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Alkylations by hydrogen autotransfer : from experiments to reaction mechanisms and vice-versa.

Nicolas Joly

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Normandie Université



UNIVERSITÉ
CAEN
NORMANDIE

THÈSE

Pour obtenir le diplôme de doctorat

Spécialité CHIMIE

Préparée au sein de l'Université de Caen Normandie

En cotutelle internationale avec GIRONA UNIVERSITAT , ESPAGNE

Alkylations by hydrogen autotransfer: from experiments to reaction mechanisms and vice-versa.

Présentée et soutenue par
NICOLAS JOLY

**Thèse soutenue le 13/10/2023
devant le jury composé de**

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Prepared in both:

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and

The University of Girona, Spain

Alkylations by Hydrogen Autotransfer:

From Experiments to Reaction Mechanisms and *Vice-Versa*

Presented and defended by:

Nicolas JOLY

on the 13th of October 2023



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ABBREVIATIONS AND ACRONYMS

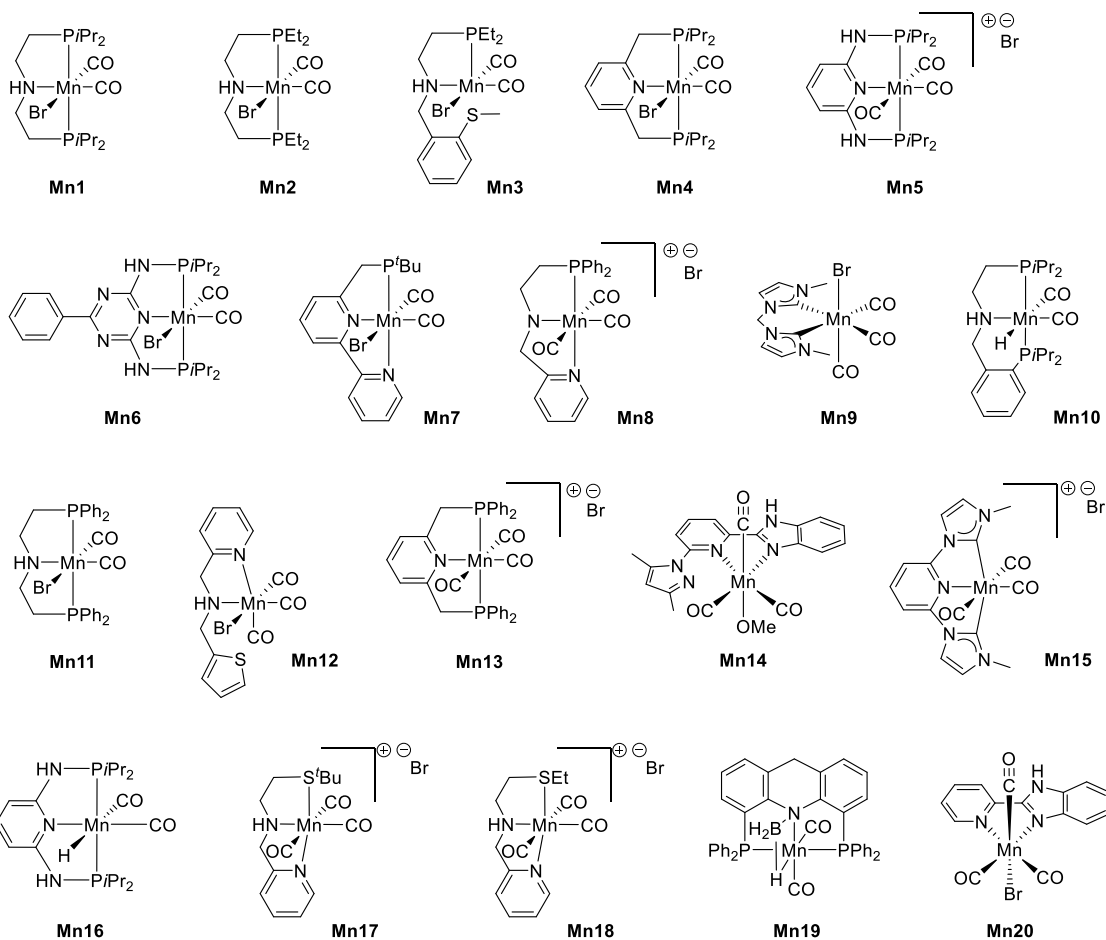
A	Ac	Acetyl
	acac	Acetyl acetonate
	Am	Amyl
	atm.	Atmosphere
	Ar	Aryl
B	BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
	Boc	<i>tert</i> -butoxycarbonyl
	bpy	2,2'-bipyridine
	Bu	Butyl
C	Cp*	1,2,3,4,5-pentamethylcyclopentadienyl
	CPME	Cyclopentyl-Methyl Ether
	Cy	Cyclohexyl
D	dba	Dibenzylideneacetone
	DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
	DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
	dcpe	1,2-bis(dicyclohexylphosphino)ethane
	dcpp	1,3-bis(diphenylphosphino)propane
	DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
	DFT	Density Functional Theory
	DIBAL-H	Diisobutyl aluminium hydride
	DIPEA	<i>N,N</i> -diisopropylethylamine
	DMAP	4-dimethylaminopyridine
	dme	Dimethoxyethane
	DMF	<i>N,N</i> -Dimethylformamide
	DMSO	Dimethyl sulfoxide
	dppf	1,1'-bis(diphenylphosphino)ferrocene
	dppm	1,1-bis(diphenylphosphino)methane
	d.r.	Diastereoisomeric ratio
	E	EDA

	EDG	Electron-Donating Group
	equiv.	Equivalent
	e.r.	Enantiomeric ratio
	Et	Ethyl
	EWG	Electron-Withdrawing Group
H	HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
	HOMO	Highest Occupied Molecular Orbital
	HRMS	High Resolution Mass Spectrometry
K	KHMDS	Potassium bis(trimethylsilyl)amide
L	LED	Light Emitting Diode
	LUMO	Lowest Unoccupied Molecular Orbital
M	Me	Methyl
	mol	Mole
	MS	Molecular Sieve
N	NHC	<i>N</i> -Heterocyclic Carbene
	NMR	Nuclear Magnetic Resonance
	NOESY	Nuclear Overhauser Effect Spectroscopy
P	Ph	Phenyl
	Phen	1,10-phenanthroline
	ppm	Parts per million
	Pr	Propyl
R	rds	Rate determining step
	r.t.	Room temperature
T	TBDMS	<i>tert</i> -butyl-dimethylsilyl
	TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
	Tf	Trifluoromethane sulfonyl
	THF	Tetrahydrofuran
	TIPS	Triisopropyl silyl
	TMB	1,2,4-trimethylbenzene
	TMEDA	Tetramethylethylenediamine

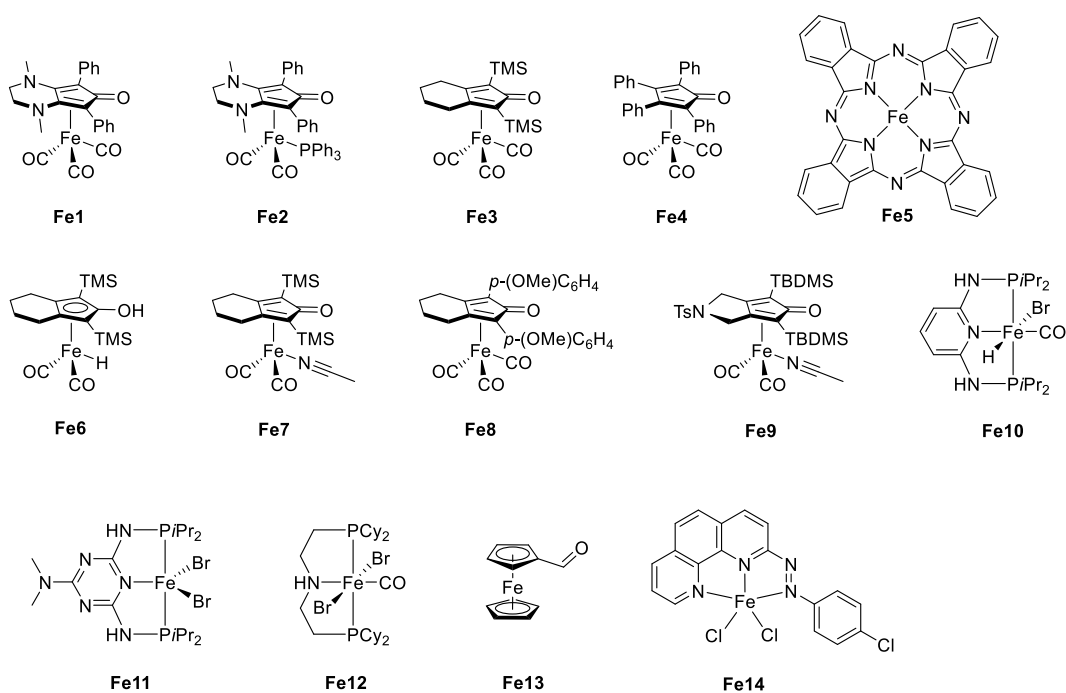
TMS	Trimethylsilyl
TON	Turn Over Number
TRIP	3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate
Ts	Tosyl

ORGANOMETALLIC COMPLEXES STUDIED

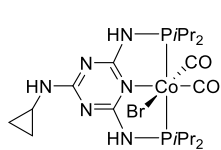
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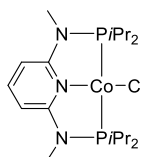
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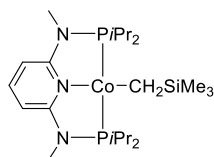
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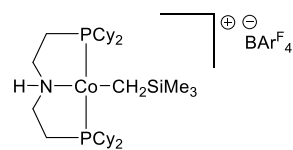
Co1



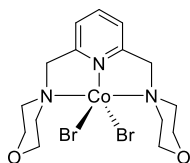
Co2



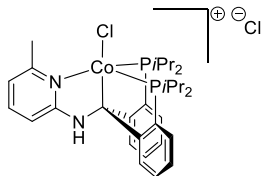
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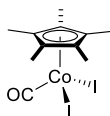
Co4



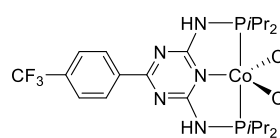
Co5



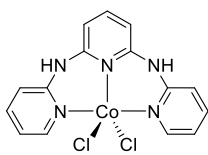
Co6



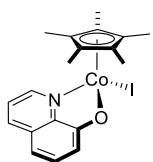
Co7



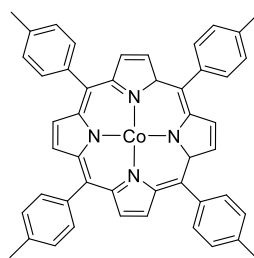
Co8



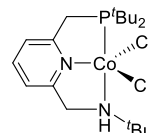
Co9



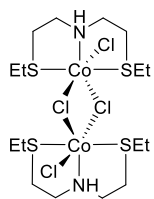
Co10



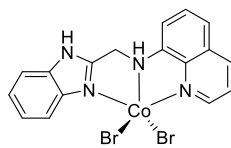
Co11



Co12

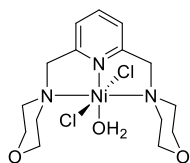


Co13

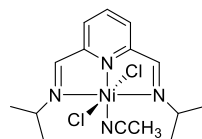


Co14

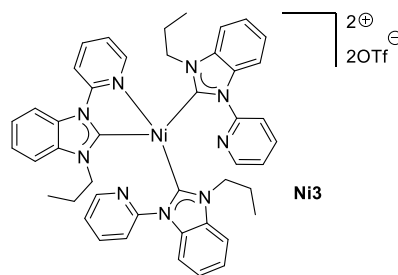
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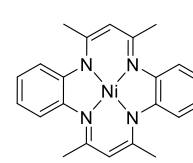
Ni1



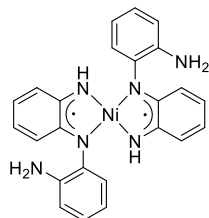
Ni2



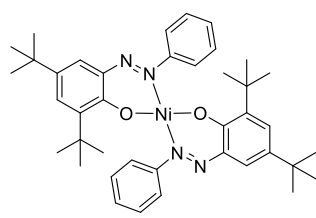
Ni3



Ni4

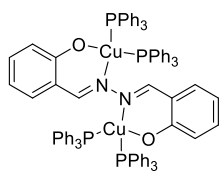


Ni5

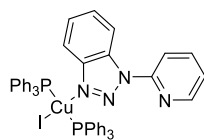


Ni6

Copper complexes:

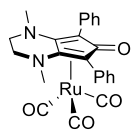


Cu1

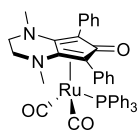


Cu2

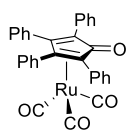
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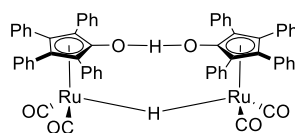
Ru1



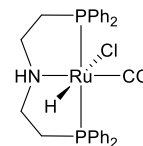
Ru2



Ru3

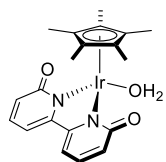


Ru4



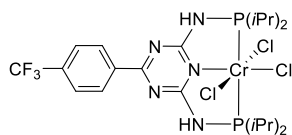
Ru5

Iridium complex:



Ir1

Chromium complex:



Cr1

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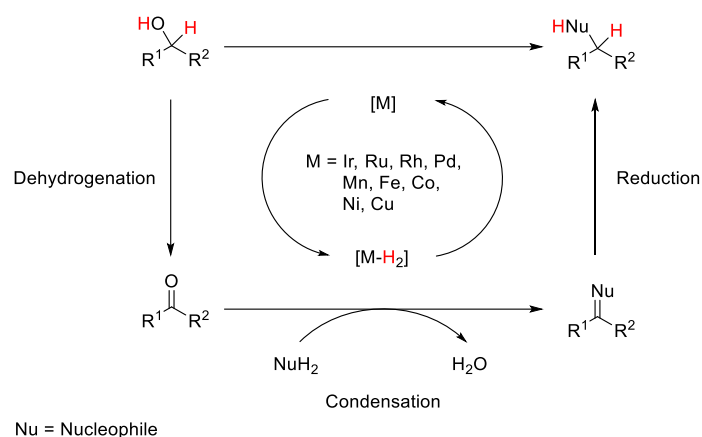
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GENERAL INTRODUCTION

In the last decades, new methodologies were developed for the formation of C-N and C-C bonds, using hydrogen autotransfer reactions. These reactions were defined for the first time by Williams in 2004 and named as “Borrowing Hydrogen”,¹ despite several examples already reported in the past.² Such reactions consist of the use of alcohols as alkylating agents, instead of halide derivatives, the latter being prepared from alcohols, thus leading to additional synthetic steps and waste generation.³ Therefore, the use of alcohols in the synthesis of carbon- and nitrogen-containing compounds is of great interest thanks to their occurrence in nature and direct availability from biomass.⁴ In that way, hydrogen autotransfer strategy falls within green and sustainable chemistry. The general mechanism of these reactions is as follows: an alcohol is dehydrogenated in the presence of an organometallic complex to generate the corresponding carbonyl derivative and a metal-hydride complex (Scheme 1). The presence of a nucleophile allows the condensation with the carbonyl function, leading to an unsaturated species which is finally reduced by the metal-hydride complex.



Scheme 1: General mechanism of hydrogen autotransfer reactions.

Numerous noble metals such as iridium,⁵ rhodium⁶ or ruthenium⁷ were reported to perform such reactions. The alkylation of various nucleophiles was described such as ketones,⁸ amides or esters,⁹ as

¹ Edwards, M. G.; Jazzar, R. F. R.; Paine, B. M.; Shermer, D. J.; Whittlesey, M. K.; Williams, J. M. J. *Chem. Commun.* **2004**, 4, 90-91.

² (a) Winans, C. F.; Adkins, H. *J. Am. Chem. Soc.* **1932**, 54, 306-312. (b) Pratt, E. F.; Frazza, E. J. *J. Am. Chem. Soc.* **1954**, 76, 6174-6179. (c) Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S.; Tongpenyai, N. *Tetrahedron Lett.* **1981**, 22, 4107-4111. (d) Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S.; Tongpenyai, N. *J. Chem. Soc. Chem. Commun.* **1981**, 611-612.

³ (a) Lamoureux, G.; Agüero, C. *Arkivoc* **2009**, 251-264. (b) Szekely, G.; Amores de Sousa, M. C.; Gil, M.; Castelo Ferreira, F.; Heggie, W. *Chem. Rev.* **2015**, 115, 8182-8229.

⁴ (a) Vispute, T. P.; Zhang, H.; Sanna, A.; Xiao, R.; Huber, G. W. *Science* **2010**, 330, 1222-1227. (b) Sun, Z.; Bottari, G.; Afanasenko, A.; Stuart, M. C. A.; Deuss, P. J.; Fridrich, B.; Barta, K. *Nat. Catal.* **2018**, 1, 82-92.

⁵ Saidi, O.; Blacker, A. J.; Lamb, G. W.; Marsden, S. P.; Taylor, J. E.; Williams, J. M. J. *Org. Process Res. Dev.* **2010**, 14, 1046-1049.

⁶ (a) Gülcemal, S. *Appl. Organomet. Chem.* **2012**, 26, 246-251. (b) Mata, J. A.; Povyatos, M.; Peris, E. *Coord. Chem. Rev.* **2007**, 251, 841-859.

⁷ (a) Chelucci, G. *Coord. Chem. Rev.* **2017**, 331, 1-36. (b) Slatford, P. A.; Whittlesey, M. K.; Williams, J. M. J. *Tetrahedron Lett.* **2006**, 47, 6787-6789.

⁸ Cho, C.S.; Kim, B.T.; Kim, T.-J.; Shim, S.C. *Tetrahedron Lett.* **2002**, 43, 7987-7989.

⁹ Gong, D.; Hu, B.; Yang, W.; Chen, D. *ChemCatChem* **2019**, 11, 4841-4847.

well as amines,¹⁰ nitriles¹¹ and nitro derivatives (Figure 1).¹² Alkylations or syntheses of heterocycles were also described.^{13,14}

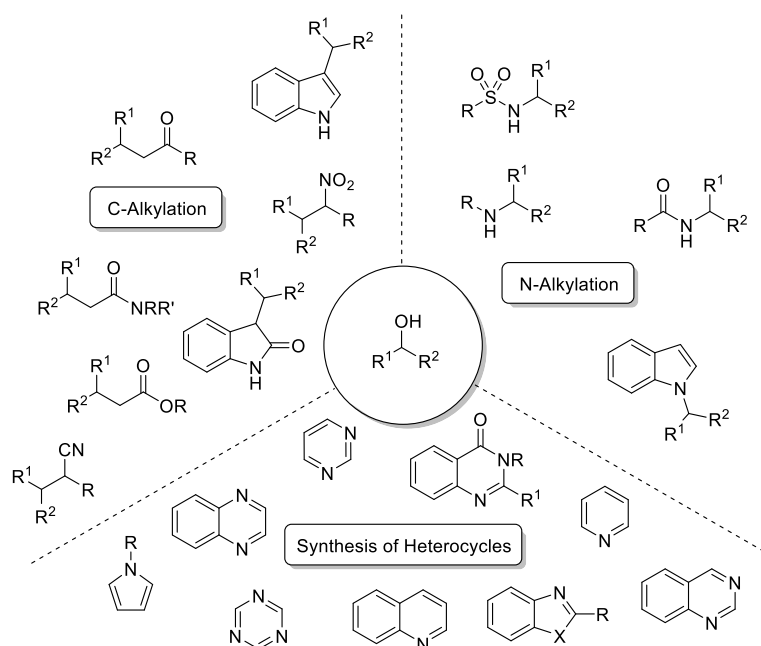


Figure 1: Examples of alkylated products and heterocycles.

Nevertheless, the rarefication of these metals and the always increasing demand make their use always more expensive. In the last years, Earth-abundant transition-metal complexes such as manganese, iron or cobalt, have proven their efficiency and competitiveness in alkylation reactions, compared to noble metals.¹⁵ Our group get particularly interested in iron which is, among all transition-metals, the most abundant in Earth crust and therefore the cheapest one (few dozens of cents per kilogram). Thanks to the use of organophosphorus ligands, iron chemistry advanced in the last years.¹⁶ However, these ligands are often air- and moisture-sensitive and too expensive. The development of cheaper ligands such as cyclopentadienones aims to solve these issues. Following the work of Knölker (**Fe3**, Figure 2),¹⁷ our group has developed different iron complexes bearing cyclopentadienone ligands (**Fe1** and **Fe2**, among others) and contributed to the employment of these complexes in homogenous

¹⁰ (a) Li, F.; Xie, J.; Shan, H.; Sun, C.; Chen, L. *RSC Adv.* **2012**, *2*, 8645-8652. (b) Michlik, S.; Hillie, T.; Kempe, R. *Adv. Synth. Catal.* **2012**, *354*, 847-862. (c) Liang, R.; Li, S.; Wang, R.; Lu, L.; Li, F. *Org. Lett.* **2017**, *19*, 5790-5793.

¹¹ Sagawushi, T.; Obara, Y. *Chem. Lett.* **2011**, *40*, 1055-1057.

¹² Black, P. J.; Cami-Kobeci, G.; Edwards, M. G.; Slatford, P. A.; Whittlesey, M. K.; Williams, J. M. J. *Org. Biomol. Chem.* **2006**, *4*, 116-125.

¹³ (a) Blank, B.; Kempe, R. *J. Am. Chem. Soc.* **2010**, *132*, 924-925. (b) Obara, Y.; Ogawa, S.; Yamamoto, N. *J. Org. Chem.* **2012**, *77*, 9429-9433. (c) Feng, T.-Y.; Li, H.-X.; Young, D. J.; Lang, J.-P. *J. Org. Chem.* **2017**, *82*, 4113-4120.

¹⁴ (a) Paul, B.; Maji, M.; Chakrabartia, K.; Kundu, S. *Org. Biomol. Chem.* **2020**, *18*, 2193-2214. (b) Mondal, A.; Sharma, R.; Pal, D.; Srimani, D. *Eur. J. Org. Chem.* **2021**, *2021*, 3690-3720. (c) Maji, M.; Panja, D.; Borthakur, I.; Kundu, S. *Org. Chem. Front.* **2021**, *8*, 2673-2709.

¹⁵ Irrgang, T.; Kempe, R. *Chem. Rev.* **2019**, *119*, 2524-2549.

¹⁶ Bauer, I.; Knölker, H.-J. *Chem. Rev.* **2015**, *115*, 3170-3387.

¹⁷ (a) Knölker, H.-J.; Heber, J.; Malher, C. H. *Synlett* **1992**, 1002-1007. (b) Knölker, H.-J.; Heber, J. *Synlett* **1993**, 924-927. (c) Knölker, H.-J.; Goesmann, H.; Klauss, R. *Angew. Chem. Int. Ed.* **1999**, *38*, 702-705.

catalysis, more particularly for the reduction of carbonyls¹⁸ and reductive amination.¹⁹ Iron complex **Fe1** demonstrated a higher activity and selectivity than the Knölker complex **Fe3** and was engaged in various alkylation reactions with anilines,²⁰ indoles,²¹ alcohols,²² or ketones.²³

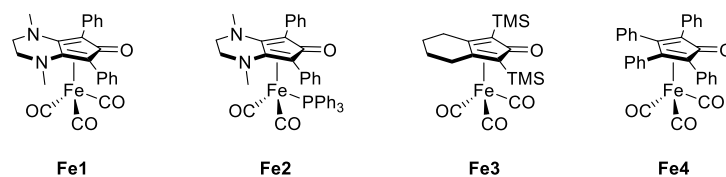


Figure 2: Iron complexes employed during this thesis.

In the continuity of these works, the main objectives of this thesis were the development of new methodologies for C-N and C-C bond formation, the investigation of reaction mechanism and the improvement of Knölker-type catalysts. The manuscript will be organised as followed: Chapter I will present a state of the art on the C-N and C-C bond formation through hydrogen borrowing methodology. The focus will be made on 3d-metal catalysed reactions using alcohols as alkylating agent. Chapter II will focus on the alkylation with hydrazide derivatives, under evaluated *N*-nucleophiles. The limits of iron complexes will be shown. Therefore, the ruthenium analogues will be studied (Figure 3). The synthesis of a heterocyclic compound will be investigated in Chapter III. More precisely the synthesis of 3-arylquinolin-2(1*H*)-ones *via* a dehydrogenative coupling approach will be presented. In Chapter IV, complex **Fe1** will be evaluated in a reductive amination reaction and examined by Density Functional Theory (DFT). Substitution effects of the phenyl rings of the ligand will be scrutinised *in silico* to improve the activity of the complex. Finally, the last chapter will concern a novel room temperature alkylation methodology using light as energy source.

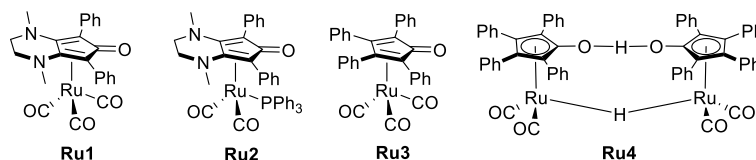


Figure 3: Ruthenium complexes employed during this thesis.

¹⁸ Mérel, D. S.; Elie, M.; Lohier, J.-F.; Gaillard, S.; Renaud, J.-L. *ChemCatChem* **2013**, *5*, 2939-2945.

¹⁹ Pagnoux-Ozherelyeva, A.; Pannetier, N.; Mbaye, M. D.; Gaillard, S.; Renaud, J.-L. *Angew. Chem. Int. Ed.* **2012**, *51*, 4976-4980.

²⁰ Lator, A.; Gaillard, S.; Poater, A.; Renaud, J.-L. *Org. Lett.* **2018**, *20*, 5985-5990.

²¹ Seck, C.; Mbaye, M. D.; Gaillard, S.; Renaud, J.-L. *Adv. Synth. Catal.* **2018**, *360*, 4640-4645.

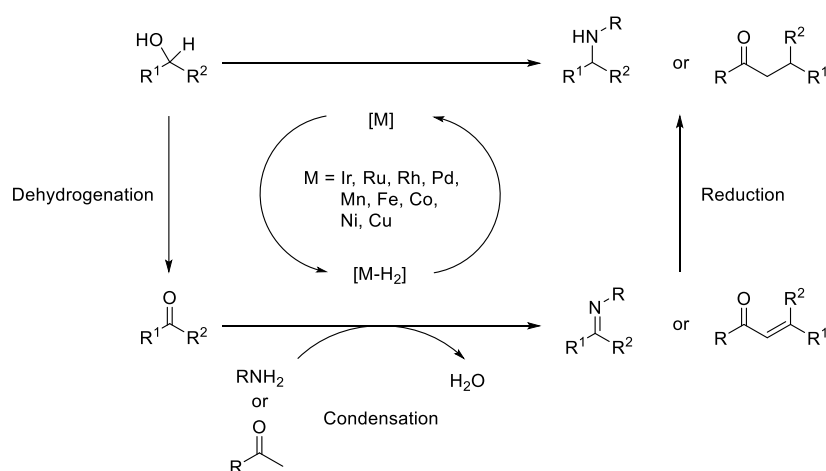
²² Bettoni, L.; Gaillard, S.; Renaud, J.-L. *Org. Lett.* **2019**, *21*, 8404-8408.

²³ (a) Seck, C.; Mbaye, M. D.; Coufourier, S.; Lator, A.; Lohier, J.-F.; Poater, A.; Ward, T. R.; Gaillard, S.; Renaud, J.-L. *ChemCatChem* **2017**, *9*, 4410-4416. (b) Bettoni, L.; Seck, C.; Mbaye, M. D.; Gaillard, S.; Renaud, J.-L. *Org. Lett.* **2019**, *21*, 3057-3061. (c) Bettoni, L.; Gaillard, S.; Renaud, J.-L. *Chem. Commun.* **2020**, *56*, 12909-12912. (d) Bettoni, L.; Gaillard, S.; Renaud, J.-L. *Org. Lett.* **2020**, *22*, 2064-2069.

**CHAPTER I: BIBLIOGRAPHIC STUDY: C-N AND C-C
BOND FORMATION THROUGH HYDROGEN
AUTOTRANSFER STRATEGY.**

I. General principle.

Alkylation of amines or ketones usually requires the use of alkyl halides as electrophiles and a stoichiometric amount of base.²⁴ Such strategy suffers from the lack of selectivity (due to over-alkylation reaction) and generation of by-products (halogen salts for example) which can be difficult to manage. For these reasons, new methodologies were developed, and among them, hydrogen autotransfer.²⁵ Following this strategy, the formation of C-N bonds usually proceeds using a nucleophilic nitrogen-containing nucleophile. After the dehydrogenation of an alcohol into the corresponding carbonyl by a metal complex, a condensation step takes place providing an imine/iminium intermediate (Scheme 1.1). The latter is finally reduced by the metal-hydrogen species to give the N-alkylated product. The C-C bonds formation proceeds using ketones as pro-nucleophiles. The unsaturated intermediate is generated by a Knoevenagel condensation between the ketone and the dehydrogenated alcohol. The C=C bond of the α,β -unsaturated ketone is finally reduced by the metal-hydrogen species to give the α -alkylated ketone (Scheme 1.1). That way, the only by-product of the reaction is water resulting from the condensation step.



Scheme 1.1: Simplified mechanism for the alkylation of amines and ketones by hydrogen autotransfer.

Hydrogen autotransfer reaction were extensively studied during the last decades. Many noble and non-nobles metal catalysts were reported to catalyse such reactions.^{26,27} This part will be dedicated to the formation of C-N and C-C bonds through hydrogen autotransfer reactions using alcohols catalysed by homogeneous first-row transition-metal catalysts.

²⁴ (a) Marvin, C. C. in *Comprehensive Organic Synthesis* (Second Edition), Vol. 6 (Ed.: P. Knochel), Elsevier. **2014**, 34-99. (b) Stoltz, B. M.; Bennett, N. B.; Duquette, D. C.; Goldberg, A. F. G.; Liu, Y.; Loewinger, M. B.; Reeves, C. M. in *Comprehensive Organic Synthesis* (Second Edition), Vol. 3 (Ed.: P. Knochel), Elsevier. **2014**, 1-55.

²⁵ (a) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681-703. (b) Guillena, G.; Ramón, D. J.; Yus, M. *Chem. Rev.* **2010**, *110*, 1611-1641.

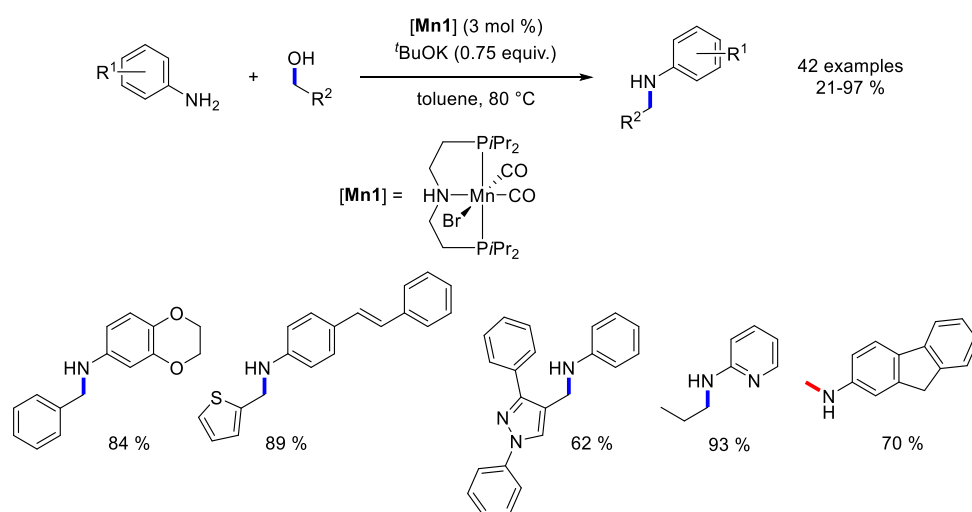
²⁶ For recent reviews see: (a) Huang, F.; Liu, Z.; Yu, Z. *Angew. Chem. Int. Ed.* **2016**, *55*, 862-875. (b) Chelucci, G. *Coord. Chem. Rev.* **2017**, *331*, 1-36. (c) Corma, A.; Navas, J.; Sabater, M. J. *Chem. Rev.* **2018**, *118*, 1410-1459.

²⁷ For recent reviews on the use of Earth-abundant metal-based complexes in auto-transfer strategy, see: (a) Irrgang, T.; Kempe, R. *Chem. Rev.* **2019**, *119*, 2524-2549. (b) Reed-Berendt, B. G.; Polidano, K.; Morrill, L. C. *Org. Biomol. Chem.* **2019**, *17*, 1595-1607. (c) Maji, B.; Barman, M. K. *Synthesis* **2017**, *49*, 3377-3393. (d) Renaud, J.-L.; Gaillard, S. *Synthesis* **2016**, *48*, 3659-3683. (e) Bauer, I.; Knölker, H.-J. *Chem. Rev.* **2015**, *115*, 3170-3387.

II. *N*-alkylation reactions catalysed by non-noble metals.

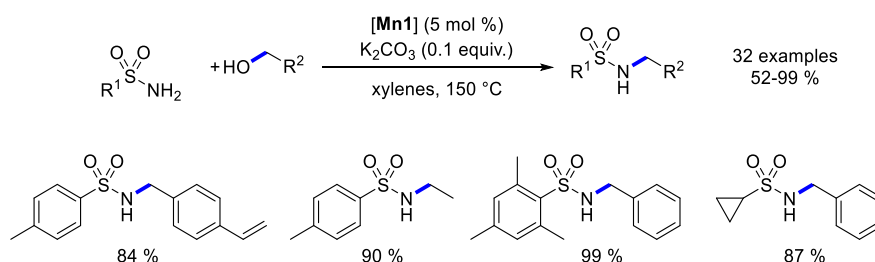
1) Manganese-catalysed *N*-alkylation reactions.

In 2016, Beller and co-workers described the first alkylation of amines with alcohols using Mn-Macho catalyst.²⁸ Anilines derivatives were alkylated with primary alcohols and only the mono-alkylated product was observed (Scheme 1.2). This reaction tolerated a variety of functional groups allowing the formation of substituted products. Methylation is a greater challenge as the dehydrogenation of methanol required higher energy than those of other alcohols ($\Delta H = +84$ kJ/mol for methanol *versus* $\Delta H = +68$ kJ/mol for ethanol for example). The Mn-Macho complex was able to catalyse the methylation of aniline-type derivatives in the presence of 1 equiv. of base at 100 °C (Scheme 1.2). The corresponding methylated anilines were isolated in 52 to 94 % yields.



Scheme 1.2: Manganese-catalysed alkylation of amines.

In 2019, the Mn-Macho complex-catalysed alkylation of sulphonamides was reported by Morill.²⁹ A variety of *N*-substituted sulphonamides were prepared following this methodology, perhaps, a high temperature (150 °C) was required to achieve this alkylation reaction in good yields (Scheme 1.3).

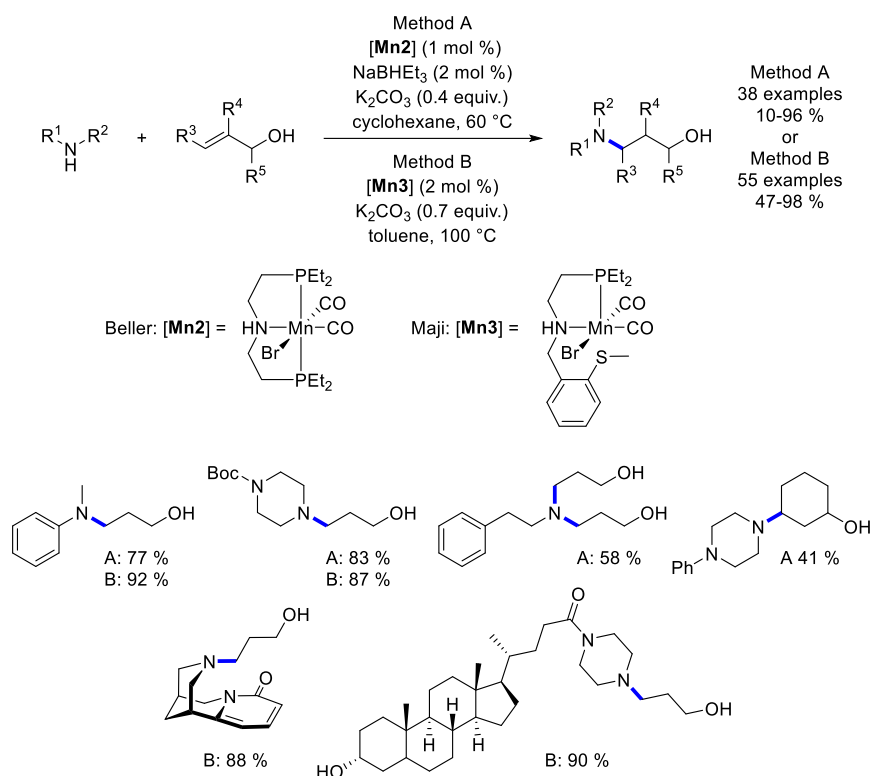


Scheme 1.3: Alkylation of sulfonylamides.

²⁸ Elangovan, S.; Neumann, J.; Sortais, J.-B.; Junge, K.; Darcel, C.; Beller, M. *Nat. Commun.* **2016**, *7*, 12641.

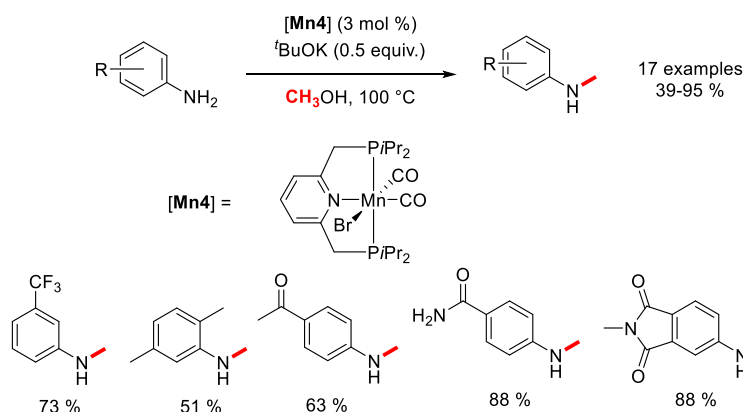
²⁹ Reed-Berendt, B. G.; Morrill, L. C. *J. Org. Chem.* **2019**, *84*, 3715-3724.

More recently, Beller and Maji reported the hydroamination of allylic alcohols.³⁰ This reaction differs from the previous alkylations since a 1,4-addition reaction takes place on the α,β -unsaturated aldehyde intermediate, to give a γ -amino-alcohol as final product (Scheme 1.4).



Scheme 1.4: Synthesis of γ -amino-alcohols described by Beller and Maji.

Replacement of the Macho ligand by a PNP pincer-type ligand (a pyridine-diphosphine ligand) led to the improvement of the methylation reaction. At 100 °C, in the presence of 0.5 equiv. of base, the *N*-methyl anilines were obtained in 39 to 95 % yields (Scheme 1.5).³¹

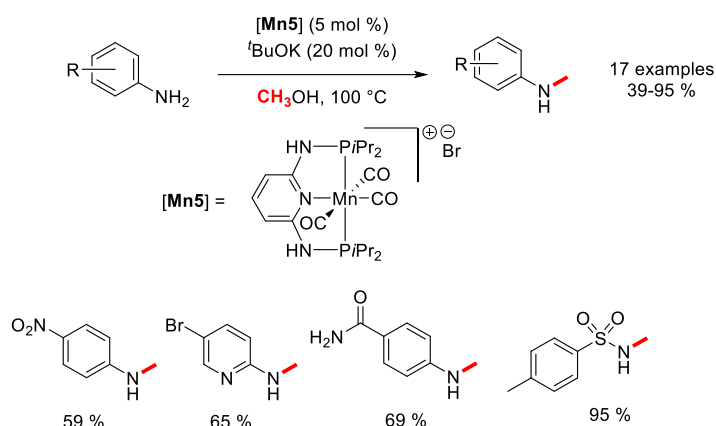


Scheme 1.5: Methylation of anilines derivatives.

³⁰ (a) Duarte de Almeida, L.; Bourriquen, F.; Junge, K.; Beller, M. *Adv. Synth. Catal.* **2021**, *363*, 4177-4181. (b) Das, K.; Sarkar, K.; Maji, B. *ACS Catal.* **2021**, *11*, 7060-7069.

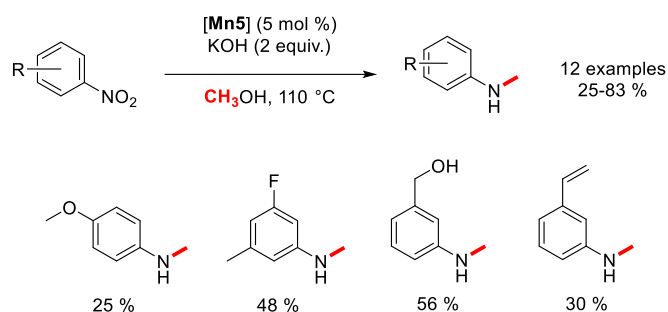
³¹ Neumann, J.; Elangovan, S.; Spannenberg, A.; Junge, K.; Beller, M. *Chem. Eur. J.* **2017**, *23*, 5410-5413.

At the same time than Beller,²⁸ Sortais described the application of another PNP-Mn complex in the methylation of aniline derivatives.³² The *N*-methylated anilines were obtained in 39-95 % yield (Scheme 1.6) and various electron-withdrawing groups (EWG) and electron-donating groups (EDG) were evaluated to delineate the scope of this reaction.



Scheme 1.6: Methylation of aniline derivatives reported by Sortais.

Morill developed a synthetic method for the one-pot conversion of nitroarenes into *N*-methylaryl amines.³³ In a first step, the cationic manganese complex dehydrogenates methanol and reduces the nitro moiety into amine. Then, a methylation takes place yielding the methylated aniline (Scheme 1.7).



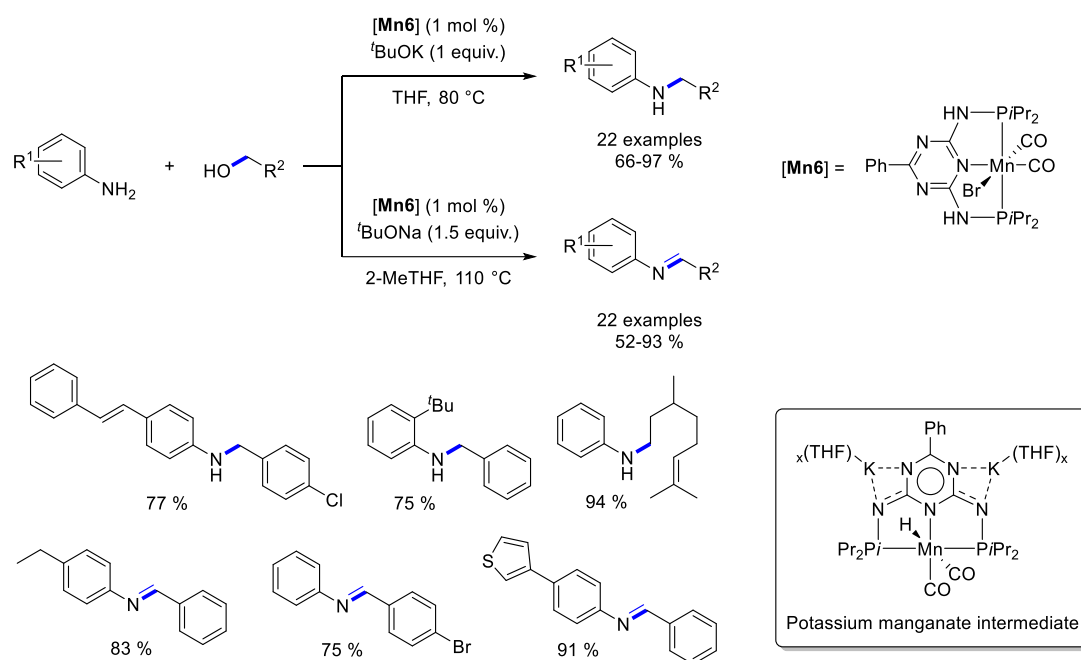
Scheme 1.7: Synthesis of methylaryl amines.

In 2018, Kempe described a base-switchable synthesis of amines or imines.³⁴ A PNP ligand incorporating a triazine motif was developed and the corresponding Mn-complex applied in the alkylation of anilines. Depending on the cation of the base (K^+ or Na^+), starting from the same amine and alcohol, either the *N*-alkyl amine, via a hydrogen autotransfer process, or the imine, via dehydrogenative condensation, was isolated (Scheme 1.8). This reactivity switch was attributed to the chelation ability of the cation, and the reactivity of the corresponding manganese hydride intermediate. The potassium manganate hydride reduced faster the imine than the sodium salt.

³² Bruneau-Voisine, A.; Wang, D.; Dorcet, V.; Roisnel, T.; Darcel, C.; Sortais, J.-B. *J. Catal.* **2017**, *347*, 57-62.

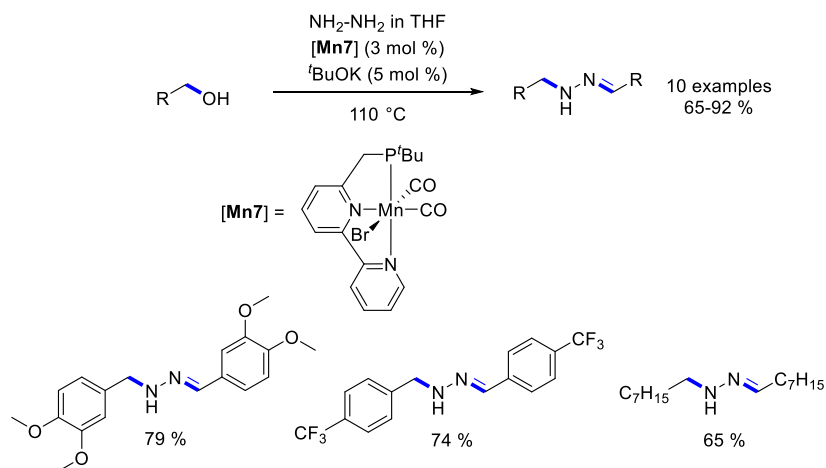
³³ Reed-Berendt, B. G.; Mast, N.; Morrill, L. C. *Eur. J. Org. Chem.* **2020**, 1136-1140.

³⁴ Fertig, R.; Irrgang, T.; Freitag, F.; Zander, J.; Kempe, R. *ACS Catal.* **2018**, *8*, 8525-8530.



Scheme 1.8: Alkylation of anilines derivatives.

Modification of the ligand allowed a fine tuning of the reactivity. In 2017, Milstein replaced the PNP ligand by a phosphine-bipyridine one (PNN ligand) and applied the corresponding Mn-complex in the alkylation of hydrazine (Scheme 1.9).³⁵ Surprisingly, *N*-substituted hydrazones were obtained in this reaction *via* a hydrogen transfer process for the alkylation step and a dehydrogenation step for the hydrazone moiety formation.



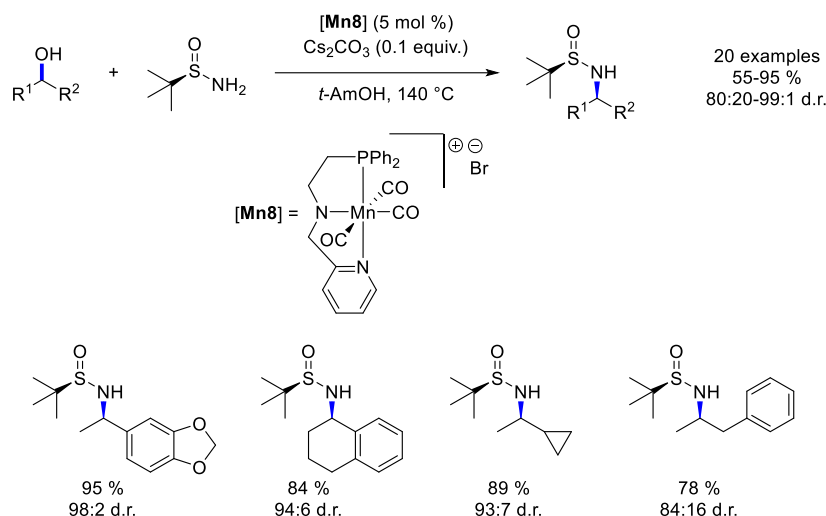
Scheme 1.9: Synthesis of *N*-substituted hydrazones.

Rueping replaced the central pyridine ring of the ligand into an amine to generate a novel cationic manganese complex.³⁶ The latter was involved in an asymmetric amination of secondary alcohols (Scheme 1.10). Asymmetric reduction of the imine intermediate was obtained by the presence

³⁵ Das, U. K.; Ben-David, Y.; Diskin-Posner, Y.; Milstein, D. *Angew. Chem. Int. Ed.* **2018**, *57*, 2179-2182.

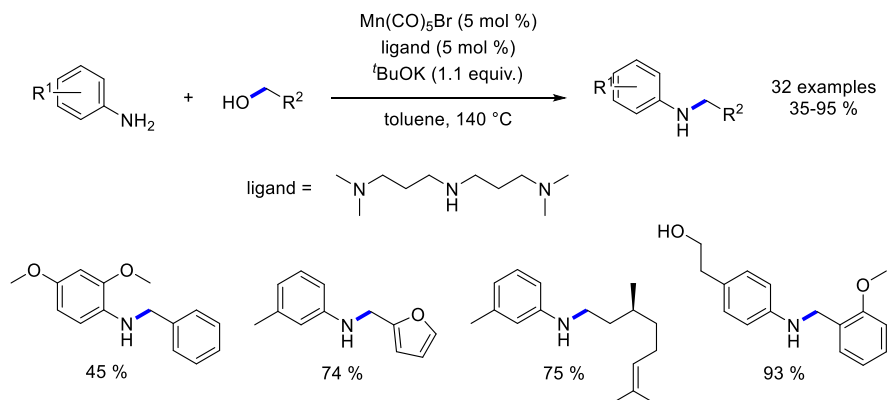
³⁶ Azofra, L. M.; Tran, M. A.; Zubar, V.; Cavallo, L.; Rueping, M.; El-Sepelgy, O. *Chem. Commun.* **2020**, *56*, 9094-9097.

of the *tert*-butyl group. The latter forces the Mn-H complex to approach the less hindered side of the imine, thus generating a diastereoselective reduction.



Scheme 1.10: Asymmetric amination of secondary alcohols.

In 2018, Balaraman reported an inexpensive *N*-alkylation of anilines with benzylic and aliphatic alcohols.³⁷ A manganese salt ($\text{Mn}(\text{CO})_5\text{Br}$) was associated with *N*¹-(3-(Dimethylamino)propyl)-*N*³,*N*³-dimethylpropane-1,3-diamine (NNN ligand) to form the catalytic species. Electron-rich and electron-deficient *N*-substituted anilines were isolated in 35 to 95 % yields. (Scheme 1.11). This methodology is competitive compared to the catalytic systems of Beller²⁸ or Kempe³⁴ since the catalytic species is prepared *in situ*, even though the products are obtained in slightly lower yields.



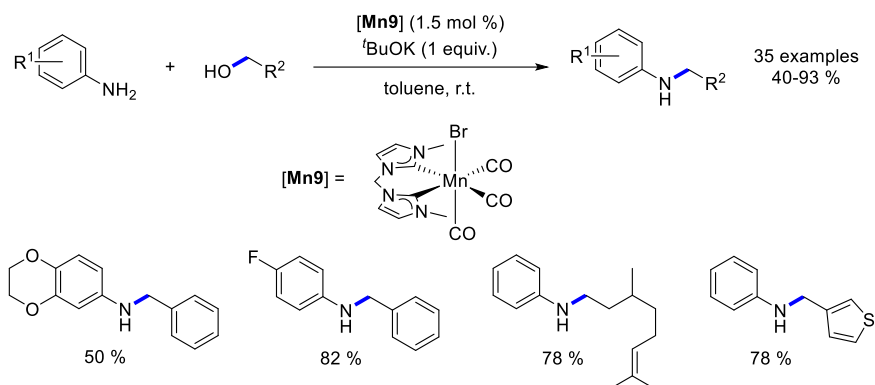
Scheme 1.11: Alkylation of aniline derivatives.

The following year, Ke described the first room temperature non-noble metal system for the alkylation of anilines derivatives.³⁸ A manganese complex bearing *N*-heterocyclic carbene (NHC) ligand catalysed the reaction of anilines with benzylic and aliphatic alcohols at room temperature. The corresponding *N*-substituted products were isolated in 40 to 93 % (Scheme 1.12). The methylation was also investigated and a temperature of 100 °C was required to obtain the methylated products in 53 to 94 % yields. Mechanistic investigation by means of Density Functional Theory (DFT) calculations

³⁷ Landge, V. G.; Mondal, A.; Kumar, V.; Nandakumar, A.; Balaraman, E. *Org. Biomol. Chem.* **2018**, *16*, 8175-8180.

³⁸ Huang, M.; Li, Y.; Li, Y.; Liu, J.; Shu, S.; Liu, Y.; Ke, Z. *Chem. Commun.* **2019**, *55*, 6213-6216.

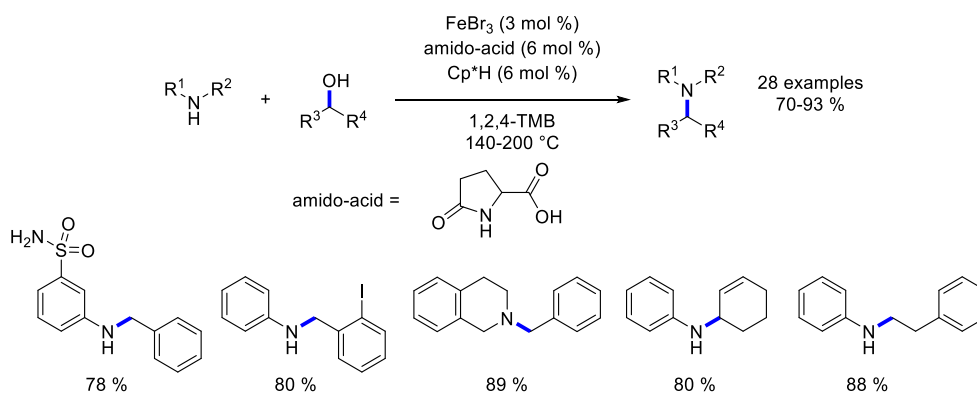
highlighted an outer-sphere mechanism with a maximum energy barrier of 23.7 kcal/mol, compared to the inner-sphere mechanism which required the de-coordination of a CO ligand to perform this reaction with a maximum of 46.4 kcal/mol energy barrier.



Scheme 1.12: Alkylation of anilines derivatives.

2) Iron-catalysed *N*-alkylation reactions.

One of the first iron-catalysed alkylation of amines with alcohols was reported by Saito in 2011.³⁹ Iron tribromide (3 mol %) in combination with an amido-acid (6 mol %) and Cp*H (6 mol %) catalysed the alkylation of a variety of primary and secondary amines with benzylic and aliphatic alcohols to form secondary and tertiary amines at 140-200 °C (Scheme 1.13). Unsaturated alcohols were also alkylated without any reduction of the C=C bond. High temperatures were required and the catalytic species was not clearly defined. Very few substituents were also reported in this work.



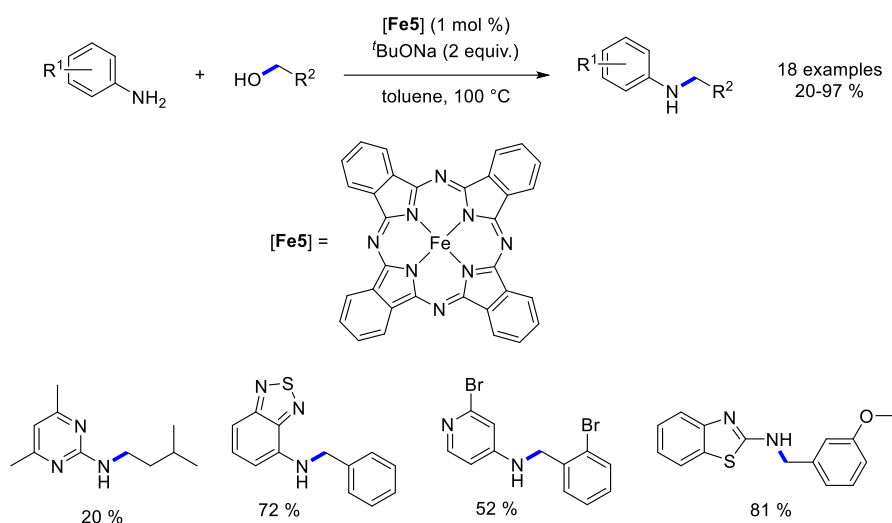
Scheme 1.13: Iron-catalysed alkylation of amines reported by Saito.

In 2013, Singh described an iron(II)-phthalocyanine as a catalyst for the alkylation of aromatic amines with alcohols.⁴⁰ This catalyst allowed the mono-alkylation of arylamines with benzylic and aliphatic alcohols (Scheme 1.14). Low yields were obtained with aliphatic alcohols due to the higher energy required for the dehydrogenation step compared to benzylic alcohols. A Fe(III)-phthalocyanine

³⁹ Zhao, Y.; Foo, S. W.; Saito, S. *Angew. Chem. Int. Ed.* **2011**, *50*, 3006-3009.

⁴⁰ Bala, M.; Verma, P. K.; Sharma, U.; Kumar, N.; Singh, B. *Green Chem.* **2013**, *15*, 1687-1693.

chloride was also reported by Minakawa for the same reaction, but less functional groups were tolerated and higher temperatures were required (130 °C).⁴¹



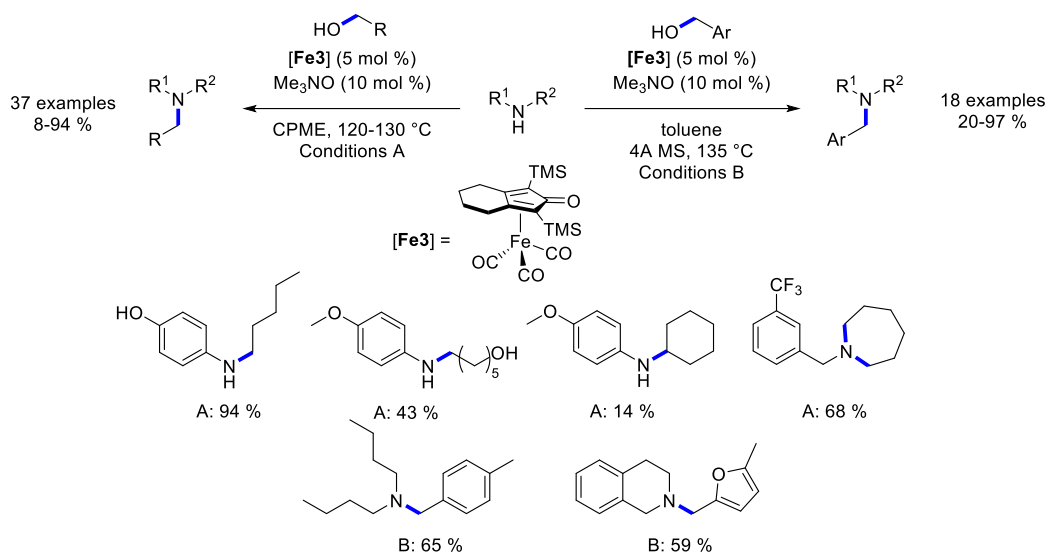
Scheme 1.14: Alkylation of amines reported by Singh.

Feringa and Barta described the alkylation of aryl and benzyl amines using a cyclopentadienone iron complex in the absence of base, a great advantage in the context of sustainable chemistry.⁴² Surprisingly, aliphatic alcohols afforded the alkylated amines in good yields while the reaction with benzylic alcohols was less efficient, moreover the reaction of anilines with diols led to the amino-alcohols products instead of the *N*-aryl cyclic amines. To overcome the lower reactivity of benzylic alcohols, the use of benzylamines in the presence of aliphatic alcohols (or diols) was proposed. The *N*-benzylamines were synthesised in good yields (Scheme 1.15). Worth to note, *N*-alkyl benzylamine derivatives were prepared by monoalkylation of benzylamines with alcohols. Finally, if benzyl alcohols have to be engaged in such alkylation procedure, then CPME has to be replaced by toluene and molecular sieve has to be added.⁴³ Nevertheless, this modification did not permit to increase the reactivity with secondary alcohols.

⁴¹ Minakawa, M.; Okubo, M.; Kawatsura, M. *Bull. Chem. Soc. Jpn.* **2015**, *88*, 1680-1682.

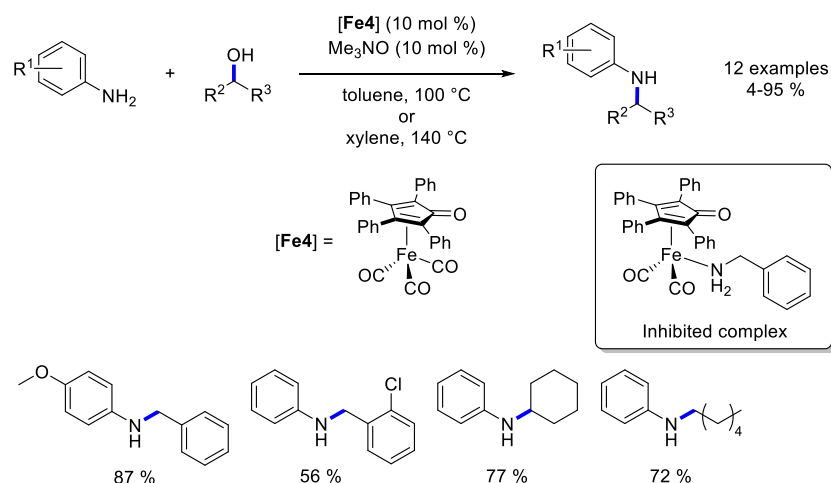
⁴² Yan, T.; Feringa, B. L.; Barta, K. *Nat Commun* **2014**, *5*, 5602.

⁴³ Yan, T.; Feringa, B. L.; Barta, K. *ACS Catal.* **2016**, *6*, 381-388.



Scheme 1.15: Knölker-catalysed alkylation of amines described by Feringa and Barta.

Wills described a tetraphenylcyclopentadienone iron complex (also known as Schrauzer's complex⁴⁴) for the alkylation of anilines with primary alcohols.⁴⁵ This reaction was limited to methoxy- and chloro-substituted anilines and led to lower conversion than the Knölker's complex,^{42,43} even with higher catalyst loading and temperature were required (Scheme 1.16). When benzylamine was introduced, no product was formed. The authors suggested that benzylamine inhibited the catalytic activity by forming a stable amino-iron complex with the active species, as already observed by Beller with the Shvo's complex.⁴⁶



Scheme 1.16: Alkylation of anilines.

In 2016, Sundararaju reported the alkylation of amines with allyl alcohols catalysed by the Knölker's complex.⁴⁷ Contrary to the hydroamination reaction reported by Maji and Beller,³⁰ the C-N

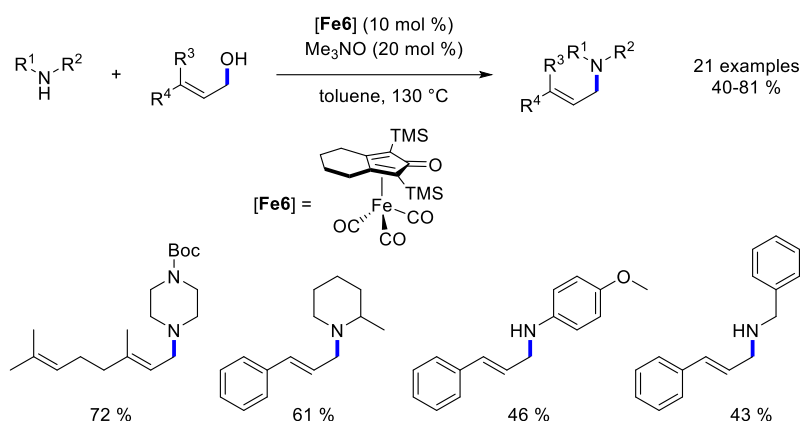
⁴⁴ Schrauzer, G. N. *J. Am. Chem. Soc.* **1959**, *81*, 5307-5310.

⁴⁵ Rawlings, A. J.; Diorazio, L. J.; Wills, M. *Org. Lett.* **2015**, *17*, 1086-1089.

⁴⁶ Hollmann, D.; Jiao, H.; Spannenberg, A.; Bähn, S.; Tillack, A.; Parton, P.; Altink, R.; Beller, M. *Organometallics* **2009**, *28*, 473-479.

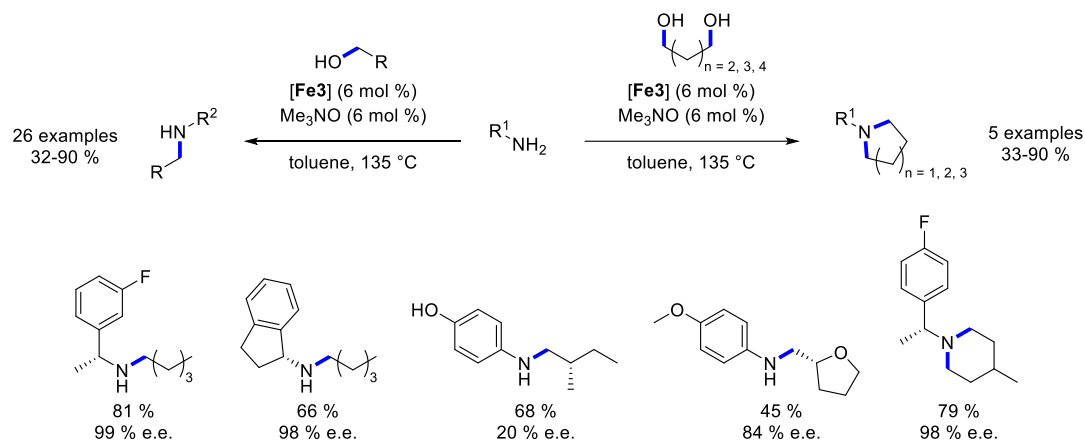
⁴⁷ Emayavaramban, B.; Roy, M.; Sundararaju, B. *Chem. Eur. J.* **2016**, *22*, 3952-3955.

bond was formed by condensation between the amine and the *in situ* generated carbonyl intermediate, to furnish the allyl amines instead of the γ -amino-alcohols (Scheme 1.17).



Scheme 1.17: Alkylation of amines with allylic alcohols.

The synthesis of chiral compounds starting from chiral amine or alcohols was also investigated by Barta.⁴⁸ Chiral benzylamines were reacted with aliphatic alcohols (or diols) to furnish the mono- or di-alkylated products in good yields (61-90 %, Scheme 1.18). The same procedure was used starting from optically active alcohols affording the corresponding product in moderate to good yields (32-68 %, Scheme 1.18). Lower enantiomeric excesses were obtained in this case as racemization could occur via enol (or enamine) formation after the dehydrogenation step.



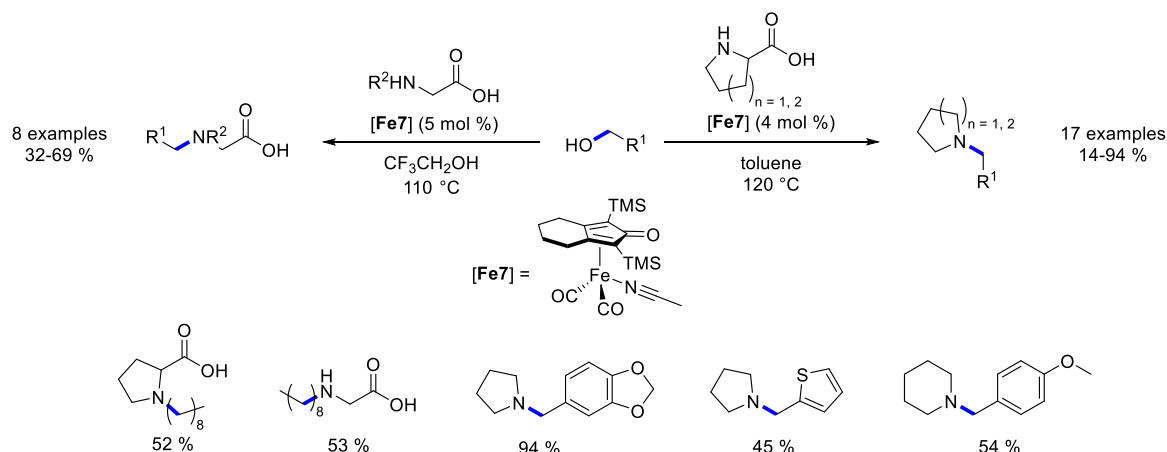
Scheme 1.18: Synthesis of chiral amines.

The *N*-alkylation of unprotected amino-acids was then investigated by the same group.⁴⁹ A derivative of the Knölker complex bearing an acetonitrile ligand replacing one CO was used. Various primary alcohols were engaged in this reaction in acidic conditions, affording the mono-alkylated product in moderate to good yields (32-69 %, Scheme 1.19). This work was extended to the synthesis of pyrrolidine and piperidine derivatives using proline derivatives.⁵⁰ The non-acidic conditions allowed the removal of the acid function by decarboxylation *in situ*.

⁴⁸ Bottari, G.; Afanasenko, A.; Castillo-Garcia, A. A.; Feringa, B. L.; Barta, K. *Adv. Synth. Catal.* **2021**, *363*, 5436-5442.

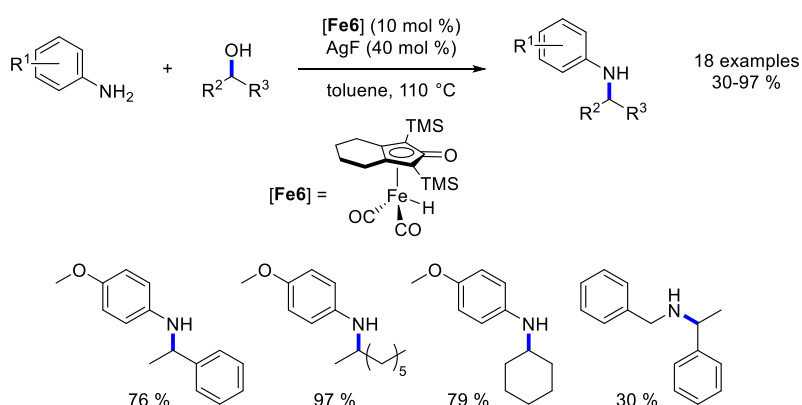
⁴⁹ Yan, T.; Feringa, B. L.; Barta, K. *Sci. Adv.* **2017**, *3*, eaao6494.

⁵⁰ Afanasenko, A.; Hannah, R.; Yan, T.; Elangovan, S.; Barta, K. *ChemSusChem* **2019**, *12*, 3801-3807.



Scheme 1.19: Alkylation of amino-acids and synthesis of *N*-substituted cyclic amines.

As mentioned previously in Barta's work, secondary alcohols are more reluctant pro-electrophiles. To enhance their reactivity, Zhao described their activation in the presence of silver fluoride as Lewis acid.⁵¹ Even if the iron complex and silver salt loading remained high (10 mol %), this methodology opened an access to *N*-aryl and *N*-benzyl α,α' -disubstituted amines in moderate to good yields (Scheme 1.20).

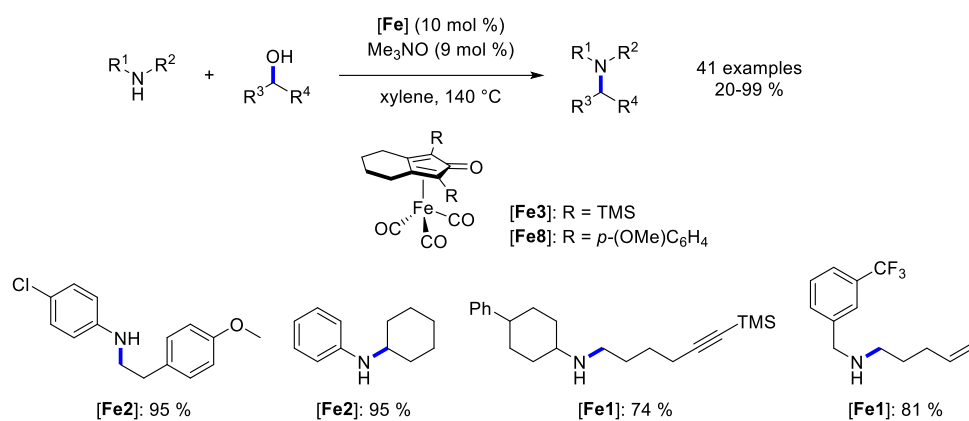


Scheme 1.20: Alkylation of amines with secondary alcohols.

Later on, Wills re-investigated the alkylation of amines with a small library of Knölker-type complexes.⁵² The trimethylsilyl groups of the cyclopentadienone were replaced by aryl rings bearing electron-donating or electron-withdrawing groups, and the different catalysts were evaluated. The results were case-sensitive, depending on the substrates engaged in the reaction. Even though a methoxy-aryl containing complex performed well for most of the substrates, the original Knölker complex was used to exemplify the reaction (Scheme 1.21).

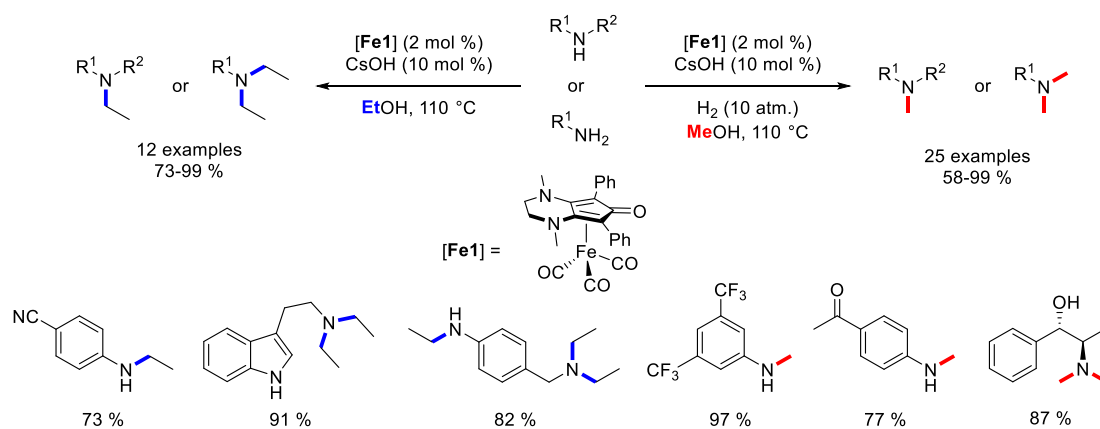
⁵¹ Pan, H.-J.; Ng, T. W.; Zhao, Y. *Chem. Commun.* **2015**, 51, 11907-11910.

⁵² Brown, T. J.; Cumbes, M.; Diorazio, L. J.; Clarkson, G. J.; Wills, M. *J. Org. Chem.* **2017**, 82, 10489-10503.



Scheme 1.21: Alkylation of amines with Knölker complex and analogues.

Renaud and Poater pursued this study and reported a modified Knölker-type complex with an electron-rich ligand for the methylation and ethylation of amines.²⁰ This diaminocyclopentadienone iron tricarbonyl complex was previously reported by the same authors for reductive amination reactions.⁵³ Alkylation with methanol and ethanol as pro-electrophiles has been scarcely studied and is more challenging due to the higher dehydrogenation energy of ethanol and methanol with respect to other alcohols. Nevertheless, this new complex afforded the ethyl- and methyl-substituted amines in good to excellent yields with a low catalyst loading (Scheme 1.22). Worth to note, the presence of base in catalytic amount was necessary to perform the reactions. Also, hydrogen pressure (10 atm.) was required to achieve the methylation reaction in good yields.



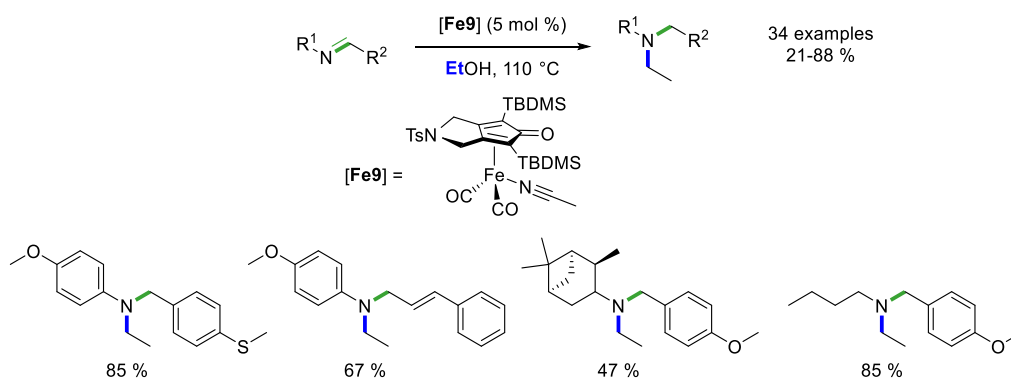
Scheme 1.22: Methylation and ethylation of amines reported by Renaud.

The same year, Bour *et al.* described a reductive ethylation of *N*-arylimines catalysed by a Knölker-type complex.⁵⁴ This complex was initially described by Renaud *et al.* in reductive amination.⁵⁵ In this sequential reaction, ethanol served both as alkylating agent and hydride source. *N*-aryl-*N*-ethyl amines were obtained in yields ranging from 21 to 88 % (Scheme 1.23).

⁵³ Thai, T.-T.; Mérel, D. S.; Poater, A.; Gaillard, S.; Renaud, J.-L. *Chem. Eur. J.* **2015**, *21*, 7066-7070.

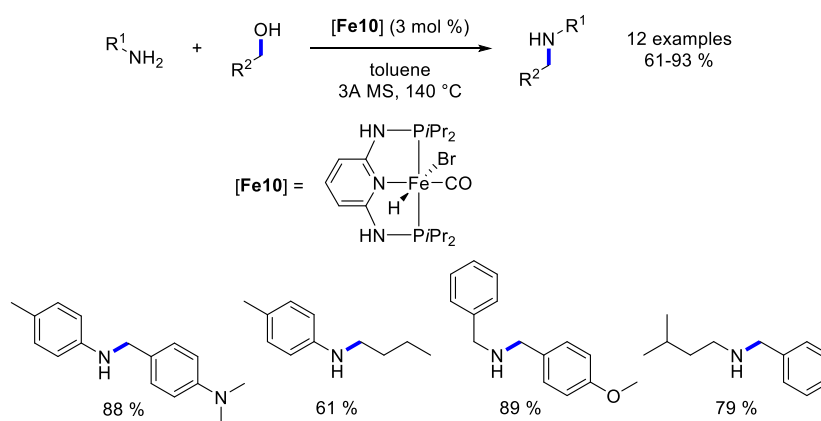
⁵⁴ Vayer, M.; Morcillo, S. P.; Dupont, J.; Gandon, V.; Bour, C. *Angew. Chem. Int. Ed.* **2018**, *57*, 3228-3232.

⁵⁵ Moulin, S.; Dentel, H.; Pagnoux-Ozherelyeva, A.; Gaillard, S.; Poater, A.; Cavallo, L.; Lohier, J.-F.; Renaud, J.-L. *Chem. Eur. J.* **2013**, *19*, 17881-17890.



Scheme 1.23: Ethylation of imines reported by Bour.

Kirchner described an iron complex, analogue of Sortai's PNP-Mn complex.³² This iron-hydride complex catalysed the alkylation of amines with primary alcohols.⁵⁶ Low catalyst loadings were used but high temperatures were required to reach good yields (Scheme 1.24).

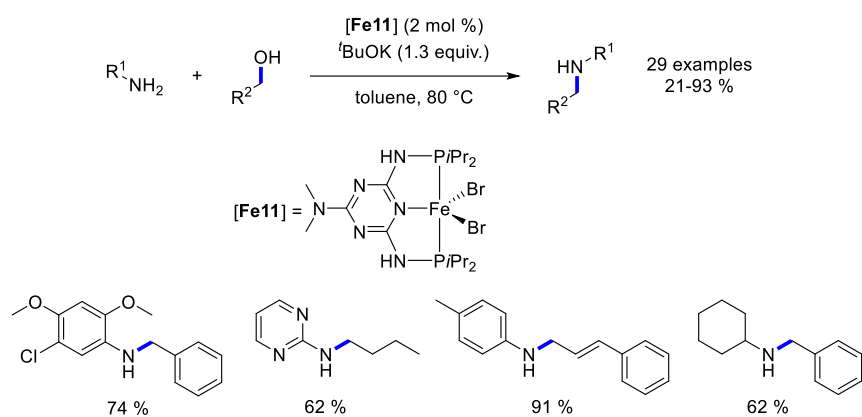


Scheme 1.24: Alkylation of amines.

Changing the pyridine ring of the ligand by a dimethylamino triazine ring improve the catalytic efficiency as the reaction temperature decrease from 140 to 80 °C, and no molecular sieve were required (Scheme 1.25).⁵⁷ However, secondary alcohols were not reactive in these conditions and the average yield of the reaction was not improved.

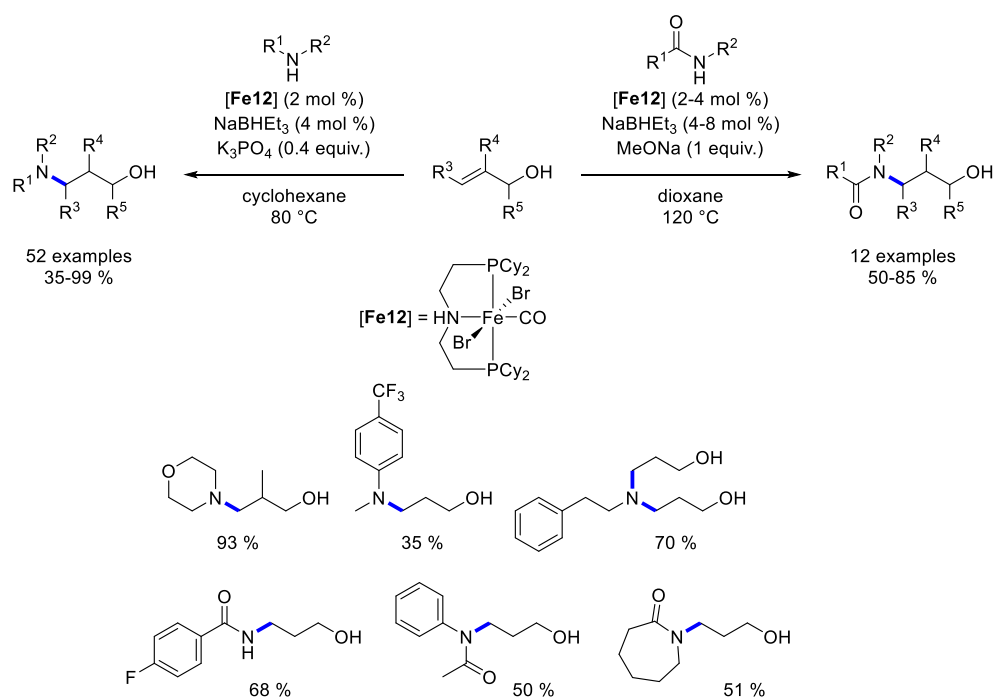
⁵⁶ Mastalir, M.; Glatz, M.; Gorgas, N.; Stöger, B.; Pittenauer, E.; Allmaier, G.; Veiros, L. F.; Kirchner, K. *Chem. Eur. J.* **2016**, *22*, 12316-12320.

⁵⁷ Mastalir, M.; Stöger, B.; Pittenauer, E.; Puchberger, M.; Allmaier, G.; Kirchner, K. *Adv. Synth. Catal.* **2016**, *358*, 3824-3831.



Scheme 1.25: Iron(II)-catalysed alkylation of amines reported by Kirchner.

In 2019, the hydroamination of allylic alcohols was reported by Wang.⁵⁸ The PNP-Fe complex oxidises the alcohol into α,β -unsaturated aldehyde. An 1,4-addition by the amine gives the amino-aldehyde which is finally reduced by the complex to give the γ -amino-alcohols (Scheme 1.26). This methodology was used afterwards by Maji and Beller with manganese pincer complexes.³⁰ Amides were also suitable for this reaction, but a higher temperature was required.

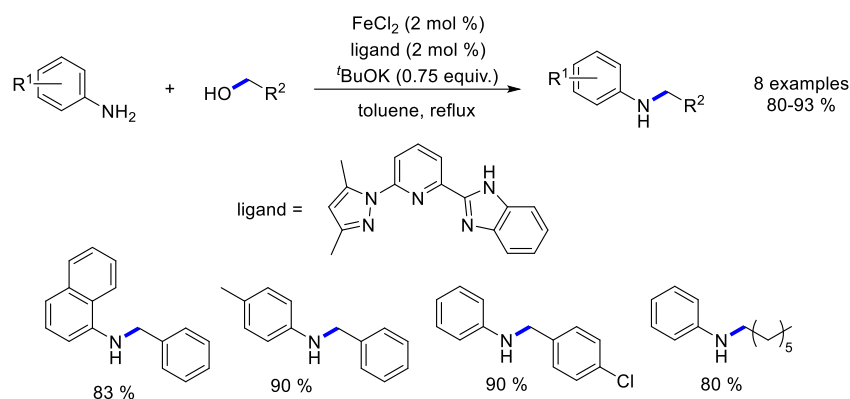


Scheme 1.26: Hydroamination of allylic alcohols reported by Wang.

Liu described a NNN-Fe(II) complex bearing pyrazoyl and imidazolyl moiety for the alkylation of amines.⁵⁹ This catalyst afforded the alkylated anilines with primary alcohols in good yields (Scheme 1.27). However, only few examples with limited functional groups were described.

⁵⁸ Ma, W.; Zhang, X.; Fan, J.; Liu, Y.; Tang, W.; Xue, D.; Li, C.; Xiao, J.; Wang, C. *J. Am. Chem. Soc.* **2019**, *141*, 13506-13515.

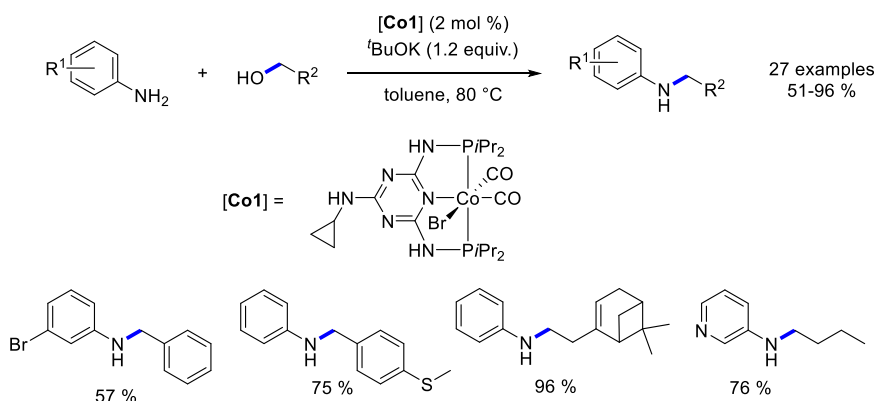
⁵⁹ Chen, H.; Wang, Q.; Liu, T.; Chen, H.; Zhou, D.; Qu, F. *J. Coord. Chem.* **2021**, *74*, 877-884.



Scheme 1.27: Alkylation of anilines reported by Liu.

3) Cobalt-catalysed *N*-alkylation reactions.

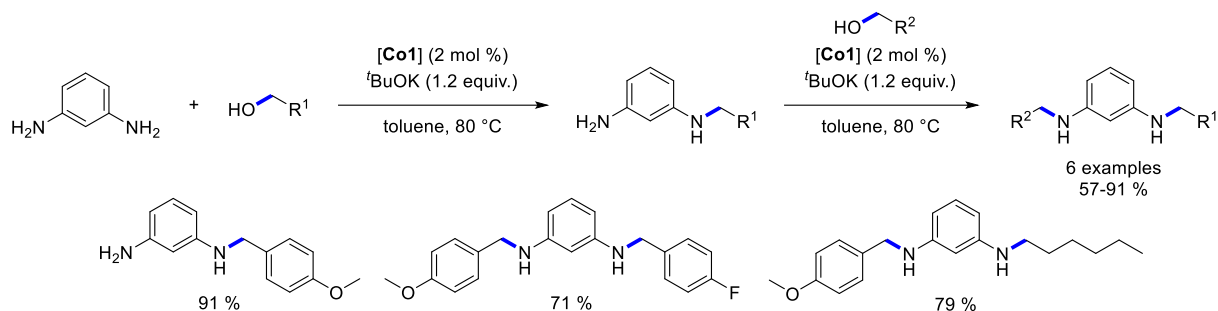
Kempe described the first cobalt-catalysed alkylation of amines with alcohols.⁶⁰ A PNP ligand containing a triazine ring was associated with CoCl_2 to generate the pre-catalyst. This metal complex catalysed the alkylation of various anilines derivatives with benzylic and aliphatic primary alcohols, the latter being as good pro-electrophiles as benzyl alcohols (Scheme 1.28). No example with secondary alcohols or aliphatic amines were reported in this work.



Scheme 1.28: Cobalt-catalysed alkylation of anilines.

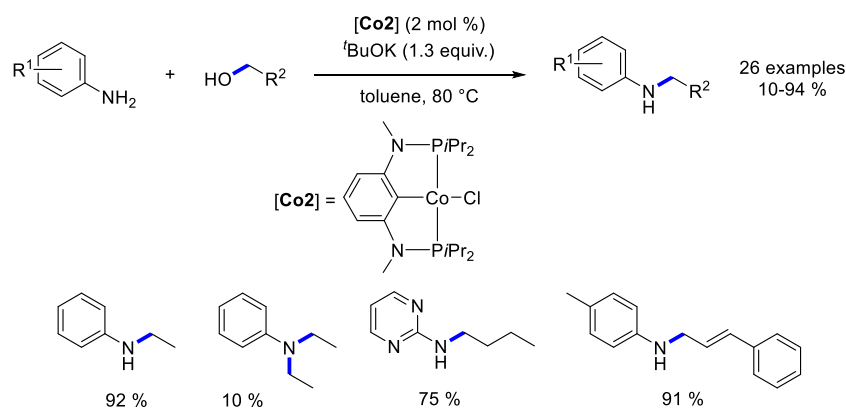
Alkylation of diamines was also performed in a sequential process, allowing the formation of non-symmetric *N,N'*-di-substituted diamines. The mono-substituted diamine could also be isolated using the diamine in excess with respect to the alcohol (Scheme 1.29).

⁶⁰ Rösler, S.; Ertl, M.; Irrgang, T.; Kempe, R. *Angew. Chem. Int. Ed.* **2015**, *54*, 15046-15050.



Scheme 1.29: Synthesis of non-symmetric diamines reported by Kempe.

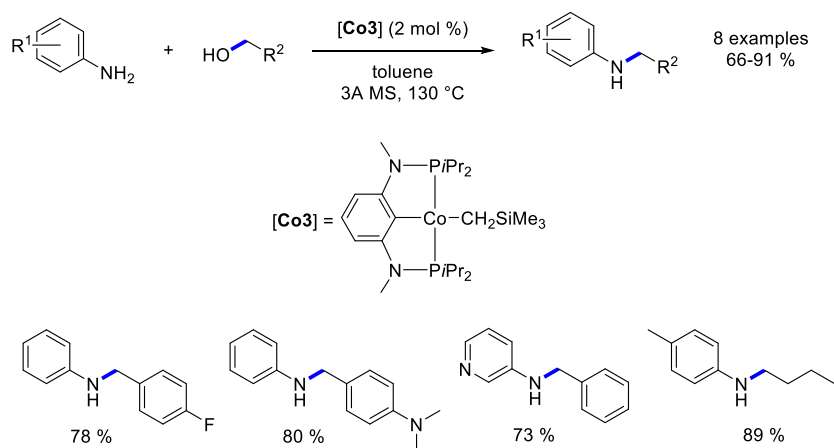
Kirchner developed a PCP pincer-type ligand and the corresponding cobalt(II) complex.⁶¹ Its application in the alkylation of arylamines with primary alcohols led to the alkylated amines in 10-94 % yields (Scheme 1.30). Only aromatic amines were introduced in this reaction, aliphatic amines might inhibit the catalytic activity as described by Wills with the Schrauzer-Reppe complex (Scheme 1.30).⁴⁵ Interestingly, the alkylation of cinnamyl alcohol was performed without reduction of the C=C bond. The dimethylation of aniline led to the corresponding dialkylated amine, albeit in very low yield (10 %). However, this example represents the first dialkylation of an aniline catalysed by an Earth-abundant metal complex.



Scheme 1.30: Cobalt-catalysed alkylation of anilines reported by Kirchner.

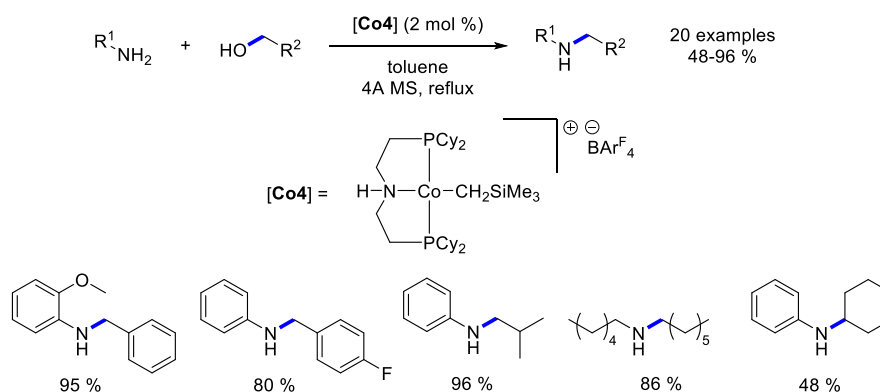
A congener of this catalyst bearing strongly basic CH_2SiMe_3 ligand was also tested. This catalyst was also effective for the studied reaction and did not necessitate the addition of base, but higher temperatures were required (Scheme 1.31).

⁶¹ Mastalir, M.; Tomsu, G.; Pittenauer, E.; Allmaier, G.; Kirchner, K. *Org. Lett.* **2016**, *18*, 3462-3465.



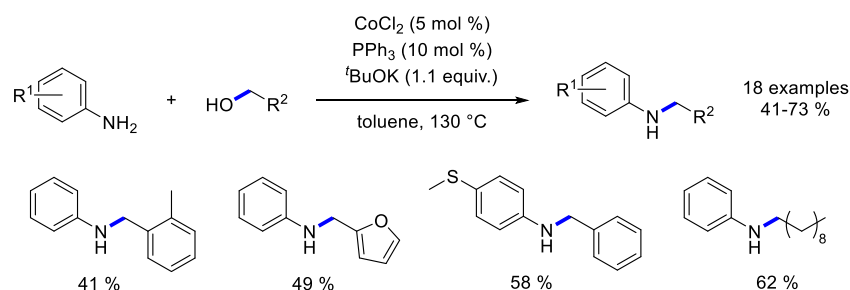
Scheme 1.31: Base-free alkylation of amines reported by Kirchner.

This methylene trimethylsilyl ligand was then reported by Zhang on a Macho-type cationic cobalt complex.⁶² Once again this ligand avoided the use of base, and aryl as well as aliphatic amines were alkylated with various primary alcohols in good to excellent yields (Scheme 1.32). One example with cyclohexanol as secondary alcohol afforded the alkylated aniline in 48 % yield.



Scheme 1.32: Alkylation of amines described by Zhang.

Balaraman reported the combination of CoCl_2 with PPh_3 for the alkylation of anilines with primary alcohols.⁶³ Various substituted anilines were alkylated with benzylic and aliphatic alcohols, but lower yields were obtained with this reaction compared to previously reported cobalt-catalysed hydrogen autotransfer reactions (Scheme 1.33).

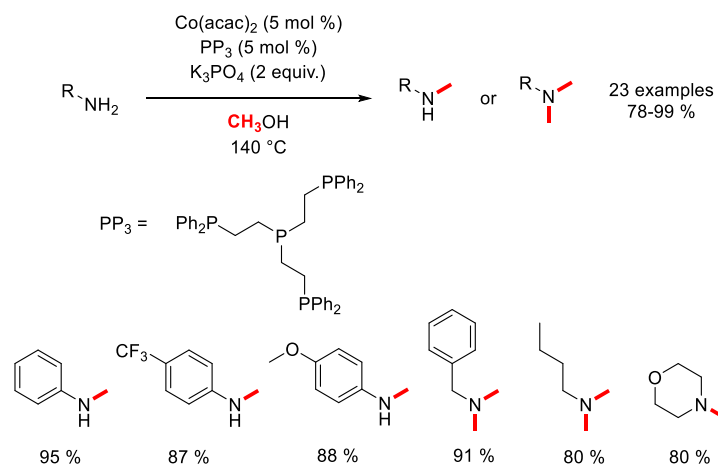


Scheme 1.33: Cobalt-catalysed alkylation of anilines reported by Balaraman.

⁶² Zhang, G.; Yin, Z.; Zheng, S. *Org. Lett.* **2016**, *18*, 300-303.

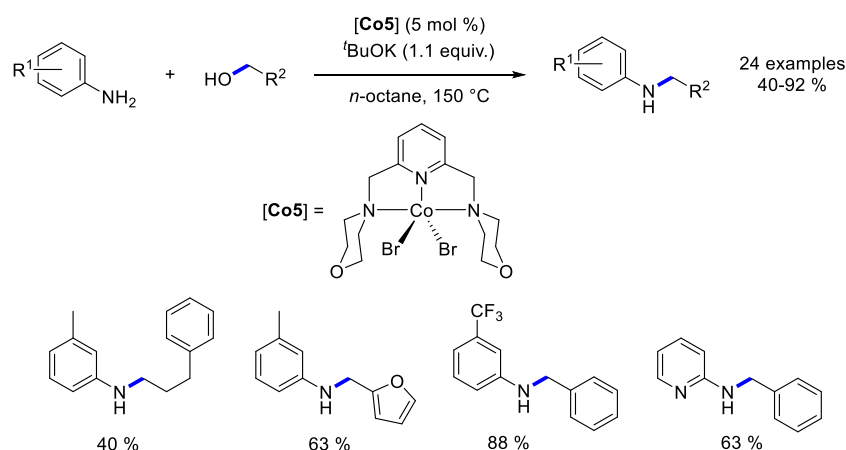
⁶³ Midya, S. P.; Mondal, A.; Begum, A.; Balaraman, E. *Synthesis* **2017**, *49*, 3957-3961.

In 2017, Liu investigated the methylation of aryl and aliphatic amines.⁶⁴ Combining $\text{Co}(\text{acac})_2$ and a tetra-phosphine ligand, aromatic amines yielded the mono-methylated anilines while aliphatic amines yielded the dimethylated product exclusively (Scheme 1.34).



Scheme 1.34: Methylation of amines reported by Liu.

Balaraman *et al.* designed a new NNN-Co complex.⁶⁵ This complex was active in the alkylation of aniline derivatives with alcohols, even if higher temperature was required, the *N*-alkylated aniline compounds were isolated in 40-92 % yields (Scheme 1.35).



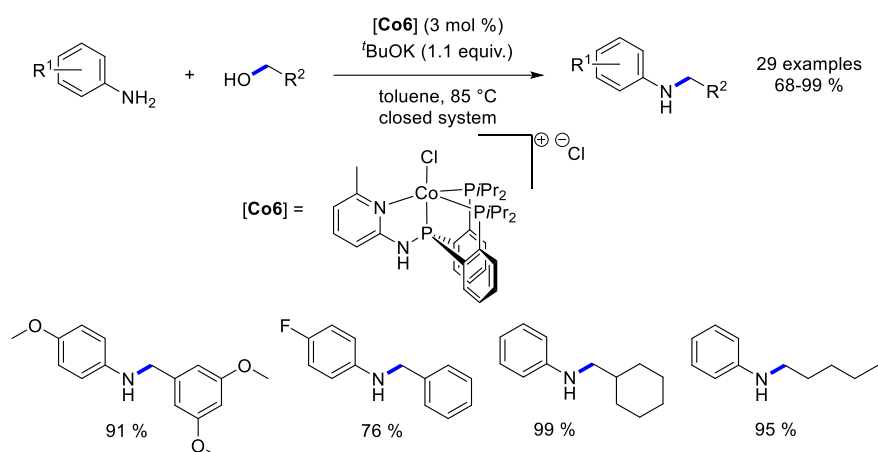
Scheme 1.35: Cobalt-pincer complex-catalysed alkylation of anilines.

More recently, Ding described a switchable imine and amine synthesis catalysed by a PNPP ligand.⁶⁶ Modulation of the base loading, temperature, and type of system (close or open) afforded either the imine or the amine product. This catalytic system was efficient for the alkylation of anilines with primary alcohols, but alkylated aliphatic amines were not obtained (Scheme 1.36).

⁶⁴ Liu, Z.; Yang, Z.; Yu, X.; Zhang, H.; Yu, B.; Zhao, Y.; Liu, Z. *Adv. Synth. Catal.* **2017**, *359*, 4278-4283.

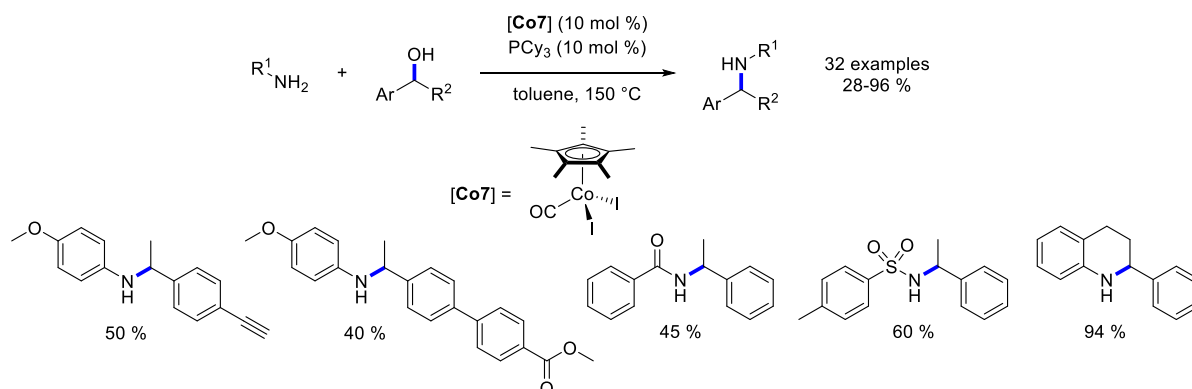
⁶⁵ Midya, S. P.; Pitchaimani, J.; Landge, V. G.; Madhu, V.; Balaraman, E. *Catal. Sci. Technol.* **2018**, *8*, 3469-3473.

⁶⁶ Paudel, K.; Xu, S.; Hietsoi, O.; Pandey, B.; Onuh, C.; Ding, K. *Organometallics* **2021**, *40*, 418-426.



Scheme 1.36: Alkylation of anilines.

Among the previously discussed cobalt-catalysed alkylations of amines, only one example of alkylation with secondary alcohol was reported by Zhang.⁶² The alkylation with secondary alcohols remains a challenge since ketones are less electrophilic than aldehydes. In 2019, Sundararaju reported a Cp*Co(III) complex for the alkylation of amines with secondary alcohols.⁶⁷ The reaction was performed in toluene at 150 °C without additional base (Scheme 1.37). This reaction afforded the alkylated anilines and amide derivatives with a variety of secondary benzylic alcohols.



Scheme 1.37: Alkylation of amines and amides with secondary alcohols.

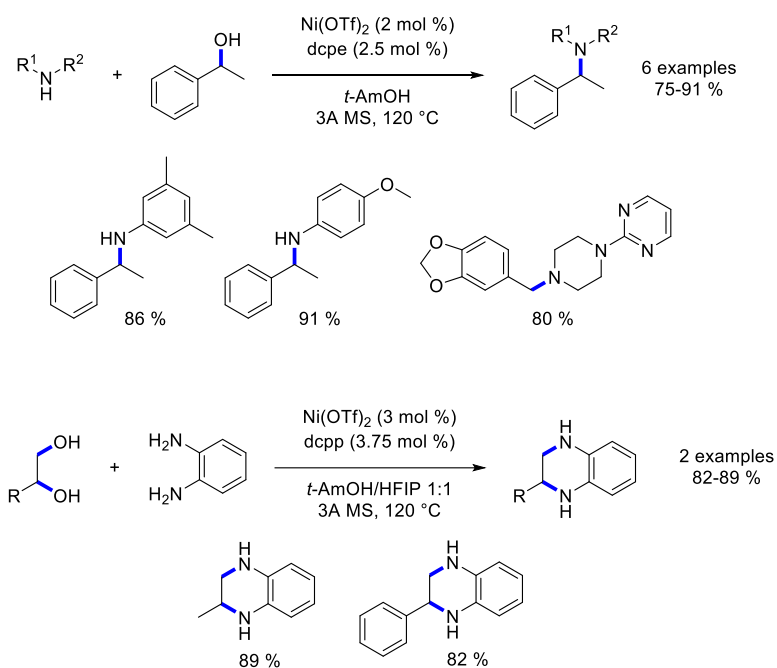
4) Nickel-catalysed *N*-alkylation reactions.

The first homogeneous nickel-complex-catalysed alkylation of amines was reported by Zhou in 2017.⁶⁸ A nickel salt was associated with a diphosphine ligand to catalyse the alkylation of amines with alcohols. This reaction allowed the synthesis of substituted anilines, piperazines and trisubstituted amines (Scheme 1.38). The alkylation of acylhydrazides with alcohols was also reported but it will be discussed in detail later.⁶⁹

⁶⁷ Emayavaramban, B.; Chakraborty, P.; Manoury, E.; Poli, R.; Sundararaju, B. *Org. Chem. Front.* **2019**, *6*, 852-857.

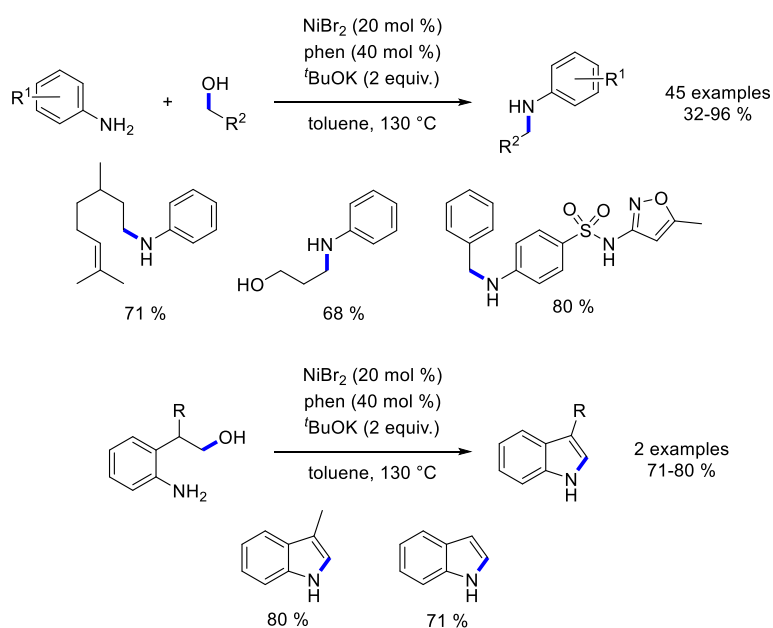
⁶⁸ Yang, P.; Zhang, C.; Ma, Y.; Zhang, C.; Li, A.; Tang, B.; Zhou, J. S. *Angew. Chem. Int. Ed.* **2017**, *56*, 14702-14706.

⁶⁹ C.f. Chapter II.



Scheme 1.38: Alkylation of amines reported by Zhou.

Banerjee described a very simple *in situ* generated nickel-phenanthroline complex-catalysed alkylation of aniline derivatives.⁷⁰ Indole derivatives could be synthesised in the same reaction conditions via an intramolecular cyclisation and isomerization in the aromatic form (Scheme 1.39).



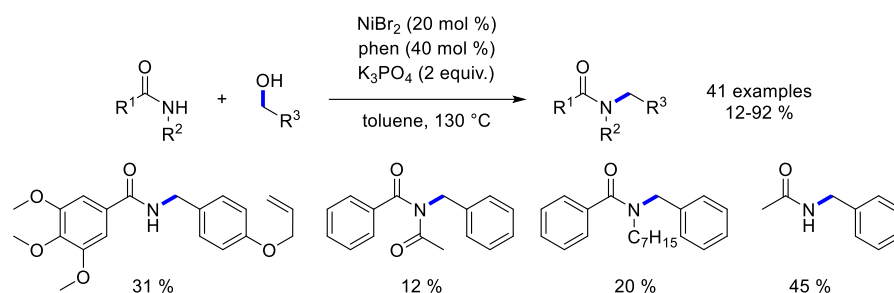
Scheme 1.39: Alkylation of anilines reported by Banerjee.

By using K_3PO_4 as base and decreasing the catalyst loading, the alkylation of amide could also be achieved.⁷¹ This reaction allowed the alkylation of a variety of amides, *N*-substituted amides and

⁷⁰ Vellakkaran, M.; Singh, K.; Banerjee, D. *ACS Catal.* **2017**, *7*, 8152-8158.

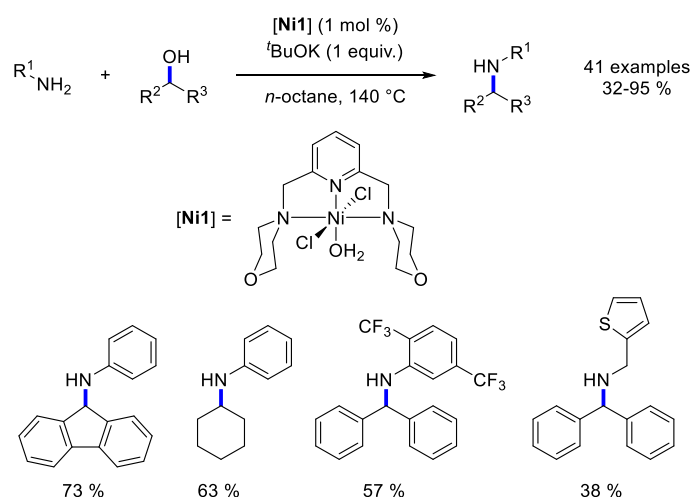
⁷¹ Das, J.; Banerjee, D. *J. Org. Chem.* **2018**, *83*, 3378-3384.

secondary amides. Lower yields were obtained with less nucleophilic amides or aliphatic alcohols (Scheme 1.40).



Scheme 1.40: Alkylation of amides reported by Banerjee.

Based on the same NNN-ligand, Balaraman developed a nickel-catalysed alkylation of aniline and benzylic amines with a variety of secondary alcohols at 140 °C in *n*-octane (Scheme 1.41).⁷² In the same conditions, aliphatic amines and non-cyclic aliphatic secondary alcohols did not yield any product. In similar reaction conditions, only primary alcohols were engaged with the cobalt analogue of this complex previously reported by the same group.⁶⁵

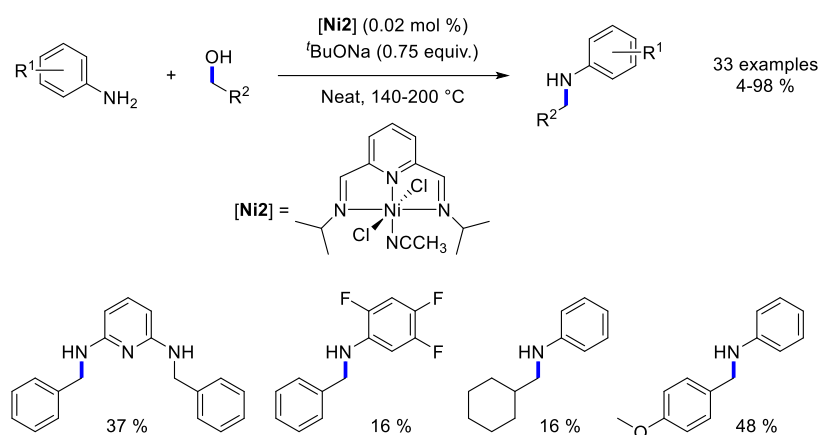


Scheme 1.41: Alkylation of amines with secondary alcohols reported by Balaraman.

Following the work of Balaraman, Kumar described a pyridine-diimine base containing nickel complex and its application in alkylation of aniline compounds with benzylic alcohols at 140-200 °C and substoichiometric amount of *t*BuOK (0.75 equiv., Scheme 1.42). Catalytic activities were good (TONs up to 4500) at 140 °C. Higher TONs (up to 34 000) were reached at elevated temperatures (200 °C) in the presence of only 0.002 mol % of nickel complex.⁷³

⁷² Subaramanian, M.; Midya, S. P.; Ramar, P. M.; Balaraman, E. *Org. Lett.* **2019**, *21*, 8899-8903.

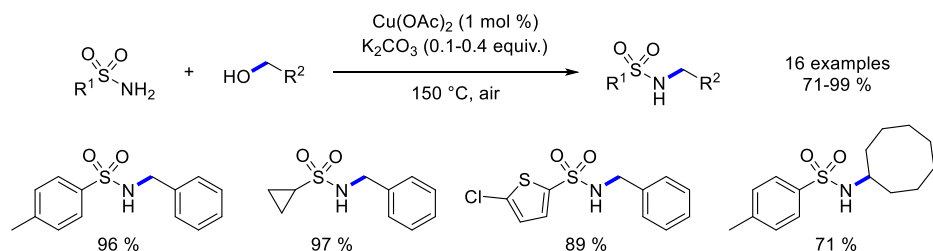
⁷³ Arora, V.; Dutta, M.; Das, K.; Das, B.; Srivastava, H. K.; Kumar, A. *Organometallics* **2020**, *39*, 2162-2176.



Scheme 1.42: Alkylation of amines reported by Kumar.

5) Copper-catalysed *N*-alkylation reactions.

Beller reported the first ligand-free copper-catalysed alkylation of sulphonamides with alcohols in 2009.⁷⁴ Various sulphonamides reacted with benzylic and aliphatic primary and secondary alcohols to yield the *N*-substituted sulfonamides. A variety of functionalised compounds were tolerated (Scheme 1.43).



Scheme 1.43: Copper-catalysed alkylation of sulphonamides reported by Beller.

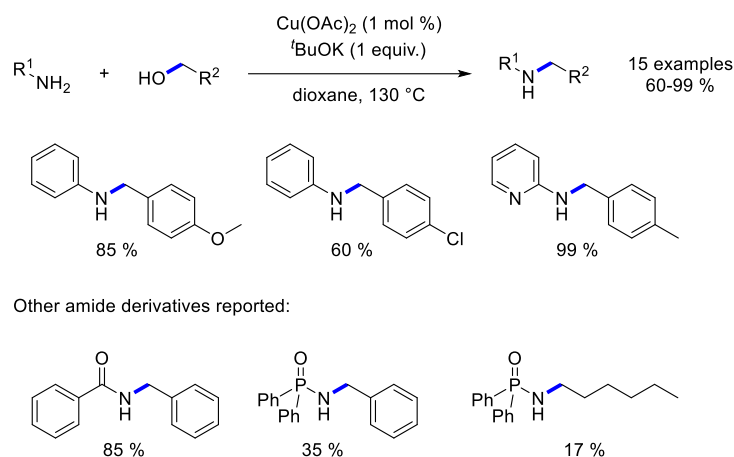
In 2010, Yus extended this work to the alkylation of anilines derivatives at lower temperature with a stronger base and at higher base loading, and longer reaction time (2 days).⁷⁵ *N*-alkylated anilines were isolated in 60-99 % yields (Scheme 1.44). This work was completed by the *N*-alkylation of amides and amide derivatives.⁷⁶ A mechanistic investigation by means of Density Functional Theory (DFT) calculations highlighted an outer sphere mechanism for both the dehydrogenation and the reduction steps of this reaction.⁷⁷

⁷⁴ (a) Shi, F.; Tse, M. K.; Cui, X.; Gördes, D.; Michalik, D.; Thurow, K.; Deng, Y.; Beller, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 5912-5915. (b) Cui, X.; Shi, F.; Tse, M. K.; Gördes, D.; Thurow, K.; Beller, M.; Deng, D. *Adv. Synth. Catal.* **2009**, *351*, 2949-2958.

⁷⁵ Martínez-Asencio, A.; Ramón, D. J.; Yus, M. *Tetrahedron Lett.* **2010**, *51*, 325-327.

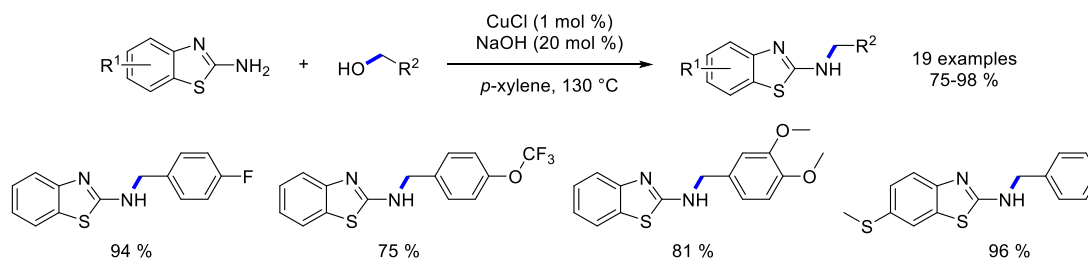
⁷⁶ Martínez-Asencio, A.; Ramón, D. J.; Yus, M. *Tetrahedron* **2011**, *67*, 3140-3149.

⁷⁷ Zhao, G.-m.; Liu, H.-l.; Zhang, D.-d.; Huang, X.-r.; Yang, X. *ACS Catal.* **2014**, *4*, 2231-2240.



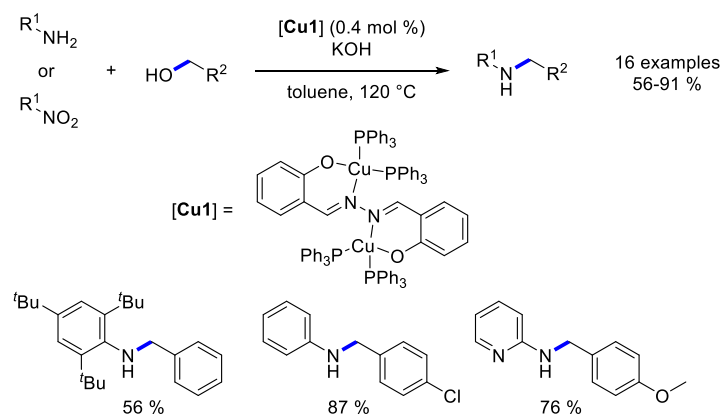
Scheme 1.44: Copper-catalysed alkylation of anilines and amides derivatives.

The following year, Li reported the use of CuCl as a catalyst for the alkylation of 2-aminobenzothiazoles with benzyl alcohols.⁷⁸ The reaction afforded the *N*-alkylated amino benzothiazoles in very good yields (Scheme 1.45).



Scheme 1.45: Alkylation of amino benzothiazoles described by Li.

In 2015, Viswanathamurthi described a new heteroleptic binuclear copper(I) complex to catalyse the alkylation of anilines with benzylic alcohols.⁷⁹ Worth to note, sterically hindered anilines were also alkylated in good yields (Scheme 1.46). Nitroarenes were also engaged and reduced *in situ* to give the corresponding *N*-alkylated compounds after subsequent alkylation.

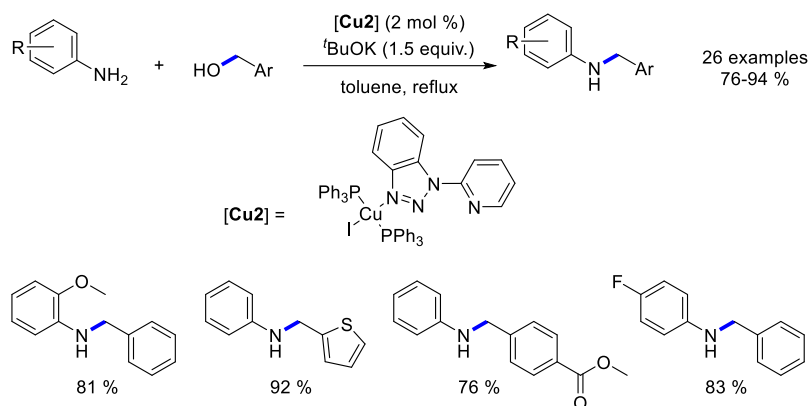


Scheme 1.46: Alkylation of anilines and nitroarenes.

⁷⁸ Li, F.; Shan, H.; Kang, Q.; Chen, L. *Chem. Commun.* **2011**, 47, 5058-5060.

⁷⁹ Prakash, G.; Nirmala, M.; Ramachandran, R.; Viswanathamurthi, P.; Malecki, J. G.; Sanmartin, J. *Polyhedron* **2015**, 89, 62-69.

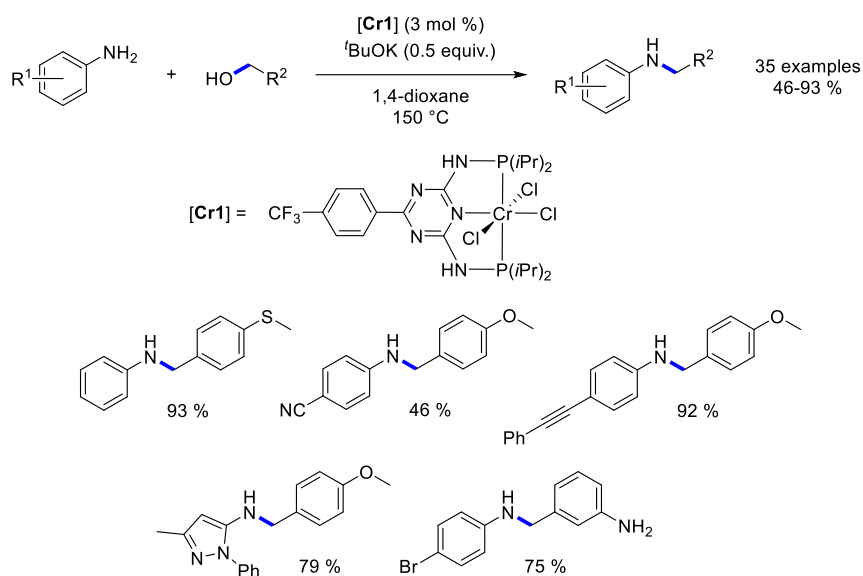
In 2017, Wang reported a Triazole-Phosphine-copper complex for the synthesis of benzimidazoles and the alkylation of arylamines.⁸⁰ This system allowed the alkylation of various anilines with benzylic alcohols and tolerated substituted benzylic alcohols (Scheme 1.47). This method allowed to reduce the temperature of the reaction compared to ligand-free copper salt catalysts,^{74,75,76,77,78} but was limited to anilines and benzylic alcohols.



Scheme 1.47: Alkylation of anilines reported by Wang.

6) Other 3d-metal catalysed *N*-alkylation reactions.

In 2020, Kempe reported a chromium-PNP complex-catalysed alkylation of anilines with alcohols.⁸¹ This reaction was limited to benzylic and homobenzylic alcohols, but the reaction tolerated a wide range of functionalised pro-electrophiles and pro-nucleophiles and led to the *N*-alkyl anilines in good to excellent yields (46 to 93 %, Scheme 1.48), albeit at high temperature.

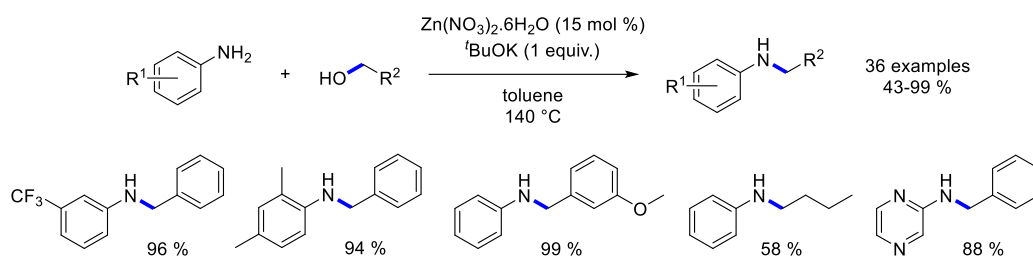


Scheme 1.48: Chromium-catalysed alkylation of anilines.

⁸⁰ Xu, Z.; Wang, D.-S.; Yu, X.; Yang, Y.; Wang, D. *Adv. Synth. Catal.* **2017**, *359*, 3332-3340.

⁸¹ Kallmeier, F.; Fertig, R.; Irrgang, T.; Kempe, R. *Angew. Chem. Int. Ed.* **2020**, *132*, 11887-11891.

The same year, Sivakumar and Mannathan described a zinc-catalysed alkylation of anilines.⁸² Thus, simple zinc nitrate salt afforded the desired alkylated anilines from benzylic and aliphatic alcohols as pro-electrophiles (Scheme 1.49).



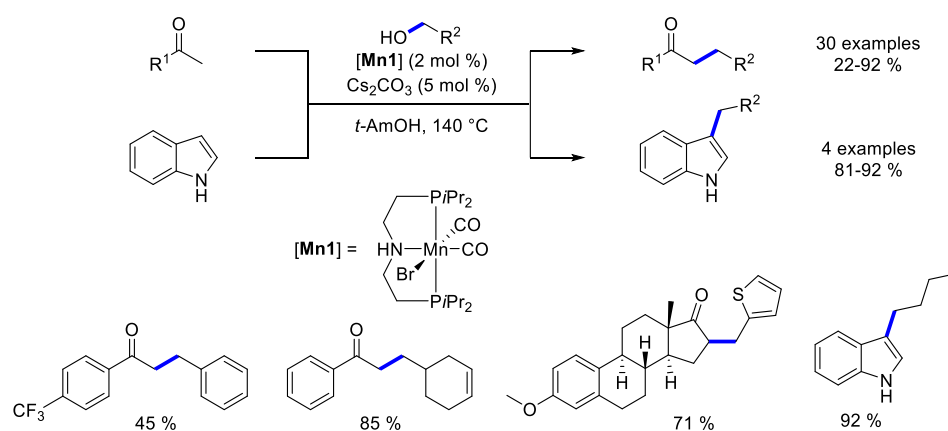
Scheme 1.49: Zinc-catalysed alkylation of anilines.

⁸² Sankar, V.; Kathiresan, M.; Sivakumar, B.; Mannathan, S. *Adv. Synth. Catal.* **2020**, *362*, 4409-4414.

III. C-alkylation reaction catalysed by first row transition-metals.

1) Manganese-catalysed C-alkylation reactions.

In 2016, Beller described the first alkylation of ketones with primary alcohols catalysed by a manganese complex.⁸³ The complex used in this work was also reported by the same group for the alkylation of amines with alcohols.²⁸ In the case of this C-C bond formation, catalytic amount of Cs₂CO₃ (5 mol %) was used as base and the reaction was performed in *tert*-amyl alcohol at 140 °C. Various substituted ketones and alcohols were engaged leading to functionalised products in moderate to good yields (Scheme 1.50). The reaction was affected by electronic effects as the ketones bearing electron-withdrawing groups gave lower yields. This reaction was also extended to oxindole derivatives, and the alkylated products were obtained in good yields. Liu and Jones used the same complex to upgrade ethanol to 1-butanol at high temperature (150-160 °C).⁸⁴



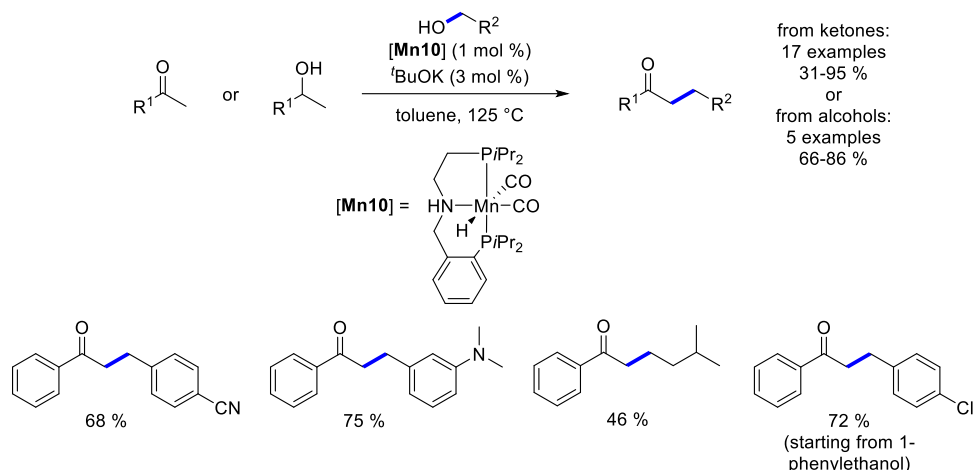
Scheme 1.50: Alkylation of ketones and oxindoles.

Milstein also reported the alkylation of ketones along with the alkylation of amides and esters.⁸⁵ A PNP-Mn complex was used to perform these reactions. Aromatic ketones were alkylated with various benzylic and aliphatic alcohols. Nevertheless, lower yields were obtained with aliphatic alcohols. Using the same reaction conditions, one example of alkylation of oxindole, and 5 examples of alkylation of 1-phenylethanol with benzyl alcohols to give α -substituted ketones were also described. This reaction was perhaps limited to aryl ketones and benzylic alcohols as pro-nucleophiles (Scheme 1.51).

⁸³ Peña-López, M.; Piehl, P.; Elangovan, S.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 14967-14971.

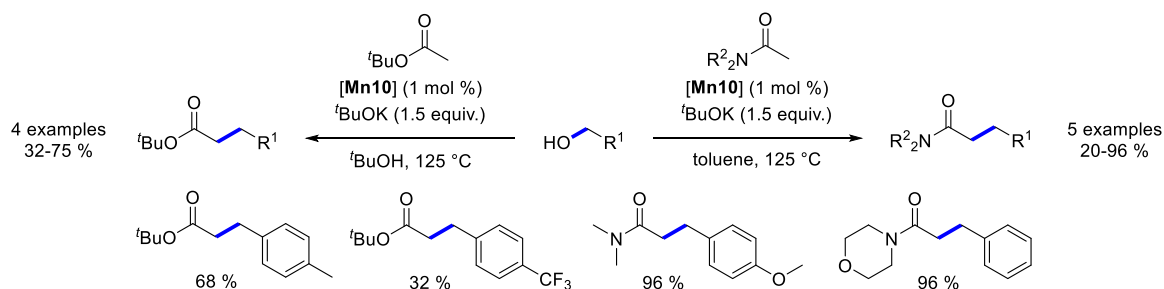
⁸⁴ (a) Fu, S.; Shao, Z.; Wang, Y.; Liu, Q. *J. Am. Chem. Soc.* **2017**, *139*, 11941-11948. (b) Kulkarni, N. V.; Brennessel, W. W.; Jones, W. D. *ACS Catal.* **2018**, *8*, 997-1002.

⁸⁵ Chakraborty, S.; Daw, P.; Ben-David, Y.; Milstein, D. *ACS Catal.* **2018**, *8*, 10300-10305.



Scheme 1.51: Alkylation of ketones and secondary alcohols described by Milstein.

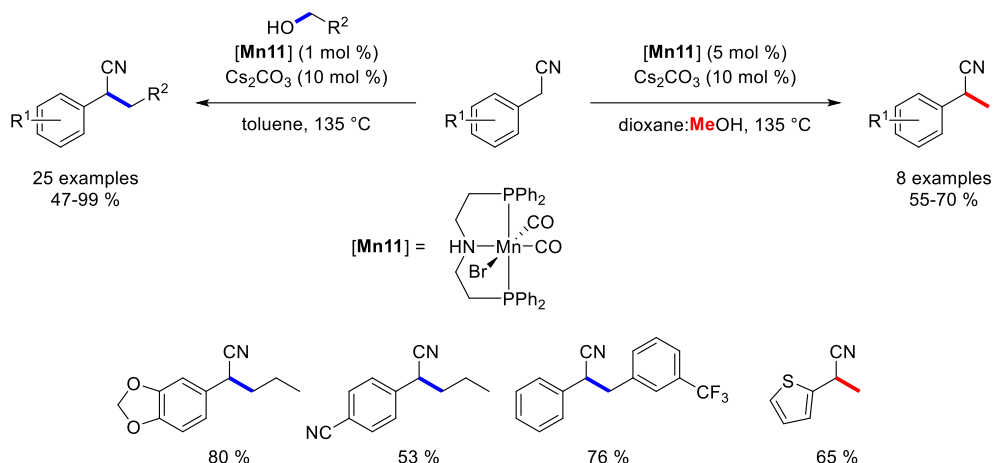
The same Macho-type manganese complex allowed the alkylation of esters and amides. In this reaction, a stoichiometric amount of base was necessary to obtain high conversions and good yields (20-96 %, Scheme 1.52).



Scheme 1.52: Alkylation of amides and esters described by Milstein.

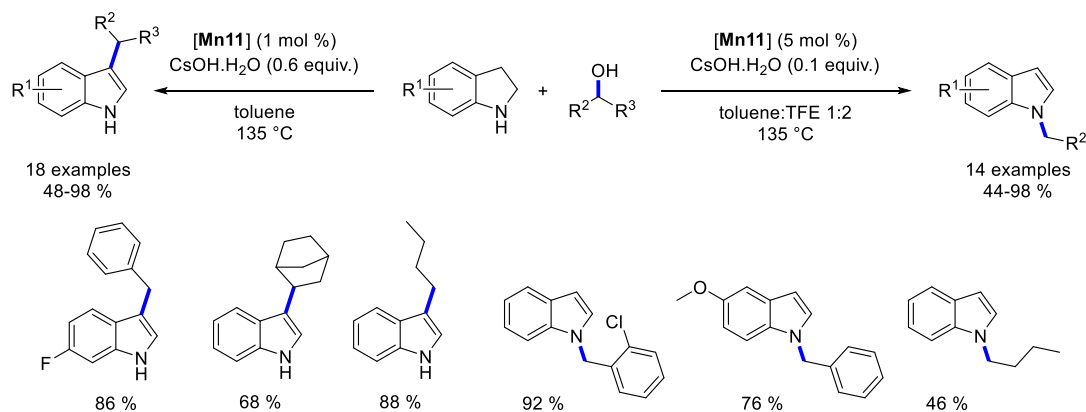
The alkylation of nitriles was then investigated by Rueping.⁸⁶ Various benzyl nitriles were engaged in this reaction, affording the alkylated products in moderate to good yields. Methanol was also introduced leading to α -methylated benzyl nitriles; however, this reaction was limited to primary alcohols (Scheme 1.53).

⁸⁶ Borghs, J. C.; Tran, M. A.; Sklyaruk, J.; Rueping, M.; El-Sepelgy, O. *J. Org. Chem.* **2019**, *84*, 7927-7935.



Scheme 1.53: Alkylation of nitriles reported by Rueping.

Following this work, the alkylation of indolines was investigated, with the same manganese catalyst.⁸⁷ In this work, both N- and C3- alkylation of indoline could be hypothesized. First, whatever the conditions, indole derivatives were formed. Second, the selectivity between N- and C- alkylation can be controlled by the amount of base and the nature of the solvent. Then, depending on the selected conditions, C3-alkylated indoles were isolated in 48-98 % yields and the N-alkylated indoles in 44-98 % yields (Scheme 1.54).



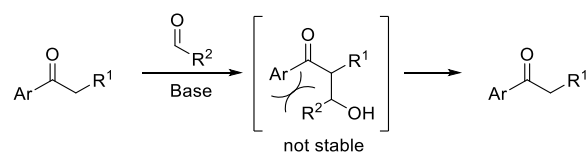
Scheme 1.54: Selective alkylation of indoline to N- or C3-substituted indoles.

While the mono-alkylation of various nucleophiles was widely studied with transition-metals, the use of diols to form cycloalkanes was not scarcely described with Earth-abundant metal-based complexes. The alkylation of α -substituted ketones is more challenging than methyl ketones because of the steric hindrance generated in the α -position by the aromatic ring, favouring the retro-aldol reaction instead of the elimination of water (Scheme 1.55). The introduction of *ortho*-substituted acetophenones allowed to overcome this limitation.⁸⁸ In fact, due to the substitution in *ortho*, the aromatic ring and the keto group are no more in the same plan but perpendicular to limit the steric interactions. Thus, they are not conjugated. Also, the reduction of the ketone is avoided due to the steric hindrance generated by the *ortho* substituents. During the alkylation step, steric interactions are minimised and, therefore, favours the elimination than the retro-aldol reaction. Such strategy was introduced for the first time by the group

⁸⁷ Borghs, J. C.; Zubar, V.; Azofra, L. M.; Sklyaruk, J.; Rueping, M. *Org. Lett.* **2020**, *22*, 4222-4227.

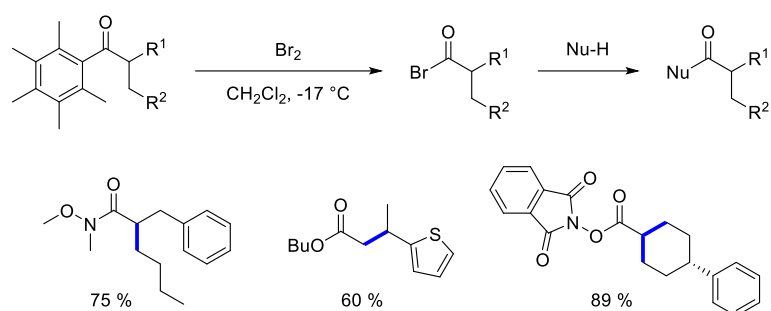
⁸⁸ Frost, J. R.; Cheong, C. B.; Akhtar, W. M.; Caputo, D. F. J.; Stevenson, N. G.; Donohoe, T. J. *J. Am. Chem. Soc.* **2015**, *137*, 15664-15667.

of Donohoe and was applied for the synthesis of α,α -disubstituted ketones,⁸⁸ the alkylation of ketones with secondary alcohols,⁸⁹ and the synthesis of cycloalkanes.⁹⁰



Scheme 1.55: Steric hindrance generated by the aromatic moiety of the starting ketone.

The 1-(2,3,4,5,6-pentamethyl)ethan-1-one was particularly used by this group, which highlighted the possibility to substitute the pentamethylphenyl group in the presence of bromine *via* a retro Friedel-Craft reaction.⁹¹ This reaction generates an acyl bromide which can react with various nucleophiles, giving access to functionalised products (Scheme 1.56).



Scheme 1.56: Functionalisation of α -substituted ketones.

In 2019, Leitner described the di-alkylation of ketones or secondary alcohols using diols as pro-electrophiles in the presence of the Macho-Mn complex (Scheme 1.57).⁹² A variety of 5-, 6- and 7-membered rings were obtained with this methodology. This work was completed by Maji who extended the scope of this reaction using a NNS-Mn complex, lower base loading and temperature.⁹³ As explained above, the use of ortho-substituted ketones avoided the final reduction of the carbonyl.

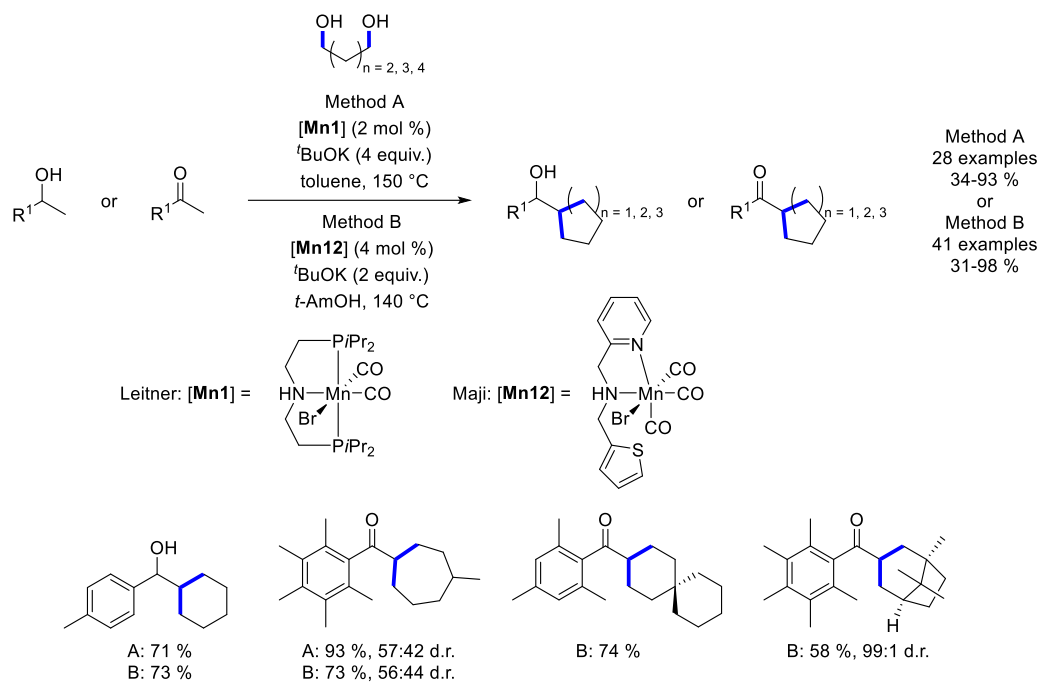
⁸⁹ Akhtar, W. M.; Cheong, C. B.; Frost, J. R.; Christensen, K. E.; Stevenson, N. G.; Donohoe, T. J. *J. Am. Chem. Soc.* **2017**, *139*, 2577-2580.

⁹⁰ (a) Akhtar, W. M.; Armstrong, R. J.; Frost, J. R.; Stevenson, N. G.; Donohoe, T. J. *J. Am. Chem. Soc.* **2018**, *140*, 11916-11920. (b) Armstrong, R. J.; Akhtar, W. M.; Frost, J. R.; Christensen, K. E.; Stevenson, N. G.; Donohoe, T. J. *Tetrahedron* **2019**, *75*, 130680.

⁹¹ Schubert, W. M.; Latourette, H. K. *J. Am. Chem. Soc.* **1952**, *74*, 1829.

⁹² Kaithal, A.; Gracia, L.-L.; Camp, C.; Quadrelli, E. A.; Leitner, W. *J. Am. Chem. Soc.* **2019**, *141*, 17487-17492.

⁹³ Jana, A.; Das, K.; Kundu, A.; Thorve, P. R.; Adhikari, D.; Maji, B. *ACS Catal.* **2020**, *10*, 2615-2626.

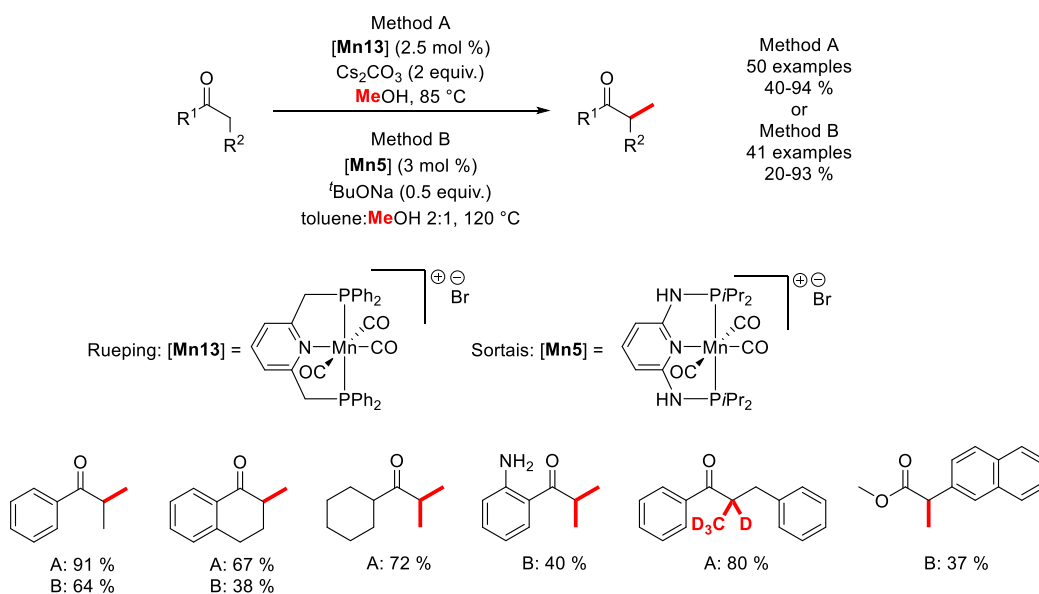


Scheme 1.57: Synthesis of cycloalkanes described by Leitner and Maji.

The methylation using methanol remains a challenging reaction due to its higher dehydrogenation energy ($\Delta H = +84$ kJ/mol for methanol *versus* $\Delta H = +68$ kJ/mol for ethanol for example). In 2019, Rueping described the methylation of ketones using methanol or deuterated methanol.⁹⁴ The reaction was performed in relatively mild conditions (85-105 °C), yielding the mono- or di-methylated products in good yields (Scheme 1.58). This reaction was also described almost simultaneously with another pincer Mn complex by Sortais.⁹⁵ Lower base loading was used but the reaction needed a higher temperature (120 °C). Nevertheless, methylation of esters was also described through this methodology (Scheme 1.58).

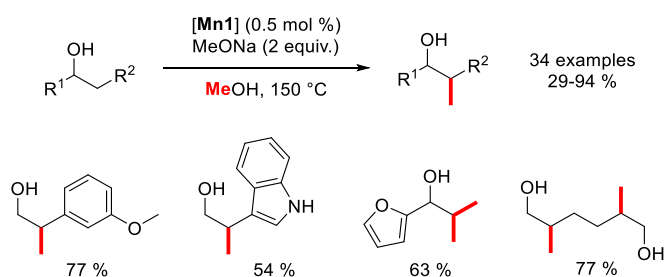
⁹⁴ Sklyaruk, J.; Borghs, J. C.; El-Sepelgy, O.; Rueping, M. *Angew. Chem. Int. Ed.* **2019**, *58*, 775-779.

⁹⁵ Bruneau-Voisine, A.; Pallova, L.; Bastin, S.; César, V.; Sortais, J.-B. *Chem. Commun.* **2019**, *55*, 314-317.



Scheme 1.58: Methylation of ketones and esters reported by Rueping and Sortais.

Leitner reported the β -methylation of alcohols using stoichiometric amount of base at 150 °C in the presence of the Macho-Mn complex, leading to β -branched products (Scheme 1.59).⁹⁶ While the alkylation was limited to homo-benzylic alcohols with iron complexes,⁹⁷ in the presence of the manganese complex both homobenzylic and aliphatic alcohols can be introduced without any detrimental effect.



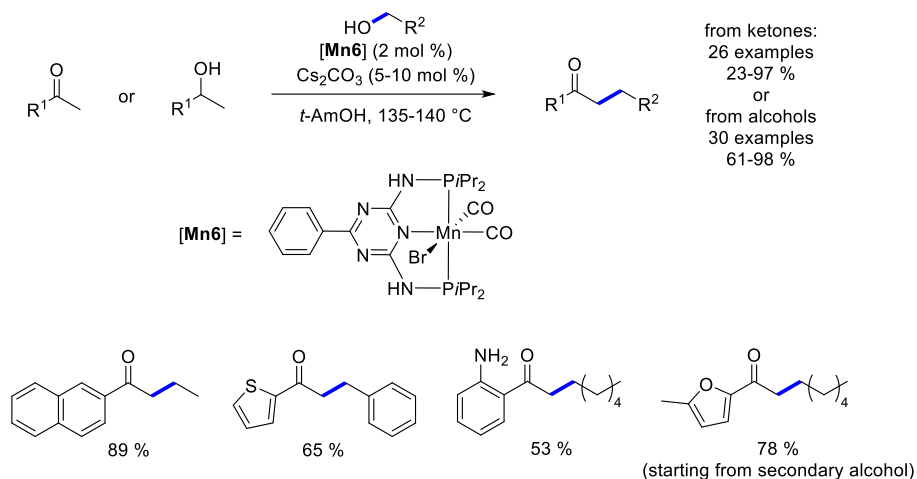
Scheme 1.59: Methylation of alcohols.

In 2019, Gunanathan described the α -alkylation of ketones and β -alkylation of alcohols leading to α -substituted ketones in both cases.⁹⁸ The main difference between the two methodologies was the base loading varying from 10 to 5 %. Aliphatic and benzylic alcohols afforded the desired products in good yields. Mono-ethylation of ketones was performed using a mixture of solvent (*t*-AmOH:EtOH 1:1). Keto-aniline derivatives were engaged, leading selectively to the C-alkylated product and highlighting the chemoselectivity of the reaction (Scheme 1.60).

⁹⁶ Kaithal, A.; van Bonn, P.; Hölscher, M.; Leitner, W. *Angew. Chem. Int. Ed.* **2020**, *59*, 215-220.

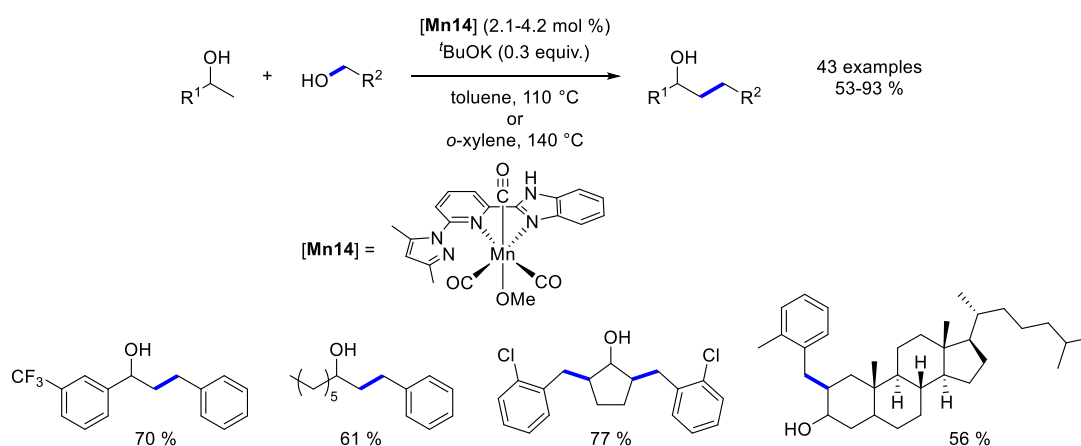
⁹⁷ see Chapter I, part II.2.

⁹⁸ Gawali, S. S.; Pandia, B. K.; Pal, S.; Gunanathan, C. *ACS Omega* **2019**, *4*, 10741-10754.



Scheme 1.60: Synthesis of α -substituted ketones.

Yu reported the alkylation of secondary alcohols with primary alcohols using a bifunctional NNN-Mn(I) complex bearing a pyridine-benzimidazole-pyrrole ligand.⁹⁹ In contrast with Milstein results,⁸⁵ the C=O bond of the alkylated ketone was reduced leading to β -substituted alcohol as products (Scheme 1.61).

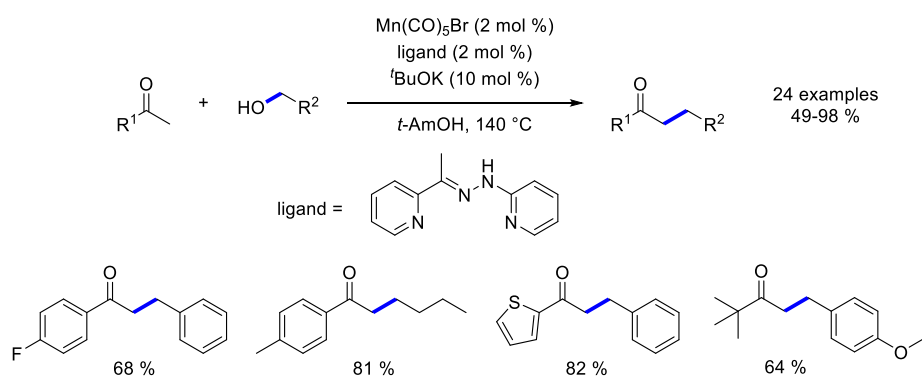


Scheme 1.61: Alkylation of secondary alcohols.

In 2018, Maji reported a phosphine-free NNN-Mn complex for the alkylation of ketones.¹⁰⁰ A variety of aryl and aliphatic ketones reacted with primary alcohols to give the α -substituted ketones bearing different functionalities (Scheme 1.62). Aliphatic alcohols proceeded as well as benzylic alcohols. Methylation was also attempted but did not yield any methylated product.

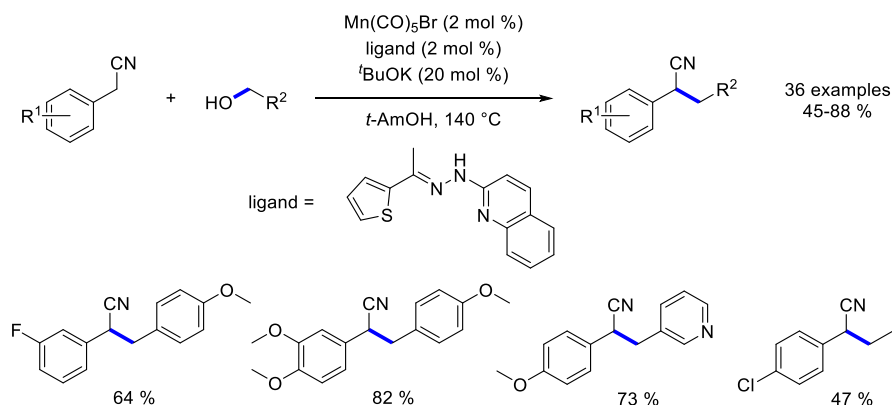
⁹⁹ Liu, T.; Wang, L.; Wu, K.; Yu, Z. *ACS Catal.* **2018**, *8*, 7201-7207.

¹⁰⁰ Barman, M. K.; Jana, A.; Maji, B. *Adv. Synth. Catal.* **2018**, *360*, 3233-3238.



Scheme 1.62: Alkylation of ketones.

Changing the pyridine hydrazone ligand by a thiophene hydrazone one allowed the alkylation of nitrile derivatives with a variety of primary alcohols.¹⁰¹ With the exception of the amount of base (which was increased from 10 to 20 mol %), the reaction conditions were similar in this reaction than those for the C-C bond formation between a ketone and an alcohol.¹⁰⁰ Alkylated nitriles were prepared in moderate to good yields (45-88 %, Scheme 1.63). This reaction tolerated a variety of functional groups but was limited to benzyl nitriles. Methanol was also introduced but again no methylation was observed.

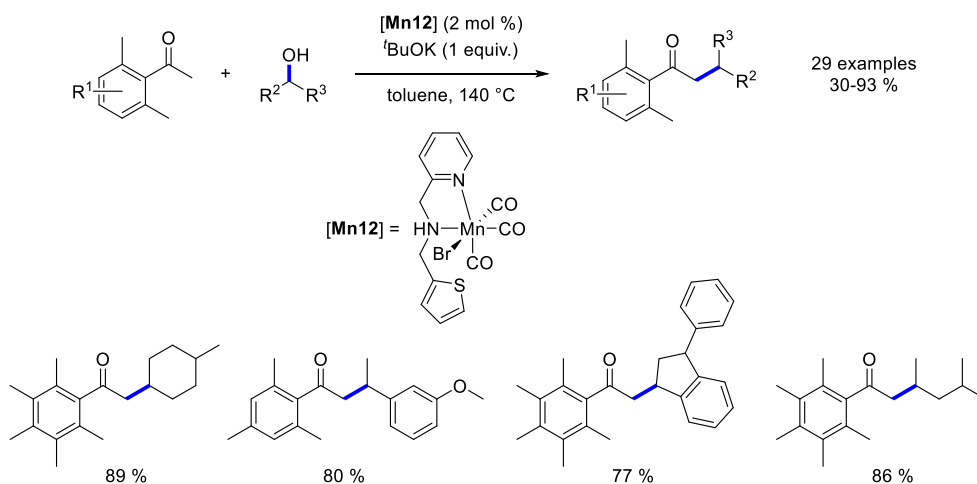


Scheme 1.63: Alkylation of nitriles.

In 2020, Maji investigated the alkylation of ketones with secondary alcohols with his phosphine free bidentate NN-ligand containing Mn-complex.¹⁰² To avoid any cross-alkylation products, only 2,5-dimethyl acetophenones derivatives were used as pro-nucleophiles. In the optimised conditions, a variety of benzylic and aliphatic secondary alcohols were engaged, leading to β -branched ketones in good yields (Scheme 1.64).

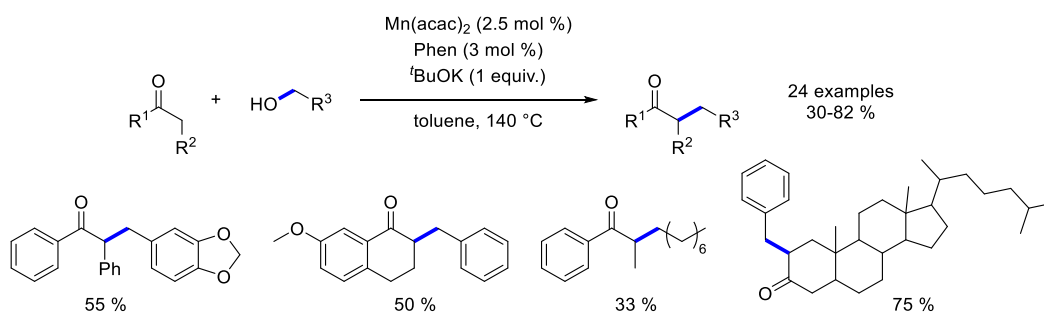
¹⁰¹ Jana, A.; Reddy, C. B.; Maji, B. *ACS Catal.* **2018**, *8*, 9226-9231.

¹⁰² Waiba, S.; Jana, S. K.; Jati, A.; Jana, A.; Maji, B. *Chem. Commun.* **2020**, *56*, 8376-8379.



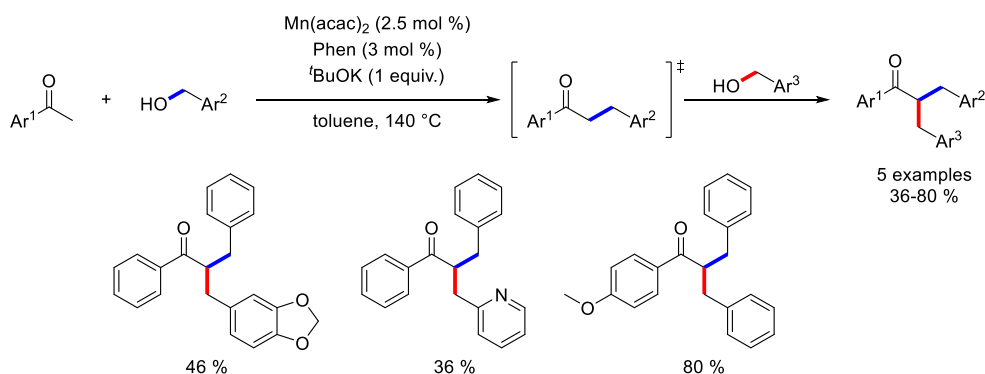
Scheme 1.64: Alkylation of ketones with secondary alcohols.

Banerjee investigated the alkylation of α -substituted ketones with primary alcohols using a combination of $\text{Mn}(\text{acac})_2$ and 1,10-phenanthroline.¹⁰³ Stoichiometric amount of base was required to afford the alkylated products (Scheme 1.65).



Scheme 1.65: Alkylation of α -substituted ketones reported by Banerjee.

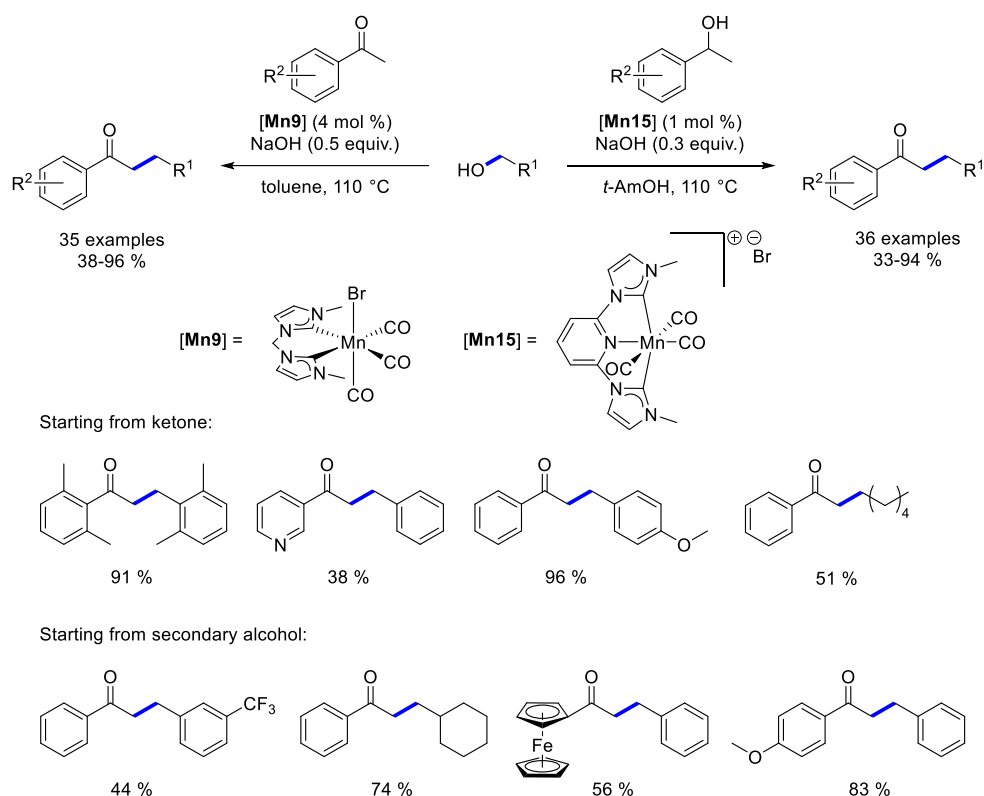
A two-step one-pot dialkylation of acetophenones was also investigated. After 2 hours of reaction, a second alcohol is added to the reaction mixture. The dialkylated products were isolated in moderate to good yields (Scheme 1.66).



Scheme 1.66: Two-step one-pot dialkylation of ketones.

¹⁰³ Kabadwal, L. M.; Das, J.; Banerjee, D. *Chem. Commun.* **2018**, 54, 14069-14072.

Organometallic complexes used for borrowing hydrogen reaction usually bear bifunctional or hemilabile ligands which are involved in the mechanism of the reaction. Such ligand could be expensive to prepare, air- or moisture-sensitive and difficult to synthesise at a large scale. For these reasons, a non-bifunctional manganese complex was investigated by Ke and involved in the α -alkylation of ketones with alcohols.¹⁰⁴ Preliminary DFT calculations compared the reduction of α,β -unsaturated ketones catalysed by this non-bifunctional complex and different catalytic systems described before.^{83,100,85} This theoretical study showed a much lower hydrogenation energy using the non-bifunctional complex (14.9 kcal/mol), while Beller, Maji and Milstein systems were more energy demanding (22.8, 23.7 and 26.6 kcal/mol, respectively). This observation was confirmed by experiments as this complex catalysed the α -alkylation of ketones at 110 °C (*versus* 125-140 °C for the other systems) in short reaction time (2 hours, Scheme 1.67). Even though this reaction required catalytic amount of base (NaOH, 0.5 equiv.), lower base loading was used by Beller, Maji or Milstein. This non-bifunctional complex was then modified, allowing the β -alkylation of secondary alcohols to α -substituted ketones.¹⁰⁵ Nevertheless, both systems were limited to the alkylation of aryl ketones with primary alcohols.



Scheme 1.67: Synthesis of α -substituted ketones described by Ke.

2) Iron-catalysed C-alkylation reactions.

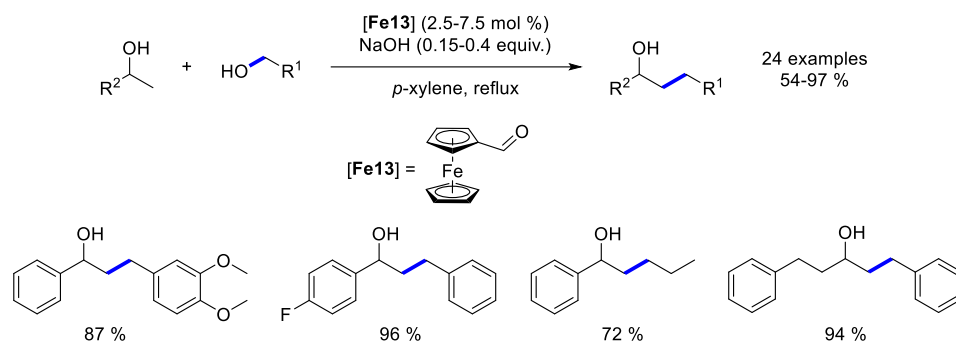
Following the first iron-catalysed alkylation of amines described by Saito,³⁹ the first iron-catalysed C-C bond formation through borrowing hydrogen was described by Sun in 2012.¹⁰⁶ In the

¹⁰⁴ Lan, X.-B.; Ye, Z.; Huang, M.; Liu, J.; Liu, Y.; Ke, Z. *Org. Lett.* **2019**, *21*, 8065-8070.

¹⁰⁵ Lan, X.-B.; Ye, Z.; Liu, J.; Huang, M.; Shao, Y.; Cai, X.; Liu, Y.; Ke, Z. *ChemSusChem* **2020**, *13*, 2557-2563.

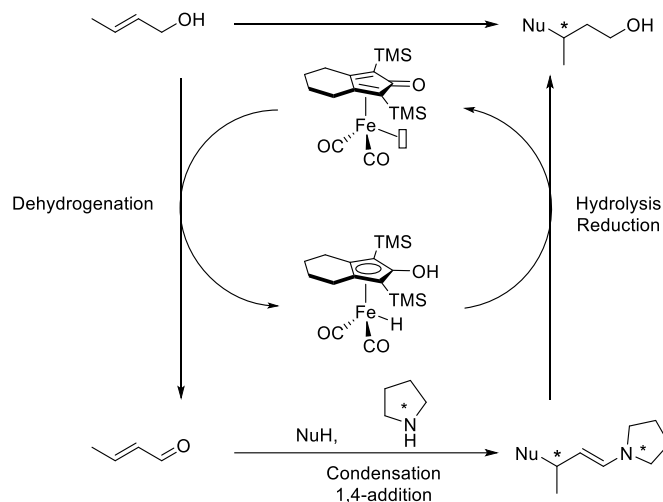
¹⁰⁶ Yang, J.; Liu, X.; Meng, D.-L.; Chen, H.-Y.; Zong, Z.-H.; Feng, T.-T.; Sun, K. *Adv. Synth. Catal.* **2012**, *354*, 328-334.

presence of a simple ferrocene carboxaldehyde as a catalyst, various secondary alcohols were alkylated with benzylic and aliphatic alcohols to give β -substituted alcohols. This reaction tolerated few functional groups but allowed the formation of substituted alcohols in good to excellent yields (Scheme 1.68).



Scheme 1.68: Iron-catalysed β -alkylation of alcohols.

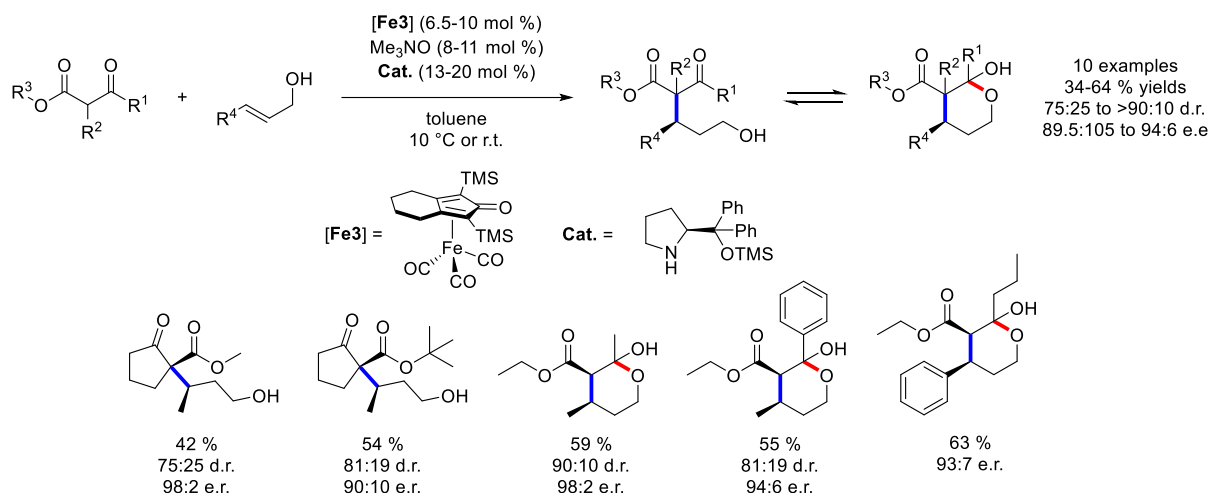
In 2013, Quintard and Rodriguez described a dual catalytic cascade process for enantioselective functionalisation of allylic alcohols.¹⁰⁷ In a first step, the Knölker complex dehydrogenates an allylic alcohol to give an enal intermediate. Condensation with a prolinol-type amine and subsequent 1,4-addition by a nucleophile afford a chiral enamine. Final hydrolysis and reduction give the β -substituted chiral alcohol as product (Scheme 1.69).



Scheme 1.69: Dual iron/organocatalysed alkylation of allylic alcohols.

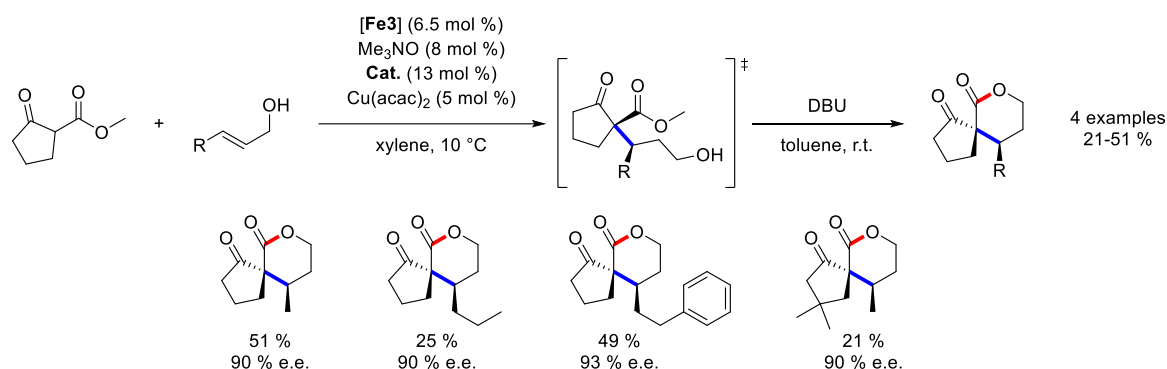
This methodology was evaluated using β -ketoesters as pro-nucleophiles. Moderate to good yields were obtained (35-64 %, Scheme 1.70) with excellent enantiomeric ratios (89.5:10.5 to 96:6) and good diastereomeric ratios (75:25 to >90:10) from crotyl and cinnamyl alcohols. The iminium intermediate ensured both the enantiocontrol and the formation of the desired product (less than 10 % conversion without the amine catalyst).

¹⁰⁷ Quintard, A.; Constantieux, T.; Rodriguez, J. *Angew. Chem. Int. Ed.* **2013**, 52, 12883-12887.



Scheme 1.70: Enantioselective alkylation of allylic alcohols.

In contrast with other substrates, cyclopentanone derivatives were not isolated in the cyclic form. A final transesterification was thus investigated, opening the route to chiral γ -lactones from 1,3-keto-esters.¹⁰⁸ To do so, DBU was added after the alkylation with allylic alcohol, allowing the formation of the lactone product. Using copper salt as additive increased the enantiomeric ratios of the reaction (Scheme 1.71).



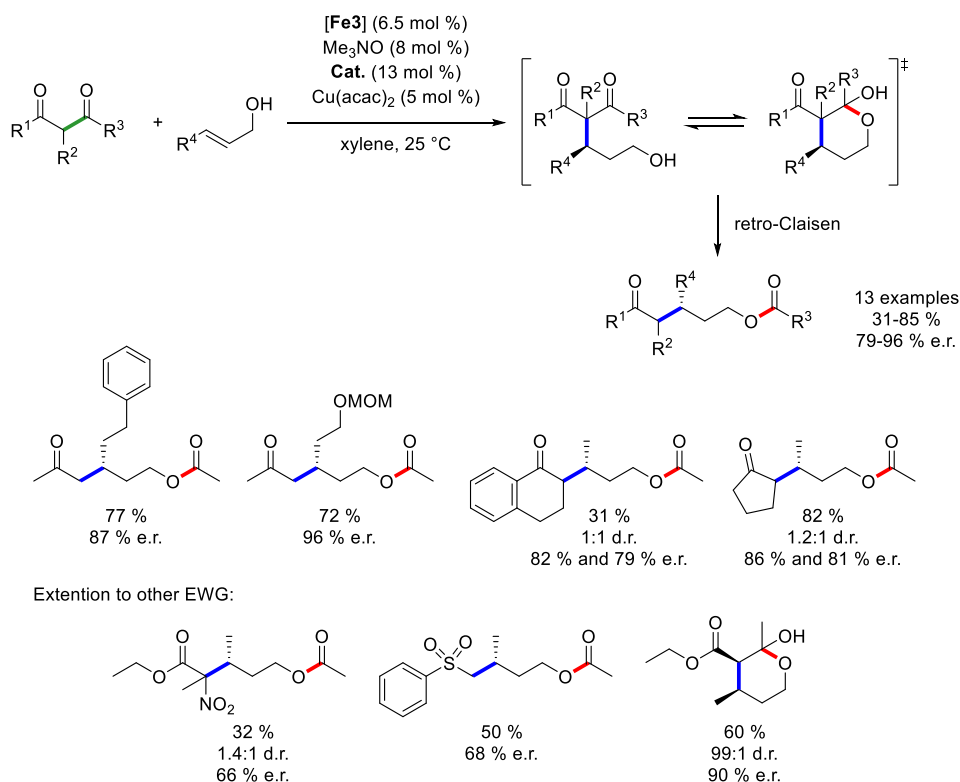
Scheme 1.71: Synthesis of γ -lactones.

The same group extended this dual catalytic strategy to the synthesis of 3-alkyl pentanols fragments.¹⁰⁹ The cascade process was associated to a final retro-Claisen reaction (Scheme 1.72). In this case, electron-withdrawing groups were not tolerated and the nature of the organocatalyst depended on the diketone involved in the reaction. The products were isolated in moderate to good yields (34 to 96 %) with good enantiomeric ratios (70:30 to >96:4). No diastereoselectivity was obtained with cyclic β -diketones, probably due to a non-selective protonation during the last step of the retro-Claisen fragmentation. Final optimisation by adding a copper salt as chelating agent in the Michael addition improved the enantiomeric ratio of the reaction (31-85 %, 79-96 % e.e., Scheme 1.72).¹¹⁰ Other β -EWG-substituted ketones as pro-nucleophiles were also engaged to extend the scope of this reaction and were isolated in moderate to good yields and good enantiomeric ratios (66-90 % e.e.).

¹⁰⁸ Quintard, A.; Roudier, M.; Rodriguez, J. *Synthesis* **2018**, 50, 785-792.

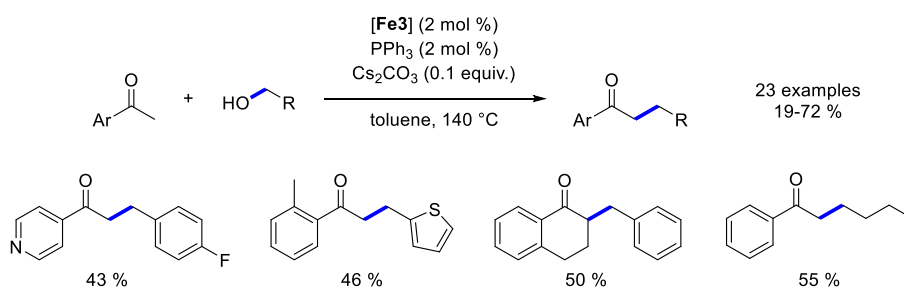
¹⁰⁹ Roudier, M.; Constantieux, T.; Quintard, A.; Rodriguez, J. *Org. Lett.* **2014**, 16, 2802-2805.

¹¹⁰ Roudier, M.; Constantieux, T.; Quintard, A.; Rodriguez, J. *ACS Catal.* **2016**, 6, 5236-5244.



Scheme 1.72: Insertion of allylic alcohol in 1,3-diketones.

In 2015, Darcel described the α -alkylation of ketones with primary alcohols catalysed by the Knölker complex at 140 °C.¹¹¹ Interestingly, addition of triphenylphosphine increased the activity of the catalyst. This additive was supposed to increase the lifetime of the catalytic species. Nevertheless, only aromatic ketones were involved as only reduction was observed when aliphatic ketones were evaluated in these reaction conditions (Scheme 1.73).

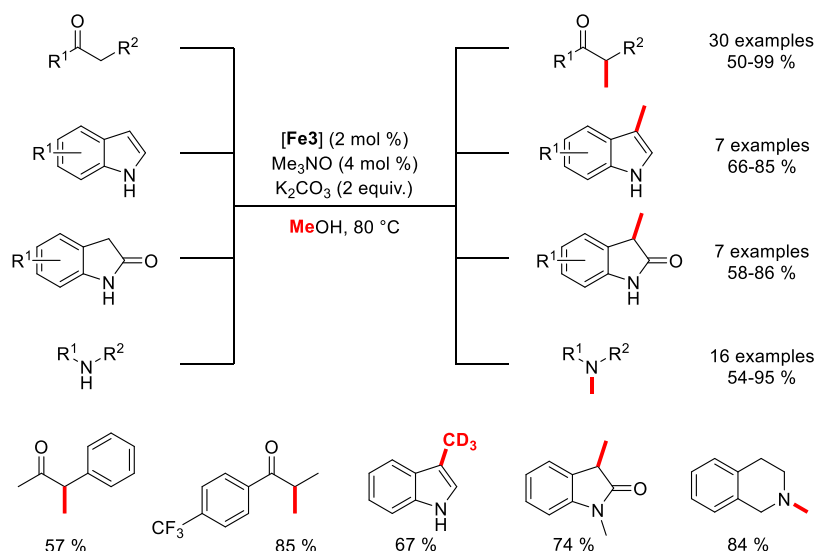


Scheme 1.73: Alkylation of ketones reported by Darcel.

Methylation reactions were then investigated by Morrill.¹¹² Various nucleophiles reacted with methanol in the presence of the Knölker complex in mild conditions to afford the methylated products in good to excellent yields (Scheme 1.74).

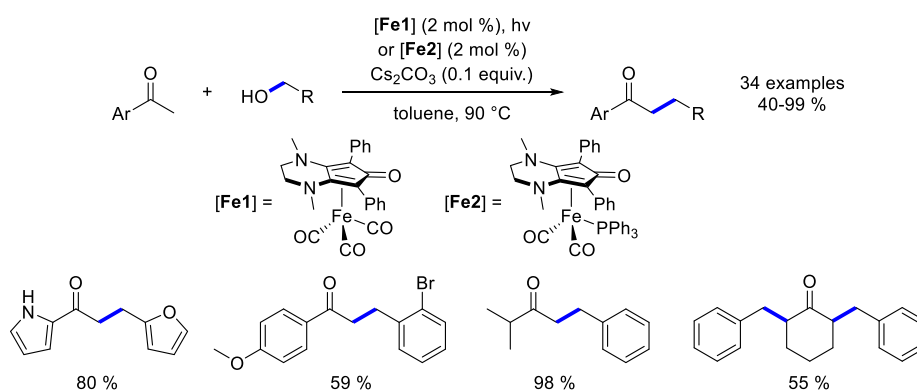
¹¹¹ Elangovan, S.; Sortais, J.-B.; Beller, M.; Darcel, C. *Angew. Chem. Int. Ed.* **2015**, *54*, 14483-14486.

¹¹² Polidano, K.; Allen, B. D. W.; Williams, J. M. J.; Morrill, L. C. *ACS Catal.* **2018**, *8*, 6440-6445.



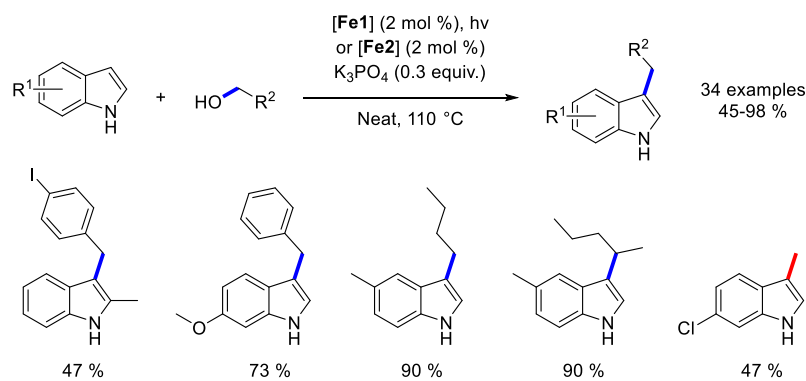
Scheme 1.74: Methylation of various nucleophiles.

In 2017, the modified Knölker catalyst described by Renaud⁵³ was reported for the same reaction.^{23a} DFT calculation compared the original Knölker and Renaud's catalysts along the catalytic cycle. This study showed lower energy barriers for the diamino derivative. Furthermore, the reduction step was found to be exothermic for the latter. Taking this information into account, α -alkylation of aryl ketones was performed and confirmed the theoretical study: using the conditions described by Darcel,¹¹¹ the temperature could be decreased to $90\text{ }^\circ\text{C}$ with shorter reaction times, and the alkylated products were obtained with better yields (Scheme 1.75). In contrast with the work of Darcel,¹¹¹ the alkylation of aliphatic ketones could be achieved without any reduction of the ketones.



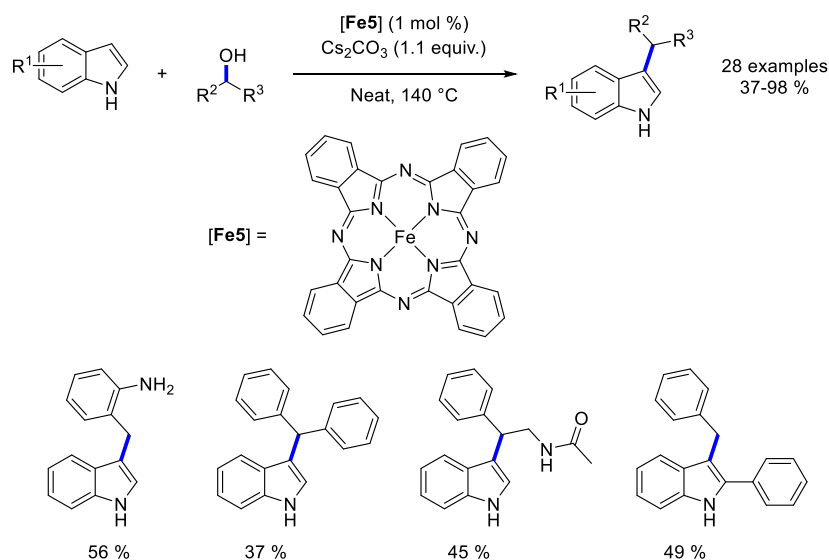
Scheme 1.75: Alkylation of ketones reported by Renaud.

Following this work, the alkylation of indoles was investigated.²¹ Higher temperatures were required due to the lower nucleophilicity of indoles. The alkylated products were obtained in moderate to good yields. Also, two examples with secondary alcohols as pro-electrophiles were isolated in good yields (45-55 %, Scheme 1.76).



Scheme 1.76: Alkylation of indoles reported by Renaud.

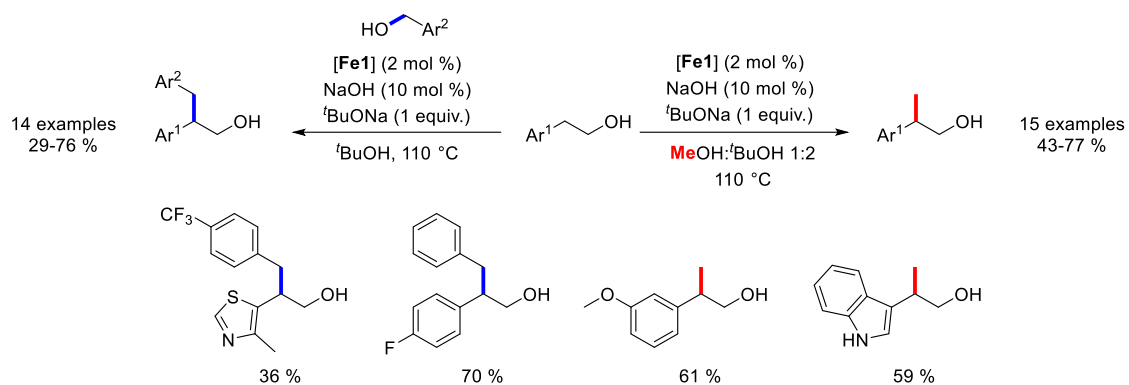
This reaction was also described with an iron-phthalocyanine complex as a catalyst.¹¹³ Lower yields were obtained with secondary alcohols compared to the alkylation with primary alcohols. Furthermore, high temperatures were required (Scheme 1.77).



Scheme 1.77: Alkylation of indoles reported by Piersanti.

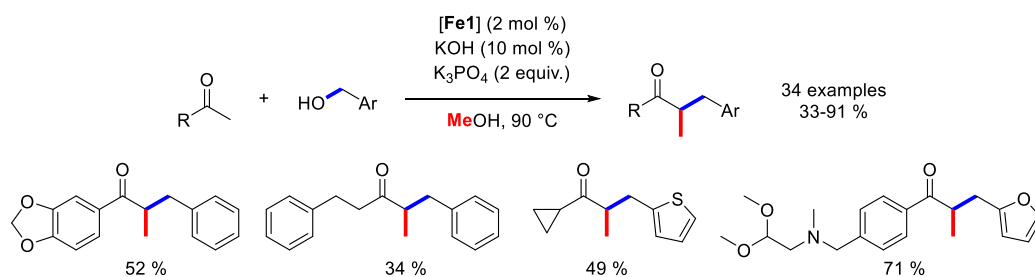
While the alkylation of ketones or secondary alcohols has been widely explored, the β -alkylation of primary alcohols using earth-abundant metals was not described. In 2019, our group reported the β -alkylation of homobenzylic alcohols with benzylic alcohols and methanol.²² Various substituted alcohols were engaged, leading to functionalised β -branched primary alcohols in moderate to good yields (Scheme 1.78). This reaction couldn't be extended to aliphatic alcohols since cross-alkylation products could be obtained as well. Nevertheless, this procedure is an atom-efficient alternative to hydroformylation-reduction sequence and allows the synthesis of functionalised alcohols.

¹¹³ Di Gregorio, G.; Mari, M.; Bartoccini, F.; Piersanti, G. *J. Org. Chem.* **2017**, *82*, 8769-8775.



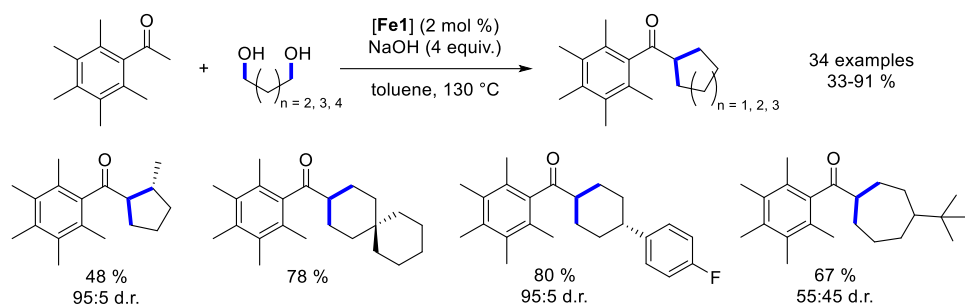
Scheme 1.78: Alkylation of primary alcohols.

The same year, a three-component alkylation reaction was described by our group.^{23b} In this reaction, a ketone reacted with a primary alcohol in methanol to give an α -disubstituted ketone. Various functionalised products were obtained with this methodology (Scheme 1.79). The proposed mechanism was the following one. After a first alkylation with benzyl alcohol, the α -substituted ketone undergoes a second alkylation with methanol, giving rise to the α -benzylmethyl ketone. This reaction was limited to benzylic primary alcohols as pro-electrophile. Nevertheless, these results represent an atom-economical approach to the synthesis of functionalised ketones.



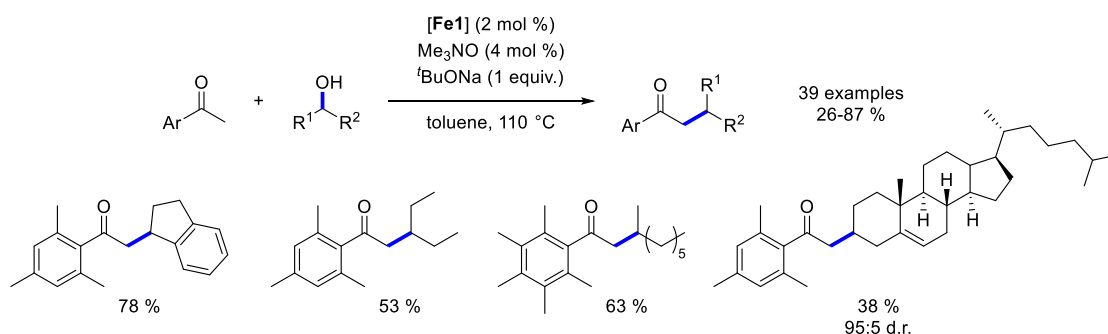
Scheme 1.79: One-pot three-component alkylation of ketones reported by Renaud.

To further explore the capability of this complex, the synthesis of cycloalkanes was explored.^{23c} Following the same methodology than Leitner and Maji,^{92,93} various diols were engaged with pentamethyl acetophenone to provide the corresponding cyclic di-alkylated ketones in moderate to good yields. 5- to 7-membered substituted cycloalkanes were obtained with this methodology. Good control of the diastereoselectivity was obtained with cyclopentanes and cyclohexanes, while cycloheptanes gave lower diastereomeric ratios (Scheme 1.80).



Scheme 1.80: Synthesis of cycloalkanes.

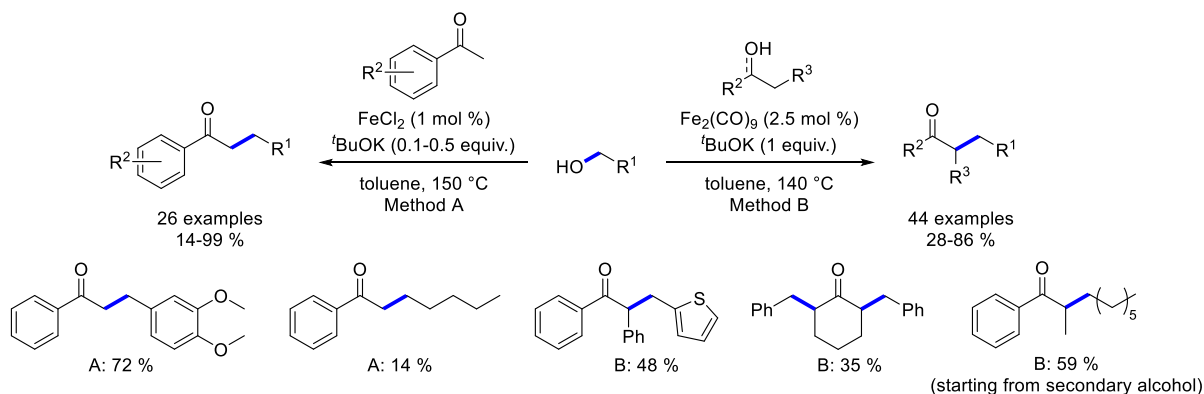
Numerous works described the alkylation of ketones with primary alcohols. The use of secondary alcohols as pro-electrophiles is still a stimulating problem as few examples have been described, whatever the metal-based complex. To complete this work, the α -alkylation of ketones with secondary alcohols was finally investigated.^{23d} Pentamethyl acetophenone was again used to avoid cross-alkylation reactions. Various benzylic and aliphatic secondary alcohols were engaged in this reaction, leading to β -branched ketones in moderate to good yields, with good functional groups tolerance. To highlight the methodology, functionalised cholesterol derivative was obtained in 38 % yield with a complete control of the diastereoselectivity (Scheme 1.81).



Scheme 1.81: Alkylation with secondary alcohols.

In 2019, Yang and Banerjee described the synthesis of α -substituted ketones using ligand free catalysts.¹¹⁴ Yang used FeCl_2 as a catalyst while Banerjee used $\text{Fe}_2(\text{CO})_9$, two precursors of previously reported bifunctional iron catalysts. Both required high temperatures to catalyse the alkylation reactions. The methodology of Banerjee was more general as it was not limited to benzylic ketones and better yields were obtained with aliphatic alcohols. Furthermore, secondary alcohols could be employed as pro-nucleophiles, yielding the substituted ketones in similar yields (Scheme 1.82).

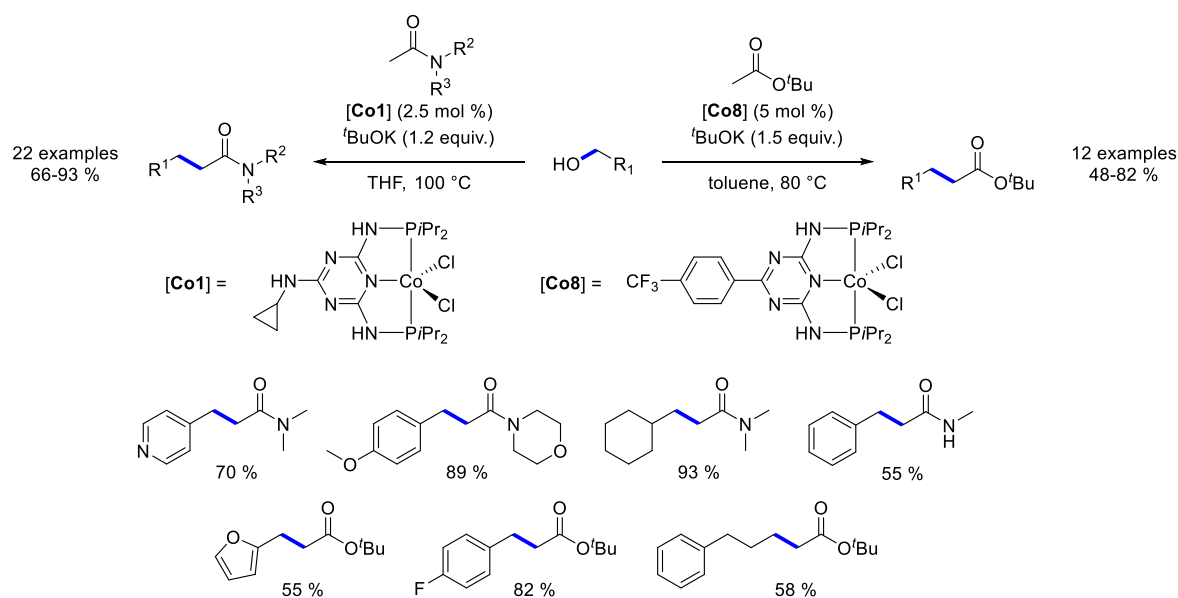
¹¹⁴ (a) Ibrahim, J. J.; Reddy, C. B.; Zhang, S.; Yang, Y. *Asian J. Org. Chem.* **2019**, *8*, 1858-1861. (b) Alanthadka, A.; Bera, S.; Banerjee, D. *J. Org. Chem.* **2019**, *84*, 11676-11686.



Scheme 1.82: Synthesis of α -substituted ketones.

3) Cobalt-catalysed C-alkylation reactions.

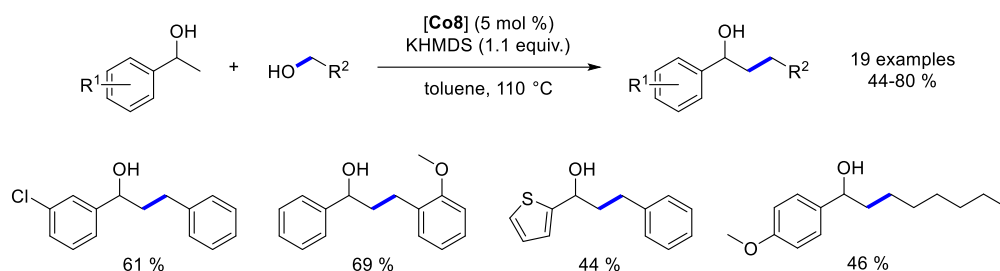
The first cobalt-catalysed C-alkylation reaction was reported by Kempe in 2016.¹¹⁵ A cobalt complex bearing a triazine-containing pincer PNP-type ligand was able to promote either the alkylation of various acetamide derivatives, or the alkylation of *tert*-butyl acetate, with primary alcohols. The reaction conditions depended on the pro-nucleophile. In sharp contrast with the alkylation of ketones, the pro-electrophiles were used as limiting reagent due to the less acidic character of amide and esters. In the optimised conditions, a variety of amides and esters were alkylated with benzylic and aliphatic alcohols to give α -substituted products in good to excellent yields (Scheme 1.83). *N*-mono-substituted amides led to lower yields due to the favoured deprotonation of the acidic hydrogen. Worth to mention, the scope was limited to *tert*-butyl esters due to a possible transesterification with ^tBuOK in the process.



Scheme 1.83: C-alkylation of amides and esters.

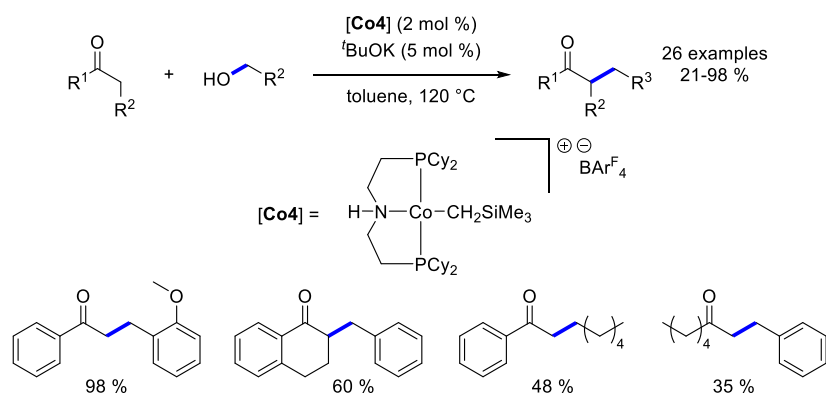
¹¹⁵ Deibl, N.; Kempe, R. *J. Am. Chem. Soc.* **2016**, *138*, 10786-10789.

The cobalt complex **Co8** was also engaged in the alkylation of secondary benzylic alcohols.¹¹⁶ Various benzylic and aliphatic alcohols were engaged in this process, giving the β -alkylated products in moderate to good yields. Lower yields were obtained with aliphatic alcohols (Scheme 1.84).



Scheme 1.84: Alkylation of secondary alcohols.

Zhang *et al.* investigated also the alkylation of ketones in the presence of cobalt complex.¹¹⁷ The Macho-Co complex previously described by the same group for the alkylation of amines⁶² allowed the alkylation of aromatic ketones with benzylic alcohols and primary aliphatic alcohols, albeit in lower yields (Scheme 1.85). Also, when the pro-nucleophile was an aliphatic ketone, the alkylated ketone was isolated in a modest yield.



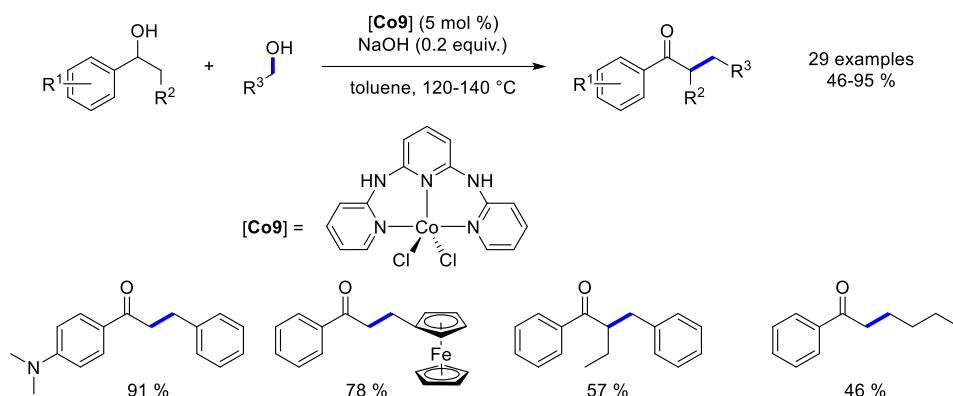
Scheme 1.85: Alkylation of ketones reported by Zhang.

Li *et al.* synthesised and applied a cobalt(II) complex bearing phosphine-free NNN pincer ligand in alkylation of benzylic secondary alcohols with primary benzylic and aliphatic alcohols in toluene at 120 °C, in the presence of a catalytic amount of NaOH (20 mol %).¹¹⁸ Various ketones were thus isolated in 46-95 % yields (Scheme 1.86).

¹¹⁶ Freitag, F.; Irrgang, T.; Kempe, R. *Chem. Eur. J.* **2017**, *23*, 12110-12113.

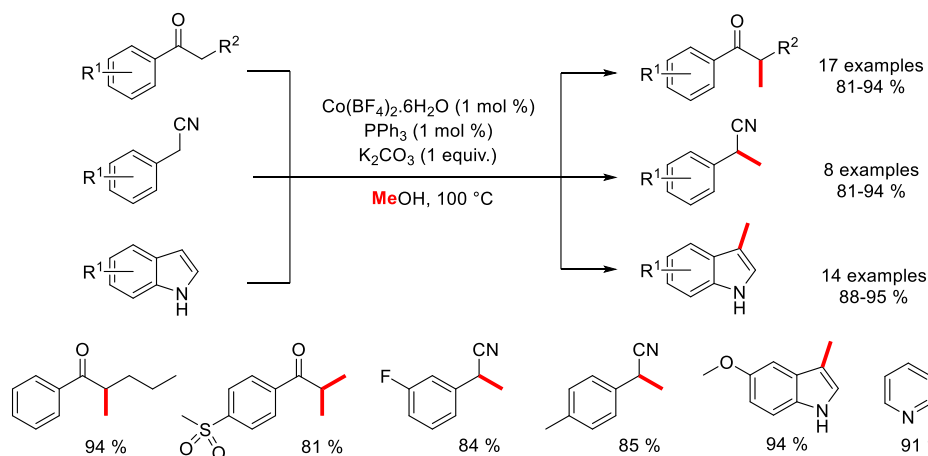
¹¹⁷ Zhang, G.; Wu, J.; Zeng, H.; Zhang, S.; Yin, Z.; Zheng, S. *Org. Lett.* **2017**, *19*, 1080-1083.

¹¹⁸ Zhang, S.-Q.; Guo, B.; Xu, Z.; Li, H.-X.; Li, H.-Y.; Lang, J.-P. *Tetrahedron* **2019**, *75*, 130640.



Scheme 1.86: Synthesis of α -substituted ketones reported by Li.

In 2017, Liu reported the methylation of ketones, benzyl nitriles and indoles using a combination of $\text{Co}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ and PPh_3 .¹¹⁹ Various substituted nucleophiles were methylated with methanol as pro-electrophile and isolated in good to excellent yields, with tolerance for a variety of functional groups (Scheme 1.87).



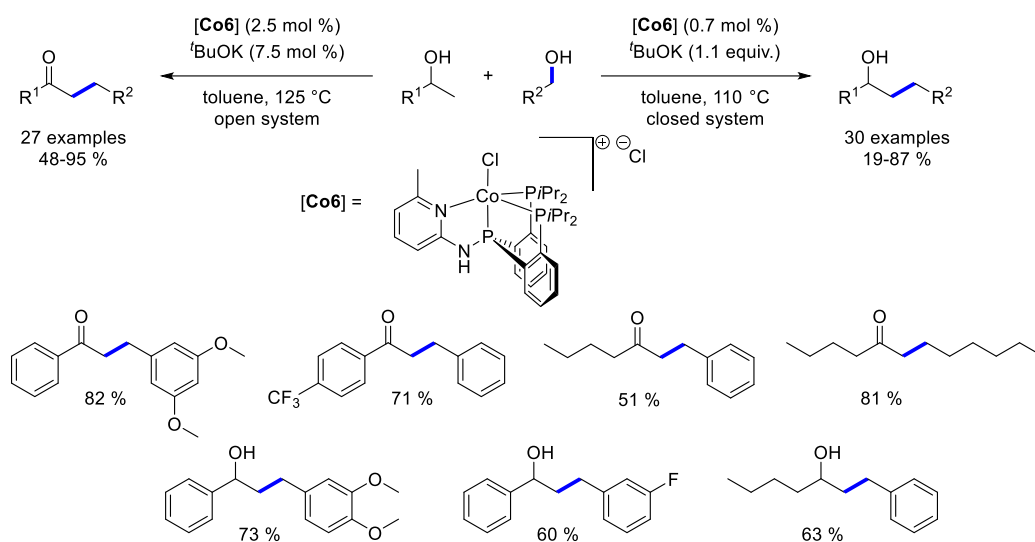
Scheme 1.87: Cobalt-catalysed methylation of various nucleophiles reported by Liu.

Ding presented a well-defined PNPP-Co catalyst for the β -alkylation of secondary with primary alcohols leading either to the corresponding β -alkylated alcohol or the α -alkylated ketone at 110-125 °C.^{120, 121} This switchable synthesis can be controlled by modifying the reaction parameters (amount of base, closed or open system). Worth to mention is the low catalyst loading employed in this process (Scheme 1.88).

¹¹⁹ Liu, Z.; Yang, Z.; Yu, X.; Zhang, H.; Yu, B.; Zhao, Y.; Liu, Z. *Org. Lett.* **2017**, *19*, 5228-5231.

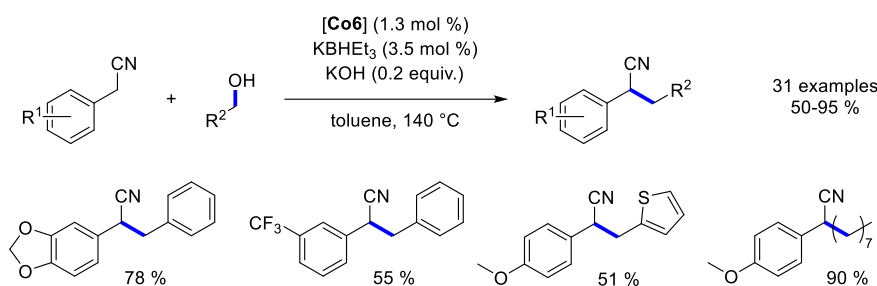
¹²⁰ Pandey, B.; Xu, S.; Ding, K. *Org. Lett.* **2019**, *21*, 7420-7423.

¹²¹ Pandey, B.; Xu, S.; Ding, K. *Organometallics* **2021**, *40*, 1207-1212.



Scheme 1.88: Synthesis of α -substituted ketones and β -substituted alcohols.

Alkylation of nitriles with primary alcohols was also achieved with the same PNPP-Co complex.¹²² Up to 95 % yield were reached with a variety of benzyl nitriles and either benzyl or aliphatic alcohols (Scheme 1.89). Other nitrile derivatives did not work under these conditions.

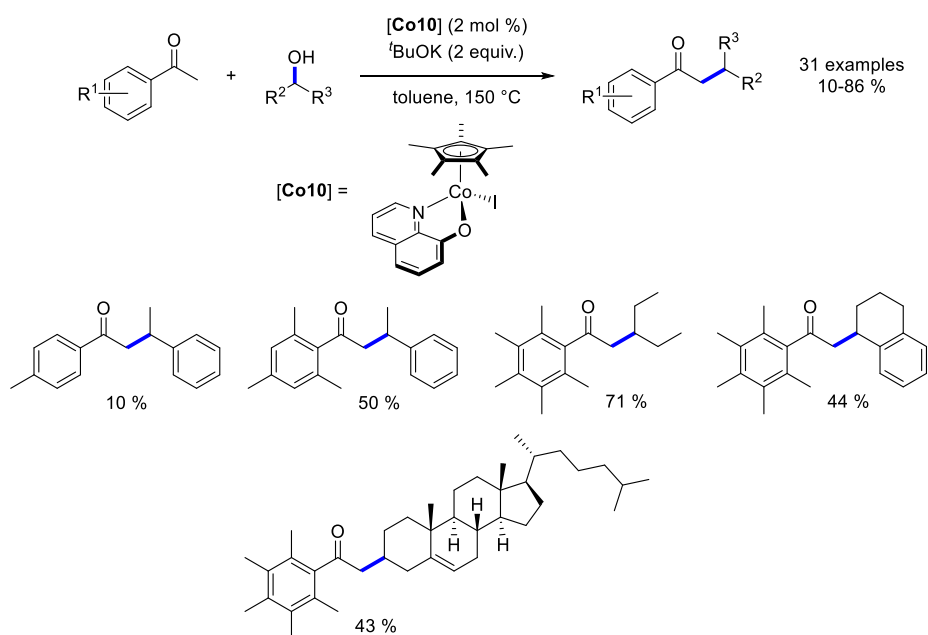


Scheme 1.89: Alkylation of nitriles reported by Ding.

In 2019, Sundararaju reported the α -alkylation of ketones using a $\text{Cp}^*\text{Co(III)}$ complex.¹²³ A related complex was also able to catalyse the alkylation of amines with secondary alcohols.⁶⁷ The reaction between substituted acetophenone derivatives with benzylic or aliphatic secondary alcohols afforded the β -disubstituted ketones in good yields (Scheme 1.90). Also noticed in Mn and Fe chemistry, *ortho,ortho*-disubstitution of the acetophenone derivative is necessary to avoid cross-alkylation and to enhance the reactivity.

¹²² Paudel, K.; Xu, S.; Ding, K. *J. Org. Chem.* **2020**, *85*, 14980-14988.

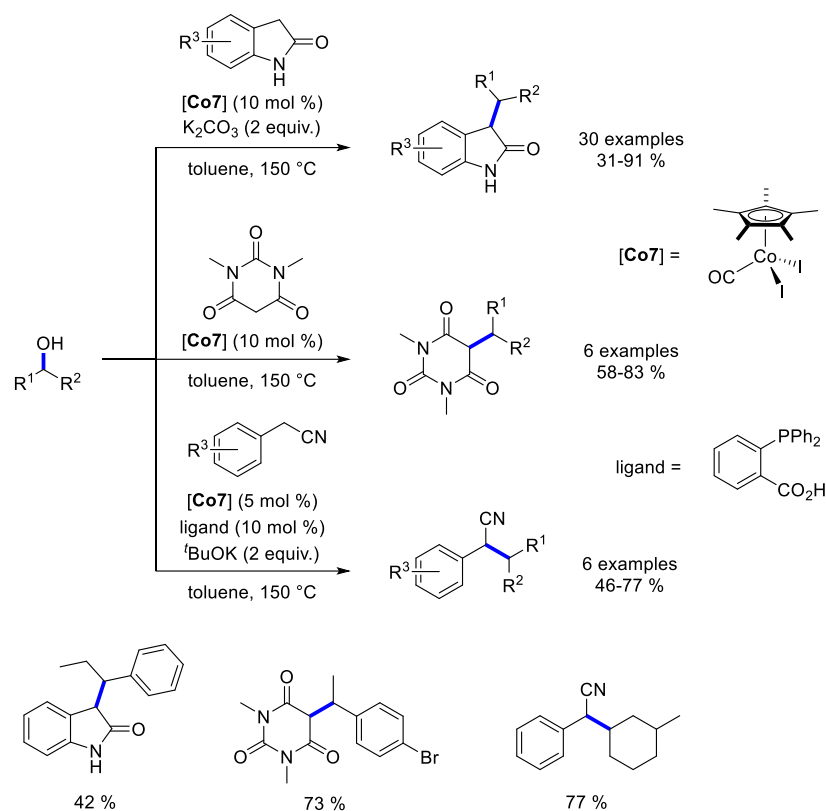
¹²³ Chakraborty, P.; Gangwar, M. K.; Emayavaramban, B.; Manoury, E.; Poli, R.; Sundararaju, B. *ChemSusChem* **2019**, *12*, 3463-3467.



Scheme 1.90: Alkylation of ketones with secondary alcohols.

Another phosphine-free cobalt complex was also described by Sundararaju et al. for the alkylation of oxindoles, *N,N*-dimethyl barbituric acid and benzyl nitriles with secondary alcohols.¹²⁴ The bench-stable cobalt(III) catalysed selectively the oxindole derivative in 31-91 % yields (Scheme 1.91). Alkylation of barbituric acid did not require additional base due to the acidic character of this substrate, the alkylated derivatives were obtained in 58-83 % yields (Scheme 1.91). In this case, only benzylic alcohols were introduced in the reaction while the alkylation of benzyl nitriles was performed only with cyclic aliphatic alcohols in 46-77 % yields (Scheme 1.91).

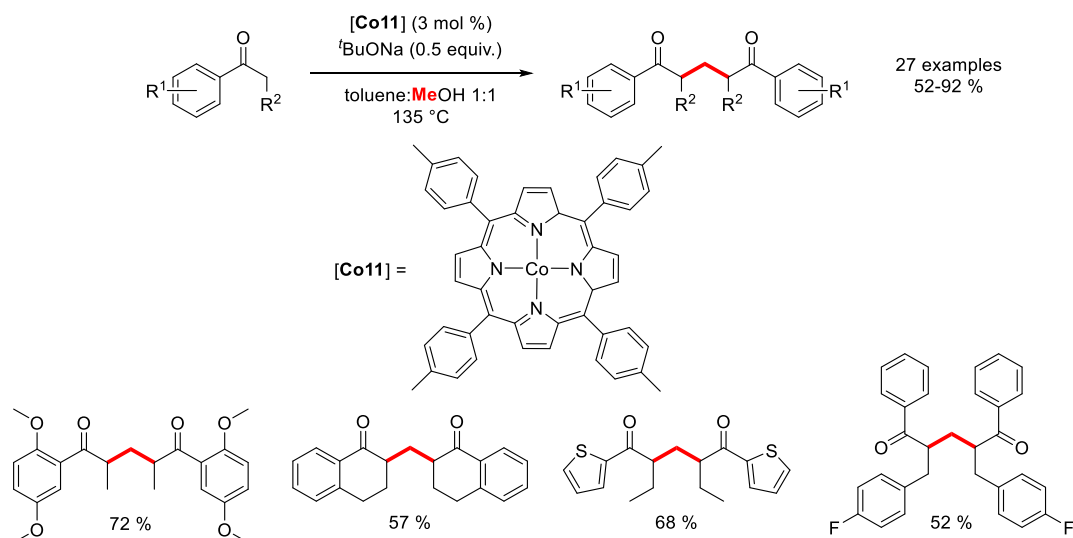
¹²⁴ Chakraborty, P.; Garg, N.; Manoury, E.; Poli, R.; Sundararaju, B. *ACS Catal.* **2020**, *10*, 8023-8031.



Scheme 1.91: Alkylation of oxindoles, barbituric acid and nitriles.

More recently, Chandrasekhar and Venkatasubbaiah described a porphyrin cobalt complex for the synthesis of 1,5-diketones via a dehydrogenative coupling reaction using methanol as a C1 source.¹²⁵ In this process, condensation of the *in situ* generated formaldehyde led to the α,β -unsaturated aromatic ketones. A Michael-type addition of the aromatic enolate furnished the corresponding 1,5-diketones in 52-92 % yields (Scheme 1.92). The catalytic cobalt active species was regenerated after release of hydrogen. A variety of methylenated products were obtained with this methodology, albeit limited to α -substituted benzylic ketones.

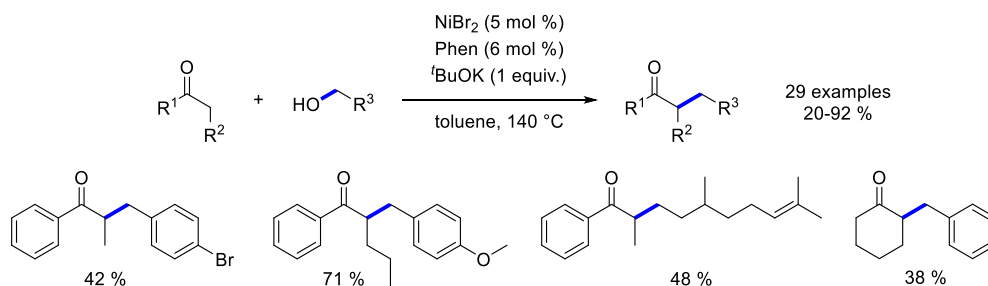
¹²⁵ Biswal, P.; Samsar, S.; Nayak, P.; Chandrasekhar, V.; Venkatasubbaiah, K. *J. Org. Chem.* **2021**, *86*, 6744-6754.



Scheme 1.92: Synthesis of 1,5-diketones.

4) Nickel-catalysed C-alkylation reactions.

The first nickel-catalysed alkylation of ketones with alcohols was described by Banerjee in 2018.¹²⁶ The catalyst was generated *in situ* by associating NiBr₂ with 1,10-phenanthroline. Various α -substituted aryl ketones were alkylated with benzylic alcohols in moderate to good yield while aliphatic alcohols or aliphatic ketones yielded the products in lower yields and required a higher base loading (2 equiv. and 2.5 equiv., respectively). This system was further studied using a catalytic amount of base (Cs₂CO₃ (10 mol %) or tBuOK (20 mol %)) but aliphatic alcohols did not provide any alkylated compounds in these conditions (Scheme 1.93).¹²⁷



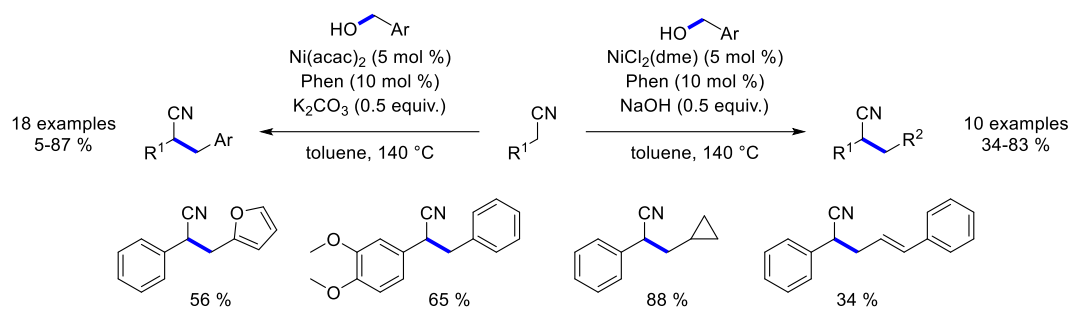
Scheme 1.93: Alkylation of α -substituted ketones.

Following these works, the same group reported the alkylation of nitriles with primary alcohols.¹²⁸ In this work, 1,10-phenanthroline was associated with Ni(acac)₂ to form the catalytic species *in situ*. The reaction of benzyl nitriles with benzyl alcohols afforded the alkylated products in low to good yields (Scheme 1.94). Aliphatic nitriles such as 3-propionitrile led to the alkylated product in very low yields and no reaction was observed with acetonitrile. Replacement of Ni(acac)₂ and K₂CO₃ by NiCl₂(dme) and NaOH allowed the alkylation with aliphatic and allylic alcohols.

¹²⁶ Das, J.; Singh, K.; Vellakkaran, M.; Banerjee, D. *Org. Lett.* **2018**, *20*, 5587-5591.

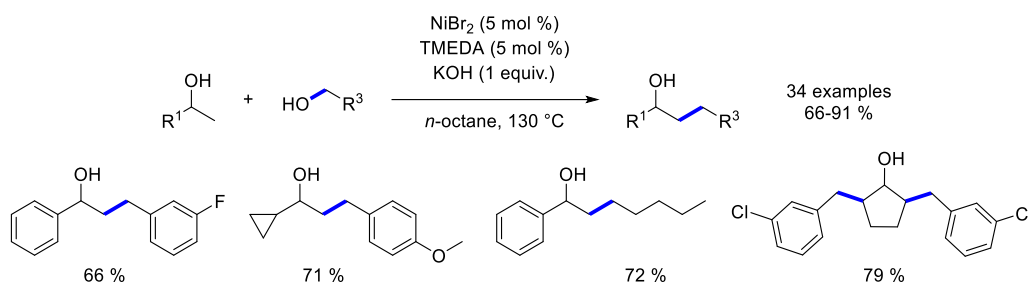
¹²⁷ Das, J.; Vellakkaran, M.; Banerjee, D. *J. Org. Chem.* **2019**, *84*, 769-779.

¹²⁸ Bera, S.; Bera, A.; Banerjee, B. *Chem. Commun.* **2020**, *56*, 6850-6853.



Scheme 1.94: Nickel-catalysed alkylation of nitriles.

In 2021, Balaraman reported the β -alkylation of secondary alcohols with primary alcohols to give β -substituted alcohols catalysed by a combination of tetramethylethylenediamine (TMEDA) and NiBr_2 .¹²⁹ A variety of alcohols were engaged as pro-electrophiles and yielded the desired products, without significant decrease in yields with aliphatic and benzylic alcohols. Aliphatic secondary alcohols also afforded the desired products in good yields without modification of the reaction conditions which makes this reaction applicable for a wide range of substrates (Scheme 1.95).

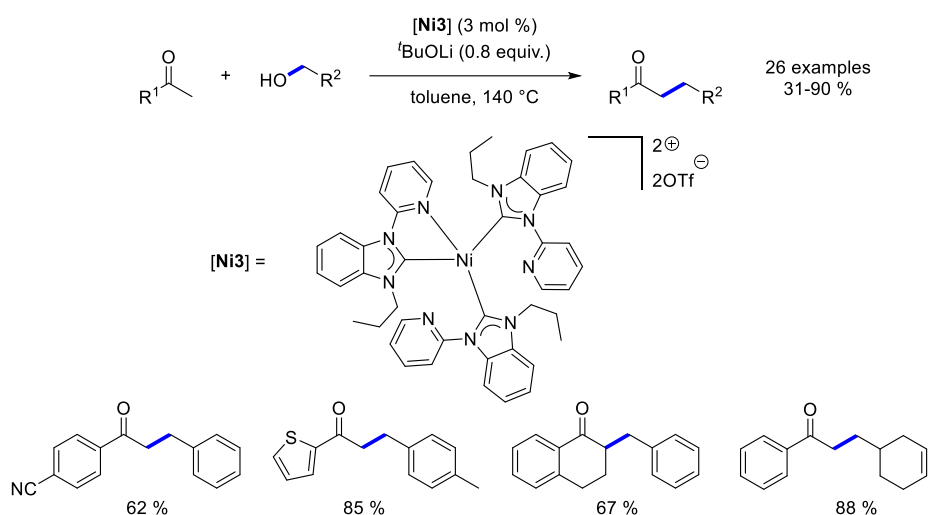


Scheme 1.95: Nickel-catalysed β -alkylation of alcohols.

Liu described a Ni-NHC complex for the α -alkylation of ketones with benzyl alcohols.¹³⁰ This new catalyst allowed the formation of a variety of alkylated ketones in low to good yields with catalytic amount of base at 140 °C (Scheme 1.96).

¹²⁹ Babu, R.; Subaramanian, M.; Midya, S. P.; Balaraman, E. *Org. Lett.* **2021**, *23*, 3320-3325.

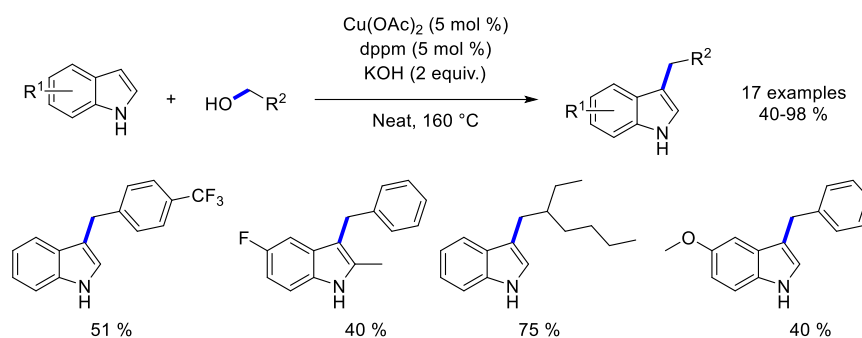
¹³⁰ Wu, D.; Wang, Y.; Li, M.; Shi, L.; Liu, J.; Liu, N. *Appl Organomet Chem.* **2022**, *36*, e6493.



Scheme 1.96: Alkylation of ketones reported by Liu.

5) Copper-catalysed C-alkylation reactions.

Recently, Dang described the first copper-catalysed alkylation of indoles with alcohols.¹³¹ Copper acetate was associated with the bis-diphenylphosphinomethane (dppm) ligand to form the catalytic species. Benzylic and aliphatic alcohols led to the alkylated indoles in moderate to good yields (Scheme 1.97). Nevertheless, high temperatures were required and only few examples of functionalised products were described which limits the scope of this reaction. Also, no reaction was observed with *N*-substituted indoles which highlight the necessity of this hydrogen atom in the process.

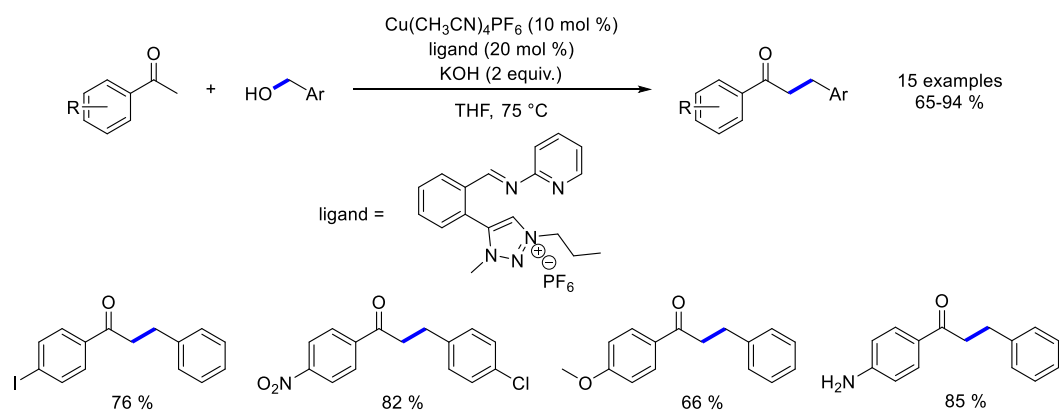


Scheme 1.97: C3-alkylation of indoles.

The same year, Bala reported the alkylation of aryl ketones with benzyl alcohols.¹³² The catalyst was also generated *in situ* associating $\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6$ with the ligand. This reaction allowed the formation of a variety of functionalised ketones in good yields at 75 °C which makes this reaction competitive compared to other alkylation reactions which requires high temperatures (Scheme 1.98).

¹³¹ Nguyen, N.-K.; Nam, D. H.; Phuc, B. V.; Nguyen, V. H.; Trinh, Q. T.; Hung, T. Q.; Dang, T. T. *Mol. Catal.* **2021**, *505*, 111462.

¹³² Lawal, N. S.; Ibrahim, H.; Bala, M. D. *Monatsh. fur Chem.* **2021**, *152*, 275-285.



Scheme 1.98: Copper-catalysed alkylation of ketones.

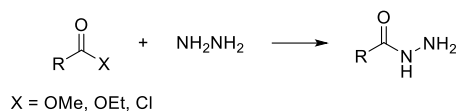
IV. Conclusion.

Among the reported works for the alkylation of N- and C-nucleophiles, rare are the methodologies using moisture- and air-stable organometallic complexes. Furthermore, the tricky synthesis of these sensitive catalysts raises the question of the relevance and applicability of such methodologies at an industrial level. Other methods report the use of metal salts, but higher temperatures and base loadings are usually required, sometimes at a stoichiometric amount. Cyclopentadienone iron tricarbonyl complexes already shown their effectiveness in various alkylation reactions in mild conditions, and thus presents a particular interest in this purpose.

**CHAPTER II: ALKYLATION OF BENZOYL
HYDRAZINES: ACCESS TO MONO- OR DI-
SUBSTITUTED COMPOUNDS.**

I. Introduction.

Hydrazides are a class of nitrogen containing compounds, bearing an acyl substituent on one of the two nitrogens of the hydrazine moiety. These compounds can be easily synthesized from acyl chlorides or esters¹³³ (Scheme 2.1).



Scheme 2.1: General synthesis of hydrazides.

Hydrazides derivatives are important synthons as they have applications in the synthesis of drugs, agrochemicals, and in polymer manufacturing, among others (Figure 2.1).¹³⁴ As examples, Iproniazid and Isocarboxazide are two drugs used in the treatment of psychiatric disorders, Rimonabant is an anorectic anti-obesity drug, and Daminozide is a plant growth regulator. They are also often used as precursors for the synthesis of heterocyclic compounds.¹³⁵

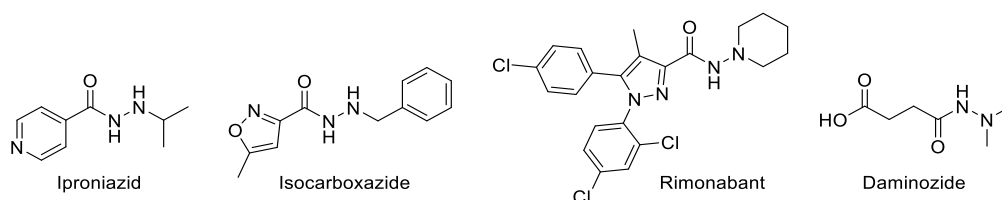


Figure 2.1: Examples of bioactive compounds presenting a hydrazide fragment.

II. Alkylation of hydrazides *via* hydrogen autotransfer reaction.

1) *N'*-Alkylation of hydrazides.

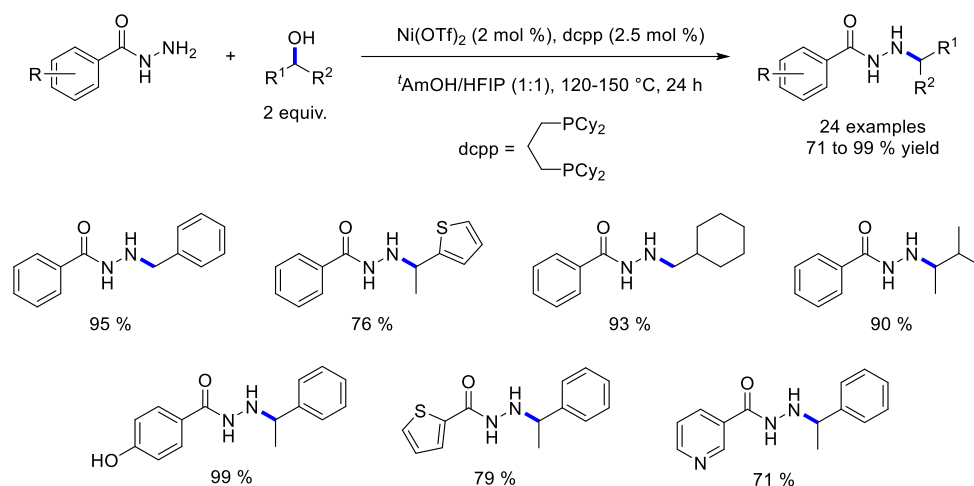
Zhou reported in 2017 the first *N'*-alkylation of hydrazides derivatives *via* hydrogen autotransfer (Scheme 2.2).¹³⁶ A nickel (II) precatalyst associated with a diphosphine ligand was used, allowing the *N'*-alkylation of benzoyl, acetyl and carboxybenzyl hydrazines. Various primary, secondary, benzylic or aliphatic alcohols were employed, generating the corresponding products in very good yields (71 to 99 %) with perfect selectivity for the mono-alkylated hydrazide even if two equivalents of alcohols were introduced. Furthermore, slightly acidic conditions (presence of HFIP or AcOH) were necessary to achieve good reactivities, whereas the product was not observed in strongly basic, acidic or neutral conditions.

¹³³ (a) Shamsabadi, A.; Chudasama, V. *Org. Biomol. Chem.* **2017**, *15*, 17-33. (b) Majumdar, P.; Pati, A.; Patra, M.; Behera, R. K.; Behera, A. K. *Chem. Rev.* **2014**, *114*, 2942-2977.

¹³⁴ Grekov, A. P. *Organic Chemistry of Hydrazine*; Technika Publishers: Kiev, **1966**; 23.

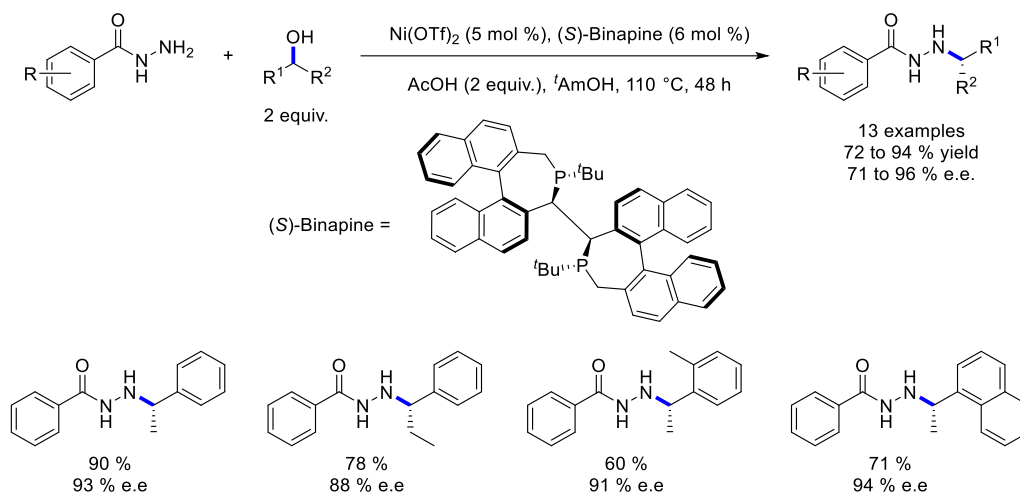
¹³⁵ Majumdar, P.; Pati, A.; Patra, M.; Behera, R. K.; Behera, A. K. *Chem. Rev.* **2014**, *114*, 2942-2977.

¹³⁶ Yang, P.; Zhang, C.; Ma, Y.; Zhang, C.; Li, A.; Tang, B.; Zhou, J. S. *Angew. Chem. Int. Ed.* **2017**, *56*, 14702-14706.



Scheme 2.2: *N'*-Alkylation of hydrazides reported by Zhou.

To further enhance the value of this methodology, the (*S*)-Binapine, a chiral diphosphine, was used in order to develop an enantioselective alkylation (Scheme 2.3). Only tert-amyl alcohol was used as solvent, but an excess of acetic acid was required to give the product in similar yield and good enantiomeric excess (71 to 96 % e.e., Scheme 3)

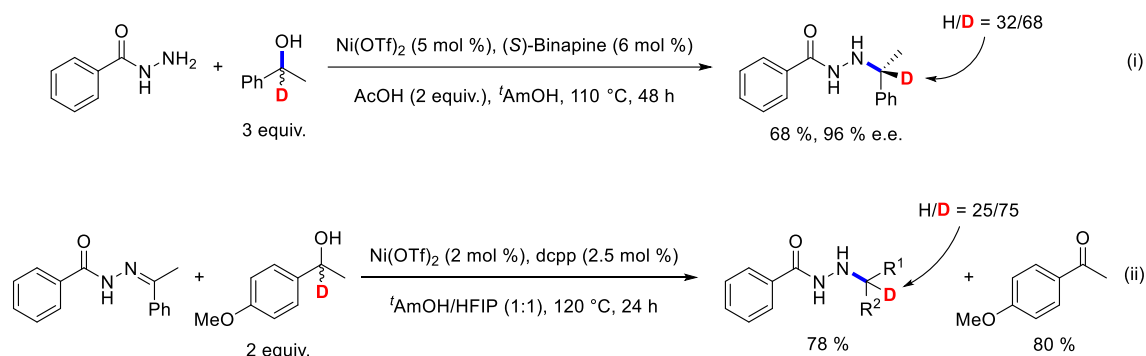


Scheme 2.3: Enantioselective *N'*-alkylation of hydrazides reported by Zhou.

In order to gain insight into the mechanism and validate the hydrogen autotransfer mechanism and not a nucleophilic substitution, deuterium labelling experiments were conducted (Scheme 2.4). In the first experiment (i), rac-deuterated 1-phenylethanol was used as a pro-electrophile in the alkylation of phenyl hydrazide in the presence of nickel salt and (*S*)-Binapine. The product was isolated with 68 % of deuterium incorporation at the benzylic position and 96 % e.e. The authors explained this loss of deuterium by a parasitic equilibrium between (*L-L*)Ni⁰ and cationic [(*L-L*)NiD]⁺ in the presence of acidic proton and alcoholic solvents, as already observed in previous works.¹³⁷ In a second experiment (ii), the benzoyl hydrazone reacted with deuterated 1-(4-anisyl)ethanol as a hydride donor in racemic conditions to yield the reduced benzoyl hydrazide with 75 % incorporation of deuterium, and the 4-methoxy acetophenone. These experiments suggest that a nucleophilic substitution or radical pathway

¹³⁷ (a) Guo, S.; Yang, P.; Zhou, J. *Chem. Commun.* **2015**, *51*, 12115-12117. (b) Guo, S.; Zhou, J. *Org. Lett.* **2016**, *18*, 5344-5347.

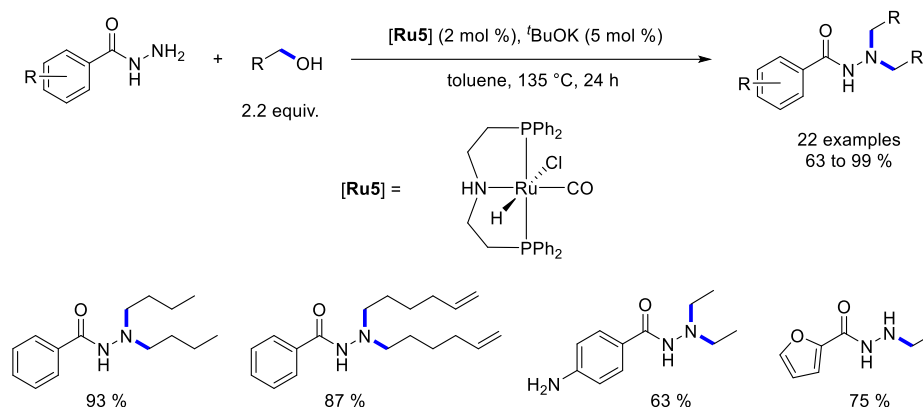
could be discarded and directly support a hydrogen transfer mechanism between the alcohol and the hydrazone.



Scheme 2.4: Deuterium labelling experiments proposed by Zhou.

2) *N,N'*-Dialkylation of hydrazides

In 2020, Gunanathan reported a ruthenium-catalysed *N,N'*-dialkylation of acyl hydrazides with alcohols.¹³⁸ The Ru-Macho pincer complex, used in this reaction, was previously reported for the β -alkylation of secondary alcohols by the same group.¹³⁹ In this work, only a catalytic amount of base was necessary to obtain the dialkylated products in good to excellent yields (63 to 99 %, Scheme 2.5). It is worth noting that an aniline derivative was engaged in the reaction without any alkylation of the amine function. When the 2-furoylhydrazide was used as pro-nucleophile, the monoalkylated product was isolated exclusively in 75 % yield.

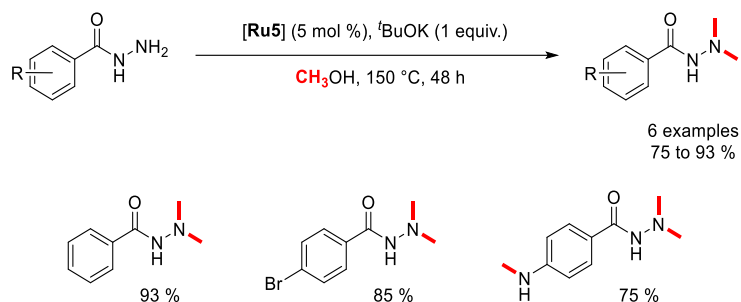


Scheme 2.5: *N,N'*-Dialkylation of benzoyl hydrazines proposed by Gunanathan.

The dimethylation of acyl hydrazides was also explored. To do so, the reaction was performed directly in methanol at higher temperature (150 °C), base (1 equiv. of *t*BuOK) and catalyst loadings were needed (5 mol % of ruthenium complex, Scheme 2.6). Also, the reaction time was longer (48 hours). It is worth noting that under these conditions both nitrogen atoms of 4-aminophenylhydrazide were methylated.

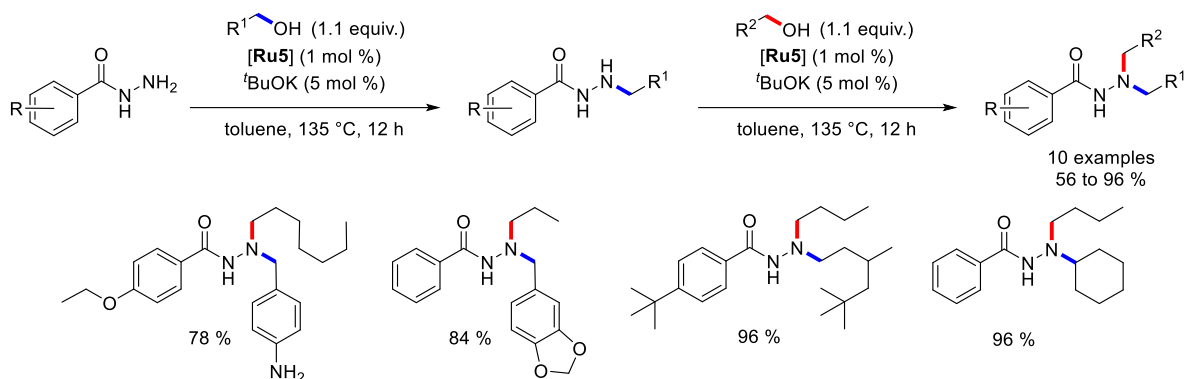
¹³⁸ Thiyagarajan, S.; Gunanathan, C. *Org. Lett.* **2020**, *22*, 6617-6622.

¹³⁹ Thiyagarajan, S.; Gunanathan, C. *J. Am. Chem. Soc.* **2019**, *141*, 3822-3827.



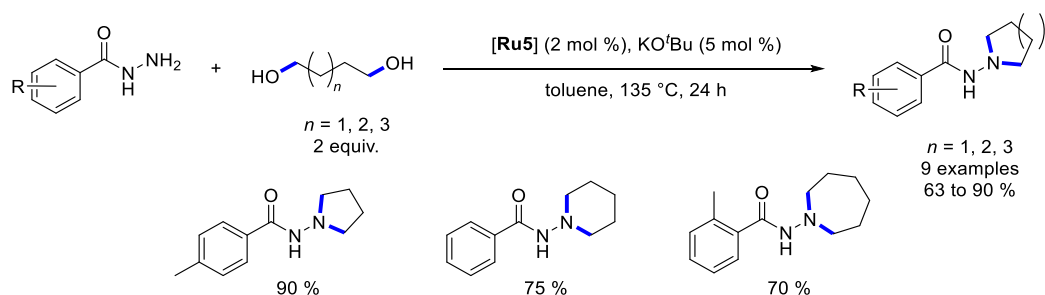
Scheme 2.6: *N,N'*-dimethylation of hydrazides reported by Gunanathan.

To obtain unsymmetrical *N,N'*-dialkylated products, the reaction was decomposed in a sequential two-steps one-pot alkylation (Scheme 2.7). After a first alkylation of the acylhydrazide with an alcohol as pro-electrophile in presence of 1 mol % of ruthenium complex, 5 mol % of ^tBuOK in toluene at 135 °C, a second alkylation was carried with another alcohol and after addition of 1 mol % of ruthenium complex and 5 mol % of ^tBuOK (Scheme 2.7). In this sequential alkylation, the products were isolated in yields ranging from 56 to 96 % (Scheme 2.7).



Scheme 2.7: Synthesis of unsymmetrical hydrazides reported by Gunanathan.

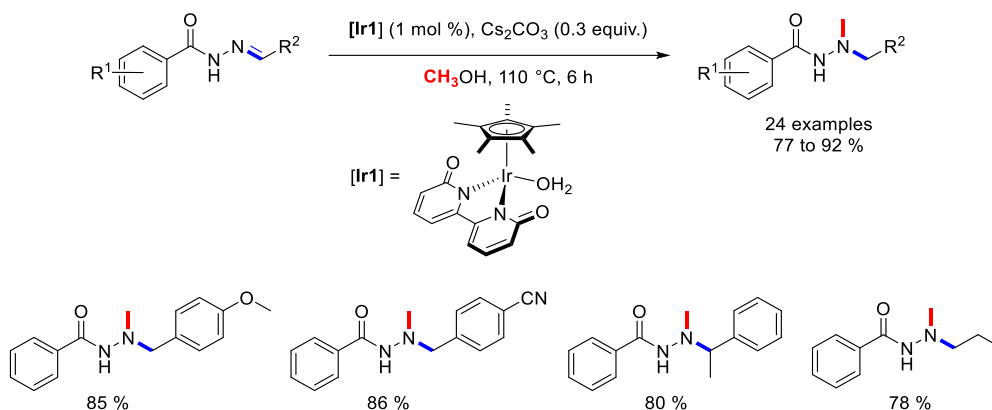
To extend the scope of pro-electrophiles, diols were engaged in this reaction in order to obtain nitrogen-containing heterocycles. Then, 5-, 6- and 7-member rings were obtained *via* an intermolecular alkylation of the first alcohol, followed by an intramolecular alkylation with the second one, in 63 to 90 % yield (Scheme 2.8).



Scheme 2.8: *N,N'*-Dialkylation of hydrazides with diols described by Gunanathan.

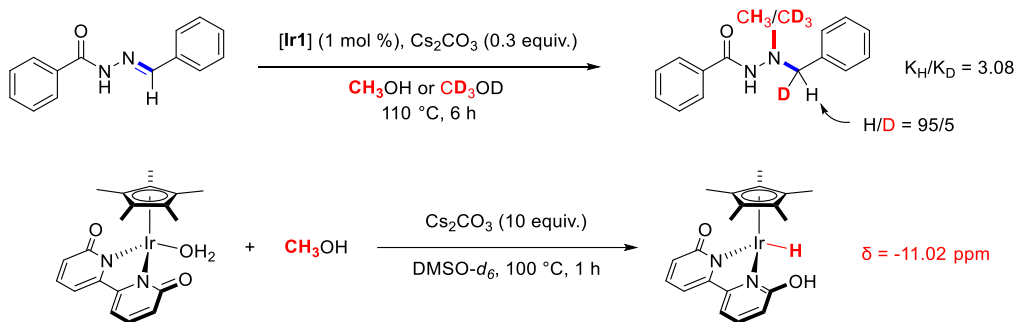
3) *N'*-methyl-*N'*-alkyl hydrazides from acylhydrazones.

In 2022, Li reported the synthesis of *N'*-methyl-*N'*-alkyl hydrazides from acylhydrazones *via* a transfer hydrogenation approach.¹⁴⁰ In this work, a Cp*-iridium complex bearing a [2,2'-bipyridine]-6,6'-dione ligand was employed in the presence of a catalytic amount of Cs₂CO₃ in methanol (Scheme 2.9). Benzylic and aliphatic acylhydrazones were involved in this process and the desired products were obtained in good to excellent yields (77 to 92 %, Scheme 2.9). Cyano substituents were tolerated in these conditions and neither the reduction of the C=N bond nor lower activity of the catalyst was observed.



Scheme 2.9: Synthesis of *N'*-methyl-*N'*-alkyl hydrazides reported by Li.

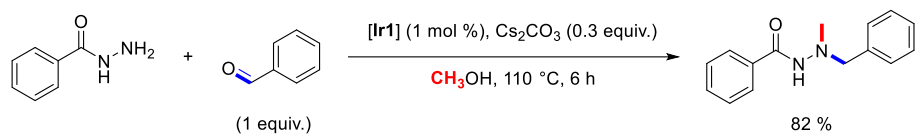
Investigations of the reaction mechanism in Scheme 2.10 showed a significant kinetic isotopic effect when methanol was replaced by CD₃OD ($K_H/K_D = 3.08$), revealing that the C-H bond cleavage of methanol is the rate determining step (rds). Deuterium incorporation at the benzylic position confirmed the hydrogen borrowing mechanism. Furthermore, the iridium-hydride species was observed by ¹H NMR, which further complete this mechanistic study.



Scheme 2.10: Mechanistic investigation performed by Li.

Finally, a one-pot three-components synthesis of *N'*-benzyl-*N'*-methyl benzoyl hydrazide starting from benzoyl hydrazine, benzaldehyde and methanol was performed under the optimized conditions and the desired non-symmetric product was obtained in 82 % yield (Scheme 2.11).

¹⁴⁰ Luo, S.; Xu, X.; Zhang, P.; Shi, Q.; Yang, X.; Li, F. *Org. Lett.* **2022**, *24*, 9081-9085.



Scheme 2.11: One-pot, three component synthesis of *N'*-methyl-*N'*-benzyl benzoyl hydrazide.

III. Cyclopentadienone ruthenium tricarbonyl complex-catalysed mono- and dialkylation of benzoyl hydrazides.

1) Optimisation of the reaction.

While the diaminocyclopentadienone iron tricarbonyl complexes had proven their efficiency for the formation of C-C bonds in the alkylation of ketones,^{23,112} indoles,²¹ oxindoles,¹⁴¹ and alcohols,^{22,142,143} but also for the formation of C-N bonds through the methylation and ethylation of amines,^{7,20} the alkylation of hydrazides derivatives has not yet been explored. It was preliminary hypothesised that iron complexes **Fe1-Fe4** may also catalyse the synthesis of substituted acyl hydrazides with alcohols (Figure 2.2). Unfortunately, none of these complexes were able to furnish the alkylated product. The first result was obtained with their ruthenium congeners **Ru1-Ru4**. The ruthenium complex **Ru1**, analogue of **Fe1**, was developed by Haak and used for the activation of propargyl alcohols.¹⁴⁴ Complex **Ru2** was synthesized for the first time in our group starting from **Ru1** and triphenylphosphine, **Ru3** is the ruthenium analogue of Reppe's complex **Fe4** and a precursor of the Shvo's complex **Ru4** which is already known to catalyse hydrogen transfer reactions.¹⁴⁵

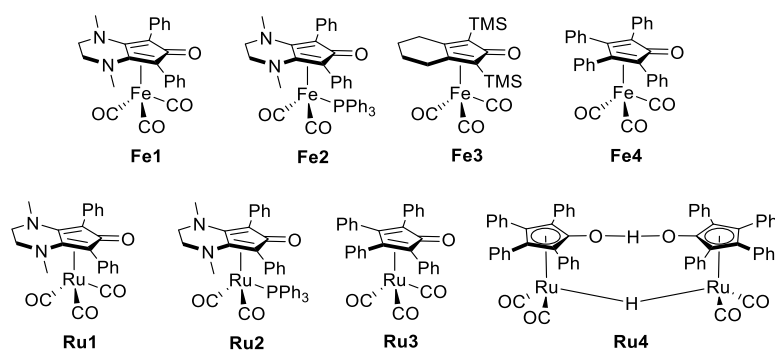


Figure 2.2: Iron and ruthenium complexes studied.

The alkylation of benzoyl hydrazine with 1-hexanol was chosen as a model reaction (Table 2.1). To allow the formation of the dialkylated product with good selectivity, a large excess of alcohol (5 equiv.) was mandatory. A decrease, to 1.5 and 3 equiv. (Entries 1 and 2), lead to both a lower conversion of the starting material and lower selectivity as a mixture of mono- and di-alkylated products was obtained. Diminishing the temperature (Entries 12 and 13) also resulted in lower conversion and only the mono-alkylated product was observed. Sodium *tert*-butoxide was found to be the most effective base, while inorganic ones did not give full conversion (Entries 14 to 16). Lowering the quantity of base only led to lower conversion and selectivity (Entries 5 to 8) and the optimum was obtained with 0.5 equiv. (Entry 4). A final solvent study showed that *tert*-butanol gave the best result (Entry 3). Toluene

¹⁴¹ Dambatta, M. B.; Polidano, K.; Northey, A. D.; Williams, J. M. J.; Morrill, L. C. *ChemSusChem* **2019**, *12*, 2345-2349.

¹⁴² Latham, D. E.; Polidano, K.; Williams, J. M. J.; Morrill, L. C. *Org. Lett.* **2019**, *21*, 7914-7918.

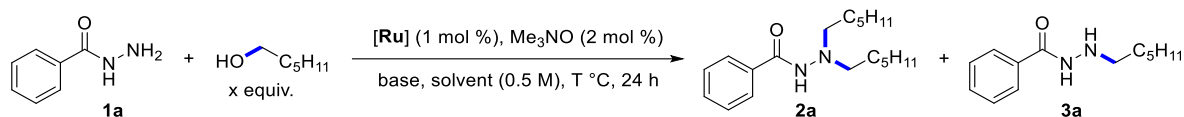
¹⁴³ Polidano, K.; Williams, J. M. J.; Morrill, L. C. *ACS Catal.* **2019**, *9*, 8575-8580.

¹⁴⁴ (a) Haak, E. *Eur. J. Org. Chem.* **2007**, *2007*, 2815-2824. (b) Haak, E. *Eur. J. Org. Chem.* **2008**, *2008*, 788-792. (c) Berger, S.; Haak, E. *Tetrahedron Lett.* **2010**, *51*, 6630-6634. (d) Thies, N.; Hrib, C. G.; Haak, E. *Chem. Eur. J.* **2012**, *18*, 6302-6308. (e) Jonek, A.; Berger, S.; Haak, E. *Chem. Eur. J.* **2012**, *18*, 15504-15511. (f) Thies, N.; Gerlach, M.; Haak, E. *Eur. J. Org. Chem.* **2013**, *2013*, 7354-7365. (g) Thies, N.; Haak, E. *Angew. Chem. Int. Ed.* **2015**, *54*, 4097-4101. (h) Thies, N.; Stürminger, M.; Haak, E. *Synlett.* **2017**, *28*, 701-704. (i) Kaufmann, J.; Jäckel, E.; Haak, E. *Angew. Chem. Int. Ed.* **2018**, *57*, 5908-5911. (j) Jäckel, E.; Kaufmann, J.; Haak, E. *Synthesis* **2018**, *50*, 742-752. (k) Kaufmann, J.; Jäckel, E.; Haak, E. *Arkivoc* **2019**, *part iv*, 91-101.

¹⁴⁵ Warner, M. C.; Casey, C. P.; Backvall, J.-E. *Top. Organomet. Chem.* **2011**, *37*, 85-125.

was also suitable for the reaction (Entry 10), while no dialkylated product was observed in CPME (Entry 11). The ruthenium complex **Ru2** also permitted the alkylation (Entry 17), while **Ru3** and **Ru4** had shown lower reactivity and selectivity (Entries 18 and 19). It should be noted that none of the conditions allowed the mono-alkylated product to be obtained with good selectivity.

Table 2.1: Optimisation table for the *N,N*-dialkylation of hydrazides.



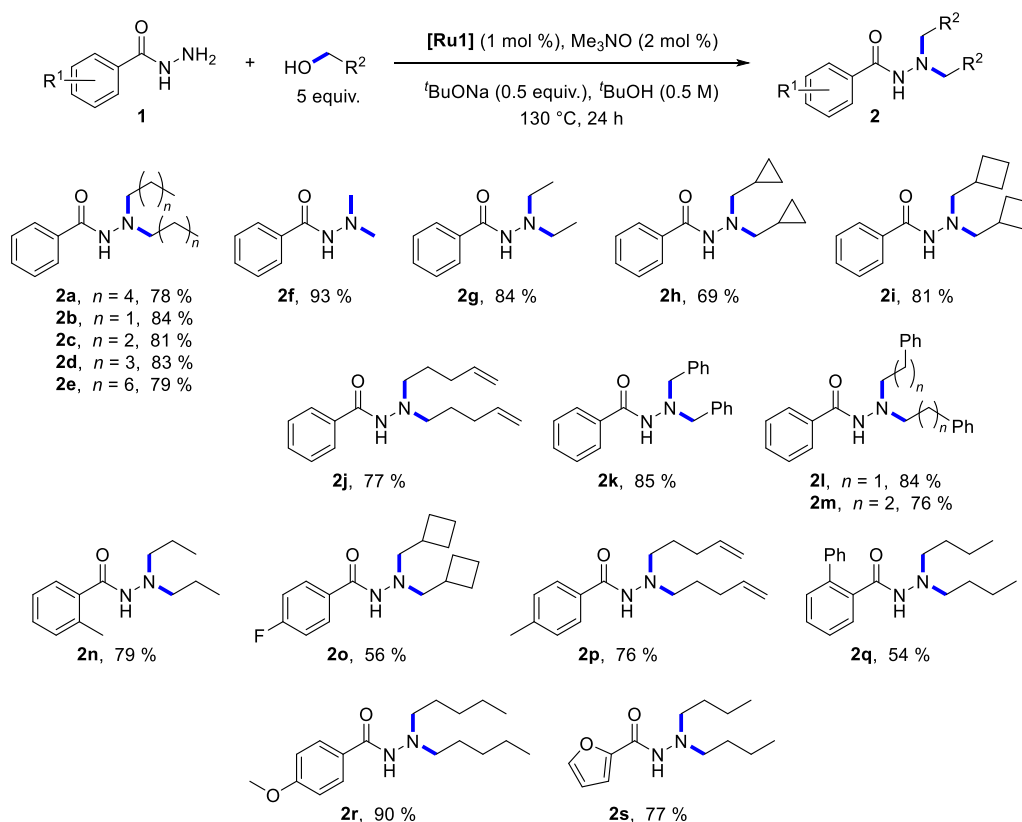
Entry ^a	Catalyst	1-hexanol (equiv.)	Solvent	Temperature (°C)	Base (equiv.)	1a (%)	2a (%)	3a (%)
1	Ru1	1.5	^t BuOH	130	NaO ^t Bu (0.5)	94	-	6
2	Ru1	3	^t BuOH	130	NaO ^t Bu (0.5)	44	22	34
3	Ru1	5	^tBuOH	130	NaO^tBu (0.5)	-	98 (78)^b	2
4	Ru1	7	^t BuOH	130	NaO ^t Bu (0.5)	-	98	2
5	Ru1	5	^t BuOH	130	NaO ^t Bu (0.1)	61	-	39
6	Ru1	5	^t BuOH	130	NaO ^t Bu (0.2)	36	22	42
7	Ru1	5	^t BuOH	130	NaO ^t Bu (0.3)	13	51	36
8	Ru1	5	^t BuOH	130	NaO ^t Bu (0.4)	-	71	29
9	Ru1	5	^t BuOH	130	NaO ^t Bu (1.0)	-	98	2
10	Ru1	5	toluene	130	NaO ^t Bu (0.5)	-	92	8
11	Ru1	5	CPME	130	NaO ^t Bu (0.5)	82	-	18
12	Ru1	5	^t BuOH	110	NaO ^t Bu (0.5)	48	-	52
13	Ru1	5	^t BuOH	90	NaO ^t Bu (0.5)	77	-	23
14	Ru1	5	^t BuOH	130	Na ₂ CO ₃ (0.5)	41	49	10
15	Ru1	5	^t BuOH	130	NaOH (0.5)	77	-	23
16	Ru1	5	^t BuOH	130	KO ^t Bu (0.5)	-	91	9
17^c	Ru2	5	^t BuOH	130	NaO ^t Bu (0.5)	3	92	5
18	Ru3	5	^t BuOH	130	NaO ^t Bu (0.5)	62	23	15
19^c	Ru4	5	^t BuOH	130	NaO ^t Bu (0.5)	59	32	19
20	-	5	^t BuOH	130	NaO ^t Bu (0.5)	100	-	-

^a Reactions performed with 0.5 mmol of acylhydrazide, conversion was determined by ¹H-NMR analysis of the crude mixture. ^b Yield of the isolated product after purification. ^c Reaction performed without using Me₃NO.

According to this study, the optimized conditions were as follows: the *N,N'*-dialkylation of benzoyl hydrazide processes in presence of alcohol (5 equiv.), the ruthenium complex **Ru1** (1 mol %) activated with Me₃NO (2 mol %), sodium *tert*-butoxide (0.5 equiv.) in *tert*-butanol (0.5 M) at 130 °C for 24 hours.

2) Scope of the reaction.

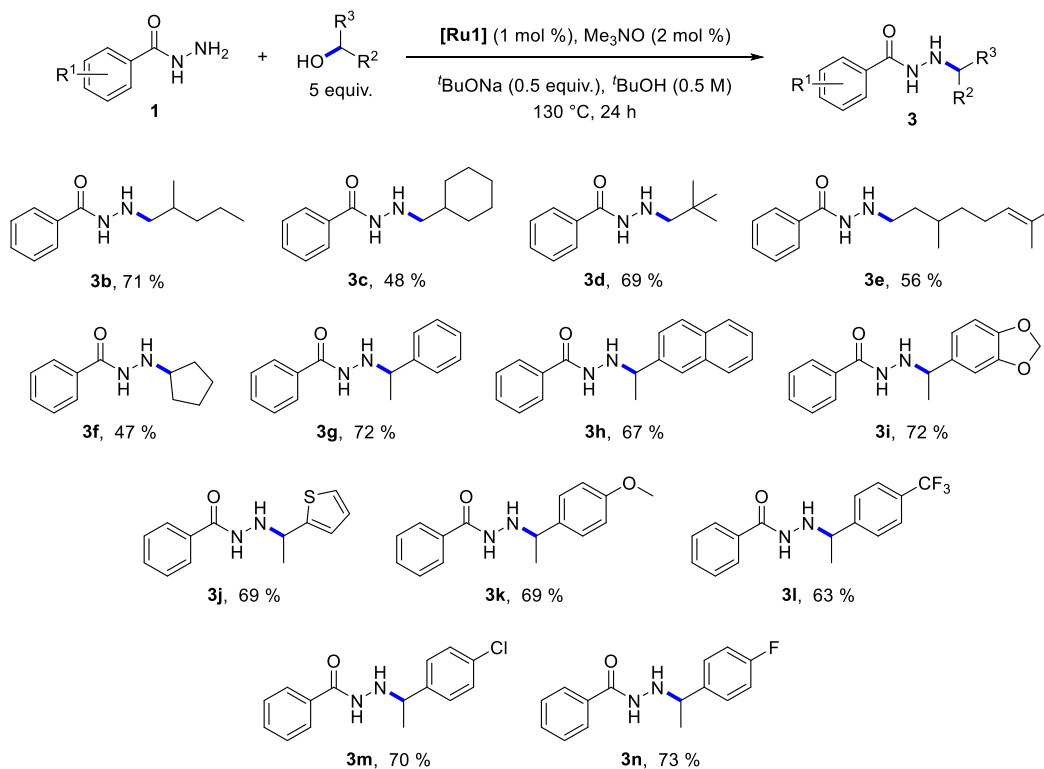
With the optimized conditions in hand, we explored the scope of this *N,N'*-dialkylation reaction with various alcohols and hydrazides (Scheme 2.12).¹⁴⁶ Linear aliphatic alcohols from C1 to C8 led to the *N,N'*-dialkylated products in very good yields (78 to 93 %) as well as primary alcohols bearing a strained small ring (compounds **2h**, **2i** and **2o**, 56 to 81 % yield). Unsaturated alcohols were tolerated and compounds **2j** and **2p** were isolated in 77 % and 76 % yield, respectively, without any reduction of the C=C double bond. Benzylic and homobenzylic alcohols also led to the dialkylated hydrazides **2k** and **2l** in good yields (85 % and 84 % respectively). Electron-donating groups on the aromatic ring of the acyl moiety, such as methyl (**2n**, **2p**), methoxy (**2r**), or electron-withdrawing substituent (fluorine, **2o**) were tolerated and yielded the dialkylated products without affecting the reactivity (**2n-r**, 54 to 90 % yield). Interestingly, furyl hydrazide led to the *N,N'*-dialkylated compound **2s**, while Gunanathan obtained only the mono-alkylated product.¹³⁹



Scheme 2.12: *N,N'*-Dialkylation of hydrazides.

¹⁴⁶ Joly, N.; Bettoni, L.; Gaillard, S.; Poater, A.; Renaud, J.-L. *J. Org. Chem.* **2021**, *86*, 6813-6825.

To extend the scope of this reaction, secondary and α -substituted alcohols were evaluated in this process. Surprisingly, these alcohols led only to the monoalkylated hydrazides, whatever the reaction conditions. Considering these results, we extended this work to various secondary and sterically hindered alcohols (Scheme 2.13). Compounds **3b** to **3e** were obtained from α - or β -substituted primary alcohols in moderate to good yields (48 to 71 %). In sharp contrast to Gunanathan's work,¹³⁹ citronellol led only to the monoalkylated hydrazide **3e**. Secondary alcohols can also be used as pro-electrophiles. Cyclopentanol gave the *N'*-alkylated hydrazide **3f** in 47 % yield. Benzylic secondary alcohols bearing electron-donating or electro-withdrawing groups furnished the mono-alkylated products **3g** to **3n** in good yields (63 to 73 %), whatever the nature of the substituent on the aryl ring.



Scheme 2.13: *N'*-mono-alkylation of hydrazides.

3) Mechanistic study and deuterium labelling.

Having delineated the scope of this alkylation reaction, DFT calculations were performed (Figure 2.3). The mechanism of alkylation can be separated in three steps. The first is the dehydrogenation of the alcohol into aldehyde or ketone catalysed by the ruthenium complex. Then, a condensation step between the carbonyl and the hydrazide, leading the hydrazone intermediate which is finally reduced by the ruthenium-hydride complex generated in the first step. Calculations highlighted that the rate determining step (rds) was the one non-metal-catalysed, that is, the formation of the hydrazone intermediate. As the dialkylation proceed *via* two condensation steps, and the mono-alkylation is always performed regardless the alcohol used, the second condensation of the ketone or aldehyde on the mono-alkylated hydrazide leading to the hydrazone intermediate is the rds. This intermediate is generated by the addition of the mono-alkylated hydrazide on the carbonyl followed by the release of water. Figure 2.3 shows the energy profile of the second alkylation of benzoyl hydrazide with methanol (black), leading to compound **2f**; alkylation of product **3b** with 2-methylpentan-1-ol

(purple); and alkylation of product **3d** with neopentyl alcohol (red). As shown in the energy profile, the elimination of water is the most energetically demanding step, with an energy barrier of 31.9 kcal/mol to afford product **2f**, while the second alkylation of compounds **3b** and **3d** has an energy barrier of 33.6 and 37.6 kcal/mol respectively, too high to be feasible in these conditions. The kinetic costs for the second alkylation affording *N,N'*-diethyl benzoyl hydrazide **2g** and *N,N'*-dibutyl furyl hydrazide **2s** were found to be similar to compound **2f** (31.6 and 31.8 kcal/mol respectively), which means the elongation of the alkyl chain of the alcohol did not influence the kinetics of this reaction and steric effects play the main role in this process.

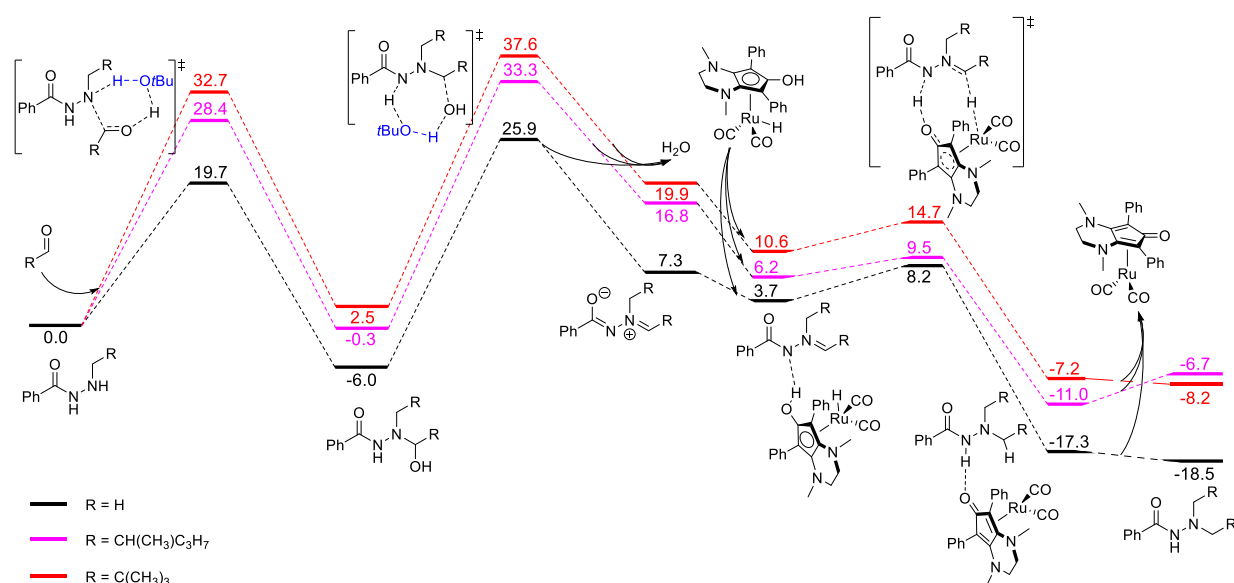


Figure 2.3: Energy profile for the dialkylation of the mono-alkylated acyl hydrazides (relative Gibbs energies in kcal/mol).

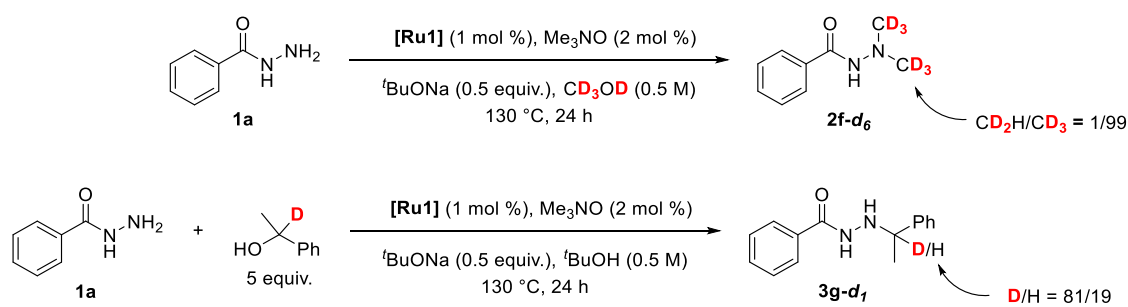
To show up the threshold between mono- and dialkylation and avoid the study of the overall pathway for all alcohols, calculations of the buried volume ($\%V_{\text{Bur}}$) measurement index, introduced by Cavallo *et al.*, was applied to the alcohols used in this study.¹⁴⁷ This index corresponds to the percentage of a sphere, around a chosen atom centre, that is occupied by other atoms (substituents, ligands, etc...). The results on the alcohols highlight a $\%V_{\text{Bur}}$ limit between 45.2 and 47.7 $\%V_{\text{Bur}}$ above which the dialkylation is no longer feasible (Table 2.2). These two values correspond to the highest value for an alcohol giving the dialkylated product (2-phenylethan-1-ol), and the lowest value for an alcohol giving the monoalkylated product (cyclohexylmethanol). As expected, the $\%V_{\text{Bur}}$ is much higher for secondary alcohols, and it can be seen that the β -substitution of primary alcohols is sufficient to prevent dialkylation. The results also suggest that the length of the alkyl chain does not affect the process. Citronellol is a particular case as it furnishes the monoalkylated product **3e** while its $\%V_{\text{Bur}}$ is similar to those of alcohols giving the dialkylated product (45.4 $\%V_{\text{Bur}}$). This could be due to other steric effects. In that way, calculations of the $\%V_{\text{Bur}}$ gave more information about the mechanism, allowing to explain the selectivity and anticipate whether the mono- or di-alkylated product will be obtained with this system.

¹⁴⁷ (a) Falivene, L.; Cao, Z.; Petta, A.; Serra, L.; Poater, A.; Oliva, R.; Scarano, V.; Cavallo, L. *Nat. Chem.* **2019**, *11*, 872-879. (b) Falivene, L.; Credentino, R.; Poater, A.; Petta, A.; Serra, L.; Oliva, R.; Scarano, V.; Cavallo, L. *Organometallics* **2016**, *35*, 2286-2293.

Table 2.2: % V_{Bur} of the alcohols studied (sphere radius: 3.5 Å, the α carbon of the alcohol is at the origin of the sphere).

Alcohol (leading to dialkylation)	% V_{Bur}	Alcohol (leading to monoalkylation)	% V_{Bur}
Methanol	25.6	Citronellol	45.4
Ethanol	36.9	Cyclohexylmethanol	47.7
Propan-1-ol	42.3	2-methylpentan-1-ol	47.9
Butan-1-ol	42.3	2,2-dimethylpropan-1-ol	53.1
Pent-4-en-1-ol	42.3	Cyclopentanol	53.9
3-phenylethan-1-ol	42.4	1-(thiophen-2-yl)ethan-1-ol	55.5
Cyclopropylmethanol	43.9	1-phenylethan-1-ol	55.8
Cyclobutylmethanol	44.6	1-(benzo[d][1,3]dioxol-5-yl)ethan-1-ol	57.3
Benzyl alcohol	44.7	1-(naphthalen-2-yl)ethan-1-ol	59.0
2-phenylethan-1-ol	45.2		

To confirm the hydrogen transfer mechanism, deuterium labelling experiments were performed (Scheme 2.14). In the first, benzoyl hydrazide was reacted with deuterated methanol to furnish product **2f-d₆**. A similar yield to non-deuterated methanol (88 % for CD₃OD *versus* 93 % for CH₃OH) was obtained with complete deuterium incorporation into both methyl groups. In the second experiment, benzyl-methyl alcohol **d₁** was used instead of deuterated methanol and product **3g-d₁** was obtained in 68 % yield (72 % yield for non-deuterated benzyl-methyl alcohol) with 81 % incorporation of deuterium on the α carbon. These results confirm the formation of a hydrazone intermediate which is then reduced by a ruthenium deuteride type complex.



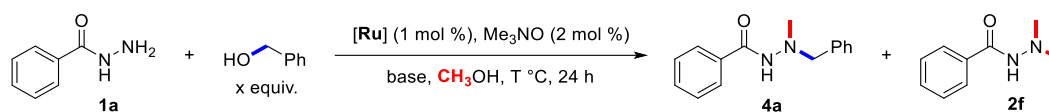
Scheme 2.14: Deuterium labelling experiments.

IV. Cross *N,N*-dialkylation of hydrazides: access to non-symmetric acyl hydrazides *via* a three components cascade reaction.

1) Optimisation of the reaction.

Regarding the previously described results on the mono- and di-alkylation of benzoyl hydrazides and based on previous results on tandem multicomponent alkylation of ketones, it was hypothesised that multicomponent alkylation of acylhydrazides might be developed to access unsymmetrical *N',N'*-dialkylated hydrazides starting from two different alcohols in one pot. To initiate this study, benzylic alcohol and methanol were initially chosen as pro-electrophiles for the optimisation of this reaction (Table 2.3). In this case, the tricky issue was to minimize the formation of the dimethylated product **8** whereas the dibenzylated product was never observed. Temperature was a key parameter. In this case, 110 °C appeared to be optimal, while the higher temperature favoured the dimethylation, and lower temperature led to uncomplete conversion of the starting material (Entries 5-7 and 10-11). Decreasing the amount of benzyl alcohol or increasing the quantity of methanol benefits the dimethylated product (Entries 1 to 4). Variation of the base or base loading also favoured product **2f** (Entries 4-5 and 12-14). Once the optimal conditions were in hands, complexes **Ru2**, **Ru3** and **Ru4** were evaluated in the reaction. Not surprisingly, complex **Ru2** gave the same results than **Ru1**, while **Ru3** and **Ru4** favoured the demethylated product (Entries 16-18).

Table 2.3: Optimisation table for the unsymmetrical dialkylation of hydrazides.



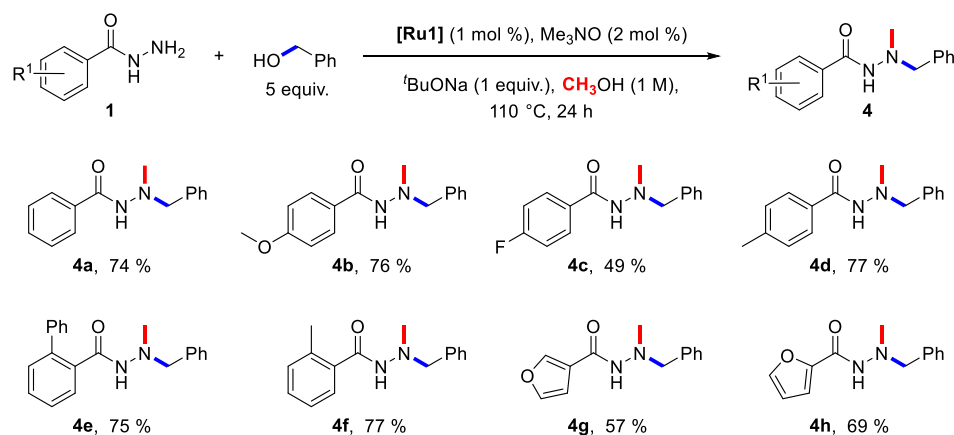
Entry ^a	Catalyst	Benzyl alcohol (equiv.)	Methanol (mL)	Temperature (°C)	Base (equiv.)	1a ^a (%)	4a ^a (%)	2f ^a (%)
1	Ru1	1.5	1.0	110	^t BuONa (0.5)	-	9	91
2	Ru1	2.5	1.0	110	^t BuONa (0.5)	-	34	66
3	Ru1	5	1.0	110	^t BuONa (0.5)	-	51	49
4	Ru1	5	0.5	110	^t BuONa (0.5)	-	63	37
5	Ru1	5	0.5	110	^tBuONa (1.0)	-	81 (74)^b	19
6	Ru1	5	0.5	100	^t BuONa (1.0)	28	41	31
7	Ru1	5	0.5	90	^t BuONa (1.0)	55	29	16
8	Ru1	7	0.5	110	^t BuONa (1.0)	-	81	19
9	Ru1	5	1.0	110	^t BuONa (1.0)	-	64	36
10	Ru1	5	0.5	120	^t BuONa (1.0)	-	74	26

11	Ru1	5	0.5	130	^t BuONa (1.0)	-	65	35
12	Ru1	5	0.5	110	^t BuOK (1.0)	-	78	22
13	Ru1	5	0.5	110	MeONa (1.0)	-	63	37
14	Ru1	5	0.5	110	Na ₂ CO ₃ (1.0)	28	40	32
15	Ru1	5	0.25	110	^t BuONa (1.0)	15	56	29
16 ^c	Ru2	5	0.5	110	^t BuONa (1.0)	-	81	19
17	Ru3	5	0.5	110	^t BuONa (1.0)	11	34	55
18 ^c	Ru4	5	0.5	110	^t BuONa (1.0)	18	37	45
19	-	5	0.5	110	^t BuONa (1.0)	100	-	-

^a Reactions performed with 0.5 mmol of acylhydrazide, conversion was determined by ¹H-NMR analysis of the crude mixture. ^b Yield of the isolated product after purification. ^c Reaction performed without using Me₃NO.

2) Scope of the reaction.

To explore the scope of this unsymmetrical *N',N'*-dialkylation of hydrazides, the variation of the acyl substituent was first studied (Scheme 2.15).¹⁴⁸ Electron donating and electron withdrawing groups were well tolerated, except for compound **4c** which was obtained in lower yield (49 %). The steric hindrance around the aromatic ring was also meaningless as the *ortho*-phenyl benzoylhydrazide **4e** was obtained in good yield (75 %). Heteroaryl acyl hydrazides also underwent the reaction and compounds **4g** and **4h** were obtained in 57 and 69 % yield respectively.

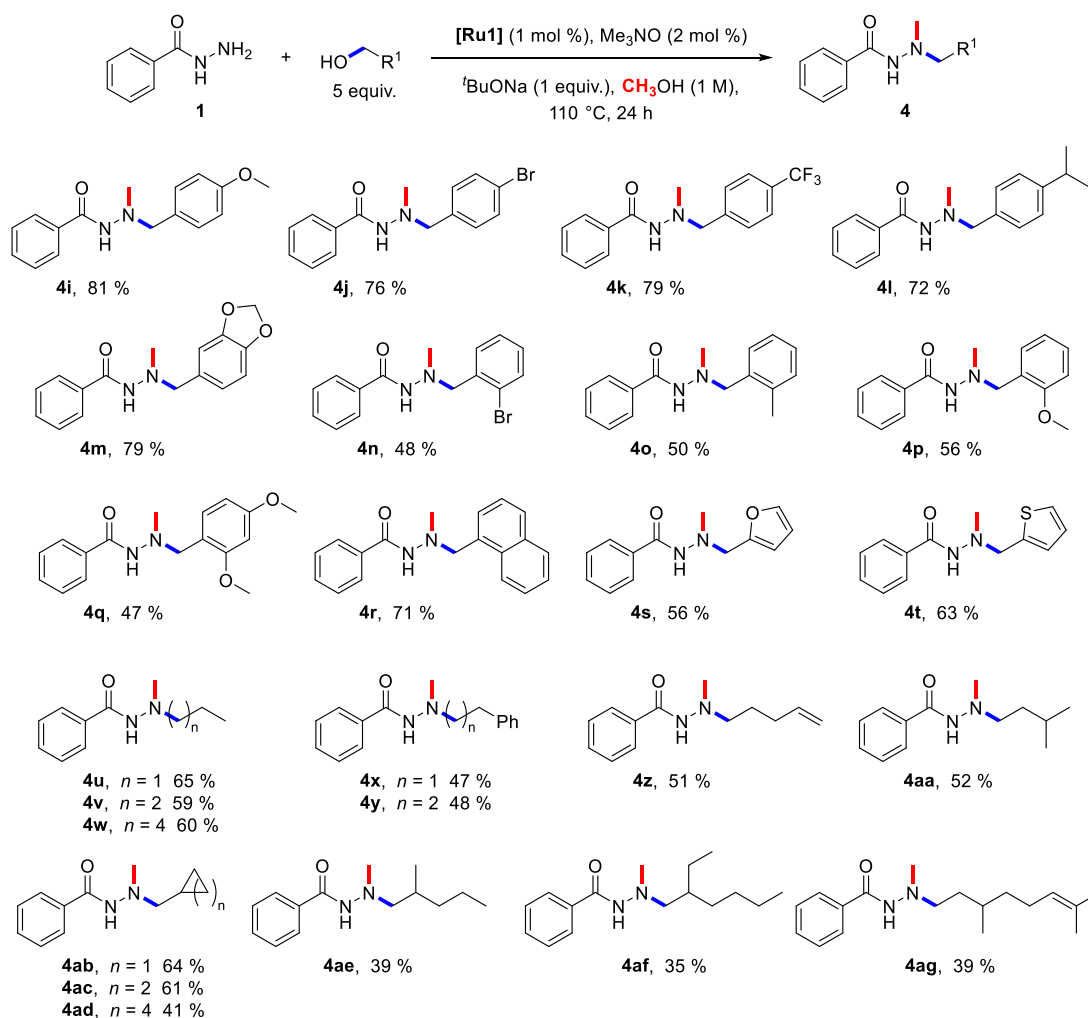


Scheme 2.15: Cross *N',N'*-dialkylation of hydrazides: variation of the acyl substituent.

Several primary alcohols were then implicated in this reaction (Scheme 2.16). Benzyl alcohols containing electron donating and electron withdrawing groups gave the desired products **4i** to **4r** in good

¹⁴⁸ Bettoni, L.; Joly, N.; Lohier, J.-F.; Gaillard, S.; Poater, A.; Renaud, J.-L. *Adv. Synth. Catal.* **2021**, *363*, 4009-4017.

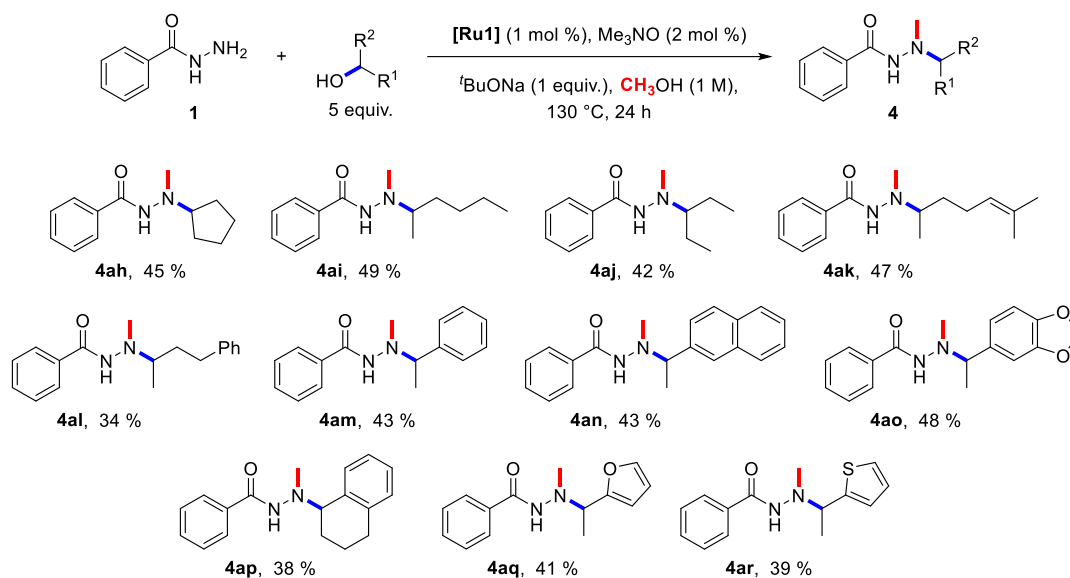
yields (47 to 81 %). The yield may be influenced by the steric hindrance of the benzyl alcohol as *ortho*-substituted aromatic rings led to the dialkylated products in lower yields (compounds **4n** to **4r**, 47 to 56 %). This decrease is due to a greater selectivity for the dimethylated product. Furfuryl and thiophenyl alcohols were also engaged in this reaction and compounds **4s** and **4t** were isolated in 56 and 63 % yield. It was then envisaged to extend the scope to primary aliphatic alcohols. Different aliphatic alcohols were engaged and the corresponding dialkylated hydrazides **4u** to **4ag** were obtained in moderate to good yields (35 to 65 %). The lower yields were explained by the energy of dehydrogenation of aliphatic alcohols that is higher than the one of benzyl alcohols, and closer to the energy of dehydrogenation of methanol, making this three-component alkylation more challenging. Aliphatic alcohols such as propan-1-ol, butan-1-ol and hexan-1-ol were involved in this reaction and led to compounds **4u**, **4v** and **4w** in 65, 59 and 60 % yield respectively. Cycloalkyl methanol derivatives were also tolerated and compounds **4ab**, **4ac** and **4ad** were obtained in 64, 61 and 41 % yield respectively. Unsaturated alcohols were engaged as well and the corresponding products **4z** and **4ag** were obtained without any reduction of the C=C double bond. Alcohols which led only to the monoalkylation in the previous study furnished in this case the dialkylated product **4ad** to **4ag**, but lower yields were obtained (35 to 41 %) due to the steric hindrance which favoured the dimethylation.



Scheme 2.16: Cross *N',N'*-dialkylation of hydrazides: variation of the primary alcohol.

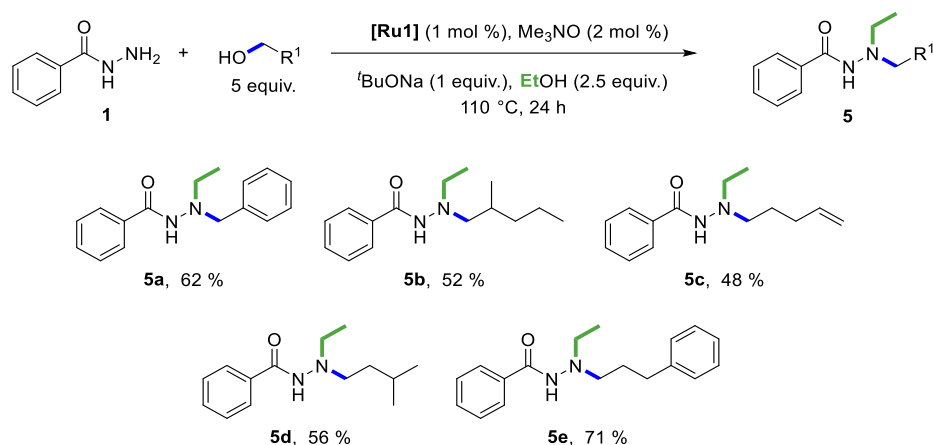
The same trend was observed when secondary alcohols were used as the steric hindrance as well as the % V_{Bur} are higher. Furthermore, formaldehyde is more electrophilic than a ketone, and the

reduction of the aldimine is faster than the reduction of the ketimine. On the other hand, dehydrogenation of secondary alcohols is faster than the dehydrogenation of methanol ($\Delta H = +55$ kJ/mol for isopropanol *versus* $\Delta H = +84$ kJ/mol for methanol). As a consequence, both monoalkylated hydrazides can be produced in similar rate, favouring the dimethylated product. After a modification of the reaction conditions, a temperature of 130 °C instead of 110 °C was found to be more suitable (Scheme 2.17). Products **4ah** to **4ar** were obtained from linear aliphatic and cyclic alcohols in moderate yields (34 to 49 %). Secondary benzylic alcohols were also used and compounds **4an** to **4ar** were obtained in similar yields (38 to 48 %).



Scheme 2.17: Cross N',N' -dialkylation of hydrazides: variation of the secondary alcohol.

To further explore this three components alkylation reaction, it was proposed to replace methanol by ethanol. The latter makes this process even more challenging as its energy of dehydrogenation is lower ($\Delta H = +68$ kJ/mol for ethanol *versus* $\Delta H = +84$ kJ/mol for methanol). As a consequence, it becomes even more difficult to make the difference between ethanol and the second alcohol involved in this process. After modification of the reaction conditions, lowering the amount of ethanol to 2.5 equiv. (*versus* 25 equiv. when methanol was used) and a temperature of 110 °C favoured the cross N',N' -dialkylation products (Scheme 2.18). Compounds **5a** to **5e** were isolated in moderate to good yields (48 to 71 %).



Scheme 2.18: Cross N',N' -dialkylation of hydrazides: ethanol and primary alcohols.

3) Mechanistic study and deuterium labelling.

Regarding the mono- and dialkylation of hydrazides, DFT calculation were performed to unveil the mechanism behind this three-component alkylation reaction (Figure 2.4). Different energy profiles were calculated: in black is the profile corresponding to the dimethylation product **2f**; in red is the profile of product **4a** with first the alkylation with benzyl alcohol and second the alkylation with methanol; in pink is the profile for the same product, but with first the alkylation with methanol and second the alkylation with benzyl alcohol; the profile in red corresponds to product **4v** with first the alkylation of butanol and second the alkylation with methanol. For the first alkylation step, the alkylation with benzyl alcohol appears to be more energetically demanding, compared to the alkylation with butanol and methanol. Once the monoalkylated products are formed, the energy for the second alkylation with methanol is very close, regardless of the monoalkylated acyl hydrazide. The highest energy barrier for the methylation of the N' -methyl, N' -butyl and N' -benzyl hydrazides are 31.2, 32.3 and 31.9 kcal/mol respectively. In contrast, benzylation of the N' -methyl hydrazide (pink profile) presents an energy barrier of 36.5 kcal/mol, which is 5 kcal/mol higher compared to the methylation. As a consequence, the methylation is favoured. According to these results, the synthesis of unsymmetrical acyl hydrazides seems to occur in a single order: a first alkylation with benzylic or aliphatic alcohol followed by the methylation with methanol. The obtention of the non-symmetrical acyl hydrazide only depends on the formation of the first alkylated intermediate. Nevertheless, the N',N' -dialkylated acyl hydrazide was the major product in most of the cases. It has to be considered that, even if methanol is introduced in large excess, formaldehyde and methanol are in gas phase in the reaction conditions, which means that their quantity is reduced with respect to less volatile alcohols or aldehydes. Consequently, the possible pathway may not be driven by the energetics but by the concentration of formaldehyde and methanol in both liquid and gas phase.

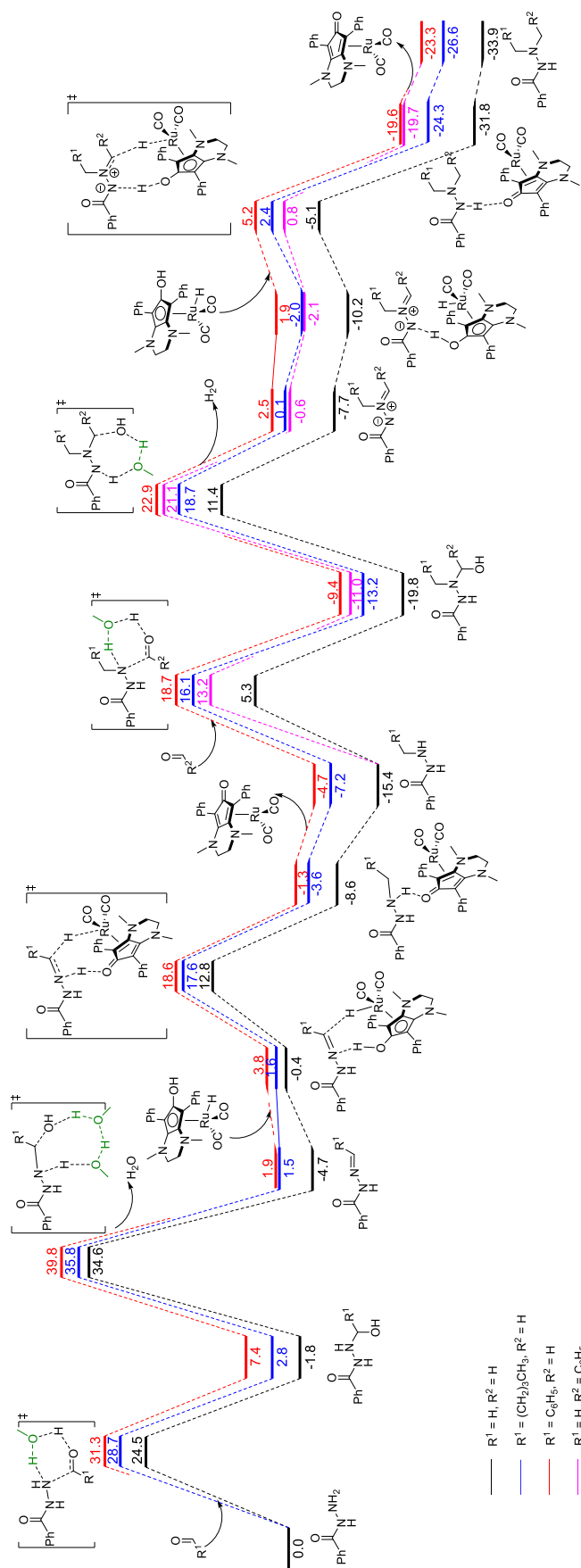
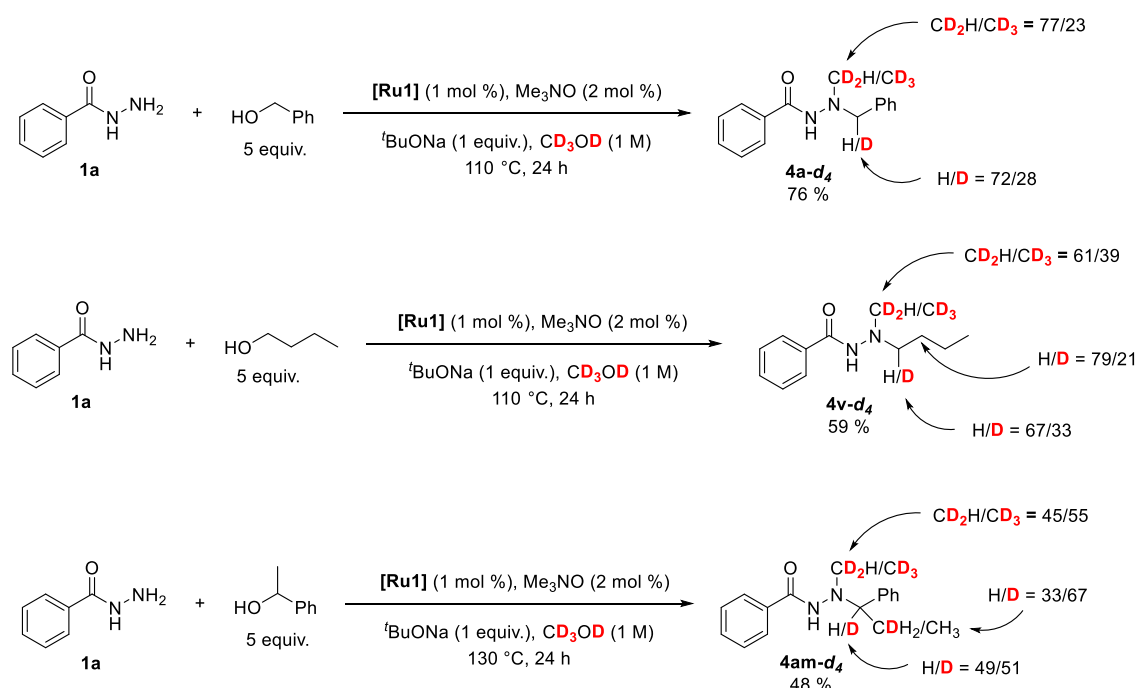


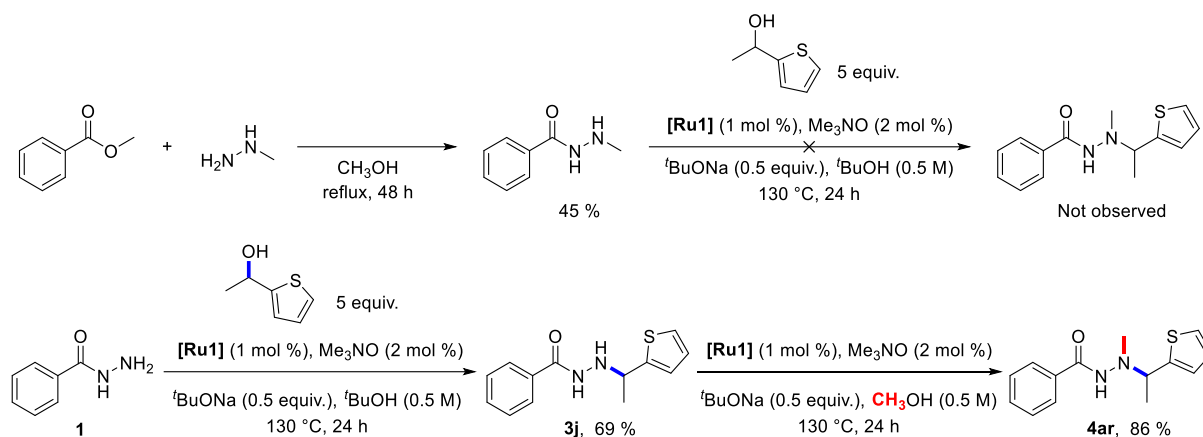
Figure 2.4: Energy profile for the dialkylation of hydrazides leading to products **2f**, **4a** and **4v** (relative Gibbs energies in kcal/mol).

Deuterium labelling experiments were performed to unveil which alcohol was the hydride source in this process (Scheme 2.19). In the first experiment, benzohydrazide reacted with benzyl alcohol and deuterated methanol. The deuterated product was obtained in similar yield than the non-deuterated one (76 % *versus* 81 % for product **4a**). Low incorporation of deuterium was observed on the two α carbons (23 and 28 %) which means the benzyl alcohol is the principal hydride source in this reaction. The same experiment was performed using butan-1-ol and 1-phenylethan-1-ol instead of benzyl alcohol. With butanol, the deuterium incorporation is a bit higher which confirms that the dehydrogenation of methanol becomes more competitive with butanol. In the last experiment with a secondary alcohol, 55 and 51 % of deuterium incorporation was obtained meaning that the two alcohols contribute equally as a hydride source. It can be noticed that in the case of butan-1-ol and phenylethan-1-ol, incorporation of deuterium was observed at the β -carbon. This implies an imine/enamine equilibrium during the condensation between the hydrazide and the corresponding carbonyl compound.



Scheme 2.19: Deuterium labelling experiments.

To show the order of alkylation of the two alcohols, two experiments were performed (Scheme 2.20). In the first, *N*'-methyl benzoyl hydrazide was synthesized from *N*-methyl hydrazine and methyl benzoate as the monomethylated hydrazide could not be obtained by our methodologies. Alkylation of the *N*'-methyl benzoylhydrazide in the optimised reaction conditions with 1-(thiophen-2-yl)ethan-1-ol did not furnish any product, meaning that the alkylation of *N*'-methyl hydrazide with a sterically hindered alcohol is a highly energetically demanding process due to steric hindrance and/or kinetic issue. In contrast, reaction of compound **3j** with methanol afforded the disubstituted product **4ar** in good yield (86 %). These experiments confirm both the experimental results and DFT calculations. The reaction occurs only in one possible way: an initial alkylation with the secondary alcohol as pro-electrophile followed by alkylation with methanol.



Scheme 2.20: Consecutive addition of two different alcohols.

V. Conclusion.

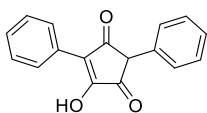
The first phosphine-free ruthenium complex-catalysed monoalkylation, dialkylation and cross dialkylation of acyl hydrazide using alcohols as pro-electrophiles was disclosed. Various benzylic, cyclic and aliphatic primary and secondary alcohols were engaged in these processes. The first ruthenium-catalysed one-pot cross dialkylation of hydrazides was described with methanol and ethanol. DFT calculations clearly explained the observed selectivity favouring the mono or the dialkylation with the calculation of the % V_{Bur} . They also confirmed that methanol was the most reactive pro-electrophile, favouring the formation of the dimethylated product. Although this result is the opposite of what is observed experimentally, it highlights the compromise between energy of dehydrogenation and electrophilicity.

VI. Experimental Part.

1) General considerations.

All air- and moisture-sensitive manipulations were carried out using standard vacuum line Schlenk tubes techniques. Dry toluene was dried using a solvent purification system from Innovative Technologies, by passage through towers containing activated alumina. Xylene was purchased from Carlo Erba and was distilled over sodium and stocked over 4Å molecular sieves. Other solvents and chemicals were purchased from different suppliers and used as received. Neutral alumina was purchased from Alfa Aesar (Brockmann Grade I, 58 Angstroms, -60 Mesh Powder, S.A. 150 m²/g) and silica from Carlo Erba (60Å 40-63µ). Deuterated solvents for NMR spectroscopy were purchased from Eurisotop and used as received. NMR spectra were recorded on a 500 MHz Brücker spectrometer. Proton (¹H) NMR information is given in the following format: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quint, quintuplet; sext, sextuplet; sept, septuplet; m, multiplet), coupling constant(s) (*J*) in Hertz (Hz), number of protons. The prefix app is occasionally applied when the true signal multiplicity was unresolved and br indicates the signal in question broadened. Carbon (¹³C) NMR spectra are reported in ppm (δ) relative to CDCl₃ unless noted otherwise. Infrared spectra were recorded over a PerkinElmer Spectrum 100 FT-IR Spectrometer using neat conditions. HRMS (ESI-TOF) m/z analyses were performed by Laboratoire de Chimie Moléculaire et Thioorganique analytical Facilities.

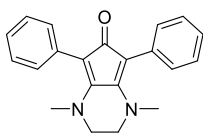
2) Synthesis of ruthenium complexes.



- **4-hydroxy-2,5-diphenylcyclopent-4-ene-1,3-dione**¹⁴⁹

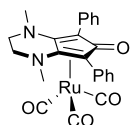
In a Schlenk tube under an argon atmosphere, freshly cut pieces of sodium (2 equiv., 1.31 g, 57.1 mmol) were dropped into freshly distilled ethanol (20 equiv.) at 0 °C. After its complete dissolution, 1,3-diphenylpropan-2-one (1 equiv., 6.0 g, 28.5 mmol) and diethyl oxalate (1 equiv., 3.9 mL, 28.5 mmol) were added. The solution was slowly warmed up to room temperature and stirred for 48 h at room temperature. The color of the reaction mixture changed from yellow to dark purple. The reaction mixture was then poured into ice/water and the aqueous layer was acidified to pH=1 by careful dropwise addition of concentrated sulfuric acid (96 %). The resulting precipitate was filtered, washed twice with water and dried by azeotropic distillation with toluene. The product was obtained as a yellow powder (5.79 g, 77 %). ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 7.80 (d, *J* = 7.3 Hz, 2H), 7.21 (t, *J* = 7.5 Hz, 2H), 7.16-7.04 (m, 4H), 6.90 (d, *J* = 7.2 Hz, 2H), 4.21 (s, 1H) ppm (OH not observed). ¹³C-NMR (DMSO-*d*₆, 125 MHz): δ 197.5, 196.8, 166.4, 134.4, 129.6, 128.9, 128.9, 128.8, 128.7, 128.2, 128.1, 127.4, 56.0 ppm.

¹⁴⁹ Claisen, L.; Ewan, T.; *Annalen*, **1895**, 284, 245-299.



- **1,4-dimethyl-5,7-diphenyl-1,2,3,4-tetrahydro-6H-cyclopenta[b]pyrazin-6-one L1¹⁵⁰**

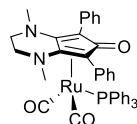
In a Schlenk tube, 4-hydroxy-2,5-diphenylcyclopent-4-ene-1,3-dione (1 equiv., 5 g, 18.9 mmol) and *N,N'*-dimethylethylenediamine (1 equiv., 2.04 mL, 18.9 mmol) were introduced in methanol (30 mL). The reaction mixture was heated under reflux overnight. After complete consumption of the starting materials, the solvent was removed under vacuum to furnish the pure product as a purple powder (5.99 g, 100 %). If necessary, the product was purified by slow diffusion of pentane into dichloromethane. ¹H-NMR (CDCl₃, 400 MHz) δ 7.30-7.25 (m, 8H), 7.17-7.12 (m, 2H), 3.33 (s, 4H), 2.82 (s, 6H) ppm. ¹³C-NMR (CDCl₃, 100 MHz) δ 195.4, 151.0, 133.7, 131.2, 127.4, 125.6, 98.9, 50.1, 42.3 ppm.



Chemical Formula: C₂₅H₂₃N₂O₄Ru

- **(1,4-dimethyl-5,7-diphenyl-1,2,3,4-tetrahydro-6H-cyclopenta[b]pyrazin-6-one)ruthenium tricarbonyl complex (Ru1)**

In a 50 mL dried Schlenk tube under an argon atmosphere, the cyclopentadienone ligand **L1** (2.53 mmol, 800 mg, 1 equiv.) and Ru₃CO₁₂ (1.26 mmol, 806 mg, 0.5 equiv.) were introduced in dry and free-O₂ toluene (12 mL). The reaction mixture was stirred under reflux overnight. After cooling down to room temperature, the resulting mixture was purified on neutral alumina oxide column chromatography (eluent: CH₂Cl₂ to CH₂Cl₂/MeOH [98:2]). Precipitation on a mixture of pentane/diethyl ether (1:1) and filtration under vacuum gave the pure complex **Ru1** as a yellow powder (973 mg, 77 %). ¹H-NMR (CDCl₃, 500 MHz): δ 7.48-7.47 (m, 4H), 7.38-7.35 (m, 4H), 7.32-7.29 (m, 2H), 3.42-3.38 (m, 2H), 2.64-2.60 (m, 2H), 2.17 (s, 6H) ppm. ¹³C-NMR (CDCl₃, 125 MHz): δ 199.1, 172.1, 132.9, 132.3, 128.5, 127.7, 116.7, 69.7, 50.1, 43.8 ppm. IR (neat) ν 2959, 2045, 2005, 1637, 1508, 1492, 1439, 1410, 1360, 200 1265, 1194, 1114, 1071, 1048, 1028, 1004, 946, 848, 785 cm⁻¹. HRMS (ESI-TOF) m/z [M+H]⁺: Calcd for C₂₄H₂₁RuN₂O₄ 503.0545; found 503.0556.



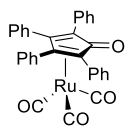
Chemical Formula: C₄₂H₃₈N₂O₃PRu

- **(1,4-dimethyl-5,7-diphenyl-1,2,3,4-tetrahydro-6H-cyclopenta[b]pyrazin-6-one)triphenylphosphine dicarbonyl ruthenium complex (Ru2)**

In a 50 mL dried Schlenk under an argon atmosphere, tricarbonyl ruthenium complex **Ru1** (0.90 mmol, 1 equiv., 451 mg) and triphenylphosphine (2.7 mmol, 3 equiv., 708 mg) were solubilized in O₂-free

¹⁵⁰ Haak, E. *Eur. J. Org. Chem.* **2007**, *17*, 2815-2824.

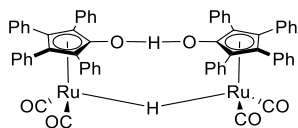
xylene (24 mL) and then refluxed at 140 °C overnight. Purification by flash column chromatography on neutral aluminium oxide (eluent: pentane/ethyl acetate [90:10] to [70:30]) afforded the pure triphenylphosphine ruthenium complex **Ru2** as a yellow powder (430 mg, 65 %). **¹H-NMR (CDCl₃, 500 MHz):** δ 7.42-7.41 (m, 4H), 7.25-7.22 (m, 6H), 7.20-7.17 (m, 3H), 7.12-7.09 (m, 2H), 7.05-7.00 (m, 10H), 3.35-3.31 (m, 2H), 3.11-3.06 (m, 2H), 2.37 (s, 6H) ppm. **¹³C-NMR (CDCl₃, 125 MHz):** δ 203.2, 166.9, 134.2, 133.9, 133.8, 133.3, 133.2, 132.0, 129.4, 128.0, 127.9, 127.6, 125.9, 111.5, 70.7, 48.7, 42.1 ppm. **³¹P-NMR (CDCl₃, 162 MHz):** δ 29.1 ppm. **IR (neat):** ν 3047, 2952, 2860, 2038, 1982, 1923, 1609, 1538, 1517, 1480, 1432, 1409, 1362, 1261, 1198, 1179, 1090, 1045, 944, 755, 735, 696, 586, 520, 496 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₄₁H₃₆RuN₂O₃P 737.1507; found 737.1522.



Chemical Formula: C₃₃H₂₃O₄Ru

- **(2,3,4,5-tetraphenylcyclopenta-2,4-dien-1-one) ruthenium tricarbonyl complex (Ru3)**

Ruthenium complex **Ru3** was prepared according a procedure described by Shvo.¹⁵¹ In a 50 mL dried Schlenk tube under an argon atmosphere, 2,3,4,5-tetraphenylcyclopenta-2,4-dien-1-one (2 mmol, 768 mg, 1 equiv.) and Ru₃CO₁₂ (1 mmol, 639 mg, 0.5 equiv.) were introduced in dry and free-O₂ toluene (12 mL). The reaction mixture was stirred under reflux overnight. After cooling to room temperature, the resulting mixture was purified on silica column chromatography (eluent: CH₂Cl₂ to CH₂Cl₂/methanol [98:2]) which afforded the pure complex **Ru3** as a pale-yellow powder (863 mg, 76 %). **¹H-NMR (CDCl₃, 500 MHz):** δ 7.48-7.47 (m, 4H), 7.25-7.22 (m, 6H), 7.20-7.17 (m, 2H), 7.13-7.10 (m, 4H), 7.07-7.05 (m, 4H) ppm. **¹³C-NMR (CDCl₃, 125 MHz):** δ 194.5, 174.0, 132.1, 131.6, 130.9, 129.9, 128.7, 128.2, 128.1, 127.5, 107.9, 82.2 ppm. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₃₂H₂₁RuO₄ 571.0483; found 571.0499.



Chemical Formula: C₆₂H₄₂O₆Ru₂

- **Dimer (2,3,4,5-tetraphenylcyclopenta-2,4-dien-1-one) ruthenium tricarbonyl complex (Ru4)**

Ruthenium complex **Ru4** was prepared according a procedure described by Shvo.¹⁵¹ In a 50 mL dried Schlenk tube under an argon atmosphere, ruthenium complex **Ru3** (0.5 mmol, 285 mg) was dissolved in acetone (20 mL) and a saturated solution of sodium carbonate (10 mL) was added. The mixture was stirred at room temperature for 0.5 hours. The reaction was neutralized with saturated ammonium chloride solution and acetone was evaporated under vacuum. The residue was extracted with dichloromethane, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude

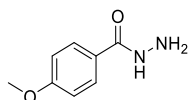
¹⁵¹ Menashe, N.; Shvo, Y. *Organometallics* **1991**, *10*, 3885-3891.

product was purified by flash chromatography on silica gel using pentane-dichloromethane (1:1) as eluent to afford the pure complex **Ru4** as an orange powder (195 mg, 72 %). **¹H-NMR (CDCl₃, 500 MHz):** δ 7.12-7.06 (m, 15H), 7.01-6.99 (m, 25H), -18.37 (s, 1H) ppm. **¹³C-NMR (CDCl₃, 125 MHz):** δ 200.9, 154.3, 132.2, 131.2, 130.7, 130.4, 128.0, 127.9, 127.7, 126.9, 103.6, 87.9 ppm. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₆₂H₄₃Ru₂O₆ 1087.1147; found 1087.1196.

3) Synthesis of acylhydrazides.

General Procedure A:

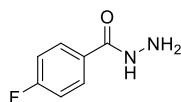
In a round bottomed flask, the desired benzoic acid (10 mmol) was dissolved in methanol (10 mL). Ten drops of sulfuric acid (96 %) were added to the solution. The mixture was refluxed for 12 h. The reaction was then dissolved in water and extracted three times with ethyl acetate. The combined organic phases were dried over MgSO₄ and concentrated under reduced pressure. The crude product was directly engaged to the next step. The ester was dissolved in methanol (5 mL), hydrazine monohydrate (5 equiv.) was then added and the mixture was refluxed for 16 h. Solvent was then removed under reduced pressure. The residue was dissolved in water and extracted with dichloromethane. The organic layer was washed with water and dried over Na₂SO₄. Solvent was then removed to afford the desired product without further purification.



Chemical Formula: C₈H₁₀N₂O₂

- **4-methoxybenzohydrazide (1b)**¹⁵²

According to general procedure A, product was obtained from 4-methoxybenzoic acid (10 mmol, 1.66 g) as a white solid (1.49 g, 90 %) without further purification. **¹H-NMR (CDCl₃, 500 MHz):** δ 7.70 (d, *J* = 8.8 Hz, 2H), 7.43 (br. s, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 4.08 (br. s, 2H), 3.85 (s, 3H) ppm. **¹³C-NMR (CDCl₃, 125 MHz):** δ 168.5, 162.6, 128.8, 125.0, 114.1, 55.5 ppm.



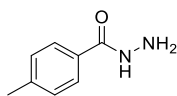
Chemical Formula: C₇H₇FN₂O

- **4-fluorobenzohydrazide (1c)**¹⁵²

According to general procedure A, product was obtained from 4-fluorobenzoic acid (10 mmol, 1.54 g) as a white solid (1.42 g, 92 %) without further purification. **¹H-NMR (CDCl₃, 500 MHz):** δ 7.78-7.75 (m, 2H), 7.42 (br. s, 1H), 7.14-7.11 (m, 2H), 3.02 (br. s, 2H) ppm. **¹⁹F NMR (500 MHz, CDCl₃):** δ -

¹⁵² Rodrigues, D. A.; Guerra, F. S.; Sagrillo, F. S.; Pinheiro, P. S. M.; Alves, M. A.; Thota, S.; Chaves, L. S.; Sant'Anna, C. M. R.; Fernandes, P. D.; Fraga, C. A. M. *ChemMedChem*. **2020**, *15*, 539-551.

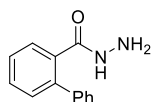
107.2 ppm. $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): δ 167.9, 165.1 (d, $J = 250.9$ Hz), 129.3 (d, $J = 8.9$ Hz), 128.9 (d, $J = 3.2$ Hz), 116.0 (d, $J = 21.8$ Hz) ppm.



Chemical Formula: $\text{C}_8\text{H}_{10}\text{N}_2\text{O}$

- **4-methylbenzohydrazide (1d)**¹⁵²

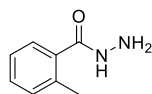
According to general procedure A, product was obtained from 4-methylbenzoic acid (10 mmol, 1.50 g) as a white solid (1.35 g, 90 %) without further purification. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ 7.63 (d, $J = 8.1$ Hz, 2H), 7.37 (br. s, 1H), 7.24 (d, $J = 8.0$ Hz, 2H), 4.08 (br. s, 2H), 2.40 (s, 3H) ppm. $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): δ 168.8, 142.6, 129.9, 129.5, 127.0, 21.6 ppm.



Chemical Formula: $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}$

- **2-phenylbenzohydrazide (1e)**

According to general procedure A, product was obtained from 2-phenylbenzoic acid (10 mmol, 2.12 g) as a white solid (1.73 g, 82 %) without further purification. Mp 102.3-102.7 °C. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ 7.65 (dd, $J = 1.1$; 7.6 Hz, 1H), 7.49 (td, $J = 1.3$; 7.6 Hz, 1H), 7.44-7.36 (m, 7H), 6.53 (br. s, 1H), 3.84 (br. s, 2H) ppm. $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): δ 170.6, 140.0, 140.0, 133.6, 130.7, 130.5, 129.0, 128.9, 128.6, 128.1, 127.8 ppm. IR (neat): ν 3248, 1649, 1541, 1446, 1292, 1162, 1072, 969, 909, 854, 749, 691, 664, 527 cm^{-1} . HRMS (ESI-TOF) m/z $[\text{M}+\text{H}]^+$: Calcd for $\text{C}_{13}\text{H}_{13}\text{N}_2\text{O}$ 213.1028; found 213.1030.

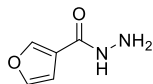


Chemical Formula: $\text{C}_8\text{H}_{10}\text{N}_2\text{O}$

- **2-methylbenzohydrazide (1f)**¹⁵³

According to general procedure A, product was obtained from 2-methylbenzoic acid (10 mmol, 1.36 g) as a white solid (1.39 g, 93 %) without further purification. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ 7.36-7.33 (m, 2H), 7.25-7.20 (m, 2H), 6.98 (br. s, 1H), 4.10 (br. s, 2H), 2.45 (s, 3H) ppm. $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): δ 171.0, 136.8, 134.2, 131.3, 130.6, 127.1, 126.0, 19.9 ppm.

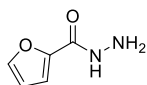
¹⁵³ Nisa, M.; Munawar, M. A.; Iqbal, A.; Ahmed, A.; Ashraf, M.; Gardener, Q. A.; Khan, M. A. *Eur. J. Med. Chem.* **2017**, *138*, 396-406.



Chemical Formula: C₅H₆N₂O₂

- **furan-3-carbohydrazide (1g)**¹⁵²

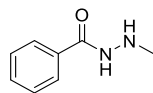
According to general procedure A, product was obtained from furan-3-carboxylic acid (10 mmol, 1.12 g) as a white solid (1.06 g, 84 %) without further purification. ¹H-NMR (CDCl₃, 500 MHz): δ 7.95 (br. s, 1H), 7.45 (br. s, 1H), 7.12 (br. s, 1H), 6.60 (br. s, 1H), 4.08 (br. s, 2H). ¹³C-NMR (CDCl₃, 125 MHz): δ 164.0, 161.9, 144.9, 144.2, 108.0 ppm.



Chemical Formula: C₅H₆N₂O₂

- **furan-2-carbohydrazide (1h)**¹⁵²

According to general procedure A, product was obtained from furan-2-carboxylic acid (10 mmol, 1.12 g) as a white solid (1.12 g, 88 %) without further purification. ¹H-NMR (CDCl₃, 500 MHz): δ 7.56 (br. s, 1H), 7.45 (dd, *J* = 0.7; 1.7 Hz, 1H), 7.14 (dd, *J* = 0.7; 3.5 Hz, 1H), 6.51 (dd, *J* = 1.7; 3.5 Hz, 1H), 4.02 (br. s, 2H) ppm. ¹³C-NMR (CDCl₃, 125 MHz): δ 159.6, 146.8, 144.4, 115.0, 112.2 ppm.



Chemical Formula: C₈H₁₀N₂O

- **N'-methylbenzohydrazide (1i)**¹⁵⁴

According to a modified general procedure A using methylhydrazine (50 mmol, 2.63 mL), product was obtained from benzohydrazide (10 mmol, 1.36 g) as a white solid (0.68 g, 45 %) by silica flash column chromatography (pure ethyl acetate). ¹H-NMR (CDCl₃, 500 MHz): δ 8.04 (br. s, 1H), 7.81-7.78 (m, 2H), 7.57-7.54 (m, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 4.72 (br. s, 1H) ppm. ¹³C-NMR (CDCl₃, 125 MHz): δ 167.4, 133.0, 132.0, 128.8, 127.0, 39.6 ppm.

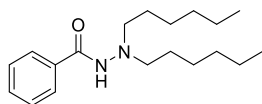
4) Synthesis of mono- or di-substituted acylhydrazides.

General Procedure B:

In a 15 mL flame-dried Schlenk tube equipped with a stirring bar, the desired hydrazide (0.5 mmol), the desired alcohol (5 equiv.), Me₃NO (1.1 mg, 2 mol %), ruthenium complex **Ru1** (2.51 mg, 1 mol %), ^tBuONa (24 mg, 0.5 equiv.) and ^tBuOH (1.0 mL) were poured in under an argon atmosphere. The mixture was then placed into a pre-heated oil bath and stirred at 130 °C for 24 hours. The mixture was cooled-down to room temperature, filtrated over celite with diethyl ether and concentrated under reduced

¹⁵⁴ Rai Deja, J. K.; Sahariah, B.; Baruah, K.; Bar, A. K.; Sarma, B. K. *Chem. Commun.* **2020**, 56, 4874-4877.

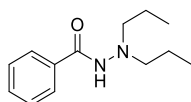
pressure. The conversion was determined by $^1\text{H-NMR}$ spectroscopy and the residue was purified by flash chromatography on silica gel using pentane-ethyl acetate as eluent to afford the desired product. For some compounds, a distillation using a glass oven Kugelrohr was necessary in order to remove the excess of alcohol.



Chemical Formula: $\text{C}_{19}\text{H}_{32}\text{N}_2\text{O}$

- ***N',N'*-dihexylbenzohydrazide (2a)**¹³⁹

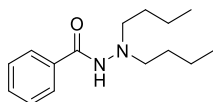
According to general procedure B, alkylation of benzohydrazide (0.5 mmol, 68 mg) with hexan-1-ol (5 equiv., 309 μL) afforded the pure product as a white solid (119 mg, 78 %) by silica flash column chromatography (pentane/ethyl acetate 9:1). $^1\text{H NMR}$ (500 MHz, CDCl_3): δ 7.74-7.72 (m, 2H), 7.52-7.49 (m, 1H), 7.45-7.42 (m, 2H), 6.52 (br. s, 1H), 2.83-2.80 (m, 4H), 1.58-1.54 (m, 4H), 1.34-1.24 (m, 12H), 0.85 (t, $J = 6.9$ Hz, 6H) ppm. $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ 166.9, 134.4, 131.7, 128.9, 127.2, 58.8, 32.0, 27.3, 27.2, 22.8, 14.3 ppm.



Chemical Formula: $\text{C}_{13}\text{H}_{20}\text{N}_2\text{O}$

- ***N',N'*-dipropylbenzohydrazide (2b)**

According to general procedure B, alkylation of benzohydrazide (0.5 mmol, 68 mg) with propan-1-ol (5 equiv., 187 μL) afforded the pure product as a white solid (92 mg, 84 %) by silica flash column chromatography (pentane/ethyl acetate 9:1). Mp 80.8-81.8 $^\circ\text{C}$. $^1\text{H NMR}$ (500 MHz, CDCl_3): δ 7.73 (d, $J = 7.0$ Hz, 2H), 7.50 (t, $J = 7.4$ Hz, 1H), 7.43 (t, $J = 7.5$ Hz, 2H), 6.54 (br. s, 1H), 2.80 (t, $J = 7.6$ Hz, 4H), 1.65-1.55 (m, 4H), 0.94 (t, $J = 7.4$ Hz, 6H) ppm. $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ 166.8, 134.2, 131.7, 128.8, 127.1, 60.4, 20.5, 11.8 ppm. IR (neat): ν 3228, 2960, 1648, 1539, 1290, 1067, 946, 913, 695, 668, 604, 523 cm^{-1} . HRMS (ESI-TOF) m/z $[\text{M}+\text{H}]^+$: Calcd for $\text{C}_{13}\text{H}_{21}\text{N}_2\text{O}$ 221.1654; found 221.1658.



Chemical Formula: $\text{C}_{15}\text{H}_{24}\text{N}_2\text{O}$

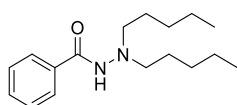
- ***N',N'*-dibutylbenzohydrazide (2c)**¹³⁹

According to general procedure B, alkylation of benzohydrazide (0.5 mmol, 68 mg) with butan-1-ol (5 equiv., 229 μL) afforded the pure product as a white solid (101 mg, 81 %) by silica flash column chromatography (pentane/ethyl acetate 9:1). $^1\text{H NMR}$ (500 MHz, CDCl_3): δ 7.69 (d, $J = 7.3$ Hz, 2H), 7.42 (t, $J = 7.4$ Hz, 1H), 7.33 (t, $J = 7.5$ Hz, 2H), 6.87 (br. s, 1H), 2.79-2.76 (m, 4H), 1.53-1.47 (m, 4H),

1.27 (sext, $J = 7.3$ Hz, 4H), 0.84 (t, $J = 7.3$ Hz, 6H) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ 166.7, 134.1, 131.4, 128.5, 127.0, 58.1, 29.2, 20.4, 14.0 ppm.

- **Scale up of the reaction to 5 mmol starting material**

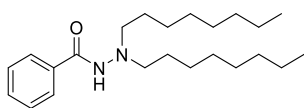
In a 30 mL flame-dried Schlenk tube equipped with a stirring bar, benzohydrazide (5 mmol, 680 mg), butan-1-ol (5 equiv., 2.29 mL), ruthenium complex **Ru1** (25.1 mg, 1 mol %), Me_3NO (11.1 mg, 2 mol %), $t\text{BuONa}$ (240 mg, 1 equiv.) and $t\text{BuOH}$ (10 mL, 0.5 M) were poured in under an argon atmosphere. The mixture was rapidly stirred at room temperature for 2 min and then placed into a pre-heated oil bath at 130 °C and stirred over 24 hours. The mixture was cooled-down to room temperature, filtrated over celite with diethyl ether and concentrated under reduced pressure. The conversion was determined by ^1H -NMR spectroscopy and the residue was purified by flash chromatography on silica gel using pentane-ethyl acetate (9:1) as eluent to afford the pure product as a white solid (968 mg, 78 %). ^1H -NMR data were comparable with the previous NMR data.



Chemical Formula: $\text{C}_{17}\text{H}_{28}\text{N}_2\text{O}$

- **N',N' -dipentylbenzohydrazide (2d)**

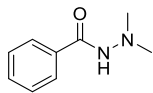
According to general procedure B, alkylation of benzohydrazide (0.5 mmol, 68 mg) with pentan-1-ol (5 equiv., 271 μL) afforded the pure product as a white solid (114 mg, 83 %) by silica flash column chromatography (pentane/ethyl acetate 9:1). Mp 80.8-82.1 °C. ^1H NMR (500 MHz, CDCl_3): δ 7.73 (d, $J = 7.0$ Hz, 2H), 7.50 (t, $J = 7.4$ Hz, 1H), 7.43 (t, $J = 7.5$ Hz, 2H), 6.53 (br. s, 1H), 2.84-2.79 (m, 4H), 1.61-1.54 (m, 4H), 1.33-1.29 (m, 8H), 0.88 (t, $J = 7.1$ Hz, 6H) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ 166.8, 134.3, 131.6, 128.8, 127.1, 58.6, 29.6, 26.9, 22.7, 14.2 ppm. IR (neat): ν 3229, 2943, 2929, 1651, 1541, 1470, 1314, 1080, 937, 695, 680, 669, 604, 527, 506, 444 cm^{-1} . HRMS (ESI-TOF) m/z $[\text{M}+\text{H}]^+$: Calcd for $\text{C}_{17}\text{H}_{29}\text{N}_2\text{O}$ 277.2280; found 277.2284.



Chemical Formula: $\text{C}_{23}\text{H}_{40}\text{N}_2\text{O}$

- **N',N' -dioctylbenzohydrazide (2e)**

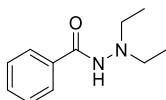
According to general procedure B, alkylation of benzohydrazide (0.5 mmol, 68 mg) with octan-1-ol (5 equiv., 392 μL) afforded the pure product as a white solid (142 mg, 79 %) by silica flash column chromatography (pentane/ethyl acetate 9:1). The excess of octan-1-ol was then removed by distillation ($T = 120$ °C, $P = 110$ mbar). Mp 82.1-84.5 °C. ^1H NMR (500 MHz, CDCl_3): δ 7.71 (d, $J = 7.0$ Hz, 2H), 7.47 (t, $J = 7.4$ Hz, 1H), 7.40 (t, $J = 7.5$ Hz, 2H), 6.61 (br. s, 1H), 2.82-2.79 (m, 4H), 1.53 (app t, $J = 7.3$ Hz, 4H), 1.32-1.24 (m, 20H), 0.84 (t, $J = 7.0$ Hz, 6H) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ 166.8, 207 134.3, 131.6, 128.72, 127.1, 58.6, 31.9, 29.6, 29.4, 27.4, 27.2, 22.8, 14.2 ppm. IR (neat): ν 32232, 2941, 1650, 1542, 1472, 1316, 1081, 932, 680, 672, 604, 527, 506, 482 cm^{-1} . HRMS (ESI-TOF) m/z $[\text{M}+\text{H}]^+$: Calcd for $\text{C}_{23}\text{H}_{41}\text{N}_2\text{O}$ 361.3123; found 361.3122.



Chemical Formula: C₉H₁₂N₂O

- ***N,N'*-dimethylbenzohydrazide (2f)**¹³⁹

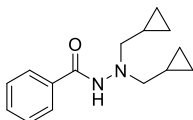
According to a modified general procedure B, alkylation of benzohydrazide (0.5 mmol, 68 mg) with methanol used as solvent (0.5 M) afforded the pure product as a white solid (76 mg, 93 %) by silica flash column chromatography (pure ethyl acetate). **¹H NMR (500 MHz, CDCl₃):** δ 7.69 (d, *J* = 7.0 Hz, 2H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.24 (br. s, 1H), 2.64 (s, 6H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ 165.8, 133.8, 131.6, 128.5, 127.1, 47.6 ppm.



Chemical Formula: C₁₁H₁₆N₂O

- ***N,N'*-diethylbenzohydrazide (2g)**¹³⁹

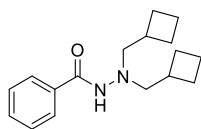
According to a modified general procedure B, alkylation of benzohydrazide (0.5 mmol, 68 mg) with ethanol (10 equiv., 292 μL) afforded the pure product as a white solid (81 mg, 84 %) by silica flash column chromatography (pentane/ethyl acetate 2:8). **¹H NMR (500 MHz, CDCl₃):** δ 7.74 (d, *J* = 7.2 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 2H), 6.41 (br. s, 1H), 2.86 (q, *J* = 7.1 Hz, 4H), 1.16 (t, *J* = 7.1 Hz, 6H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ 167.1, 134.2, 131.7, 128.8, 127.1, 52.5, 12.2 ppm.



Chemical Formula: C₁₅H₂₀N₂O

- ***N,N'*-bis(cyclopropylmethyl)benzohydrazide (2h)**

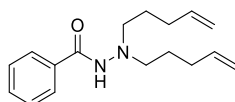
According to general procedure B, alkylation of benzohydrazide (0.5 mmol, 68 mg) with cyclopropylmethanol (5 equiv., 202 μL) afforded the pure product as a white solid (84 mg, 69 %) by silica flash column chromatography (pentane/ethyl acetate 3:1). Mp 73.9-75.8 °C. **¹H NMR (500 MHz, CDCl₃):** δ 7.74 (d, *J* = 7.0 Hz, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 2H), 6.98 (br. s, 1H), 2.86 (d, *J* = 6.7 Hz, 4H), 1.06-0.98 (m, 2H), 0.55-0.50 (m, 4H), 0.16 (q, *J* = 4.7 Hz, 4H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ 166.7, 134.5, 131.6, 128.8, 127.0, 61.9, 8.4, 3.6 ppm. **IR (neat):** ν 3232, 208 3070, 2995, 1649, 1543, 1313, 1177, 1017, 935, 892, 698, 670, 597, 520, 448, 409 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₁₅H₂₁N₂O 245.1654; found 245.1651.



Chemical Formula: C₁₇H₂₄N₂O

- ***N',N'*-bis(cyclobutylmethyl)benzohydrazide (2i)**

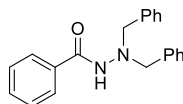
According to general procedure B, alkylation of benzohydrazide (0.5 mmol, 68 mg) with cyclobutylmethanol (5 equiv., 242 μ L) afforded the pure product as a white solid (110 mg, 81 %) by silica flash column chromatography (pentane/ethyl acetate 3:1). Mp 75.6-77.7 °C. **¹H NMR (500 MHz, CDCl₃):** δ 7.69 (d, J = 7.2 Hz, 2H), 7.46 (t, J = 7.4 Hz, 1H), 7.39 (t, J = 7.5 Hz, 2H), 6.71 (br. s, 1H), 2.87 (d, J = 6.9 Hz, 4H), 2.64-2.53 (m, 2H), 2.06-1.98 (m, 4H), 1.92-1.81 (m, 2H), 1.78-1.66 (m, 6H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ 166.4, 134.3, 131.5, 128.7, 127.0, 64.0, 34.0, 27.6, 19.1 ppm. **IR (neat):** ν 3226, 3065, 2957, 2937, 2853, 1641, 1545, 1306, 1059, 938, 926, 695, 670, 637, 409 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₁₇H₂₅N₂O 173.1967; Found: 273.1971.



Chemical Formula: C₁₇H₂₄N₂O

- ***N',N'*-di(pent-4-en-1-yl)benzohydrazide (2j)**

According to general procedure B, alkylation of benzohydrazide (0.5 mmol, 68 mg) with pent-4-en-1-ol (5 equiv., 256 μ L) afforded the pure product as a white solid (105 mg, 77 %) by silica flash column chromatography (pentane/ethyl acetate 3:1). Mp 70.7-71.3 °C. **¹H NMR (500 MHz, CDCl₃):** δ 7.69 (d, J = 7.1 Hz, 2H), 7.43 (t, J = 7.4 Hz, 1H), 7.34 (t, J = 7.6 Hz, 2H), 7.00 (br. s, 1H), 5.74 (td, J = 6.7; 16.9 Hz, 2H), 4.98-4.95 (m, 2H), 4.92-4.88 (m, 2H), 2.83-2.78 (m, 4H), 2.12-2.08 (m, 4H), 1.65- 1.57 (m, 4H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ 166.8, 138.3, 134.0, 131.6, 128.5, 127.0, 114.9, 57.6, 31.3, 26.4 ppm. **IR (neat):** ν 3231, 3062, 2951, 2841, 1645, 1536, 1302, 1288, 1073, 991, 909, 801, 694, 669 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₁₇H₂₅N₂O 273.1967; found 273.1968.



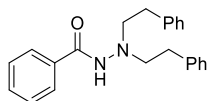
Chemical Formula: C₂₁H₂₀N₂O

- ***N',N'*-dibenzylbenzohydrazide (2k)¹⁵⁵**

According to general procedure B, alkylation of benzohydrazide (0.5 mmol, 68 mg) with benzyl alcohol (5 equiv., 265 μ L) afforded the pure product as a white solid (134 mg, 85 %) by silica flash column chromatography (pentane/ethyl acetate 9:1). The excess of benzyl alcohol was then removed by distillation (T = 105 °C, P = 110 mbar). **¹H NMR (500 MHz, CDCl₃):** δ 7.42 (t, J = 7.7 Hz, 7H), 7.36-

¹⁵⁵ Kawase, Y.; Yamagishi, T.; Kato, J.-Y.; Kutsuma, T.; Kataoka, T.; Iwakuma, T.; Yokomatsu, T. *Synthesis* **2014**, *46*, 455-464.

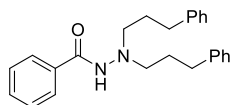
7.27 (m, 8H), 7.00 (br. s, 1H), 4.33 (s, 4H) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ 167.5, 137.5, 134.1, 131.5, 129.4, 128.6, 128.5, 127.6, 126.9, 59.4 ppm.



Chemical Formula: $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}$

- ***N,N'*-diphenethylbenzohydrazide (2l)**

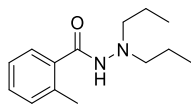
According to general procedure B, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 2-phenylethan-1-ol (5 equiv., 299 μL) afforded the pure product as a white solid (145 mg, 84 %) by silica flash column chromatography (pentane/ethyl acetate 3:1). The excess of 2-phenylethan-1-ol was then removed by distillation ($T = 120\text{ }^\circ\text{C}$, $P = 110\text{ mbar}$). Mp 87.3-88.4 $^\circ\text{C}$. ^1H NMR (500 MHz, CDCl_3): δ 7.52 (d, $J = 7.4\text{ Hz}$, 2H), 7.40 (t, $J = 7.4\text{ Hz}$, 1H), 7.30 (t, $J = 7.5\text{ Hz}$, 2H), 7.20-7.17 (m, 5H), 7.12-7.09 (m, 5H), 6.75 (br. s, 1H), 3.15-3.12 (m, 4H), 2.85-2.81 (m, 4H) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ 166.9, 139.9, 133.7, 131.8, 128.8, 128.7, 128.6, 127.1, 126.3, 59.4, 34.0 ppm. IR (neat): ν 3223, 3059, 3026, 2961, 2839, 1643, 1547, 1494, 1453, 1293, 1124, 1027, 934, 752, 727, 694, 671, 613, 498, 471 cm^{-1} . HRMS (ESI-TOF) m/z $[\text{M}+\text{H}]^+$: Calcd for $\text{C}_{23}\text{H}_{25}\text{N}_2\text{O}$ 345.1967; found 345.1967.



Chemical Formula: $\text{C}_{25}\text{H}_{28}\text{N}_2\text{O}$

- ***N,N'*-bis(3-phenylpropyl)benzohydrazide (2m)**

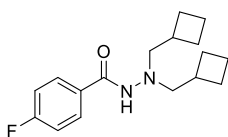
According to general procedure B, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 3-phenylpropan-1-ol (5 equiv., 327 μL) afforded the pure product as a white solid (141 mg, 76 %) by silica flash column chromatography (pentane/ethyl acetate 3:1). The excess of 3-phenylpropan-1-ol was then removed by distillation ($T = 130\text{ }^\circ\text{C}$, $P = 110\text{ mbar}$). Mp 85.5-88.9 $^\circ\text{C}$. ^1H NMR (500 MHz, CDCl_3): δ 7.59 (d, $J = 7.4\text{ Hz}$, 2H), 7.38 (t, $J = 7.5\text{ Hz}$, 1H), 7.29 (t, $J = 7.5\text{ Hz}$, 2H), 7.18-7.15 (m, 5H), 7.10-7.07 (m, 5H), 6.52 (br. s, 1H), 2.74 (t, $J = 7.2\text{ Hz}$, 4H), 2.61 (t, $J = 7.3\text{ Hz}$, 4H), 1.76 (quint, $J = 7.3\text{ Hz}$, 4H) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ 166.8, 142.1, 134.0, 131.7, 128.7, 128.6, 128.4, 128.4, 127.0, 125.9, 57.7, 33.4, 28.9 ppm. IR (neat): ν 3245, 3026, 2946, 2851, 1650, 1533, 1312, 1286, 1107, 1028, 938, 800, 751, 694, 669, 607, 596, 503, 489, 460 cm^{-1} . HRMS (ESI-TOF) m/z $[\text{M}+\text{H}]^+$: Calcd for $\text{C}_{25}\text{H}_{29}\text{N}_2\text{O}$ 373.2280; found 373.2284.



Chemical Formula: C₁₄H₂₂N₂O

- **2-methyl-*N',N'*-dipropylbenzohydrazide (2n)**

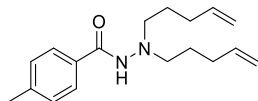
According to general procedure B, alkylation of 2-methylbenzohydrazide (0.5 mmol, 75 mg) with propan-1-ol (5 equiv., 187 μ L) afforded the pure product as a white solid (92 mg, 79 %) by silica flash column chromatography (pentane/ethyl acetate 9:1). Mp 74.0-78.9 °C. **¹H NMR (500 MHz, CDCl₃):** δ 7.32-7.29 (m, 2H), 7.23-7.17 (m, 2H), 6.15 (br. s, 1H), 2.76 (t, $J = 7.7$ Hz, 4H), 2.45 (s, 3H), 1.60 (sext, $J = 7.6$ Hz, 4H), 0.95 (t, $J = 7.4$ Hz, 6H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ 169.0, 136.5, 135.6, 131.1, 130.1, 126.7, 125.8, 60.4, 20.5, 19.8, 11.9 ppm. **IR (neat):** ν 3214, 3056, 2961, 2937, 2857, 2833, 1653, 1538, 1466, 1375, 1314, 1281, 1165, 1067, 948, 914, 867, 750, 723, 691, 660, 466, 455 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₁₄H₂₃N₂O 221.1654; found 221.1658.



Chemical Formula: C₁₇H₂₃FN₂O

- ***N',N'*-bis(cyclobutylmethyl)-4-fluorobenzohydrazide (2o)**

According to general procedure B, alkylation of 4-fluorobenzohydrazide (0.5 mmol, 77 mg) with cyclobutylmethanol (5 equiv., 242 μ L) afforded the pure product as a white solid (81 mg, 56 %) by silica flash column chromatography (pentane/ethyl acetate 3:1). Mp 77.9-79.2 °C. **¹H NMR (500 MHz, CDCl₃):** δ 7.72-7.69 (m, 2H), 7.07 (t, $J = 8.6$ Hz, 2H), 6.59 (br. s, 1H), 2.87 (d, $J = 6.9$ Hz, 4H), 2.61-2.55 (m, 2H), 2.06-12.00 (m, 4H), 1.91-1.83 (m, 2H), 1.81-1.68 (m, 6H) ppm. **¹⁹F NMR (500 MHz, CDCl₃):** δ -108.1 ppm. **¹³C NMR (125 MHz, CDCl₃):** δ 165.4, 132.4, 129.2 (d, $J = 8.8$ Hz), 115.7 (d, $J = 22.5$ Hz), 114.6, 64.0, 34.1, 27.6, 19.2 ppm. **IR (neat):** ν 3280, 3048, 2957, 2933, 2855, 1650, 1603, 1553, 1500, 1454, 1322, 1292, 1277, 1236, 1225, 1159, 1097, 930, 855, 765, 654, 625, 603 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₁₇H₂₄N₂OF 291.1873; found 291.1879.

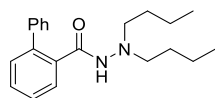


Chemical Formula: C₁₈H₂₆N₂O

- **4-methyl-*N',N'*-di(pent-4-en-1-yl)benzohydrazide (2p)**

According to general procedure B, alkylation of 4-methylbenzohydrazide (0.5 mmol, 75 mg) with pent-4-en-1-ol (5 equiv., 256 μ L) afforded the pure product as a white solid (109 mg, 76 %) by silica flash column chromatography (pentane/ethyl acetate 3:1). Mp 71.2-72.4 °C. **¹H NMR (500 MHz, CDCl₃):** δ 7.62 (d, $J = 8.1$ Hz, 2H), 7.22 (d, $J = 8.0$ Hz, 2H), 6.59 (br. s, 1H), 5.75 (td, $J = 6.7$; 16.9 Hz, 2H), 5.03-4.98 (m, 2H), 4.95-4.93 (m, 2H), 2.86-2.83 (m, 4H), 2.39 (s, 3H), 2.14-2.10 (m, 4H), 1.69- 1.63 (m, 4H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ 166.7, 142.2, 138.4, 131.2, 129.4, 127.1, 115.0, 57.8,

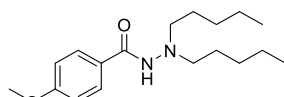
31.4, 26.5, 21.6 ppm. **IR (neat):** ν 3230, 2949, 1646, 1492, 1312, 1288, 1071, 909, 774, 694, 669 cm^{-1} . **HRMS (ESI-TOF) m/z $[M+H]^+$:** Calcd for $\text{C}_{18}\text{H}_{27}\text{N}_2\text{O}$ 287.2123; found 287.2127.



Chemical Formula: $\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}$

- ***N',N'*-dibutyl-[1,1'-biphenyl]-2-carbohydrazide (2q)**

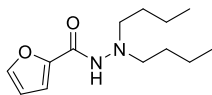
According to general procedure B, alkylation of [1,1'-biphenyl]-2-carbohydrazide (0.5 mmol, 106 mg) with butan-1-ol (5 equiv., 229 μL) afforded the pure product as a white solid (88 mg, 54 %) by silica flash column chromatography (pentane/ethyl acetate 9:1). Mp 77.5-80.9 $^{\circ}\text{C}$. **^1H NMR (500 MHz, CDCl_3):** δ 7.65 (dd, $J = 1.3$; 7.6 Hz, 1H), 7.49-7.45 (m, 3H), 7.43-7.37 (m, 5H), 5.76 (br. s, 1H), 2.43 (t, $J = 7.3$ Hz, 4H), 1.20-1.18 (m, 8H), 0.82 (t, $J = 7.1$ Hz, 6H) ppm. **^{13}C NMR (125 MHz, CDCl_3):** δ 168.3, 140.4, 139.6, 135.1, 130.3, 130.1, 129.0, 128.9, 128.8, 128.0, 127.7, 57.5, 28.4, 20.5, 14.0 ppm. **IR (neat):** ν 3215, 3058, 2955, 2861, 1651, 1543, 1466, 1317, 1304, 1073, 919, 760, 741, 696, 660, 565, 521 cm^{-1} . **HRMS (ESI-TOF) m/z $[M+H]^+$:** Calcd for $\text{C}_{21}\text{H}_{29}\text{N}_2\text{O}$ 325.2280; found 325.2286.



Chemical Formula: $\text{C}_{18}\text{H}_{30}\text{N}_2\text{O}_2$

- **4-methoxy-*N',N'*-dipentylbenzohydrazide (2r)**

According to general procedure B, alkylation of 4-methoxybenzohydrazide (0.5 mmol, 83 mg) with pentan-1-ol (5 equiv., 271 μL) afforded the pure product as a white solid (138 mg, 90 %) by silica flash column chromatography (pentane/ethyl acetate 9:1). Mp 77.2-78.8 $^{\circ}\text{C}$. **^1H NMR (500 MHz, CDCl_3):** δ 7.70 (d, $J = 8.8$ Hz, 2H), 6.91 (d, $J = 8.8$ Hz, 2H), 6.46 (br. s, 1H), 3.85 (s, 3H), 2.82-2.79 (m, 4H), 1.57-1.53 (m, 4H), 1.31-1.29 (m, 8H), 0.86 (t, $J = 7.0$ Hz, 6H) ppm. **^{13}C NMR (125 MHz, CDCl_3):** δ 166.3, 162.3, 128.9, 126.5, 114.0, 58.7, 55.6, 29.6, 26.9, 22.7, 14.2 ppm. **IR (neat):** ν 3243, 2932, 2858, 1647, 1607, 1537, 1508, 1459, 1289, 1253, 1182, 1082, 1026, 942, 929, 848, 771, 668, 631, 609, 534, 515 cm^{-1} . **HRMS (ESI-TOF) m/z $[M+H]^+$:** Calcd for $\text{C}_{18}\text{H}_{31}\text{N}_2\text{O}_2$ 307.2386; found 307.2383.

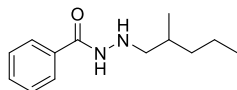


Chemical Formula: $\text{C}_{13}\text{H}_{22}\text{N}_2\text{O}_2$

- ***N',N'*-dibutylfuran-2-carbohydrazide (2s)**

According to general procedure B, alkylation of furan-2-carbohydrazide (0.5 mmol, 63 mg) with butan-1-ol (5 equiv., 229 μL) afforded the pure product as a white solid (92 mg, 77 %) by silica flash column chromatography (pentane/ethyl acetate 3:1). Mp 68.9-71.1 $^{\circ}\text{C}$. **^1H NMR (500 MHz, CDCl_3):** δ 7.41 (dd, $J = 0.7$; 1.7 Hz, 1H), 7.14 (dd, $J = 0.7$; 3.5 Hz, 1H), 6.78 (br. s, 1H), 6.49 (dd, $J = 1.7$; 3.5 Hz, 1H), 2.79-2.76 (m, 4H), 1.55-1.49 (m, 4H), 1.30 (sext, $J = 7.4$ Hz, 4H), 0.87 (t, $J = 7.4$ Hz, 6H) ppm. **^{13}C**

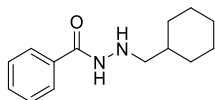
NMR (125 MHz, CDCl₃): δ 157.5, 147.4, 143.9, 115.0, 112.2, 58.6, 29.1, 20.5, 14.1 ppm. **IR (neat):** ν 3238, 2956, 2865, 1655, 1591, 1470, 1293, 1082, 1008, 885, 748, 596 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₁₃H₂₃N₂O₂ 239.1760; found 239.1763.



Chemical Formula: C₁₃H₂₀N₂O

- **N'-(2-methylpentyl)benzohydrazide (3b)**

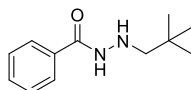
According to general procedure B, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 2-methylpentan-1-ol (5 equiv., 309 μ L) afforded the pure product as a white solid (92 mg, 79 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). Mp 96.7-97.8 °C. **¹H NMR (500 MHz, CDCl₃):** δ 8.03 (br. s, 1H), 7.76-7.73 (m, 2H), 7.51-7.48 (m, 1H), 7.40 (t, J = 7.5 Hz, 2H), 4.93 (br. s, 1H), 2.84 (dd, J = 5.8; 11.2 Hz, 1H), 2.69 (dd, J = 7.5; 11.2 Hz, 1H), 1.69-1.63 (m, 1H), 1.42-1.33 (m, 2H), 1.31-1.24 (m, 1H), 1.17-1.11 (m, 1H), 0.96 (d, J = 6.7 Hz, 3H), 0.85 (t, J = 7.0 Hz, 3H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ 167.3, 133.1, 131.8, 128.7, 127.0, 58.8, 37.2, 31.9, 20.1, 18.1, 14.4 ppm. **IR (neat):** ν 2988, 2901, 1648, 1493, 1392, 1232, 1067, 895, 694, 615, 432 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₁₃H₂₁N₂O 221.1654; found 221.1658.



Chemical Formula: C₁₄H₂₀N₂O

- **N'-(cyclohexylmethyl)benzohydrazide (3c)**

According to general procedure B, alkylation of benzohydrazide (0.5 mmol, 68 mg) with cyclohexylmethanol (5 equiv., 307 μ L) afforded the pure product as a white solid (56 mg, 48 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). Mp 98.2-99.9 °C. **¹H NMR (500 MHz, CDCl₃):** δ 7.73 (d, J = 7.3 Hz, 2H), 7.50 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.5 Hz, 2H), 2.78 (d, J = 6.7, 2H), 1.83-1.81 (m, 2H), 1.74-1.67 (m, 2H), 1.54-1.49 (m, 1H), 1.29-1.14 (m, 4H), 1.02-0.95 (m, 2H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ 167.3, 133.1, 131.9, 128.8, 126.9, 59.1, 36.8, 31.4, 26.7, 26.1 ppm. **IR (neat):** ν 3243, 2972, 2941, 1648, 1532, 1492, 1376, 1218, 1082, 896, 679, 652, 414 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₁₄H₂₁N₂O 233.1654; found 233.1651.

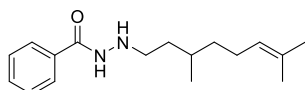


Chemical Formula: C₁₂H₁₈N₂O

- **N'-neopentylbenzohydrazide (3d)**

According to general procedure B, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 2,2-dimethylpropan-1-ol (5 equiv., 220 mg) afforded the pure product as a white solid (71 mg, 69 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). Mp 95.8-96.9 °C. **¹H NMR (500 MHz,**

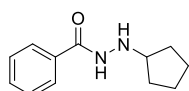
CDCl₃): δ 7.97 (br. s, 1H), 7.73 (d, $J = 7.3$ Hz, 2H), 7.47 (t, $J = 7.4$ Hz, 1H), 7.39 (t, $J = 7.5$ Hz, 2H), 4.88 (br. s, 1H), 2.72 (s, 2H), 0.98 (s, 9H) ppm. **¹³C NMR (125 MHz, CDCl₃)**: δ 167.3, 133.1, 131.8, 128.8, 126.9, 64.4, 31.3, 27.8 ppm. **IR (neat)**: ν 3231, 2954, 2843, 1628, 1460, 1364, 1328, 1160, 888, 695, 550 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺**: Calcd for C₁₂H₁₉N₂O 207.1497; found 207.1499.



Chemical Formula: C₁₇H₂₆N₂O

- ***N'*-(3,7-dimethyloct-6-en-1-yl)benzohydrazide (3e)**

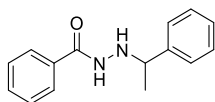
According to general procedure B, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 3,7-dimethyloct-6-en-1-ol (5 equiv., 456 μ L) afforded the pure product as a light yellow solid (77 mg, 56 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). Mp 98.7-99.4 °C. **¹H NMR (500 MHz, CDCl₃)**: δ 7.87 (br. s, 1H), 7.74 (d, $J = 7.3$ Hz, 2H), 7.50 (t, $J = 7.4$ Hz, 1H), 7.42 (t, $J = 7.6$ Hz, 2H), 5.09-5.06 (m, 1H), 3.00-2.90 (m, 2H), 2.02-1.91 (m, 2H), 1.73-1.62 (m, 5H), 1.59-1.49 (m, 5H), 1.83-1.81 (m, 2H), 0.89 (d, $J = 6.6$ Hz, 3H) ppm. **¹³C NMR (125 MHz, CDCl₃)**: δ 167.4, 133.0, 131.9, 131.4, 128.8, 127.0, 124.8, 50.5, 37.3, 35.2, 30.6, 25.8, 25.6, 19.7, 17.8 ppm. **IR (neat)**: ν 3243, 2985, 2905, 1649, 1497, 1421, 1364, 1292, 1068, 982, 926, 692, 617, 418 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺**: Calcd for C₁₇H₂₇N₂O 275.2053; found 275.2055.



Chemical Formula: C₁₂H₁₆N₂O

- ***N'*-cyclopentylbenzohydrazide (3f)**

According to general procedure B, alkylation of benzohydrazide (0.5 mmol, 68 mg) with cyclopentanol (5 equiv., 218 μ L) afforded the pure product as a white solid (48 mg, 47 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). Mp 94.5-96.8 °C. **¹H NMR (500 MHz, CDCl₃)**: δ 7.76-7.74 (m, 2H), 7.68 (br. s, 1H), 7.53-7.50 (m, 1H), 7.46-7.43 (m, 2H), 4.87 (br. s, 1H), 3.59-3.58 (m, 1H), 1.79-1.70 (m, 4H), 1.61-1.51 (m, 4H) ppm. **¹³C NMR (125 MHz, CDCl₃)**: δ 167.4, 133.2, 131.9, 128.9, 127.0, 61.9, 31.4, 24.3 ppm. **IR (neat)**: ν 3062, 2956, 1634, 1578, 1536, 1455, 1075, 989, 798, 693 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺**: Calcd for C₁₂H₁₇N₂O 205.1341; found 205.1342.

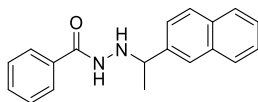


Chemical Formula: C₁₅H₁₆N₂O

- ***N'*-(1-phenylethyl)benzohydrazide (3g)¹³⁶**

According to general procedure B, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 1-phenylethan-1-ol (5 equiv., 299 μ L) afforded the pure product as a white solid (86 mg, 72 %) by silica flash column chromatography (pentane/ethyl acetate 13:1). **¹H NMR (500 MHz, CDCl₃)**: δ 7.76 (br. s, 1H), 7.64-7.63

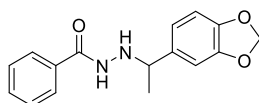
(m, 2H), 7.49-7.46 (m, 2H), 7.40-7.33 (m, 5H), 7.30-7.27 (m, 1H), 5.12 (br. s, 1H), 4.23 (q, $J = 6.6$ Hz, 1H), 1.42 (d, $J = 6.6$ Hz, 3H) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ 167.4, 143.1, 132.9, 131.9, 128.7, 128.7, 127.7, 127.3, 127.0, 60.1, 21.2 ppm.



Chemical Formula: $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}$

- ***N'*-(1-(naphthalen-2-yl)ethyl)benzohydrazide (3h)**

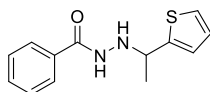
According to general procedure B, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 1-(naphthalen-2-yl)ethan-1-ol (5 equiv., 430 mg) afforded the pure product as a white solid (97 mg, 67 %) by silica flash column chromatography (pentane/ethyl acetate 3:1). Mp 100.1-100.6 °C. ^1H NMR (500 MHz, CDCl_3): δ 7.87-7.81 (m, 4H), 7.61-7.57 (m, 3H), 7.51-7.44 (m, 4H), 7.37-7.34 (m, 2H), 5.19 (br. s, 1H), 4.41 (q, $J = 6.6$ Hz, 1H), 1.51 (d, $J = 6.6$ Hz, 3H) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ 167.5, 140.8, 133.6, 133.2, 133.0, 132.0, 128.8, 128.6, 128.0, 127.8, 127.0, 126.3, 126.0, 125.3, 60.4, 21.5 ppm. IR (neat): ν 3266, 2962, 1648, 1519, 1392, 1285, 912, 893, 751, 693, 486 cm^{-1} . HRMS (ESI-TOF) m/z $[\text{M}+\text{H}]^+$: Calcd for $\text{C}_{19}\text{H}_{19}\text{N}_2\text{O}$ 291.1422; found 291.1426.



Chemical Formula: $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_3$

- ***N'*-(1-(benzo[*d*][1,3]dioxol-5-yl)ethyl)benzohydrazide (3i)**

According to general procedure B, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 1-(benzo[*d*][1,3]dioxol-5-yl)ethan-1-ol (5 equiv., 415 mg) afforded the pure product as a light yellow solid (94 mg, 66 %) by silica flash column chromatography (pentane/ethyl acetate 3:1). Mp 99.2-99.8 °C. ^1H NMR (500 MHz, CDCl_3): δ 7.65-7.63 (m, 3H), 7.47 (t, $J = 7.5$ Hz, 1H), 7.37 (t, $J = 7.5$ Hz, 2H), 6.93 (d, $J = 1.4$ Hz, 1H), 6.80 (dd, $J = 1.4$; 7.9 Hz, 1H), 6.74 (d, $J = 7.9$ Hz, 1H), 5.93 (s, 2H), 5.04 (br. s, 1H), 4.15 (q, $J = 6.6$ Hz, 1H), 1.36 (d, $J = 6.6$ Hz, 3H) ppm. ^{13}C NMR (125 MHz, CDCl_3): δ 167.5, 148.0, 147.0, 137.2, 133.0, 131.9, 128.8, 127.0, 120.8, 108.3, 107.4, 101.1, 59.9, 21.4 ppm. IR (neat): ν 3061, 2970, 2888, 1634, 1485, 1438, 1239, 1037, 934, 806, 692, 638, 442 cm^{-1} . HRMS (ESI-TOF) m/z $[\text{M}+\text{H}]^+$: Calcd for $\text{C}_{16}\text{H}_{17}\text{N}_2\text{O}_3$ 285.1563; found 285.1562.

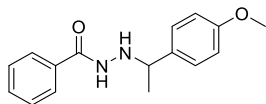


Chemical Formula: $\text{C}_{13}\text{H}_{14}\text{N}_2\text{OS}$

- ***N'*-(1-(thiophen-2-yl)ethyl)benzohydrazide (3j)¹³⁶**

According to general procedure B, alkylation of benzohydrazide (0.5 mmol, 68 mg) with (thiophen-2-yl)ethan-1-ol (5 equiv., 320 mg) afforded the pure product as a light yellow solid (85 mg, 69 %) by silica

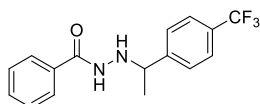
flash column chromatography (pentane/ethyl acetate 3:1). **¹H NMR (500 MHz, CDCl₃):** δ 7.71 (br. s, 1H), 7.67 (d, *J* = 7.2 Hz, 2H), 7.48 (t, *J* = 7.3 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.26-7.24 (m, 1H), 6.98-6.95 (m, 2H), 5.13 (br. s, 1H), 4.54 (q, *J* = 6.5 Hz, 1H), 1.50 (d, *J* = 6.5 Hz, 3H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ 167.6, 147.1, 132.9, 132.0, 128.8, 127.0, 126.8, 124.9, 124.7, 55.8, 22.0 ppm.



Chemical Formula: C₁₆H₁₈N₂O₂

- ***N'*-(1-(4-methoxyphenyl)ethyl)benzohydrazide (3k)**¹³⁶

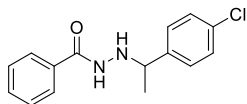
According to general procedure B, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 1-(4-methoxyphenyl)ethan-1-ol (5 equiv., 380 mg) afforded the pure product as a white solid (93 mg, 69 %) by silica flash column chromatography (pentane/ethyl acetate 3:1). **¹H NMR (500 MHz, CDCl₃):** δ 7.56-7.55 (m, 2H), 7.43-7.40 (m, 1H), 7.34-7.31 (m, 3H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 4.12 (q, *J* = 6.6 Hz, 1H), 3.73 (s, 3H), 1.34 (d, *J* = 6.6 Hz, 3H) ppm. **¹³C NMR (125 MHz, CDCl₃):** δ 167.4, 159.2, 135.2, 133.1, 131.9, 128.8, 128.5, 127.0, 114.1, 59.5, 55.4, 21.3 ppm.



Chemical Formula: C₁₆H₁₅F₃N₂O

- ***N'*-(1-(4-(trifluoromethyl)phenyl)ethyl)benzohydrazide (3l)**¹³⁶

According to general procedure B, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 1-(4-(trifluoromethyl)phenyl)ethan-1-ol (5 equiv., 475 mg) afforded the pure product as a white solid (97 mg, 63 %) by silica flash column chromatography (pentane/ethyl acetate 3:1). **¹H NMR (500 MHz, CDCl₃):** δ 7.63-7.61 (m, 4H), 7.53 (d, *J* = 8.1 Hz, 2H), 7.52-7.49 (m, 1H), 7.42-7.37 (m, 3H), 5.07 (br. s, 1H), 4.33 (q, *J* = 6.6 Hz, 1H), 1.43 (d, *J* = 6.6 Hz, 3H) ppm. **¹⁹F NMR (500 MHz, CDCl₃):** δ -62.4 ppm. **¹³C NMR (125 MHz, CDCl₃):** δ 167.8, 147.6, 132.8, 132.2, 128.9, 128.7 (d, *J* = 139 Hz), 127.7, 127.0, 125.7 (q, *J* = 3.7 Hz), 59.9, 21.6 ppm.

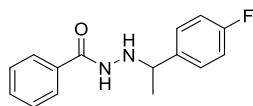


Chemical Formula: C₁₅H₁₅ClN₂O

- ***N'*-(1-(4-chlorophenyl)ethyl)benzohydrazide (3m)**

According to general procedure B, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 1-(4-chlorophenyl)ethan-1-ol (5 equiv., 390 mg) afforded the pure product as a white solid (96 mg, 70 %) by silica flash column chromatography (pentane/ethyl acetate 3:1). Mp 98.3-99.9 °C. **¹H NMR (500 MHz, CDCl₃):** δ 7.63-7.61 (m, 2H), 7.51-7.48 (m, 1H), 7.45 (br. s, 1H), 7.41-7.38 (m, 2H), 7.35-7.31 (m, 4H), 5.05 (br. s, 1H), 4.22 (q, *J* = 6.6 Hz, 1H), 1.39 (d, *J* = 6.6 Hz, 3H) ppm. **¹³C NMR (125 MHz, CDCl₃):**

δ 167.6, 141.9, 133.4, 132.9, 132.1, 128.9, 128.8, 128.7, 127.0, 59.6, 21.4 ppm. **IR (neat):** ν 2968, 1636, 1462, 1312, 1129, 1075, 1017, 867, 805, 716, 692, 483, 413 cm^{-1} . **HRMS (ESI-TOF) m/z $[M+H]^+$:** Calcd for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{OCl}$ 275.1602; found 275.1608.



Chemical Formula: $\text{C}_{15}\text{H}_{15}\text{FN}_2\text{O}$

- ***N'*-(1-(4-fluorophenyl)ethyl)benzohydrazide (3n)¹³⁶**

According to general procedure B, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 1-(4-fluorophenyl)ethan-1-ol (5 equiv., 350 mg) afforded the pure product as a white solid (94 mg, 73 %) by silica flash column chromatography (pentane/ethyl acetate 3:1). **¹H NMR (500 MHz, CDCl_3):** δ 7.71 (br. s, 1H), 7.63 (d, $J = 7.2$ Hz, 2H), 7.50-7.47 (m, 1H), 7.40-7.34 (m, 4H), 7.06-6.99 (m, 2H), 5.00 (br. s, 1H), 4.24 (q, $J = 6.6$ Hz, 1H), 1.38 (d, $J = 6.6$ Hz, 3H) ppm. **¹⁹F NMR (500 MHz, CDCl_3):** δ -115.1 ppm. **¹³C NMR (125 MHz, CDCl_3):** δ 167.5, 161.3 (d, $J = 243.8$ Hz), 138.9 (d, $J = 3.1$ Hz), 132.9, 132.0, 128.9 (d, $J = 7.9$ Hz), 128.8, 127.0, 115.4 (d, $J = 21.1$ Hz), 59.4, 21.3 ppm.

5) Synthesis of non-symmetric di-substituted acylhydrazides.

General Procedure C:

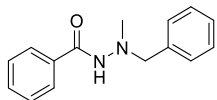
In a 15 mL flame-dried Schlenk tube equipped with a stirring bar, the desired acylhydrazide (0.5 mmol, 1 equiv.), the desired primary alcohol (5 equiv.), Me_3NO (1.11 mg, 2 mol %), methanol (25 equiv., 0.5 mL), ruthenium complex **Ru1** (2.51 mg, 1 mol %) and $^t\text{BuONa}$ (48 mg, 1 equiv.) were poured in under an argon atmosphere. The mixture was then placed into a pre-heated oil bath at 110 °C and stirred over 24 hours. The mixture was cooled-down to room temperature, filtrated over celite with diethyl ether and concentrated under reduced pressure. The conversion was determined by ¹H-NMR spectroscopy and the residue was purified by flash chromatography on silica gel using pentane-ethyl acetate as eluent to afford the desired product.

General Procedure D:

In a 15 mL flame-dried Schlenk tube equipped with a stirring bar, the desired acylhydrazide (0.5 mmol, 1 equiv.), the desired secondary alcohol (5 equiv.), Me_3NO (1.11 mg, 2 mol %), methanol (25 equiv., 0.5 mL), ruthenium complex **Ru1** (2.51 mg, 1 mol %) and $^t\text{BuONa}$ (48 mg, 1 equiv.) were poured in under an argon atmosphere. The mixture was then placed into a pre-heated oil bath at 130 °C and stirred over 24 hours. The mixture was cooled-down to room temperature, filtrated over celite with diethyl ether and concentrated under reduced pressure. The conversion was determined by ¹H-NMR spectroscopy and the residue was purified by flash chromatography on silica gel using pentane-ethyl acetate as eluent to afford the desired product.

General Procedure E:

In a 15 mL flame-dried Schlenk tube equipped with a stirring bar, the desired acylhydrazide (0.5 mmol, 1 equiv.), the desired primary alcohol (5 equiv.), Me₃NO (1.11 mg, 2 mol %), ethanol (2.5 equiv., 73 μL), ruthenium complex **Ru1** (2.51 mg, 1 mol %) and ^tBuONa (48 mg, 1 equiv.) were poured in under an argon atmosphere. The mixture was then placed into a pre-heated oil bath at 110 °C and stirred over 24 hours. The mixture was cooled-down to room temperature, filtrated over celite with diethyl ether and concentrated under reduced pressure. The conversion was determined by ¹H-NMR spectroscopy and the residue was purified by flash chromatography on silica gel using pentane-ethyl acetate as eluent to afford the desired product.



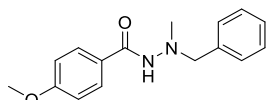
Chemical Formula: C₁₅H₁₆N₂O

- ***N'*-benzyl-*N'*-methylbenzohydrazide (4a)**

According to general procedure C, alkylation of benzohydrazide (0.5 mmol, 68 mg) with benzyl alcohol (5 equiv., 0.265 mL) afforded the pure product as a white solid (89 mg, 74 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by ¹H-NMR spectroscopy in the crude product with 19 % of dimethylated derivative observed. **¹H-NMR (CDCl₃, 500 MHz):** δ 7.59-7.58 (m, 2H), 7.46-7.43 (m, 1H), 7.37-7.31 (m, 6H), 7.29-7.26 (m, 1H), 7.06 (br. s, 1H), 4.09 (s, 2H), 2.78 (s, 3H) ppm. **¹³C-NMR (CDCl₃, 125 MHz):** δ 166.4, 136.0, 133.9, 131.6, 129.5, 128.6, 128.5, 127.8, 127.0, 62.5, 44.7 ppm. **IR (neat):** ν 3248, 1649, 1541, 1446, 1292, 1162, 1072, 969, 909, 854, 218 749, 691, 664, 527 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₁₅H₁₇N₂O 241.1341; found 241.1343.

- **Scale up of the reaction to 5 mmol starting material**

In a 30 mL flame-dried Schlenk tube equipped with a stirring bar, benzohydrazide (5 mmol, 680 mg), benzyl alcohol (5 equiv., 2.65 mL), ruthenium complex **Ru1** (25.1 mg, 1 mol %), Me₃NO (11.1 mg, 2 mol %), ^tBuONa (480 mg, 1 equiv.) and methanol (5 mL, 1 M) were poured in under an argon atmosphere. The mixture was rapidly stirred at room temperature for 2 min and then placed into a pre-heated oil bath at 110 °C and stirred over 24 hours. The mixture was cooled-down to room temperature, filtrated over celite with diethyl ether and concentrated under reduced pressure. The conversion was determined by ¹H-NMR spectroscopy and the residue was purified by flash chromatography on silica gel using pentane-ethyl acetate (9:1) as eluent to afford the pure product as a white solid (968 mg, 78 %). ¹H-NMR data were comparable with the previous NMR data.

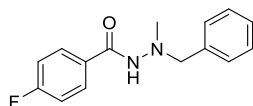


Chemical Formula: C₁₆H₁₈N₂O₂

- ***N'*-benzyl-4-methoxy-*N'*-methylbenzohydrazide (4b)**

According to general procedure C, alkylation of 4-methoxybenzohydrazide (0.5 mmol, 83 mg) with benzyl alcohol (5 equiv., 0.265 mL) afforded the pure product as a white solid (89 mg, 76 %) by silica

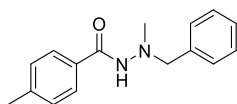
flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by $^1\text{H-NMR}$ spectroscopy in the crude product with 11 % of dimethylated derivative observed. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ 7.56 (d, $J = 8.6$ Hz, 2H), 7.35-7.26 (m, 5H), 7.03 (br. s, 1H), 6.82 (d, $J = 8.6$ Hz, 2H), 4.08 (s, 2H), 3.79 (s, 3H), 2.76 (s, 3H) ppm. $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): δ 165.9, 162.2, 136.0, 129.6, 128.8, 128.5, 127.7, 126.1, 113.8, 62.5, 55.4, 44.6 ppm. IR (neat): ν 3186, 2990, 1633, 1564, 1323, 1246, 1177, 1154, 1066, 1036, 904, 840, 742, 700, 632, 525, 452 cm^{-1} . HRMS (ESI-TOF) m/z $[\text{M}+\text{H}]^+$: Calcd for $\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}_2$ 271.1447; found 271.1447.



Chemical Formula: $\text{C}_{15}\text{H}_{15}\text{FN}_2\text{O}$

- ***N'*-benzyl-4-fluoro-*N'*-methylbenzohydrazide (4c)**

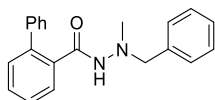
According to general procedure C, alkylation of 4-fluorobenzohydrazide (0.5 mmol, 77 mg) with benzyl alcohol (5 equiv., 0.265 mL) afforded the pure product as a white solid (63 mg, 49 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by $^1\text{H-NMR}$ spectroscopy in the crude product with 16 % of dimethylated derivative observed. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ 7.61-7.58 (m, 2H), 7.35-7.29 (m, 5H), 7.02 (t, $J = 8.5$ Hz, 2H), 6.88 (br. s, 1H), 4.10 (s, 2H), 2.80 (s, 3H) ppm. $^{19}\text{F-NMR}$ (CDCl_3 , 500 MHz): δ -107.8 ppm. $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): δ 165.4, 135.9, 130.1, 129.6, 129.3 (d, $J = 8.8$ Hz), 128.6, 127.9, 115.7 (d, $J = 21.3$ Hz), 62.5, 44.7 ppm. IR (neat): ν 3194, 3025, 2848, 1637, 1558, 1446, 1308, 1292, 1106, 920, 904, 850, 744, 696, 666, 528, 433 cm^{-1} . HRMS (ESI-TOF) m/z $[\text{M}+\text{H}]^+$: Calcd for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{OF}$ 259.1247; found 259.1243.



Chemical Formula: $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}$

- ***N'*-benzyl-*N'*-4-dimethylbenzohydrazide (4d)**

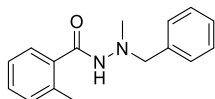
According to general procedure C, alkylation of 4-methylbenzohydrazide (0.5 mmol, 75 mg) with benzyl alcohol (5 equiv., 0.265 mL) afforded the pure product as a white solid (98 mg, 77 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by $^1\text{H-NMR}$ spectroscopy in the crude product with 18 % of dimethylated derivative observed. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ 7.49 (d, $J = 8.1$ Hz, 2H), 7.36-7.30 (m, 4H), 7.28-7.26 (m, 1H), 7.14 (d, $J = 8.1$ Hz, 2H), 7.02 (br. s, 1H), 4.09 (s, 2H), 2.77 (s, 3H), 2.35 (s, 3H) ppm. $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): δ 166.3, 142.0, 136.0, 131.0, 129.6, 129.2, 128.5, 127.7, 127.0, 62.5, 44.6, 21.5 ppm. IR (neat): ν 3241, 3033, 2921, 1648, 1542, 1362, 1307, 1189, 1005, 909, 832, 746, 698, 614, 540, 409 cm^{-1} . HRMS (ESI-TOF) m/z $[\text{M}+\text{H}]^+$: Calcd for $\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}$ 255.1497; found 255.1503.



Chemical Formula: C₂₁H₂₀N₂O

- ***N'*-benzyl-*N'*-methyl-[1,1'-biphenyl]-2-carbohydrazide (4e)**

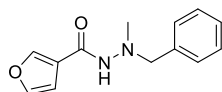
According to general procedure C, alkylation of [1,1'-biphenyl]-2-carbohydrazide (0.5 mmol, 106 mg) with benzyl alcohol (5 equiv., 0.265 mL) afforded the pure product as a white solid (119 mg, 75 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by ¹H-NMR spectroscopy in the crude product with 18 % of dimethylated derivative observed. **¹H-NMR (CD₃OD, 500 MHz):** δ 7.44 (td, *J* = 1.3; 7.6 Hz, 1H), 7.36-7.32 (m, 6H), 7.31-7.26 (m, 7H), 7.04 (dd, *J* = 1.3; 7.6 Hz, 1H), 3.68 (s, 2H), 2.33 (s, 3H) ppm. **¹³C-NMR (CD₃OD, 125 MHz):** δ 171.0, 141.5, 141.5, 138.0, 136.0, 131.1, 131.1, 130.6, 129.8, 129.3, 129.2, 128.8, 128.6, 128.6, 128.2, 63.8, 44.8 ppm. **IR (neat):** ν 3032, 1649, 1547, 1374, 1312, 1201, 1015, 965, 909, 816, 746, 696, 614, 542, 412 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₂₁H₂₁N₂O 317.1654; found 317.1659.



Chemical Formula: C₁₆H₁₈N₂O

- ***N'*-benzyl-*N'*,2-dimethylbenzohydrazide (4f)**

According to general procedure C, alkylation of 2-methylbenzohydrazide (0.5 mmol, 75 mg) with benzyl alcohol (5 equiv., 0.265 mL) afforded the pure product as a white solid (98 mg, 77 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by ¹H-NMR spectroscopy in the crude product with 16 % of dimethylated derivative observed. **¹H-NMR (CD₃OD, 500 MHz):** δ 7.43 (d, *J* = 7.2 Hz, 2H), 7.33-7.29 (m, 2H), 7.28-7.23 (m, 2H), 7.14-7.09 (m, 2H), 6.98 (d, *J* = 7.6 Hz, 1H), 3.91 (s, 2H), 2.73 (s, 3H), 2.05 (s, 3H) ppm. **¹³C-NMR (CD₃OD, 125 MHz):** δ 171.2, 138.4, 136.9, 136.4, 131.5, 130.9, 130.6, 129.2, 128.6, 128.0, 126.5, 64.0, 46.0, 19.1 ppm. **IR (neat):** ν 3243, 3021, 2956, 1648, 1517, 1375, 1312, 1201, 1006, 917, 833, 746, 696, 616, 536, 475, 409 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₁₆H₁₉N₂O 255.1497; found 255.1501.

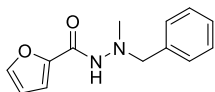


Chemical Formula: C₁₃H₁₄N₂O₂

- ***N'*-benzyl-*N'*-methylfuran-3-carbohydrazide (4g)**

According to general procedure C, alkylation of furan-3-carbohydrazide (0.5 mmol, 63 mg) with benzyl alcohol (5 equiv, 0.265 mL) afforded the pure product as a white solid (66 mg, 57 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by ¹H-NMR spectroscopy in the crude product with 23 % of dimethylated derivative observed. **¹H-NMR (CD₃OD, 500 MHz):** δ 7.91 (d, *J* = 0.5 Hz, 1H), 7.49 (t, *J* = 1.7 Hz, 1H), 7.36 (d, *J* = 7.1 Hz, 2H), 7.27-7.24 (m, 2H), 7.22-7.19 (m, 1H), 3.91 (s, 2H), 2.65 (s, 3H) ppm. **¹³C-NMR (CD₃OD, 125 MHz):** δ 163.6, 146.3,

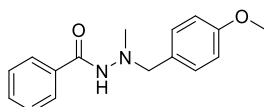
145.1, 138.1, 130.5, 129.2, 128.5, 122.2, 109.4, 64.0, 45.4 ppm. **IR (neat):** ν 3242, 3023, 2958, 1645, 1522, 1423, 1375, 1312, 1211, 1008, 922, 862, 816, 747, 694, 615, 535, 475, 411 cm^{-1} . **HRMS (ESI-TOF) m/z $[M+H]^+$:** Calcd for $\text{C}_{13}\text{H}_{15}\text{N}_2\text{O}_2$ 231.1134; found 231.1133.



Chemical Formula: $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_2$

- ***N'*-benzyl-*N'*-methylfuran-2-carbohydrazide (4h)**

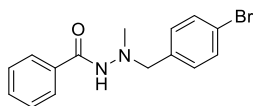
According to general procedure C, alkylation of furan-2-carbohydrazide (0.5 mmol, 63 mg) with benzyl alcohol (5 equiv., 0.265 mL) afforded the pure product as a white solid (79 mg, 69 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by $^1\text{H-NMR}$ spectroscopy in the crude product with 20 % of dimethylated derivative observed. **$^1\text{H-NMR}$ (CDCl_3 , 500 MHz):** δ 7.34-7.30 (m, 5H), 7.27-7.26 (m, 1H), 7.22 (br. s, 1H), 7.09 (d, $J = 3.2$ Hz, 1H), 6.43 (d, $J = 1.3$ Hz, 1H), 4.04 (s, 2H), 2.72 (s, 3H) ppm. **$^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz):** δ 156.8, 147.2, 144.0, 135.6, 129.5, 128.5, 127.8, 114.9, 112.0, 62.9, 44.8 ppm. **IR (neat):** ν 3242, 3021, 2958, 1645, 1521, 1375, 1313, 1201, 1006, 922, 833, 746, 694, 615, 536, 475, 412 cm^{-1} . **HRMS (ESI-TOF) m/z $[M+H]^+$:** Calcd for $\text{C}_{13}\text{H}_{15}\text{N}_2\text{O}_2$ 231.1134; found 231.1138.



Chemical Formula: $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_2$

- ***N'*-(4-methoxybenzyl)-*N'*-methylbenzohydrazide (4i)**

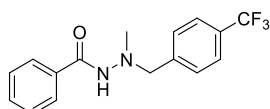
According to general procedure C, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 4-methoxybenzyl alcohol (5 equiv., 345 mg) afforded the pure product as a white solid (109 mg, 81 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by $^1\text{H-NMR}$ spectroscopy in the crude product with 10 % of dimethylated derivative observed. **$^1\text{H-NMR}$ (CDCl_3 , 500 MHz):** δ 7.53 (d, $J = 8.6$ Hz, 2H), 7.39-7.36 (m, 1H), 7.27 (t, $J = 7.6$ Hz, 2H), 7.19 (d, $J = 8.6$ Hz, 2H), 6.98 (br. s, 1H), 6.87 (d, $J = 8.6$ Hz, 2H), 3.95 (s, 2H), 3.70 (s, 3H), 2.68 (s, 3H) ppm. **$^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz):** δ 166.3, 159.2, 133.9, 131.5, 130.8, 128.6, 127.9, 127.0, 113.9, 61.9, 55.3, 44.5 ppm. **IR (neat):** ν 3188, 2991, 2839, 1637, 1561, 1491, 1314, 1257, 1236, 1108, 1035, 908, 694, 529, 441 cm^{-1} . **HRMS (ESI-TOF) m/z $[M+H]^+$:** Calcd for $\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}_2$ 271.1447; found 271.1445.



Chemical Formula: $\text{C}_{15}\text{H}_{15}\text{BrN}_2\text{O}$

- ***N'*-(4-bromobenzyl)-*N'*-methylbenzohydrazide (4j)**

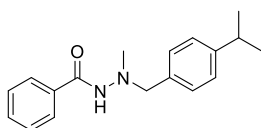
According to general procedure C, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 4-bromobenzyl alcohol (5 equiv., 465 mg) afforded the pure product as a white solid (106 mg, 67 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by ¹H-NMR spectroscopy in the crude product with 19 % of dimethylated derivative observed. **¹H-NMR (CDCl₃, 500 MHz):** δ 7.42 (d, *J* = 7.3 Hz, 2H), 7.33-7.28 (m, 3H), 7.20 (t, *J* = 7.6 Hz, 2H), 7.09 (d, *J* = 7.3 Hz, 2H), 6.83 (br. s, 1H), 3.90 (s, 2H), 2.65 (s, 3H) ppm. **¹³C-NMR (CDCl₃, 125 MHz):** δ 166.5, 135.5, 133.8, 131.8, 131.7, 131.1, 128.7, 127.0, 121.7, 61.8, 44.8 ppm. **IR (neat):** ν 3253, 2969, 1648, 1637, 1464, 1303, 1070, 1012, 866, 804, 723, 690, 655, 544, 485, 412 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₁₅H₁₆BrN₂O 319.0446; found 319.0454.



Chemical Formula: C₁₆H₁₅F₃N₂O

- ***N'*-methyl-*N'*-(4-(trifluoromethyl)benzyl)benzohydrazide (4k)**

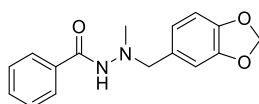
According to general procedure C, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 4-trifluoromethylbenzyl alcohol (5 equiv., 440 mg) afforded the pure product as a white solid (122 mg, 79 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by ¹H-NMR spectroscopy in the crude product with 9 % of dimethylated derivative observed. **¹H-NMR (CDCl₃, 500 MHz):** δ 7.51-7.47 (m, 4H), 7.43-7.41 (m, 2H), 7.39-7.36 (m, 1H), 7.25 (t, *J* = 6.9 Hz, 2H), 7.15 (br. s, 1H), 4.08 (s, 2H), 2.75 (s, 3H) ppm. **¹⁹F-NMR (CDCl₃, 500 MHz):** δ -62.4 ppm. **¹³C-NMR (CDCl₃, 125 MHz):** δ 166.6, 140.9, 136.7, 131.8, 129.8 (q, *J* = 32.1 Hz), 129.4, 128.7, 127.0, 125.4 (q, *J* = 3.4 Hz), 124.2 (d, *J* = 270.2 Hz), 62.0, 45.0 ppm. **IR (neat):** ν 3248, 2988, 2901, 1647, 1638, 1326, 1160, 1066, 872, 692, 656, 422 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₁₆H₁₆N₂OF₃ 309.1215; found 309.1226.



Chemical Formula: C₁₈H₂₂N₂O

- ***N'*-(4-isopropylbenzyl)-*N'*-methylbenzohydrazide (4l)**

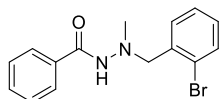
According to general procedure C, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 4-isopropylbenzyl alcohol (5 equiv., 375 mg) afforded the pure product as a white solid (101 mg, 72 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by ¹H-NMR spectroscopy in the crude product with 11 % of dimethylated derivative observed. **¹H-NMR (CDCl₃, 500 MHz):** δ 7.60 (d, *J* = 8.0 Hz, 2H), 7.47-7.44 (m, 1H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 4.08 (s, 2H), 2.90 (sept, *J* = 6.9 Hz, 1H), 2.78 (s, 3H), 1.23 (d, *J* = 6.9 Hz, 6H) ppm. **¹³C-NMR (CDCl₃, 125 MHz):** δ 166.3, 148.4, 134.0, 133.1, 131.5, 129.6, 128.5, 127.0, 126.5, 62.1, 44.4, 33.8, 24.0 ppm. **IR (neat):** ν 3216, 2961, 2867, 1644, 1538, 1304, 1118, 1002, 914, 849, 808, 689, 663, 554, 445 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₁₈H₂₃N₂O 283.1810; found 283.1812.



Chemical Formula: C₁₆H₁₆N₂O₃

- ***N'*-(benzo[*d*][1,3]dioxol-5-ylmethyl)-*N'*-methylbenzohydrazide (4m)**

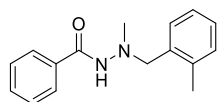
According to general procedure C, alkylation of benzohydrazide (0.5 mmol, 68 mg) with benzo[*d*][1,3]dioxol-5-ylmethanol (5 equiv., 380 mg) afforded the pure product as a white solid (112 mg, 79 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by ¹H-NMR spectroscopy in the crude product with 12 % of dimethylated derivative observed. **¹H-NMR (CDCl₃, 500 MHz):** δ 7.59 (d, *J* = 7.7 Hz, 2H), 7.41 (t, *J* = 7.3 Hz, 1H), 7.32 (t, *J* = 7.7 Hz, 2H), 7.19 (br. d, *J* = 8.8 Hz, 1H), 6.87 (br. s, 1H), 6.75 (d, *J* = 7.7 Hz, 1H), 6.70 (d, *J* = 7.7 Hz, 1H), 5.89 (s, 2H), 3.96 (s, 2H), 2.73 (s, 3H) ppm. **¹³C-NMR (CDCl₃, 125 MHz):** δ 166.3, 147.8, 147.1, 133.9, 131.5, 129.9, 128.6, 127.0, 122.8, 109.9, 108.1, 101.0, 62.2, 44.4 ppm. **IR (neat):** ν 3252, 3064, 2791, 1651, 1551, 1490, 1445, 1307, 1288, 1231, 1097, 1035, 925, 871, 693, 650, 544 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₁₆H₁₇N₂O₃ 285.1239; found 285.1245.



Chemical Formula: C₁₅H₁₅BrN₂O

- ***N'*-(2-bromobenzyl)-*N'*-methylbenzohydrazide (4n)**

According to general procedure C, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 2-bromobenzyl alcohol (5 equiv., 465 mg) afforded the pure product as a white solid (76 mg, 48 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by ¹H-NMR spectroscopy in the crude product with 38 % of dimethylated derivative observed. **¹H-NMR (CDCl₃, 500 MHz):** δ 7.64 (d, *J* = 7.2 Hz, 2H), 7.59-7.55 (m, 2H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.27 (t, *J* = 7.4 Hz, 1H), 7.25 (br. s, 1H), 7.12 (td, *J* = 1.5; 7.6 Hz, 1H), 4.24 (s, 2H), 2.90 (s, 3H) ppm. **¹³C-NMR (CDCl₃, 125 MHz):** δ 166.5, 136.2, 133.8, 132.8, 131.7, 131.5, 129.2, 128.6, 127.6, 127.0, 124.6, 61.7, 45.4 ppm. **IR (neat):** ν 3211, 2967, 1639, 1548, 1407, 1310, 1066, 1026, 929, 761, 693, 452 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₁₅H₁₆BrN₂O 319.0446; found 319.0449.

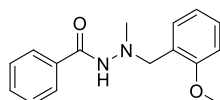


Chemical Formula: C₁₆H₁₈N₂O

- ***N'*-methyl-*N'*-(2-methylbenzyl)benzohydrazide (4o)**

According to general procedure C, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 2-methylbenzyl alcohol (5 equiv., 305 mg) afforded the pure product as a white solid (64 mg, 50 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by ¹H-NMR spectroscopy in the crude product with 35 % of dimethylated derivative observed. **¹H-NMR**

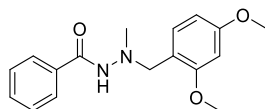
(CDCl₃, 500 MHz): δ 7.59 (d, J = 7.3 Hz, 2H), 7.44 (t, J = 7.4 Hz, 1H), 7.35 (t, J = 7.6 Hz, 2H), 7.29 (d, J = 7.3 Hz, 1H), 7.19-7.11 (m, 3H), 7.08 (br. s, 1H), 4.11 (s, 2H), 2.83 (s, 3H), 2.45 (s, 3H) ppm. ¹³C-NMR (CDCl₃, 125 MHz): δ 166.7, 137.9, 135.0, 134.1, 131.6, 130.5, 130.4, 128.6, 127.8, 127.0, 125.8, 60.4, 224.4, 19.3 ppm. IR (neat): ν 3240, 2966, 1639, 1537, 1467, 1302, 1288, 1075, 911, 711, 697, 629, 448 cm⁻¹. HRMS (ESI-TOF) m/z [M+H]⁺: Calcd for C₁₆H₁₉N₂O 255.1497; found 255.1508.



Chemical Formula: C₁₆H₁₈N₂O₂

- ***N'*-methyl-*N'*-(2-methoxybenzyl)benzohydrazide (4p)**

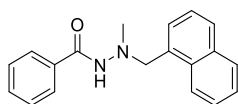
According to general procedure C, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 2-methoxybenzyl alcohol (5 equiv., 345 mg) afforded the pure product as a white solid (76 mg, 56 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by ¹H-NMR spectroscopy in the crude product with 32 % of dimethylated derivative observed. ¹H-NMR (CDCl₃, 500 MHz): δ 7.65 (d, J = 7.3 Hz, 2H), 7.46 (t, J = 7.4 Hz, 1H), 7.42 (br. s, 1H), 7.40-7.35 (m, 3H), 7.31-7.28 (m, 1H), 6.95 (t, J = 7.4 Hz, 1H), 6.89 (d, J = 8.1 Hz, 1H), 4.15 (s, 2H), 3.79 (s, 3H), 2.76 (s, 3H) ppm. ¹³C-NMR (CDCl₃, 125 MHz): δ 165.8, 157.8, 134.1, 132.2, 131.4, 129.3, 128.5, 126.9, 123.8, 120.8, 110.6, 56.5, 55.4, 44.7 ppm. IR (neat): ν 3234, 2986, 1639, 1579, 1495, 1245, 1052, 913, 756, 689, 573, 494 cm⁻¹. HRMS (ESI-TOF) m/z [M+H]⁺: Calcd for C₁₆H₁₉N₂O₂ 271.1447; found 271.1448.



Chemical Formula: C₁₇H₂₀N₂O₃

- ***N'*-(2,4-dimethoxybenzyl)-*N'*-methylbenzohydrazide (4q)**

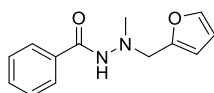
According to general procedure C, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 2,4-dimethoxybenzyl alcohol (5 equiv., 420 mg) afforded the pure product as a white solid (71 mg, 47 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by ¹H-NMR spectroscopy in the crude product with 32 % of dimethylated derivative observed. ¹H-NMR (CDCl₃, 500 MHz): δ 7.62 (d, J = 7.6 Hz, 2H), 7.43 (t, J = 7.3 Hz, 1H), 7.35 (t, J = 7.2 Hz, 2H), 7.24 (s, 1H), 7.20 (d, J = 8.1 Hz, 1H), 6.47-6.44 (m, 2H), 4.04 (s, 2H), 3.78 (s, 3H), 3.73 (s, 3H), 2.70 (s, 3H) ppm. ¹³C-NMR (CDCl₃, 125 MHz): δ 165.8, 160.8, 158.9, 134.2, 133.1, 131.4, 128.5, 127.0, 116.1, 104.4, 98.7, 56.1, 55.5, 55.4, 44.6 ppm. IR (neat): ν 3234, 2986, 1640, 1579, 1495, 1306, 1245, 1066, 924, 756, 689, 573, 494, 467 cm⁻¹. HRMS (ESI-TOF) m/z [M+Na]⁺: Calcd for C₁₇H₂₀N₂O₃Na 323.1372; found 323.1369.



Chemical Formula: C₁₉H₁₈N₂O

- ***N'*-methyl-*N'*-(naphthalen-1-ylmethyl)benzohydrazide (4r)**

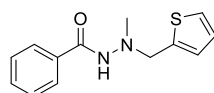
According to general procedure C, alkylation of benzohydrazide (0.5 mmol, 68 mg) with naphthalen-1-ylmethanol (5 equiv., 395 mg) afforded the pure product as a white solid (103 mg, 71 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by ¹H-NMR spectroscopy in the crude product with 18 % of dimethylated derivative observed. **¹H-NMR (CDCl₃, 500 MHz):** δ 8.47 (d, *J* = 8.3 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 7.4 Hz, 3H), 7.52-7.43 (m, 3H), 7.41-7.33 (m, 3H), 7.17 (br. s, 1H), 4.58 (s, 2H), 2.88 (s, 3H) ppm. **¹³C-NMR (CDCl₃, 125 MHz):** δ 166.9, 133.9, 132.6, 132.5, 131.6, 128.7, 128.6, 128.5, 128.3, 127.0, 126.4, 125.9, 125.3, 124.8, 60.2, 44.4 ppm. **IR (neat):** ν 3257, 2988, 1647, 1623, 1394, 1284, 1066, 905, 800, 692, 559, 442, 413 cm⁻¹. **HRMS (ESI-TOF) m/z [M+Na]⁺:** Calcd for C₁₉H₁₈N₂ONa 313.1317; found 313.1313.



Chemical Formula: C₁₃H₁₄N₂O₂

- ***N'*-(furan-2-ylmethyl)-*N'*-methylbenzohydrazide (4s)**

According to general procedure C, alkylation of benzohydrazide (0.5 mmol, 68 mg) with furan-2-ylmethanol (5 equiv., 0.217 mL) afforded the pure product as a light yellow solid (64 mg, 56 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by ¹H-NMR spectroscopy in the crude product with 24 % of dimethylated derivative observed. **¹H-NMR (CDCl₃, 500 MHz):** δ 7.67 (d, *J* = 7.9 Hz, 2H), 7.49-7.46 (m, 1H), 7.42-7.38 (m, 3H), 7.24 (br. s, 1H), 6.35 (br. s, 1H), 6.29 (br. s, 1H), 4.10 (s, 2H), 2.71 (s, 3H) ppm. **¹³C-NMR (CDCl₃, 125 MHz):** δ 166.2, 150.3, 143.0, 133.8, 131.7, 128.7, 127.1, 110.5, 110.3, 54.1, 44.1 ppm. **IR (neat):** ν 3239, 2961, 1643, 1579, 1445, 1293, 1128, 1007, 916, 802, 632, 530, 479, 413 cm⁻¹. **HRMS (ESI-TOF) m/z [M+Na]⁺:** Calcd for C₁₃H₁₄N₂O₂Na 253.0953; found 253.0961.

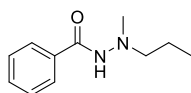


Chemical Formula: C₁₃H₁₄N₂OS

- ***N'*-methyl-*N'*-(thiophen-2-ylmethyl)benzohydrazide (4t)**

According to general procedure C, alkylation of benzohydrazide (0.5 mmol, 68 mg) with thiophen-2-ylmethanol (5 equiv., 0.238 mL) afforded the pure product as a light-yellow solid (78 mg, 63 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by ¹H-NMR spectroscopy in the crude product with 22 % of dimethylated derivative observed. **¹H-NMR**

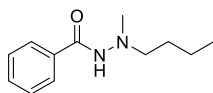
(CDCl₃, 500 MHz): δ 7.65 (d, J = 7.4 Hz, 2H), 7.47 (t, J = 7.4 Hz, 1H), 7.38 (t, J = 7.6 Hz, 2H), 7.29 (br. d, J = 4.4 Hz, 1H), 7.04 (br. s, 1H), 7.01-6.99 (m, 2H), 4.34 (s, 2H), 2.79 (s, 3H) ppm. ¹³C-NMR (CDCl₃, 125 MHz): δ 166.3, 137.2, 133.8, 131.8, 128.7, 128.1, 127.1, 127.1, 126.1, 56.0, 44.0 ppm. IR (neat): ν 3240, 2958, 1645, 1544, 1445, 1293, 1228, 1075, 916, 831, 691, 478, 413 cm⁻¹. HRMS (ESI-TOF) m/z [M+H]⁺: Calcd for C₁₃H₁₅N₂OS 247.0905; found 247.0901.



Chemical Formula: C₁₁H₁₆N₂O

- ***N'*-methyl-*N'*-propylbenzohydrazide (4u)**

According to general procedure C, alkylation of benzohydrazide (0.5 mmol, 68 mg) with *n*-propanol (5 equiv., 0.186 mL) afforded the pure product as a white solid (62 mg, 65 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by ¹H-NMR spectroscopy in the crude product with 28 % of dimethylated derivative observed. ¹H-NMR (CDCl₃, 500 MHz): δ 7.69 (d, J = 7.3 Hz, 2H), 7.43 (t, J = 7.3 Hz, 1H), 7.34 (t, J = 7.4 Hz, 2H), 6.96 (br. s, 1H), 2.69 (t, J = 7.5 Hz, 2H), 2.67 (s, 3H), 1.51 (sext, J = 7.5 Hz, 2H), 0.88 (t, J = 7.4 Hz, 3H) ppm. ¹³C-NMR (CDCl₃, 125 MHz): δ 166.2, 134.0, 131.5, 128.5, 127.1, 61.6, 46.2, 20.5, 11.6 ppm. IR (neat): ν 2971, 2917, 2901, 1691, 1610, 1450, 1425, 1380, 1251, 1066, 1057, 984, 925, 849, 725, 596, 515, 455 cm⁻¹. HRMS (ESI-TOF) m/z [M+H]⁺: Calcd for C₁₁H₁₇N₂O 194.1341; found 194.1345.



Chemical Formula: C₁₂H₁₈N₂O

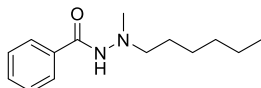
- ***N'*-butyl-*N'*-methylbenzohydrazide (4v)**

According to general procedure C, alkylation of benzohydrazide (0.5 mmol, 68 mg) with *n*-butanol (5 equiv., 0.228 mL) afforded the pure product as a white solid (61 mg, 59 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by ¹H-NMR spectroscopy in the crude product with 37 % of dimethylated derivative observed. ¹H-NMR (CDCl₃, 500 MHz): δ 7.71 (d, J = 7.3 Hz, 2H), 7.45 (t, J = 7.3 Hz, 1H), 7.37 (t, J = 7.4 Hz, 2H), 6.85 (br. s, 1H), 2.74 (t, J = 7.5 Hz, 2H), 2.69 (s, 3H), 1.56-1.50 (m, 2H), 1.31 (sext, J = 7.5 Hz, 2H), 0.87 (t, J = 7.5 Hz, 3H) ppm. ¹³C-NMR (CDCl₃, 125 MHz): δ 166.2, 134.0, 131.6, 128.6, 127.1, 59.6, 46.3, 29.4, 20.4, 14.1 ppm. IR (neat): ν 3236, 2901, 1649, 1563, 1452, 1381, 1250, 1028, 923, 722, 692, 613 cm⁻¹. HRMS (ESI-TOF) m/z [M+H]⁺: Calcd for C₁₂H₁₉N₂O 207.1497; found 207.1505.

- **Scale up of the reaction to 5 mmol starting material**

In a 30 mL flame-dried Schlenk tube equipped with a stirring bar, benzohydrazide (5 mmol, 680 mg), *n*-butanol (5 equiv., 2.28 mL), ruthenium complex **Ru1** (25.1 mg, 1 mol %), Me₃NO (11.1 mg, 2 mol %), ^tBuONa (480 mg, 1 equiv.) and methanol (5 mL, 1 M) were poured in under an argon atmosphere. The mixture was rapidly stirred at room temperature for 2 min and then placed into a pre-heated oil bath at 110 °C and stirred over 24 hours. The mixture was cooled-down to room temperature, filtrated over

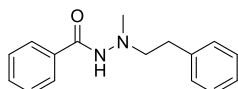
celite with diethyl ether and concentrated under reduced pressure. The conversion was determined by $^1\text{H-NMR}$ spectroscopy and the residue was purified by flash chromatography on silica gel using pentane-ethyl acetate (1:1) as eluent to afford the pure product as a white solid (548 mg, 57 %). $^1\text{H-NMR}$ data were comparable with the previous NMR data.



Chemical Formula: $\text{C}_{14}\text{H}_{22}\text{N}_2\text{O}$

- ***N'*-hexyl-*N'*-methylbenzohydrazide (4w)**

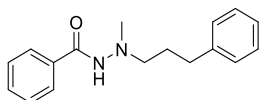
According to general procedure C, alkylation of benzohydrazide (0.5 mmol, 68 mg) with *n*-hexanol (5 equiv., 0.312 mL) afforded the pure product as a white solid (70 mg, 60 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by $^1\text{H-NMR}$ spectroscopy in the crude product with 30 % of dimethylated derivative observed. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ 7.71 (d, $J = 7.2$ Hz, 2H), 7.48-7.46 (m, 1H), 7.37 (t, $J = 7.4$ Hz, 2H), 6.83 (br. s, 1H), 2.74 (t, $J = 7.7$ Hz, 2H), 2.69 (s, 3H), 1.56-1.51 (m, 2H), 1.33-1.23 (m, 6H), 0.83 (t, $J = 6.9$ Hz, 3H) ppm. $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): δ 166.2, 134.0, 131.61, 128.7, 127.1, 60.0, 46.3, 31.8, 27.3, 27.0, 22.7, 14.1 ppm. IR (neat): ν 3237, 2988, 2971, 1649, 1548, 1394, 1230, 1076, 921, 694, 660, 550 cm^{-1} . HRMS (ESI-TOF) m/z $[\text{M}+\text{H}]^+$: Calcd for $\text{C}_{14}\text{H}_{23}\text{N}_2\text{O}$ 235.1810; found 235.1810.



Chemical Formula: $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}$

- ***N'*-methyl-*N'*-phenethylbenzohydrazide (4x)**

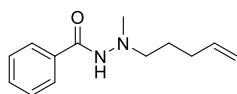
According to general procedure C, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 2-phenylethan-1-ol (5 equiv., 0.299 mL) afforded the pure product as a white solid (60 mg, 47 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by $^1\text{H-NMR}$ spectroscopy in the crude product with 44 % of dimethylated derivative observed. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ 7.67 (d, $J = 7.2$ Hz, 2H), 7.49 (t, $J = 7.3$ Hz, 1H), 7.40 (t, $J = 7.5$ Hz, 2H), 7.30-7.27 (m, 2H), 7.23-7.18 (m, 3H), 6.93 (br. s, 1H), 3.14-3.10 (m, 2H), 2.94-2.91 (m, 2H), 2.79 (s, 3H) ppm. $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): δ 166.3, 139.8, 133.8, 131.7, 128.7, 128.6, 128.6, 127.1, 126.3, 60.9, 46.2, 228 34.0 ppm. IR (neat): ν 3215, 2988, 1639, 1557, 1452, 1394, 1230, 1075, 786, 694, 503 cm^{-1} . HRMS (ESI-TOF) m/z $[\text{M}+\text{H}]^+$: Calcd for $\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}$ 255.1497; found 255.1504.



Chemical Formula: $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}$

- ***N'*-methyl-*N'*-(3-phenylpropyl)benzohydrazide (4y)**

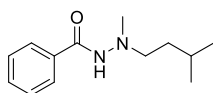
According to general procedure C, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 3-phenylpropan-1-ol (5 equiv., 0.338 mL) afforded the pure product as a white solid (64 mg, 48 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by ¹H-NMR spectroscopy in the crude product with 41 % of dimethylated derivative observed. **¹H-NMR (CDCl₃, 500 MHz):** δ 7.71 (d, *J* = 7.2 Hz, 2H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.26-7.23 (m, 2H), 7.17-7.15 (m, 3H), 7.02 (br. s, 1H), 2.78 (t, *J* = 7.3 Hz, 2H), 2.70-2.67 (m, 5H), 1.85 (quint, *J* = 7.4 Hz, 2H) ppm. **¹³C-NMR (CDCl₃, 125 MHz):** δ 166.3, 141.9, 133.9, 131.6, 128.6, 128.5, 128.4, 127.1, 125.8, 59.0, 46.3, 33.3, 29.0 ppm. **IR (neat):** ν 3234, 2972, 1646, 1545, 1448, 1394, 1076, 912, 804, 717, 657, 528, 408 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₁₇H₂₁N₂O 269.1654; found 269.1660.



Chemical Formula: C₁₃H₁₈N₂O

- ***N'*-methyl-*N'*-(pent-4-en-1-yl)benzohydrazide (4z)**

According to general procedure C, alkylation of benzohydrazide (0.5 mmol, 68 mg) with pent-4-en-1-ol (5 equiv., 0.256 mL) afforded the pure product as a white solid (55 mg, 51 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by ¹H-NMR spectroscopy in the crude product with 40 % of dimethylated derivative observed. **¹H-NMR (CDCl₃, 500 MHz):** δ 7.71 (d, *J* = 7.2 Hz, 2H), 7.46 (t, *J* = 7.3 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 2H), 6.86 (br. s, 1H), 5.73 (ddt, *J* = 6.7; 10.2; 17.0 Hz, 1H), 5.00 (dd, *J* = 1.5 Hz; 17.0 Hz, 1H), 4.92 (dd, *J* = 1.5; 10.2 Hz, 1H), 2.79-2.76 (m, 2H), 2.70 (s, 3H), 2.08 (t, *J* = 7.2 Hz, 2H), 1.62 (quint, *J* = 7.2 Hz, 2H) ppm. **¹³C-NMR (CDCl₃, 125 MHz):** δ 166.3, 138.3, 134.0, 131.6, 128.7, 127.1, 115.0, 59.2, 46.3, 31.3, 26.5 ppm. **IR (neat):** ν 3242, 2971, 2902, 1648, 1596, 1463, 1422, 1346, 1249, 1063, 983, 926, 724, 583, 462 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₁₃H₁₉N₂O 219.1497; found 219.1503.

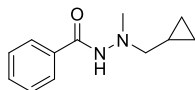


Chemical Formula: C₁₃H₂₀N₂O

- ***N'*-isopentyl-*N'*-methylbenzohydrazide (4aa)**

According to general procedure C, alkylation of benzohydrazide (0.5 mmol, 68 mg) 3-methylbutan-1-ol (5 equiv., 0.271 mL) afforded the pure product as a white solid (57 mg, 52 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by ¹H-NMR spectroscopy in the crude product with 40 % of dimethylated derivative observed. **¹H-NMR (CDCl₃, 500 MHz):** δ 7.70 (d, *J* = 7.2 Hz, 2H), 7.43 (t, *J* = 7.3 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 2H), 6.97 (br. s, 1H), 2.77-2.74 (m, 2H), 2.67 (s, 3H), 1.56 (sept, *J* = 6.7 Hz, 1H), 1.44-1.40 (m, 2H), 0.84 (d, *J* = 6.7 Hz, 2H) ppm. **¹³C-**

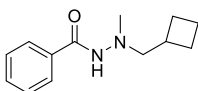
NMR (CDCl₃, 125 MHz): δ 166.2, 134.0, 131.5, 128.6, 127.1, 58.1, 46.3, 36.1, 26.2, 22.7 ppm. **IR (neat):** ν 3242, 2988, 2901, 1647, 1451, 1394, 1230, 1076, 897, 695, 432 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₁₃H₂₁N₂O 221.1654; found 221.1660.



Chemical Formula: C₁₂H₁₆N₂O

- ***N'*-(cyclopropylmethyl)-*N'*-methylbenzohydrazide (4ab)**

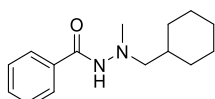
According to general procedure C, alkylation of benzohydrazide (0.5 mmol, 68 mg) with cyclopropylmethanol (5 equiv., 0.202 mL) afforded the pure product as a white solid (65 mg, 64 %) by silica flash column chromatography (pentane/ethyl acetate 2:8). The conversion was determined by ¹H-NMR spectroscopy in the crude product with 28 % of dimethylated derivative observed. **¹H-NMR (CDCl₃, 500 MHz):** δ 7.71 (d, *J* = 7.2 Hz, 2H), 7.46 (t, *J* = 7.3 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.05 (br. s, 1H), 2.75 (s, 3H), 2.71 (d, *J* = 6.7 Hz, 2H), 1.02-0.97 (m, 1H), 0.53-0.49 (m, 2H), 0.16-0.13 (m, 2H) ppm. **¹³C-NMR (CDCl₃, 125 MHz):** δ 166.2, 134.1, 131.6, 128.7, 127.1, 64.0, 45.5, 8.1, 3.5 ppm. **IR (neat):** ν 2988, 2901, 1629, 1382, 1075, 891, 672, 432 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₁₂H₁₇N₂O 205.1341; found 205.1342.



Chemical Formula: C₁₃H₁₈N₂O

- ***N'*-(cyclobutylmethyl)-*N'*-methylbenzohydrazide (4ac)**

According to general procedure C, alkylation of benzohydrazide (0.5 mmol, 68 mg) with cyclobutylmethanol (5 equiv., 0.241 mL) afforded the pure product as a white solid (66 mg, 61 %) by silica flash column chromatography (pentane/ethyl acetate 4:6). The conversion was determined by ¹H-NMR spectroscopy in the crude product with 34 % of dimethylated derivative observed. **¹H-NMR (CDCl₃, 500 MHz):** δ 7.69 (d, *J* = 7.2 Hz, 2H), 7.45 (t, *J* = 7.3 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 2H), 6.86 (br. s, 1H), 2.82 (d, *J* = 7.0 Hz, 2H), 2.68 (s, 3H), 2.62-2.56 (m, 1H), 2.08-2.02 (m, 2H), 1.92-1.83 (m, 1H), 1.81-1.68 (m, 3H) ppm. **¹³C-NMR (CDCl₃, 125 MHz):** δ 166.1, 134.0, 131.6, 128.7, 127.1, 65.7, 46.3, 33.9, 27.5, 19.0 ppm. **IR (neat):** ν 3246, 2971, 1648, 1545, 1379, 1249, 1076, 913, 695, 655, 404 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₁₃H₁₉N₂O 219.1497; found 219.1501.

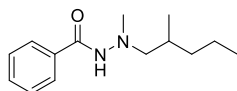


Chemical Formula: C₁₅H₂₂N₂O

- ***N'*-(cyclohexylmethyl)-*N'*-methylbenzohydrazide (4ad)**

According to general procedure C, alkylation of benzohydrazide (0.5 mmol, 68 mg) with cyclohexylmethanol (5 equiv., 0.320 mL) afforded the pure product as a white solid (50 mg, 41 %) by

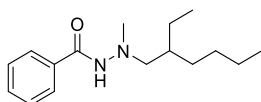
silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by $^1\text{H-NMR}$ spectroscopy in the crude product with 53 % of dimethylated derivative observed. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ 7.70 (d, $J = 7.2$ Hz, 2H), 7.45 (t, $J = 7.3$ Hz, 1H), 7.37 (t, $J = 7.4$ Hz, 2H), 6.87 (br. s, 1H), 2.68 (s, 3H), 2.60 (d, $J = 7.1$ Hz, 2H), 1.86-1.84 (m, 2H), 1.68-1.66 (m, 2H), 1.63-1.61 (m, 1H), 1.52-1.44 (m, 1H), 1.23-1.09 (m, 3H), 0.95-0.88 (m, 2H) ppm. $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): δ 166.1, 134.1, 131.6, 128.6, 127.1, 66.6, 46.8, 36.1, 31.6, 26.7, 26.1 ppm. IR (neat): ν 3243, 2972, 1649, 1532, 1386, 1223, 1084, 907, 696, 652, 413 cm^{-1} . HRMS (ESI-TOF) m/z $[\text{M}+\text{H}]^+$: Calcd for $\text{C}_{15}\text{H}_{23}\text{N}_2\text{O}$ 247.1810; found 247.1816.



Chemical Formula: $\text{C}_{14}\text{H}_{22}\text{N}_2\text{O}$

- ***N'*-methyl-*N'*-(2-methylpentyl)benzohydrazide (4ae)**

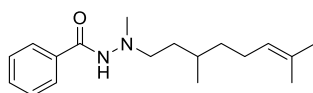
According to general procedure C, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 2-methylpentan-1-ol (5 equiv., 0.309 mL) afforded the pure product as a white solid (46 mg, 39 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by $^1\text{H-NMR}$ spectroscopy in the crude product with 47 % of dimethylated derivative observed. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ 7.70 (d, $J = 7.3$ Hz, 2H), 7.46 (t, $J = 7.3$ Hz, 1H), 7.38 (t, $J = 7.5$ Hz, 2H), 6.81 (br. s, 1H), 2.71 (s, 3H), 2.70-2.67 (m, 1H), 2.58-2.53 (m, 1H), 1.67-1.63 (m, 1H), 1.48-1.33 (m, 2H), 1.28-1.21 (m, 1H), 1.13-1.09 (m, 1H), 0.96 (d, $J = 6.6$ Hz, 3H), 0.85 (t, $J = 7.2$ Hz, 3H) ppm. $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): δ 166.1, 134.2, 131.6, 128.7, 127.1, 66.7, 46.7, 37.2, 31.3, 20.1, 18.3, 14.4 ppm. IR (neat): ν 3243, 2988, 1647, 1394, 1250, 1057, 897, 695, 432 cm^{-1} . HRMS (ESI-TOF) m/z $[\text{M}+\text{H}]^+$: Calcd for $\text{C}_{14}\text{H}_{23}\text{N}_2\text{O}$ 235.1810; found 235.1815.



Chemical Formula: $\text{C}_{16}\text{H}_{26}\text{N}_2\text{O}$

- ***N'*-(2-ethylhexyl)-*N'*-methylbenzohydrazide (4af)**

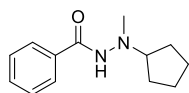
According to general procedure C, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 2-ethylhexan-1-ol (5 equiv., 0.392 mL) afforded the pure product as a white solid (46 mg, 35 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by $^1\text{H-NMR}$ spectroscopy in the crude product with 41 % of dimethylated derivative observed. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ 7.69 (d, $J = 7.3$ Hz, 2H), 7.46 (t, $J = 7.3$ Hz, 1H), 7.39 (t, $J = 7.5$ Hz, 2H), 6.77 (br. s, 1H), 2.72 (s, 3H), 2.67 (d, $J = 6.5$ Hz, 2H), 1.50-1.45 (m, 2H), 1.41-1.35 (m, 2H), 1.33-1.21 (m, 5H), 0.88-0.84 (m, 6H) ppm. $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): δ 166.1, 134.2, 131.6, 128.7, 127.0, 63.8, 46.6, 37.4, 31.1, 29.0, 24.3, 23.2, 14.3, 10.7 ppm. IR (neat): ν 3242, 2972, 1648, 1374, 1239, 1062, 912, 694, 412 cm^{-1} . HRMS (ESI-TOF) m/z $[\text{M}+\text{H}]^+$: Calcd for $\text{C}_{16}\text{H}_{27}\text{N}_2\text{O}$ 263.2123; found 263.2126.



Chemical Formula: C₁₈H₂₈N₂O

- ***N'*-(3,7-dimethyloct-6-en-1-yl)-*N'*-methylbenzohydrazide (4ag)**

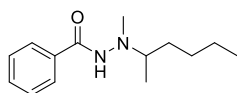
According to general procedure C, alkylation of benzohydrazide (0.5 mmol, 68 mg) with citronellol (5 equiv., 0.457 mL) afforded the pure product as a light yellow solid (56 mg, 39 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by ¹H-NMR spectroscopy in the crude product with 35 % of dimethylated derivative observed. **¹H-NMR (CDCl₃, 500 MHz):** δ 7.70 (d, *J* = 7.3 Hz, 2H), 7.45 (t, *J* = 7.3 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 2H), 6.85 (br. s, 1H), 5.03 (app t, *J* = 7.1 Hz, 1H), 2.82-2.73 (m, 2H), 2.69 (s, 3H), 1.99-1.88 (m, 2H), 1.64 (s, 3H), 1.62-1.57 (m, 1H), 1.55 (s, 3H), 1.50-1.45 (m, 1H), 1.41-1.26 (m, 3H), 1.17-1.10 (m, 1H), 0.86 (d, *J* = 6.6 Hz, 3H) ppm. **¹³C-NMR (CDCl₃, 125 MHz):** δ 166.2, 134.0, 131.6, 131.3, 128.6, 127.1, 124.8, 58.0, 46.3, 37.2, 34.2, 30.7, 25.8, 25.5, 19.7, 17.7 ppm. **IR (neat):** ν 3243, 2987, 2901, 1648, 1592, 1496, 1421, 1392, 1076, 982, 695, 581, 423 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₁₈H₂₉N₂O 289.2286; found 289.2282.



Chemical Formula: C₁₃H₁₈N₂O

- ***N'*-cyclopentyl-*N'*-methylbenzohydrazide (4ah)**

According to general procedure D, alkylation of benzohydrazide (0.5 mmol, 68 mg) with cyclopentanol (5 equiv., 0.218 mL) afforded the pure product as a light yellow solid (49 mg, 45 %) by silica flash column chromatography (pentane/ethyl acetate 2:8). The conversion was determined by ¹H-NMR spectroscopy in the crude product with 51 % of dimethylated derivative observed. **¹H-NMR (CDCl₃, 500 MHz):** δ 7.69 (d, *J* = 7.2 Hz, 2H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.35 (t, *J* = 7.4 Hz, 2H), 6.97 (br. s, 1H), 3.12 (quint, *J* = 7.4 Hz, 1H), 2.65 (s, 3H), 1.80-1.76 (m, 2H), 1.72-1.66 (m, 2H), 1.62-1.51 (m, 4H) ppm. **¹³C-NMR (CDCl₃, 125 MHz):** δ 166.1, 134.1, 131.5, 128.6, 127.1, 69.1, 45.0, 30.3, 24.5 ppm. **IR (neat):** ν 3218, 2938, 1645, 1549, 1446, 1304, 1289, 933, 895, 723, 695, 609 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₁₃H₁₉N₂O 219.1497; found 219.1504.

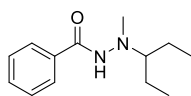


Chemical Formula: C₁₄H₂₂N₂O

- ***N'*-(hexan-2-yl)-*N'*-methylbenzohydrazide (4ai)**

According to general procedure D, alkylation of benzohydrazide (0.5 mmol, 68 mg) with hexan-2-ol (5 equiv., 0.315 mL) afforded the pure product as a light yellow solid (57 mg, 49 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by ¹H-NMR spectroscopy

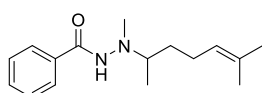
in the crude product with 32 % of dimethylated derivative observed. **¹H-NMR (CDCl₃, 500 MHz):** δ 7.71 (d, *J* = 7.2 Hz, 2H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.4 Hz, 2H), 6.70 (br. s, 1H), 2.92-2.87 (m, 1H), 2.68 (s, 3H), 1.68-1.64 (m, 2H), 1.40-1.25 (m, 4H), 1.10 (d, *J* = 6.5 Hz, 3H), 0.88 (t, *J* = 7.0 Hz, 3H) ppm. **¹³C-NMR (CDCl₃, 125 MHz):** δ 166.4, 134.3, 131.6, 128.8, 127.1, 61.3, 42.8, 33.0, 28.7, 23.0, 14.4, 14.2 ppm. **IR (neat):** ν 3248, 1649, 1541, 1446, 1292, 1162, 1072, 969, 909, 854, 749, 691, 664, 527 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₁₄H₂₃N₂O 235.1810; found 235.1813.



Chemical Formula: C₁₃H₂₀N₂O

- ***N'*-methyl-*N'*-(pentan-3-yl)benzohydrazide (4aj)**

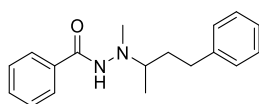
According to general procedure D, alkylation of benzohydrazide (0.5 mmol, 68 mg) with pentan-3-ol (5 equiv, 0.269 mL) afforded the pure product as a light yellow solid (46 mg, 42 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by ¹H-NMR spectroscopy in the crude product with 48 % of dimethylated derivative observed. **¹H-NMR (CDCl₃, 500 MHz):** δ 7.71 (d, *J* = 7.3 Hz, 2H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.40 (t, *J* = 7.4 Hz, 2H), 6.76 (br. s, 1H), 2.70 (s, 3H), 2.61-2.56 (m, 1H), 1.63-1.55 (m, 2H), 1.50-1.42 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 6H) ppm. **¹³C-NMR (CDCl₃, 125 MHz):** δ 166.2, 134.4, 131.6, 128.7, 127.1, 68.7, 42.8, 22.3, 11.1 ppm. **IR (neat):** ν 3249, 1649, 1536, 1435, 1362, 1253, 1086, 963, 914, 856, 763, 684, 612, 485 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₁₃H₂₁N₂O 221.1654; found 221.1661.



Chemical Formula: C₁₆H₂₄N₂O

- ***N'*-methyl-*N'*-(6-methylhept-5-en-2-yl)benzohydrazide (4ak)**

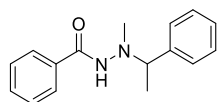
According to general procedure D, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 6-methylhept-5-en-2-ol (5 equiv., 320 mg) afforded the pure product as a white solid (61 mg, 47 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by ¹H-NMR spectroscopy in the crude product with 44 % of dimethylated derivative observed. **¹H-NMR (CDCl₃, 500 MHz):** δ 7.72 (d, *J* = 7.3 Hz, 2H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.4 Hz, 2H), 6.71 (br. s, 1H), 5.08 (t, *J* = 7.1 Hz, 1H), 2.93-2.87 (m, 1H), 2.68 (s, 3H), 2.16-2.02 (m, 2H), 1.72-1.68 (m, 1H), 1.67 (s, 3H), 1.60 (s, 3H), 1.38-1.30 (m, 1H), 1.11 (d, *J* = 6.5 Hz, 3H) ppm. **¹³C-NMR (CDCl₃, 125 MHz):** δ 166.4, 134.3, 132.1, 131.7, 128.8, 127.1, 124.2, 60.8, 42.9, 33.4, 25.8, 25.0, 17.8, 14.3 ppm. **IR (neat):** ν 3242, 2971, 2901, 1649, 1583, 1461, 1436, 1362, 1248, 1074, 965, 712, 583, 462 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₁₆H₂₅N₂O 261.1657; found 261.1654.



Chemical Formula: C₁₈H₂₂N₂O

- ***N'*-methyl-*N'*-(4-phenylbutan-2-yl)benzohydrazide (4al)**

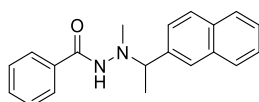
According to general procedure D, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 4-phenylbutan-2-ol (5 equiv., 375 mg) afforded the pure product as a light yellow solid (48 mg, 34 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by ¹H-NMR spectroscopy in the crude product with 55 % of dimethylated derivative observed. **¹H-NMR (CDCl₃, 500 MHz):** δ 7.71 (d, *J* = 7.2 Hz, 2H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.4 Hz, 2H), 7.28-7.20 (m, 4H), 7.15 (t, *J* = 7.2 Hz, 1H), 6.71 (br. s, 1H), 2.90 (quint, *J* = 6.4 Hz, 1H), 2.82-2.72 (m, 2H), 2.68 (s, 3H), 1.99-1.92 (m, 1H), 1.67-1.60 (m, 1H), 1.15 (d, *J* = 6.4 Hz, 3H) ppm. **¹³C-NMR (CDCl₃, 125 MHz):** δ 166.4, 142.4, 134.2, 131.7, 128.8, 128.6, 128.5, 127.1, 125.9, 60.6, 42.9, 35.6, 32.6, 14.0 ppm. **IR (neat):** ν 3242, 2971, 2903, 1649, 1582, 1467, 1418, 1348, 1263, 1192, 912, 853, 644, 416 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₁₈H₂₃N₂O 283.1341; found 283.1343.



Chemical Formula: C₁₆H₁₈N₂O

- ***N'*-methyl-*N'*-(1-phenylethyl)benzohydrazide (4am)**

According to general procedure D, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 1-phenylethan-1-ol (5 equiv., 0.300 mL) afforded the pure product as a white solid (55 mg, 43 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by ¹H-NMR spectroscopy in the crude product with 49 % of dimethylated derivative observed. **¹H-NMR (CDCl₃, 500 MHz):** δ 7.61-7.59 (m, 2H), 7.48-7.46 (m, 1H), 7.39-7.36 (m, 6H), 7.31-7.29 (m, 1H), 6.75 (br. s, 1H), 4.11 (q, *J* = 6.8 Hz, 1H), 2.65 (s, 3H), 1.49 (d, *J* = 6.8 Hz, 1H) ppm. **¹³C-NMR (CDCl₃, 125 MHz):** δ 166.5, 140.5, 134.1, 131.6, 128.7, 128.7, 128.0, 127.9, 127.0, 65.6, 43.3, 20.1 ppm. **IR (neat):** ν 3236, 3057, 2926, 1650, 1529, 1371, 1284, 1116, 862, 746, 692, 515, 467 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₁₆H₁₉N₂O 255.1497; found 255.1503.

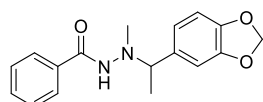


Chemical Formula: C₂₀H₂₀N₂O

- ***N'*-methyl-*N'*-(1-(naphthalen-2-yl)ethyl)benzohydrazide (4an)**

According to general procedure D, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 1-(naphthalen-2-yl)ethan-1-ol (5 equiv., 430 mg) afforded the pure product as a white solid (65 mg, 43 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by ¹H-NMR spectroscopy in the crude product with 51 % of dimethylated derivative observed. **¹H-NMR (CDCl₃,**

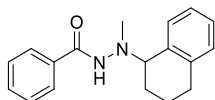
500 MHz): δ 7.87-7.80 (m, 4H), 7.63-7.61 (m, 2H), 7.56 (dd, $J = 1.5; 8.4$ Hz, 1H), 7.51-7.44 (m, 3H), 7.35 (t, $J = 7.5$ Hz, 2H), 6.86 (br. s, 1H), 4.30 (q, $J = 6.7$ Hz, 1H), 2.70 (s, 3H), 1.57 (d, $J = 6.7$ Hz, 1H) ppm. **$^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz):** δ 166.5, 138.5, 134.0, 133.4, 133.2, 131.6, 128.7, 128.4, 128.0, 127.8, 127.0, 126.8, 126.3, 126.0, 125.9, 65.8, 43.4, 20.3 ppm. **IR (neat):** ν 3236, 2959, 1651, 1532, 1287, 1066, 900, 862, 748, 691, 482 cm^{-1} . **HRMS (ESI-TOF) m/z $[\text{M}+\text{Na}]^+$:** Calcd for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{ONa}$ 327.1473; found 327.1477.



Chemical Formula: $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_3$

- ***N'*-(1-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-*N'*-methylbenzohydrazide (4a0)**

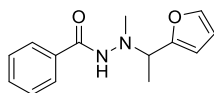
According to general procedure D, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 1-(benzo[*d*][1,3]dioxol-5-yl)ethan-1-ol (5 equiv., 415 mg) afforded the pure product as a white solid (72 mg, 48 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by $^1\text{H-NMR}$ spectroscopy in the crude product with 49 % of dimethylated derivative observed. **$^1\text{H-NMR}$ (CDCl_3 , 500 MHz):** δ 7.58-7.56 (m, 2H), 7.43-7.40 (m, 1H), 7.35-7.32 (m, 2H), 6.82 (br. s, 1H), 6.74-6.69 (m, 3H), 5.89-5.88 (m, 2H), 3.98 (q, $J = 6.7$ Hz, 1H), 2.57 (s, 3H), 1.37 (d, $J = 6.7$ Hz, 1H) ppm. **$^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz):** δ 166.4, 148.0, 147.2, 134.6, 134.1, 131.7, 128.8, 127.0, 121.3, 108.2, 108.1, 101.2, 65.2, 43.2, 20.3 ppm. **IR (neat):** ν 3233, 2972, 1652, 1580, 1308, 1097, 900, 862, 748, 679, 478 cm^{-1} . **HRMS (ESI-TOF) m/z $[\text{M}+\text{Na}]^+$:** Calcd for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_3\text{Na}$ 321.1215; found 321.1221.



Chemical Formula: $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}$

- ***N'*-methyl-*N'*-(1,2,3,4-tetrahydronaphthalen-1-yl)benzohydrazide (4ap)**

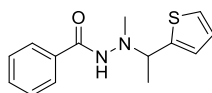
According to general procedure D, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 1,2,3,4-tetrahydronaphthalen-1-ol (5 equiv., 368 mg) afforded the pure product as a light yellow solid (53 mg, 38 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by $^1\text{H-NMR}$ spectroscopy in the crude product with 48 % of dimethylated derivative observed. **$^1\text{H-NMR}$ (CDCl_3 , 500 MHz):** δ 7.66-7.65 (m, 1H), 7.59 (d, $J = 7.3$ Hz, 2H), 7.48-7.45 (m, 1H), 7.36 (t, $J = 7.4$ Hz, 2H), 7.18-7.16 (m, 2H), 7.11-7.09 (m, 1H), 6.89 (br. s, 1H), 4.22 (t, $J = 6.1$ Hz, 1H), 2.88-2.84 (m, 1H), 2.74 (s, 3H), 2.13-2.09 (m, 1H), 2.06-2.00 (m, 1H), 1.98-1.91 (m, 1H), 1.76-1.69 (m, 2H) ppm. **$^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz):** δ 166.3, 138.4, 135.5, 134.3, 131.6, 129.7, 129.1, 128.7, 127.4, 127.1, 125.8, 63.6, 42.1, 29.3, 24.0, 20.4 ppm. **IR (neat):** ν 3249, 2972, 1648, 1543, 1447, 1346, 1182, 1074, 976, 919, 862, 775, 684, 643, 532 cm^{-1} . **HRMS (ESI-TOF) m/z $[\text{M}+\text{Na}]^+$:** Calcd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{ONa}$ 303.1473; found 303.1478.



Chemical Formula: C₁₄H₁₆N₂O₂

- ***N'*-(1-(furan-2-yl)ethyl)-*N'*-methylbenzohydrazide (4aq)**

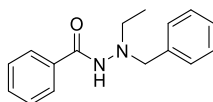
According to general procedure D, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 1-(furan-2-yl)ethan-1-ol (5 equiv., 280 mg) afforded the pure product as a light yellow solid (50 mg, 41 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by ¹H-NMR spectroscopy in the crude product with 52 % of dimethylated derivative observed. **¹H-NMR (CDCl₃, 500 MHz):** δ 7.72 (d, *J* = 7.3 Hz, 2H), 7.52-7.41 (m, 4H), 7.00 (br. s, 1H), 6.38 (dd, *J* = 1.9; 236 3.2 Hz, 1H), 6.27 (d, *J* = 3.2 Hz, 1H), 4.17 (q, *J* = 7.0 Hz, 1H), 2.57 (s, 3H), 1.50 (d, *J* = 7.0 Hz, 1H) ppm. **¹³C-NMR (CDCl₃, 125 MHz):** δ 166.2, 153.7, 142.6, 134.0, 131.7, 128.7, 127.1, 111.9, 110.3, 108.7, 58.3, 43.0, 17.3 ppm. **IR (neat):** ν 3263, 2977, 1651, 1548, 1307, 1288, 1078, 911, 749, 691, 644, 609, 478, 414 cm⁻¹. **HRMS (ESI-TOF) m/z [M+Na]⁺:** Calcd for C₁₄H₁₆N₂O₂Na 267.1109; found 267.1114.



Chemical Formula: C₁₄H₁₆N₂OS

- ***N'*-methyl-*N'*-(1-(thiophen-2-yl)ethyl)benzohydrazide (4ar)**

According to general procedure D, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 1-(thiophen-2-yl)ethan-1-ol (5 equiv., 320 mg) afforded the pure product as a light yellow solid (51 mg, 39 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). The conversion was determined by ¹H-NMR spectroscopy in the crude product with 53 % of dimethylated derivative observed. **¹H-NMR (CDCl₃, 500 MHz):** δ 7.73 (d, *J* = 7.3 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.4 Hz, 2H), 7.31 (d, *J* = 4.9 Hz, 1H), 7.05 (dd, *J* = 3.4; 4.9 Hz, 1H), 6.99 (d, *J* = 3.1 Hz, 1H), 6.75 (br. s, 1H), 4.45 (q, *J* = 6.9 Hz, 1H), 2.62 (s, 3H), 1.58 (d, *J* = 6.9 Hz, 1H) ppm. **¹³C-NMR (CDCl₃, 125 MHz):** δ 166.4, 141.0, 133.8, 131.8, 128.8, 127.2, 127.1, 126.6, 125.1, 60.5, 42.9, 20.8 ppm. **IR (neat):** ν 3262, 2982, 1650, 1552, 1312, 1293, 1083, 921, 753, 693, 652, 612, 523, 414 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₁₄H₁₆N₂OS 261.1065; found 261.1066.

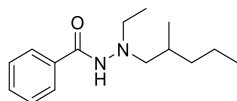


Chemical Formula: C₁₆H₁₈N₂O

- ***N'*-benzyl-*N'*-ethylbenzohydrazide (5a)**

According to general procedure E, alkylation of benzohydrazide (0.5 mmol, 68 mg) with benzyl alcohol (5 equiv., 0.265 mL) afforded the pure product as a light yellow solid (79 mg, 62 %) by silica flash column chromatography (pentane/ethyl acetate 3:1). **¹H-NMR (CDCl₃, 500 MHz):** δ 7.58-7.57 (m, 2H), 7.47-7.44 (m, 1H), 7.38-7.32 (m, 6H), 7.29-7.28 (m, 1H), 6.78 (br. s, 1H), 4.16 (s, 2H), 3.02 (q, *J* = 7.1 Hz, 2H), 1.17 (t, *J* = 7.1 Hz, 3H) ppm. **¹³C-NMR (CDCl₃, 125 MHz):** δ 167.0, 136.4, 134.1, 131.6, 129.7, 128.7, 128.5, 127.7, 127.0, 61.0, 50.7, 12.6 ppm. **IR (neat):** ν 3248, 2972, 1649, 1541, 1446,

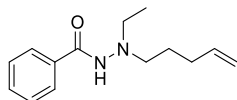
1292, 1162, 1072, 1002, 969, 909, 854, 749, 691, 664, 527 cm^{-1} . **HRMS (ESI-TOF) m/z $[\text{M}+\text{H}]^+$:** Calcd for $\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}$ 255.1497; found 255.1501.



Chemical Formula: $\text{C}_{15}\text{H}_{24}\text{N}_2\text{O}$

- ***N'*-ethyl-*N'*-(2-methylpentyl)benzohydrazide (5b)**

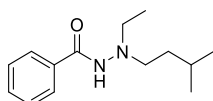
According to general procedure E, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 2-methylpentan-1-ol (5 equiv., 0.309 mL) afforded the pure product as a white solid (65 mg, 52 %) by silica flash column chromatography (pentane/ethyl acetate 3:1). **$^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ** 7.70 (d, $J = 7.3$ Hz, 2H), 7.46 (t, $J = 7.3$ Hz, 1H), 7.38 (t, $J = 7.5$ Hz, 2H), 6.70 (br. s, 1H), 2.88 (q, $J = 7.1$ Hz, 2H), 2.71 (dd, $J = 6.2$; 12.3 Hz, 1H), 2.55 (dd, $J = 8.0$; 12.3 Hz, 1H), 1.69-1.63 (m, 1H), 1.49-1.33 (m, 2H), 1.27-1.22 (m, 1H), 1.11 (t, $J = 7.1$ Hz, 1H), 1.09-1.05 (m, 1H), 0.96 (d, $J = 6.6$ Hz, 3H), 0.85 (t, $J = 7.2$ Hz, 3H) ppm. **$^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): δ** 166.7, 134.4, 131.5, 128.7, 127.0, 64.6, 52.6, 37.3, 31.3, 20.1, 18.4, 14.4, 12.2 ppm. **IR (neat): ν** 3248, 2972, 1648, 1394, 1380, 1296, 1239, 1062, 912, 694, 432 cm^{-1} . **HRMS (ESI-TOF) m/z $[\text{M}+\text{H}]^+$:** Calcd for $\text{C}_{15}\text{H}_{25}\text{N}_2\text{O}$ 249.1967; Found 249.1972.



Chemical Formula: $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}$

- ***N'*-ethyl-*N'*-(pent-4-en-1-yl)benzohydrazide (5c)**

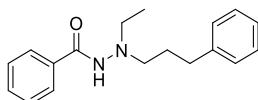
According to general procedure E, alkylation of benzohydrazide (0.5 mmol, 68 mg) with pent-4-en-1-ol (5 equiv., 0.256 mL) afforded the pure product as a light yellow solid (56 mg, 48 %) by silica flash column chromatography (pentane/ethyl acetate 3:1). **$^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ** 7.71 (d, $J = 7.2$ Hz, 2H), 7.47 (t, $J = 7.3$ Hz, 1H), 7.39 (t, $J = 7.4$ Hz, 2H), 6.64 (br. s, 1H), 5.73 (ddt, $J = 6.7$; 10.2; 16.9 Hz, 1H), 5.02-4.97 (m, 1H), 4.94-4.92 (m, 1H), 2.86 (q, $J = 7.1$ Hz, 2H), 2.82-2.79 (m, 2H), 2.12- 2.08 (m, 2H), 1.64 (quint, $J = 7.4$ Hz, 2H), 1.12 (t, $J = 7.1$ Hz, 3H) ppm. **$^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): δ** 167.0, 138.3, 134.1, 131.6, 128.7, 127.1, 115.0, 57.6, 52.6, 31.4, 26.4, 12.1 ppm. **IR (neat): ν** 3248, 2971, 2902, 1648, 1596, 1462, 1422, 1382, 1347, 1223, 1098, 982, 912, 748, 582, 462 cm^{-1} . **HRMS (ESI-TOF) m/z $[\text{M}+\text{H}]^+$:** Calcd for $\text{C}_{14}\text{H}_{21}\text{N}_2\text{O}$ 233.1615; found 233.1617.



Chemical Formula: $\text{C}_{14}\text{H}_{22}\text{N}_2\text{O}$

- ***N'*-isopentyl-*N'*-ethylbenzohydrazide (5d)**

According to general procedure E, alkylation of benzohydrazide (0.5 mmol, 68 mg) 3-methylbutan-1-ol (5 equiv., 0.271 mL) afforded the pure product as a white solid (66 mg, 56 %) by silica flash column chromatography (pentane/ethyl acetate 3:1). **¹H-NMR (CDCl₃, 500 MHz):** δ 7.73 (d, *J* = 7.2 Hz, 2H), 7.48 (t, *J* = 7.3 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 6.51 (br. s, 1H), 2.86 (q, *J* = 7.1 Hz, 2H), 2.84-2.80 (m, 2H), 1.59 (sept, *J* = 6.7 Hz, 1H), 1.50-1.46 (m, 2H), 1.13 (t, *J* = 7.1 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 2H) ppm. **¹³C-NMR (CDCl₃, 125 MHz):** δ 166.9, 134.2, 131.7, 128.8, 127.1, 56.7, 52.7, 36.0, 26.5, 22.8, 12.1 ppm. **IR (neat):** ν 3232, 3024, 2970, 1649, 1535, 1288, 1078, 911, 759, 693, 564, 499 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₁₄H₂₃N₂O 235.1810; found 235.1812.

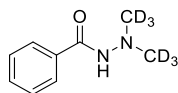


Chemical Formula: C₁₈H₂₂N₂O

- ***N'*-ethyl-*N'*-(3-phenylpropyl)benzohydrazide (5e)**

According to general procedure E, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 3-phenylpropan-1-ol (5 equiv., 0.338 mL) afforded the pure product as a white solid (100 mg, 71 %) by silica flash column chromatography (pentane/ethyl acetate 3:1). **¹H-NMR (CDCl₃, 500 MHz):** δ 7.73 (d, *J* = 7.2 Hz, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.30-7.27 (m, 2H), 7.21-7.18 (m, 3H), 6.57 (br. s, 1H), 2.86 (q, *J* = 7.1 Hz, 2H), 2.85 (t, *J* = 7.7 Hz, 2H), 2.71 (t, *J* = 7.7 Hz, 2H), 1.91 (quint, *J* = 7.7 Hz, 1H), 1.16 (t, *J* = 7.1 Hz, 3H) ppm. **¹³C-NMR (CDCl₃, 125 MHz):** δ 167.0, 142.0, 134.1, 131.7, 128.7, 128.6, 128.4, 127.1, 125.9, 57.6, 52.7, 33.5, 28.9, 12.1 ppm. **IR (neat):** ν 3235, 2964, 1647, 1538, 1373, 1285, 1155, 1081, 904, 805, 692, 654, 571, 494 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** Calcd for C₁₈H₂₃N₂O 283.1341; found 283.1345.

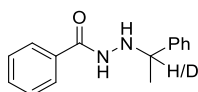
6) Deuterium labelling.



Chemical Formula: C₉H₆D₆N₂O

- ***N'*,*N'*-dimethylbenzohydrazide-*d*₆ (2f-*d*₆)**

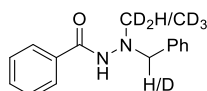
According to a modified general procedure B, alkylation of benzohydrazide (0.5 mmol, 68 mg) with methanol-*d*₄ used as solvent (0.5 M) afforded the pure deuterated product as a white solid (75 mg, 88 %) by silica flash column chromatography (pure ethyl acetate). **¹H NMR (500 MHz, CDCl₃):** δ 8.05 (br. s, 1H), 7.76-7.74 (m, 2H), 7.52-7.49 (m, 1H), 7.41 (t, *J* = 7.5 Hz, 2H) ppm.



Chemical Formula: C₁₅H₁₆DN₂O

- ***N'*-(1-phenylethyl)benzohydrazide-*d*₁ (3g-*d*₁)**

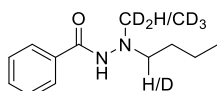
According to general procedure B, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 1-phenylethan-1-*d*₁-ol (5 equiv., 308 mg) afforded the pure deuterated product as a white solid (82 mg, 68 %) by silica flash column chromatography (pentane/ethyl acetate 3:1). **¹H NMR (500 MHz, CDCl₃):** δ 7.63-7.61 (m, 2H), 7.50-7.47 (m, 1H), 7.43-7.34 (m, 7H), 7.31-7.28 (m, 1H), 5.09 (br. s, 1H), 1.43 (br. s, 3H) ppm.



Chemical Formula: C₁₆H₁₄D₆N₂O

- ***N'*-benzyl-*N'*-methylbenzohydrazide-*d*₄ (4a-*d*₄)**

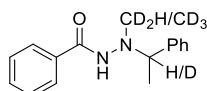
According to general procedure C, alkylation of benzohydrazide (0.5 mmol, 68 mg) with benzyl alcohol (5 equiv, 0.265 mL) using methanol-*d*₄ (1 M) afforded the pure deuterated product as a white solid (92 mg, 76 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). **¹H-NMR (CDCl₃, 500 MHz):** δ 7.58 (d, *J* = 7.1 Hz, 2H), 7.42 (t, *J* = 6.9 Hz, 1H), 7.34-7.30 (m, 6H), 7.28-7.25 (m, 1H), 7.06 (br. s, 1H), 4.08 (s, 2H), 2.73 (s, 1H) ppm. **HRMS (ESI-TOF) m/z [M+H]⁺** of major compound observed: Calcd for C₁₅H₁₅D₂ON₂ 243.1466; found 243.1464.



Chemical Formula: C₁₃H₁₆D₆N₂O

- ***N'*-butyl-*N'*-methylbenzohydrazide-*d*₄ (4v-*d*₄)**

According to general procedure C, alkylation of benzohydrazide (0.5 mmol, 68 mg) with *n*-butanol (5 equiv, 0.228 mL) using methanol-*d*₄ (1 M) afforded the pure deuterated product as a white solid (66 mg, 63 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). **¹H-NMR (CDCl₃, 500 MHz):** δ 7.70 (d, *J* = 7.3 Hz, 2H), 7.45 (t, *J* = 7.3 Hz, 1H), 7.35 (t, *J* = 7.4 Hz, 2H), 6.88 (br. s, 1H), 2.77-2.71 (m, 1.67H), 2.64 (s, 1H), 1.55-1.49 (m, 2H), 1.31 (sext, *J* = 7.5 Hz, 2H), 0.85 (t, *J* = 7.4 Hz, 3H) ppm. **HRMS (ESI-TOF) m/z [M+H]⁺** of majors compounds observed: Calcd for C₁₂H₁₆D₃ON₂ 210.1686; found 210.1681. Calcd for C₁₂H₁₅D₄ON₂ 211.1748; found 211.1741.



Chemical Formula: C₁₇H₁₆D₆N₂O

- ***N'*-benzyl-*N'*-methylbenzohydrazide-*d*₄ (4am-*d*₄)**

According to general procedure D, alkylation of benzohydrazide (0.5 mmol, 68 mg) with 1-phenylethan-1-ol (5 equiv, 0.300 mL) using methanol-*d*₄ (1 M) afforded the pure deuterated product as a white solid (55 mg, 42 %) by silica flash column chromatography (pentane/ethyl acetate 1:1). **¹H-NMR (CDCl₃, 500 MHz):** δ 7.61-7.59 (m, 2H), 7.48-7.45 (m, 1H), 7.40-7.34 (m, 6H), 7.32-7.29 (m, 1H), 6.72 (br. s,

1H), 4.13-4.12 (m, 0.49 H), 2.61 (s, 0.45 H), 1.49-1.46 (m, 0.33 H) ppm. **HRMS (ESI-TOF) m/z** [M+Na]⁺ of majors compounds observed: Calcd for C₁₆H₁₃D₅ONa₂ 282.1631; found 282.1627. Calcd for C₁₆H₁₂D₆ONa₂ 283.1693; found 283.1687.

7) Computational Details.

DFT static calculations were performed with the Gaussian16 set of programs,¹⁵⁶ using the BP86 functional of Becke and Perdew.¹⁵⁷ The electronic configuration of the molecular systems was described with the double- ζ basis set with polarization of Ahlrichs for main-group atoms (SVP keyword in Gaussian),¹⁵⁸ using the SDD ECP on Ru.¹⁵⁹ The geometry optimizations were performed without symmetry constraints, and analytical frequency calculations performed the characterization of the located stationary points. These frequencies were used to calculate unscaled zero-point energies (ZPEs), as well. Energies were obtained by single-point calculations on the optimized geometries with the M06 functional¹⁶⁰ and the triple- ζ basis set cc-pVTZ, which is a dunning's correlation consistent basis set which has redundant function removed and has been rotated in order to increase computational efficiency,¹⁶¹ using the SDD ECP on Ru. And estimating solvent effects with the polarizable continuous solvation model (PCM) as implemented in Gaussian16,¹⁶² using *t*-BuOH as solvent. The reported free energies in this work include energies obtained at the M06/cc-pVTZ~sdd level of theory corrected with zero-point energies, thermal corrections and entropy effects achieved at the BP86/SVP~sdd level. The resulting solvation Gibbs energies were added to the final Gibbs energies in the gas phase to obtain Gibbs energies in solution. Standard Gibbs energies in solution refer to a 1 M standard-state concentration for all species. The change of conventional 1 atm standard state for gas-phase calculations to a standard state of 1 M concentration in solution requires the introduction of a correction in the Gibbs energy term of 2.62 kcal/mol.¹⁶³

¹⁵⁶ Gaussian 16, Revision C.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2016.

¹⁵⁷ (a) Becke, A. *Phys. Rev. A* **1988**, *38*, 3098-3100. (b) Perdew, J. P. *Phys. Rev. B* **1986**, *33*, 8822-8824. (c) Perdew, J. P. *Phys. Rev. B* **1986**, *34*, 7406-7406.

¹⁵⁸ Schäfer, S.; Horn, H.; Ahlrichs, R. *J. Chem. Phys.* **1992**, *97*, 2571-2577.

¹⁵⁹ (a) Haeusermann, U.; Dolg, M.; Stoll, H.; Preuss, H. *Mol. Phys.* **1993**, *78*, 1211-1224. (b) Küchle, W.; Dolg, M.; Stoll, H.; Preuss, H. *J. Chem. Phys.* **1994**, *100*, 7535-7542. (c) Leininger, T.; Nicklass, A.; Stoll, H.; Dolg, M.; Schwerdtfeger, P. *J. Chem. Phys.* **1996**, *105*, 1052-1059.

¹⁶⁰ (a) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215-241. (b) Zhao, Y.; Truhlar, D. G. *J. Chem. Phys.* **2006**, *125*, 194101:1-18.

¹⁶¹ Kendall, R. A.; Dunning Jr., T. H.; Harrison, R. J. *J. Chem. Phys.* **1992**, *96*, 6796-6806.

¹⁶² (a) Barone, V.; Cossi, M. *J. Phys. Chem. A* **1988**, *102*, 1995-2001. (b) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027-2094.

¹⁶³ (a) Kelly, C. P.; Cramer, C. J.; Truhlar, D. G. *J. Chem. Theory Comput.* **2005**, *1*, 1133-1152. (b) Kelly, C. P.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2006**, *110*, 16066-16081. (c) Bryantsev, V. S.; Diallo, M. S.; Goddard III, W. A. *J. Phys. Chem. B* **2008**, *112*, 9709-9719.

8) Xyz coordinates and absolute energies (in a.u.) of all computed DFT species.

See the Supporting Information of [146] and [148].

**CHAPTER III: DEHYDROGENATIVE COUPLING OF
AMIDO-ALCOHOLS: SYNTHESIS OF 3-
ARYLQUINOLIN-2(1*H*)-ONES.**

I. Introduction

Quinolin-2(1*H*)-one is a class of *N*-heterocyclic compounds and is classified as cyclic amide. Such a structure can be observed in many kinds of products, such as biological and pharmaceutical molecules,¹⁶⁴ and presents interesting bioactivities. For example, Brexpiprazole is a serotonin-dopamine activity modulator used as an adjunct in the treatment of major depressive disorder,¹⁶⁵ Indacaterol and Procaterol are used in the treatment of asthma¹⁶⁶ and CHIR-124 is a Checkpoint kinase 1 inhibitor (Figure 3.1).¹⁶⁷

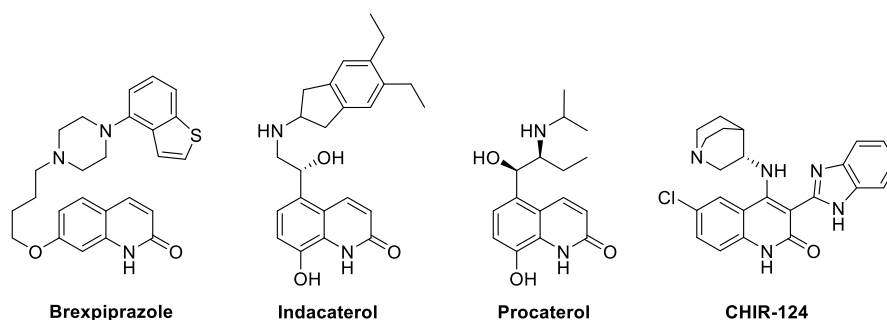


Figure 3.1: Example of bioactive compounds presenting a quinoline-2(1*H*)-one fragment.

Such motifs are commonly prepared using the Vilsmeier-Haak¹⁶⁸ or Friedlander¹⁶⁹ reactions, but alternative syntheses of quinolinones using transition metal catalysts have been developed in the past years.

II. Recent syntheses of quinoline-2(1*H*)-ones catalysed by transition metals.

The first metal-catalysed synthesis of quinoline-2(1*H*)-one was described by Takahashi in 1995.¹⁷⁰ Aiming to synthesize 1,3-dihydroindol-2-ones from 2-alkynylaniline and carbon monoxide using a rhodium catalyst, the quinoline derivative was obtained as a by-product in 11% yield (Scheme 3.1).

¹⁶⁴ (a) Reisch, J.; Gunaherath, G. M. K. B.; Kamal, G. M. *Monatsh. Chem.* **1988**, *119*, 1169-1178. (b) Michael, J. P. *Nat. Prod. Rep.* **1995**, *12*, 465-475. (c) Carling, R. W.; Leeson, P. D.; Moore, K. W.; Moyer, C. R.; Duncton, M.; Hudson, M. L.; Baker, R.; Foster, A. C.; Grimwood, S.; Kemp, J. A.; Marshall, G. R.; Tricklebank, M. D.; Saywell, K. L. *J. Med. Chem.* **1997**, *40*, 754-765. (d) Chung, H. S.; Woo, W. S. *J. Nat. Prod.* **2001**, *64*, 1579-1580. (e) Peifer, C.; Urich, R.; Schattel, V.; Abadleh, M.; Röttig, M.; Kohlbacher, O.; Laufer, S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1431-1435.

¹⁶⁵ Maeda, K.; Sugino, H.; Akazawa, H.; Amada, N.; Shimada, J.; Futamura, T.; Yamashita, H.; Ito, N.; McQuade, R. D.; Mork, A.; Pehrson, A. L.; Hentzer, M.; Nielsen, V.; Bundgaard, C.; Arnt, J.; Stensbol, T. B.; Kikuchi, T. *J. Pharmacol. Exp. Ther.* **2014**, *350*, 589-604.

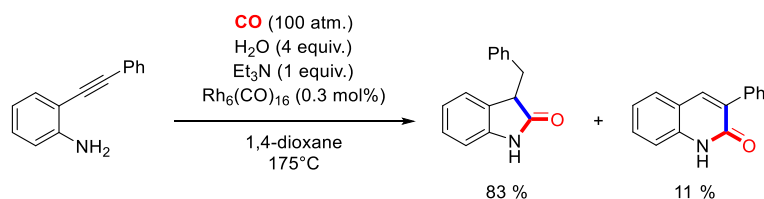
¹⁶⁶ (a) Cazzola, M.; Matera, M. G.; Lotvall, J. *Expert. Opin. Investig. Drugs* **2005**, *14*, 775-783. (b) Aizawa, H.; Inoue, H.; Ikeda, T.; Hirose, T.; Ito, Y. *Respiration* **1991**, *58*, 163-166.

¹⁶⁷ Berman, H. M.; Westbrook, J.; Feng, Z.; Gilliland, G.; Bhat, T. N.; Weissig, H.; Shindyalov, I. N.; Bourne, P. E. *Nucleic Acids Res.* **2000**, *28*, 235-242.

¹⁶⁸ (a) Joseph, B.; Darro, F.; Behard, A.; Lesur, B.; Collignon, F.; Decaestecker, C.; Frydman, A.; Guillaumet, G.; Kiss, R. J. *J. Med. Chem.* **2002**, *45*, 2543-2555. (b) Zhang, Y.; Fang, Y.; Liang, H.; Wang, H.; Hu, K.; Liu, X.; Yi, X.; Peng, Y. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 107-111.

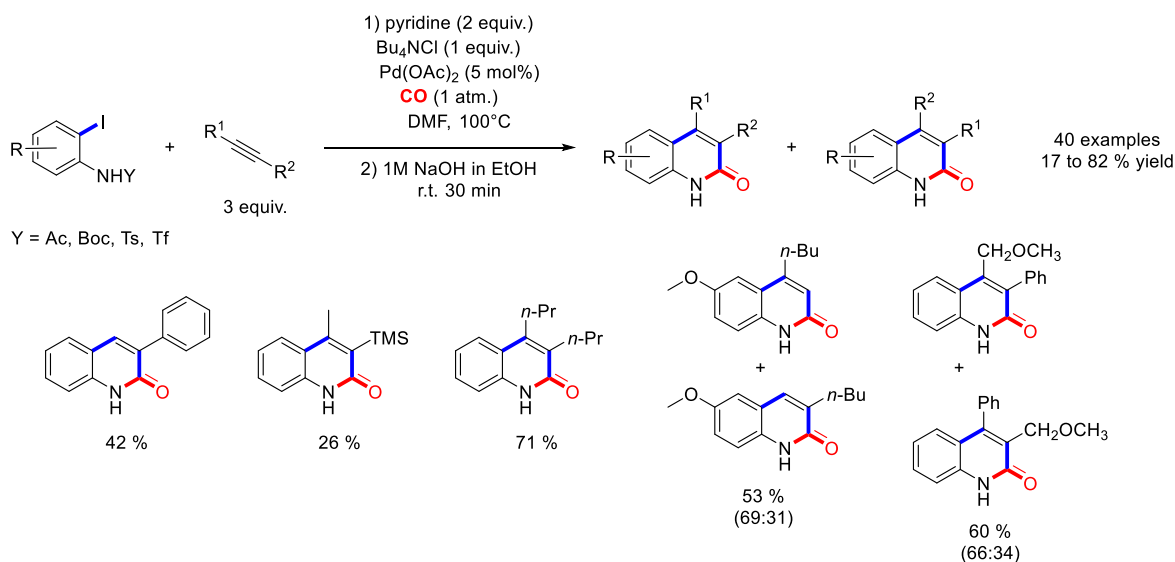
¹⁶⁹ Han, S.-Y.; Choi, J. W.; Yang, J.; Chae, C. H.; Lee, J.; Jung, H.; Lee, K.; Ha, J. D.; Kim, H. R.; Cho, S. Y. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2837-2844.

¹⁷⁰ Hirao, K.; Morii, N.; Joh, T.; Takahashi, S. *Tetrahedron Lett.* **1995**, *36*, 6243-6246.



Scheme 3.1: First metal-catalysed synthesis of quinolinone described by Takahashi.

Later on, Larock described a palladium-catalysed carbonylative annulation of alkynes for the synthesis of 2-quinolones (Scheme 3.2).¹⁷¹ The reaction of 2-iodoanilines derivatives with various alkynes in the presence of Pd(OAc)₂ under a CO atmosphere afforded the desired products in moderate to good yields (17 to 82 %). Modest selectivity was obtained when unsymmetrical alkynes were employed, except when one of the substituents was much more hindered, as for phenylacetylene or trimethyl(prop-1-yn-1-yl)silane. The use of non-protected anilines was also detrimental in this process. This methodology was then applied by Liu & Jia for the synthesis of 4,5-fused tricyclic 2-quinolones from alkyne-tethered *ortho*-iodoaniline.¹⁷²



Scheme 3.2: Palladium-catalysed synthesis of quinolones.

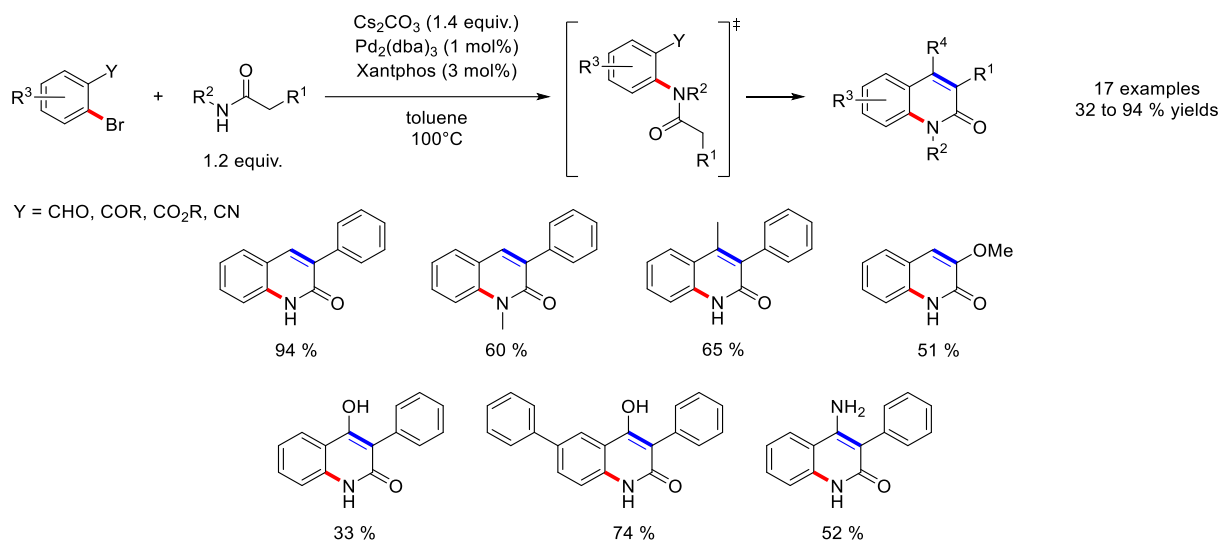
In 2004, Manley envisioned an alternative cascade reaction to the Friedlander condensation.¹⁷³ A Buchwald¹⁷⁴ cross-coupling reaction between 2-halogenobenzaldehyde and acetamides catalysed by a palladium/Xantphos complex afforded the corresponding *N*-arylacetamides intermediates, which cyclised afterwards, *via* an enol condensation, giving rise to the desired quinolinones in moderate to very good yields (32 to 94 %, Scheme 3.3). Even though *N*-methyl quinolinone could be obtained in these conditions, this methodology suffered from the steric hindrance of other *N*-substituted arylacetamides that failed to couple. Nevertheless, 4-hydroxy and 4-aminoquinolinones were obtained following this procedure.

¹⁷¹ (a) Kadnikov, D. V.; Larock, R. C. *J. Organomet. Chem.* **2003**, 687, 425-435. (b) Kadnikov, D. V.; Larock, R. C. *J. Org. Chem.* **2004**, 69, 6772-6780.

¹⁷² Zhang, X.; Liu, H.; Jia, Y. *Chem. Commun.* **2016**, 52, 7665-7667.

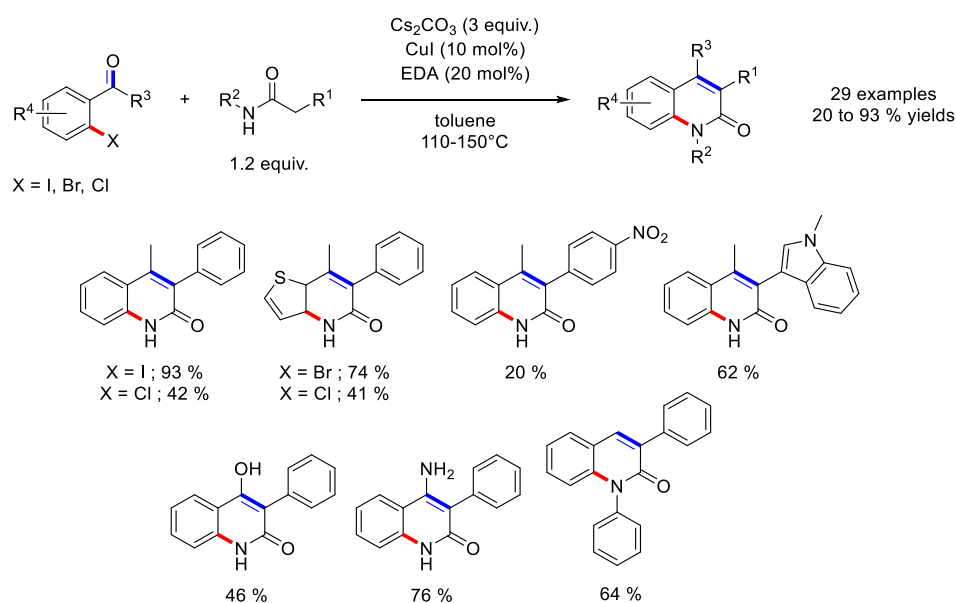
¹⁷³ Manley, P. J.; Bilodeau, M. T. *Org. Lett.* **2004**, 6, 2433-2435.

¹⁷⁴ (a) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, 2, 1101-1104. (b) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, 124, 6043-6048.



Scheme 3.3: Synthesis of quinolinones via amide coupling/enol condensation.

Following up on this cascade reaction, Ding¹⁷⁵ further explored the synthesis of quinolinones using the conditions reported by Buchwald¹⁷⁶ for the copper-catalysed coupling of amides with aryl halides. Aryl iodide and bromides performed well at 110°C and the corresponding products were obtained in moderate to very good yields (20 to 93 %, Scheme 3.4). 4-hydroxy and 4-aminoquinolinones were obtained as well in good yields (46 and 76 % respectively). This strategy was also extended to less reactive aryl chlorides, however a temperature threshold of 150°C was required to give the desired quinolinones in moderate yields (35 to 42 %).



Scheme 3.4: Synthesis of quinolinones via a copper-catalysed arylation of amide.

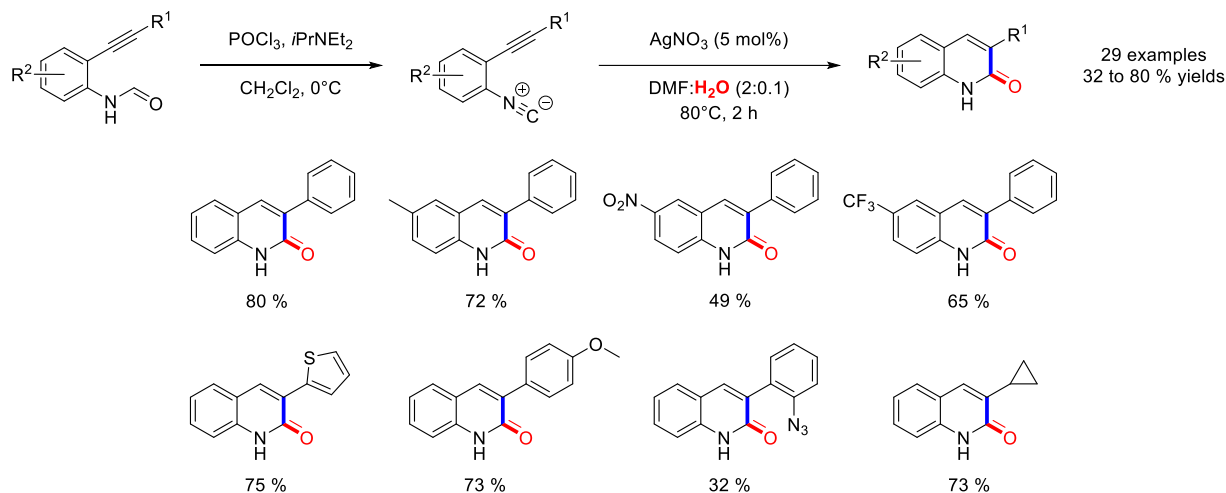
In 2018, Kuhakarn described a two-step synthesis of quinolinones starting from *N*-(2-alkynylaryl)formamides.¹⁷⁷ In a first step, the formamides derivatives were converted to the

¹⁷⁵ Fu, L.; Huang, X.; Wang, D.; Zhao, P.; Ding, K. *Synthesis* **2011**, *10*, 1547-1554.

¹⁷⁶ Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421-7428.

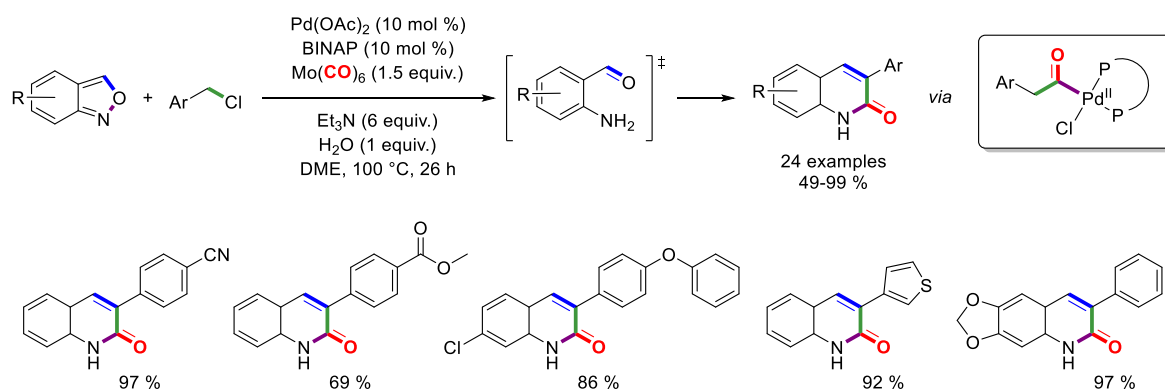
¹⁷⁷ Charoenpol, A.; Meesin, J.; Khaikate, O.; Reutrakul, V.; Pohmakotr, M.; Leowanawat, P.; Soorukram, D.; Kuhakarn, C. *Org. Biomol. Chem.* **2018**, *16*, 7050-7054.

corresponding isonitriles (Scheme 3.5). The latter were then engaged in a silver-catalysed cyclisation reaction. A mixture of DMF and water at 80°C in the presence of silver nitrate afforded the desired quinoline-2-(1*H*)-ones in moderate to good yields (32 to 80 %). Various electro-donating and electro-withdrawing groups were tolerated in these conditions, and more specifically an azido-substituted 3-arylquinolin-2(1*H*)-one was obtained in 32 % yield.



Scheme 3.5: Silver-catalysed synthesis of quinolinone.

More recently, Qi and Wu reported the use of anthranil and benzyl chloride derivatives for the synthesis of quinolinones.¹⁷⁸ Anthranil compounds were previously reported in various transition-metal-catalysed C-N bond formation thanks to their good coordination ability.¹⁷⁹ The latter were converted *in situ* into 2-aminobenzaldehydes before being engaged in a carbonylative Buchwald-type coupling with benzyl chlorides, followed by intramolecular condensation to give the quinolinone products. This reaction tolerated a variety of electron-donating and electron-withdrawing groups and allowed the formation of functionalised 3-arylquinolin-2-(1*H*)-ones in yields ranging from 49 to 99 % (Scheme 3.6).



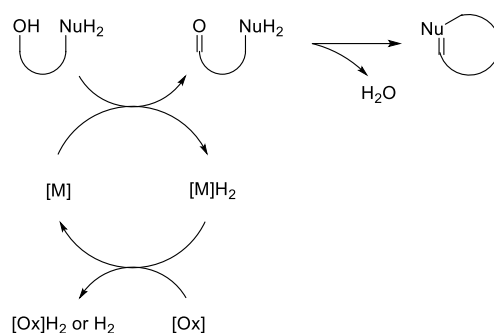
Scheme 3.6: Synthesis of quinolinones from anthranil derivatives.

¹⁷⁸ Liu, J.-L.; Xu, R.-R.; Wang, W.; Qi, X.; Wu, X.-F. *Org. Biomol. Chem.* **2021**, *19*, 3584-3589.

¹⁷⁹ Gao, Y.; Nie, J.; Huo Y.; Hu, X.-Q. *Org. Chem. Front.* **2020**, *7*, 1177-1196.

III. Dehydrogenative coupling approach to heterocycles synthesis.

The transition-metal catalyzed synthesis of heterocycles has been well studied during the last decades.¹⁸⁰ Recently, the borrowing hydrogen and dehydrogenative coupling approaches became attractive strategies due to the non-toxicity of the generated by-products (H_2O , H_2 , ...).¹⁴ Noble and first-row metals catalysts were reported to perform such reaction. Only the synthesis of heterocycles *via* dehydrogenative couplings catalyzed by 3d metals will be discussed in this chapter. The general mechanism of such reaction is depicted in Scheme 3.7. In a first step, the metal catalyst dehydrogenates an alcohol to generate the corresponding carbonyl and a metal-hydrogen species. Contrary to alkylation reactions, the latter releases molecular hydrogen to regenerate the catalytic species, assisted or not by an oxidant. The carbonyl undergoes an intramolecular condensation leading to a cyclic unsaturated product.



Scheme 3.7: General mechanism of dehydrogenative coupling.

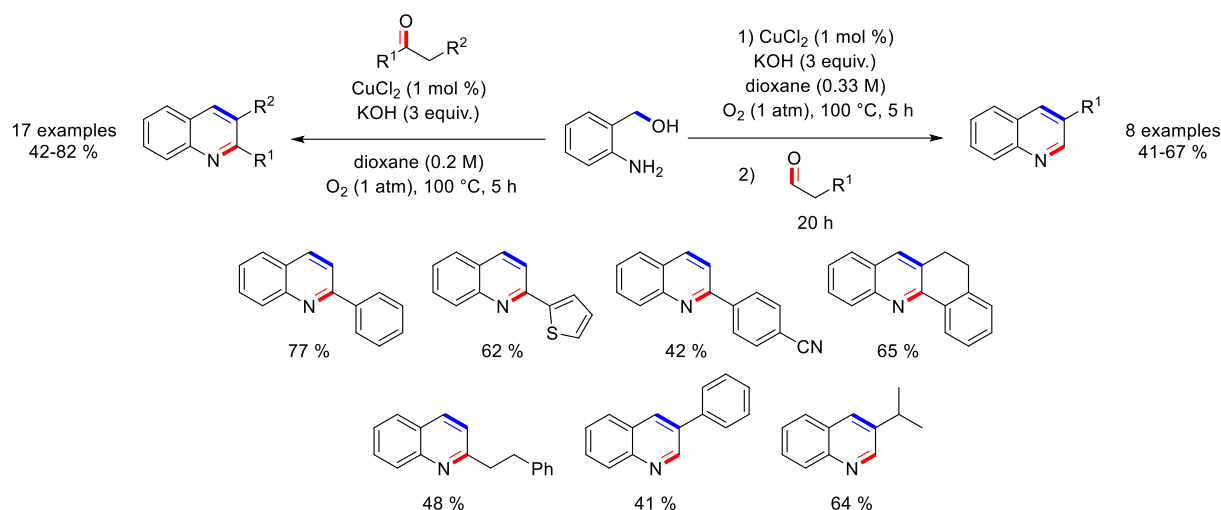
1) Copper-catalysed dehydrogenative synthesis of heterocycles.

In 2006, Cho *et al.* described the first copper-catalysed synthesis of quinolines.¹⁸¹ The reaction of 2-aminobenzyl alcohol and ketones in presence of KOH (3 equiv.) and a catalytic amount of CuCl_2 (1 mol %) in dioxane (100°C) gave the desired 2-substituted quinolines (Scheme 3.8). Different aromatic and aliphatic ketones were engaged allowing the formation of 2-alkyl or 2-arylquinolines in good yields (42 to 82 %). Modification of the conditions permitted to engage aldehydes leading to 3-alkyl or 3-arylquinolines (41 to 67 % yields). Few years later, a recyclable version of this methodology was reported by the same group and the system could be reused up to 10 times without any loss of catalytic activity.¹⁸²

¹⁸⁰ (a) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127-2198. (b) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev.* **2013**, *113*, 3084-3213.

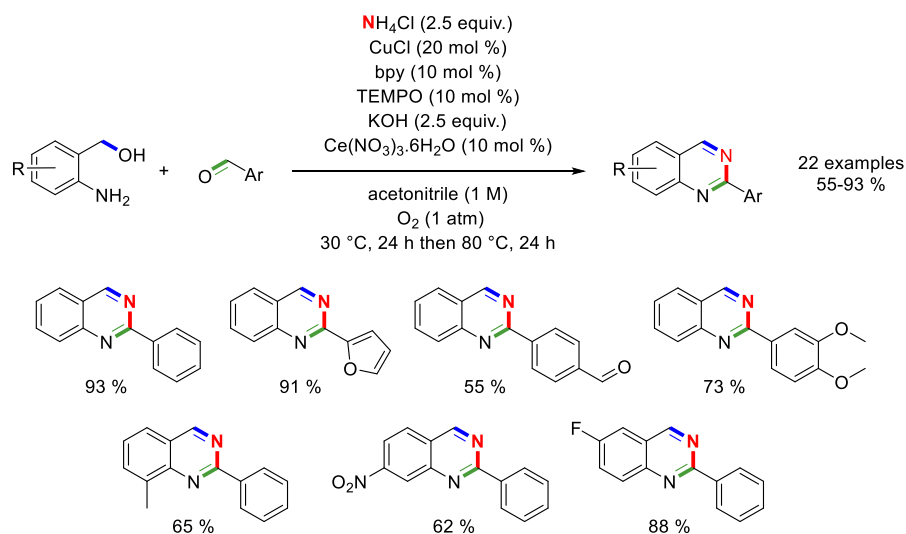
¹⁸¹ Cho, C. S.; Ren, W. X.; Shim, S. C. *Tetrahedron Lett.* **2006**, *47*, 6781-6785.

¹⁸² Cho, C. S.; Ren, W. X.; Yoon, N. S. *J. Mol. Catal. A: Chem.* **2009**, *299*, 117-120.



Scheme 3.8: Copper-catalysed synthesis of quinolines.

Later on, the synthesis of quinazolines was described by Chen.¹⁸³ CuCl (20 mol %) was used along with Ce(NO₃)₃ (10 mol %) and TEMPO (10 mol %) to afford the desired 2-substituted quinazolines (Scheme 3.9). Despite the important catalytic charge, this methodology allowed to use various benzaldehydes and substituted 2-aminobenzyl alcohols, leading to functionalised quinazolines in good to excellent yields (55 to 93 %).

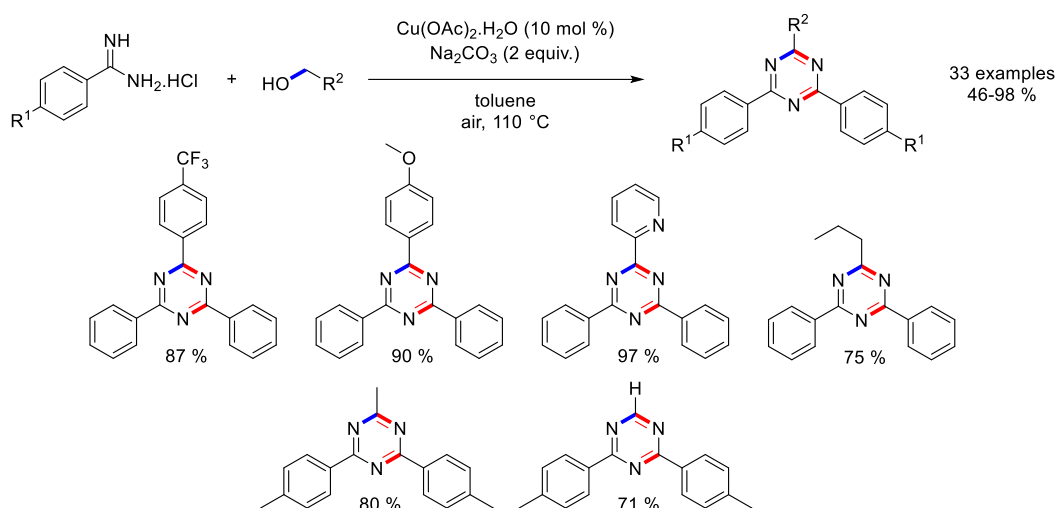


Scheme 3.9: Synthesis of quinazolines.

In 2015, Zang reported the synthesis of 1,3,5-triazines.¹⁸⁴ Benzamidines hydrochlorides were reacted with alkyl and benzyl alcohols in the presence of copper acetate (10 mol %) and sodium carbonate (2 equiv.) in refluxing toluene (Scheme 3.10). The cyclic products were isolated in good to excellent yields (46 to 98 %) without significant decrease in yield when less reactive aliphatic alcohols were engaged. Various electro-donating and electro withdrawing groups were tolerated as well as heteroaryl substituents.

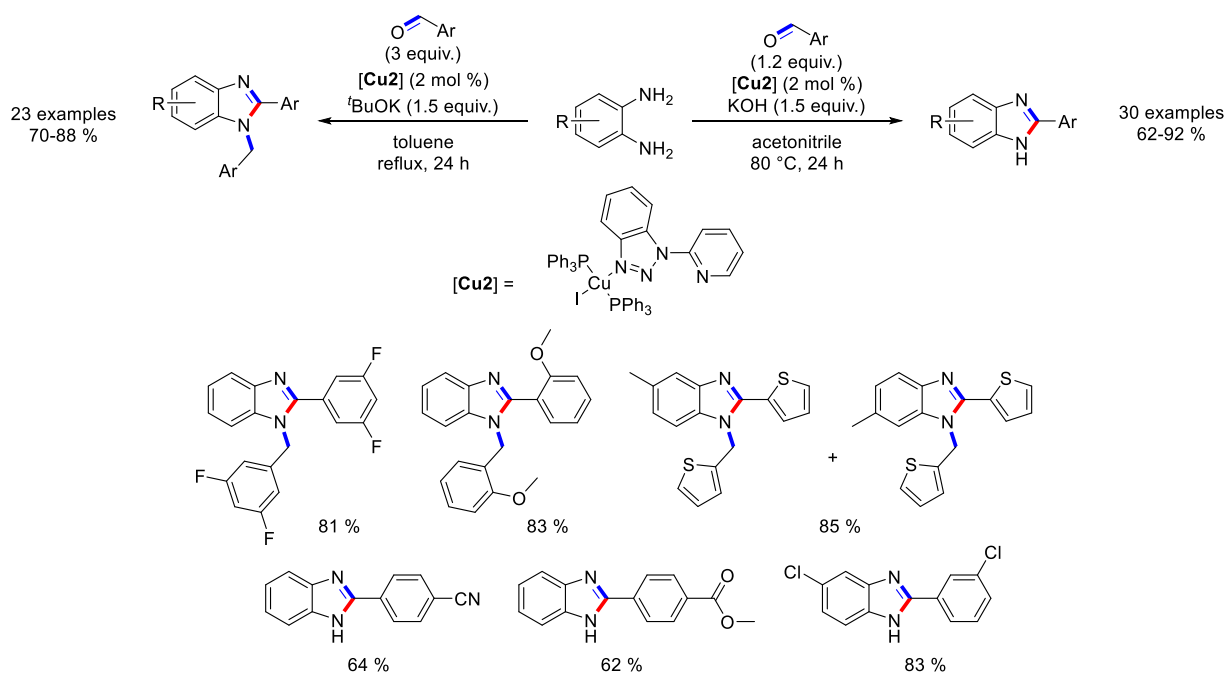
¹⁸³ Chen, Z.; Chen, J.; Liu, M.; Ding, J.; Gao, W.; Huang, X.; Wu, H. *J. Org. Chem.* **2013**, *78*, 11342-11348.

¹⁸⁴ You, Q.; Wang, F.; Wu, C.; Shi, T.; Min, D.; Chen, H.; Zhang, W. *Org. Biomol. Chem.* **2015**, *13*, 6723-6727.



Scheme 3.10: Copper-catalysed synthesis of triazines.

In 2017, Wang described the synthesis of benzimidazoles from 1,2-diamines and benzyl alcohols.⁸⁰ The triazole-phosphine-copper complex **Cu2** was used as a catalyst in basic conditions to achieve the synthesis of 1-benzyl-2-aryl-1*H*-benzo[*d*]imidazoles or 2-aryl-1*H*-benzo[*d*]imidazoles. This methodology allowed the formation of the desired products in good yields (62 to 91 %) and a variety of functionalised benzimidazoles were synthesized (Scheme 3.11).

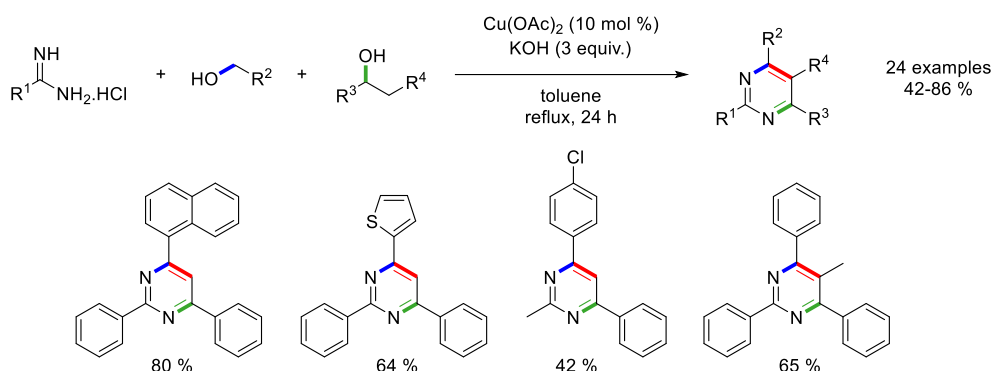


Scheme 3.11: Copper-catalysed synthesis of benzimidazoles.

Zang reported in 2018 a three-component synthesis of pyrimidines starting from alkylamidines or benzamidines hydrochlorides, benzyl alcohols and 1-aryl ethanols, in the presence of potassium hydroxide (3 equiv.) and copper acetate (10 mol %) in refluxing toluene (Scheme 3.12).¹⁸⁵ Various

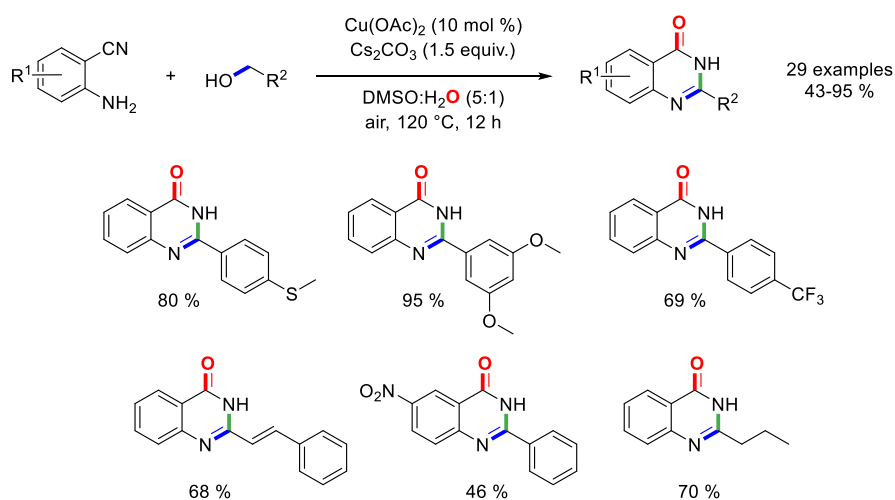
¹⁸⁵ Shi, T.; Qin, F.; Li, Q.; Zhang, W. *Org. Biomol. Chem.* **2018**, *16*, 9487-9491.

electro-donating and electro-withdrawing groups were tolerated and the corresponding pyrimidines were isolated in moderate to good yields (42 to 86 %).



Scheme 3.12: Copper-catalysed synthesis of pyrimidines.

In 2019, a copper-catalysed synthesis of quinazolinones was described by Li.¹⁸⁶ Various 2-aminobenzonitriles and primary alcohols reacted in presence of Cs_2CO_3 (1.5 equiv.) and a catalytic amount of copper acetate (10 mol %) in a mixture of DMSO and water (5:1) at 120 °C (Scheme 3.13). The desired quinazolinones bearing diverse functions were isolated in yields ranging from 43 to 95 %. A mechanism was also proposed by the authors: the catalytic cycle was initiated by the hydration of the nitrile function, leading to a 2-aminobenzamide intermediate. Condensation of the aldehyde on the amine moiety generates an imine. Intramolecular cyclisation by addition of the amide to the imine gives a 2,3-dihydroquinazolinone which is rapidly oxidised into the corresponding quinazolinone.



Scheme 3.13: Copper-catalysed synthesis of quinazolinones.

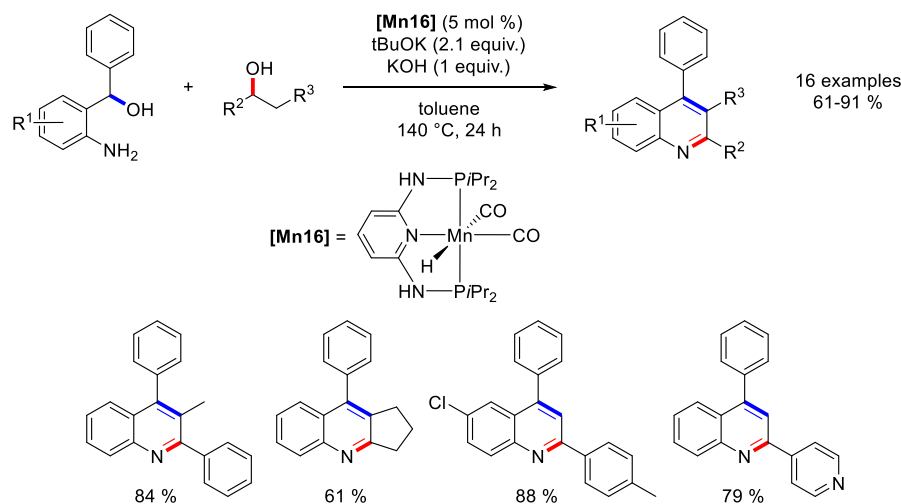
2) Manganese-catalysed dehydrogenative synthesis of heterocycles.

In 2016, Kirchner reported the first manganese-catalysed synthesis of nitrogen-containing heterocycles following a dehydrogenative coupling.¹⁸⁷ Various 2-aminobenzyl alcohols and secondary alcohols reacted in presence of stoichiometric amount of $t\text{BuOK}$ (2.1 equiv.), KOH (1 equiv.) and a

¹⁸⁶ Hu, Y.; Li, S.; Li, H.; Li, Y.; Li, J.; Duanmu, C.; Li, B. *Org. Chem. Front.* **2019**, *6*, 2744-2748.

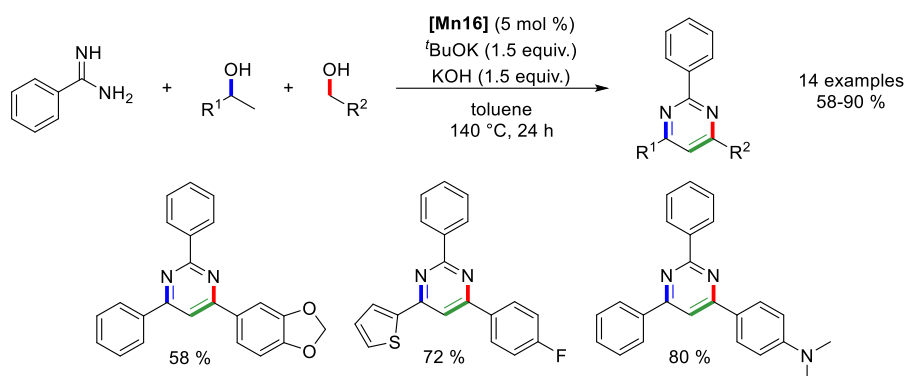
¹⁸⁷ Mastalir, M.; Glatz, M.; Pittenauer, E.; Allmaier, G.; Kirchner, K. *J. Am. Chem. Soc.* **2016**, *138*, 15543-15546.

catalytic amount of PNP-Mn complex (5 mol %) at 140 °C in toluene. The corresponding quinolines were prepared in good to very good yields (61 to 91 %, Scheme 3.14). Compared to the method proposed by Cho,¹⁸¹ this strategy allowed the substitution on the position 4 of the quinoline product, as highlighted in Scheme 3.14.



Scheme 3.14: Manganese-catalysed synthesis of quinolines.

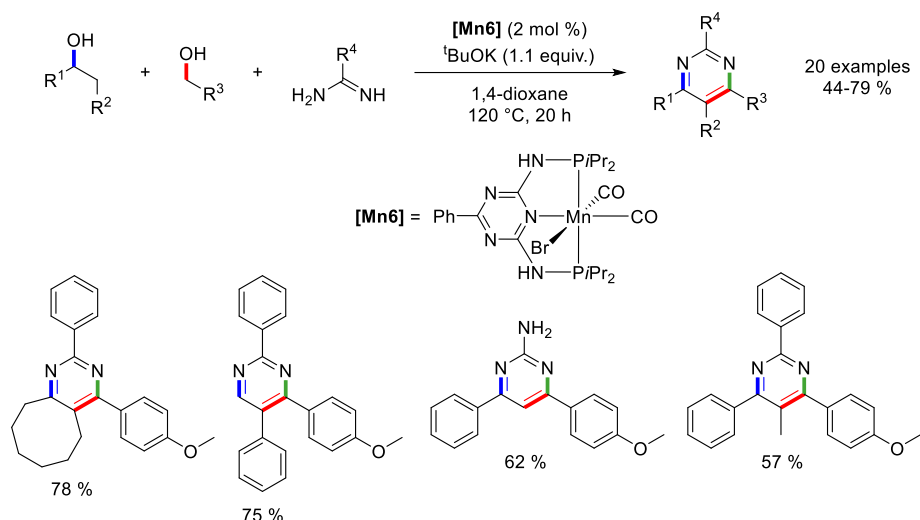
To further explore the potential of such a reaction, the synthesis of pyrimidines starting from benzamidine, primary and secondary alcohols was also explored. This approach led to the synthesis of a variety of substituted pyrimidines in good yields (58 to 90 %, Scheme 3.15).



Scheme 3.15: Manganese-catalysed synthesis of pyrimidines.

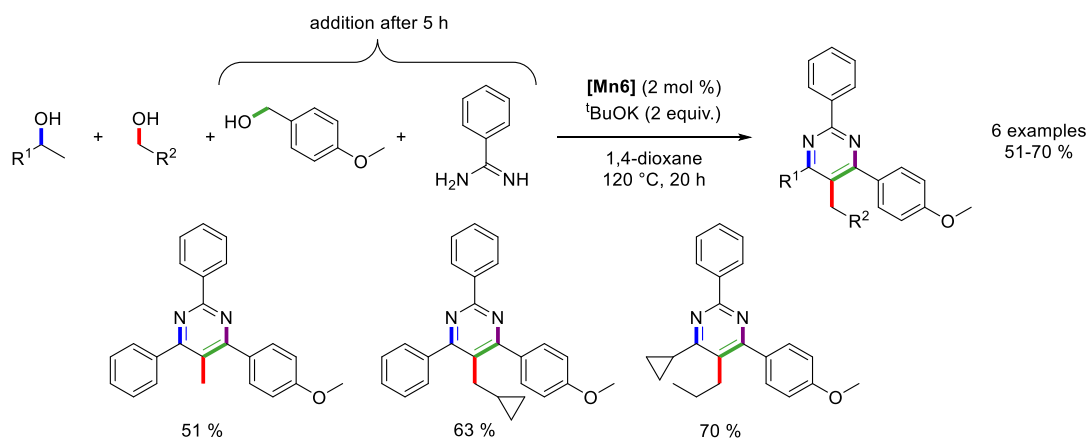
At the same time, Kempe reported a three-component synthesis of pyrimidines.¹⁸⁸ A modified PNP-Mn complex was used to catalyse this reaction. Various alkyl, aryl, heteroaryl moieties were tolerated and the substituted pyrimidines were isolated in moderate to good yields (44 to 79 %, Scheme 3.16). Even if various electron-donating groups were tolerated, electron-withdrawing groups were not introduced using this methodology.

¹⁸⁸ Deibl, N.; Kempe, R. *Angew. Chem. Int. Ed.* **2017**, *56*, 1663-1666.



Scheme 3.16: Synthesis of pyrimidines reported by Kempe.

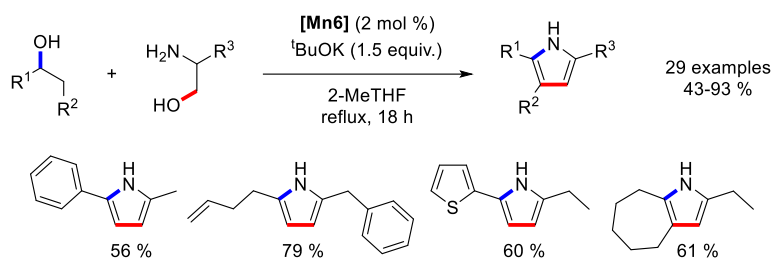
Using a sequential method, a four-component synthesis of pyrimidines was also described. In this second approach, a first alkylation of the secondary alcohol with a primary alcohol is performed before the amidine and a second primary alcohol were added. This methodology allowed the synthesis of tetrasubstituted pyrimidines in good yields (51 to 70 %, Scheme 3.17).



Scheme 3.17: Four-component synthesis of pyrimidines.

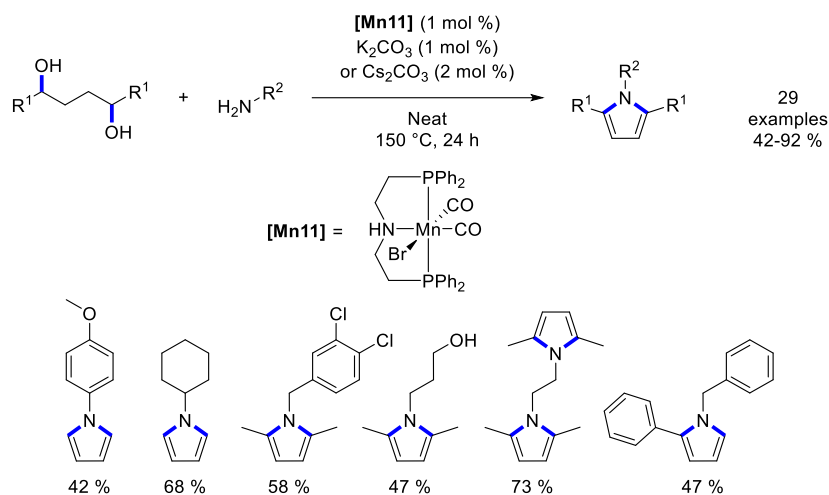
The synthesis of pyrroles was also described by Kempe using the same manganese catalyst.¹⁸⁹ Starting from secondary alcohols and amino-alcohols in the presence of ^tBuOK (1.5 equiv.) and PNP-Mn complex (0.5 mol %) in refluxing 2-methyl-THF, various non-symmetric substituted pyrroles were isolated in 51 to 93 % yields (Scheme 3.18).

¹⁸⁹ Kallmeier, F.; Dudzic, B.; Irrgang, T.; Kempe, R. *Angew. Chem. Int. Ed.* **2017**, *56*, 7261-7265.



Scheme 3.18: Manganese-catalysed synthesis of pyrroles.

Later on, Rueping and El-Sepelgy reported an alternative manganese-catalysed synthesis of pyrroles using 1,4-diols and primary amines.¹⁹⁰ Various benzylic or aliphatic amines as well as diamines were engaged allowing the formation of *N*-substituted pyrroles which were isolated in yields ranging from 42 to 92 % (Scheme 3.19). Compared to complex **Mn2**, electron-withdrawing groups were also tolerated in this reaction and aryl groups bearing halide substituents could be also introduced in the final product.

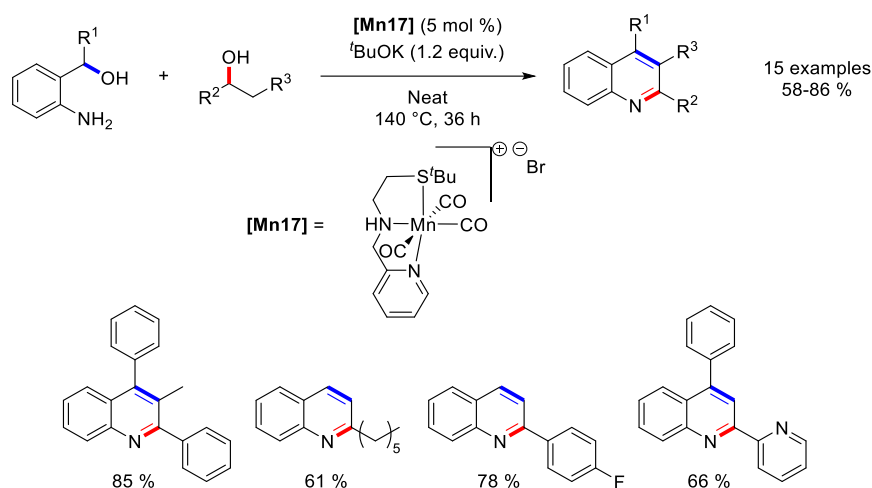


Scheme 3.19: Manganese-catalysed synthesis of pyrroles.

In 2018, Srimani reported the synthesis of quinolines, quinoxalines, pyrazines, and benzothiazoles in neat conditions.¹⁹¹ A tridentate NNS-Mn(I) complex **Mn4** was used to catalyse these dehydrogenative coupling reactions. The synthesis of quinolines was performed starting from 2-aminobenzyl alcohols and secondary alcohols, following the same methodology than Cho¹⁸¹ and Kirchner.¹⁸⁷ Various alkyl- and aryl-substituted quinolines were obtained in yields ranging from 58 to 86 %, but this reaction was limited to non-functionalised starting materials as only two examples of substituted quinoline (F, Cl) were reported (Scheme 3.20).

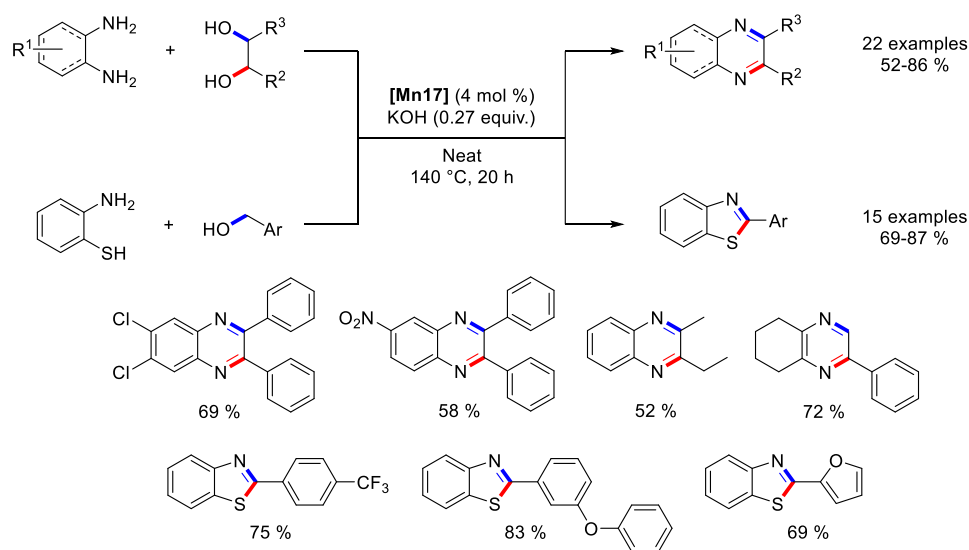
¹⁹⁰ Borghs, J. C.; Lebedev, Y.; Rueping, M.; El-Sepelgy, O. *Org. Lett.* **2019**, *21*, 70-74.

¹⁹¹ Das, K.; Mondal, A.; Srimani, D. *Chem. Commun.* **2018**, *54*, 10582-10585.



Scheme 3.20: Synthesis of quinolines reported by Srimani.

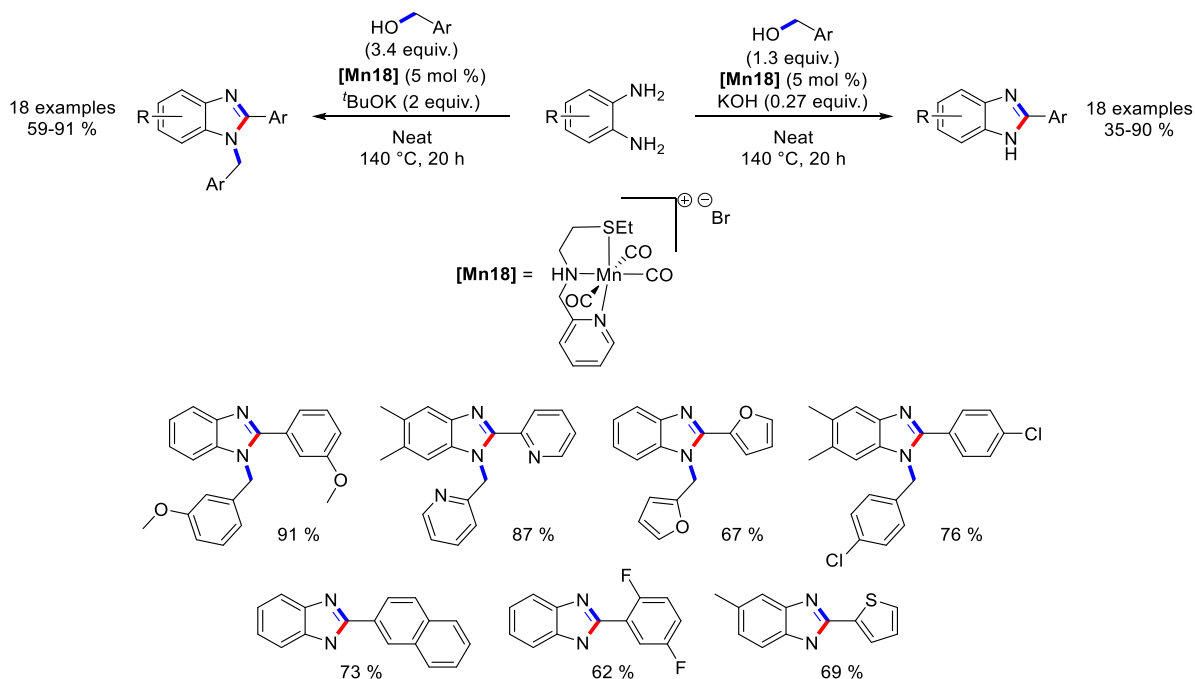
The same catalyst was then used for the synthesis of quinoxalines and pyrazines starting from 1,2-diamines and 1,2-diols. Alkyl, halogen or nitro substituents were tolerated and the products were obtained in good yields (52 to 86 %, Scheme 3.21). The same conditions were used for the synthesis of benzothiazoles from 2-amino thiophenol and benzyl alcohols. The desired cyclic products were obtained in good yields with a good tolerance over electro-donating, electro-withdrawing and heteroaryl groups (69 to 87 %, Scheme 3.21).



Scheme 3.21: Synthesis of quinoxalines, pyrimidines and benzothiazoles.

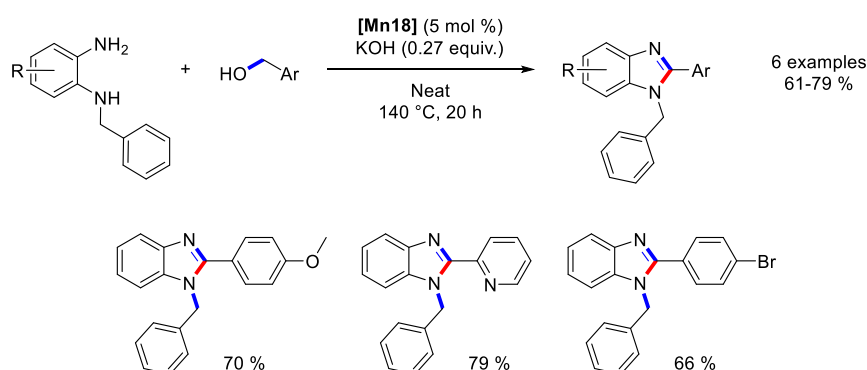
The same group described also the synthesis of 2-substituted and 1,2-disubstituted benzimidazoles.¹⁹² Contrary to Wang who started from benzaldehydes,⁸⁰ Srimani used benzyl alcohols as pro-electrophiles for this reaction. Various diamines and alcohols were engaged in basic conditions ($t\text{BuOK}$ or KOH) in presence of the NNS-Mn catalyst (5 mol %) to afford the desired mono- or di-substituted products (35 to 91 %, Scheme 3.22).

¹⁹² Das, K.; Mondal, A.; Srimani, D. *J. Org. Chem.* **2018**, *83*, 9553-9560.



Scheme 3.22: Manganese-catalysed synthesis of mono- or disubstituted benzimidazoles.

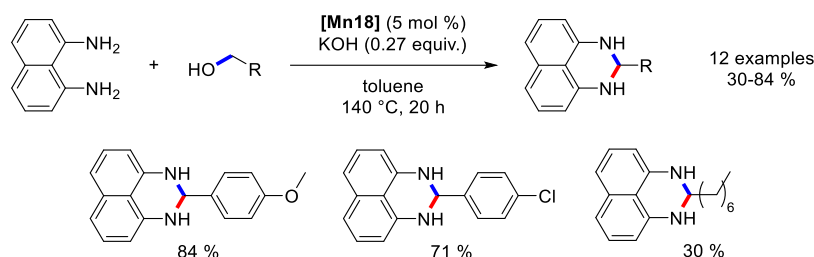
The synthesis of 1-benzyl-2-aryl-1*H*-benzo[*d*]imidazoles was also explored. Starting from *N*-benzyl diamines, disubstituted benzimidazoles bearing different aryl groups were isolated in good yields (61 to 79 %, Scheme 3.23).



Scheme 3.23: Synthesis of disubstituted benzimidazoles bearing different substituents.

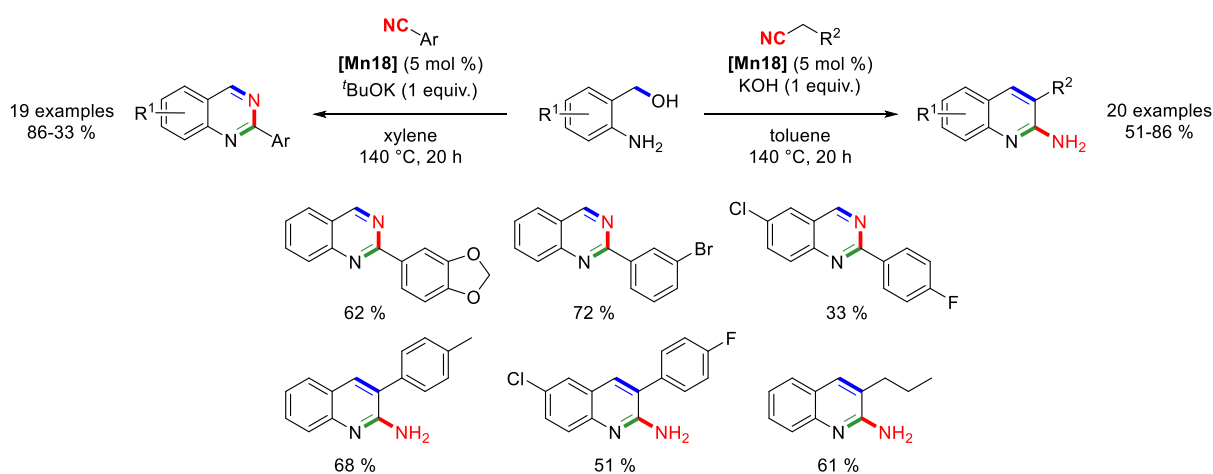
This NNS-Mn catalyst was later engaged for the synthesis of 2,3-dihydro-1*H*-perimidine derivatives using 1,8-diaminonaphthalene and various primary alcohols (Scheme 3.23).¹⁹³

¹⁹³ Das, K.; Mondal, A.; Pal, D.; Srivastava, H. K.; Srimani, D. *Organometallics* **2019**, *38*, 1815-1825.



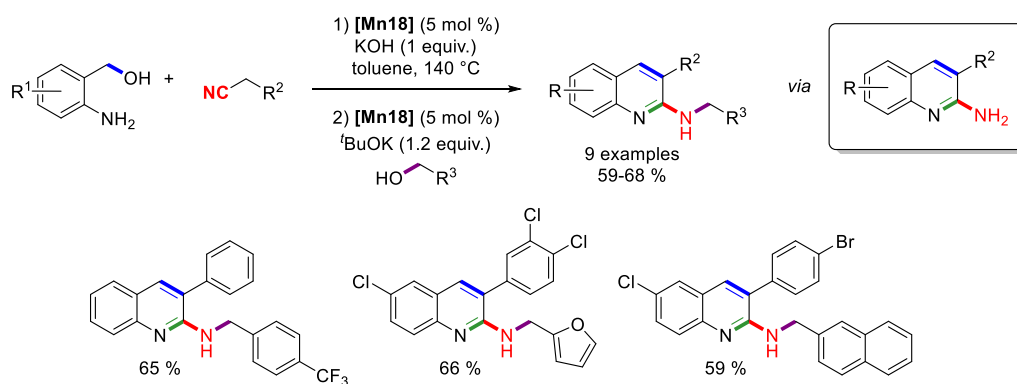
Scheme 3.23: Synthesis of dihydropyrimidines.

By varying the base (^tBuOK or KOH) and solvent, the NNS-Mn catalyst allowed the synthesis of quinazolines or 2-aminoquinolines starting from 2-aminobenzyl alcohols and nitriles.¹⁹⁴ Various nitrogen-containing heterocycles bearing electron-donating and electron-withdrawing groups were obtained following this methodology (Scheme 3.24).



Scheme 3.24: Synthesis of quinazolines and 2-aminoquinolines from nitriles.

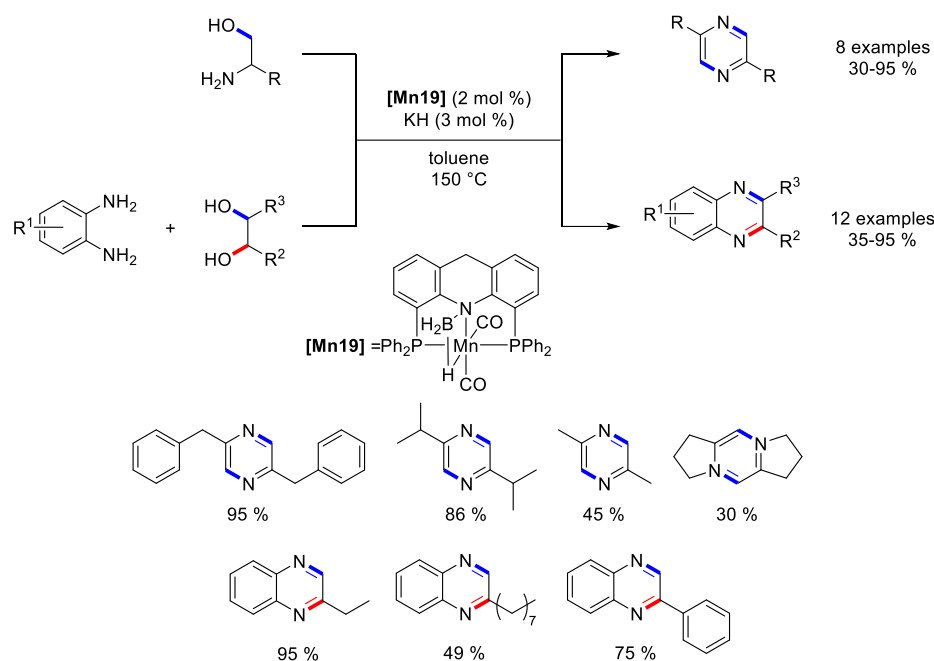
The authors also envisioned a two-step one-pot synthesis of 2-alkylaminoquinolines. After the formation of the 2-aminoquinoline intermediate, a primary alcohol was added to the reaction mixture in order to further functionalise the amine. Diverse electro-donating and electro-withdrawing groups were tolerated and the desired 2-aminoalkylquinolines were obtained in yields ranging from 59 to 68 % (Scheme 3.25).



Scheme 3.25: Manganese-catalysed synthesis of 2-alkylaminoquinolines.

¹⁹⁴ Das, K.; Mondal, A.; Pal, D.; Srimani, D. *Org. Lett.* **2019**, *21*, 3223-3227.

In 2018, Milstein reported the synthesis of pyrazines and quinoxalines catalysed by a PNP-Mn complex.¹⁹⁵ The homocoupling of amino alcohols in the presence of potassium hydride (3 mol %) and the manganese complex (2 mol %) in toluene at 150 °C afforded the symmetric pyrazines with low to very good yields (30 to 95 %, Scheme 3.26). In the same conditions, the reaction of 1,2-diamines and 1,2-diols led to the corresponding quinoxalines in low to very good yields (35 to 95 %). Perhaps, only alkyl and aryl-substituted heterocycles were obtained with this approach.

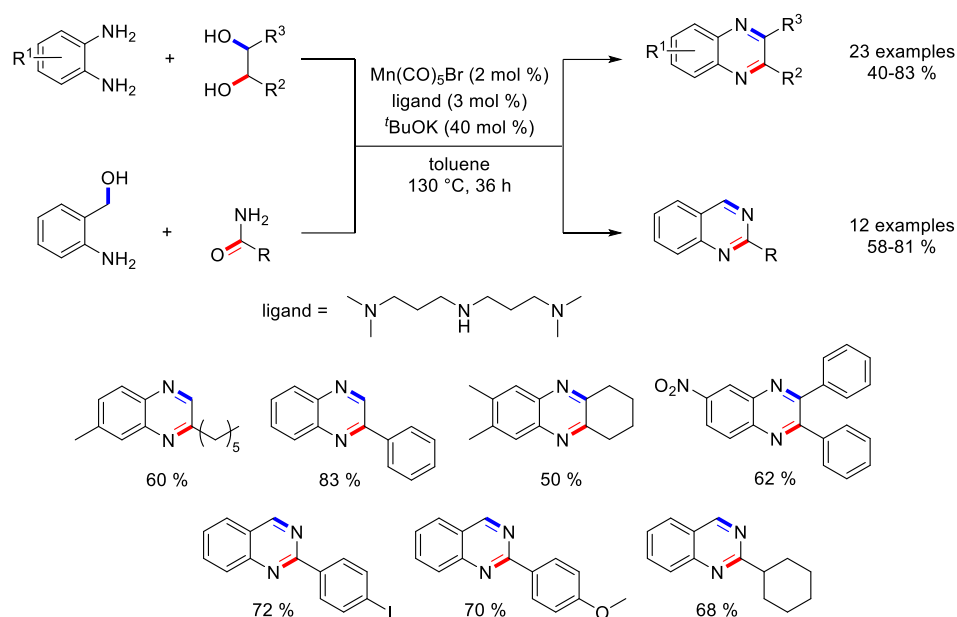


Scheme 3.26: Synthesis of pyrazines and quinoxalines reported by Milstein.

More recently, Balaraman described the synthesis of quinoxalines and quinazolines catalysed by an *in situ* generated NNN-Mn complex.¹⁹⁶ Following the same strategy than Milstein,¹⁹⁵ the desired quinoxalines were obtained by reaction of diamines and diols in the presence of *t*BuOK (40 mol %), ligand (3 mol %) and Mn(CO)₅Br (2 mol %) in toluene at 130 °C. Various alkyl- and aryl-substituted quinoxalines were isolated in good yields (40 to 83 %, Scheme 3.27). Under the same reaction conditions, starting from 2-aminobenzyl alcohol and substituted amides, the quinazoline derivatives were obtained in good yields as well (58 to 81 %, Scheme 3.27). A greater functional groups tolerance was obtained with this catalyst.

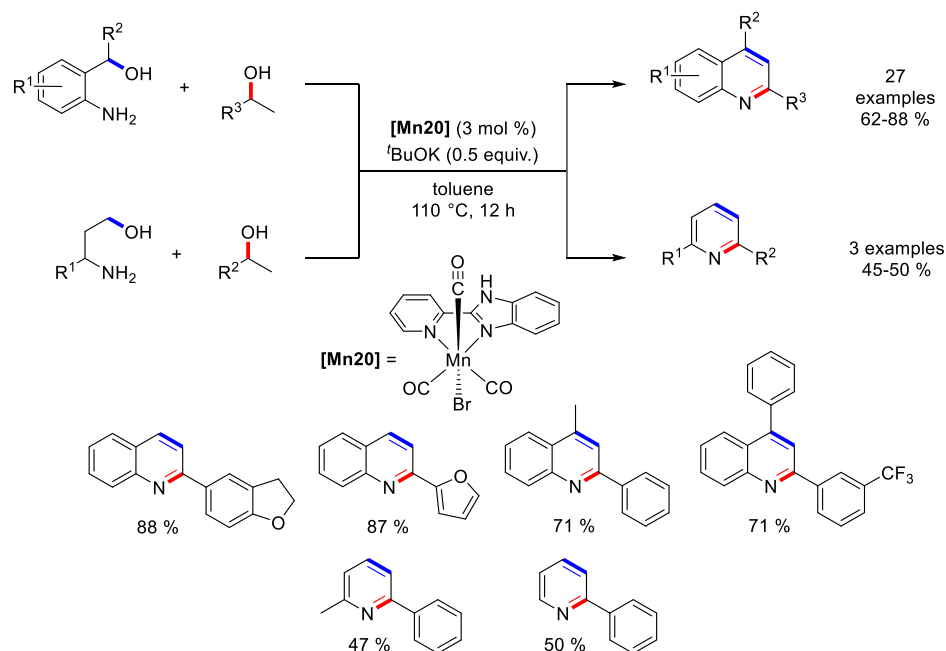
¹⁹⁵ Daw, P.; Kumar, A.; Espinosa-Jalapa, N. A.; Diskin-Posner, Y.; Ben-David, Y.; Milstein, D. *ACS Catal.* **2018**, *8*, 7734-7741.

¹⁹⁶ Mondal, A.; Sahoo, M. K.; Subramanian, M.; Balaraman, E. *J. Org. Chem.* **2020**, *85*, 7181-7191.



Scheme 3.27: Synthesis of quinazolines and quinoxalines reported by Balaraman.

The same year, Chai and Zang described the synthesis of quinolines and pyridines using a NN-pyridine-benzimidazole bidentate manganese complex.¹⁹⁷ The reaction of secondary alcohols with 2-aminobenzyl alcohols or 1,3-amino-alcohols in the presence of a catalytic amount of $t\text{BuOK}$ (0.5 equiv.) and NN-Mn complex (3 mol %) in toluene at 110 °C led to the desired heterocycles in moderate to good yields (45 to 88 %, Scheme 3.28) and a high functional groups compatibility compared to the system described by Srimani (limited to benzophenone derivatives to generate substitution in position 4 of the quinoline).¹⁹¹

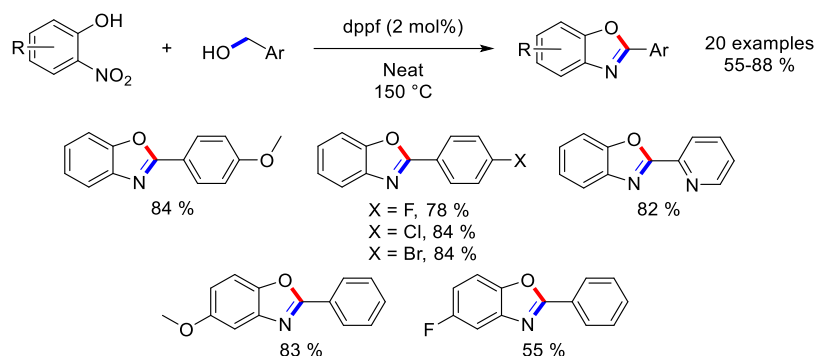


Scheme 3.28: Synthesis of quinolines and pyridines.

¹⁹⁷ Chai, H.; Tan, W.; Lu, Y.; Zhang, G.; Ma, J. *Appl. Organomet. Chem.* **2020**, *34*, e5685.

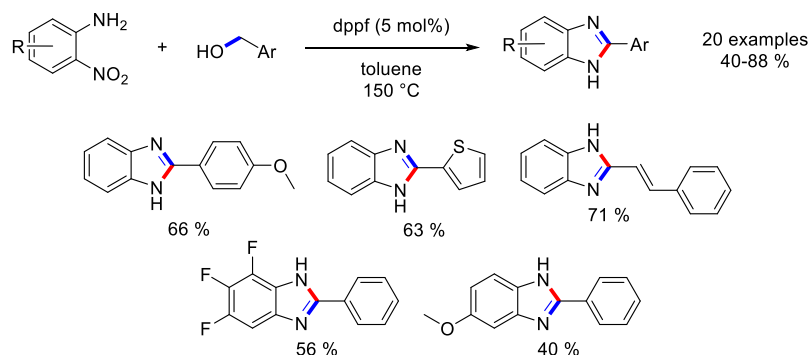
3) Iron-catalysed dehydrogenative synthesis of heterocycles.

In 2012, Deng reported the first iron-catalysed synthesis of heterocycle derivatives through a dehydrogenative coupling strategy.¹⁹⁸ Starting from *ortho*-nitrophenols and benzyl alcohols in the presence of diphenylphosphino-ferrocene (dppf) (2 mol %) as catalyst in neat conditions at 150 °C, various 2-arylbenzoxazoles bearing halogen (F, Cl, Br), methoxy, alkyl or heteroaryl substituents were isolated in good yields (55-88 %, Scheme 3.29).



Scheme 3.29: Iron-catalysed synthesis of benzoxazoles.

Following this work, Huang described the synthesis of benzimidazoles.¹⁹⁹ *Ortho*-nitroanilines were used as precursors along with benzyl alcohols in the presence of dppf (5 mol %) in toluene at 150 °C. Various substituted nitroanilines as well as benzyl alcohols bearing electro-donating or electro-withdrawing groups were engaged in this reaction and the corresponding products were prepared in moderate to good yields (40-88 %, Scheme 3.30).



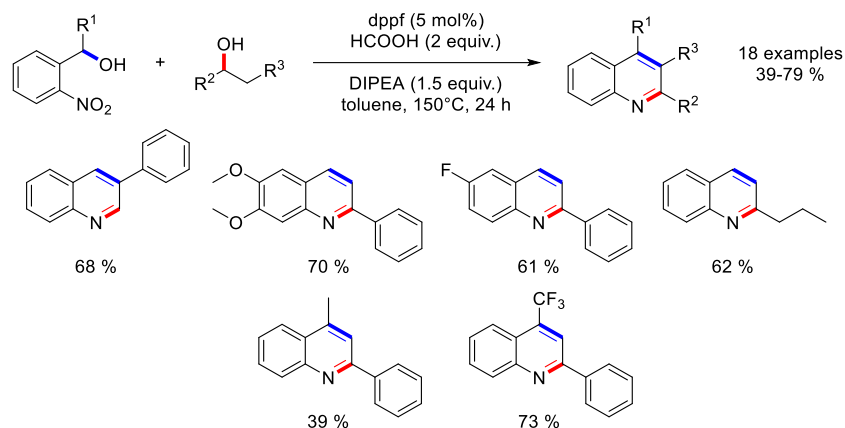
Scheme 3.30: Iron-catalysed synthesis of benzimidazoles.

In 2016, Wang described a dppf catalyzed synthesis of quinolines (Scheme 3.31).²⁰⁰ Differently substituted quinolines were prepared from 2-nitrobenzylalcohols and secondary alcohols. In this process, formic acid served as a hydride source to reduce the nitro function into the corresponding amine, allowing the subsequent condensation and cyclisation. Nevertheless, this system requires higher temperature and base loading compared to Zang's system (110 °C and ^tBuOK 0.5 equiv., Scheme 3.28).¹⁹⁷

¹⁹⁸ Wu, M.; Hu, X.; Liu, J.; Liao, Y.; Deng, G.-J. *Org. Lett.* **2012**, *14*, 2722-2725.

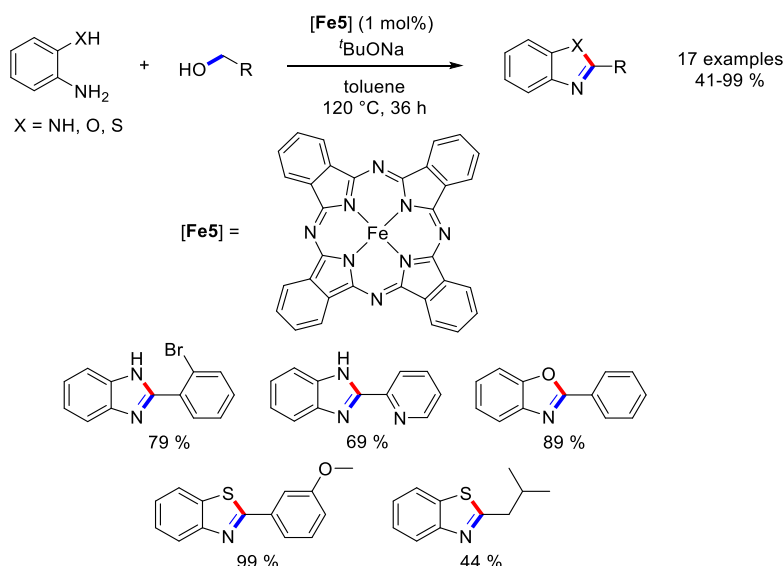
¹⁹⁹ Li, G.; Wang, J.; Yuan, B.; Zhang, D.; Lin, Z.; Li, P.; Huang, H. *Tetrahedron Lett.* **2013**, *54*, 6934-6936.

²⁰⁰ Liu, Y.; Wu, Y.-C.; Wang, Q.; Wang, M.; Li, H.-J.; Zhu, S. *Synthesis* **2016**, *48*, 3985-3995.



Scheme 3.31: Synthesis of quinolines.

Singh described an iron(II) phthalocyanine complex-catalysed synthesis of benzimidazoles, benzoxazoles and benzothiazoles.²⁰¹ 2-amino, 2-hydroxy and 2-thioanilines reacted with alkyl and benzyl alcohols in the presence of ^tBuONa (2 equiv.) and Fe(II)Pc (1 mol %) in toluene at 120 °C to yield the 2-substituted heterocycles (41 to 99 %, Scheme 3.32). Lower yields were obtained with aliphatic alcohols due to a greater activation energy of these alcohols over the oxidation step.

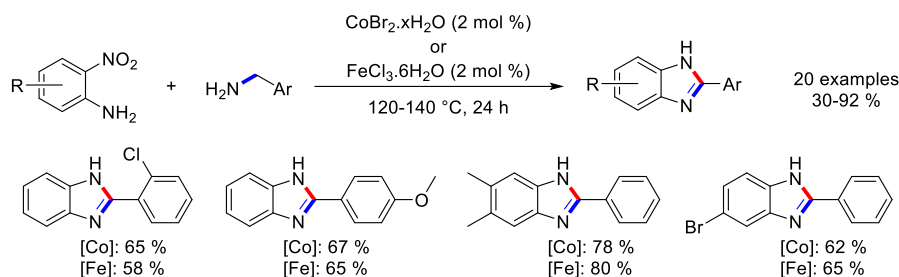


Scheme 3.32: Synthesis of benzimidazoles, benzoxazoles and benzothiazoles reported by Singh.

Such derivatives can be also synthesised from benzylamines as pro-electrophiles, as described by Nguyen and co-workers, in the presence of FeCl₃ or CoBr₂ at 120-140 °C.²⁰² Ortho-nitroanilines reacted with various benzyl amines to yield the desired five-member rings in good yields (62-92 % with cobalt and 30-87 % with iron, Scheme 3.33).

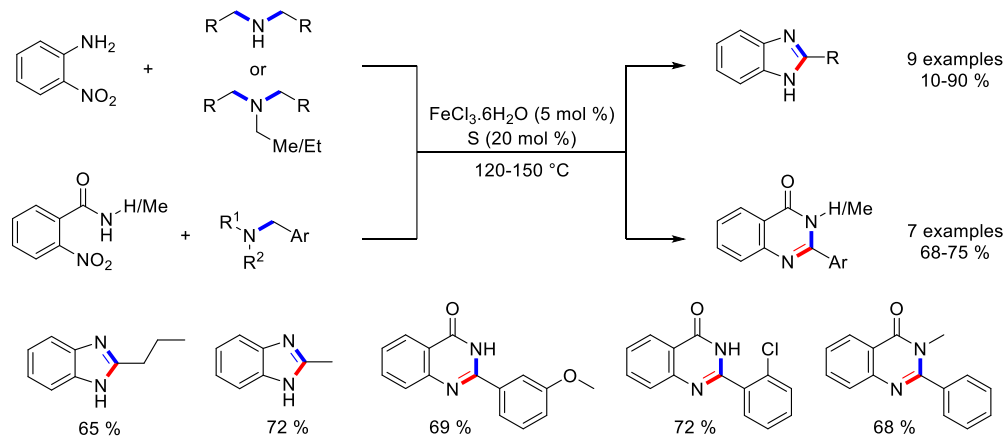
²⁰¹ Bala, M.; Verma, P. K.; Sharma, U.; Kumar, N.; Singh, B. *Green Chem.* **2013**, *15*, 1687-1693.

²⁰² Nguyen, T. B.; Le Bescont, J.; Ermolenko, L.; Al-Mourabit, A. *Org. Lett.* **2013**, *15*, 6218-6221.



Scheme 3.33: Synthesis of 2-arylbenzimidazoles reported by Nguyen.

To allow the synthesis of 2-alkylbenzimidazoles, 20 mol % of elemental sulfur has to be added. Actually, sulfur served as an electron-donor to efficiently reduce the nitro function, thus increasing the conversion and yields of the reaction. In these conditions, 2-alkylbenzimidazoles were isolated in low to good yields (10 to 90 %, Scheme 3.34). The authors extended this work to the synthesis of 2-arylquinazolin-4(3*H*)-ones. 2-nitrobenzamide reacted with benzylamines in the same conditions, and the desired quinazolinones were isolated in good yields (68-75 %, Scheme 3.34). However, this methodology is more limited compared to the process developed by Li in the presence of copper complex.¹⁸⁶ Aiming to improve this catalytic system, a modified version in which elemental sulfur (20 mol %) was replaced by Na₂S.nH₂O (40 mol %) was described then, and the benzimidazoles products were obtained in comparable yields (44 to 90 %) than those described by Li.²⁰³

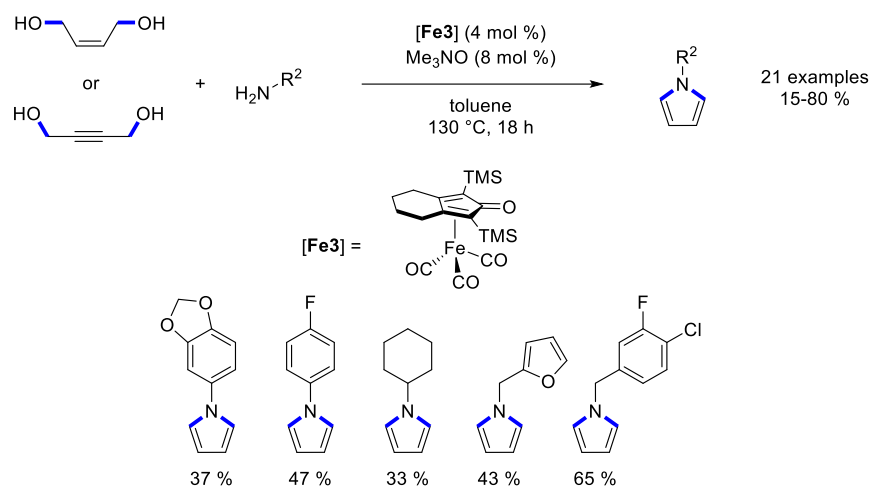


Scheme 3.34: Synthesis of 2-alkylbenzimidazoles and quinazolinones.

Barta reported the use of the Knölker's complex for the synthesis of *N*-substituted pyrroles.²⁰⁴ Various primary alkyl and aryl amines reacted with 1,4-diols in the presence of the Knölker complex (4 mol %) and Me₃NO (8 mol %) in toluene at 130 °C to yield the pyrrole derivatives in 15 to 80 % (Scheme 3.35). A wide range of functions as well as heteroaryl rings were tolerated, making this methodology competitive compared to the one proposed by Rueping¹⁹⁰ or Kempe¹⁸⁹ (Scheme 3.18 and Scheme 3.19).

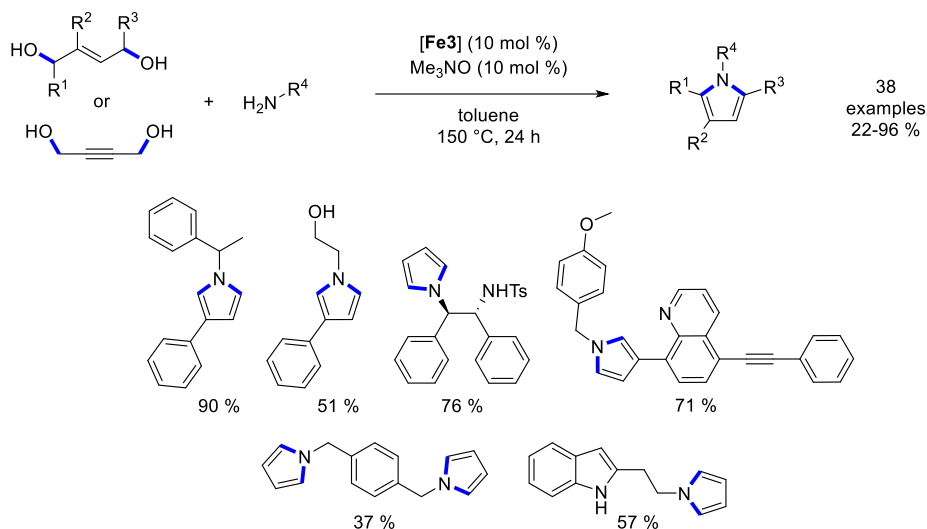
²⁰³ Nguyen, T. B.; Ermolenko, L.; Al-Mourabit, A. *Synthesis* **2015**, 47, 1741-1748.

²⁰⁴ Yan, T.; Barta, K. *ChemSusChem* **2016**, 9, 2321-2325.



Scheme 3.35: Synthesis of pyrroles reported by Barta.

Increasing the catalytic loading up to 10 mol % and the temperature to 150 °C, Sundararaju extended the scope of this reaction and various substituted pyrroles were isolated (22 to 96 % yields, Scheme 3.36).²⁰⁵ Barta and Sundararaju reported almost simultaneously the synthesis of *N*-substituted pyrroles from various primary alkyl and arylamines and 1,4-alkene-diols or 1,4-butyndiols.

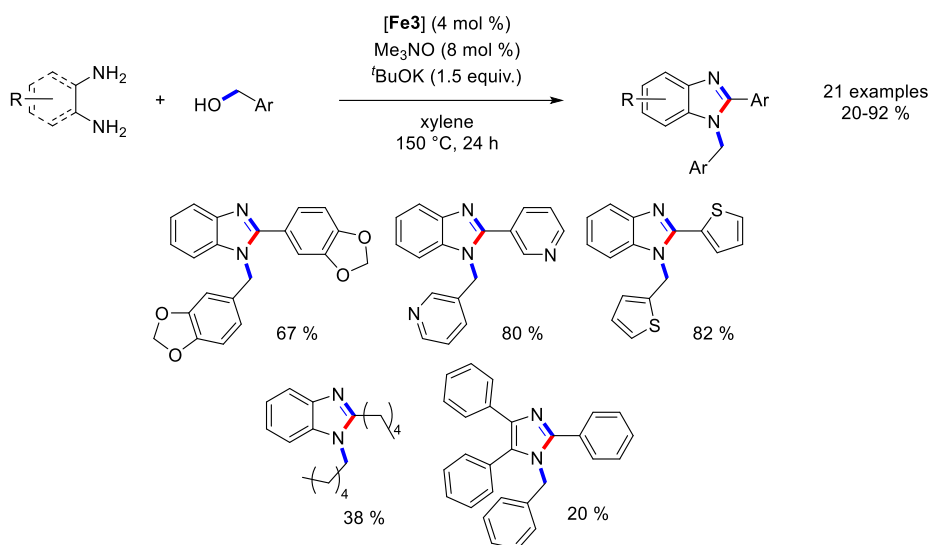


Scheme 3.36: Synthesis of pyrroles reported by Sundararaju.

Knölker's complex is also able to catalyse the synthesis of benzimidazoles.²⁰⁶ Following the same strategy than Srimani,¹⁹² 1,2-diamines reacted with primary alcohols in the presence of ^tBuOK (1.5 equiv.) Me₃NO (8 mol %) and Knölker's complex (4 mol %) in xylene at 150 °C to give the desired disubstituted benzimidazoles in low to good yields (20 to 92 %, Scheme 3.37). Compared to Wang⁸⁰ or Srimani,¹⁹² this methodology appears to be less efficient, nevertheless, aliphatic alcohols could also be engaged in this process.

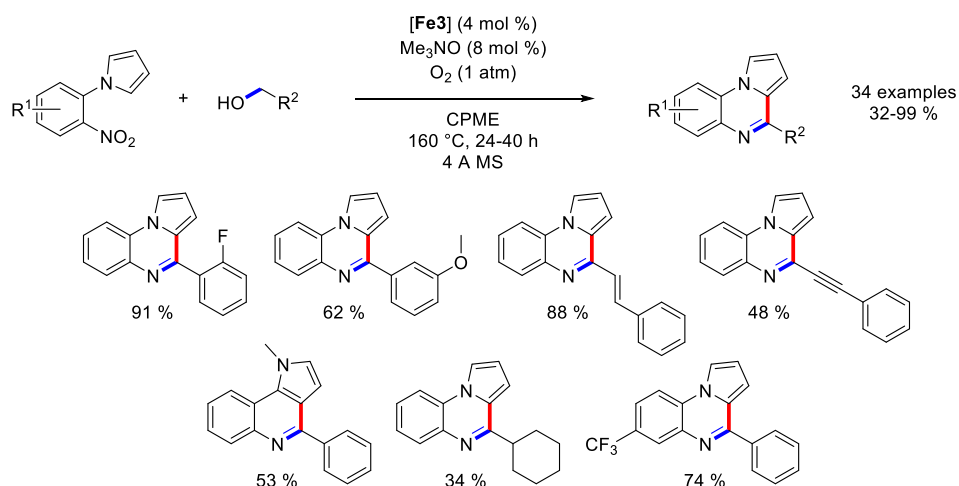
²⁰⁵ Emayavaramban, B.; Sen, M.; Sundararaju, B. *Org. Lett.* **2017**, *19*, 6-9.

²⁰⁶ Putta, R. R.; Chun, S.; Lee, S. B.; Oh, D.-C.; Hong, S. *Front. Chem.* **2020**, *8*, 429.



Scheme 3.37: Knölker complex-catalysed synthesis of benzimidazoles.

This methodology was extended to the synthesis of pyrrolo[1,2- α]quinoxalines.²⁰⁷ Using the Knölker complex (6 mol %) and Me₃NO (12 mol %) in cyclopentyl-methyl ether (CPME) at 160 °C under oxygen atmosphere, various 2-pyrrole nitroarenes reacted with primary alcohols to give the tricyclic products in low to very good yields (32-99 %, Scheme 3.38).

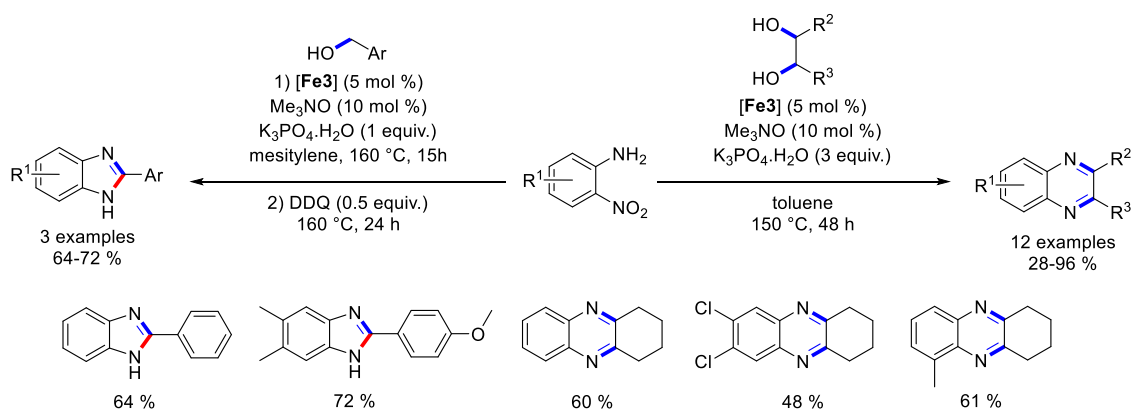


Scheme 3.38: Synthesis of pyrroloquinoxalines.

Recently, Darcel described the synthesis of benzimidazoles and quinoxalines catalyzed by the same iron complex.²⁰⁸ Starting from either primary alcohols or 1,2-diols and *ortho*-nitroaniline in the presence of K₃PO₄·H₂O (1 or 3 equiv.), Me₃NO (10 mol %) and the Knölker complex (5 mol %) in mesitylene (160 °C) or toluene (150 °C), the desired heterocyclic compounds were obtained in low to very good yields (28 to 96 %, Scheme 3.39). The addition of DDQ (0.5 equiv.) after 15 h of reaction was necessary for the obtention of benzimidazoles derivatives. This methodology was limited as only three examples of benzimidazoles, and only methyl- or halogen-substituted quinoxalines were reported.

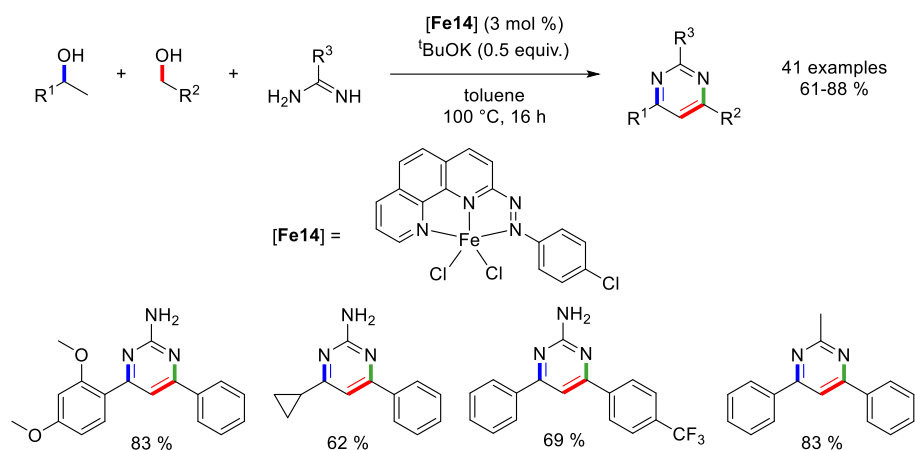
²⁰⁷ Chun, S.; Ahn, J.; Putta, R. R.; Lee, S. B.; Oh, D.-C.; Hong, S. *J. Org. Chem.* **2020**, *85*, 15314-15324.

²⁰⁸ Wu, J.; Darcel, C. *J. Org. Chem.* **2021**, *86*, 1023-1036.



Scheme 3.39: Synthesis of heterocycles reported by Darcel.

In 2020, Paul *et al.* introduced an NNN-Fe complex for the synthesis of 2-amino- or 2-alkyl-pyrimidines via a three-component reaction.²⁰⁹ Various alkyl- and aryl-substituted pyrimidines were prepared by this method in yields ranging from 61 to 88 % (Scheme 3.40). This method allowed the introduction of electron-withdrawing substituents, unlike previous methods (Scheme 3.12 and Scheme 3.16).^{185,188}



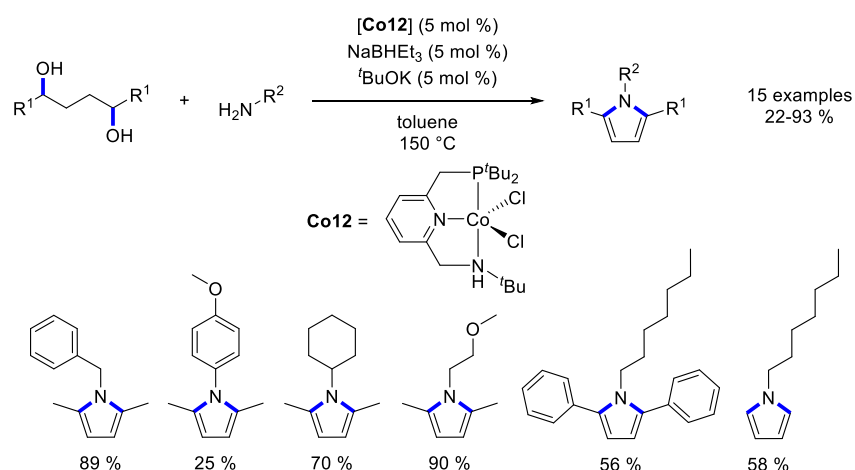
Scheme 3.40: Synthesis of pyrimidines.

4) Cobalt-catalysed dehydrogenative synthesis of heterocycles.

In 2016, Milstein reported the first cobalt-catalysed synthesis of pyrroles starting from 1,4-diols and primary amines.²¹⁰ A PNN pincer Co complex (5 mol %) was used with tBuOK (5 mol %) and NaBHET₃ (5 mol %) to activate the catalyst. Various alkyl- or aryl-substituted pyrroles were prepared by this methodology (22 to 93 % yields, Scheme 3.41). This methodology tolerated electron-donating (methoxy, methyl) and electron-withdrawing groups (CF₃) without impeding the yield of the reaction.

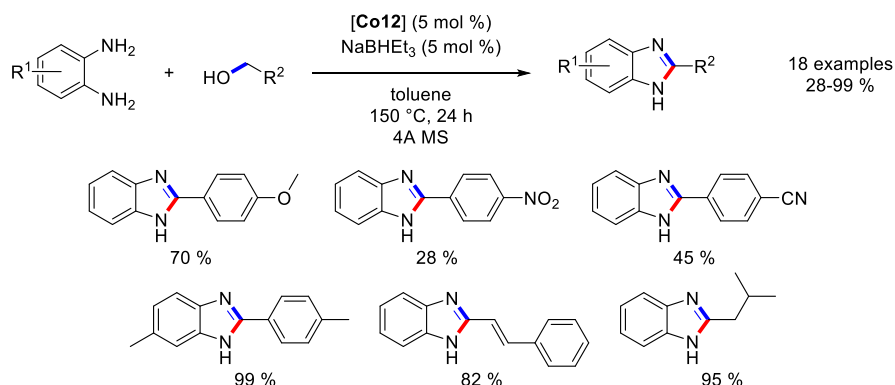
²⁰⁹ Mondal, R.; Sinha, S.; Das, S.; Chakraborty, G.; Paul, N. D. *Adv. Synth. Catal.* **2020**, 362, 594-600.

²¹⁰ Daw, P.; Chakraborty, S.; Garg, J. A.; Ben-David, Y.; Milstein, D. *Angew. Chem. Int. Ed.* **2016**, 55, 14373-14377.



Scheme 3.41: Cobalt-catalysed synthesis of pyrroles.

Following this work, the same catalyst was used for the synthesis of benzimidazoles.²¹¹ Diamines reacted with various primary alcohol in the presence of NaBHET₃ (5 mol %) and the PNN-Co catalyst (5 mol %), without any additional base. The desired benzimidazoles were isolated in 28 to 99 % yields (Scheme 3.42). Various functional groups were tolerated allowing the formation of functionalised heterocycles.

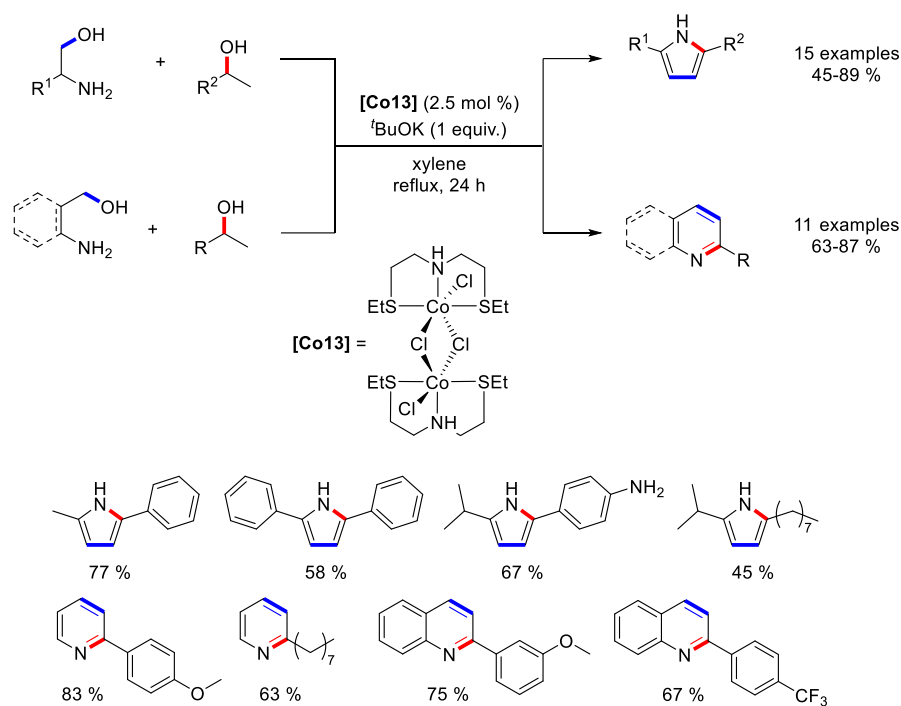


Scheme 3.42: Cobalt-catalysed synthesis of benzimidazoles.

Later on, Balaraman reported the synthesis of pyrroles and quinolines using a dimeric-cobalt complex bearing a SNS ligand.²¹² 1,2-amino-alcohols reacted with secondary alcohols in the presence of ^tBuOK (1 equiv.) and the dimeric complex (2.5 mol %) in refluxing xylene. Various non-symmetric alkyl- and aryl-substituted pyrroles were isolated following this methodology in 45 to 89 % yields (Scheme 3.43). The same conditions were used for the reaction between 1,3-amino-alcohols and secondary alcohols, allowing the synthesis of pyridines and quinolines in 63 to 78 % yields (Scheme 3.43). This complex, compared to Milstein's,²¹⁰ can be easily prepared as the ligand is not air-sensitive. In addition, more functional groups are tolerated with this methodology.

²¹¹ Daw, P.; Ben-David, Y.; Milstein, D. *ACS Catal.* **2017**, *7*, 7456-7460.

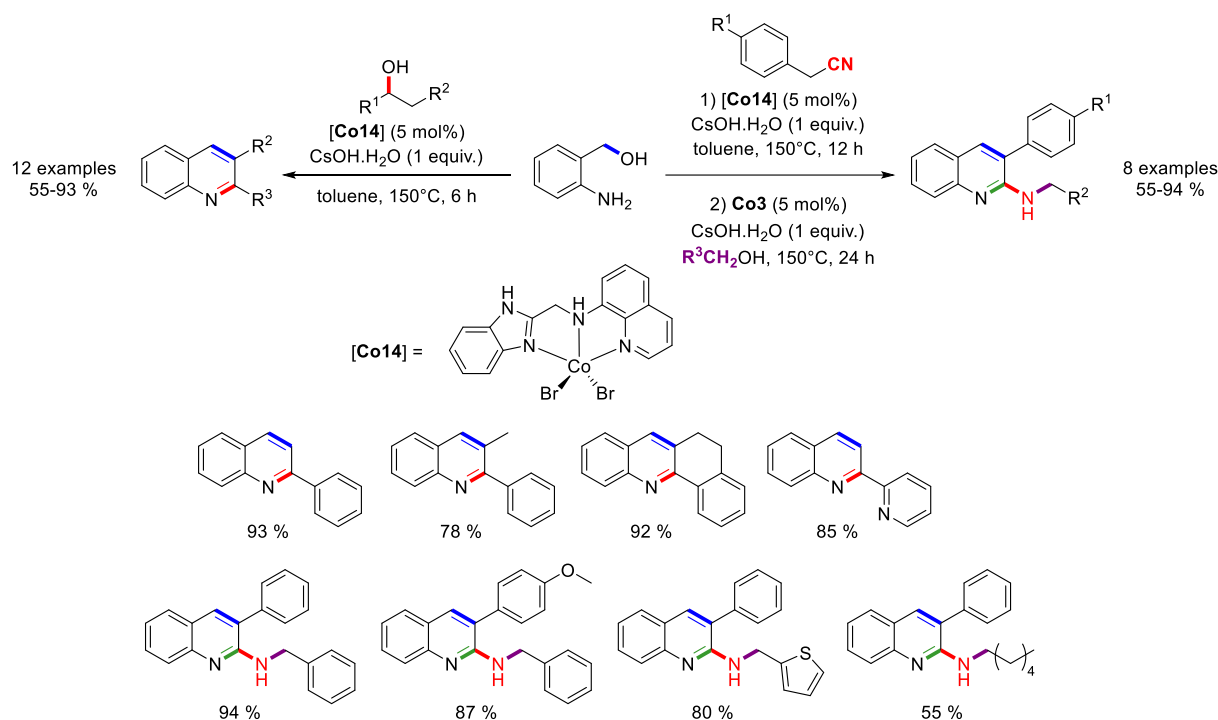
²¹² Midya, S. P.; Landge, V. G.; Sahoo, M. K.; Rana, J.; Balaraman, E. *Chem. Commun.* **2018**, *54*, 90-93.



Scheme 3.43: Synthesis of pyrroles, pyridines and quinolines.

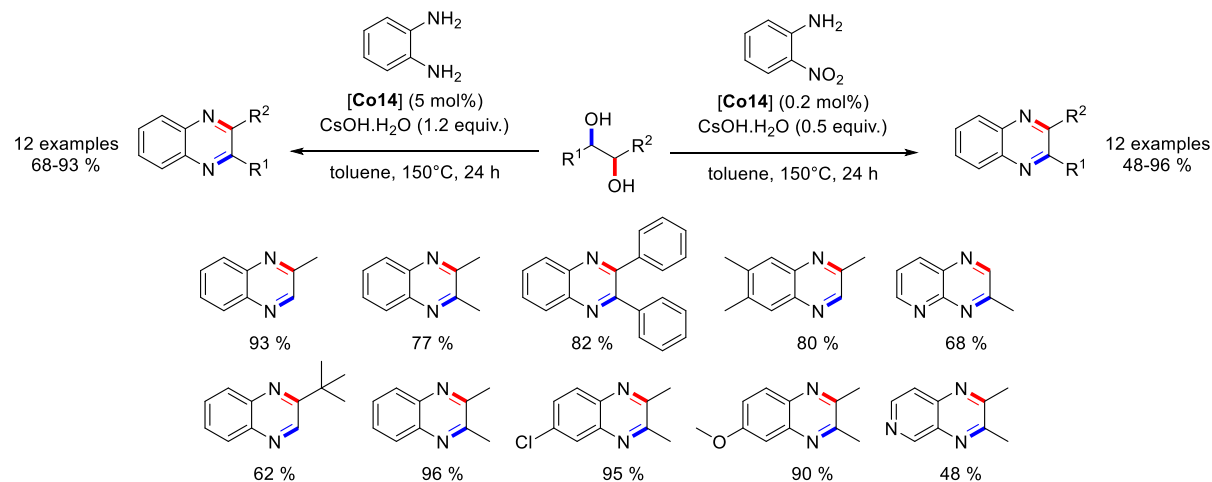
In 2018, a cobalt-catalysed synthesis of quinolines, 2-alkylaminoquinolines and quinoxalines was reported by Kundu.²¹³ Starting from 2-aminobenzylalcohols and secondary alcohols, various 2-arylquinolinones were obtained in 55 to 93 % yields (Scheme 3.44). 2-aminoquinolines were also obtained in two steps using 2-aminobenzylalcohols and benzonitrile (Scheme 3.44). As reported by Srimani,¹⁹⁴ an initial Co-catalysed dehydrogenation leading to 2-aminoquinoline derivative was then followed by a Co-catalysed amino-alkylation in a second step.

²¹³ Shee, S.; Ganguli, K.; Jana, K.; Kundu, S. *Chem. Commun.* **2018**, 54, 6883-6886.



Scheme 3.44: Cobalt-catalysed synthesis of quinolines and 2-aminoalkylquinolines.

The same complex was applied to the synthesis of quinoxalines using vicinal diols and 2-aminoanilines or 2-nitroanilines. Alkyl- and aryl-substituted quinoxalines were isolated in good to excellent yields (48-96 %, Scheme 3.45).

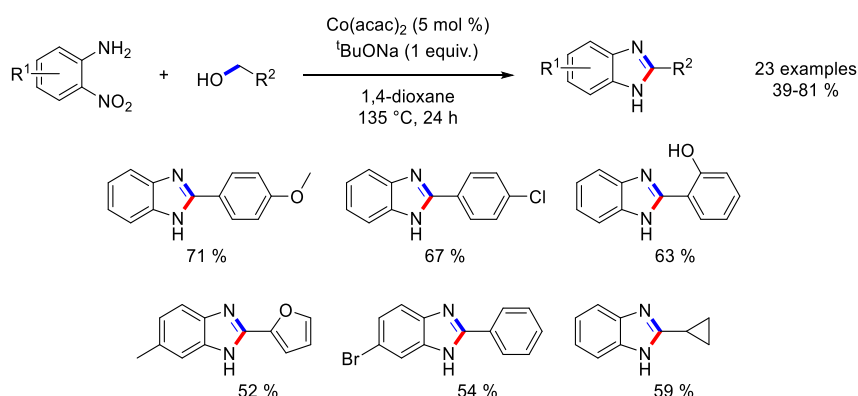


Scheme 3.45: Synthesis of quinoxalines.

In 2019, De Sarkar reported the use of Co(acac)₂ as a catalyst for the synthesis of benzimidazoles.²¹⁴ Starting from ortho-nitroanilines and benzyl alcohols in the presence of ^tBuONa (1 equiv.) and Co(acac)₂ (5 mol %) in 1,4-dioxane at 135 °C, the desired heterocyclic compounds were obtained in moderate to good yields (39 to 81 %, Scheme 3.46). Both in terms of group tolerance and reactivity, this simple catalytic system is competitive with the Co-pincer complex described by

²¹⁴ Das, S.; Mallick, S.; De Sarkar, S. *J. Org. Chem.* **2019**, *84*, 12111-12119.

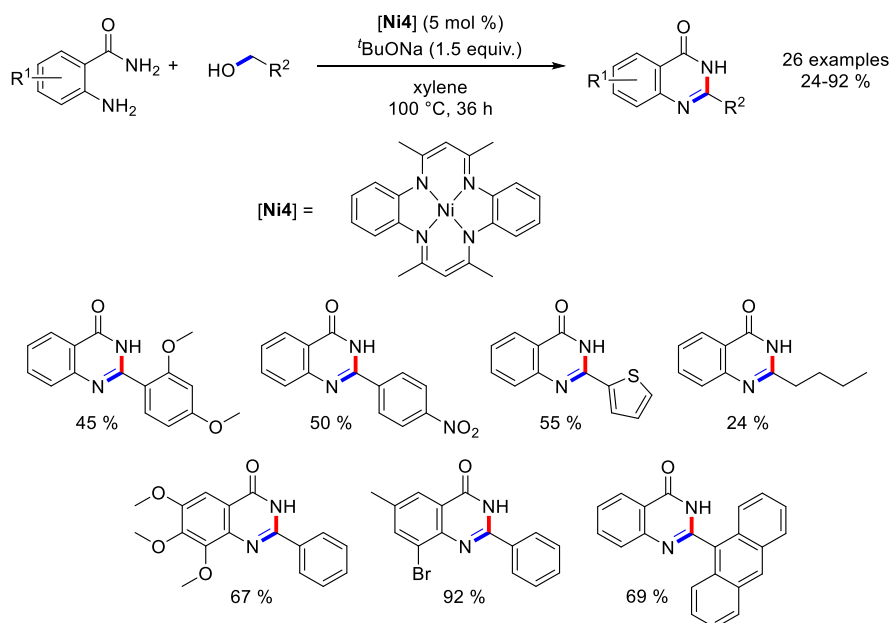
Milstein.²¹¹ To highlight this reactivity, the 2-cyclopropylbenzimidazole, a heterocyclic compound with a strained and reactive cyclopropyl substituent, was prepared in 59 % yield following this procedure.



Scheme 3.46: Cobalt-catalysed synthesis of benzimidazoles.

5) Nickel-catalysed dehydrogenative synthesis of heterocycles.

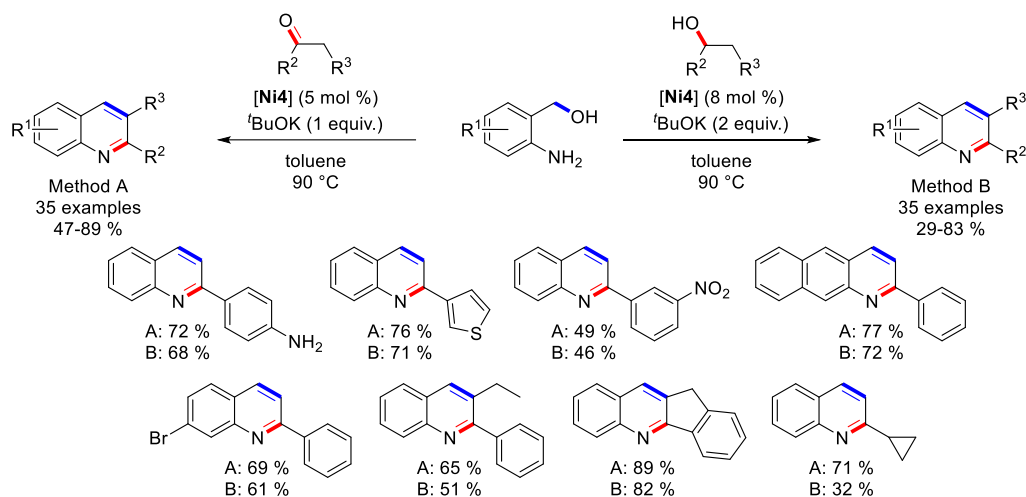
In 2017, Paul reported the first nickel-catalysed synthesis of heterocycle derivatives following a dehydrogenative coupling methodology.²¹⁵ In the optimised reaction conditions, benzyl alcohols reacted with 2-aminobenzamides in the presence of ^tBuONa (1.5 equiv.) and a nickel complex bearing a tetraaza macrocyclic ligand (5 mol %) in xylene at 100 °C (Scheme 3.47). Both the yields and the diversity of substituent for the reported small library of quinazolin-4(3*H*)-ones are similar to those described previously by Li¹⁸⁶ in the presence of Cu(OAc)₂ or by Nguyen in the presence of FeCl₃.²⁰²



Scheme 3.47: Nickel-catalysed synthesis of quinazolinones.

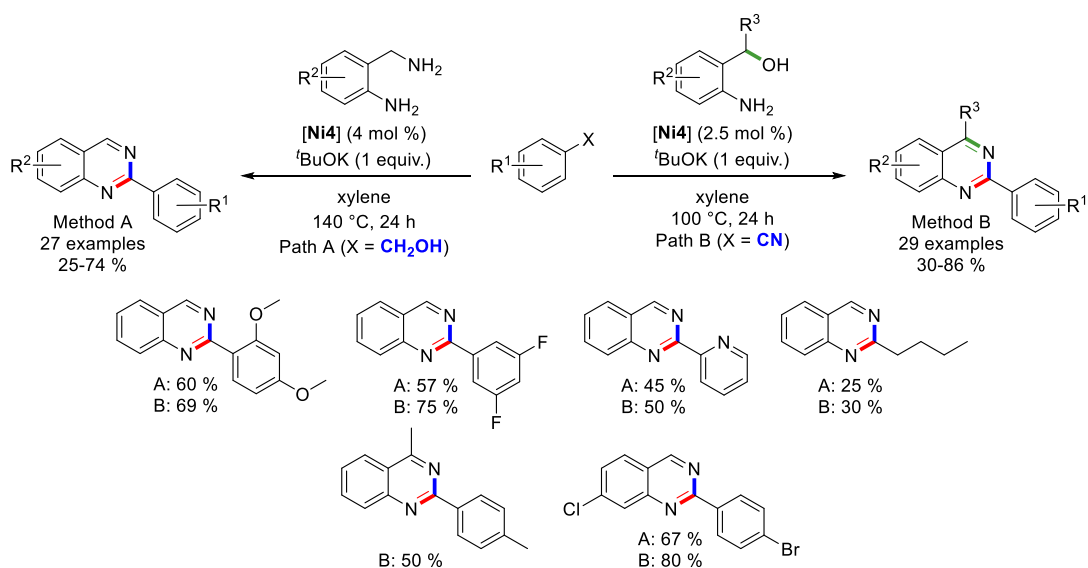
²¹⁵ Parua, S.; Das, S.; Sikari, R.; Sinha, S.; Paul, N. D. *J. Org. Chem.* **2017**, *82*, 7165-7175.

The same complex allowed also to open the route to quinolines *via* either a mono- or double-dehydrogenative coupling process.²¹⁶ Various substituted aryl and aliphatic alcohols or ketones were engaged with 2-aminobenzyl alcohol in the presence of stoichiometric ^tBuOK and catalytic amount of the nickel complex in toluene at 90 °C. Both methods led to the desired heterocycles in moderate to good yields (29-89 %, Scheme 3.48), albeit, the double-dehydrogenative methodology furnished the quinolines products in slightly lower yields.



Scheme 3.48: Synthesis of quinolines from ketones or secondary alcohols.

Paul *et al.* also described the synthesis of quinazolines using 2-aminobenzylamine and alcohols, or 2-aminobenzyl alcohol and benzonitrile.²¹⁷ The quinazolines products were isolated in low to good yields using whatever methods (25 to 86 %, Scheme 3.49). Again, the mono-dehydrogenative coupling (*i.e.* Method B, Scheme 3.49) led to better results.

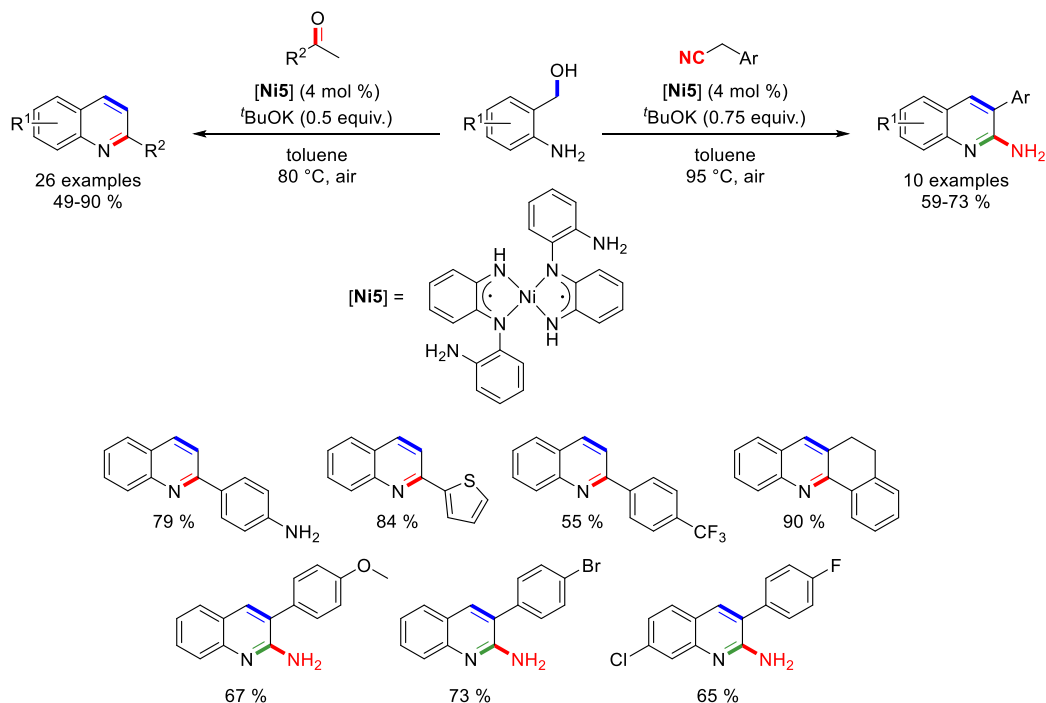


Scheme 3.49: Synthesis of quinazolines from benzylamines or benzonitriles.

²¹⁶ Parua, S.; Sikari, R.; Sinha, S.; Das, S.; Chakraborty, G.; Paul, N. D. *Org. Biomol. Chem.* **2018**, *16*, 274-284.

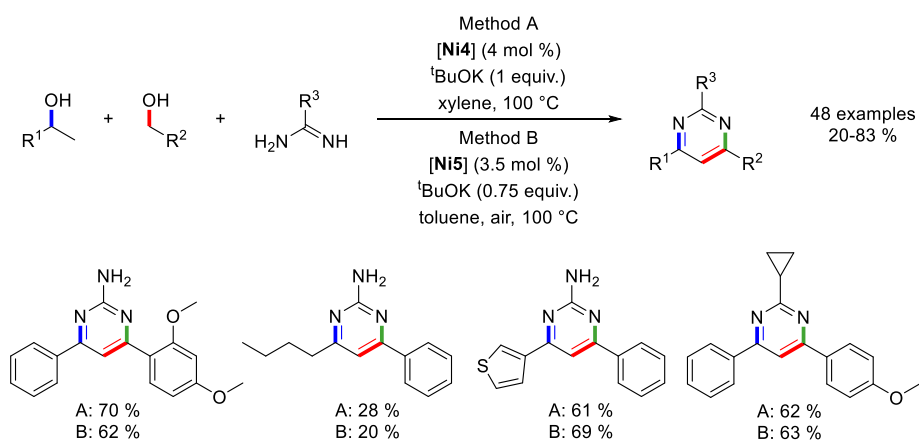
²¹⁷ Parua, S.; Sikari, R.; Sinha, S.; Chakraborty, G.; Mondal, R.; Paul, N. D. *J. Org. Chem.* **2018**, *83*, 11154-11166.

In 2019, Paul reported another nitrogen ligand-based nickel complex and its application in dehydrogenative processes, i.e. the synthesis of quinolines, aminoquinolines and quinazolines (Scheme 3.50).²¹⁸ The main feature of these catalytic reactions are the following: (i) less amount of base required and (ii) the reaction can be carried out under an air atmosphere, otherwise, the reaction conditions and the isolated yields are very similar.



Scheme 3.50: Synthesis of quinolines and 2-aminoquinolines reported by Paul.

Finally, the activities of **Ni4** and **Ni5** in the synthesis of pyrimidines were compared.²¹⁹ Very similar conditions were used for both complexes. Nevertheless, the second **Ni4** led to slightly higher yields in most cases (20-83 %, Scheme 3.51).

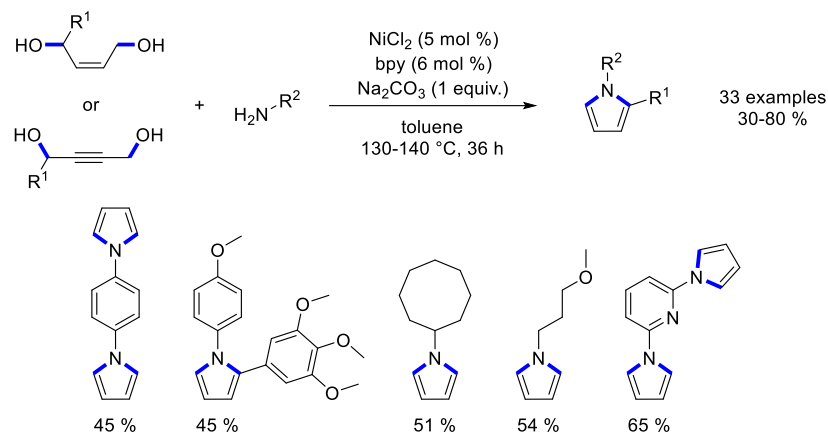


Scheme 3.51: Synthesis of pyrimidines reported by Paul.

²¹⁸ Chakraborty, G.; Sikari, R.; Das, S.; Mondal, R.; Sinha, S.; Banerjee, S.; Paul, N. D. *J. Org. Chem.* **2019**, *84*, 2626-2641.

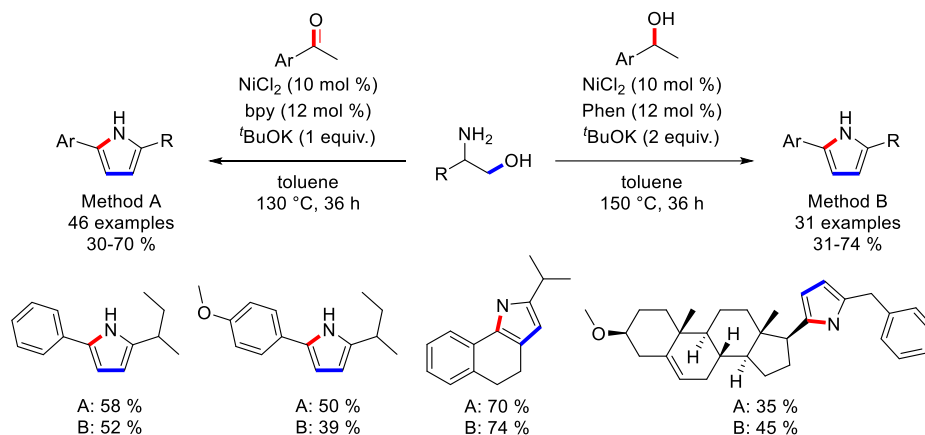
²¹⁹ Chakraborty, C.; Sikari, R.; Mondal, R.; Mandal, S.; Paul, N. D. *Asian J. Org. Chem.* **2020**, *9*, 431-436.

In 2018, Banerjee described a very simple and inexpensive 2,2'-bipyridine NiCl₂ complex catalysed synthesis of pyrroles.²²⁰ Following the same strategy than Barta,²⁰⁴ various unsaturated 1,4-diols reacted with aromatic and aliphatic amines to provide the pyrrole derivatives in 30 to 80 % yields (Scheme 3.52). Similar results were obtained with Barta or Sundararaju's methodologies.^{204,205} Nevertheless, this methodology does not require the synthesis of the catalyst *a priori*.



Scheme 3.52: Synthesis of pyrroles.

Following the methodology proposed by Kempe,¹⁸⁹ amino-alcohols can be pro-nucleophiles/pro-electrophiles partners in this process. Thus, they can react with either ketones²²¹ or secondary alcohols,²²² in the presence of ^tBuOK (1 or 2 equiv.), bipyridine-type ligand (12 mol %) and NiCl₂ (10 mol %) at elevated temperatures. Various non-symmetric pyrroles were obtained in yields ranging from 30 to 70 % (Scheme 3.53).



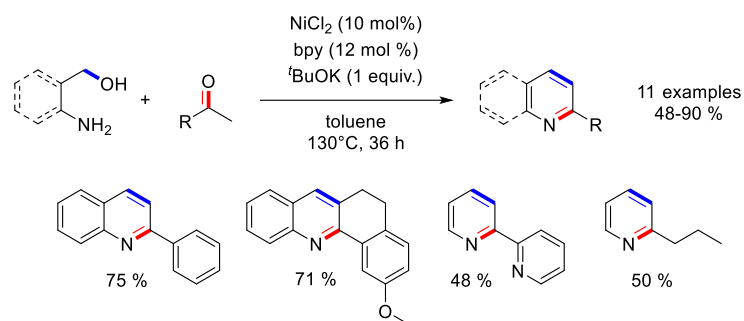
Scheme 3.53: Synthesis of pyrroles from amino-alcohols.

The NiCl₂(bpy) complex was then applied for the synthesis of quinolines and from amino-alcohols and ketones as also observed by Paul.²¹⁸ The quinoline products were obtained in moderate to good yields (48-90 %, Scheme 3.54). Few substituents were described in this work, and consequently the scope appeared limited compared to other works.

²²⁰ Singh, K.; Kabadwal, L. M.; Bera, S.; Alanthadka, A.; Banerjee, D. *J. Org. Chem.* **2018**, *83*, 15406-15414.

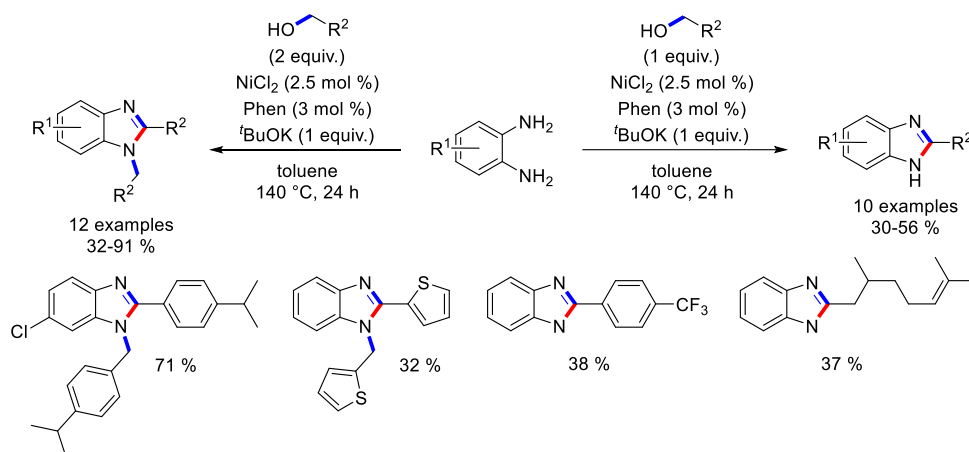
²²¹ Singh, K.; Vellakaran, M.; Banerjee, D. *Green Chem.* **2018**, *20*, 2250-2256.

²²² Alanthadka, A.; Bera, S.; Vellakaran, M.; Banerjee, D. *J. Org. Chem.* **2019**, *84*, 13557-13564.



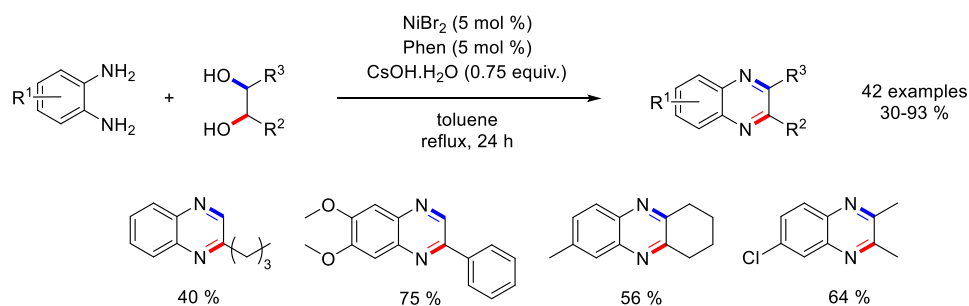
Scheme 3.54: Synthesis of quinolines and pyridines.

Concerning the $\text{NiCl}_2(1,10\text{-phenanthroline})$ complex, it was further used for the synthesis of benzimidazoles (Scheme 3.55).²²³ Contrary to the work of Wang⁸⁰ or Srimani,¹⁹² for which the nature and the loading of the base changed the selectivity for the final product, the selectivity for the mono- or disubstituted benzimidazole was only driven by the amount of the alkylating agent.



Scheme 3.55: Synthesis of benzimidazoles.

In 2020, Kundu described the synthesis of quinoxalines using Ni(II)/phen complex.²²⁴ The desired heterocycles were obtained following a similar methodology previously reported by this group using a cobalt catalyst.²¹³ Lower yields were obtained with the nickel system and more specifically with alkyl substituents (Scheme 3.56).

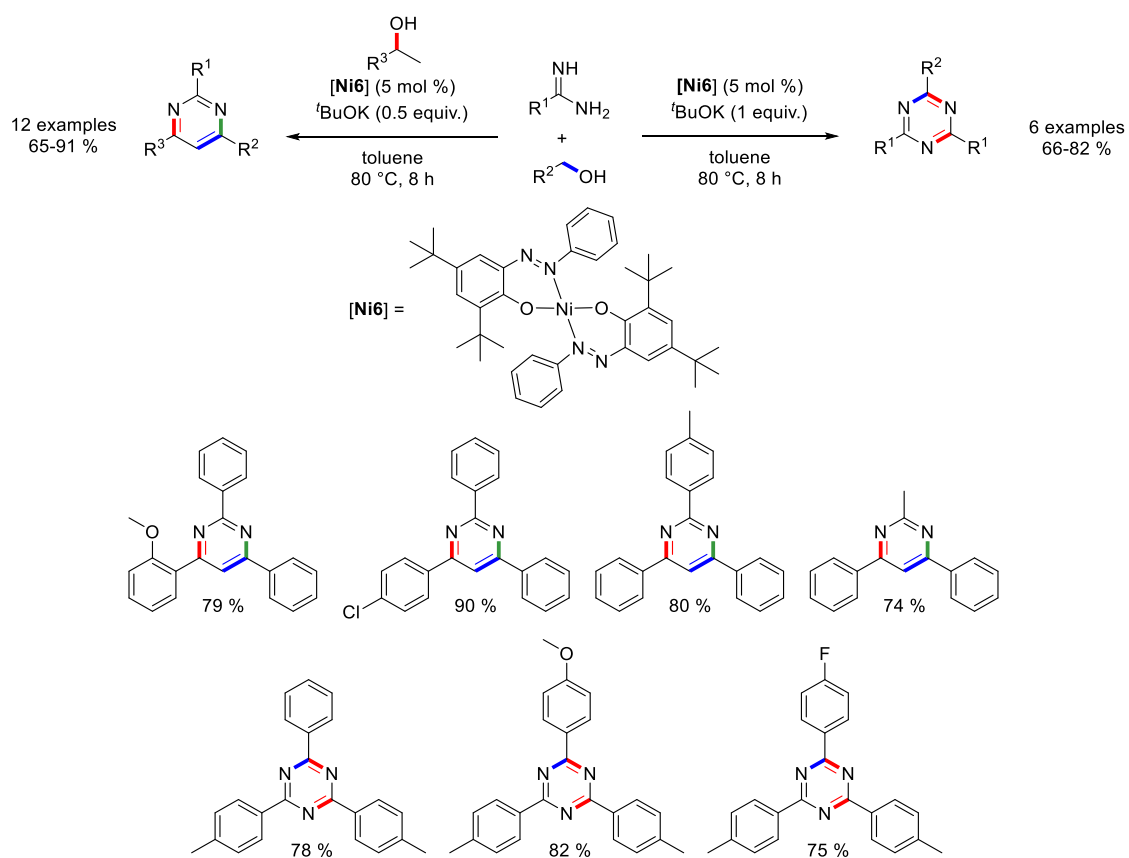


Scheme 3.56: Nickel-catalysed synthesis of quinoxalines.

²²³ Bera, A.; Sk, M.; Singh, K.; Banerjee, D. *Chem. Commun.* **2019**, 55, 5958-5961.

²²⁴ Shee, S.; Panja, D.; Kundu, S. *J. Org. Chem.* **2020**, 85, 2775-2784.

The same year, the synthesis of pyrimidines and triazines was reported by Adhikari.²²⁵ Following previously reported methods for the synthesis of pyrimidines^{187,188,209} or 1,3,5-triazines¹⁸⁴ and using a new nickel(II) complex, various heterocyclic products were isolated in good to very good yields (65-91 %, Scheme 3.57). Nevertheless, this reaction was limited to benzamidines and benzyl alcohols.



Scheme 3.57: Synthesis of pyrimidines and triazines.

Regarding the state of the art on the synthesis of quinolinones and dehydrogenative coupling reactions, catalysed by non-noble metals and leading to heterocyclic products, it was proposed to evaluate the feasibility of the synthesis of quinolinone-type products via dehydrogenative coupling reaction. This would be the first synthesis of quinoline-2(1*H*)-ones using such a strategy.

²²⁵ Bains, A. K.; Adhikari, D. *Catal. Sci. Technol.* **2020**, *10*, 6309-6318.

IV. Iron-catalysed dehydrogenative coupling of amido-alcohols: Synthesis of 3-Arylquinolin-2(1H)-ones.

3-Arylquinolin-2(1H)-ones presents 3 different cycles (A, B and C, Figure 3.2) which can be substituted prior to the cyclization, or by *post*-functionalization of the quinolinone product. In order to bring diversity to our reaction, various substituted *N*-(2-(hydroxymethyl)phenyl)-2-arylacamide were prepared.

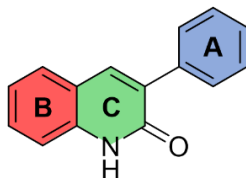


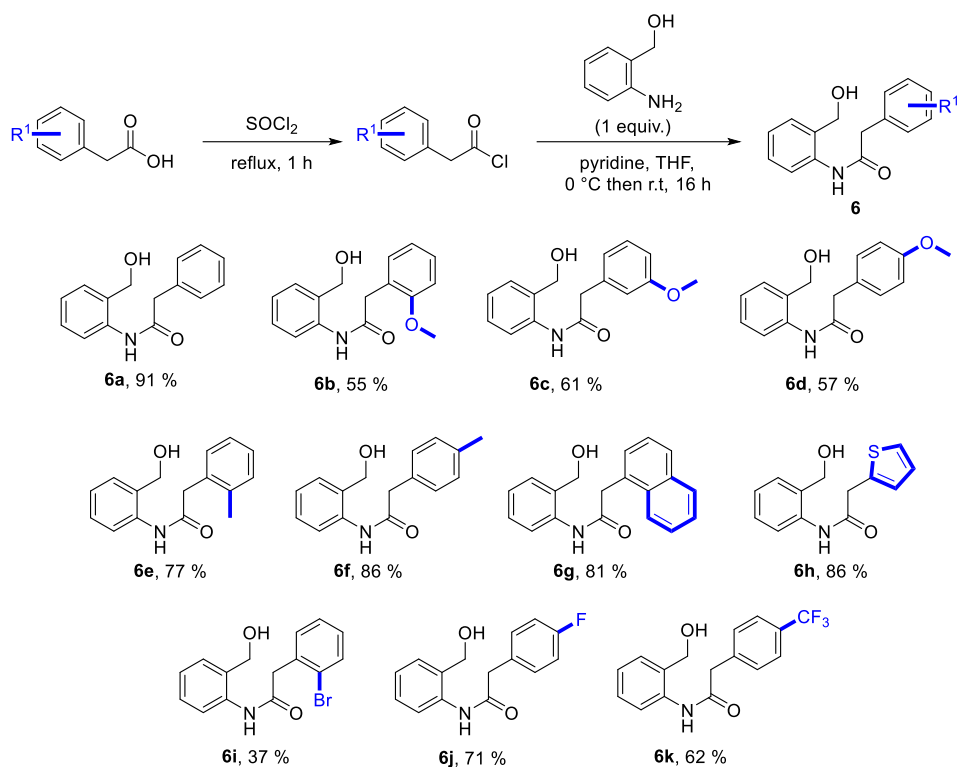
Figure 3.2: Representation of the different cycles A, B and C discussed.

1) Synthesis of starting materials.

a) Modification of Cycle A.

In order to bring diversity on cycle A, substituted amido-alcohols **6** were targeted. Compounds **6a-k** were easily prepared in two steps from various substituted arylacetic acids in 37 to 91 % overall yields (Scheme 3.58).²²⁶ Neither electronic effects nor the steric hindrance generated in *ortho* position of the substituents impeded the reaction.

²²⁶ Wissner, A.; Carroll, M. L.; Johnson, B. D.; Kerwar, S. S.; Pickett, W. C.; Schaub, R. E.; Torley, L. W.; Trova, M. P.; Kohler, C. A. *J. Med. Chem.* **1992**, *35*, 4779-4789.

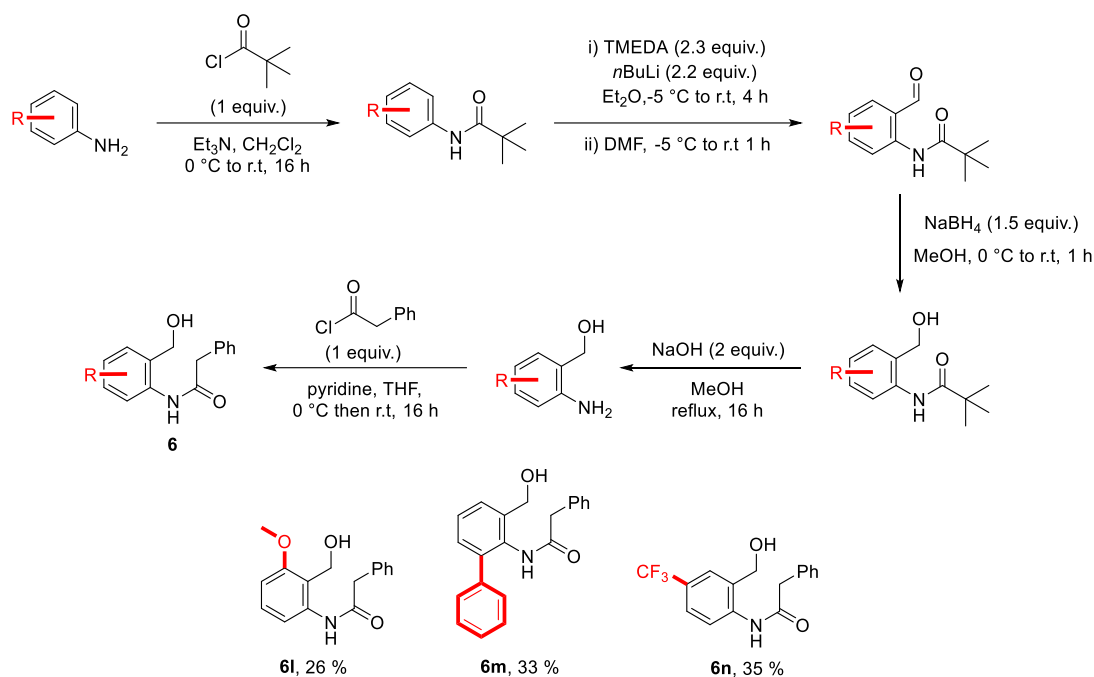


Scheme 3.58: Synthesis of amido-alcohols from substituted arylacetic acids.

b) Substitution on Cycle B.

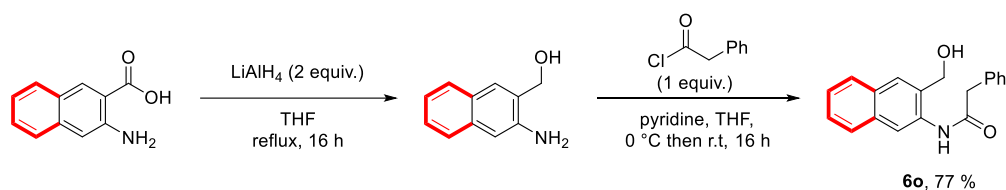
To bring diversity, a second small library of amido-alcohols (**6l-n**) was prepared from substituted 2-aminobenzyl alcohols (Scheme 3.59). Starting from substituted anilines, *ortho*-formylation was achieved in two steps to give *N*-(2-formylaryl)pivalamide.²²⁷ Reduction with sodium borohydride, deprotection of the amine and subsequent amidation afforded the substituted amido-alcohols in 26 to 35 % overall yields (Scheme 3.59).

²²⁷ Adelstein, G. W.; Yen, C. H.; Haack, R. A.; Yu, S.; Gullikson, G.; Price, D. V.; Anglin, C.; Dektor, D. L.; Tsai, H.; Keith, R. H. *J. Med. Chem.* **1988**, *31*, 1215-1220.



Scheme 3.59: Synthesis of amido-alcohols starting from substituted anilines.

Starting from 3-amino-2-naphthoic acid, compound **6o** was obtained after reduction with lithium-aluminium hydride (LiAlH_4), followed by amidation with phenylacetyl chloride, **6o** was isolated in 77 % overall yield (Scheme 3.60).

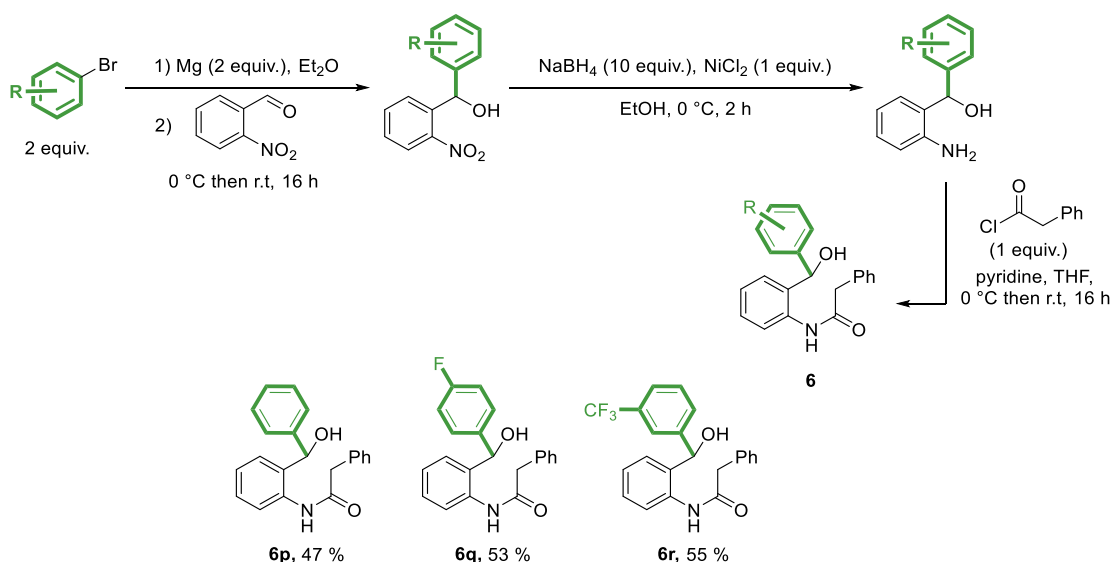


Scheme 3.60: Synthesis of naphthyl derivative **6o**.

c) Substitution on Cycle C.

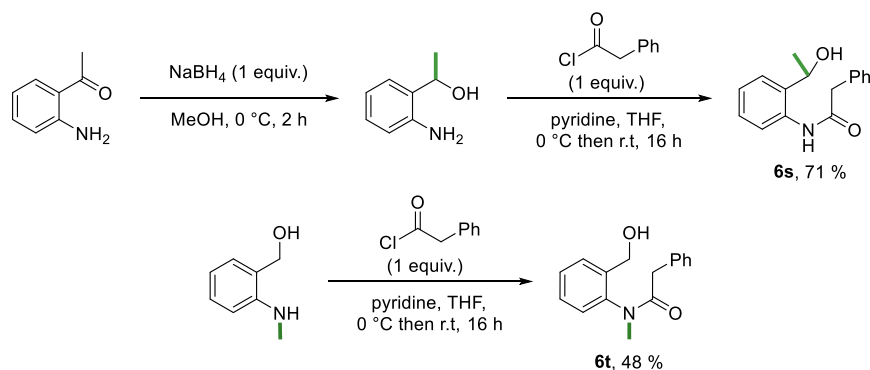
In order to prepare 3,4-disubstituted quinolinones, secondary benzylic alcohols have been synthesized. Initially, these benzylic alcohols were prepared as reported in Scheme 3.61. (2-amidophenyl)(aryl)methanol derivatives **6p-r** were prepared in three steps from aryl Grignard reagents and 2-nitrobenzaldehyde. The (2-nitrophenyl)(aryl)methanol intermediates were reduced into the corresponding amino-alcohol using nickel chloride and sodium borohydride as hydride source.²²⁸ The final step was achieved using phenylacetyl chloride as mentioned previously.

²²⁸ Nose, A.; Kudo, T. *Chem. Pharm. Bull.* **1981**, *29*, 1159-1161.



Scheme 3.61: Synthesis of *N*-(2-(hydroxy(phenyl)methyl)phenyl)-2-phenylacetamides **6p-r**.

Alkyl derivative **1s** was synthesized in two steps from 2-aminoacetophenone in 71 % yield and compound **1t** was obtained from (2-(methylamino)phenyl)methanol in fair yield due to a competition between amidation and esterification (Scheme 3.62). When other *N*-alkyl (Et, Pr, ^tBu...) or *N*-benzylanilines were engaged, the ester derivative was the main or the exclusive product.

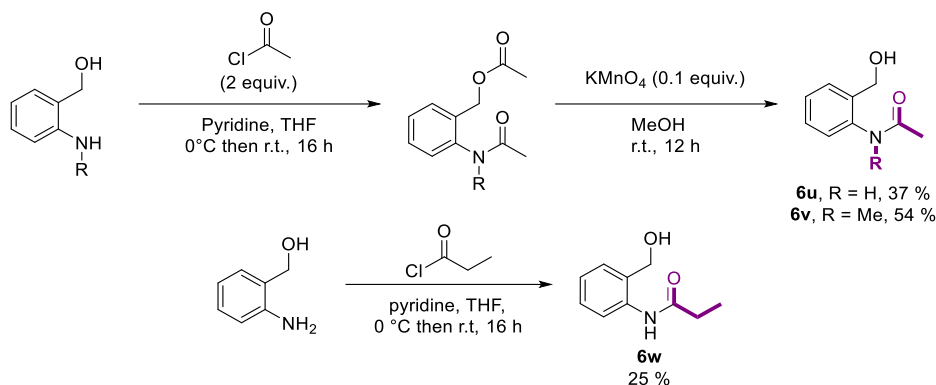


Scheme 3.62: Synthesis of compounds **6s-t**.

d) Synthesis of 2-alkylacetanilides

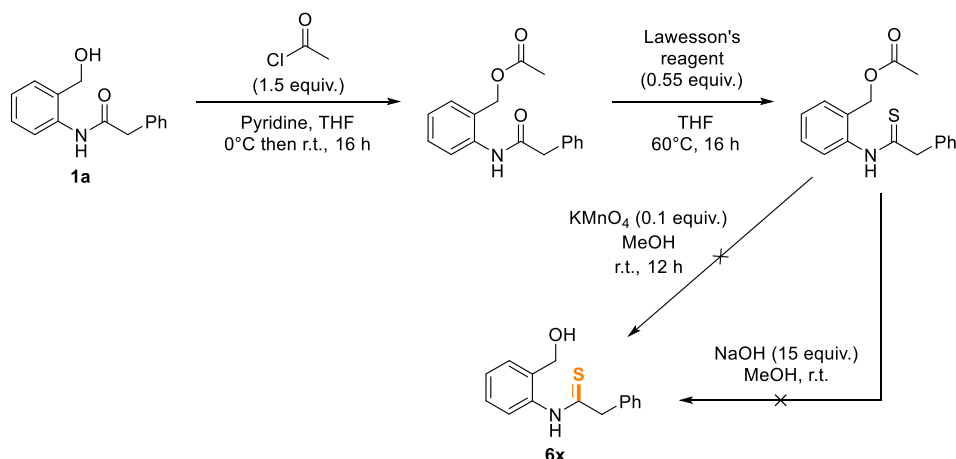
To complete the range of starting material for our reaction, anilides **6u-v** were prepared by diacetylation of 2-aminobenzylalcohol with acetylchloride. Selective deacetylation of the alcohol was performed using catalytic potassium permanganate in methanol and the desired amido-alcohols in 37-54 % (Scheme 3.63).²²⁹ Propionyl derivative **6w** was obtained directly from 2-aminobenzyl alcohol in low yield (25 %, the amido-ester being the major product).

²²⁹ Gurawa, A.; Kumar, M.; Rao, D. S.; Kashyap, S. *New J. Chem.* **2020**, *44*, 16702-16707.



Scheme 3.63: Synthetic pathway to alkyl derivatives **6u-w**.

Finally, to further exemplify this reaction, the preparation of thioamide **6x** was envisioned. After protection of the benzyl alcohol **6a** with acetyl chloride, the reaction with Lawesson's reagent afforded the thioamido-ester intermediate (Scheme 3.64).²³⁰ Unfortunately, final deacetylation using potassium permanganate led only to unreacted starting material. Reaction with sodium hydroxide at room temperature did not permit the saponification of the ester as well, and an increase of the temperature resulted in the degradation of the thioamido-ester.

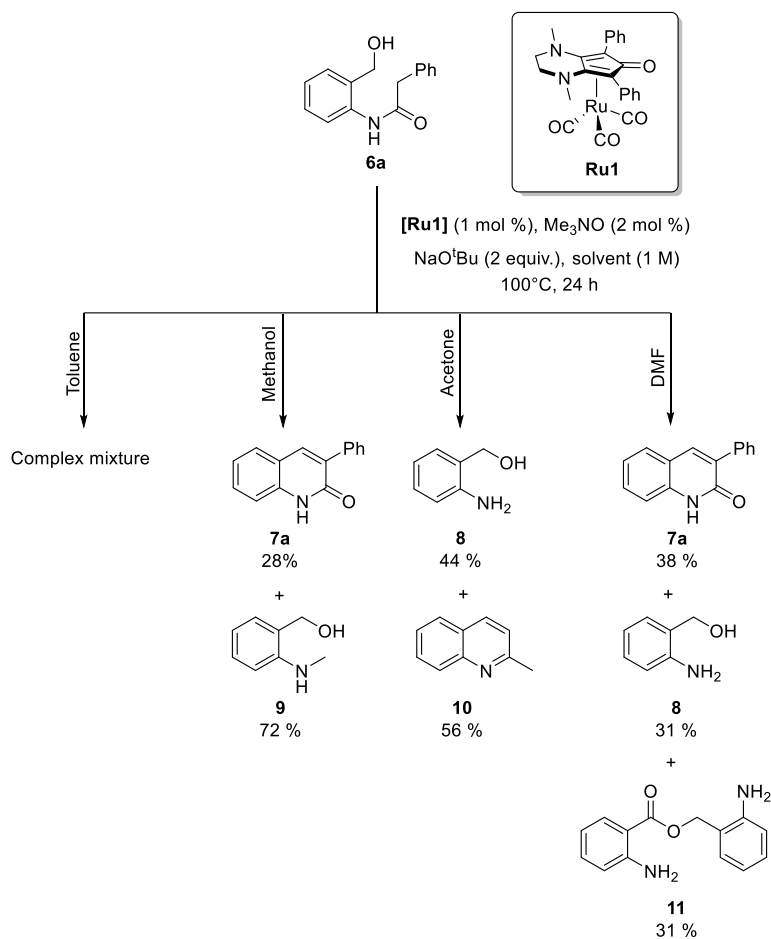


Scheme 3.64: Synthetic pathway to access thioamido-alcohol **6x**.

2) Optimization of the reaction.

Having prepared a variety of amido-alcohols, the synthesis of quinolinones via dehydrogenative coupling was initiated. Following our previous work on the alkylation of benzoyl hydrazides, we decided to start our study using the ruthenium complex **Ru1** at 100 °C in the presence of 2 equivalents of base (Scheme 3.65).

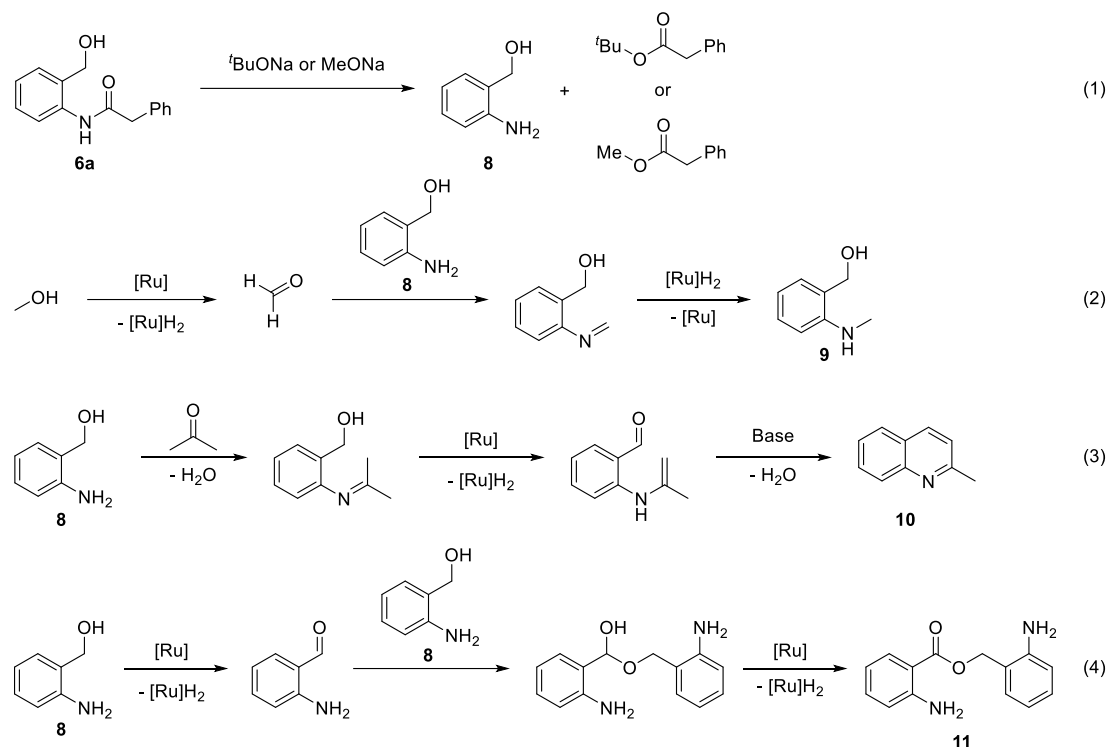
²³⁰ Ransborg, L. K.; Albrecht, L.; Weise, C. F.; Bak, J. R.; Jørgensen, K. A. *Org. Lett.* **2012**, *14*, 724-727.



Scheme 3.65: Ruthenium-catalysed synthesis of 3-phenylquinolinone.

The use of *tert*-butanol or methanol as a solvent was detrimental in this reaction. In fact, the degradation of the starting material into 2-aminobenzyl alcohol and *tert*-butyl or methyl ester was mainly observed (Scheme 3.66, Eq. 1). The formation of *N*-methylated 2-aminobenzyl alcohol resulted from the dehydrogenation of methanol, condensation of formaldehyde and subsequent reduction of the imine intermediate (Scheme 3.66, Eq. 2). In acetone, 2-methyl quinoline was observed as main product (Scheme 3.66, Eq. 3). The use of toluene as a solvent led only to a complex mixture. Consequently, it was supposed that a polar and non-nucleophilic solvent was necessary for the reaction to occur. DMF was finally the solvent giving the best conversion for the quinolinone product. However, the side-product **11** was observed (Scheme 3.66, Eq. 4). This product results from the dehydrogenative coupling of two benzyl alcohol moieties. Such a reaction was already described with various conditions and catalysts and is known as the Tishchenko reaction.²³¹

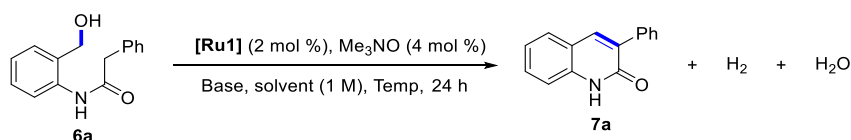
²³¹ Koskinen, A. M. P.; Kataja, A.O. (2015). The Tishchenko Reaction. In *Organic Reactions*. Vol. 86, pp 105-410.



Scheme 3.66: Plausible mechanism for the formation of side-products.

The role of the base was next studied. As described above, alkoxides bases led to the C-N bond cleavage of the amide and consequently to the formation of side-products. As a consequence, sodium *tert*-butoxide was replaced by inorganic bases. Best selectivity and conversions were obtained with carbonates as described in Table 3.1. In these conditions (DMF, Na₂CO₃, 100 °C), compound **7a** was obtained in 96 % conversion.

Table 3.1: Optimisation of the ruthenium-catalysed synthesis of 3-phenylquinolinone.

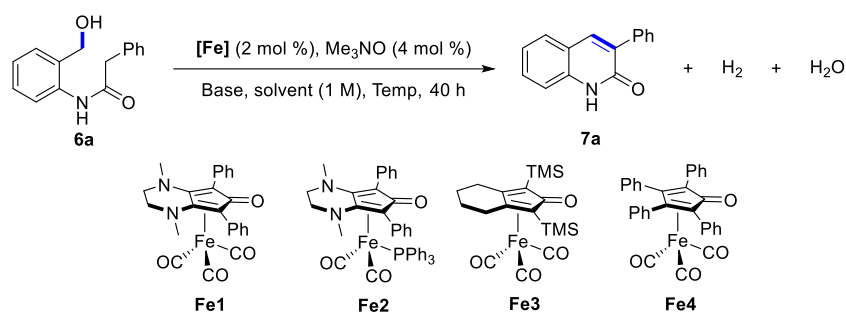


Entry	Ru	Base (equiv.)	Solvent	Temp (°C)	6a/7a/8/11 ^b
1	Ru1	NaO ^t Bu (2.0)	DMF	100	-/38/31/31
2	Ru1	NaOH (2.0)	DMF	100	75/25/-/-
3	Ru1	Cs ₂ CO ₃ (2.0)	DMF	100	28/72/-/-
4	Ru1	K ₂ CO ₃ (2.0)	DMF	100	3/65/17/15
5	Ru1	Na ₂ CO ₃ (2.0)	DMF	100	1/96/3/-
6	Ru1	NaHCO ₃ (2.0)	DMF	100	24/37/39/-

^a General Conditions: Amido-alcohol **6a** (0.5 mmol), **Ru** (2 mol %), Me₃NO (4 mol %), base (2 equiv.), DMF (1 M) for 24 h. ^b Conversions and selectivities were determined by ¹H-NMR analysis of the crude mixture.

With the aim of making this reaction more competitive, we focused our attention on iron complexes **Fe1-Fe4**. The study began with the complex **Fe1**, the iron congener of **Ru1**, in the same solvents than before (Table 3.2, Entry 1-5). DMF was found to be the best solvent. Evaluation of the iron cyclopentadienone complexes in DMF at 90 °C with 1 equiv. of Na₂SO₄ showed the Knölker complex led to the best conversion in favor of quinolinone **7a** (78 %, Table 2, Entry 8). This result could be explained by the higher propensity of the Knölker complex to release hydrogen and consequently perform a new catalytic cycle. Optimisation of the base (Entries 15 to 21) and its loadings (Entries 11 to 14) showed that higher conversion into the quinolinone product was reached with 2 equivalents of sodium carbonate. The temperature was also an important parameter. An optimum was found at 100°C (Entry 9 and 13) while lower temperature led to lower conversion, and higher temperature led to degradation products. Finally, while maximum conversion was obtained in 24 hours with ruthenium, 40 hours of reaction were necessary with iron complexes to give similar conversion. Even if ruthenium complex **Ru1** was slightly more efficient in terms of reaction time and conversions for this reaction, it was chosen to continue our study with iron, which represent a greater economic interest.

Table 3.2: Optimisation table of the iron-catalysed synthesis of 3-phenylquinolin-2(1H)-one **2a**.



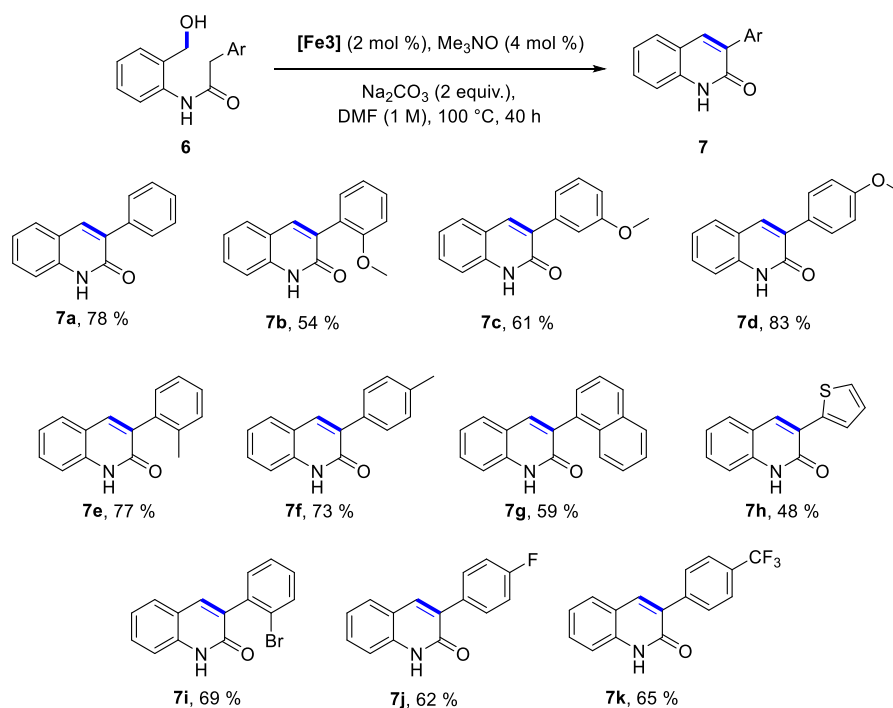
Entry	Fe	Base (equiv.)	Solvent	Temp (°C)	6a/7a ^b
1	Fe1	NaO ^t Bu (1.0)	toluene	90	-/-
2	Fe1	NaO ^t Bu (1.0)	CPME	90	-/-
3	Fe1	NaO ^t Bu (1.0)	MeOH	90	-/17
4	Fe1	NaO ^t Bu (1.0)	ⁱ PrOH	90	-/21
5	Fe1	NaO ^t Bu (1.0)	DMF	90	-/29
6	Fe1	Na ₂ CO ₃ (1.0)	DMF	90	65/35
7 ^d	Fe2	Na ₂ CO ₃ (1.0)	DMF	90	72/28
8	Fe3	Na ₂ CO ₃ (1.0)	DMF	90	22/78
9	Fe4	Na ₂ CO ₃ (1.0)	DMF	90	41/59
10	Fe3	Na ₂ CO ₃ (1.0)	toluene	100	-/-
11	Fe3	Na ₂ CO ₃ (0.1)	DMF	100	82/18
12	Fe3	Na ₂ CO ₃ (0.5)	DMF	100	63/37
13	Fe3	Na ₂ CO ₃ (1.0)	DMF	100	14/86

14	Fe3	Na ₂ CO ₃ (1.0)	DMF	110	-/77 (48) ^c
15	Fe3	Na ₂ CO ₃ (2.0)	DMF	100	8/92 (78) ^c
16	Fe3	K ₂ CO ₃ (2.0)	DMF	100	26/74
17	Fe3	K ₃ PO ₄ (2.0)	DMF	100	28/72
18	Fe3	K ₂ HPO ₄ (2.0)	DMF	100	41/59
19	Fe3	Cs ₂ CO ₃ (2.0)	DMF	100	28/72
20	Fe3	NaHCO ₃ (2.0)	DMF	100	63/37
21	Fe3	NaOH (2.0)	DMF	100	-/25

^a General Conditions: Amido-alcohol **6a** (0.5 mmol), **Fe** or **Ru** (2 mol %), Me₃NO (4 mol %), base (x equiv.), solvent (1 M) for 40 h. ^b Conversions and selectivities **6a/7a** were determined by ¹H-NMR analysis of the crude mixture. ^c Isolated yield. ^d Without Me₃NO.

3) Scope of the reaction.

With the optimized conditions in hands, the scope and limitations were then delineated. Initial experiments were conducted with the first library of compounds (amido-alcohols **6a-k**). The corresponding 3-arylquinolin-2(1H)-ones were isolated in 48-83 % yields (Scheme 3.67). The *ortho* substitution did not hamper the reactivity as compounds **7b**, **7e** and **7g** were obtained in good yields (54, 77 and 59 %, respectively). Electron-donating as well as electron-withdrawing groups were also well tolerated in this reaction and products **7b-f**, **7i-k** were isolated in good yields (54-83 % and 62-69 % yields, respectively). The introduction of a heterocycle such as thiophene was possible and compound **7h** was obtained in 48 % yield.



Scheme 3.67: Synthesis of 3-arylquinolin-2(1H)-ones with diversity on the A ring.

X-RAY diffraction analysis of compounds **7a** and **7j** confirmed the tricyclic structure of the desired 3-arylquinolin-2(1*H*)-ones (Figure 3.3). Interestingly, the aryl substituent in position 3 was not coplanar to the quinolinone structure. This could be due to steric interaction with the oxygen in position 2 which could block the free rotation of this substituent.

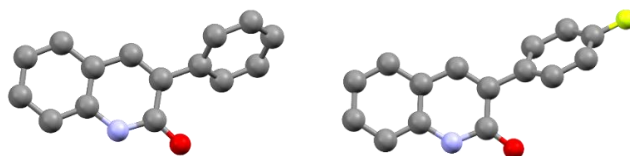
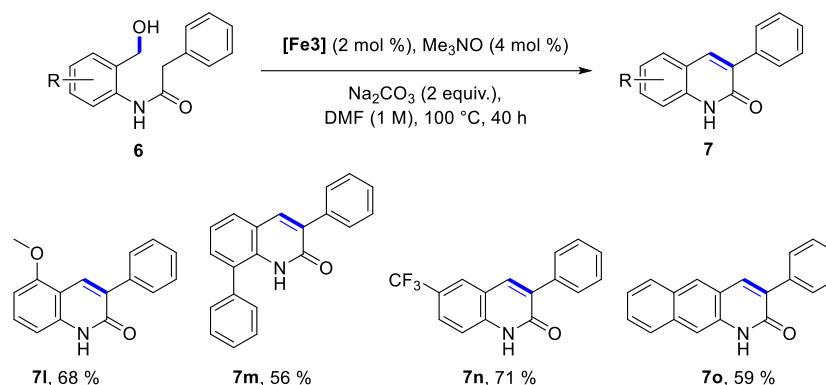


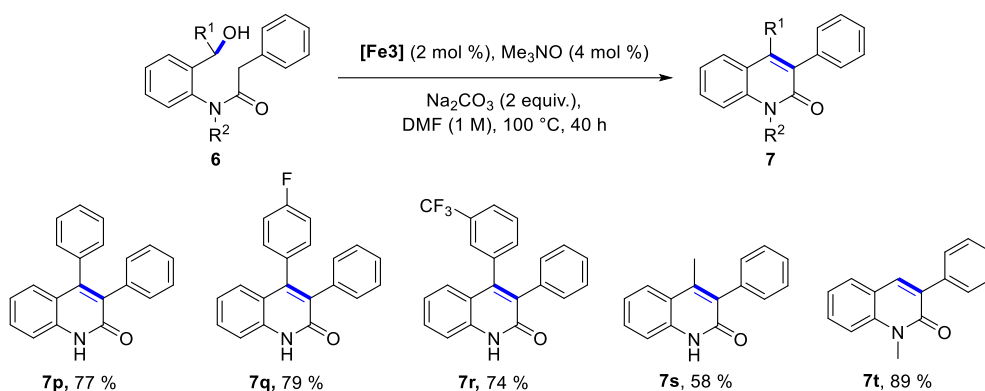
Figure 3.3: X-RAY structures of compounds **7a** (left) and **7j** (right).

Next, phenylacetanilides **6l-o** were engaged in this catalytic process (Scheme 3.68). The electro-donating and electro-withdrawing substituted quinolinones **7l** and **7n** were isolated in good yields (68 and 71 % respectively). Neither the steric hindrance generated by the biphenyl motif in **6m** nor the extension of the aromatic system hampered the reactivity and compounds **7m** and **7o** were obtained within 56 and 59 % yield respectively.



Scheme 3.68: Synthesis of 3-phenylquinolin-2(1*H*)-ones with substituents on the B ring.

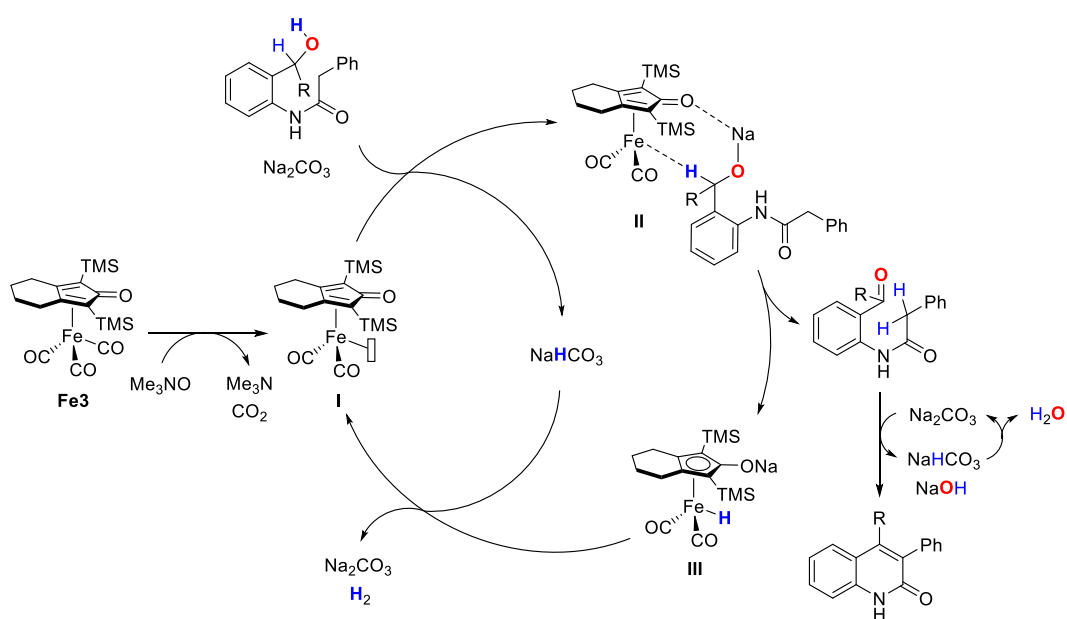
Finally, the methodology was applied to secondary amido-alcohols **6p-t**. Compounds **7p-r** were obtained in good yields (74 to 79 %, Scheme 3.69). Alkyl-substituted quinolinone **7s** was obtained in lower yield (58 %) while *N*-substituted anilide **6t** yielded compound **7t** in very good yield (89 %). Among the reported methods allowing the formation of substituted quinolines derivatives, few reported the possibility to bring substitution on any position of this type of heterocycle.^{187,191,197,202} Among them, Kirchner¹⁸⁷ and Srimani¹⁹¹ were limited to aryl substituents on the position 4 of the quinoline ring, while Wang reported only 4-methyl or 4-trifluoromethyl quinolines.²⁰⁰ The manganese-catalysed synthesis of quinolines reported by Zang is the only method allowing alkyl and aryl substitution on the position 4 of the quinoline product.¹⁹⁷ However, all these methodologies allowed the obtention of the desired heterocycles in similar yields than the present method.



Scheme 3.69: Synthesis of 3-phenylquinolin-2(1H)-ones with substitution on the C ring.

Unfortunately, no conversion was obtained when compounds **6u-w** were engaged in this reaction. This non-reactivity may be due to a less acidic character of the acetamide.

A simplified mechanism was proposed for this iron-catalysed cyclisation reaction (Scheme 3.70). The first step is the activation of the catalyst by the removal of a CO ligand using Me_3NO . The activated species **I** dehydrogenates the alcohol through intermediate **II**, generating the amido-aldehyde which cyclises *via* intramolecular condensation to lead to the desired 3-arylquinolin-2(1H)-one. Iron complex **III** then recombines with sodium bicarbonate to release hydrogen and the activated catalyst **I**.



Scheme 3.70: Proposed mechanism for the iron-catalyzed synthesis of quinolinones.

V. Conclusion.

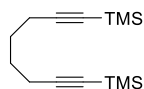
In conclusion we have developed an original way to access highly substituted quinoline-2(1*H*)-ones using iron catalysis. This reaction relies on an intramolecular dehydrogenative coupling of amido-alcohols leading to a cyclisation product. Different strategies were employed to prepare these starting materials. This methodology opens the way to the synthesis of various substituted 3-arylquinolin-2(1*H*)-ones with substitution on any of the position of the bicyclic product. Also, it is of particular interest for the preparation of highly functionalised quinolinones.

VI. Experimental Part.

1) General considerations.

All air- and moisture-sensitive manipulations were carried out using standard vacuum line Schlenk tubes techniques. Dry toluene was dried using a solvent purification system from Innovative Technologies, by passage through towers containing activated alumina. Xylene was purchased from Carlo Erba and was distilled over sodium and stocked over 4Å molecular sieves. Both were degassed prior to use by bubbling argon gas directly in the solvent. Other solvents and chemicals were purchased from different suppliers and used as received. Neutral alumina was purchased from Alfa Aesar (Brockmann Grade I, 58 Angstroms, -60 Mesh Powder, S.A. 150 m²/g) and silica from Carlo Erba (60Å 40-63µ). Deuterated solvents for NMR spectroscopy were purchased from Eurisotop and used as received. NMR spectra were recorded on a 500 MHz Brücker spectrometer. Proton (¹H) NMR information is given in the following format: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; qui, quintet; sept, septet; m, multiplet), coupling constant(s) (*J*) in Hertz (Hz), number of protons. The prefix *app* is occasionally applied when the true signal multiplicity was unresolved and *br* indicates the signal in question broadened. Carbon ¹³C{¹H} NMR spectra are reported in ppm (δ) relative to CDCl₃ unless noted otherwise. Infrared spectra were recorded over a PerkinElmer Spectrum 100 FT-IR Spectrometer using neat conditions. HRMS analyses were performed by Laboratoire de Chimie Moléculaire et Thioorganique analytical Facilities.

2) Synthesis of iron complexes.

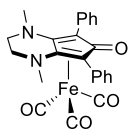


Chemical Formula: C₁₄H₂₆Si₂

- **1,8-bis(trimethylsilyl)octa-1,7-diyne²³² (L2)**

In a 50 mL dried Schlenk tube under an argon atmosphere, to a solution of diyne (10 mmol) in dried THF (20 mL) at -78 °C was added *n*-BuLi (22 mmol, 2.2 equiv.). The reaction mixture was stirred for 10 minutes at -78 °C then 1 hour at room temperature. Trimethylsilylchloride (22 mol, 2.2 equiv.) was added and the resulting solution was stirred 3 hours at room temperature. A saturated aqueous solution of NH₄Cl was added, then the aqueous layer was extracted with diethyl ether (2 x 50 mL). Combined organic layers were dried over MgSO₄. After filtration, solvent was removed under vacuum. The crude product was purified by silica gel column chromatography using pentane/ethyl acetate (90:10) to afford the pure product as a colorless oil (2.45 g, 98 %). ¹H-NMR (CDCl₃, 500 MHz): δ 2.27-2.19 (m, 4H), 1.65-1.57 (m, 4H), 0.13 (s, 18H) ppm. ¹³C-NMR (CDCl₃, 125 MHz): δ 107.0, 84.6, 27.6, 19.3, 0.1 ppm.

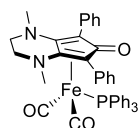
²³² Bushnell, L. M.; Evitt, E. R.; Bergman, R. G. *J. Organomet. Chem.* **1978**, *157*, 445-456.



Chemical Formula: $C_{25}H_{23}FeN_2O_4$

- **(1,4-dimethyl-5,7-diphenyl-1,2,3,4-tetrahydro-6H-cyclopenta[b]pyrazin-6-one)tricarbonyl iron complex (Fe2)**

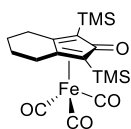
In a 15 mL dried Schlenk tube under an argon atmosphere, the cyclopentadienone ligand **L1** (2.52 mmol, 800 mg, 1 equiv.) and $Fe_2(CO)_9$ (5.06 mmol, 1.84 g, 2 equiv.) were introduced in dry and free- O_2 toluene (10 mL). The reaction mixture was stirred under reflux overnight. The resulting mixture was cooled to room temperature and purified on neutral alumina oxide column chromatography surrounded by a pad of celite (eluent: CH_2Cl_2 to $CH_2Cl_2/MeOH$ [98:2]). Precipitation on a mixture of pentane/diethyl ether (10:1) and filtration under vacuum gave the pure complex **Fe1** as a yellow powder (560 mg, 49 %). **1H -NMR ($CDCl_3$, 500 MHz):** δ 7.54 (d, $J = 7.1$ Hz, 4H), 7.40-7.31 (m, 6H), 3.44 (ddd, $J = 3.9$; 6.9; 11.0 Hz, 2H), 2.92 (ddd, $J = 3.9$; 6.9; 11.0; Hz, 2H), 2.37 (s, 6H) ppm. **^{13}C -NMR ($CDCl_3$, 125 MHz):** δ 210.2 (3C), 165.7, 132.4 (4C), 131.9 (2C), 128.4 (4C), 128.0 (2C), 114.6 (2C), 71.1 (2C), 50.1 (2C), 41.5 (2C) ppm. **IR (neat):** ν 3023, 2957, 2911, 2868, 2027, 1962, 1947, 1917, 1666, 1620, 1573, 1555, 1514, 1495, 1441, 1415, 1359, 1265, 1192, 1117, 1074, 1058, 951, 850, 755, 728, 699 cm^{-1} . **HRMS (ESI-TOF) m/z $[M+H]^+$:** Calcd for $C_{24}H_{21}FeN_2O_4$ 457.0851; found 457.0841.



Chemical Formula: $C_{42}H_{38}FeN_2O_3P$

- **(1,4-dimethyl-5,7-diphenyl-1,2,3,4-tetrahydro-6H-cyclopenta[b]pyrazin-6-one) triphenylphosphine dicarbonyl iron complex (Fe2)**

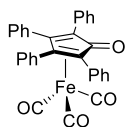
In a 15 mL dried Schlenk under an argon atmosphere, tricarbonyl iron complex **Fe1** (0.44 mmol, 200 mg, 1 equiv.) and triphenylphosphine (1.33 mmol, 366 mg, 3 equiv.) were solubilized in O_2 -free xylene (6 mL) and then refluxed at 140 $^{\circ}C$ overnight. Purification by flash column chromatography on neutral aluminium oxide topped with a pad of celite (eluent: pentane/AcOEt [90:10] to [70:30]) afforded the pure triphenylphosphine iron complex **Fe2** as an orange powder (195 mg, 65 %). **1H -NMR ($CDCl_3$, 500 MHz):** δ 7.82 (d, $J = 7.0$ Hz, 4H), 7.39 (s, 2H), 7.34-7.20 (m, 9H), 7.16 (t, $J = 7.0$ Hz, 4H), 7.07-7.03 (m, 6H), 3.49 (s, 4H), 2.59 (s, 6H) ppm. **^{13}C -NMR ($CDCl_3$, 125 MHz):** δ 216.9, 160.9, 133.9, 133.8, 133.3, 133.2, 130.8, 128.9, 127.5, 127.4, 125.9, 108.6, 71.3, 47.1, 40.2 ppm. **^{31}P -NMR ($CDCl_3$, 162 MHz):** δ 50.68 ppm. **IR (neat):** ν 3058, 2925, 1969, 1902, 1603, 1573, 1542, 1498, 1484, 1470, 1434, 86 1417, 1380, 1354, 1332, 1251, 1175, 1089, 1029, 930, 846, 762, 750, 740, 693 cm^{-1} . **HRMS (ESI-TOF) m/z $[M+H]^+$:** Calcd for $C_{41}H_{36}N_2O_3PFe$ 691.1813; found 691.1812.



Chemical Formula: $C_{19}H_{29}FeO_4Si_2$

- **(1,3-bis(trimethylsilyl)-4,5,6,7-tetrahydro-2H-inden-2-one) tricarbonyl iron complex (Fe3)**

In a 50 mL dried Schlenk tube under an argon atmosphere, Fe_2CO_9 (2 mmol, 727 mg, 1 equiv.) was added to a solution of diyne **L1** (2 mmol, 500 mg, 1 equiv.) in dry and free- O_2 toluene (10 mL). The reaction mixture was stirred under reflux overnight. The resulting mixture was cooled to room temperature. The crude product was purified by column chromatography on neutral alumina oxide (eluent: pentane/ethyl acetate [50:50]) to afford the pure complex **Fe3** as a yellow solid (711 mg, 85 %). 1H -NMR ($CDCl_3$, 500 MHz): δ 2.66-2.48 (m, 4H), 1.90-1.76 (m, 4H), 0.27 (s, 18H) ppm. ^{13}C -NMR ($CDCl_3$, 125 MHz): δ 209.2, 181.4, 111.1, 71.9, 24.9, 22.5, 0.1 ppm. IR (neat): ν 2053, 1987, 1604, 1441, 1410, 1398, 1371, 1310, 1241, 1085, 1043, 960, 887, 842, 827, 769, 747, 692 cm^{-1} . HRMS (ESI-TOF) m/z $[M+H]^+$: Calcd for $C_{18}H_{27}O_4Si_2Fe$ 419.0797; found 419.0785.



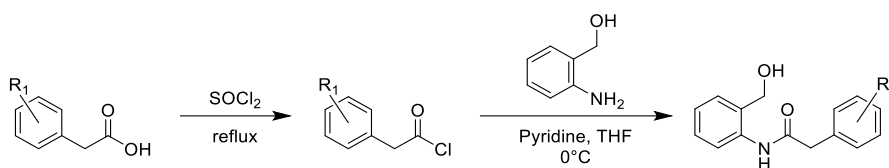
Chemical Formula: $C_{33}H_{23}FeO_4$

- **(tetraphenylcyclopentadienone) tricarbonyl iron complex²³³ (Fe4)**

In a 15 mL dried Schlenk tube under an argon atmosphere, Fe_2CO_9 (2 mmol, 727 mg, 1 equiv.) was added to a solution of 2,3,4,5-tetraphenylcyclopenta-2,4-dien-1-one (2 mmol, 769 mg, 1 equiv.) in dry and free- O_2 toluene (10 mL). The reaction mixture was stirred under reflux overnight. The resulting mixture was cooling down to room temperature. The crude product was purified by column chromatography on neutral alumina oxide (eluent: pentane/ethyl acetate [50:50]) to afford the pure complex **Fe4** as a yellow solid (954 mg, 91 %). 1H -NMR ($CDCl_3$, 500 MHz): δ 7.61-7.55 (m, 4H) 7.28-7.20 (m, 8H), 7.16-7.13 (m, 8H) ppm. ^{13}C -NMR ($CDCl_3$, 125 MHz): δ 208.5, 169.7, 131.7, 130.7, 130.2, 129.8, 128.6, 128.0, 127.9, 127.8, 104.0, 82.4 ppm.

²³³ Johnson, T. C.; Clarkson, G. J.; Wills, M. *Organometallics*, **2011**, *30*, 1859-1868.

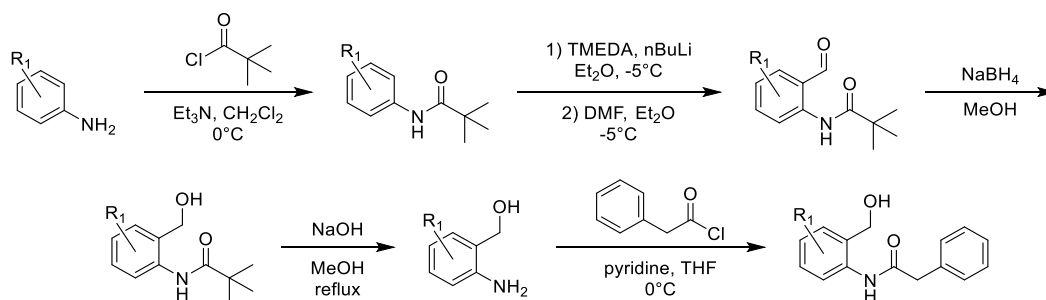
3) Synthesis of starting materials.



General Procedure A:

Step 1: In a round bottomed flask, the desired phenylacetic acid (10 mmol) was dissolved in thionyl chloride (2.18 mL, 3 equiv.). The mixture was stirred under reflux for 1 hour. After cooling to room temperature, the solvent was evaporated in vacuo to give the desired phenylacetyl chloride, which was directly used for the next step.

Step 2²²⁶: To a stirred solution of 2-aminobenzyl alcohol (10 mmol, 1 equiv.) in dry THF (15 mL) was added 5 mL of pyridine. A solution of the desired phenylacetyl chloride (10 mmol, 1 equiv.) in dry THF (10 mL) was added dropwise at 0 °C under argon. The mixture was warmed to room temperature and stirred overnight. Solvent was evaporated, water and chloroform were added and the organic phase was washed with aqueous HCl (5 %), brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. Depending on the purity of the crude, the product was purified by silica gel chromatography using pentane-ethyl acetate as eluent.



General Procedure B:

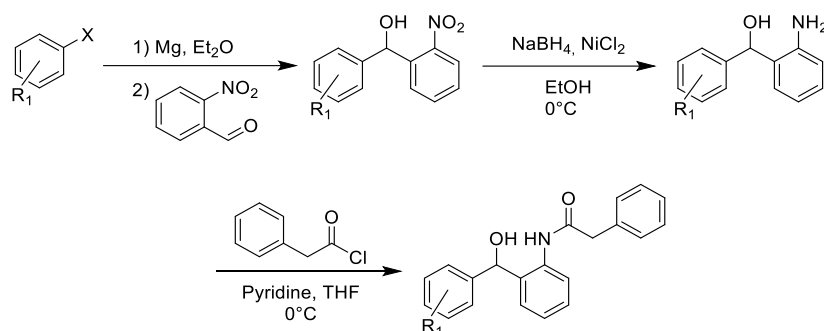
Step 1: In a round bottomed flask, the desired aniline (15 mmol, 1 equiv.) was dissolved in dichloromethane (24 mL) and triethylamine (2.3 mL, 1.1 equiv.) was added. The mixture was cooled to 0 °C and pivaloyl chloride (1.84 mL, 1 equiv.) was added dropwise. The mixture was stirred at room temperature overnight and then poured into water. The water phase was washed with dichloromethane and the organic layers were combined. The organic phase was washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure, giving the *N*-pivaloyl aniline which was directly used for the next step.

Step 2²²⁷: Under argon, *N*-pivaloyl aniline (1 equiv.) was dissolved in dry diethyl ether (0.25 M) and TMEDA (2.25 equiv.) was added. The mixture was cooled to -5 °C. A solution of *n*-butyllithium (2.5 M in hexane, 2.2 equiv.) was added dropwise. The mixture was warmed to room temperature, stirred for 2 hours, and cooled again to -5 °C. DMF (3 equiv.) was added dropwise and the mixture was stirred for 1 hour. Water was added, the water layer was extracted with additional Et₂O and the organic extracts were combined, dried over Na₂SO₄, filtered and concentrated under reduced pressure.

Step 3: The crude *N*-pivaloyl aniline-benzaldehyde (1 equiv.) was dissolved in methanol (0.5 M). Sodium borohydride (1.5 equiv.) was added portionwise at 0 °C, the mixture was warmed at room temperature, stirred for 2 hours and quenched with water. The product was extracted with ethyl acetate, washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure.

Step 4: The crude amido-alcohol (1 equiv.) was dissolved in methanol (0.38 M) and sodium hydroxide (5 equiv.) was added. The mixture was stirred and refluxed overnight. After cooling down to room temperature, water was added and the product was extracted with ethyl acetate, washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure.

Step 5²²⁶: To a stirred solution of 2-aminobenzyl alcohol (1 equiv.) in 15 mL of dry THF was added 5 mL of pyridine. A solution of phenylacetyl chloride (1 equiv.) in 10 mL of dry THF was added dropwise at 0°C under argon. The mixture was warmed to room temperature and stirred overnight. Solvent was evaporated, water and chloroform were added and the organic phase was washed with aqueous HCl (5 %), brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. Depending on the purity of the crude, the product was purified on silica gel chromatography using pentane-ethyl acetate as eluent.



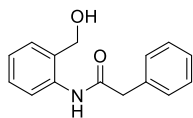
General Procedure C:

Step 1: In a two necks flask, a minimum of diethyl ether was added to small pieces of magnesium (20 mmol, 486 mg, 2 equiv.) and a small amount of diiodide. A first part of the halogen derivative (7 mmol, 0.67 equiv.) was added. The mixture was heated until the reaction starts. A second part of the halogen derivative (13 mmol, 1.33 equiv.) was added and the reaction mixture was heated at reflux for 30 minutes. After cooling down to room temperature, 2-nitrobenzaldehyde (10 mmol, 1 equiv.) was added dropwise at 0 °C and the mixture was stirred at room temperature overnight. The reaction was quenched with saturated aqueous NH₄Cl solution and the product was extracted with ethyl acetate, washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure.

Step 2: To a stirred solution of the crude nitro-alcohol (1 equiv.) and nickel (II) chloride hexahydrate (1 equiv.) in ethanol (0.33 M) was added portionwise sodium borohydride (10 equiv.) at 0 °C. The mixture was stirred for 2 hours at 0 °C and quenched with a minimum of water, filtered on celite and poured into water. The aqueous phase was then extracted twice with ethyl acetate. The combined organic phases were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure.

Step 3²²⁶: To a stirred solution of the crude 2-aminobenzyl alcohol (1 equiv.) in 15 mL of dry THF was added 5 mL of pyridine. A solution of phenylacetyl chloride (1 equiv.) in 10 mL of dry THF was added dropwise at 0 °C under argon. The mixture was warmed to room temperature and stirred overnight. Solvent was evaporated, water and chloroform were added and the organic phase was washed with

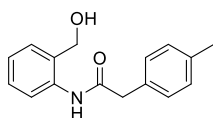
aqueous HCl (5 %), brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. Depending on the purity of the crude, the product was purified on silica gel chromatography using pentane-ethyl acetate as eluent.



Chemical Formula: C₁₅H₁₅NO₂

- **N-[2-(hydroxymethyl)phenyl]-2-phenylacetamide (6a)**

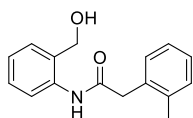
According to general procedure A, the product was obtained from 2-aminobenzyl alcohol (10 mmol, 1 equiv.) and phenylacetyl chloride (10 mmol, 1 equiv.), as a white solid (2.19 g, 91 %) without further purification. **¹H-NMR (CDCl₃, 500 MHz):** δ 8.37 (br. s, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.43-7.36 (m, 3H), 7.36-7.29 (m, 3H), 7.13 (d, *J* = 6.4 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 4.46 (s, 2H), 3.78 (s, 2H). **¹³C-NMR (CDCl₃, 125 MHz):** δ 169.9, 137.4, 134.8, 129.8, 129.5, 129.2, 129.2, 128.9, 127.6, 124.5, 122.5, 64.3, 45.2. **IR (neat):** ν 3254, 1652, 1585, 1525, 1451, 1394, 1066, 1028, 968, 754, 699 cm⁻¹. **HRMS (ESI-TOF) m/z [M+Na]⁺:** calcd for C₁₅H₁₅NO₂Na 264.1000; found 264.1001.



Chemical Formula: C₁₆H₁₇NO₂

- **N-(2-(hydroxymethyl)phenyl)-2-(p-tolyl)acetamide (6b)**

According to general procedure A, the product was obtained from 2-aminobenzyl alcohol (10 mmol, 1 equiv.) and 2-(p-tolyl)acetic acid (10 mmol, 1 equiv.) as a white solid (2.20 g, 86 %) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 6:4). **¹H-NMR (CDCl₃, 500 MHz):** δ 8.33 (br. s, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.32-7.29 (m, 1H), 7.26-7.25 (m, 2H), 7.19 (app. d, *J* = 7.9 Hz, 2H), 7.15-7.14 (m, 1H), 7.04 (t, *J* = 7.4 Hz, 1H), 4.47 (s, 2H), 3.73 (s, 2H), 2.36 (s, 3H). **¹³C-NMR (CDCl₃, 125 MHz):** δ 170.3, 137.4, 137.4, 131.7, 129.9, 129.8, 129.7, 129.3, 129.1, 124.6, 122.6, 64.3, 44.8, 21.3. **IR (neat):** ν 3254, 1652, 1587, 1527, 1455, 1341, 1245, 1188, 1035, 763, 702, 493 cm⁻¹. **HRMS (ESI-TOF) m/z [M+Na]⁺:** calcd for C₁₆H₁₇NO₂Na 278.1157; found 278.1160.

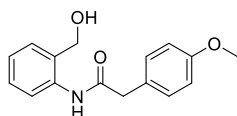


Chemical Formula: C₁₆H₁₇NO₂

- **N-(2-(hydroxymethyl)phenyl)-2-(o-tolyl)acetamide (6c)**

According to general procedure A, the product was obtained from 2-aminobenzyl alcohol (10 mmol, 1 equiv.) and 2-(o-tolyl)acetic acid (10 mmol, 1 equiv.) as a white solid (1.97 g, 77 %) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 6:4). **¹H-NMR (CDCl₃, 500 MHz):**

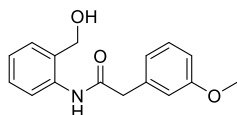
δ 8.33 (br. s, 1H), 8.03 (dd, $J = 3.8; 8.1$ Hz, 1H), 7.32-7.29 (m, 2H), 7.26-7.24 (m, 2H), 7.10 (app. d, $J = 7.5$ Hz, 2H), 7.03 (t, $J = 7.4$ Hz, 1H), 4.39 (s, 2H), 3.76 (d, $J = 7.5$ Hz, 2H), 2.37 (d, $J = 2.6$ Hz, 3H). **$^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz):** δ 169.8, 137.7, 137.3, 133.3, 131.0, 130.9, 129.5, 129.3, 129.0, 128.1, 126.9, 124.5, 122.4, 64.3, 43.2, 19.7. **IR (neat):** ν 3251, 3047, 1660, 1526, 1489, 1345, 1203, 1032, 967, 757, 745, 661, 501 cm^{-1} . **HRMS (ESI-TOF) m/z [$\text{M}+\text{Na}$] $^+$:** calcd for $\text{C}_{16}\text{H}_{17}\text{NO}_2\text{Na}$ 278.1157; found 278.1159.



Chemical Formula: $\text{C}_{16}\text{H}_{17}\text{NO}_3$

- ***N*-(2-(hydroxymethyl)phenyl)-2-(4-methoxyphenyl)acetamide (6d)**

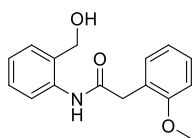
According to general procedure A, the product was obtained from 2-aminobenzyl alcohol (10 mmol, 1 equiv.) and 2-(3-methoxyphenyl)acetic acid (10 mmol, 1 equiv.) as a white solid (1.55 g, 57 %) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 6:4). **$^1\text{H-NMR}$ (CDCl_3 , 500 MHz):** δ 8.38 (br. s, 1H), 8.00 (d, $J = 8.1$ Hz, 1H), 7.32-7.29 (m, 1H), 7.27 (d, $J = 8.6$ Hz, 2H), 7.14-7.13 (dd, $J = 1.0; 7.4$ Hz, 1H), 7.07-7.04 (td, $J = 1.0; 7.4$ Hz, 1H), 6.91 (d, $J = 8.6$ Hz, 1H), 4.48 (s, 2H), 3.81 (s, 3H), 3.70 (s, 2H). **$^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz):** δ 170.5, 159.2, 137.4, 130.9, 129.7, 129.3, 129.0, 126.7, 124.6, 122.6, 114.6, 64.3, 55.5, 44.31. **IR (neat):** ν 3259, 1657, 1585, 1512, 1409, 1302, 1243, 1175, 1034, 971, 772, 711, 574, 514, 437 cm^{-1} . **HRMS (ESI-TOF) m/z [$\text{M}+\text{Na}$] $^+$:** calcd for $\text{C}_{16}\text{H}_{17}\text{NO}_3\text{Na}$ 294.1106; found 294.1107.



Chemical Formula: $\text{C}_{16}\text{H}_{17}\text{NO}_3$

- ***N*-(2-(hydroxymethyl)phenyl)-2-(3-methoxyphenyl)acetamide (6e)**

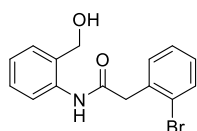
According to general procedure A, the product was obtained from 2-aminobenzyl alcohol (10 mmol, 1 equiv.) and 2-(3-methoxyphenyl)acetic acid (10 mmol, 1 equiv.) as a white solid (1.67 g, 61 %) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 6:4). **$^1\text{H-NMR}$ (CDCl_3 , 500 MHz):** δ 8.42 (br. s, 1H), 8.01 (d, $J = 8.2$ Hz, 1H), 7.29 (t, $J = 7.9$ Hz, 2H), 7.14-7.12 (m, 1H), 7.04 (t, $J = 7.3$ Hz, 1H), 6.94 (d, $J = 7.4$ Hz, 1H), 6.90 (s, 1H), 6.88-6.86 (m, 1H), 4.47 (s, 2H), 3.82 (s, 3H), 3.73 (s, 2H), 1.79 (br. s, 1H). **$^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz):** δ 169.8, 160.3, 137.4, 136.2, 130.3, 129.7, 129.3, 129.0, 124.6, 122.6, 122.1, 115.2, 113.4, 64.4, 55.4, 45.3. **IR (neat):** ν 3257, 1655, 1585, 1525, 1491, 1463, 1345, 1263, 1158, 1037, 970, 759, 706, 587 cm^{-1} . **HRMS (ESI-TOF) m/z [$\text{M}+\text{Na}$] $^+$:** calcd for $\text{C}_{16}\text{H}_{17}\text{NO}_3\text{Na}$ 294.1106; found 294.1109.



Chemical Formula: C₁₆H₁₇NO₃

- ***N*-(2-(hydroxymethyl)phenyl)-2-(2-methoxyphenyl)acetamide (6f)**

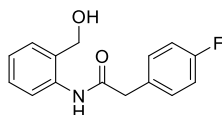
According to general procedure A, the product was obtained from 2-aminobenzyl alcohol (10 mmol, 1 equiv.) and 2-(2-methoxyphenyl)acetic acid (10 mmol, 1 equiv.) as a white solid (1.49 g, 55 %) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 6:4). **¹H-NMR (CDCl₃, 500 MHz):** δ 8.43 (br. s, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.33-7.27 (m, 3H), 7.14 (d, *J* = 7.4 Hz, 1H), 7.03 (d, *J* = 7.4 Hz, 1H), 6.96 (d, *J* = 7.4 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 4.45 (s, 2H), 3.88 (s, 3H), 3.75 (s, 2H), 1.94 (br. s, 1H). **¹³C-NMR (CDCl₃, 125 MHz):** δ 170.4, 157.6, 137.3, 131.6, 130.4, 129.2, 129.1, 129.1, 124.6, 123.4, 122.9, 121.2, 110.8, 64.0, 55.6, 40.0. **IR (neat):** ν 3243, 1653, 1586, 1522, 1453, 1239, 1043, 970, 747, 686, 589, 509 cm⁻¹. **HRMS (ESI-TOF) m/z [M+Na]⁺:** calcd for C₁₆H₁₇NO₃Na 294.1106; found 294.1110.



Chemical Formula: C₁₅H₁₄BrNO₂

- **2-(2-bromophenyl)-*N*-(2-(hydroxymethyl)phenyl)acetamide (6g)**

According to general procedure A, the product was obtained from 2-aminobenzyl alcohol (10 mmol, 1 equiv.) and 2-(2-bromophenyl)acetic acid (10 mmol, 1 equiv.) as a white solid (1.18 g, 37 %) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 6:4). **¹H-NMR (CDCl₃, 500 MHz):** δ 8.40 (br. s, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.64 (dd, *J* = 1.0; 8.1 Hz, 1H), 7.44 (dd, *J* = 1.5; 7.5 Hz, 1H), 7.34 (td, *J* = 1.1; 7.5 Hz, 1H), 7.33-7.30 (m, 1H), 7.19 (td, *J* = 1.7; 7.8 Hz, 1H), 7.14 (dd, *J* = 1.0; 7.4 Hz, 1H), 7.05 (td, *J* = 1.0; 7.4 Hz, 1H), 4.54 (s, 2H), 3.93 (s, 2H). **¹³C-NMR (CDCl₃, 125 MHz):** δ 168.4, 137.4, 134.7, 133.4, 132.2, 129.8, 129.5, 129.3, 129.0, 128.3, 125.5, 124.7, 122.8, 64.5, 45.4. **IR (neat):** ν 3249, 1662, 1532, 1499, 1362, 1253, 1054, 922, 762, 674, 503 cm⁻¹. **HRMS (ESI-TOF) m/z [M+Na]⁺:** calcd for C₁₅H₁₄NO₂BrNa 342.0106; found 342.0111.

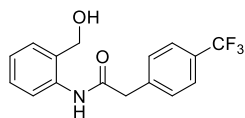


Chemical Formula: C₁₅H₁₄FNO₂

- **2-(4-fluorophenyl)-*N*-(2-(hydroxymethyl)phenyl)acetamide (6h)**

According to general procedure A, the product was obtained from 2-aminobenzyl alcohol (10 mmol, 1 equiv.) and 2-(4-fluorophenyl)acetic acid (10 mmol, 1 equiv.) as a light yellow solid (1.84 g, 71 %) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 6:4). **¹H-NMR (500 MHz, CDCl₃):** δ 8.49 (br. s, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.34-7.30 (m, 3H), 7.12 (d, *J* = 7.4 Hz, 1H),

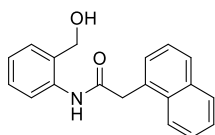
7.08-7.04 (m, 3H), 4.51 (s, 2H), 3.72 (s, 2H). **¹⁹F-NMR (CDCl₃, 500 MHz):** δ - 114.8. **¹³C-NMR (125 MHz, CDCl₃):** δ 169.7, 161.5 (d, *J* = 244.5 Hz), 137.4, 131.3 (d, *J* = 8.0 Hz), 130.4 (d, *J* = 3.3 Hz), 129.5, 129.3, 128.9, 116.0 (d, *J* = 21.3 Hz), 64.5, 44.3. **IR (neat):** ν 3211, 1656, 1588, 1530, 1507, 1354, 1286, 1220, 1157, 1019, 842, 752, 512, 471 cm⁻¹. **HRMS (ESI-TOF) m/z [M+Na]⁺:** calcd for C₁₅H₁₄NO₂FNa 282.0906; found 282.0906.



Chemical Formula: C₁₆H₁₄F₃NO₂

- ***N*-(2-(hydroxymethyl)phenyl)-2-(4-(trifluoromethyl)phenyl)acetamide (6i)**

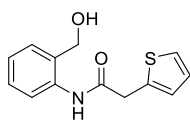
According to general procedure A, the product was obtained from 2-aminobenzyl alcohol (10 mmol, 1 equiv.) and 2-(4-(trifluoromethyl)phenyl)acetic acid (10 mmol, 1 equiv.) as a white solid (1.92 g, 62 %) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 6:4). **¹H-NMR (500 MHz, CDCl₃):** δ 8.56 (br. s, 1H), 8.06 (d, *J* = 8.1 Hz, 1H), 7.63 (d, *J* = 8.1 Hz, 2H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.34-7.30 (m, 1H), 7.13 (d, *J* = 7.4 Hz, 1H), 7.05 (t, *J* = 7.4 Hz, 1H), 4.56 (s, 2H), 3.81 (s, 2H). **¹⁹F-NMR (CDCl₃, 500 MHz):** δ - 62.5. **¹³C-NMR (125 MHz, CDCl₃):** δ 168.7, 138.8, 137.5, 130.0, 129.4, 129.3, 128.9, 128.0 (d, *J* = 65.3 Hz) 126.0 (q, *J* = 3.7 Hz), 124.6, 124.2 (d, *J* = 270 Hz), 122.4, 64.7, 44.9. **IR (neat):** ν 3219, 1663, 1585, 1525, 1486, 1309, 1237, 1198, 1095, 1002, 944, 714, 569 cm⁻¹. **HRMS (ESI-TOF) m/z [M+Na]⁺:** calcd for C₁₆H₁₄NO₂F₃Na 332.0874; found 332.0874.



Chemical Formula: C₁₉H₁₇NO₂

- ***N*-(2-(hydroxymethyl)phenyl)-2-(naphthalen-1-yl)acetamide (6j)**

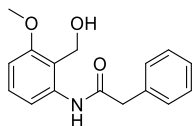
According to general procedure A, the product was obtained from 2-aminobenzyl alcohol (10 mmol, 1 equiv.) and 2-(naphthalen-1-yl)acetic acid (10 mmol, 1 equiv.) as a light yellow solid (2.36 g, 81 %) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 6:4). **¹H-NMR (CDCl₃, 500 MHz):** δ 8.30 (br. s, 1H), 8.06 (d, *J* = 8.2 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 1H), 7.90 (dd, *J* = 2.2; 7.1 Hz, 1H), 7.86 (dd, *J* = 2.2; 7.1 Hz, 1H), 7.57-7.49 (m, 4H), 7.28-7.25 (m, 1H), 6.99-6.97 (m, 2H), 4.21 (s, 2H), 4.02 (s, 2H). **¹³C-NMR (CDCl₃, 125 MHz):** δ 169.9, 137.2, 134.0, 132.4, 131.0, 129.5, 129.1, 129.0, 128.9, 128.9, 128.7, 127.1, 126.5, 126.0, 124.5, 124.0, 122.5, 64.0, 43.2. **IR (neat):** ν 3237, 1650, 1534, 1456, 1399, 1205, 1090, 1045, 886, 779, 529 cm⁻¹. **HRMS (ESI-TOF) m/z [M+Na]⁺:** calcd for C₁₉H₁₇NO₂Na 314.1157; found 314.1160.



Chemical Formula: C₁₃H₁₃NO₂S

- ***N*-(2-(hydroxymethyl)phenyl)-2-(thiophen-2-yl)acetamide (6k)**

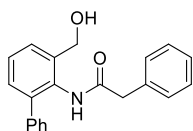
According to general procedure A, the product was obtained from 2-aminobenzyl alcohol (10 mmol, 1 equiv.) and 2-(thiophen-2-yl)acetic acid (10 mmol, 1 equiv.) as a white solid (2.13 g, 86 %) after purification by flash column chromatography on silica gel (pentane/ethyl acetate 6:4). **¹H-NMR (CDCl₃, 500 MHz):** δ 8.63 (br. s, 1H), 8.03 (d, *J* = 8.1 Hz, 1H), 7.33-7.29 (m, 2H), 7.13 (d, *J* = 7.4 Hz, 1H), 7.08-7.03 (m, 3H), 4.52 (s, 2H), 3.96 (s, 3H), 3.75 (s, 2H), 1.94 (br. s, 1H). **¹³C-NMR (CDCl₃, 125 MHz):** δ 168.8, 137.2, 135.9, 129.7, 129.3, 129.0, 128.1, 127.7, 126.1, 124.7, 122.5, 64.4, 38.8. **IR (neat):** ν 3250, 1654, 1587, 1532, 1454, 1342, 1248, 1039, 967, 765, 697, 533 cm⁻¹. **HRMS (ESI-TOF) m/z [M+Na]⁺:** calcd for C₁₃H₁₃NO₂SNa 270.0565; found 270.0566.



Chemical Formula: C₁₆H₁₇NO₃

- ***N*-(2-(hydroxymethyl)-3-methoxyphenyl)-2-phenylacetamide (6l)**

According to the general procedure B, the product was obtained over 5 steps from 3-methoxyaniline (15 mmol, 1.85 g) as a white solid (1.052 g, 26 % overall yield) by flash column chromatography on silica gel (pentane/ethyl acetate 1:1). **¹H-NMR (CDCl₃, 500 MHz):** δ 8.23 (br. s, 1H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.41-7.36 (m, 4H), 7.34-7.31 (m, 1H), 7.22 (t, *J* = 8.2 Hz, 1H), 6.66 (d, *J* = 8.2 Hz, 1H), 4.58 (s, 2H), 3.79 (s, 3H), 3.76 (s, 2H), 1.82 (br. s, 1H). **¹³C-NMR (CDCl₃, 125 MHz):** δ 170.2, 157.4, 138.3, 134.8, 129.8, 129.4, 129.3, 127.7, 119.3, 115.6, 107.5, 56.2, 55.9, 45.2. **IR (neat):** ν 3241, 1655, 1579, 1533, 1476, 1394, 1196, 1039, 968, 744, 576 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** calcd for C₂₁H₂₀NO₂ 318.1494; found 318.1495.

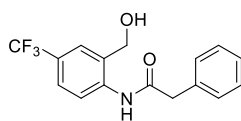


Chemical Formula: C₂₁H₁₉NO₂

- ***N*-(3-(hydroxymethyl)-[1,1'-biphenyl]-2-yl)-2-phenylacetamide (6m)**

According to the general procedure B, the product was obtained over 5 steps from [1,1'-biphenyl]-2-amine (15 mmol, 2.54 g) as a white solid (1.57 g, 33 % overall yield) by flash column chromatography on silica gel (pentane/ethyl acetate 1:1). **¹H-NMR (CDCl₃, 500 MHz):** δ 7.49 (dd, *J* = 1.4; 7.6 Hz, 1H), 7.40-7.38 (m, 3H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.27-7.23 (m, 4H), 7.18-7.17 (m, 2H), 7.01-6.99 (m, 2H), 6.73 (br. s, 1H), 4.50 (s, 2H), 3.61 (s, 2H), 3.51 (br. s, 1H). **¹³C-NMR (CDCl₃, 125 MHz):** δ 172.0, 139.2, 139.2, 138.1, 134.0, 131.9, 130.3, 130.2, 129.6, 129.3, 128.9, 128.8, 127.9, 127.8, 127.7, 62.7,

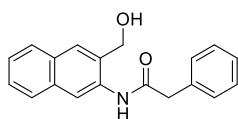
43.9. **IR (neat):** ν 3383, 3220, 1662, 1596, 1525, 1435, 1351, 1239, 1096, 1044, 992, 787, 698, 642, 512 cm^{-1} . **HRMS (ESI-TOF) m/z $[M+Na]^+$:** calcd for $\text{C}_{16}\text{H}_{17}\text{NO}_3\text{Na}$ 294.1106; found 294.1106.



Chemical Formula: $\text{C}_{16}\text{H}_{14}\text{F}_3\text{NO}_2$

- ***N*-(2-(hydroxymethyl)-4-(trifluoromethyl)phenyl)-2-phenylacetamide (6n)**

According to the general procedure B, the product was obtained over 5 steps from 4-(trifluoromethyl)aniline (15 mmol, 2.42 g) as a white solid (1.62 g, 35 % overall yield) by flash column chromatography on silica gel (pentane/ethyl acetate 1:1). **$^1\text{H-NMR}$ (500 MHz, CDCl_3):** δ 8.68 (br. s, 1H), 8.31 (d, $J = 8.5$ Hz, 1H), 7.55 (d, $J = 8.5$ Hz, 2H), 7.42-7.40 (m, 2H), 7.37-7.35 (m, 4H), 4.50 (s, 2H), 3.78 (s, 2H). **$^{19}\text{F-NMR}$ (CDCl_3 , 500 MHz):** δ -62.2. **$^{13}\text{C-NMR}$ (125 MHz, CDCl_3):** δ 170.0, 134.4, 129.9, 129.3, 128.8, 127.8, 126.8 (d, $J = 132$ Hz), 126.4 (q, $J = 3.7$ Hz), 125.7 (q, $J = 3.7$ Hz), 124.1 (d, $J = 270$ Hz), 121.8, 64.2, 45.4. **IR (neat):** ν 3256, 1660, 1524, 1408, 1330, 1274, 1166, 1079, 904, 834, 703, 571 cm^{-1} . **HRMS (ESI-TOF) m/z : $[M+Na]^+$:** calcd for $\text{C}_{16}\text{H}_{15}\text{NO}_2\text{F}_3$ 310.1055; found 310.1059.

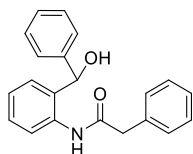


Chemical Formula: $\text{C}_{19}\text{H}_{17}\text{NO}_2$

- ***N*-(3-(hydroxymethyl)naphthalen-2-yl)-2-phenylacetamide (6o)**

Step 1: to a suspension of LiAlH_4 (20 mmol, 0.76 g, 2 equiv.) in dry THF (40 mL) under argon at 0°C a solution of 3-amino-2-naphthoic acid (10 mmol, 1.87 g, 1 equiv.) in dry THF (25 mL) was added dropwise. After addition, the reaction was heated to reflux for 16 h. After cooling to room temperature, the reaction was quenched with saturated Na_2SO_4 solution and filtered over celite. The filtrate was then washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford pure (3-aminonaphthalen-2-yl)methanol as a light brown solid (1.54 g, 89 %).

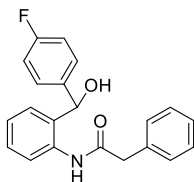
Step 2: To a stirred solution of (3-aminonaphthalen-2-yl)methanol (1.54 g, 8.9 mmol) in dry THF (15 mL) was added 5 mL of pyridine. A solution of phenylacetyl chloride (1.18 mL, 1 equiv.) in dry THF (10 mL) was added dropwise at 0°C under argon. The mixture was warmed to room temperature and stirred overnight. Solvent was evaporated, water and chloroform were added and the organic phase was washed with aqueous HCl (5 %), brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. Crude product was then purified by flash column chromatography on silica gel (pentane/ethyl acetate 1:1) to afford the pure product as a light brown solid (1.99 g, 77 %). **$^1\text{H-NMR}$ (500 MHz, CDCl_3):** δ 8.65 (br. s, 1H), 8.61 (s, 1H), 7.79 (d, $J = 8.2$ Hz, 1H), 7.69 (d, $J = 8.2$ Hz, 1H), 7.37-7.33 (m, 1H), 4.60 (s, 2H), 3.81 (s, 2H). **$^{13}\text{C-NMR}$ (125 MHz, CDCl_3):** δ 170.1, 134.8, 133.9, 130.2, 129.9, 129.3, 129.0, 128.9, 128.1, 127.9, 127.7, 127.5, 126.8, 125.5, 119.3, 64.8, 45.4. **IR (neat):** ν 3304, 1737, 1645, 1600, 1527, 1496, 1451, 1359, 1166, 1031, 974, 884, 747, 699, 477 cm^{-1} . **HRMS (ESI-TOF) m/z $[M+Na]^+$:** calcd for $\text{C}_{19}\text{H}_{17}\text{NO}_2\text{Na}$ 314.1157; found 314.1164.



Chemical Formula: C₂₁H₁₉NO₂

- ***N*-(2-(hydroxy(phenyl)methyl)phenyl)-2-phenylacetamide (6p)**

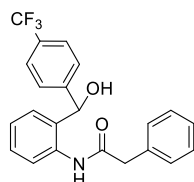
According to the general procedure C, the product was obtained from bromobenzene (10 mmol, 1.56 g) as a light yellow solid (1.49 g, 47 %) by flash column chromatography on silica gel (pentane/ethyl acetate 3:1). **¹H-NMR (CDCl₃, 500 MHz):** δ 8.48 (br. s, 1H), 8.07 (d, *J* = 8.1 Hz, 1H), 7.34-7.26 (m, 7H), 7.19-7.15 (m, 4H), 7.02 (t, *J* = 7.4 Hz, 1H), 6.97 (d, *J* = 7.4 Hz, 1H), 5.68 (s, 1H), 3.64-3.55 (m, 2H), 2.48 (br. s, 1H). **¹³C-NMR (CDCl₃, 125 MHz):** δ 169.7, 141.3, 136.8, 134.6, 132.0, 129.9, 129.1, 129.0, 128.9, 128.8, 128.7, 128.0, 127.5, 126.6, 124.5, 123.3, 45.2. **IR (neat):** ν 3340, 1664, 1589, 1520, 1446, 1310, 1019, 868, 755, 722, 695, 543, 495 cm⁻¹. **HRMS (ESI-TOF) m/z [M+Na]⁺:** calcd for C₂₁H₁₉NO₂Na 340.1313; found 340.1313.



Chemical Formula: C₂₁H₁₈FNO₂

- ***N*-(2-((4-fluorophenyl)(hydroxy)methyl)phenyl)-2-phenylacetamide (6q)**

According to the general procedure C, the product was obtained from 1-bromo-4-fluorobenzene (10 mmol, 1.74 g) as a light yellow solid (1.78 g, 53 %) by flash column chromatography on silica gel (pentane/ethyl acetate 3:1). **¹H-NMR (CDCl₃, 500 MHz):** δ 8.46 (br. s, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.33-7.26 (m, 4H), 7.17-7.15 (m, 2H), 7.09-7.04 (m, 3H), 6.99-6.95 (m, 3H), 5.65 (s, 1H), 3.63-3.53 (m, 2H), 2.79 (br. s, 1H). **¹⁹F-NMR (CDCl₃, 500 MHz):** δ -114.5. **¹³C-NMR (CDCl₃, 125 MHz):** δ 169.8, 162.4 (d, *J* = 245.0 Hz), 137.0 (d, *J* = 3.1 Hz), 136.6, 134.6, 132.0, 129.8, 129.1, 129.0, 128.8, 128.2 (d, *J* = 8.1 Hz), 127.6, 124.6, 123.4, 115.3 (d, *J* = 21.3 Hz), 74.8, 45.1. **IR (neat):** ν 3314, 1664, 1588, 1524, 1503, 1449, 1329, 1215, 1152, 1018, 585, 755, 727, 695, 572, 493 cm⁻¹. **HRMS (ESI-TOF) m/z [M+Na]⁺:** calcd for C₂₁H₁₈NO₂FNa 358.1219; found 359.1221.

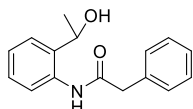


Chemical Formula: C₂₂H₁₈F₃NO₂

- ***N*-(2-(hydroxy(3-(trifluoromethyl)phenyl)methyl)phenyl)-2-phenylacetamide (6r)**

According to the general procedure C, the product was obtained from 1-bromo-3-(trifluoromethyl)benzene (10 mmol, 2.24 g) as a light yellow solid (2.12 g, 55 %) by flash column

chromatography on silica gel (pentane/ethyl acetate 3:1). **¹H-NMR (CDCl₃, 500 MHz):** δ 8.26 (br. s, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.52 (s, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.26-7.20 (m, 4H), 7.12 (d, *J* = 7.8 Hz, 1H), 7.08 (d, *J* = 6.8 Hz, 2H), 6.99 (t, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 5.65 (s, 1H), 3.56-3.45 (m, 2H). **¹⁹F-NMR (CDCl₃, 500 MHz):** δ -62.4. **¹³C-NMR (CDCl₃, 125 MHz):** δ 170.0, 142.5, 136.6, 134.3, 132.0, 129.8, 129.4, 129.2, 129.1 (d, *J* = 89.7 Hz), 129.0, 127.7, 126.4 (d, *J* = 256.7 Hz), 124.9, 124.6 (q, *J* = 3.7 Hz), 123.8, 123.2 (q, *J* = 3.7 Hz), 115.3 (d, *J* = 21.3 Hz), 74.7, 45.0. **IR (neat):** ν 3273, 1664, 1589, 1529, 1445, 1323, 1160, 1109, 1070, 1032, 797, 755, 699, 547 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** calcd for C₂₂H₁₉NO₂F₃ 386.1368; found 386.1365.

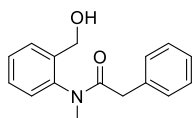


Chemical Formula: C₁₆H₁₇NO₂

- ***N*-(2-(1-hydroxyethyl)phenyl)-2-phenylacetamide (6s)**

Step 1: 2-aminoacetophenone (10 mmol, 1.35 g, 1 equiv.) was dissolved in methanol (0.5 M). Sodium borohydride (1.5 equiv.) was added portionwise at 0 °C, the mixture was stirred at room temperature for 2 hours and quenched with water. The product was extracted with ethyl acetate, washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford pure 1-(2-aminophenyl)ethan-1-ol as a light brown oil (1.27 g, 93 %).

Step 2: To a stirred solution of 1-(2-aminophenyl)ethan-1-ol (1.27 g, 9.3 mmol, 1 equiv.) in dry THF (15 mL) was added 5 mL of pyridine. A solution of phenylacetyl chloride (1.23 mL, 1 equiv.) in dry THF (10 mL) was added dropwise at 0 °C under argon. The mixture was warmed to room temperature and stirred overnight. Solvent was evaporated, water and chloroform were added and the organic phase was washed with aqueous HCl (5 %), brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. Crude product was then purified by flash column chromatography on silica gel (pentane/ethyl acetate 1:1) to afford the pure product as a brown solid (1.80 g, 76 %). **¹H-NMR (CDCl₃, 500 MHz):** δ 8.95 (br. s, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 7.40-7.30 (m, 5H), 7.27-7.24 (m, 1H), 7.08-7.01 (m, 2H), 4.72 (q, *J* = 6.6 Hz, 1H), 3.70 (d, *J* = 2.8 Hz, 2H), 1.31 (d, *J* = 6.6 Hz, 3H). **¹³C-NMR (CDCl₃, 125 MHz):** δ 169.7, 136.6, 134.7, 132.8, 129.9, 129.1, 128.5, 127.5, 126.8, 124.3, 122.5, 70.6, 45.4, 22.6. **IR (neat):** ν 2967, 1694, 1603, 1497, 1408, 1296, 1239, 1187, 1074, 925, 750, 699, 603, 479 cm⁻¹. **HRMS (ESI-TOF) m/z [M+Na]⁺:** calcd for C₁₆H₁₇NO₂Na 278.1157; found 278.1159.



Chemical Formula: C₁₆H₁₇NO₂

- ***N*-(2-(hydroxymethyl)phenyl)-*N*-methyl-2-phenylacetamide (6t)**

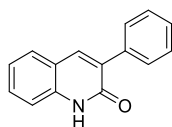
According to general procedure A, the product was obtained from (2-(methylamino)phenyl)methanol (10 mmol, 1 equiv.) and phenylacetyl chloride (10 mmol, 1 equiv.), after purification by flash column chromatography on silica gel (pentane/ethyl acetate 3:1). Brown solid (1.22 g, 48 %). **¹H-NMR (CDCl₃, 500 MHz):** δ 7.52 (d, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.2 Hz, 1H), 7.38-7.35 (m, 2H), 7.20-7.18 (m, 3H),

7.11 (d, $J = 7.5$ Hz, 1H), 6.94-6.93 (m, 2H), 4.38 (d, $J = 13.2$ Hz, 1H), 4.20 (d, $J = 13.2$ Hz, 1H), 3.43 (s, 2H), 3.18 (s, 3H). $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): δ 171.2, 141.3, 138.8, 135.1, 129.2, 129.2, 129.1, 129.1, 128.6, 128.5, 126.8, 60.7, 41.7, 37.3. IR (neat): ν 2909, 1709, 1584, 1495, 1453, 1231, 1162, 926, 748, 696, 607 cm^{-1} . HRMS (ESI-TOF) m/z $[\text{M}+\text{H}]^+$: calcd for $\text{C}_{16}\text{H}_{18}\text{NO}_2$ 256.1338; found 256.1338.

4) Iron-catalysed synthesis of quinoline-2(1H)-ones.

General Procedure D:

In a 15 mL flame-dried Schlenk tube equipped with a stirring bar, the desired amido-alcohol (0.5 mmol, 1 equiv.), Me_3NO (2.22 mg, 0.02 mmol, 4 mol%), iron complex **Fe3** (4.21 mg, 0.01 mmol, 2 mol %), and Na_2CO_3 (106 mg, 1 mmol, 2 equiv.) were added to a solution of dry DMF (0.5 mL) under an argon atmosphere. The mixture was then placed into a preheated oil bath and stirred at 100 °C for 24 h. The mixture was cooled to room temperature, filtered over a pad of Celite with diethyl ether, and concentrated under reduced pressure. The conversion was determined by $^1\text{H-NMR}$ spectroscopy and the residue was purified by flash chromatography on silica gel using dichloromethane-diethyl ether as eluent to afford the desired product.



Chemical Formula: $\text{C}_{15}\text{H}_{11}\text{NO}$

- **3-phenylquinolin-2(1H)-one (7a)**²³⁴

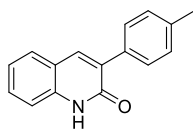
According to the general procedure D, the product was obtained from *N*-[2-(hydroxymethyl)phenyl]-2-phenylacetamide (0.5 mmol, 120 mg) as a white solid (86 mg, 78 %) by flash column chromatography on silica gel (dichloromethane/diethyl ether 3:1). $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ 11.78 (br. s, 1H), 7.93 (s, 1H), 7.83-7.81 (m, 2H), 7.60 (dd, $J = 1.0; 8.0$ Hz, 1H), 7.51-7.48 (m, 3H), 7.44-7.40 (m, 1H), 7.36 (d, $J = 8.0$ Hz, 1H), 7.24-7.21 (m, 1H). $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): δ 163.2, 138.6, 138.1, 136.3, 132.6, 130.4, 129.1, 128.4, 128.3, 128.0, 122.8, 120.5, 115.6.

- **Scale up of the reaction to 5 mmol.**

In a 30 mL flame-dried Schlenk tube equipped with a stirring bar, *N*-[2-(hydroxymethyl)phenyl]-2-phenylacetamide (5 mmol, 1.2 g), iron complex **Fe3** (42.1 mg, 2 mol %), Me_3NO (22.2 mg, 4 mol %), Na_2CO_3 (1.06 g, 2 equiv.) were added to a solution of dry DMF (5 mL) under an argon atmosphere. The mixture was rapidly stirred at room temperature for 2 min and then placed into a pre-heated oil bath at 100 °C and stirred over 24 hours. The mixture was cooled to room temperature, filtrated over a pad of celite with diethyl ether. The conversion was determined by $^1\text{H-NMR}$ spectroscopy and the residue was purified by flash chromatography on silica gel using dichloromethane-diethyl ether (3:1) as eluent to

²³⁴ Charoenpol, A.; Meesin, J.; Khaikate, O.; Reutrakul, V.; Pohmakotr, M.; Leowanawat, P.; Soorukram, D.; Kuhakarn, C. *Org. Biomol. Chem.* **2018**, *16*, 7050-7054.

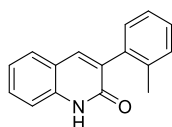
afford the pure product as a white solid (829 mg, 75 %). ¹H-NMR data were comparable with the previous NMR data.



Chemical Formula: C₁₆H₁₃NO

- **3-(*p*-tolyl)quinolin-2(1*H*)-one (7b)**²³⁴

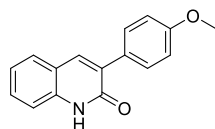
According to the general procedure D, the product was obtained from *N*-(2-(hydroxymethyl)phenyl)-2-(*p*-tolyl)acetamide (0.5 mmol, 128 mg) as a white solid (86 mg, 73 %) by flash column chromatography on silica gel (dichloromethane/diethyl ether 3:1). ¹H-NMR (CDCl₃, 500 MHz): δ 11.60 (br. s, 1H), 7.90 (s, 1H), 7.71 (d, *J* = 8.1 Hz, 2H), 7.59 (dd, *J* = 1.1; 7.8 Hz, 1H), 7.46 (ddd, *J* = 1.1; 7.3; 8.1 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 2H), 7.23-7.0 (m, 1H), 2.43 (s, 3H). ¹³C-NMR (CDCl₃, 125 MHz): δ 163.2, 138.6, 138.1, 136.3, 132.6, 130.4, 129.1, 128.4, 128.3, 128.0, 122.8, 120.5, 115.6, 21.5.



Chemical Formula: C₁₆H₁₃NO

- **3-(*o*-tolyl)quinolin-2(1*H*)-one (7c)**¹⁷⁸

According to the general procedure D, the product was obtained from *N*-(2-(hydroxymethyl)phenyl)-2-(*o*-tolyl)acetamide (0.5 mmol, 128 mg) as a white solid (91 mg, 77 %) by flash column chromatography on silica gel (dichloromethane/diethyl ether 3:1). ¹H-NMR (CDCl₃, 500 MHz): δ 12.45 (br. s, 1H), 7.76 (s, 1H), 7.56 (dd, *J* = 1.1; 7.8 Hz, 1H), 7.45-7.42 (m, 1H), 7.36-7.30 (m, 5H), 7.22-7.20 (m, 1H), 2.36 (s, 3H). ¹³C-NMR (CDCl₃, 125 MHz): δ 163.2, 140.0, 138.5, 137.4, 136.6, 134.2, 130.4, 130.2, 130.2, 128.3, 127.7, 125.9, 122.7, 120.1, 116.2, 20.3.

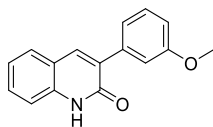


Chemical Formula: C₁₆H₁₃NO₂

- **3-(4-methoxyphenyl)quinolin-2(1*H*)-one (7d)**²³⁴

According to the general procedure D, the product was obtained from *N*-(2-(hydroxymethyl)phenyl)-2-(4-methoxyphenyl)acetamide (0.5 mmol, 136 mg) as a white solid (104 mg, 83 %) by flash column chromatography on silica gel (dichloromethane/diethyl ether 3:1). ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 11.90 (br. s, 1H), 8.04 (s, 1H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.69 (d, *J* = 7.4 Hz, 1H), 7.48-7.45 (m, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.19-7.15 (m, 1H), 6.97 (d, *J* = 8.8 Hz, 2H), 3.79 (s, 3H). ¹³C-NMR (DMSO-

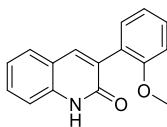
*d*₆, 125 MHz): δ 161.2, 159.1, 138.1, 136.4, 131.0, 129.9, 129.9, 128.5, 127.9, 121.8, 119.7, 114.6, 113.4, 55.2.



Chemical Formula: C₁₆H₁₃NO₂

- **3-(3-methoxyphenyl)quinolin-2(1H)-one (7e)**¹⁷⁸

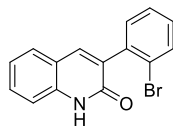
According to the general procedure D, the product was obtained from *N*-(2-(hydroxymethyl)phenyl)-2-(3-methoxyphenyl)acetamide (0.5 mmol, 136 mg) as a white solid (77 mg, 61 %) by flash column chromatography on silica gel (dichloromethane/diethyl ether 3:1). ¹H-NMR (CDCl₃, 500 MHz): δ 12.48 (br. s, 1H), 7.94 (s, 1H), 7.60 (dd, *J* = 1.0; 7.9 Hz, 1H), 7.50-7.46 (m, 1H), 7.44-7.38 (m, 4H), 7.24-7.21 (m, 1H), 6.99-6.97 (m, 1H), 3.90 (s, 3H). ¹³C-NMR (CDCl₃, 125 MHz): δ 163.4, 159.6, 138.7, 138.2, 137.7, 132.3, 130.4, 129.4, 127.9, 122.8, 121.5, 120.4, 115.9, 114.6, 114.2, 55.5.



Chemical Formula: C₁₆H₁₃NO₂

- **3-(2-methoxyphenyl)quinolin-2(1H)-one (7f)**²³⁵

According to the general procedure D, the product was obtained from *N*-(2-(hydroxymethyl)phenyl)-2-(2-methoxyphenyl)acetamide (0.5 mmol, 136 mg) as a white solid (68 mg, 54 %) by flash column chromatography on silica gel (dichloromethane/diethyl ether 3:1). ¹H-NMR (DMSO-*d*₆, 500 MHz): δ 11.80 (br. s, 1H), 7.83 (s, 1H), 7.64 (dd, *J* = 1.0; 7.8 Hz, 1H), 7.49-7.46 (m, 1H), 7.37-7.33 (m, 1H), 7.29 (d, *J* = 8.1 Hz, 1H), 7.25 (dd, *J* = 1.7; 7.4 Hz, 1H), 7.18-7.14 (m, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.99-6.96 (m, 1H), 3.71 (s, 3H). ¹³C-NMR (DMSO-*d*₆, 125 MHz): δ 160.8, 157.1, 138.7, 138.5, 130.9, 130.9, 130.0, 129.2, 127.8, 125.8, 121.7, 120.0, 119.2, 114.7, 111.3, 55.5.



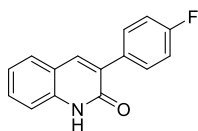
Chemical Formula: C₁₅H₁₀BrNO

- **3-(2-bromophenyl)quinolin-2(1H)-one (7g)**

According to the general procedure D, the product was obtained from 2-(2-bromophenyl)-*N*-(2-(hydroxymethyl)phenyl)acetamide (0.5 mmol, 160 mg) as a white solid (103 mg, 69 %) by flash column chromatography on silica gel (dichloromethane/diethyl ether 3:1). ¹H-NMR (CDCl₃, 500 MHz): δ 11.74 (br. s, 1H), 7.80 (s, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.57 (dd, *J* = 1.0; 7.8 Hz, 1H), 7.51-7.48 (m,

²³⁵ Modak, A.; Rana, S.; Maiti, D. *J. Org. Chem.* **2015**, *80*, 296-303.

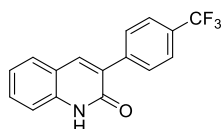
1H), 7.45-7.40 (m, 2H), 7.36 (d, $J = 8.1$ Hz, 1H), 7.31-7.27 (m, 1H), 7.24-7.21 (m, 1H). $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): δ 162.4, 140.6, 138.6, 137.5, 133.30, 133.1, 131.8, 130.8, 129.8, 128.1, 127.5, 124.2, 122.8, 119.8, 116.1. **IR (neat):** ν 2842, 1651, 1568, 1497, 1431, 1230, 1055, 1026, 904, 829, 754, 739, 596, 560, 470 cm^{-1} . **HRMS (ESI-TOF) m/z $[\text{M}+\text{H}]^+$:** calcd for $\text{C}_{15}\text{H}_{11}\text{NOBr}$ 300.0024; found 300.0028.



Chemical Formula: $\text{C}_{15}\text{H}_{10}\text{FNO}$

- **3-(4-fluorophenyl)quinolin-2(1H)-one (7h)**¹⁷⁸

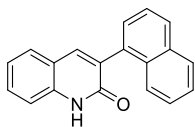
According to the general procedure D, the product was obtained from 2-(4-fluorophenyl)-*N*-(2-(hydroxymethyl)phenyl)acetamide (0.5 mmol, 130 mg) as a white solid (74 mg, 62 %) by flash column chromatography on silica gel (dichloromethane/diethyl ether 3:1). $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 500 MHz): δ 11.98 (br. s, 1H), 8.12 (s, 1H), 7.84-7.82 (m, 2H), 7.72 (dd, $J = 1.0$; 7.8 Hz, 1H), 7.52-7.50 (m, 1H), 7.34 (d, $J = 8.1$ Hz, 1H), 7.28-7.25 (m, 2H), 7.22-7.19 (m, 1H). $^{19}\text{F-NMR}$ ($\text{DMSO-}d_6$, 500 MHz): δ -114.1. $^{13}\text{C-NMR}$ ($\text{DMSO-}d_6$, 125 MHz): δ 161.8 (d, $J = 243.5$ Hz), 161.0, 138.3, 137.5 (d, $J = 5.8$ Hz), 132.5 (d, $J = 3.2$ Hz), 130.7 (d, $J = 7.9$ Hz), 130.3, 130.2, 128.1, 121.9, 119.5, 114.8, 114.7 (d, $J = 1.9$ Hz).



Chemical Formula: $\text{C}_{16}\text{H}_{10}\text{F}_3\text{NO}$

- **3-(4-(trifluoromethyl)phenyl)quinolin-2(1H)-one (7i)**¹⁷⁸

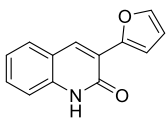
According to the general procedure D, the product was obtained from *N*-(2-(hydroxymethyl)phenyl)-2-(4-(trifluoromethyl)phenyl)acetamide (0.5 mmol, 155 mg) as a white solid (94 mg, 65 %) by flash column chromatography on silica gel (dichloromethane/diethyl ether 3:1). $^1\text{H-NMR}$ ($\text{DMSO-}d_6$, 500 MHz): δ 12.06 (br. s, 1H), 8.24 (s, 1H), 7.99 (d, $J = 8.1$ Hz, 2H), 7.78 (d, $J = 8.1$ Hz, 2H), 7.74 (d, $J = 7.4$ Hz, 1H), 7.55-7.51 (m, 1H), 7.33 (d, $J = 8.1$ Hz, 1H), 7.23-7.0 (m, 1H). $^{19}\text{F-NMR}$ ($\text{DMSO-}d_6$, 500 MHz): δ -60.9. $^{13}\text{C-NMR}$ ($\text{DMSO-}d_6$, 125 MHz): δ 160.7, 140.3, 138.8 (d, $J = 21.6$ Hz), 130.7, 129.9, 129.4, 128.4, 128.0 (d, $J = 31.7$ Hz), 124.7 (q, $J = 3.7$ Hz), 122.0, 121.5 (q, $J = 267.6$ Hz), 119.3, 114.8.



Chemical Formula: C₁₉H₁₃NO

- **3-(naphthalen-1-yl)quinolin-2(1H)-one (7j)**¹⁷⁸

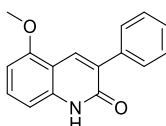
According to the general procedure D, the product was obtained from *N*-(2-(hydroxymethyl)phenyl)-2-(naphthalen-1-yl)acetamide (0.5 mmol, 146 mg) as a white solid (80 mg, 59 %) by flash column chromatography on silica gel (dichloromethane/diethyl ether 3:1). **¹H-NMR (DMSO-*d*₆, 500 MHz):** δ 12.01 (br. s, 1H), 8.00 (s, 1H), 7.95 (dd, *J* = 4.1; 8.0 Hz, 2H), 7.71 (d, *J* = 7.4 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.57-7.50 (m, 3H), 7.46-7.42 (m, 2H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.19 (t, *J* = 7.4 Hz, 1H). **¹³C-NMR (DMSO-*d*₆, 125 MHz):** δ 161.3, 139.8, 138.8, 135.0, 133.1, 132.6, 131.6, 130.3, 128.1, 128.1, 128.1, 127.4, 126.0, 125.9, 125.8, 125.4, 121.9, 119.3, 114.9.



Chemical Formula: C₁₃H₉NO₂

- **3-(thiophen-2-yl)quinolin-2(1H)-one (7k)**²³⁴

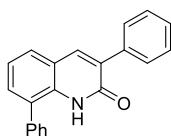
According to the general procedure D, the product was obtained from *N*-(2-(hydroxymethyl)phenyl)-2-(thiophen-2-yl)acetamide (0.5 mmol, 124 mg) as a white solid (54 mg, 48 %) by flash column chromatography on silica gel (dichloromethane/diethyl ether 3:1). **¹H-NMR (CDCl₃, 500 MHz):** δ 12.30 (br. s, 1H), 8.27 (s, 1H), 7.84 (dd, *J* = 1.0; 3.7 Hz, 1H), 7.68 (d, *J* = 7.2 Hz, 1H), 7.55 (ddd, *J* = 1.2; 7.2; 8.2 Hz, 1H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.46 (dd, *J* = 1.0; 5.1 Hz, 1H), 7.33-7.30 (m, 1H), 7.16 (dd, *J* = 3.7; 5.1 Hz, 1H). **¹³C-NMR (CDCl₃, 125 MHz):** δ 161.5, 136.8, 136.7, 135.2, 130.8, 128.0, 127.9, 127.2, 126.3, 125.0, 123.8, 120.7, 116.2.



Chemical Formula: C₁₆H₁₃NO₂

- **5-methoxy-3-phenylquinolin-2(1H)-one (7l)**

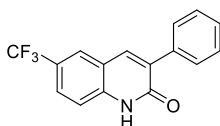
According to the general procedure D, the product was obtained from *N*-(2-(hydroxymethyl)-3-methoxyphenyl)-2-phenylacetamide (0.5 mmol, 136 mg) as a light-yellow solid (85 mg, 68 %) by flash column chromatography on silica gel (dichloromethane/diethyl ether 3:1). **¹H-NMR (CDCl₃, 500 MHz):** δ 11.42 (br. s, 1H), 8.34 (s, 1H), 7.84-7.82 (m, 2H), 7.48-7.46 (m, 2H), 7.41-7.38 (m, 2H), 6.93 (d, *J* = 8.1 Hz, 1H), 6.63 (d, *J* = 8.1 Hz, 1H), 3.96 (s, 3H). **¹³C-NMR (CDCl₃, 125 MHz):** δ 163.1, 156.3, 139.3, 136.7, 133.3, 131.2, 130.9, 129.1, 128.3, 128.1, 111.4, 108.1, 102.8, 55.9. **IR (neat):** ν 2851, 1656, 1563, 1522, 1499, 1412, 1352, 1254, 1049, 912, 833, 752, 598, 471 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** calcd for C₁₆H₁₄NO₂ 252.1025; found 252.1027.



Chemical Formula: C₂₁H₁₅NO

- **3,8-diphenylquinolin-2(1H)-one (7m)**

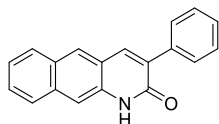
According to the general procedure D, the product was obtained from *N*-(3-(hydroxymethyl)-[1,1'-biphenyl]-2-yl)-2-phenylacetamide (0.5 mmol, 159 mg) as a white solid (83 mg, 56 %) by flash column chromatography on silica gel (pentane/ethyl acetate 6:4). **¹H-NMR (CDCl₃, 500 MHz):** δ 8.89 (br. s, 1H), 7.93 (s, 1H), 7.76-7.74 (m, 2H), 7.61 (dd, *J* = 1.3; 7.9 Hz, 1H), 7.57-7.54 (m, 2H), 7.51-7.48 (m, 1H), 7.47-7.44 (m, 4H), 7.42 (dd, *J* = 1.3; 7.4 Hz, 1H), 7.38 (ddd, *J* = 1.3; 3.9; 7.4 Hz, 1H). **¹³C-NMR (CDCl₃, 125 MHz):** δ 161.6, 138.5, 136.1, 136.0, 135.0, 133.0, 131.1, 129.8, 129.3, 128.8, 128.8, 128.5, 128.4, 128.3, 127.6, 122.6, 120.6. **IR (neat):** ν 2853, 1736, 1654, 1559, 1492, 1456, 1315, 1222, 1193, 1057, 907, 824, 766, 597 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** calcd for C₂₁H₁₆NO 298.1232; found 298.1237.



Chemical Formula: C₁₆H₁₀F₃NO

- **3-phenyl-6-(trifluoromethyl)quinolin-2(1H)-one (7n)²³⁴**

According to the general procedure D, the product was obtained from *N*-(2-(hydroxymethyl)-4-(trifluoromethyl)phenyl)-2-phenylacetamide (0.5 mmol, 155 mg) as a white solid (103 mg, 71 %) by flash column chromatography on silica gel (dichloromethane/diethyl ether 3:1). **¹H-NMR (DMSO-*d*₆, 500 MHz):** δ 11.80 (br. s, 1H), 7.83 (s, 1H), 7.64 (dd, *J* = 1.0; 7.8 Hz, 1H), 7.49-7.46 (m, 1H), 7.37-7.33 (m, 1H), 7.29 (d, *J* = 8.1 Hz, 1H), 7.25 (dd, *J* = 1.7; 7.4 Hz, 1H), 7.18-7.14 (m, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.99-6.96 (m, 1H), 3.71 (s, 3H). **¹⁹F-NMR (DMSO-*d*₆, 500 MHz):** δ -60.1. **¹³C-NMR (DMSO-*d*₆, 125 MHz):** δ 161.1, 140.7, 137.1, 135.7, 133.0, 128.7, 128.1, 128.0, 126.1 (q, *J* = 3.4 Hz), 125.5 (q, *J* = 4.2 Hz), 124.4 (d, *J* = 269.8 Hz), 121.8 (q, *J* = 32.2 Hz), 119.1, 115.6.

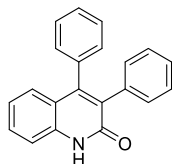


Chemical Formula: C₁₉H₁₃NO

- **3-phenylbenzo[g]quinolin-2(1H)-one (7o)**

According to the general procedure D, the product was obtained from *N*-(3-(hydroxymethyl)naphthalen-2-yl)-2-phenylacetamide (0.5 mmol, 146 mg) as a light yellow solid (80 mg, 59 %) by flash column chromatography on silica gel (dichloromethane/diethyl ether 3:1). **¹H-NMR (DMSO-*d*₆, 500 MHz):** δ 11.93 (br. s, 1H), 8.32 (s, 1H), 8.20 (s, 1H), 7.94 (d, *J* = 8.3 Hz, 1H), 7.87 (d, *J* = 8.3 Hz, 1H), 7.76-7.74 (m, 2H), 7.67 (s, 1H), 7.52-7.48 (m, 1H), 7.44-7.37 (m, 4H). **¹³C-NMR (DMSO-*d*₆, 125 MHz):** δ 161.4,

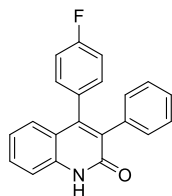
137.4, 136.1, 135.8, 133.6, 132.3, 128.9, 128.7, 128.3, 128.0, 128.0, 127.8, 127.4, 126.8, 124.4, 120.6, 109.6. **IR (neat):** ν 3029, 1662, 1568, 1497, 1431, 1230, 1055, 1026, 904, 829, 754, 739, 596, 560, 470 cm^{-1} . **HRMS (ESI-TOF) m/z $[M+H]^+$:** calcd for $\text{C}_{19}\text{H}_{14}\text{NO}$ 272.1075; found 272.1078.



Chemical Formula: $\text{C}_{21}\text{H}_{15}\text{NO}$

- **3,4-diphenylquinolin-2(1H)-one (7p)**²³⁶

According to the general procedure D, the product was obtained from *N*-(2-(hydroxy(phenyl)methyl)phenyl)-2-phenylacetamide (0.5 mmol, 159 mg) as a white solid (114 mg, 77 %) by flash column chromatography on silica gel (dichloromethane/diethyl ether 3:1). **¹H-NMR (DMSO-*d*₆, 500 MHz):** δ 12.07 (br. s, 1H), 8.32 (s, 1H), 8.20 (s, 1H), 7.94 (d, $J = 8.3$ Hz, 1H), 7.87 (d, $J = 8.3$ Hz, 1H), 7.76-7.74 (m, 2H), 7.67 (s, 1H), 7.52-7.48 (m, 1H), 7.44-7.37 (m, 4H). **¹³C-NMR (DMSO-*d*₆, 125 MHz):** δ 161.1, 148.0, 138.2, 136.1, 135.7, 131.9, 130.6, 130.1, 129.4, 127.9, 127.4, 127.0, 126.8, 126.5, 121.7, 119.9, 115.1.

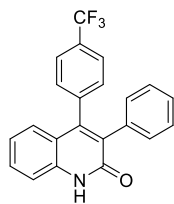


Chemical Formula: $\text{C}_{21}\text{H}_{14}\text{FNO}$

- **4-(4-fluorophenyl)-3-phenylquinolin-2(1H)-one (7q)**

According to the general procedure D, the product was obtained from *N*-(2-((4-fluorophenyl)(hydroxy)methyl)phenyl)-2-phenylacetamide (0.5 mmol, 168 mg) as a light yellow solid (124 mg, 79 %) by flash column chromatography on silica gel (dichloromethane/diethyl ether 3:1). **¹H-NMR (CDCl₃, 500 MHz):** δ 12.37 (br. s, 1H), 7.40-7.37 (m, 1H), 7.30 (d, $J = 7.7$ Hz, 1H), 7.22-7.17 (m, 4H), 7.16-7.12 (m, 2H), 7.07-7.03 (m, 3H), 6.97-6.93 (m, 2H). **¹⁹F-NMR (CDCl₃, 500 MHz):** δ -113.8. **¹³C-NMR (CDCl₃, 125 MHz):** δ 163.4, 162.2 (d, $J = 246.0$ Hz), 148.9, 138.1, 135.3, 132.4, 132.3, 131.6 (d, $J = 8.0$ Hz), 131.0, 130.5, 127.8, 127.2 (d, $J = 8.8$ Hz), 122.5, 120.9, 116.4, 115.2 (d, $J = 21.4$ Hz). **IR (neat):** ν 2848, 1640, 1598, 1496, 1430, 1376, 1219, 1154, 1013, 904, 754, 702, 690, 641, 560, 510, 462 cm^{-1} . **HRMS (ESI-TOF) m/z $[M+H]^+$:** calcd for $\text{C}_{21}\text{H}_{15}\text{NOF}$ 316.1138; found 316.1142.

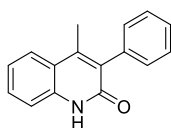
²³⁶ Luo, C.-Z.; Gandeepan, P.; Wu, Y.-C.; Chen, W.-C.; Cheng, C.-H. *RSC Adv.* **2015**, *5*, 106012-106018.



Chemical Formula: C₂₂H₁₄F₃NO

- **3-phenyl-4-(3-(trifluoromethyl)phenyl)quinolin-2(1H)-one (7r)**

According to the general procedure D, the product was obtained from *N*-(2-((4-trifluoromethylphenyl)(hydroxy)methyl)phenyl)-2-phenylacetamide (0.5 mmol, 192 mg) as a light yellow solid (135 mg, 74 %) by flash column chromatography on silica gel (dichloromethane/diethyl ether 3:1). **¹H-NMR (DMSO-*d*₆, 500 MHz):** δ 12.14 (br. s, 1H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.55-7.49 (m, 3H), 7.48 (s, 1H), 7.41 (d, *J* = 8.2 Hz, 1H), 7.14-7.08 (m, 4H), 7.07-7.05 (m, 2H), 6.94 (d, *J* = 8.2 Hz, 1H). **¹⁹F-NMR (DMSO-*d*₆, 500 MHz):** δ -61.2. **¹³C-NMR (DMSO-*d*₆, 125 MHz):** δ 161.0, 146.6, 138.4, 137.2, 135.4, 133.7, 132.7, 130.6, 130.4, 129.1, 128.8 (q, *J* = 31.6 Hz), 127.2, 126.7 (d, *J* = 45.8 Hz), 126.4 (q, *J* = 3.9 Hz), 124.3 (q, *J* = 3.2 Hz), 123.9 (q, *J* = 270.8 Hz), 122.0, 119.5, 115.3. **IR (neat):** ν 2849, 1644, 1598, 1443, 1327, 1290, 1164, 1123, 1074, 907, 759, 697, 683, 604, 559, 509, 463 cm⁻¹. **HRMS (ESI-TOF) m/z [M+H]⁺:** calcd for C₂₂H₁₅NOF₃ 366.1106; found 366.1106.

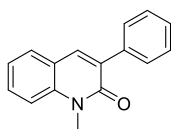


Chemical Formula: C₁₆H₁₃NO

- **4-methyl-3-phenylquinolin-2(1H)-one (7s)²³⁷**

According to the general procedure D, the product was obtained from *N*-(2-(1-hydroxyethyl)phenyl)-2-phenylacetamide (0.5 mmol, 128 mg) as a white solid (68 mg, 58 %) by flash column chromatography on silica gel (pentane/ethyl acetate 1:1). **¹H-NMR (CDCl₃, 500 MHz):** δ 11.34 (br. s, 1H), 7.74 (dd, *J* = 1.0; 8.1 Hz, 1H), 7.50-7.44 (m, 3H), 7.42-7.39 (m, 1H), 7.35-7.33 (m, 2H), 7.26-7.22 (m, 1H), 2.36 (s, 3H). **¹³C-NMR (CDCl₃, 125 MHz):** δ 163.0, 144.9, 137.5, 136.1, 132.4, 130.5, 130.2, 128.4, 127.7, 125.1, 122.5, 121.0, 116.2, 17.1.

²³⁷ Doléans-Jordheim, A.; Veron, J.-B.; Fendrich, O.; Bergeron, E.; Montagut-Romans, A.; Wong, Y.-S.; Furdul, B.; Freney, J.; Dumontet, C.; Boumendjel, A. *ChemMedChem* **2013**, *8*, 652-657.



Chemical Formula: C₁₆H₁₃NO

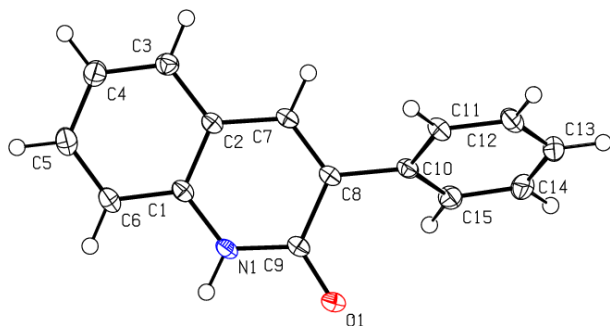
- **1-methyl-3-phenylquinolin-2(1H)-one (7t)**²³⁸

According to the general procedure D, the product was obtained from *N*-(2-(hydroxymethyl)phenyl)-*N*-methyl-2-phenylacetamide (0.5 mmol, 128 mg) as a yellow solid (105 mg, 89 %) by flash column chromatography on silica gel (dichloromethane/diethyl ether 3:1). **¹H-NMR (CDCl₃, 500 MHz):** δ 7.81 (s, 1H), 7.73-7.71 (m, 2H), 7.61 (dd, *J* = 1.4; 7.7 Hz, 1H), 7.56 (ddd, *J* = 1.4; 7.3; 8.7 Hz, 1H), 7.45-7.42 (m, 2H), 7.39-7.36 (m, 2H), 7.27-7.24 (m, 1H), 3.81 (s, 3H). **¹³C-NMR (CDCl₃, 125 MHz):** δ 161.7, 139.8, 136.9, 132.7, 130.4, 129.1, 129.0, 128.3, 128.2, 122.3, 120.9, 114.1, 30.1.

²³⁸ Nakatani, A.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2014**, *79*, 1377-1385.

5) X-Ray data of crystallized compounds.

• X-Ray diffraction analysis of compound 7a.



Crystal data

Chemical formula	C ₁₅ H ₁₁ NO
<i>M_r</i>	221.25
Crystal system, space group	Monoclinic, C2/c
Temperature (K)	150
<i>a</i> , <i>b</i> , <i>c</i> (Å)	17.8048 (14), 5.7547 (5), 21.5754 (16)
β (°)	105.736 (3)
<i>V</i> (Å ³)	2127.8 (3)
<i>Z</i>	8
Radiation type	Mo Kα
μ (mm ⁻¹)	0.09
Crystal size (mm)	0.18 × 0.09 × 0.08

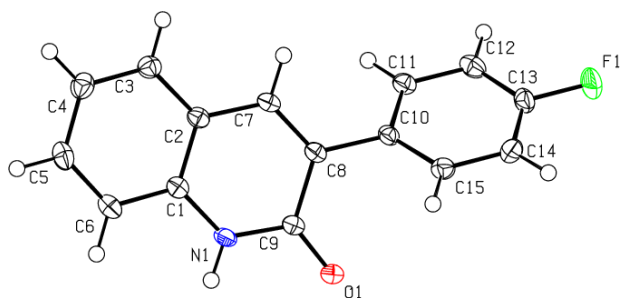
Data collection

Diffractometer	Bruker D8 QUEST
Absorption correction	Multi-scan SADABS 2016/2
No. of measured, independent and observed [<i>I</i> > 2σ(<i>I</i>)] reflections	32875, 6340, 4220
<i>R</i> _{int}	0.057
(sin θ/λ) _{max} (Å ⁻¹)	0.895

Refinement

<i>R</i> [<i>F</i> ² > 2σ(<i>F</i> ²)], <i>wR</i> (<i>F</i> ²), <i>S</i>	0.054, 0.164, 1.03
No. of reflections	6340
No. of parameters	158
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
Δρ _{max} , Δρ _{min} (e Å ⁻³)	0.55, -0.27

• **X-Ray diffraction analysis of compound 7j.**



Crystal data

Chemical formula	$C_{15}H_{10}FNO$
M_r	239.24
Crystal system, space group	Monoclinic, $C2/c$
Temperature (K)	170
a, b, c (Å)	17.5169 (8), 5.7876 (3), 22.1074 (11)
β (°)	102.879 (2)
V (Å ³)	2184.88 (19)
Z	8
Radiation type	Mo $K\alpha$
μ (mm ⁻¹)	0.10
Crystal size (mm)	0.25 × 0.07 × 0.06

Data collection

Diffractometer	Bruker D8 QUEST
Absorption correction	Multi-scan SADABS 2016/2
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	13357, 2714, 2322
R_{int}	0.029
$(\sin \theta/\lambda)_{max}$ (Å ⁻¹)	0.667

Refinement

$R[F^2 > 2\sigma(F^2)], wR(F^2), S$	0.043, 0.116, 1.03
No. of reflections	2714
No. of parameters	167
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}, \Delta\rho_{min}$ (e Å ⁻³)	0.38, -0.26

**CHAPTER IV: IMPROVING KNÖLKER CATALYSTS
FOR HYDROGENATION REACTIONS.**

I. Introduction.

Hydrogenation reactions²³⁹ of C=C or C=O bonds are extensively used for the industrial synthesis of pharmaceuticals and agrochemicals.²⁴⁰ Hydrogenation of C=N bonds are still challenging in homogenous catalysis.²⁴¹ Platinum metals have shown their efficiency in reductive amination reaction with molecular hydrogen,²⁴² formic acid,²⁴³ transfer hydrogenation or hydrogen transfer reaction,²⁴⁴ or borrowing hydrogen.^{245,246} Among all catalysts, ruthenium complexes are the most widely used. More particularly, Noyori²⁴⁷ and Shvo²⁴⁸ catalysts have been used in hydrogenation reactions of double bonds (Figure 4.1).

²³⁹ (a) Parshall, G. W.; Steven, D. I. In *Homogeneous Catalysis. In The Applications and Chemistry of Catalysis by Soluble Transition Metal Complexes*; Wiley: New York, **1992**; pp 25-50. (b) Wang, D.; Astruc, D. *Chem. Rev.* **2015**, *115*, 6621-6686. (c) Baráth, E. *Catalysts* **2018**, *8*, 671. (d) Filonenko, G. A.; van Putten, R.; Hensen, E. J. M.; Pidko, E. A. *Chem. Soc. Rev.* **2018**, *47*, 1459-1483.

²⁴⁰ (a) Klingler, F. D. *Acc. Chem. Res.* **2007**, *40*, 1367-1376. (b) Ayad, T.; Phansavath, P.; Ratovelomanana-Vidal, V. *Chem. Rec.* **2016**, *16*, 2754-2771.

²⁴¹ (a) El-Sepelgy, O.; Alandini, N.; Rueping, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 13602-13605. (b) El-Sepelgy, O.; Brzozowska, A.; Azofra, L. M.; Jang, Y. K.; Cavallo, L.; Rueping, M. *Angew. Chem. Int. Ed.* **2017**, *56*, 14863-14867.

²⁴² For some examples, see: (a) Ikenaga, T.; Matsushita, K.; Shinozawa, J.; Yada, S.; Takagi, Y. *Tetrahedron* **2005**, *61*, 2105-2109. (b) Falus, P.; Boros, Z.; Hornyanszky, G.; Nagy, J.; Darvas, F.; Üрге, L.; Poppe, L. *Tetrahedron Lett.* **2011**, *52*, 1310-1312. (c) Wei, D.; Bruneau-Voisine, A.; Valyaev, D. A.; Lugan, N.; Sortais, J.-B. *Chem. Commun.* **2018**, *54*, 4302-4305. and references cited therein. For pioneer work in iron-catalysis, see: (d) Fleischer, S.; Zhou, S.; Junge, K.; Beller, M. *Chem. - Asian J.* **2011**, *6*, 2240-2245. (e) Bhor, M. D.; Bhanushali, M. J.; Nandurkar, N. S.; Bhanage, B. M. *Tetrahedron Lett.* **2008**, *49*, 965-969.

²⁴³ For some recent examples, see: (a) Wang, C.; Pettman, A.; Basca, J.; Xiao, J. *Angew. Chem. Int. Ed.* **2010**, *49*, 7548-7552. (b) Huang, Y.-B.; Dai, J.-J.; Deng, X.-J.; Qu, Y.-C.; Guo, Q.-X.; Fu, Y. *ChemSusChem* **2011**, *4*, 1578-1581. (c) Wang, S.; Huang, H.; Bruneau, C.; Fischmeister, C. *ChemSusChem* **2017**, *10*, 4150-4154. (d) Wei, Y.; Wang, C.; Jiang, X.; Xue, D.; Li, J.; Xiao, J. *Chem. Commun.* **2013**, *49*, 5408-5410. (e) Zhu, M. *Catal. Lett.* **2014**, *144*, 1568-1572. (f) Yang, P.; Lim, L. H.; Chuanprasit, P.; Hirao, H.; Zhou, J. S. *Angew. Chem. Int. Ed.* **2016**, *55*, 12083-12087. (g) Metzker, G.; Dias, R. M. P.; Burtoloso, A. C. B. *ChemistrySelect* **2018**, *3*, 368-372.

²⁴⁴ (a) Gnanamgari, D.; Moores, A.; Rajaseelan, E.; Crabtree, R. H. *Organometallics* **2007**, *26*, 1226-1230. (b) Dou, X.; Hayashi, T. *Adv. Synth. Catal.* **2016**, *358*, 1054-1058. For examples in iron chemistry, see: (c) Vayer, M.; Morcillo, S. P.; Dupont, J.; Gandon, V.; Bour, C. *Angew. Chem. Int. Ed.* **2018**, *57*, 3228-3232. (d) Zhou, S.; Fleischer, S.; Junge, K.; Das, S.; Addis, D.; Beller, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 8121-8125. (e) Facchini, S. V.; Cettolin, M.; Bai, X.; Casamassima, G.; Pignataro, L.; Gennari, C.; Piarulli, U. *Adv. Synth. Catal.* **2018**, *360*, 1054-1059. (f) Coufourier, S.; Ndiaye, D.; Gaignard Gaillard, Q.; Bettoni, L.; Joly, N.; Mbaye, M. D.; Poater, A.; Gaillard, S.; Renaud, J.-L. *Tetrahedron* **2021**, *90*, No. 132187. (g) Petricci, E.; Santillo, N.; Castagnolo, D.; Cini, E.; Taddei, M. *Adv. Synth. Catal.* **2018**, *360*, 2560-2565.

²⁴⁵ For selected reviews: (a) Bähn, S.; Imm, S.; Neubert, L.; Zhang, M.; Neumann, H.; Beller, M. *ChemCatChem* **2011**, *3*, 1853-1864. (b) Yang, Q.; Wang, Q.; Yu, Z. *Chem. Soc. Rev.* **2015**, *44*, 2305-2329. (c) Renaud, J.-L.; Gaillard, S. *Synthesis* **2016**, *48*, 3659-3683. (d) Quintard, A.; Rodriguez, J. *ChemSusChem* **2016**, *9*, 28-30.

²⁴⁶ For some recent articles on iron complexes-catalyzed amine alkylation: (a) Yan, T.; Feringa, B. L.; Barta, K. *Nat. Commun.* **2014**, *5*, No. 5602. (b) Yan, T.; Feringa, B. L.; Barta, K. *ACS Catal.* **2016**, *6*, 381-388. (c) Yan, T.; Feringa, B. L.; Barta, K. *Sci. Adv.* **2017**, *3*, No. eaao6494. (d) Mastalir, M.; Stöger, B.; Pittenauer, E.; Puchberger, M.; Allmaries, G.; Kirchner, G. *Adv. Synth. Catal.* **2016**, *358*, 3824-3831. (e) Brown, T. J.; Cumbes, M.; Diorazio, L. J.; Clarkson, G. J.; Wills, M. J. *Org. Chem.* **2017**, *82*, 10489-10503. (f) Pan, H.-J.; Ng, T. W.; Zhao, Y. *Chem. Commun.* **2015**, *51*, 11907-11910. (g) Polidano, K.; Allen, B. D. W.; Williams, J. M. J.; Morrill, L. C. *ACS Catal.* **2018**, *8*, 6440-6445. (h) Lator, A.; Gaillard, S.; Poater, A.; Renaud, J.-L. *Org. Lett.* **2018**, *20*, 5985-5990.

²⁴⁷ (a) Ohkuma, T.; Ooka, H.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2675-2676. (b) Ohkuma, T.; Ooka, H.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 10417-10418.

²⁴⁸ Shvo, Y.; Czarkie, D.; Rahamim, Y.; Chodos, D. F. *J. Am. Chem. Soc.* **1986**, *108*, 7400-7402.

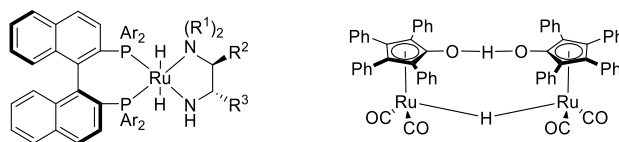
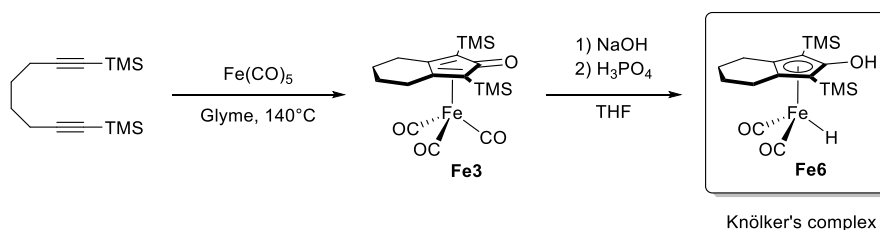


Figure 4.1: Noyori (left) and Shvo (right) catalysts.

II. Hydrogenation reactions catalysed by Knölker-type complexes.

1) Knölker complex: early works.

In recent decades, the replacement of noble metals by earth-abundant ones has become an important research topic. In the 1990s, Knölker described the synthesis of 5-membered rings through a Pauson-Khand reaction²⁴⁹ using iron pentacarbonyl (Scheme 4.1).²⁵⁰ This iron precursor served both as a CO source and as a protecting group for the cyclic product, preventing dimerization of the cyclopentadienone. At the end of the reaction, different methodologies were attempted to remove the iron metal center. One of them, based on the treatment of the tricarbonyl complex **Fe3** by sodium hydroxide followed by phosphoric acid, gave rise to an iron complex, now known as Knölker complex **Fe6**, bearing both a hydrogen on the carbonyl group of the cyclopentadienone ligand and a hydride located on the iron atom.



Scheme 4.1: Synthesis of Knölker's complex.

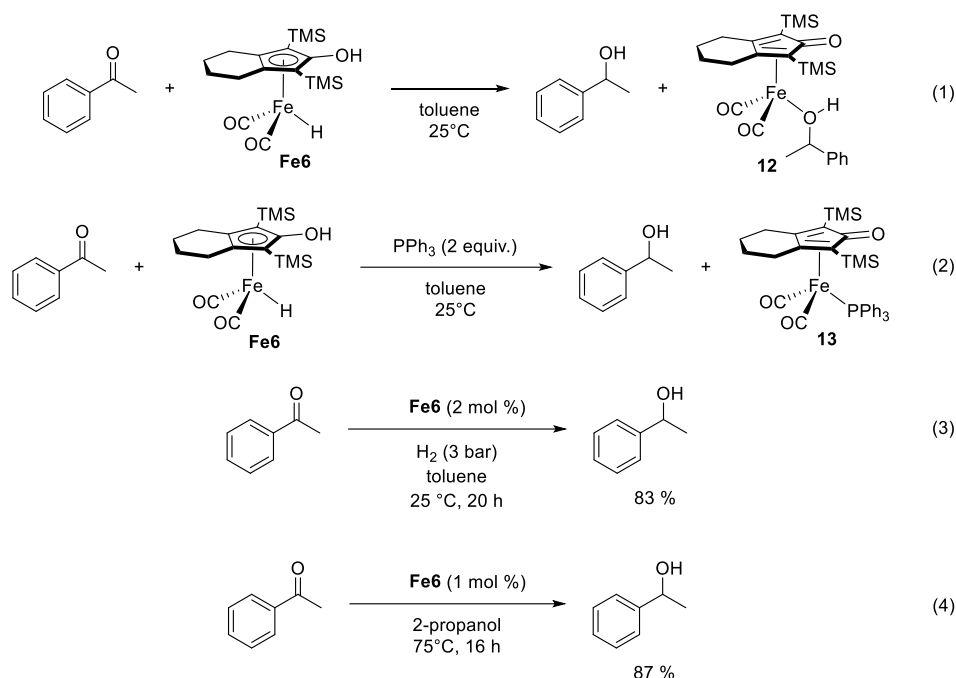
About 8 years later, Casey *et al.* proposed to test this complex in the hydrogenation of ketones.²⁵¹ The Knölker complex **Fe6** was reacted in an equimolar ratio with acetophenone in toluene at room temperature and a partial reduction of the carbonyl group was observed, as well as the formation of the phenyl ethanol complex **12** (Scheme 4.2, Eq. 1). As a consequence, it was assumed that a 16-electron species with a vacant site on the iron atom could be involved in the process and the reaction could be reversible. To confirm this hypothesis, triphenylphosphine was added as a 16-electron intermediate trap. In these conditions, total completion was obtained within 4 hours with clear formation of the triphenylphosphine iron complex **13** and the free phenyl ethanol (Scheme 4.2, Eq. 2). Thus, the authors suggested that molecular hydrogen could also be intercepted by the 16-electron species and consequently regenerate the iron-hydride complex, completing a catalytic cycle. Therefore, the reaction was performed with a catalytic amount of **Fe6** under H₂ atmosphere and phenyl ethanol was obtained in 83 % yield, confirming the catalytic ability of the iron complex (Scheme 4.2, Eq. 3). Based on these

²⁴⁹ Blanco-Urgoiti, J.; Añorbe, L.; Pérez-Serrano, L.; Domínguez, G.; Pérez-Castells, J. *Chem. Soc. Rev.* **2004**, *33*, 32-42.

²⁵⁰ (a) Knölker, H.-J.; Heber, J.; Mahler, C. H. *Synlett.* **1992**, *12*, 1002-1004. (b) Knölker, H.-J.; Baum, E.; Goesmann, H.; Klauss, R. *Angew. Chem. Int. Ed.* **1999**, *38*, 2064-2066.

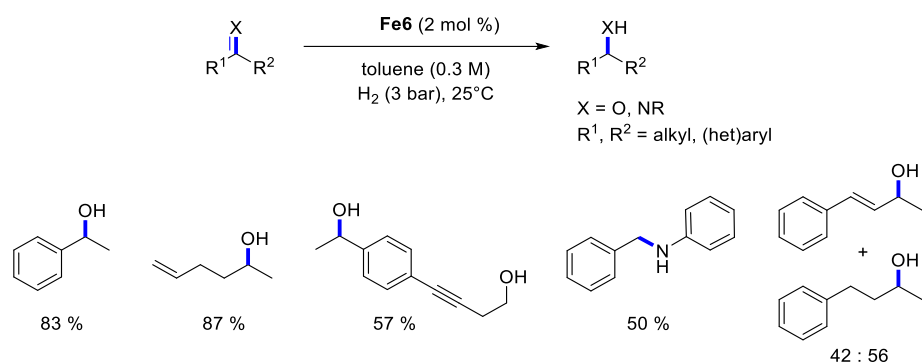
²⁵¹ (a) Casey, C. P.; Guan, H. *J. Am. Chem. Soc.* **2007**, *129*, 5816-5817. (b) Casey, C. P.; Guan, H. *J. Am. Chem. Soc.* **2009**, *131*, 2499-2507.

previous results and knowing the reversibility of the hydrogen transfer, molecular hydrogen was replaced by isopropanol as a hydrogen source and the product was obtained in similar yield (87 %) (Scheme 4.2, Eq. 4).



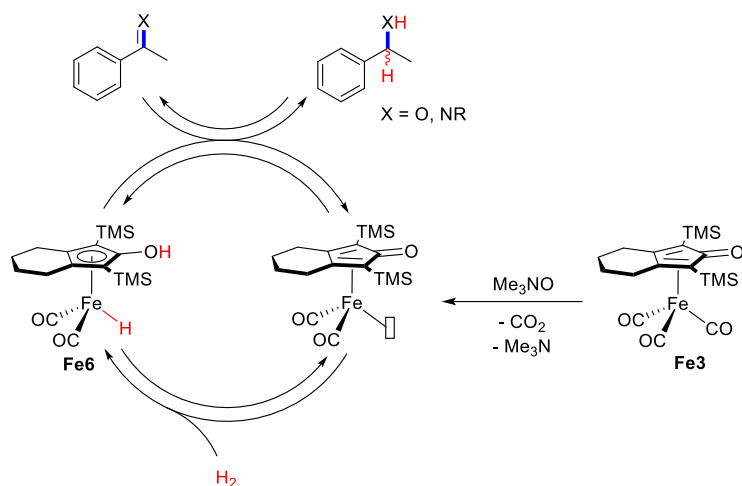
Scheme 4.2: Initial investigations performed by Casey et al.

To delineate the scope of this new hydrogenation reaction, various unsaturated compounds were used. The scope highlighted the chemoselectivity of the complex. In particular, only polarised double bonds were hydrogenated in the process. Non-conjugated alkene and alkynes remained unchanged while α,β -unsaturated ketones were partially hydrogenated into the saturated alcohol and the allylic-alcohol (Scheme 4.3).



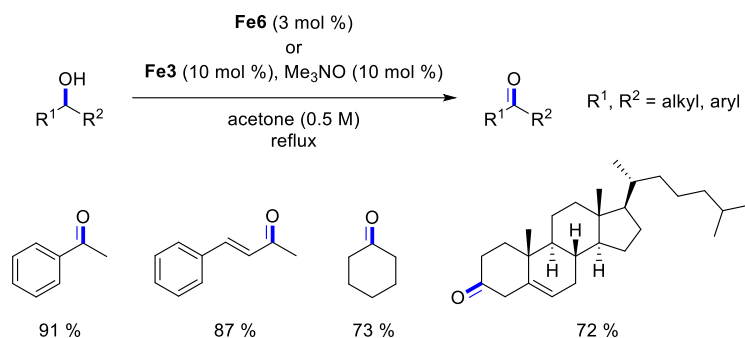
Scheme 4.3: Outline of the iron-catalysed hydrogenation of carbonyls reported by Casey et al.

With all these results, Casey proposed the first catalytic cycle for the hydrogenation process (Scheme 4.4). In a first step, the Knölker complex **Fe6** reacts with one acetophenone molecule, transferring the hydride and the proton from the complex to the carbonyl of the ketone. This hydrogen transfer led to the 16-electron species and the release of the alcohol. Molecular hydrogen then intercepted the iron dicarbonyl complex, regenerating the Knölker complex and closing the catalytic cycle.



Scheme 4.4: Mechanism proposed for the hydrogenation of ketones and imines catalysed by Knölker's complex.

Following this work, Guan²⁵² and Funk²⁵³ investigated the reverse process, that is the dehydrogenation of alcohols to carbonyls. In particular, Funk highlighted the possibility of using the iron tricarbonyl complex **Fe3** as a precatalyst (Scheme 4.4). This complex was activated *in situ* by adding Me_3NO , removing one CO ligand from the iron and leading to the 16-electron species (Scheme 4.4). This methodology appeared to be more convenient since the Knölker complex **Fe6** was air and moisture sensitive. With this strategy, different alcohols were oxidised into the corresponding carbonyls in good yields (Scheme 4.5). Nevertheless, partial oxidation was observed when primary alcohols, 2,2,2-trifluoro-1-phenylethanol, or benzoin were engaged. This result was attributed to the reversibility of the reaction, favouring the reduction of these alcohols rather than acetone.



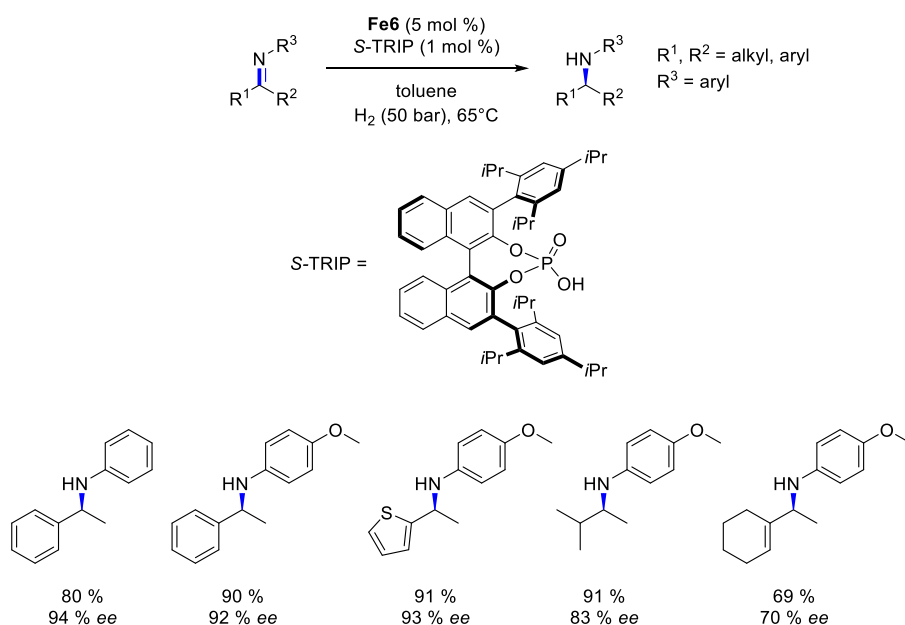
Scheme 4.5: Outline of the oxidation of alcohols reported by Guan and Funk.

Later, Beller reported the enantioselective reduction of ketimines under hydrogen pressure.²⁵⁴ The association of the Knölker complex with a chiral phosphoric acid allowed to get a stereoselective reduction of the ketimines and the corresponding chiral amines were obtained in good yields and high enantioselectivities (Scheme 4.6).

²⁵² Coleman, M. G.; Brown, A. N.; Bolton, B. A.; Guan, H. *Adv. Synth. Catal.* **2010**, *352*, 967-970.

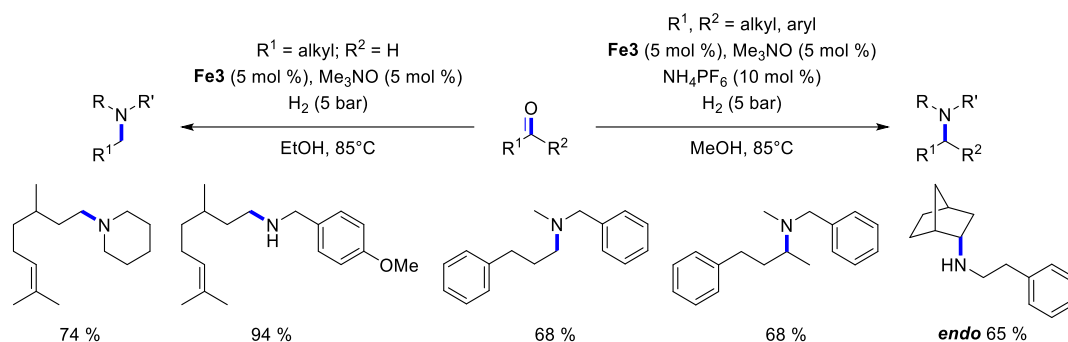
²⁵³ Moyer, S. A.; Funk, T. W. *Tetrahedron Lett.* **2010**, *51*, 5430-5433.

²⁵⁴ Zhou, S.; Fleischer, S.; Junge, K.; Beller, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 5120-5124.



Scheme 4.6: Stereoselective reduction of imines reported by Beller.

To further explore the capability of this cyclopentadienone iron complex, Renaud *et al.* investigated the feasibility of a reductive amination reaction.¹⁹ The difference with the previous works remains in the competition between the condensation of the amine on the carbonyl followed by its reduction, and the direct reduction of the carbonyl into the corresponding alcohol. Nevertheless, reductive amination of aldehydes performed well in ethanol at 85°C, and the corresponding alkylated amines were obtained in moderate to good yields (Scheme 4.7). The use of NH₄PF₆ as an additive was mandatory to obtain the desired products when ketones were used in this process.



Scheme 4.7: Reductive amination reported by Renaud.

2) Knölker complex: previous modifications.

In 2013, Renaud and Poater started a collaboration to investigate the modifications of the Knölker complex, aiming to increase its activity. Based on a “Frustrated Lewis Pair” approach,²⁵⁵ they proposed to modify the ligands to, on the one hand, increase the Lewis acidity of the iron atom and, on the other hand, increase the basicity of the carbonyl on the cyclopentadienone ligand (Figure 4.2).

²⁵⁵ (a) Flynn, S. R.; Wass, D. F. *ACS Catal.* **2013**, *3*, 2574-2581. (b) Stephan, D. W.; Erker, G. *Angew. Chem. Int. Ed.* **2015**, *54*, 6400-6441. (c) Stephan, D. W.; Erker, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 46-76.

Knowing that CO ligands are the most π -acidic ones, they focused on the modifications of the cyclopentadienone.

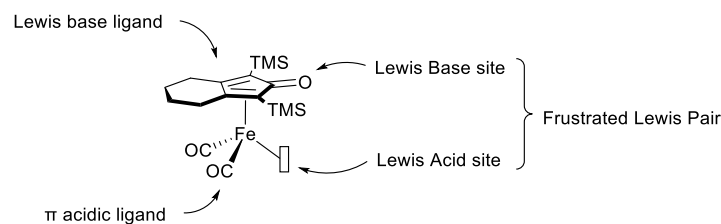
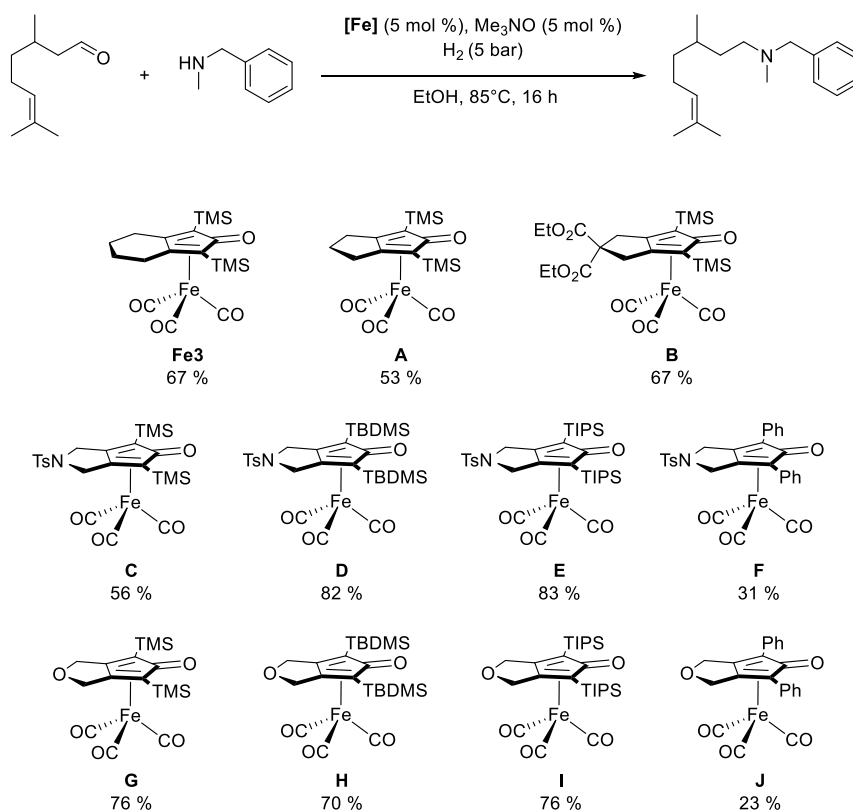


Figure 4.2: Frustrated Lewis Pair approach.

Various cyclopentadienone iron tricarbonyl complexes were prepared and evaluated in a reductive amination reaction (Scheme 4.8).⁵⁵ Complexes **a-k** catalysed the reaction but presented different activities. In particular, steric hindrance around the iron atom appeared to play a major role to keep high activities. Complexes **Fe3**, **A-E** and **G-I** bearing TMS, TBDMS or TIPS substituents catalysed well the reaction (53 to 83 % yields) while the phenyl-substituted complexes **F** and **J** led to low yields (31 and 23 % respectively).



Scheme 4.8: Screening of the modified Knölker complexes by Renaud and Poater.

For complexes **F** and **J**, X-Ray diffraction showed the coplanarity of the phenyls with the cyclopentadienone and free space around the iron atom. It was supposed that due to this lack of steric hindrance around the metal centre, the activated complex could dimerise (Figure 4.3). Density Functional Theory (DFT) calculations also confirmed this hypothesis. While dimerization was not favoured for **Fe3**, **A-E** and **G-I** (from 8.2 to 33.0 kcal/mol higher in energy, compared to the 16-electron species), the dimer of **g** and **k** was lower in energy (by 10.1 and 6.1 kcal/mol respectively, compared to

the 16-electron species), indicating the propensity of these complexes to dimerise and leading to poor catalytic activities.

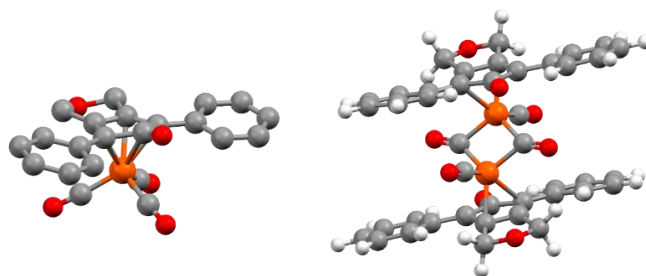
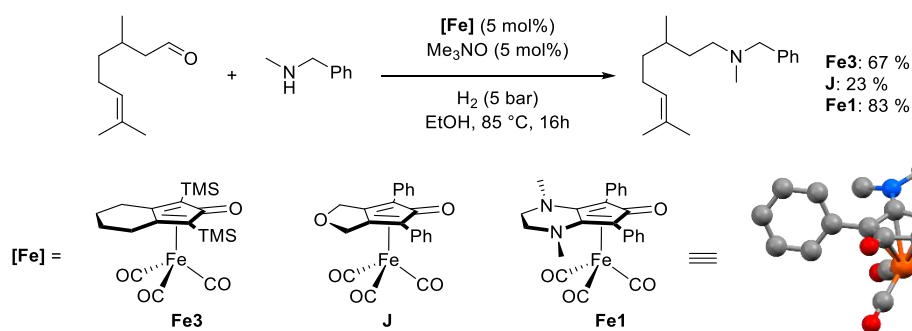


Figure 4.3: X-Ray structure of complex **J** (left), and calculated structure of **J** dimer (right).

The electronic density (*i.e.* the basicity) of the cyclopentadienone was then investigated.⁵³ To study this parameter, complex **Fe1** bearing a piperazine ring on the backbone of the cyclopentadienone was prepared. The presence of the methyl on the nitrogen atoms blocks the free rotation of the phenyl substituents on the ligand and avoids the coplanarity with the cyclopentadienone ring, as confirmed by X-Ray diffraction of the complex (Scheme 4.9). This complex was evaluated in the same reductive amination and showed a higher activity than the previous Knölker derivatives (Scheme 4.9).

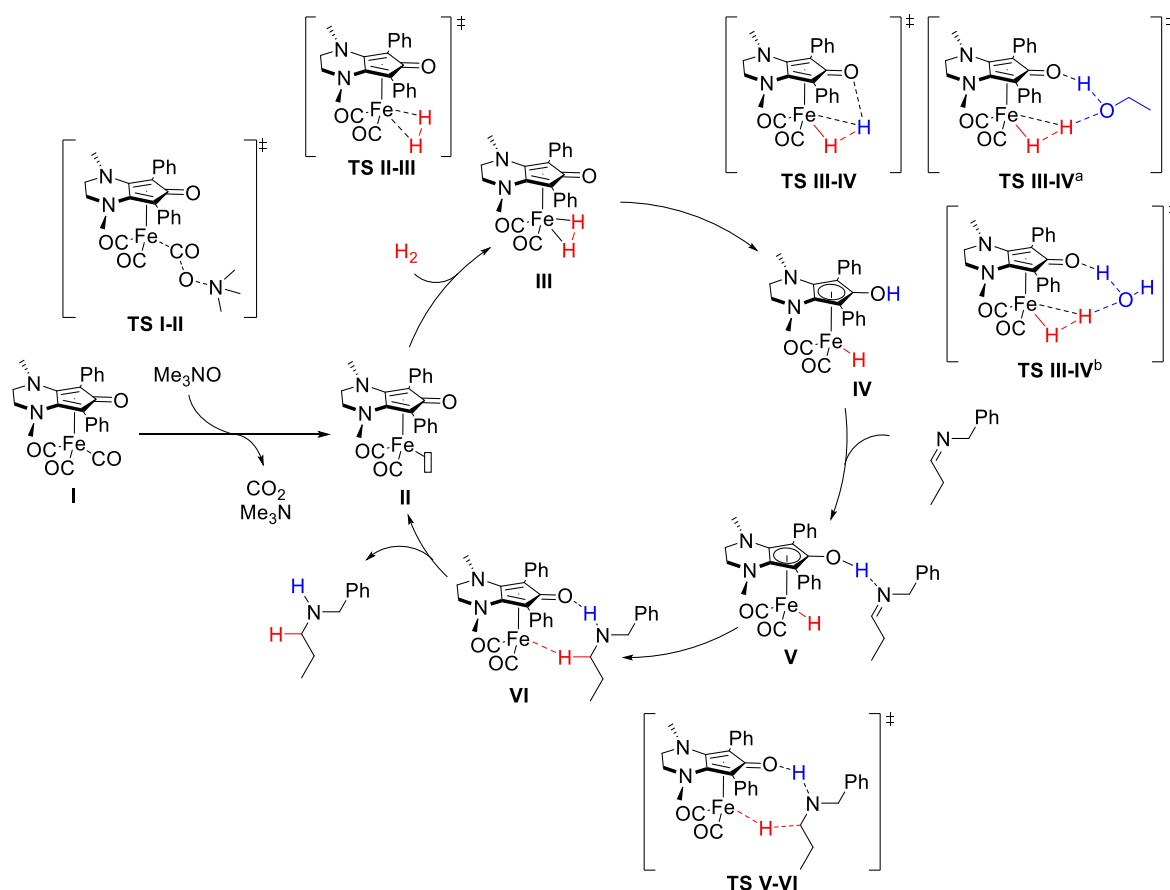


Scheme 4.9: Reductive amination catalysed by complexes **Fe3**, **J** and **Fe1**, and X-RAY structure of complex **Fe1**.

Analysis of the mechanism by DFT calculation highlighted that the reduction of the imine-iminium was an endothermic step for any of the Knölker complex derivatives, but exothermic for catalyst **Fe1** specifically. The same trend was observed for the reaction of alkylation of ketones with alcohols.^{23a} Consequently, it was concluded that the combination of an electron-rich ligand and bulky substituents around the iron atom increased the activity of the complex and the yield of the reaction.

III. Knölker catalysts for hydrogenation revisited: from DFT to experiments.

To continue this study on the modification of the Knölker-type catalysts, it was proposed to investigate the effects of the substitution on the aromatic groups of complex **Fe1**, which showed the best activity in Scheme 4.9.²⁵⁶ To avoid the synthesis of a large number of cyclopentadienone iron tricarbonyl complexes, the effects of the substitution on the cyclopentadienone ligand on the reactivity of the catalyst were studied computationally, in a similar way than Beller's study on the hydrogenation of acrolein.²⁵⁷ The different complexes were evaluated all along the reaction pathway of a reductive amination reaction (Scheme 4.10), for which two limiting steps can be observed: the first one being the activation of the catalyst (**TS I-II**) to enter the catalytic cycle; the second one being the rate determining step inside the catalytic cycle and corresponding to the hydrogen splitting (**TS III-IV**). It is important to note that this latter can be assisted by a solvent molecule (ethanol or water) as a proton shuttle to assist the migration of one hydrogen on the carbonyl of the cyclopentadienone (**TS III-IV^a** and **TS III-IV^b** respectively).



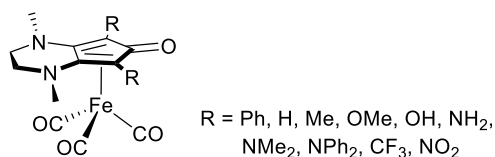
Scheme 4.10: Reaction pathway of the reductive amination process.

²⁵⁶ (a) Gimferrer, M.; Joly, N.; Escayola, S.; Viñas, E.; Gaillard, S.; Solà, M.; Renaud, J.-L.; Salvador, P.; Poater, A. *Organometallics*, **2022**, *41*, 1204-1215. (b) Joly, N.; Gimferrer, M.; Escayola, S.; Cendra, M.; Coufourier, S.; Lohier, J.-F.; Gaignard Gaillard, Q.; Gaillard, S.; Solà, M.; Renaud, J.-L.; Poater, A. *Organometallics*, **2023**, *42*, 1784-1792.

²⁵⁷ Huo, C.-F.; Li, Y.-W.; Beller, M.; Jiao, H. *Organometallics*, **2004**, *23*, 2168-2178.

In recent years, Poater and Renaud have shown that the steric hindrance generated by the substituents in position 2 and 5 of the 5-membered ring of the cyclopentadienone (*i.e.* both next to the keto group) were crucial to keep the catalytic activity and to avoid dimerization.^{21a,53,55} Taking advantage of what computational chemistry offers to study only one species at a time, without regard to the dimerization of the catalyst, the role of the substituent in position 2- and 5- of the cyclopentadienone motif was studied. The phenyl substituents of the initial cyclopentadienone iron tricarbonyl complex **Fe1** were substituted by various electron-donating groups (EDG) and electron-withdrawing groups (EWG). Table 4.1 presents the different energies of the intermediates with the different substituents and the energy barriers for the two limiting steps. A clear trend was observed with the energy barrier for the activation of the catalyst $\Delta G(\mathbf{I-II})$: EWG lowers the energy required for the removal of a carbonyl ligand, while EDG increases it. For the hydrogen splitting step (**III-IV**), the lowest energy value was obtained for the initial phenyl-substituted catalyst, whether it was solvent assisted or not. Also, in that step, the solvent is lowering the energy barrier by more or less 10 kcal/mol in all cases and makes the energies closer together. Even if the substitution led to higher energy barriers for this step, these energies were still low enough for the reaction to be done in mild conditions (typically an energy barrier of 20 kcal/mol allows the reaction to be done at room temperature while an energy barrier of 25 kcal/mol requires heating).

Table 4.1: Relative Gibbs free energies in kcal/mol at the M06/cc-pVTZ~SDD(pcm-EtOH)/BP86/SVP~SDD) level of theory, with respect to the catalytic active species **II**, for the differently substituted catalysts (*R* = substituents bonded directly on the cyclopentadienone).



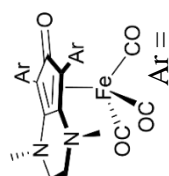
	Neutral		EDG						EWG	
	Ph	H	Me	OMe	OH	NH ₂	NMe ₂	NPh ₂	CF ₃	NO ₂
I	54.6	55.5	54.2	51.3	52.9	52.2	53.0	53.6	53.9	56.2
I-II	74.2	77.2	74.9	74.8	76.1	75.3	80.0	74.6	69.1	68.4
II	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
II-III	5.9	5.8	5.6	4.4	4.7	5.0	3.6	2.8	5.1	5.8
III	-1.1	-2.1	-2.5	-5.0	-3.1	-2.3	-3.7	-4.0	-4.2	-2.4
III-IV	23.3	24.9	24.2	25.6	28.8	24.7	25.5	27.9	28.2	29.5
III-IV ^a	13.5	15.5	15.1	14.9	17.0	16.7	16.9	18.0	14.3	12.3
III-IV ^b	16.1	17.1	16.3	15.7	19.7	17.5	17.1	17.3	15.8	14.4
IV	-8.6	-5.1	-6.7	-3.6	-2.7	-5.9	-5.4	-4.7	-3.8	-5.5
V	-3.3	-2.5	-3.6	-1.7	-1.1	-0.1	1.5	1.0	-3.1	-2.9
V-VI	3.3	5.6	3.4	4.4	4.5	5.2	5.3	3.4	-0.9	-0.3
VI	-10.6	-11.2	-11.7	-10.5	-12.4	-11.3	-7.3	-8.1	-11.9	-11.7
$\Delta G(I-II)$	19.6	21.7	20.7	23.5	23.2	23.1	27.0	21.0	15.2	12.2
$\Delta G(III-IV)$	24.4	26.9	26.8	30.5	31.9	26.9	29.2	31.8	32.4	32.0
$\Delta G(III-IV^a)$	14.7	17.5	17.7	19.8	20.1	18.9	20.6	21.9	18.5	14.8

a, b = calculated with one ethanol or one water molecule assisting the proton transfer.

Experimentally, it was observed previously that the steric hindrance around the metal centre was a key feature for good catalytic activity⁵⁵. To maintain the steric hindrance around the iron atom, this study was pursued by adding the EDG and EWG substituents on the phenyl groups instead of directly on the cyclopentadienone (Table 4.2). The positions (*-ortho*, *-meta* and *-para*) as well as different EWGs were considered. The influence of these groups was not trivial since, depending on the position on the aryl ring, the substituents could interact with the piperazine ring *via* H-bonding or with the metal centre. Focusing first on the *-para* substitution to exclude any of these interactions, the energy barriers for the hydrogen splitting step ($\Delta G(III-IV^a)$) increase from 0.6 to 3.5 kcal/mol for NMe₂, NO₂ and COOEt, whereas it decreases by 0.4 to 2.0 kcal/mol for OMe, CF₃ and COOMe. Regarding these results, no clear trend can be extracted among EDGs and EWGs. Nevertheless, looking at the activation

step, this second DFT study support the previous results as the activation of the catalyst (ΔG (I-II)) presents lower energy barriers with EWGs in most of the cases while all EDGs led to the opposite effect.

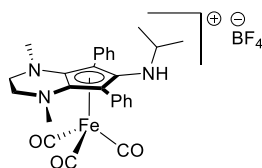
Table 4.2: Relative Gibbs energies in kcal/mol at the M06/cc-pVTZ~SDD(pcm-EtOH)//BP86/SVP~SDD level of theory, with respect to the catalytic active species **II**, for the differently substituted catalysts.



	EDG-substituted aryls						EWG-substituted aryls								
	Ph (<i>p</i> -NMe ₂)	Ph (<i>o</i> -OMe)	Ph (<i>m</i> -OMe)	Ph (<i>p</i> -OMe)	Ph (<i>o</i> , <i>o</i> -OMe)	Ph (<i>o</i> , <i>o</i> , <i>p</i> -OMe)	Ph (<i>o</i> -CF ₃)	Ph (<i>m</i> -CF ₃)	Ph (<i>p</i> -CF ₃)	C ₆ F ₅	Ph (<i>p</i> -NO ₂)	Ph (<i>p</i> -COOMe)	Ph (<i>p</i> -COOEt)	Ph (<i>o</i> , <i>o</i> -CF ₃)	Ph (<i>o</i> , <i>o</i> , <i>p</i> -CF ₃)
I	54.6	52.4	54.1	53.7	54.5	56.7	56.6	55.1	56.5	55.8	55.3	56.2	55.3	56.2	69.2
I-II	74.2	77.2	76.2	74.0	74.3	82.3	82.8	76.1	72.2	74.5	75.5	71.4	68.8	87.6	85.4
II	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
II-III	4.2	3.3	5.3	4.2	5.5	5.2	4.7	5.0	4.6	7.6	4.2	5.8	6.2	9.2	9.6
III	-3.1	-3.4	-3.3	-2.2	-2.2	-0.8	-0.5	-1.9	-0.9	-0.1	-1.4	-1.4	-1.8	5.4	5.8
III-IV ^a	13.5	16.7	15.1	13.1	14.0	18.5	18.0	14.3	14.6	15.1	15.8	13.2	15.4	26.7	27.8
IV	-8.6	-10.0	-5.6	-8.9	-8.8	-3.1	-2.9	-5.4	-7.5	-6.7	-1.1	-8.5	-8.8	5.3	5.7
V	-3.3		-3.5		-7.8	1.4	2.0	-5.4		-4.6	-2.9				
V-VI	3.3		4.8		3.3	8.7	8.2	4.3		4.1	6.0				
VI	-10.6		-10.8		-10.9	-7.7	-7.7	-9.4		-9.5	-8.3				
ΔG (I-II)	19.6	24.8	22.1	20.3	19.8	25.6	26.2	21.0	15.7	18.7	20.2	15.2	13.5	19.1	16.2
ΔG (III-IV ^a)	16.6	20.1	18.4	15.3	16.2	19.3	18.5	16.2	15.5	15.2	17.2	14.6	17.2	21.3	22.0

^a Calculated with one ethanol molecule assisting the proton transfer.

In order to complete this DFT study, the cationic complex **K** (Scheme 4.11) was evaluated because it is able to activate hydrogen and perform reductive amination reactions at room temperature.²⁵⁸



Scheme 4.11: Structure of complex **K**.

Complex **K** was evaluated along the same reductive amination reaction pathway (Table 4.3). In this case, the effect of the counter-ion BF₄⁻ was also considered. However, this parameter may not influence the results since including the counter-ion led to an increase of all the energy barriers of about 3-4 kcal/mol. Looking at the energy values, this catalyst appeared to be worse for the hydrogen splitting step (ΔG (III-IV^a)), but more prompt to be activated whether the aryl ring is substituted or not (ΔG (I-II)).

Table 4.3: Relative Gibbs energies in kcal/mol at the M06/cc-pVTZ~SDD(pcm-EtOH)/BP86/SVP~SDD level of theory, with respect to the catalytic active species **II**, for the substituted catalysts **K**.

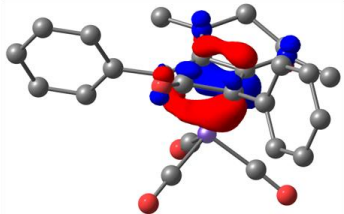
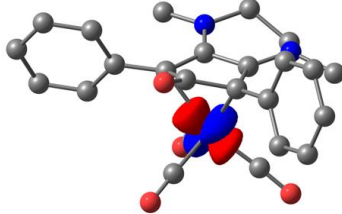
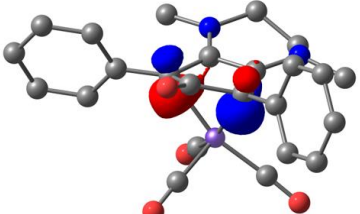
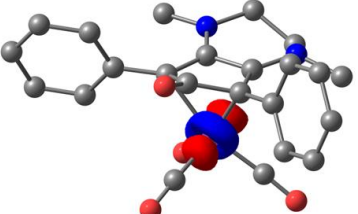
	Without BF ₄				With BF ₄		
	Ph ^b	Ph	Ph (<i>p</i> -CF ₃)	Ph (<i>o</i> -OMe)	Ph	Ph (<i>p</i> -CF ₃)	Ph (<i>o</i> -OMe)
I	54.6	56.5	56.3	55.8	55.4	56.2	55.2
I-II	74.2	69.9	66.9	70.0	71.8	70.6	72.3
II	0.0	0.0	0.0	0.0	0.0	0.0	0.0
II-III	4.2	3.6	4.3	4.0	4.8	4.5	4.8
III	-3.1	-2.2	-2.6	-4.2	-2.3	-2.0	-1.8
III-IV ^a	13.5	17.9	17.2	17.9	20.9	21.5	20.5
IV	-8.6	4.9	4.8	5.5	-0.4	0.0	-0.7
V	-3.3	-1.0	-0.9	-0.3	4.4	0.6	6.4
V-VI	3.3	1.3	1.8	-0.7	8.8	7.3	8.6
VI	-10.6	-11.0	-11.4	-12.6	-11.3	-11.8	-10.9
ΔG (I-II)	19.6	13.4	10.6	14.2	16.4	14.4	17.1
ΔG (III-IV ^a)	16.6	20.1	19.8	22.1	23.2	23.5	22.3

^a Proton transfer assisted by one ethanol molecule. ^b Catalyst **Fe1** taken as the reference.

²⁵⁸ Lator, A.; Gaignard Gaillard, Q.; Merel, D. S.; Lohier, J.-F.; Gaillard, S.; Poater, A.; Renaud, J.-L. *J. Org. Chem.* **2019**, *84*, 6813-6829.

Regarding the results in Table 4.2, the question of such a huge effect on the activation step was raised. The Effective Fragment Orbital (EFOs)²⁵⁹ occupation of the two fragments (on the one hand the cyclopentadienone ligand and on the other hand the iron tricarbonyl moiety) of the complex **1** was then evaluated (Table 4.4). The two π -type EFOs of the ligand could be put in correspondence with the π -type HOMO and π^* -type LUMO of the free cyclopentadienone. In the same way, two d-type EFOs of the metal, a d_{z^2} -type and a $d_{x^2-y^2}$ -type could be identified as the HOMO and LUMO of the metal respectively. In addition, their occupancies were complementary, allowing these EFOs to be considered as a matching pair. Consequently, two channels for charge transfer along the formation of the complex can be identified. A first one in which the HOMO of the ligand gives electron density to the LUMO of the iron and, at the same time, a second channel in which the HOMO of the iron gives electron density to the LUMO of the ligand. Careful analysis of the shapes of the HOMO orbital of the iron (d_{z^2} -type) showed that this latter is related to the C-Fe bond. This means, when forming the complex, the C-Fe bond loses electron density and becomes easier to break. As a consequence, introducing EWG on the cyclopentadienone increases the donation from the metal to the ligand and further activates the C-Fe bond. The opposite effect is obtained with EDGs.

Table 4.4: EFOs of the cyclopentadienone ligand and the iron tricarbonyl moiety.

	cyclopentadienone	iron
LUMO (electronic density)	 <p>π^*-type (0.411)</p>	 <p>$d_{x^2-y^2}$-type (0.361)</p>
HOMO (electronic density)	 <p>π-type (0.655)</p>	 <p>d_{z^2}-type (0.521)</p>

To characterise this electron density flux inside the complex, aromaticity analyses were performed using the magnetic indicator nucleus-independent chemical shift (NICS) of Schleyer and co-workers.²⁶⁰ NICS is defined as the negative value of the absolute shielding of a ring and is typically

²⁵⁹ Salvador, P.; Ramos-Cordoba, E.; Gimferrer, M. APOST-3D program, Universitat de Girona: Girona, Spain, **2019**.

²⁶⁰ (a) Schleyer, P. v. R.; Maerker, C.; Dransfeld, A.; Jiao, H.; van Eikema Hommes, N. J. R. *J. Am. Chem. Soc.* **1996**, *118*, 6317-6318. (b) Chen, Z.; Wannere, C. S.; Corminboeuf, C.; Puchta, R.; Schleyer, P. v. R. *Chem. Rev.* **2005**, *105*, 3842-3888.

evaluated at the ring centre (NICS(0)) and/or at 1 Å (above (NICS(1)_{out}) or below (NICS(1)_{in})). Also, the more negative is the NICS value, the more aromatic is the ring. Regarding the 5-membered ring of the cyclopentadienone ligand, no remarkable change in aromaticity is observed going from intermediate **I** to **II**, when EDGs or EWGs are added or not to the phenyl rings (Table 4.5). Also, looking at the 6-member rings in position 2- and 5- of the cyclopentadienone, all values for all the systems are similar, except for C₆F₆ which is the least aromatic due to its marked electro-attractive character. This observation means that both the 5-membered ring and the 6-membered rings serve as means of transport for electron density between the metal and the substituents.

Table 4.5: NICS(1)_{zz} values for the 5- and 6-membered rings for a selection of the substituents on the cyclopentadienone ligand in intermediates **I** and **II**. (The ring centre of the non-planar 5-membered ring has been obtained by adjusting the best fitted plane passing through the respective nuclei in a least-squares sense.²⁶¹ NICS values were computed by locating ghost atoms in the aforementioned points at the BP86/6-31+G**//BP86/SVP~SDD level and using the gauge-including atomic orbital method (GIAO). The z component of the NICS(1) indexes (NICS(1)_{zz}) were obtained by orienting the ring in the xy plane in a way that all the shielding corresponds only to the z component, avoiding the contamination by the d orbitals of the iron which could affect the NICS values).

		Ph	Ph (p-NMe ₂)	Ph (o-OMe)	Ph (p-OMe)	Ph (o-CF ₃)	Ph (p-CF ₃)	C ₆ F ₅	Ph (p-NO ₂)
5-membered ring	I	-12.96	-12.35	-13.02	-12.84	-13.78	-12.61	-11.83	-11.74
	II	-3.07	-1.67	-3.46	-2.48	-6.30	-2.95	-2.99	-3.04
6-membered rings	I	-27.01	-22.27	-24.41	-24.27	-23.94	-25.95	-20.09	-23.60
	II	-25.82	-21.96	-24.12	-23.29	-24.56	-24.97	-20.23	-23.43

Finally, Natural Bond Orbital (NBO) charges of the iron were calculated for the different intermediates (Table 4.6).²⁶² Even if the charge variations between the different substituents is not very significant, it can be observed that EDGs tend to give a more negative charge to the iron when EWGs make these values less negative. These observations suggest that the iron atom may release and/or compensate the electron density inside the complex.

²⁶¹ (a) Matito, E. (2015) ESI-3D; IQCC and DIPC: Donostia. Euskadi, Spain. (b) Matito, E.; Poater, J.; Duran, M.; Solà, M. *J. Mol. Struct. THEOCHEM* **2005**, 727, 165-171.

²⁶² Reed A. E.; Weinstock R. B.; Weinhold F. *J. Chem. Phys.* **1985**, 83, 735-746.

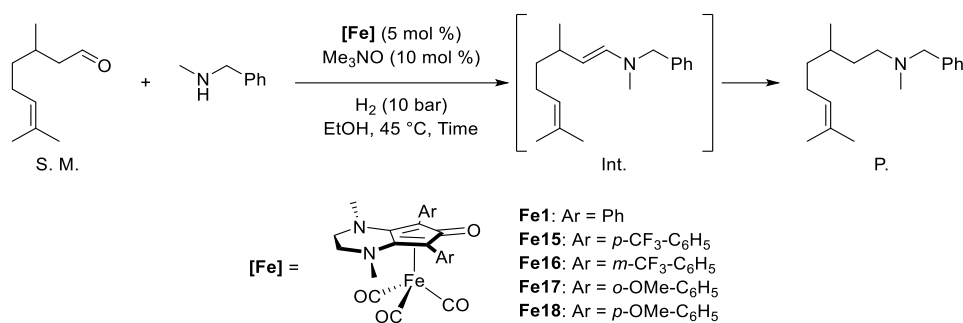
Table 4.6: NBO charges of the iron atom throughout the reaction for the different substituents on the cyclopentadienone ring.

	Ph	Ph (<i>p</i> -NMe ₂)	Ph (<i>o</i> -OMe)	Ph (<i>p</i> -OMe)	Ph (<i>o</i> -CF ₃)	Ph (<i>p</i> -CF ₃)	C ₆ F ₅	Ph (<i>p</i> -NO ₂)
I	-1.489	-1.456	-1.478	-1.468	-1.455	-1.459	-1.444	-1.433
II	-0.730	-0.734	-0.735	-0.734	-0.719	-0.721	-0.678	-0.712
III	-1.365	-1.333	-1.350	-1.337	-1.326	-1.322	-1.292	-1.311
IV	-1.373	-1.353	-1.360	-1.350	-1.351	-1.342	-1.336	-1.333

To evaluate this computational study, a reductive amination reaction was carried out with different iron catalysts bearing -CF₃ or -OMe substituents on the phenyl groups (Table 4.7). The initial non-substituted catalyst **Fe1** already showed its effectiveness under mild conditions in various hydride transfer reactions.²⁶³ The results showed faster and better activity for the -CF₃ substituted complexes while low conversion was obtained with complexes bearing methoxy groups, as predicted by the calculations. However, *m*-CF₃ substituted catalyst **Fe16** showed slightly lower activity than *p*-CF₃ substituted **Fe15**. This could be explained either by the experimental error or by the small increase in steric hindrance around the metal, making the approach of the substrate somewhat difficult. This last possibility also explains the absence of activity of catalyst **Fe17**. In fact, in the case of this *ortho*-substituted catalyst, the methoxy group is located in front of the active site of the 16-electron species (keto group and/or vacancy on the iron), thus avoiding the approach of the substrate during the hydrogenation step.

²⁶³ Coufourier, S.; Ndiaye, D.; Gaignard Gaillard, Q.; Bettoni, L.; Joly, N.; Mbaye, M. D.; Poater, A.; Gaillard, S.; Renaud, J.-L. *Tetrahedron* **2021**, *90*, 132187.

Table 4.7: Selectivity obtained for the reductive amination reaction with the different iron complexes.



Time(h)	Fe1			Fe15			Fe16			Fe17			Fe18		
	S.M.	Int.	P.	S.M.	Int.	P.	S.M.	Int.	P.	S.M.	Int.	P.	S.M.	Int.	P.
1	24	71	5	32	63	5	47	47	4	56	44	0	75	25	0
2	9	73	18	18	47	35	35	40	25	43	57	0	48	47	5
5	27	38	36	0	0	100	0	0	100	0	100	0	8	70	22

General conditions: Citronellal (1 mmol), *N*-methyl benzylamine (2 mmol), [Fe] (5 mol%), Me₃NO (10 mol%), ethanol (2 mL), H₂ (10 bar), 45 °C. Conversion was determined by ¹H NMR of the crude mixture.

IV. Conclusion.

The efficiency of iron complexes used in hydrogen autotransfer reactions needs to be improved to make these catalysts more competitive regarding noble metal catalysts used industrially. Following previous studies carried out in our group, DFT calculations have been performed to evaluate the effects induced by the modifications on the cyclopentadienone ligand, and more precisely the substitution of the aryl rings with different electron-donating and electron-attractive groups. This analysis allowed us to understand the electron density flux inside the complex and how these catalysts behave upon their activation and during the catalytic cycle. DFT calculations allowed to determine how to modify the complex to make it more efficient for hydrogenation reactions. The theoretical results were finally confirmed with experimental works.

V. Experimental part.

1) General considerations.

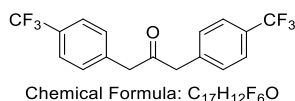
All reactions were carried out using Schlenk or autoclave under an atmosphere of dry Argon. Water was degassed prior to use by bubbling argon gas directly in the solvent. Other solvents were purchased from Carlo Erba and degassed prior to use by freeze-pump thaw procedure (3 times). NMR spectra were recorded on a 400 MHz and 500 MHz Brücker spectrometer. Proton (^1H) NMR information is given in the following format: multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintuplet; sept, septet; m, multiplet), coupling constant(s) (J) in Hertz (Hz), number of protons. The prefix app is occasionally applied when the true signal multiplicity was unresolved and br indicates the signal in question broadened. Carbon NMR spectra are reported in ppm (δ) relative to CDCl_3 unless noted otherwise. HRMS analyses were performed by LCMT analytical services. Neutral activated aluminium oxide was purchased from Alfa Aesar (Brockmann Grade I, 58 Angstroms, -60 Mesh Powder, S.A. 150 m^2/g) and from Merck (Grade I, 90 Angstroms, 70-230 Mesh ASTM). Basic aluminium oxide was purchased from Alfa Aesar (Brockmann Grade I, 58 Angstroms, -60 Mesh Powder, S.A. 150 m^2/g). NMR solvents were filtered through a pad of basic alumina for NMR analysis of iron complexes.

2) Synthesis of iron complexes.

a) Preparation of 1,3-diaryl-2-propanones.

General procedure A (according to *Bhandari and Ray*)²⁶⁴:

To a stirred solution of *N,N'*-dicyclohexylcarbodiimide (1 equiv.) and 4-dimethylaminopyridine (0.25 equiv.) in dry dichloromethane ($C = 0.3 \text{ M}$), was added the substituted arylacetic acid (1 equiv.). Reaction mixture was kept for 24 hours at room temperature and then filtered. The filtrate was distilled off and the residue was chromatographed over silica gel flash chromatography using pentane:ethyl acetate as eluant (90:10 to 70:30).

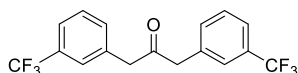


- **1,3-bis(4-(trifluoromethyl)phenyl)propan-2-one**²⁶⁵

Following the general procedure A, starting from 2-(4-(trifluoromethyl)phenyl)acetic acid (2.0 g, 9.8 mmol), DCC (2.02 g, 9.8 mmol) and DMAP (299 mg, 2.5 mmol), 1a was obtained as a white solid (1.19 g, 70 %). $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ (ppm): 7.58 (d, $J = 8.0 \text{ Hz}$, 1H), 7.27 (d, $J = 7.7 \text{ Hz}$, 1H), 3.83 (s, 1H). $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ (ppm): 203.4, 137.5, 129.9, 129.5, 125.7 (q, $J = 3.8 \text{ Hz}$, 2C), 122.7, 49.0. $^{19}\text{F-NMR}$ (CDCl_3 , 376 MHz) δ (ppm): -62.6.

²⁶⁴ Bandhari, S.; Ray, S. *Synth. Commun.* **1998**, 28, 765-771.

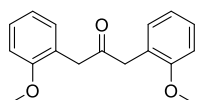
²⁶⁵ Pascal Jr., R. A.; McMillan, W. D.; Van Engen, D.; Eason, R. G. *J. Am. Chem. Soc.* **1987**, 109, 4660-4665.



Chemical Formula: C₁₇H₁₂F₆O

- **1,3-bis(3-(trifluoromethyl)phenyl)propan-2-one**²⁶⁶

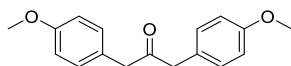
Following the general procedure A, starting from 2-(3-(trifluoromethyl)phenyl)acetic acid (3.0 g, 15.0 mmol), DCC (3.1 g, 15.0 mmol) and DMAP (458 mg, 3.75 mmol), 1b was obtained as a white solid (1.3 g, 3.75 mmol, 50 %). ¹H NMR (CDCl₃, 500 MHz) δ (ppm): 7.54 (br d, *J* = 7.5 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.38 (br s, 2H), 7.34 (br d, *J* = 7.5 Hz, 2H), 3.83 (s, 4H). ¹³C NMR (CDCl₃, 126 MHz) δ (ppm): 203.8, 134.5, 133.0 (q, *J* = 1.0 Hz), 131.2 (q, *J* = 32 Hz), 129.3, 126.4 (q, *J* = 3.8 Hz), 124.3 (q, *J* = 3.9 Hz), 124.1 (q, *J* = 272 Hz), 49.0. ¹⁹F NMR (CDCl₃, 376 MHz) δ (ppm): -62.2.



Chemical Formula: C₁₇H₁₈O₃

- **1,3-bis(2-methoxyphenyl)propan-2-one**²⁶⁷

Following the general procedure A, starting from 2-(2-methoxyphenyl)acetic acid (3.0 g, 16.1 mmol), DCC (3.72 g, 16.1 mmol) and DMAP (551 mg, 4.5 mmol), 1c was obtained as a white needles (1.26 g, 52 %). ¹H-NMR (CDCl₃, 400 MHz) δ (ppm): 7.26-7.22 (m, 2H), 7.09 (d, *J* = 6.4 Hz, 2H), 6.94-6.83 (m, 4H), 3.78 (s, 6H), 3.71 (s, 4H). ¹³C-NMR (CDCl₃, 100 MHz) δ (ppm): 206.5, 157.4, 131.3, 128.3, 123.8, 120.5, 110.4, 77.3, 77.0, 76.7, 55.3, 43.9.



Chemical Formula: C₁₇H₁₈O₃

- **1,3-bis(4-methoxyphenyl)propan-2-one**²⁶⁸

Following the general procedure A, starting from 2-(4-methoxyphenyl)acetic acid (3.0 g, 18.1 mmol), DCC (3.72 g, 18.1 mmol) and DMAP (551 mg, 4.5 mmol), 1d was obtained as a white powder (1.35 g, 55 %). ¹H-NMR (CDCl₃, 400 MHz) δ (ppm): 7.06 (d, *J* = 8.5 Hz, 4H), 6.86 (d, *J* = 8.5 Hz, 4H), 3.80 (s, 6H), 3.64 (s, 4H). ¹³C-NMR (CDCl₃, 100 MHz) δ (ppm): 206.6, 158.7, 130.5, 126.1, 114.2, 55.3, 48.1.

²⁶⁶ Shi, R.; Hu, X. *Angew. Chem. Int. Ed.* **2019**, *58*, 7454-7458.

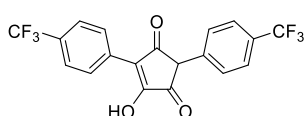
²⁶⁷ Cram, D. J.; Moran, J. R.; Maverick, E. F.; Trueblood, K. N. *J. Chem. Soc., Chem. Commun.* **1983**, 645-646.

²⁶⁸ Chaudhury, D.; Wettach, H.; van Schooten, K. J.; Liu, S.; Sigmund, E.; Höger, S.; Lupton, J. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 7714-7717.

b) Preparation of functionalised diarylcyclopentanetriones.

General procedure B (according to Claisen and Evans)²⁶⁹:

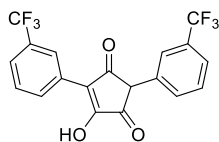
In a Schlenk tube under an argon atmosphere, freshly cut pieces of sodium (2 equiv.) were dropped into freshly distilled ethanol (20 equiv.) at 0 °C. After its complete dissolution, diethyl oxalate (1 equiv.) and the corresponding 1,3-diarylpropan-2-one (1 equiv.) were added in that order. The solution was slowly warmed up to room temperature and stirred for 48 h at room temperature. The color of the reaction mixture changed from yellow to dark purple. The reaction mixture was then poured into ice/water and the aqueous layer was acidified to pH=1 by careful dropwise addition of concentrated sulfuric acid (96 %). The resulting precipitate was filtered, washed twice with water and dried by azeotropic distillation with toluene.



Chemical Formula: C₁₉H₁₀F₆O₃

- **4-hydroxy-2,5-bis(4-(trifluoromethyl)phenyl)cyclopent-4-ene-1,3-dione**

Following the general procedure B, starting from 1,3-bis(4-(trifluoromethyl)phenyl)propan-2-one (1.0 g, 2.9 mmol), sodium (133 mg, 5.8 mmol) and diethyloxalate (392 μL, 2.9 mmol), the product was obtained as a thick yellow oil (1.08 g). The very hygroscopic crude product obtained was not isolated and was engaged without further purification in the next step because of its high sensitivity.

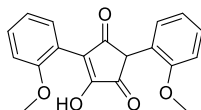


Chemical Formula: C₁₉H₁₀F₆O₃

- **4-hydroxy-2,5-bis(3-(trifluoromethyl)phenyl)cyclopent-4-ene-1,3-dione**

Following the general procedure B, starting from 1,3-bis(3-(trifluoromethyl)phenyl)propan-2-one (2.08 g, 6.0 mmol), sodium (304 mg, 13.2 mmol) and diethyloxalate (815 μL, 6.0 mmol), the product was obtained as a yellow powder (2.1 g). The very hygroscopic crude product obtained was not isolated and was engaged without further purification in the next step because of its high sensitivity.

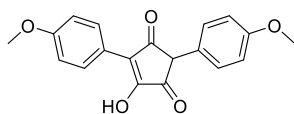
²⁶⁹ Claisen, L.; Ewan, T. *Annalen* **1895**, 284, 245-299.



Chemical Formula: C₁₉H₁₆O₅

- **4-hydroxy-2,5-bis(2-methoxyphenyl)cyclopent-4-ene-1,3-dione**

Following the general procedure B, starting from 1,3-di(2-methoxyphenyl)propan-2-one (1.0 g, 3.7 mmol), sodium (170 mg, 7.4 mmol) and diethyloxalate (502 μ L, 3.7 mmol), the product was obtained as a thick yellow oil (1.28 g). The very hygroscopic crude product obtained was not isolated and was engaged without further purification in the next step because of its high sensitivity.



Chemical Formula: C₁₉H₁₆O₅

- **4-hydroxy-2,5-bis(4-methoxyphenyl)cyclopent-4-ene-1,3-dione²⁶⁹**

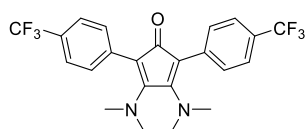
Following the general procedure B, starting from 1,3-di(4-methoxyphenyl)propan-2-one (1.0 g, 3.7 mmol), sodium (170 mg, 7.4 mmol) and diethyloxalate (0.50 mL, 3.7 mmol), the product was obtained as a yellow-brownish powder (1.03 g, 86 %). ¹H-NMR (DMSO-*d*₆, 400 MHz) δ (ppm): 8.11 (d, *J* = 8.6 Hz, 2H), 7.06 (d, *J* = 7.5 Hz, 4H), 6.91 (d, *J* = 8.6 Hz, 2H), 4.37 (s, 1H), 3.81 (s, 3H), 3.74 (s, 3H) (OH not observed). ¹³C-NMR (DMSO-*d*₆, 100 MHz) δ (ppm): 198.0, 197.8, 165.3, 160.1, 159.0, 130.9, 130.3, 128.3, 126.9, 122.5, 114.6, 114.3, 55.7, 55.6.

c) Preparation of functionalized cyclopentadienone ligands.

General procedure C (according to Haak)²⁷⁰:

In a Schlenk tube, diarylcyclopentanetrione (1 equiv.) and *N,N'*-dimethylethylenediamine (1 equiv.) were introduced in methanol (C = 0.3 M). The reaction mixture was heated under reflux overnight. After complete consumption of the starting materials, the solvent was removed under vacuum. Purification by flash chromatography on alumina with dichloromethane, and precipitation in a mixture of Et₂O/pentane (1:1) furnish the pure product as a purple powder.

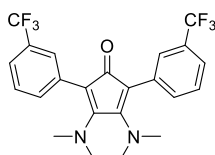
²⁷⁰ (a) Haak, E. *Eur. J. Org. Chem.* **2007**, 2007, 2815-2824. (b) Haak, E. *Eur. J. Org. Chem.* **2008**, 5, 788-792.



Chemical Formula: C₂₃H₁₈F₆N₂O

- **1,4-dimethyl-5,7-bis(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydro-6H-cyclopenta[b]pyrazin-6-one (L3)**

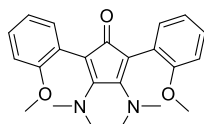
Following the general procedure C, starting from di(4-(trifluoromethyl)phenyl)cyclopentanetrione (1.08 g, 2.7 mmol) and *N,N'*-dimethylethylenediamine (290 μ L, 2.7 mmol), ligand **L3** was obtained as a purple powder (278 mg, 23 %). ¹H-NMR (CDCl₃, 400 MHz) δ (ppm): 7.43 (d, *J* = 8.1 Hz, 4H), 7.25 (d, *J* = 8.1 Hz, 4H), 3.33 (s, 4H), 2.76 (s, 6H). ¹³C-NMR (CDCl₃, 100 MHz) δ (ppm): 193.7, 151.8, 137.1, 130.8, 127.5, 127.2, 124.2 (q, *J* = 3.6 Hz, 2C), 98.0, 49.8, 42.5. ¹⁹F-NMR (CDCl₃, 376 MHz) δ (ppm): -62.24. IR (neat) ν 2859, 1641, 1587, 1517, 1458, 1439, 1407, 1353, 1315, 1264, 1246, 1203, 1185, 1167, 1150, 1133, 1106, 1070, 1062, 1014, 988, 945, 854, 834, 825, 788, 769, 732 cm⁻¹. HRMS (m/z): [M+H]⁺ calculated for C₂₃H₁₉N₂OF₆: 453.1402; found 453.1404.



Chemical Formula: C₂₃H₁₈F₆N₂O

- **1,4-dimethyl-5,7-bis(3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydro-6H-cyclopenta[b]pyrazin-6-one (L4)**

Following the general procedure C, starting from di(3-(trifluoromethyl)phenyl)cyclopentanetrione (900 mg, 2.2 mmol) and *N,N'*-dimethylethylenediamine (450 μ L, 4.0 mmol), ligand **L4** was obtained as a purple powder (310 mg, 23 %). ¹H NMR (CDCl₃, 500 MHz) δ (ppm): 7.50 – 7.46 (m, 4H), 7.43 – 7.39 (m, 4H), 3.44 (s, 4H), 2.86 (s, 6H). ¹³C NMR (CDCl₃, 126 MHz) δ (ppm): 194.1, 151.7, 134.2 – 134.1 (m), 129.8 (q, *J* = 31.4 Hz), 127.9, 127.4 (q, *J* = 3.7 Hz), 124.5 (q, *J* = 273 Hz), 122.3 (q, *J* = 3.6 Hz), 97.8, 50.0, 42.5. ¹⁹F NMR (CDCl₃, 471 MHz) δ (ppm): -62.5 ppm. IR (neat) ν 2970, 2925, 1600, 1590, 1493, 1413, 1360, 1321, 1310, 1268, 1162, 1114, 1068, 966, 835, 788, 706 cm⁻¹. HRMS (m/z): [M+H]⁺ calculated for C₂₃H₁₉N₂OF₆: 453.1396; found 453.1397.

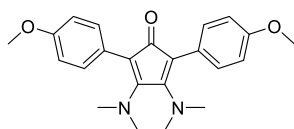


Chemical Formula: C₂₃H₂₄N₂O₃

- **1,4-dimethyl-5,7-bis(2-methoxyphenyl)-1,2,3,4-tetrahydro-6H-cyclopenta[b]pyrazin-6-one (L5)**

Following the general procedure C, starting from di(2-methoxyphenyl)cyclopentanetrione (1.0 g, 3.1 mmol) and *N,N'*-dimethylethylenediamine (332 μ L, 3.1 mmol), ligand **L5** was obtained as a dark purple powder (503 mg, 43 %). ¹H-NMR (CDCl₃, 400 MHz) δ (ppm): 7.27-7.14 (m, 4H), 6.91 (t, *J* = 7.8 Hz,

2H), 6.84 (d, $J = 7.8$ Hz, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 3.53-3.34 (m, 2H), 3.31-3.18 (m, 2H), 2.74 (s, 6H). $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ (ppm): 194.8, 158.3, 157.9, 151.4, 151.0, 133.5, 133.3, 127.4, 127.2, 123.6, 123.2, 120.0, 110.8, 110.3, 95.2, 94.7, 55.6, 55.5, 49.9, 49.8, 40.3, 40.1, 33.9, 25.0. **IR** (*neat*) ν 2836, 2159, 2028, 1610, 1587, 1497, 1456, 1434, 1409, 1360, 1269, 1238, 1180, 1121, 1048, 1020, 989, 945, 856, 839, 783, 751, 728 cm^{-1} . **HRMS** (m/z): $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{23}\text{H}_{25}\text{N}_2\text{O}_3$: 377.1865; found 377.1872.



Chemical Formula: $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_3$

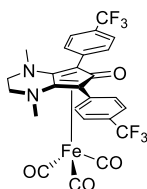
- **1,4-Dimethyl-5,7-bis(4-methoxyphenyl)-1,2,3,4-tetrahydro-6H-cyclopenta[b]pyrazin-6-one (L6)**

Following the general procedure C, starting from 4-hydroxy-2,5-bis(4-methoxyphenyl)cyclopent-4-ene-1,3-dione (800 mg, 2.5 mmol) and *N,N'*-dimethylethylenediamine (0.27 mL, 2.5 mmol), ligand **L6** was obtained as a dark purple powder (827 mg, 2.20 mmol, 89 %). $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ (ppm): 7.18 (d, $J = 8.5$ Hz, 4H), 6.84 (d, $J = 8.5$ Hz, 4H), 3.79 (s, 6H), 3.32 (s, 4H), 2.82 (s, 6H). $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) δ (ppm): 196.0, 157.7, 150.5, 132.1, 126.1, 112.9, 98.4, 55.3, 50.1, 41.9. **IR** (*neat*) ν 2955, 2346, 1649, 1588, 1567, 1509, 1465, 1454, 1408, 1350, 1306, 1288, 1221, 1174, 118, 1106, 1028, 991, 945, 838, 810, 785, 768, 729 cm^{-1} . **HRMS** (m/z): $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{23}\text{H}_{25}\text{N}_2\text{O}_3$: 377.1865; found 377.1867.

d) Preparation of iron complexes.

General procedure D:

In a dried Schlenk tube under argon, the cyclopentadienone derivative (1 equiv.) and $\text{Fe}_2(\text{CO})_9$ (2 equiv.) were introduced in dry and degassed toluene ($C = 0.3$ M). The reaction mixture was stirred overnight at 110 °C. The resulting mixture was cooled down to room temperature and purified on neutral alumina oxide column chromatography surrounded by a pad of Celite (eluent: CH_2Cl_2 to $\text{CH}_2\text{Cl}_2:\text{MeOH}$ 98:2). Precipitation with diethylether/pentane (1:1) and filtration under vacuum furnished the pure product.

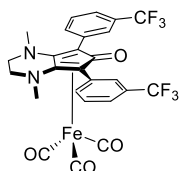


Chemical Formula: $\text{C}_{26}\text{H}_{18}\text{F}_6\text{FeN}_2\text{O}_4$

- **Iron complex (Fe15)**

Following the general procedure D, starting from ligand **L3** (120 mg, 0.27 mmol) and $\text{Fe}_2(\text{CO})_9$ (193 mg, 0.54 mmol), iron complex **Fe15** was obtained as an orange powder (98 mg, 62 %). $^1\text{H-NMR}$

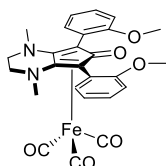
(CDCl₃, 400 MHz) δ (ppm): 7.69-7.65 (m, 8H), 3.49 (ddd, $J = 10.9, 8.0, 3.8$ Hz, 2H), 2.97 (ddd, $J = 10.9, 8.0, 3.8$ Hz, 2H), 2.41 (s, 6H). ¹³C-NMR (CDCl₃, 100 MHz) δ (ppm): 209.4, 135.9, 132.5, 130.0, 125.4, 125.3, 122.7, 114.2, 69.4, 49.8, 41.8. ¹⁹F-NMR (CDCl₃, 376 MHz) δ (ppm): -62.62. IR (neat) ν 2663, 2326, 2116, 2035, 1965, 1932, 1621, 1610, 1575, 1499, 1408, 1364, 1322, 1175, 1160, 1125, 1108, 1068, 1020, 956, 865, 847, 826, 785, 729 cm⁻¹. HRMS (m/z): [M+H]⁺ calculated for C₂₆H₁₉N₂O₄FeF₆: 593.0598; found 593.0602.



Chemical Formula: C₂₆H₁₈F₆FeN₂O₄

• Iron Complex (Fe16)

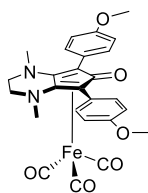
Following the general procedure D, starting from ligand **L4** (249 mg, 0.55 mmol) and Fe₂(CO)₉ (440 mg, 1.21 mmol, 2.2 equiv.), the iron complex **Fe16** was obtained as a yellow powder (120 mg, 0.20 mmol, 36%). ¹H NMR (CDCl₃, 500 MHz) δ (ppm): 7.83 (s, 2H), 7.74 (d, $J = 7.3$ Hz, 2H), 7.61 (d, $J = 7.6$ Hz, 2H), 7.54 (t, $J = 7.6$ Hz, 2H), 3.52 – 3.48 (m, 2H), 2.99 – 2.95 (m, 2H), 2.40 (s, 6H). ¹³C NMR (CDCl₃, 126 MHz) δ (ppm): 209.5, 164.7, 135.9, 132.9, 130.8 (q, $J = 33.2$ Hz), 129.1, 128.5 (q, $J = 3.8$ Hz), 125.0 (q, $J = 3.7$ Hz), 124.1 (q, $J = 274$ Hz), 114.5, 69.3, 50.0, 41.9. ¹⁹F-NMR (CDCl₃, 376 MHz) δ (ppm): -62.5. IR (neat) ν 2924, 2866, 2037, 1981, 1965, 1625, 1545, 1488, 1437, 1416, 1358, 1327, 1306, 1267, 1161, 1116, 1094, 1072, 805, 803, 700, 604 cm⁻¹. HRMS (m/z): [M+H]⁺ calculated for C₂₆H₁₉N₂O₄F₆Fe: 593.0598; found 593.0598 and [M+Na]⁺ calculated for C₂₆H₁₈N₂O₄F₆FeNa: 615.0418; found 615.0421.



Chemical Formula: C₂₆H₂₄FeN₂O₆

• Iron complex (Fe17)

Following the general procedure D, starting from ligand **L5** (375 mg, 1.0 mmol) and Fe₂(CO)₉ (725 mg, 2.0 mmol), iron complex **Fe17** was obtained as a yellow powder (331 mg, 64 %). ¹H-NMR (CDCl₃, 400 MHz) δ (ppm): 7.48-7.38 (m, 2H), 7.32 (t, $J = 7.7$ Hz, 2H), 6.99 (t, $J = 7.7$ Hz, 2H), 6.91 (d, $J = 7.7$ Hz, 2H), 3.85 (s, 6H), 3.53-3.42 (m, 2H), 2.90-2.86 (m, 2H), 2.36 (s, 6H). IR (neat) ν 2928, 2161, 2026, 1978, 1960, 1929, 1635, 1608, 1587, 1558, 1520, 1493, 1456, 1439, 1417, 1393, 1359, 1281, 1260, 1241, 1204, 1161, 1117, 1050, 1025, 1007, 952, 932, 847, 811, 757, 736 cm⁻¹. HRMS (m/z): [M+H]⁺ calculated for C₂₆H₂₅N₂O₆Fe: 517.1062; found 517.1068.



Chemical Formula: $C_{26}H_{24}FeN_2O_6$

- **Iron complex (Fe18)**

Following the general procedure D, starting from ligand **L6** (375 mg, 1.0 mmol) and $Fe_2(CO)_9$ (725 mg, 2.0 mmol), iron complex **Fe18** was obtained as a yellow powder (178 mg, 35 %). **1H -NMR (CDCl₃, 400 MHz) δ (ppm):** (d, $J = 8.3$ Hz, 4H), 6.91 (d, $J = 8.3$ Hz, 4H), 3.82 (s, 6H), 3.45-3.40 (m, 2H), 2.93-2.89 (m, 2H), 2.40 (s, 6H). **^{13}C -NMR (CDCl₃, 100 MHz) δ (ppm):** 210.3, 159.3, 133.3, 123.7, 114.6, 113.8, 70.6, 55.3, 50.0, 41.4. **IR (neat) ν** 2837, 2325, 2028, 1963, 1948, 1608, 1569, 1513, 1461, 1410, 1359, 1294, 1245, 1175, 1141, 1121, 1082, 1033, 1007, 952, 928, 837, 826, 814, 781, 724 cm^{-1} . **HRMS (m/z):** $[M+H]^+$ calculated for $C_{26}H_{25}N_2O_6Fe$: 517.1062; found 517.1064.

3) Computational Details

All calculations were performed at the DFT level with the Gaussian09 set of programs,²⁷¹ using the BP86 and M06 functionals.²⁷² The electronic configuration of the molecular systems was described with the standard split-valence basis set with a polarization function of Ahlrichs and co-workers for H, C, N, O and F (SVP keyword in Gaussian).²⁷³ For Fe, the quasi-relativistic Stuttgart/Dresden effective core potential²⁷⁴ with an associated valence basis set (standard SDD keywords in Gaussian09) was used. Geometry optimizations were carried out without symmetry constraints and normal mode analysis were computed to confirm minima on the potential energy surface. These frequencies were used to calculate unscaled zero-point energies (ZPEs) as well as thermal corrections and entropy effects at 298 K and 1 atm by using the standard statistical mechanics relationships for an ideal gas. Accurate electronic energies were obtained via single-point calculation on the BP86-optimized geometries using the M06 functional.²⁷⁵ In these calculations, the cc-pVTZ basis set was used for describing H, C, N, O and F,²⁷⁶ whereas for Fe the SDD basis set (and pseudopotential) has been employed, together with the solvent effects of ethanol estimated with the polarizable continuous solvation model (PCM).^{277,278} On top of the

²⁷¹ Gaussian 09, Revision E.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2009.

²⁷² (a) Becke, A. *Phys. Rev. A: At., Mol., Opt. Phys.* **1988**, *38*, 3098-3100. (b) Perdew, J. P. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1986**, *33*, 8822-8824.

²⁷³ Schäfer, A.; Huber, C.; Ahlrichs, R. *J. Chem. Phys.* **1994**, *100*, 5829.

²⁷⁴ (a) Küchle, W.; Dolg, M.; Stoll, H.; Preuss, H. *J. Chem. Phys.* **1994**, *100*, 7535-7542. (b) Leininger, T.; Nicklass, A.; Stoll, H.; Dolg, M.; Schwerdtfeger, P. *J. Chem. Phys.* **1996**, *105*, 1052-1059.

²⁷⁵ Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215-241.

²⁷⁶ Weigend, F.; Ahlrichs, R. *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297-3305.

²⁷⁷ Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995-2001.

²⁷⁸ Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027-2094.

M06/cc-pVTZ~SDD(pcm-EtOH) electronic energies, we added the thermal and entropy corrections obtained (gas-phase) at the BP86/SVP~SDD level.

Aromaticity was evaluated using the magnetic indicator nucleus-independent chemical shift (NICS),^{279,280} proposed by Schleyer and co-workers. NICS is defined as the negative value of the absolute shielding and typically is evaluated at the ring center (NICS(0) and/or at 1 Å above (NICS(1)_{out}) or below (NICS(1)_{in}). The ring center of the non-planar 5-membered ring has been obtained by adjusting the best fitted plane passing through the respective nuclei in a least-squares sense.^{281,282} NICS values were computed by locating ghost atoms in the aforementioned points at the BP86/6-31+G**//BP86/SVP~SDD level and using the gauge-including atomic orbital method (GIAO).

Metal and ligands oxidation states (OS) were elucidated with the effective oxidation states (EOS) analysis method, which relies on Mayer's effective fragment orbitals (EFOs) and their associated occupations. The EFOs are sorted by decreasing occupation number and then individual electrons (or pairs for closed-shell wavefunctions) are assigned to those with higher occupations, thus considering each EFO as occupied or empty. This leads to an effective configuration of the atoms/ligands within the molecule, which directly determines their OS. The difference between the occupation number of the last occupied (λ_{LO}^σ) and the first unoccupied (λ_{FU}^σ) EFOs is a pointer of how clear-cut the assignment has been performed. The larger this difference, the better the current electron distribution can be pictured into a discrete ionic model. Thus, the EOS analysis provides the OS of the fragments/atoms desired together with its reliability index ($R = \min(R_\square, R_\square)$), defined for each spin case σ as:

$$R_\sigma(\%) = 100 \cdot \min(1, \max(0, \lambda_{LO}^\sigma - \lambda_{FU}^\sigma + 1/2)).$$

The worst-case scenario is when two or more frontier EFOs sitting on different fragments exhibit the same occupation number. In those cases, two different OS distributions with $R(\%) = 50$ are equally plausible. EOS analysis has been performed at the M06/cc-pVTZ~SDD(pcm-EtOH)//BP86/SVP~SDD level of theory with the in-house developed program APOST-3D, using the Topological Fuzzy Voronoi Cells (TFVC) atomic definition,²⁸³ and a 40 x 146 atomic grid for the numerical integrations.

4) Xyz coordinates and absolute energies (in a.u.) of all computed DFT species.

See the Supporting Information of [256a] and [256b].

²⁷⁹ Schleyer, P. v. R.; Maerker, C.; Dransfeld, A.; Jiao, H.; van Eikema Hommes, N. J. R. *J. Am. Chem. Soc.* **1996**, *118*, 6317–6318.

²⁸⁰ Chen, Z.; Wannere, C. S.; Corminboeuf, C.; Puchta, R.; Schleyer, P. v. R. *Chem. Rev.* **2005**, *105*, 3842–3888.

²⁸¹ Matito, E. (2015) ESI-3D; IQCC and DIPC: Donostia. Euskadi, Spain.

²⁸² Matito, E.; Poater, J.; Duran, M.; Solà, M. *J. Mol. Struct. THEOCHEM* **2005**, *727*, 165–171.

²⁸³ Salvador, P.; Ramos-Cordoba, E. *J. Chem. Phys.* **2013**, *139*, 071103.

**CHAPTER V: LIGHT INDUCED ALKYLATION
REACTIONS THROUGH BORROWING HYDROGEN
METHODOLOGY.**

I. Introduction.

The alkylation reactions, and especially the alkylation of ketones or alcohols by hydrogen autotransfer reaction, have been well studied in the last decade. Abundant metals such as manganese, iron, cobalt and nickel have shown their efficiency in such alkylation reactions (see Chapter I). A variety of complexes and ligands were designed to increase the efficiency of the metal catalysts, allowing milder reaction conditions and/or shorter reaction times. Nevertheless, high temperatures are often still required to achieve these transformations. Recently, the association of transition-metal catalysis with photoredox chemistry opened the way to both new reactions and reactivities, using light as energy source rather than heating.²⁸⁴ Nevertheless, the photocatalyst can be incompatible with the envisioned reaction. Also, this strategy shows sometimes electron- or energy-transfer issues between the photocatalyst and the organometallic complex. In that way, the application of chromophoric transition-metal catalysts enable the use of a single catalytic species in the reaction, thus avoiding these different limitations.

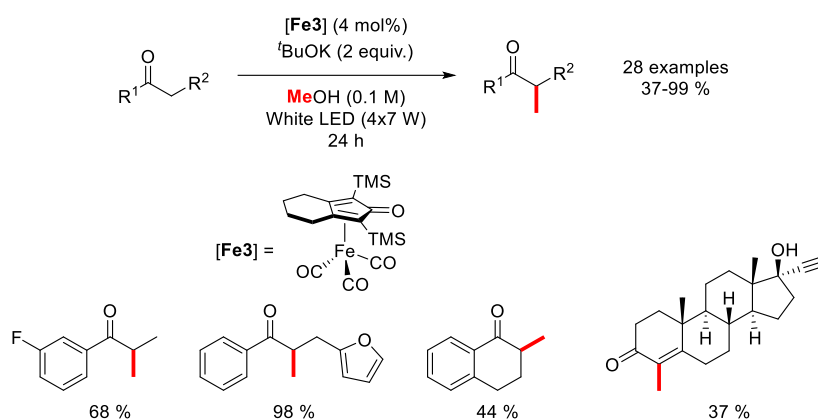
II. Light-induced alkylation reaction through borrowing hydrogen strategy.

1) Iron-catalysed α -methylation of ketones under photoirradiation.

In 2022, Sundararaju described an iron-catalysed methylation of ketones under light irradiation.²⁸⁵ Various acetophenones derivatives were introduced in the presence of the Knölker's complex (4 mol %) and ^tBuOK (2 equiv.) in methanol and the mixture was irradiated with four 7 W white LED bulb lamps in a light chamber for 24 hours. The temperature inside the chamber reached 42 °C due to continuous light irradiation. Under these conditions, α -methylated ketones were isolated in moderate to good yields (37 to 99 %, Scheme 5.1). Di-methylation of *p*-methyl acetophenone led to a lower yield (41 %). Cyclic substrates such as tetralone gave the methylated ketone in moderate yield as well (44 %). Interestingly, methylation of ethisterone did not furnish the saturated product but the tetrasubstituted olefin derivative, arising from the isomerisation of the *exo* methylene to the more stable *endo* alkene.

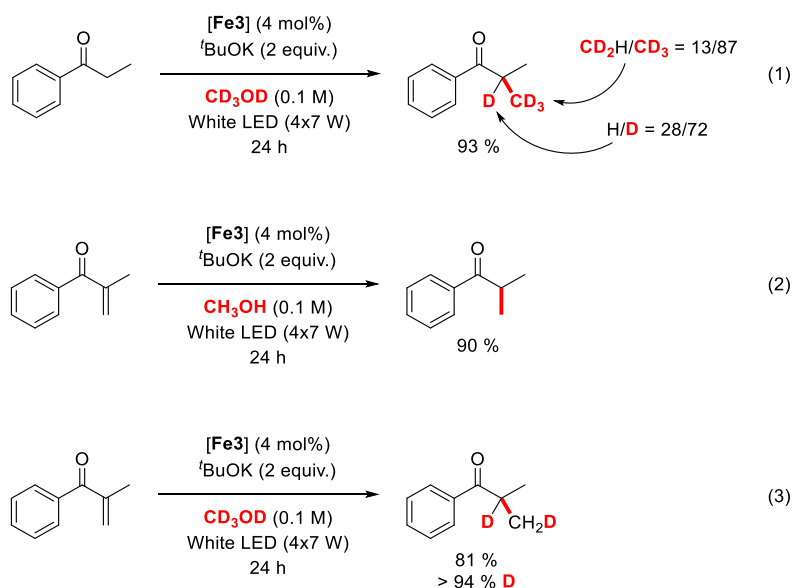
²⁸⁴ Chan, A. Y.; Perry, I. B.; Bissonnette, N. B.; Buksh, B. F.; Edwards, G. A.; Frye, L. I.; Garry, O. L.; Lavagnino, M. N.; Li, B. X.; Liang, Y.; Mao, E.; Millet, A.; Oakley, J. V.; Reed, N. L.; Sakai, H. A.; Seath, C. P.; MacMillan, D. W. C. *Chem. Rev.* **2022**, *122*, 1485-1542.

²⁸⁵ Emayavaramban, B.; Chakraborty, P.; Dahiya, P.; Sundararaju, B. *Org. Lett.* **2022**, *24*, 6219-6223.



Scheme 5.1: Methylation of ketones under light irradiation reported by Sundararaju.

To gain mechanistic insight, control experiments were carried out. First, deuterated methanol was introduced as a pro-electrophile (Scheme 5.2, Eq. 1). The deuterated product was obtained in 93 % yield with 72-87 % deuterium incorporation, confirming that methanol was the source of methyl. In a second experiment, an enone derivative was engaged in the reaction conditions and gave the reduced product in 90 % yield, suggesting that the enone was an intermediate in the alkylation reaction (Scheme 5.2, Eq. 2). Finally, the same experiment was performed using deuterated methanol as solvent (Scheme 5.2, Eq. 3). The reduced product was obtained in 81 % yield with 94 % deuterium incorporation, confirming that methanol was the hydride source.

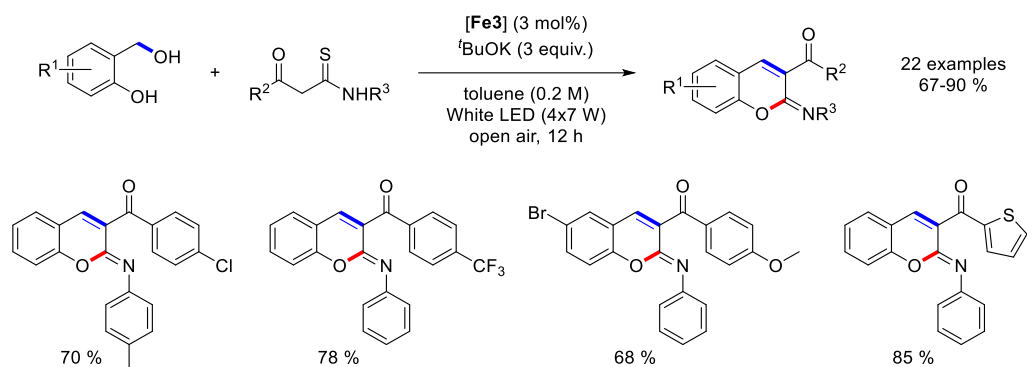


Scheme 5.2: Control experiments performed by Sundararaju.

Further investigations were performed. UV-vis spectra of the Knölker complex under light irradiation was recorded. The spectrum of the initial iron complex in methanol solution showed a maximum absorption at 319 nm. After irradiation, this maximum underwent a red shift, with an isosbestic point at 332 nm. Performing the reaction under thermal conditions did not yield any alkylated product at 40 °C, but the α -methylated ketone was obtained in 18 and 32 % yield at 50 and 60 °C, respectively. These observations confirm the importance of light in this alkylation reaction.

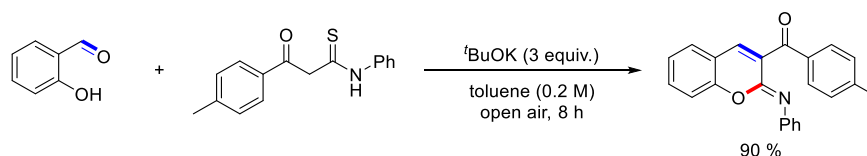
2) Iron-catalysed synthesis of 2-arylimino-2H-chromenes from 2-hydroxybenzyl alcohols and β -ketothioamides.

More recently, Waheed described the synthesis of 2-arylimino-2H-chromenes using the same iron catalyst.²⁸⁶ In this reaction, 2-hydroxybenzyl alcohols reacted with 1,3-keto-thioamides in the presence of ^tBuOK (3 equiv.) and the Knölker complex (3 mol %) in toluene under air and light irradiation (4x7 W white LED bulb lamps) for 12 hours. Under these conditions, various 2-arylimino-2H-chromenes were isolated in good yields (67-90 %, Scheme 5.3). The reaction tolerated electron-donating (alkyl, methoxy, acetal) and electron-withdrawing groups (halogen, trifluoromethyl) as well as heteroaryl derivatives.



Scheme 5.3: Synthesis of 2-arylimino-2H-chromenes reported by Waheed.

A control experiment was also carried out. Starting from salicylaldehyde, the cyclic product was obtained in 90 % yield without light irradiation (Scheme 5.4). This experiment highlights the role of the iron complex, which is only used to dehydrogenate the benzyl alcohol.



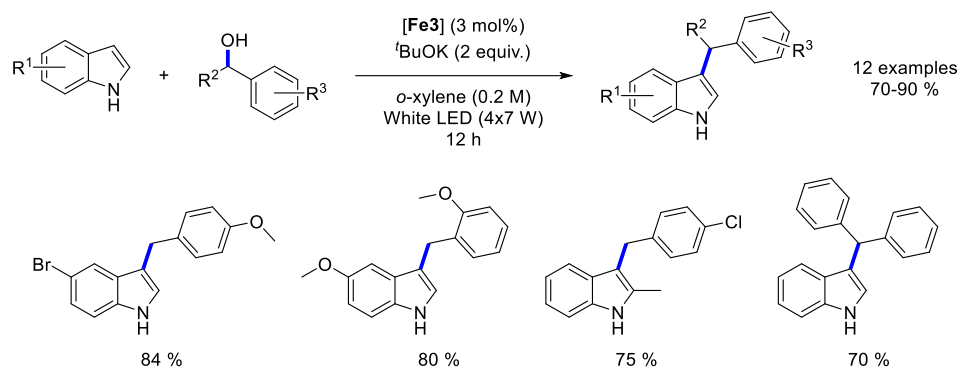
Scheme 5.4: Control experiment carried out by Waheed.

With these results, the authors proposed a mechanism for this reaction. In a first step, the Knölker complex is activated by removing one CO ligand through light irradiation. Then, the dehydrogenation of the benzylic alcohol takes place, leading to the salicylaldehyde intermediate and the iron-hydride species. The latter releases hydrogen to regenerate the catalytic species. The keto-thioamide is alkylated by enol condensation with the benzaldehyde. Final cyclisation by nucleophilic attack of the phenol moiety on the thioamide function generates the 2-arylimino-2H-chromene.

²⁸⁶ Waheed, M.; Alsharif, M. A.; Alahmadi, M. I.; Mukhtar, S.; Parveen, H. *Eur. J. Org. Chem.* **2023**, 26, e202300136.

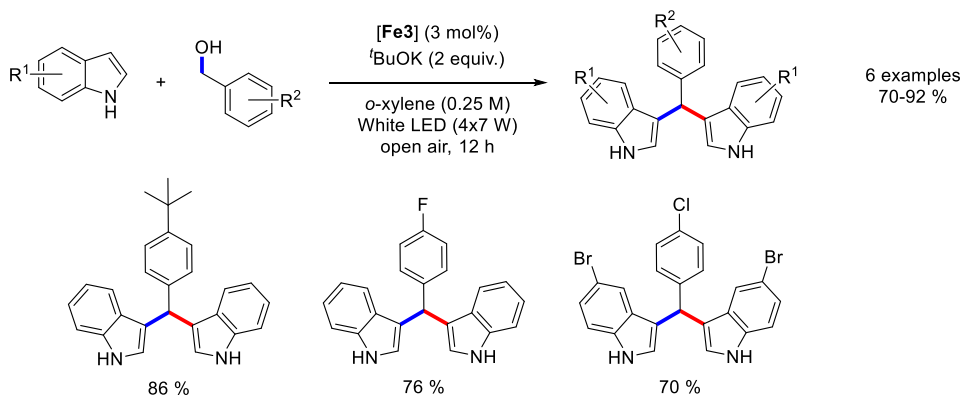
3) Iron-catalysed synthesis of C-3 alkylated indoles, bisindolymethanes and flavanones.

The same group also reported the alkylation of indoles and the synthesis of flavanones.²⁸⁷ In the optimised conditions, indole reacted with an alcohol in the presence of ^tBuOK (2 equiv.) and the Knölker complex (3 mol %) in *o*-xylene under light irradiation (4x7 W white LED bulb lamps) for 10 hours to give C3-alkylated indoles. Primary and secondary alcohols could be used as pro-electrophiles without any decrease of the yield (70-90 %, Scheme 5.5).



Scheme 5.5: Alkylation of indoles reported by Waheed.

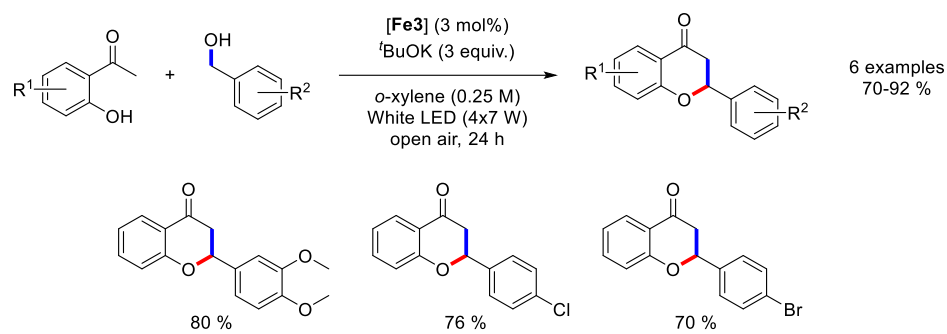
The synthesis of bisindolymethanes was also described. The previously described reaction conditions were similar, except that the reaction was carried out in an open-air environment. In these conditions, the complex does not reduce the unsaturated species intermediate, and an 1,4-addition occurs between the latter and a second indole molecule (Scheme 5.6).



Scheme 5.6: Synthesis of bisindolymethanes reported by Waheed.

Finally, the authors extended this work to the synthesis of flavanones. Increasing the amount of base and the reaction time opened a route to the desired flavanones in good yields (70 to 92 %, Scheme 5.7). More generally, the reaction described by Waheed afforded the desired products in good yields, but a limited number of functional groups were tolerated in these reactions.

²⁸⁷ Waheed, M.; Alsharif, M. A.; Alahmdi, M. I.; Mukhtar, S.; Parveen, H. *Tetrahedron Lett.* **2023**, *119*, 154428.



Scheme 5.7: Synthesis of flavanones reported by Waheed.

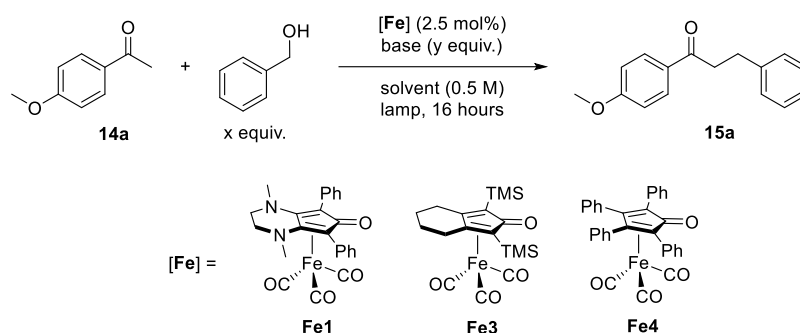
III. Blue light induced iron-catalysed α -alkylation of ketones.

1) Optimisation of the reaction.

To begin our work, the UV-visible spectra of complexes **Fe1-Fe3** were recorded.²⁸⁸ Three maxima were observed at 360, 311 and 340 nm for **Fe1**, **Fe2** and **Fe3**, respectively. Even though these maxima correspond to UV light spectra, a small absorption in the blue region can be noticed.

The study began by probing the alkylation of 4-methoxyacetophenone with benzyl alcohol in *tert*-butanol with different light sources and powers (Table 5.1, Entries 1 to 7). Both of these parameters were critical to obtain conversion of the starting materials. Total conversion into the alkylated product was obtained with the 40W blue LED lamp (Entry 4) in 16 hours, while other light sources led to lower conversions. The power of the lamp was also a key parameter. Increasing the power of the lamp increased the conversion into the alkylated product (Entries 1 to 4). Complexes **Fe3** and **Fe4** did not furnish the alkylated product (Entries 21 and 22). Base screening showed that both NaOH and *t*BuONa could be used, while carbonates did not give any conversion (Entries 4 and 8 to 11), and higher yields was obtained with sodium hydroxide compared to *t*BuONa (65 and 42 %, respectively). Decreasing the base loading led to lower conversions (Entries 12 to 14). Evaluation of different solvent showed that toluene was also suitable for this reaction, while other solvents led to lower conversion (Entries 15 to 18). Variation of the alcohol equivalents gave an optimal conversion with 2.5 equiv. of benzyl alcohol (Entries 19 and 20). The optimal conditions were the following ones: 4-methoxyacetophenone (1 equiv.) reacted with benzyl alcohol (2.5 equiv.) in the presence of NaOH (0.4 equiv.) and iron complex **Fe1** (2.5 mol %) in *t*BuOH (0.5 M) under blue light irradiation (38 W) at room temperature for 16 hours.

Table 5.1: Optimization of the alkylation of 4-methoxyacetophenone with benzyl alcohol.



Entry ^a	Catalyst	Lamp (power)	Base (equiv.)	Solvent (equiv.)	Alcohol (equiv.)	Conversion ^b
1	Fe1	Blue (5W)	NaOH (0.4)	<i>t</i> BuOH (0.5 M)	2.5	0
2	Fe1	Blue (18W)	NaOH (0.4)	<i>t</i> BuOH (0.5 M)	2.5	13
3	Fe1	Blue (2*18W)	NaOH (0.4)	<i>t</i> BuOH (0.5 M)	2.5	85
4	Fe1	Blue (38W)	NaOH (0.4)	<i>t</i> BuOH (0.5 M)	2.5	100 (65) ^c
5	Fe1	Cold white (23W)	NaOH (0.4)	<i>t</i> BuOH (0.5 M)	2.5	0

²⁸⁸ Abdallah, M.-S.; Joly, N.; Gaillard, S.; Poater, A.; Renaud, J.-L. *Org. Lett.* **2022**, *24*, 5584-5589.

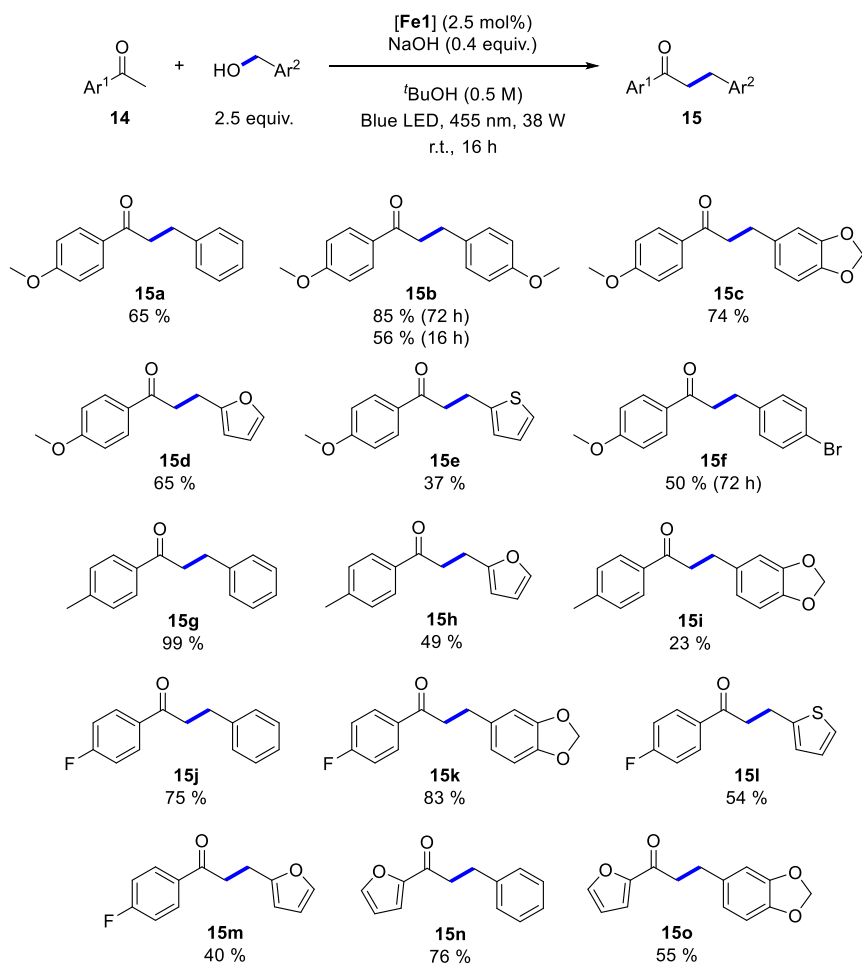
6	Fe1	Warm white (32W)	NaOH (0.4)	^t BuOH (0.5 M)	2.5	< 1
7	Fe1	Green (30W)	NaOH (0.4)	^t BuOH (0.5 M)	2.5	0
8^d	Fe1	Blue (38W)	^t BuONa (0.4)	^t BuOH (0.5 M)	2.5	100 (42) ^c
9^d	Fe1	Blue (38W)	Na ₂ CO ₃ (0.4)	^t BuOH (0.5 M)	2.5	0
10^d	Fe1	Blue (38W)	K ₂ CO ₃ (0.4)	^t BuOH (0.5 M)	2.5	0
11^d	Fe1	Blue (38W)	Cs ₂ CO ₃ (0.4)	^t BuOH (0.5 M)	2.5	0
12	Fe1	Blue (38W)	NaOH (0.3)	^t BuOH (0.5 M)	2.5	73
13	Fe1	Blue (38W)	NaOH (0.2)	^t BuOH (0.5 M)	2.5	17
14	Fe1	Blue (38W)	NaOH (0.1)	^t BuOH (0.5 M)	2.5	2
15	Fe1	Blue (38W)	NaOH (0.4)	THF (0.5 M)	2.5	0
16	Fe1	Blue (38W)	NaOH (0.4)	MeOH (0.5 M)	2.5	0
17	Fe1	Blue (38W)	NaOH (0.4)	CH ₂ Cl ₂ (0.5 M)	2.5	68
18	Fe1	Blue (38W)	NaOH (0.4)	Toluene (0.5 M)	2.5	100
19	Fe1	Blue (38W)	NaOH (0.4)	^t BuOH (0.5 M)	2.0	20
20	Fe1	Blue (38W)	NaOH (0.4)	^t BuOH (0.5 M)	3.0	50
21	Fe3	Blue (38W)	NaOH (0.4)	^t BuOH (0.5 M)	2.5	0
22	Fe4	Blue (38W)	NaOH (0.4)	^t BuOH (0.5 M)	2.5	< 1

^a General condition: 4-methoxyacetophenone (0.5 mmol), benzyl alcohol (x equiv.), base (y equiv.), **Fe** (2.5 mol%), and solvent (0.5 M), lamp, room temperature for 16 h. ^b Conversions were determined by ¹H NMR analysis of the crude mixture. ^c Isolated yields. ^d Me₃NO (2.5 mol %) was added.

2) Scope of the reaction.

With the optimised conditions in hand, we investigated the scope of this blue light induced iron-catalysed alkylation of ketones with primary alcohols. A set of benzyl alcohols bearing electron-donating and electron-withdrawing groups were engaged with aryl ketones. Methoxy, acetal, halide-substituted aryl and heteroaryl groups can be used in this hydrogen autotransfer reaction under light irradiation. The corresponding α -alkylated ketones **15a-o** were isolated in moderate to good yields (23-99 %, Scheme 5.8). Aryl ketones bearing electron-withdrawing groups led to slightly higher yields due to the higher acidity of the nucleophile (compounds **15j-m**, 40 to 83 %). Important to note, when thiophene derivatives were engaged, the desired alkylated product was not obtained. A modification of the procedure using green light (525 nm, 18 W) allowed the obtention of the alkylated products **15e** and **15l** in moderate to good yield (37 and 54 %, respectively). This result could be explained by a possible

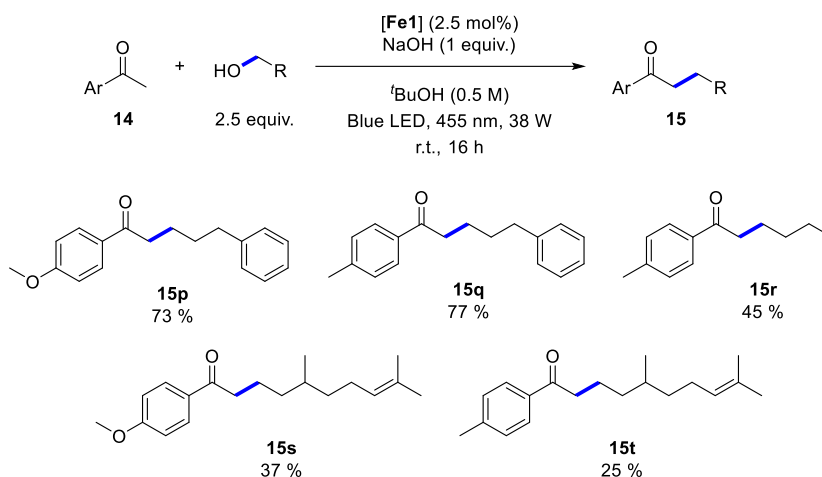
polymerization, radical formation or degradation of the thiophene 2-carboxaldehyde intermediate or other derivatives under photoirradiation.²⁸⁹



Scheme 5.8: Alkylation of aryl ketones with benzylic alcohols.

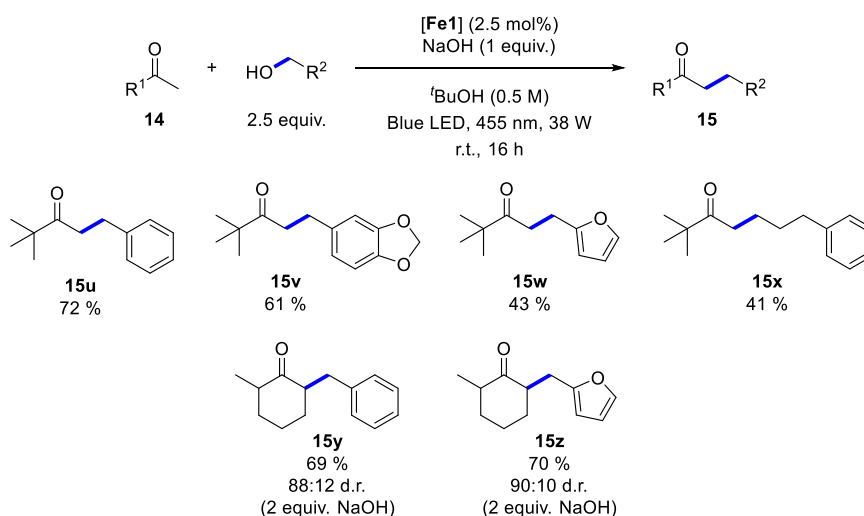
As aliphatic alcohols usually require harsher conditions, the amount of base was increased to 1 equivalent. In these conditions, 3-phenyl propanol, 1-butanol and citronellol were engaged in the reaction and the desired products **15p-t** were isolated in moderate to good yield (25 to 77 %, Scheme 5.9).

²⁸⁹ Dumur, F. *Eur. Polym. J.* **2022**, *169*, 111120.



Scheme 5.9: Alkylation of aryl ketones with aliphatic alcohols.

Finally, this reaction was extended to aliphatic ketones as pro-nucleophiles. In the same conditions than above, the alkylated products **15u-x** were isolated in moderate to good yields (41-72 %, Scheme 5.10). The first alkylation between two aliphatic partners catalysed by a cyclopentadienone iron complex is represented by **15x**. This product highlights the potential of this new methodology in organic synthesis. The alkylation of 2-methyl cyclohexanone required 2 equiv. of base due to its two possible enol forms. Increasing the amount of base afforded the alkylated products **15y-z** in pleasant yields (69-70 %).



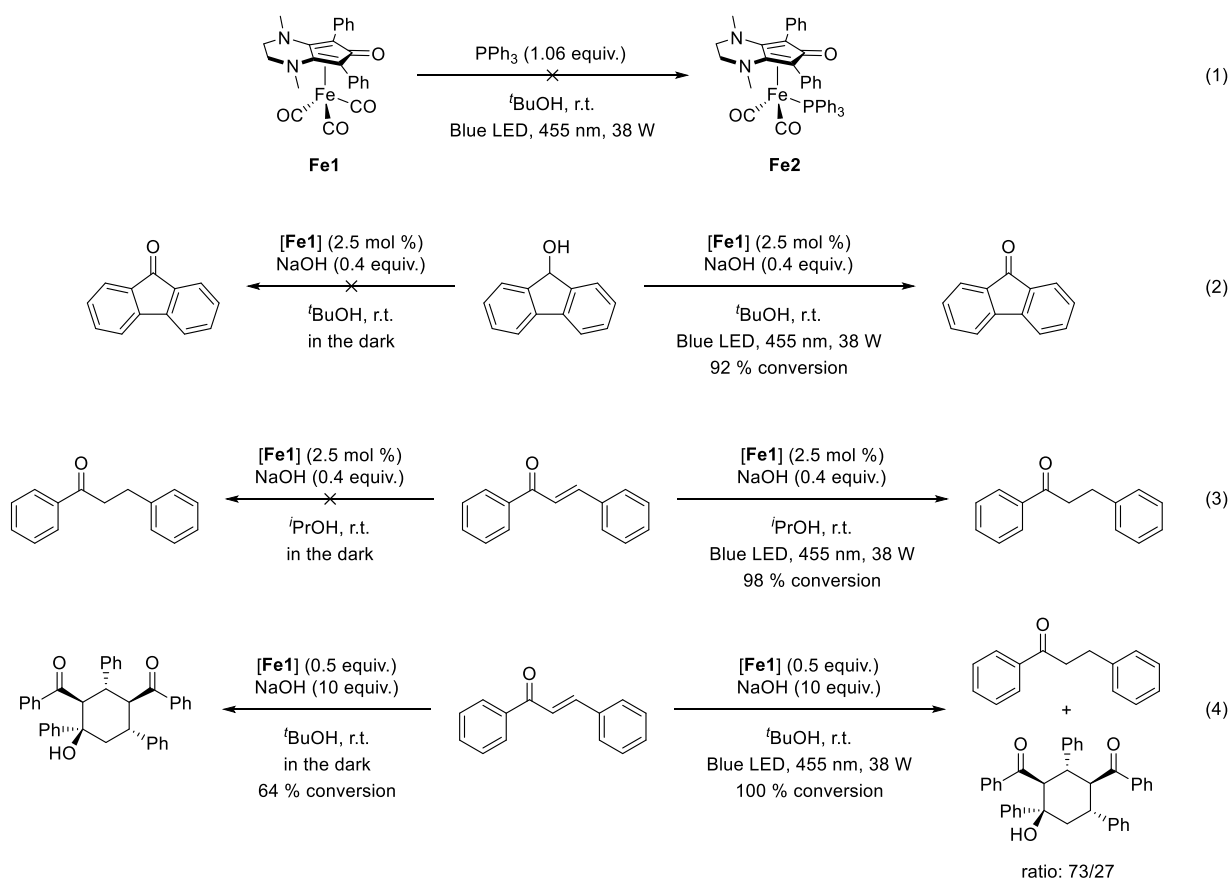
Scheme 5.10: Alkylation of aliphatic ketones with benzylic and aliphatic alcohols.

3) Mechanistic investigation.

To give more insight on the mechanism of this reaction, different experiments were performed. Photolytic removal of a CO ligand was already reported by Knölker using a 150W medium-pressure mercury lamp,^{17c, 21} or Lehnher using a blue LED lamp.²⁹⁰ To check the photolytic removal of one CO in our conditions, iron complex **Fe1** was reacted with one equivalent of triphenylphosphine in *tert*-

²⁹⁰ Lehnher, D.; Ji, Y.; Neel, A. J.; Cohen, R. D.; Brunskill, A. P. J.; Yang, J.; Reibarkh, M. *J. Am. Chem. Soc.* **2018**, *140*, 13843-13853.

butanol under light irradiation (Scheme 5.11, Eq. 1). Monitoring of the reaction by ^{31}P NMR did not show any formation of the triphenylphosphine iron complex **Fe2**. This experiment discards any role of light in the activation process. In a second experiment, fluorenone was placed in the reaction conditions, with and without light (Scheme 5.11, Eq. 2). The oxidation of the alcohol into the corresponding ketone was observed only under light irradiation, highlighting the role of the latter in this process. A third experiment using chalcone in the presence of **Fe1** (2.5 mol %) and NaOH (0.4 equiv.) in *iso*-propanol showed the reduction of the C=C bond under light irradiation (Scheme 5.11, Eq. 3), but not in the dark. Perhaps, since the light is required for the oxidation step, this experiment does not prove the role of the light in the reduction process. To check the role of the light in the reduction step, chalcone was placed in the presence of the iron complex **Fe1** (0.5 equiv.) and NaOH (10 equiv.) in *t*BuOH in order to generate the iron hydride complex *via* a Hieber base reaction.²⁹¹ In the latter, the reduction of the C=C bond was only observed under light irradiation along with the formation of a cyclohexanol by-product (identified by 2D-NMR and mass analysis) in a 73/27 ratio. In the dark, only the cyclohexanol by-product was formed with 64 % conversion (Scheme 5.11, Eq. 4). The role of the light in the reduction step was therefore confirmed.

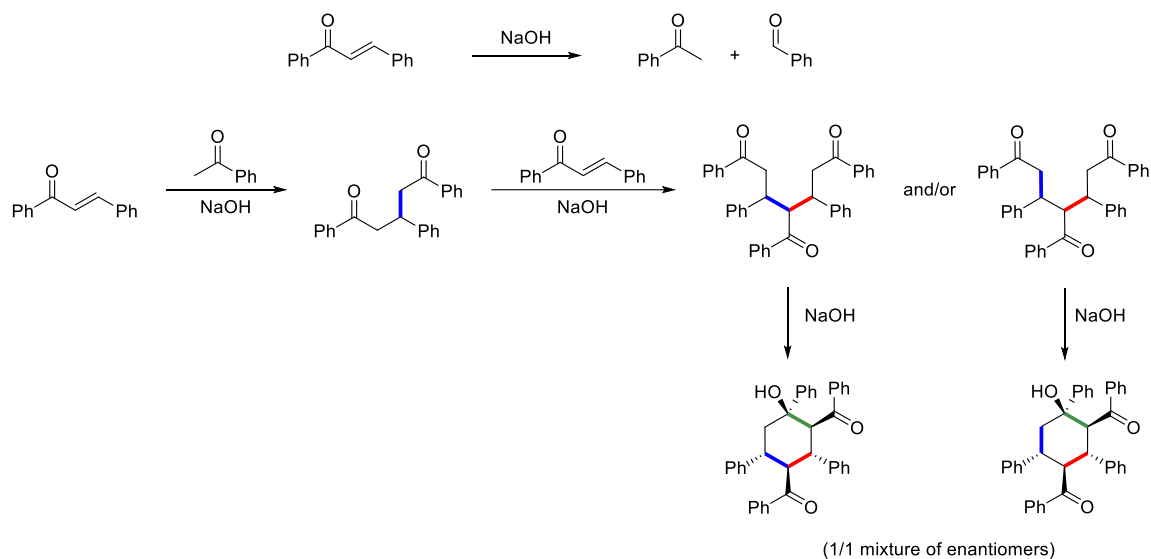


Scheme 5.11: Mechanistic experiments.

The formation of the cyclohexanol by-product results from a retro-aldol condensation giving rise to benzaldehyde and acetophenone. The addition of the latter on chalcone generates a diketone. A second addition with a second chalcone molecule led to a triketone derivative which cyclises to give the

²⁹¹ Brunet, J. J. *Chem. Rev.* **1990**, *90*, 1041-1059.

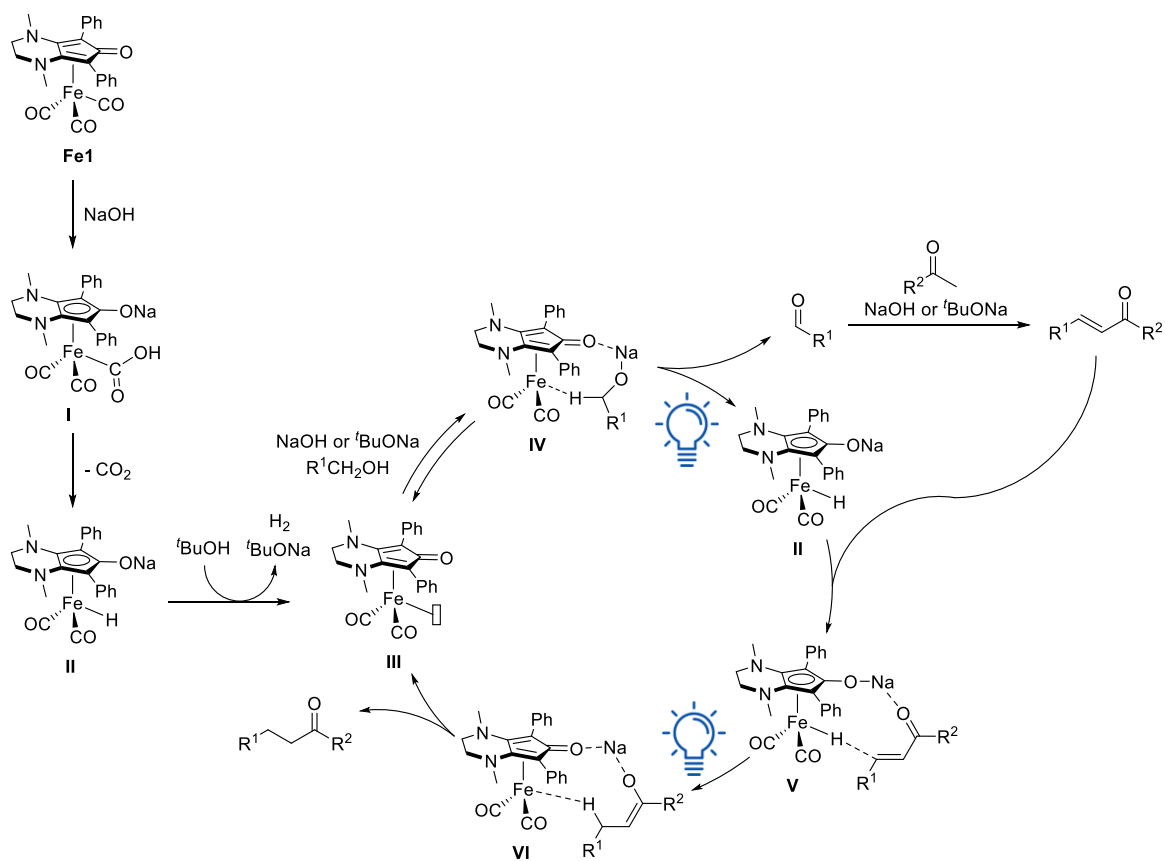
cyclohexanol product (Scheme 5.12). The stereochemistry of the product was confirmed by comparison with reported data.²⁹²



Scheme 5.12: Proposed mechanism for the formation of the cyclohexanol by product.

With these results, a mechanism was proposed for the blue-light induced α -alkylation of ketones catalysed by **Fe1** (Scheme 5.13). In a first step, the complex is activated by removal of one CO ligand with NaOH, followed by the release of hydrogen and CO₂. Coordination of the alcohol to the 16-electron species **III** gives intermediate **IV**. Dehydrogenation of the alcohol under light irradiation would be the first key step of this new approach, providing the iron-hydride intermediate **II** and the aldehyde. The mono-alkylated ketone could then be obtained thanks to a light induced activation of intermediate **V**, allowing the reduction of the unsaturated ketone at room temperature, closing the catalytic cycle with the regeneration of intermediate **III**.

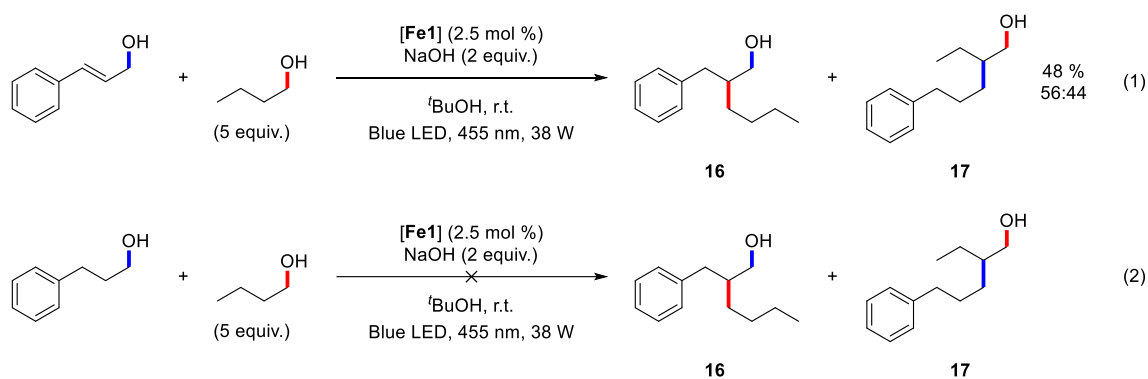
²⁹² Palamarchuka, I. V.; Shulgaub, Z. T.; Sergazyb, Sh, D.; Zhulikeevab, A. M.; Gatilovc, Yu. V.; Kulakov, I. V. *Russ. J. Gen. Chem.* **2021**, *91*, 2462-2468.



Scheme 5.13: Proposed mechanism for the light induced iron-catalyzed α -alkylation of ketones.

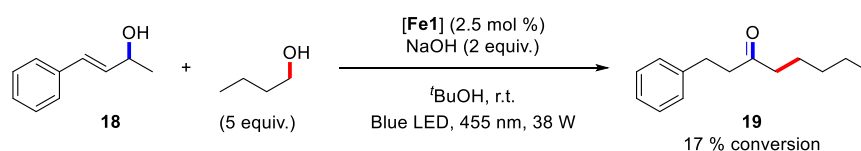
IV. Blue light induced iron-catalysed β -alkylation of allylic alcohols.

Following our previous work on the α -alkylation of ketones, we became interested in the alkylation of allylic alcohols. The reaction of cinnamyl alcohol with 1-butanol was chosen as a model reaction. A quick optimization of the reaction conditions highlighted that 2 equiv. of base were required to give >99 % conversion of the starting cinnamyl alcohol. Analysis of the crude reaction mixture by $^1\text{H-NMR}$ spectroscopy showed 20 % of 3-phenylpropan-1-ol intermediate, along with 80 % of an unidentified product. To determine its structure, purification on silica gel column chromatography was performed. Analysis of the isolated fraction allowed to identify 2-benzylhexanol **16** in mixture with a second product. 2D NMR analysis unveiled that the second product corresponds to the alkylation of butanol with the 3-phenylpropan-1-ol intermediate **17** (*i.e.* 2-ethyl 5-phenyl-pentanol). These two products were isolated in 48 % yield and couldn't be separated neither by chromatography nor by distillation (Scheme 5.14, Eq. 1). Starting from 3-phenylpropan-1-ol under the same conditions, no reaction was observed. Regarding these results, we supposed that the catalyst allows the dehydrogenation step, but immediately reduces the corresponding carbonyl function. Consequently, there is not enough pro-nucleophiles and pro-electrophiles to perform any alkylation reaction (Scheme 5.14, Eq. 2).



Scheme 5.14: Alkylation of cinnamyl alcohol and 3-phenylpropan-1-ol.

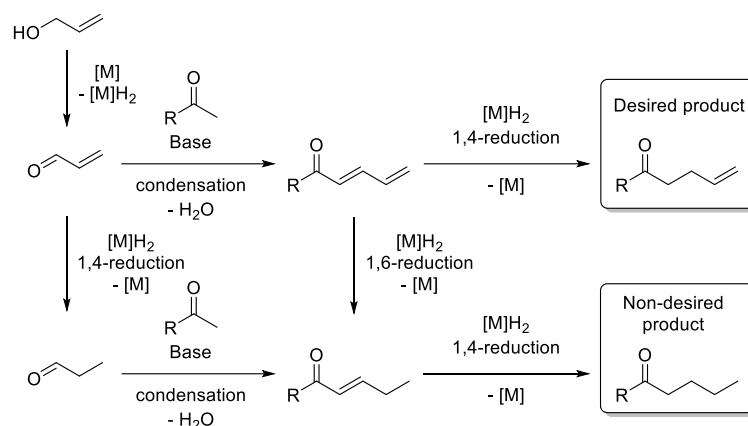
To avoid the cross-alkylation observed with cinnamyl alcohol, we decided to start from a secondary allylic alcohol, 4-phenylbut-3-en-2-ol **18**, to generate the saturated ketone intermediate, which can't be reduced with our complex, thus favouring the alkylation of this compound rather than the alkylation of butanol. Unfortunately, only 17 % conversion was obtained in favour of the alkylated product **19**, while no alkylation of butanol was detected (Scheme 5.15). Moreover, the alkylation at the terminal methyl position of the secondary alcohol was the sole alkylation site, confirming that the alkylation of α -substituted ketones is a more challenging reaction.



Scheme 5.15: Alkylation of 4-phenylbut-3-en-2-ol with butanol.

V. Alkylation reactions with allylic alcohols in thermal conditions.

Only few examples of alkylation reactions using allylic alcohols as pro-electrophiles for the formation of C-C bonds¹²⁸ or chemoselective reduction of unsaturated compounds²⁵¹ were reported in literature. Such reaction remains a challenge since a possible 1,4-reduction of the α,β -unsaturated aldehyde could furnish a saturated product at the end of the reaction (Scheme 5.16). Furthermore, a 1,6-reduction of the dienone intermediate, obtained by the condensation between the α,β -unsaturated aldehyde and the ketone, could also lead to the saturated product.

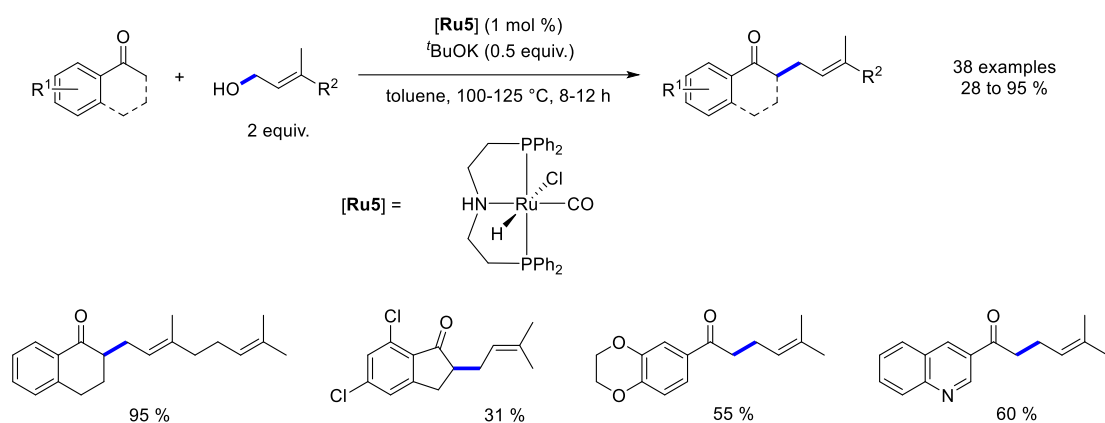


Scheme 5.16: Drawbacks due to the employment of allylic alcohols as pro-electrophiles.

1) Ruthenium-catalysed α -prenylation of ketones.

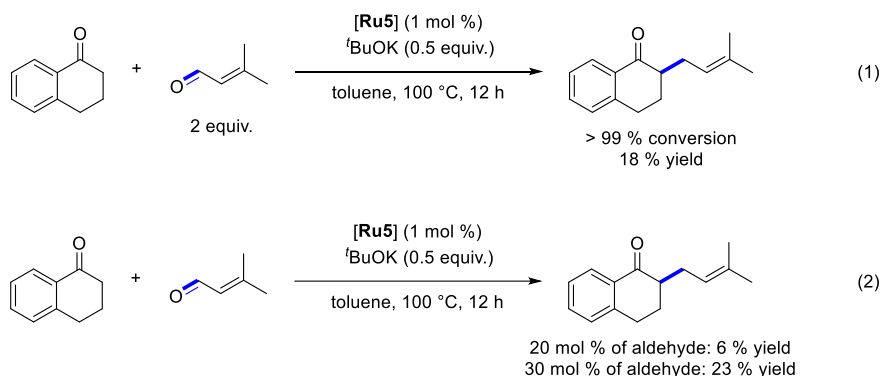
Very recently, the first alkylation of ketones with allylic alcohols to get unsaturated ketones using the hydrogen autotransfer strategy was reported by Gunanathan.²⁹³ The α -alkylation of acetophenones derivatives with terpinol compounds was achieved in the presence of ^tBuOK (0.5 equiv.) and a Ru-Macho complex (1 mol %) at 100 °C in toluene for 12 hours. In these conditions, α -tetralones and 1-indanones pro-nucleophiles were alkylated in low to excellent yields (28 to 95 %, Scheme 5.17). Aniline derivative was isolated as a mixture of the -NH₂ and the *N*-alkylated products. The alkylation of acetophenone derivatives required a higher temperature (125 °C) but also shorter reaction time (8 hours). The corresponding products were obtained in moderate to very good yields (37 to 88 %, Scheme 5.17). However, this reaction was limited to terpenols as pro-electrophiles.

²⁹³ Sankar, R. V.; Manikpuri, D.; Gunanathan, C. *Org. Biomol. Chem.* **2023**, *21*, 273-278.



Scheme 5.17: Ruthenium-catalysed alkylation of ketones with terpenols.

Mechanistic investigations were conducted by the authors. In a first experiment, tetralone reacted with 3-methyl-2-butenal in standard conditions giving 18 % yield of the alkylated product (Scheme 5.18, Eq. 1). This lower yield was attributed by the authors to the strong coordination of the aldehyde to the metal catalyst, thus inhibiting its activity. Based on this result, a second experiment using sub-stoichiometric amount of aldehyde (20 and 30 mol %) yielded the desired product in 6 and 23 % yields, respectively (Scheme 5.18, Eq. 2). The authors concluded that the inhibition of the catalyst occurs at high concentration of the aldehyde intermediate in the mixture. However, these conclusions can be discussed. First, these mechanistic investigations were carried out in standard conditions, which means no hydride source in the reaction mixture, explaining the high conversions of the starting ketone but the low yields of the reactions. Then, while no hydride source was added to the reaction, up to 23 % yield in alkylated product was obtained. It could be supposed that the reduction of the double bond could be obtained from water generated during the condensation step, which could produce the metal-hydride species able to perform the reduction of the C=C bond.



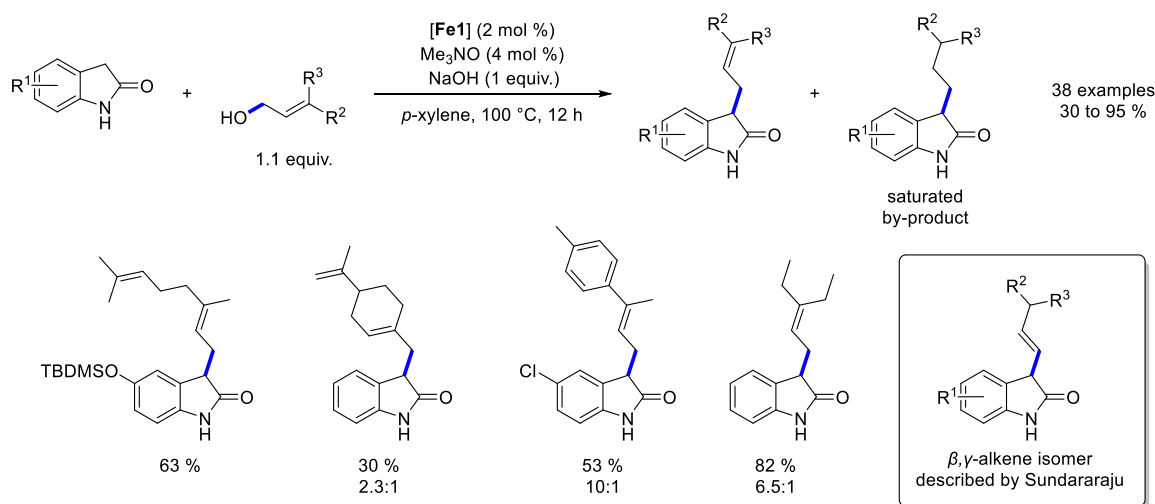
Scheme 5.18: Mechanistic investigations performed by Gunanathan.

2) Iron-catalysed alkylation of oxindoles with terpenols.

In 2023, Sundararaju described the alkylation of oxindoles with terpenols and allylic alcohols.²⁹⁴ In the optimised conditions, oxindoles reacted with 1.1 equiv. of allylic alcohol in the presence of sodium hydroxide (1 equiv.), iron complex **Fe1** (2 mol %) and Me₃NO (4 mol %) in *p*-xylene at 100 °C

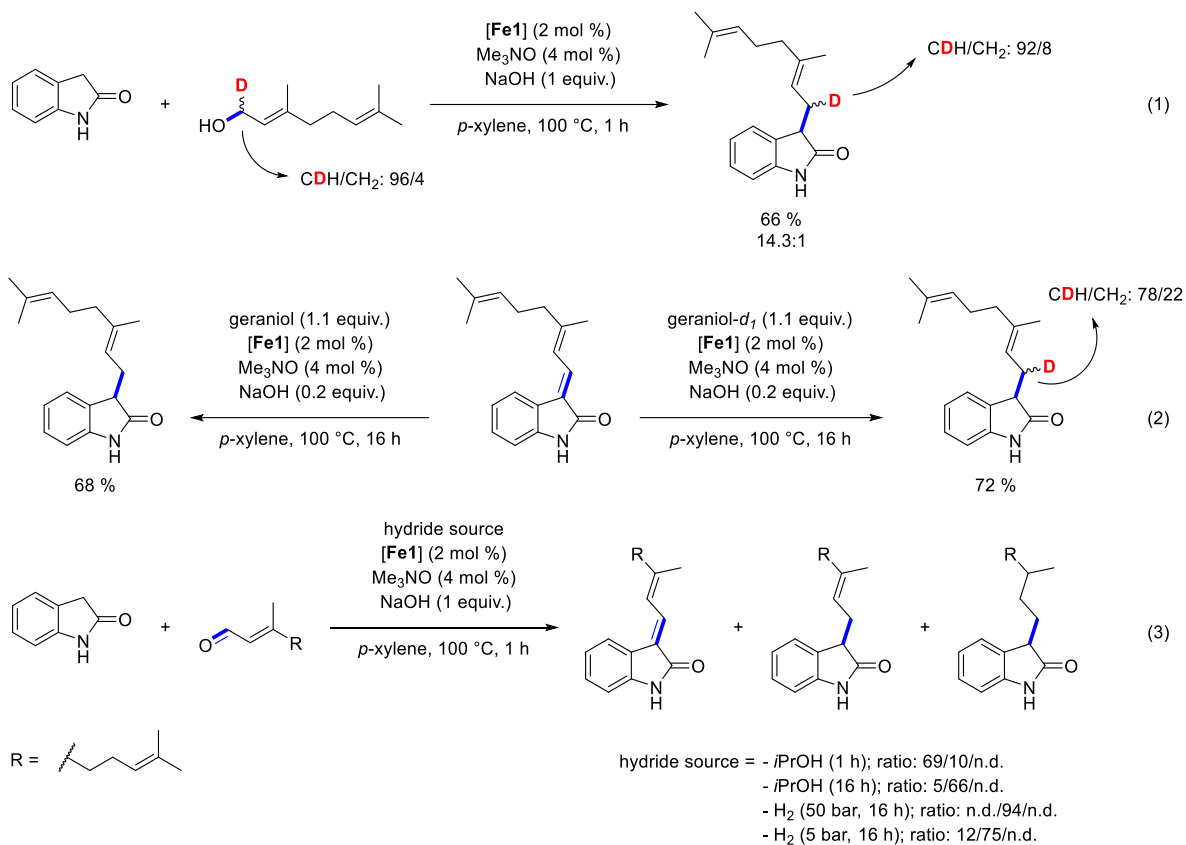
²⁹⁴ Chakraborty, P.; Pradhan, S.; Premkumar, J. R.; Sundararaju, B. *J. Catal.* **2023**, *421*, 309-318.

for 12 hours. Interestingly, the alkylated product was isolated as a mixture of alkene isomers (α,β and β,γ -alkene, Scheme 5.19) as described by the authors. The formation of this by-product was attributed to a 1,6-reduction of the dienone intermediate. However, a close analysis of the NMR spectra reported by the authors show the presence of the saturated by-product and not the β,γ -alkene isomer described by the authors. This incorrect analysis was confirmed by the mechanistic investigations discussed in the following paragraph. Regarding the scope of this reaction, various groups were tolerated on the aryl rings of the products such as halide, methoxy or silyl-protected phenols and the alkylated products were isolated in yields ranging from 30 to 95 % (Scheme 5.19).



Scheme 5.19: Alkylation of oxindoles with allylic alcohols reported by Sundararaju.

To validate the borrowing hydrogen pathway, deuterium labelling experiments were carried out. Mono-deuterated geraniol was used with oxindole in standard reaction conditions, leading to the deuterated product in 66 % yield with 92 % deuterium incorporation at the β -position, thus validating the hydrogen autotransfer (Scheme 5.20, Eq. 1). Further investigations regarding the hydrogen transfer were performed starting from the unsaturated intermediate in the presence of geraniol or deuterated isopropanol (Scheme 5.20, Eq. 2). Both experiments yielded the product in similar yields (68 and 72 % respectively), however, the deuterium incorporation was not complete (78 %). Finally, reductive alkylation using citral as electrophile and isopropanol or molecular hydrogen as hydride source gave the alkylated oxindole along with the dienone intermediate while the isomeric form previously described by the authors was not observed (Scheme 5.20, Eq. 3). Even though all these experiments also confirmed the borrowing hydrogen pathway, none of them could explain the formation of the β,γ -alkene isomer, or yielded this product, while this latter was supposed by the authors to be the by-product of the reaction. Also, the saturated product resulting from the 1,6-reduction followed by 1,4-reduction was also presented in this mechanistic investigation, however, its ratio was never determined by the authors. DFT calculations were also performed. This study highlighted the 1,6-reduction to be less energetically demanding than the 1,4-reduction by approximately 1 kcal/mol. This result could explain the formation of the saturated by-product. The latter could also come from the 1,4-reduction of the enal intermediate, after dehydrogenation of the allylic alcohol. This hypothesis is further confirmed as the saturated by-product was not observed in the second experiment starting from the dienone intermediate (Scheme 5.20, Eq. 2).



Scheme 5.20: Mechanistic investigation performed by Sundararaju.

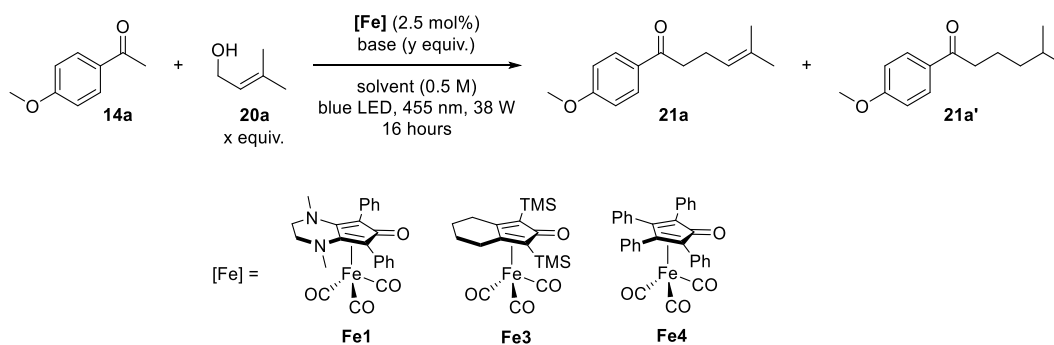
VI. Blue light induced alkylation of ketones with allylic and propargylic alcohols.

While these works were limited to terpenol derivatives or non-functionalised allylic alcohols as pro-electrophiles and based on our previous work on the alkylation of ketones under photo-irradiation, we decided to explore this alkylation reaction in our new reaction conditions.

1) Optimisation of the reaction.

We started our optimisation using 4-methoxyacetophenone as pro-nucleophile and prenol as pro-electrophile under photoirradiation with the 40W blue LED lamp in the presence of NaOH (0.5 equiv.) and **Fe1** (2.5 mol %) in *t*BuOH. In our case, the reduced product **21a'** was always present at the end of the reaction. The amount of alcohol was first scrutinised (Table 5.2, Entries 1-5). The best conversion was obtained with 4 equiv. of alcohol; however, we decided to pursue our study with 2 equiv. as it gave similar results with a much lower amount of reactant. Increasing the base loading did not improve the conversion (Table 5.2, Entries 6-8). A screening of the solvent for this reaction highlighted that more polar was the solvent, higher was the selectivity in favour of the unsaturated product (Table 5.2, Entries 2 and 9-10). This reaction was therefore tested with a variety of polar solvents (Table 5.2, Entries 12-17), however, no conversion were obtained in these conditions and *t*BuOH gave the best results and selectivities for the desired product. Variation of the concentration led to lower conversions (Table 5.2, Entries 18-19). A high concentration might lower the penetration of the light in the solution and therefore led to no conversion, while a lower concentration might slow down the reaction. Iron complexes **Fe3** and **Fe4** were also engaged but no conversion was obtained with these catalysts. The optimised conditions were as follow: 4-methoxyacetophenone reacted with 2 equiv. of prenol in the presence of NaOH (0.5 equiv.) and **Fe1** (2.5 mol %) in *t*BuOH (0.5 M) to give the alkylated product in 70 % yield.

Table 5.2: Optimisation of the alkylation of 4-methoxyacetophenone with prenol.



Entry	Catalyst (equiv.)	Base (equiv.)	Solvent (equiv.)	Alcohol (equiv.)	Conversion ^b 14a/21a/21a'
1	Fe1 (2.5 mol%)	NaOH (0.5)	<i>t</i> BuOH (0.5 M)	1.0	100/0/0
2	Fe1 (2.5 mol%)	NaOH (0.5)	<i>t</i> BuOH (0.5 M)	2.0	10/64/26 (70) ^c
3	Fe1 (2.5 mol%)	NaOH (0.5)	<i>t</i> BuOH (0.5 M)	3.0	23/55/22
4	Fe1 (2.5 mol%)	NaOH (0.5)	<i>t</i> BuOH (0.5 M)	4.0	5/67/28
5	Fe1 (2.5 mol%)	NaOH (0.5)	<i>t</i> BuOH (0.5 M)	5.0	19/60/21

6	Fe1 (2.5 mol%)	NaOH (1.0)	^t BuOH (0.5 M)	5.0	50/37/13
7	Fe1 (2.5 mol%)	NaOH (1.5)	^t BuOH (0.5 M)	5.0	15/61/24
8	Fe1 (2.5 mol%)	NaOH (2.0)	^t BuOH (0.5 M)	5.0	17/60/23
9	Fe1 (2.5 mol%)	NaOH (0.5)	toluene (0.5 M)	2.0	24/48/28
10	Fe1 (2.5 mol%)	NaOH (0.5)	CH ₂ Cl ₂ (0.5 M)	2.0	78/16/6
11	Fe1 (2.5 mol%)	NaOH (0.5)	CPME (0.5 M)	2.0	56/25/19
12	Fe1 (2.5 mol%)	NaOH (0.5)	DMF (0.5 M)	2.0	100/0/0
13	Fe1 (2.5 mol%)	NaOH (0.5)	DMSO (0.5 M)	2.0	100/0/0
14	Fe1 (2.5 mol%)	NaOH (0.5)	HFIP (0.5 M)	2.0	100/0/0
15	Fe1 (2.5 mol%)	NaOH (0.5)	trifluoroethanol (0.5 M)	2.0	100/0/0
16	Fe1 (2.5 mol%)	NaOH (0.5)	acetonitrile (0.5 M)	2.0	100/0/0
17	Fe1 (2.5 mol%)	NaOH (0.5)	^t BuOH:H ₂ O 75:25 (0.5 M)	2.0	100/0/0
18	Fe1 (2.5 mol%)	NaOH (0.5)	^t BuOH (0.25 M)	2.0	29/50/21
19	Fe1 (2.5 mol%)	NaOH (0.5)	^t BuOH (1.0 M)	2.0	100/0/0
20	Fe1 (1 mol%)	NaOH (0.5)	^t BuOH (0.5 M)	2.0	99/1/0
21	Fe1 (5 mol%)	NaOH (0.5)	^t BuOH (0.5 M)	2.0	57/32/11
22	Fe3 (2.5 mol%)	NaOH (0.5)	^t BuOH (0.5 M)	2.0	100/0/0
23	Fe4 (2.5 mol%)	NaOH (0.5)	^t BuOH (0.5 M)	2.0	100/0/0
24	-	NaOH (0.5)	^t BuOH (0.5 M)	2.0	100/0/0
25^d	Fe1 (2.5 mol%)	NaOH (0.5)	^t BuOH (0.5 M)	2.0	100/0/0

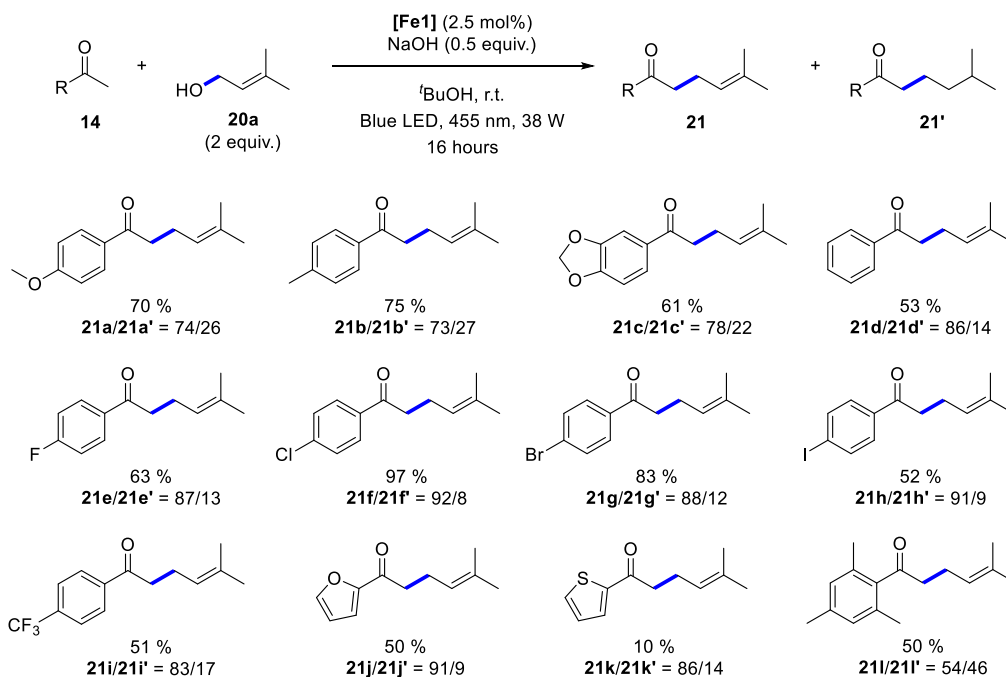
^a General condition: 4-methoxyacetophenone (0.5 mmol), prenol (x equiv.), NaOH (y equiv.), Fe (2.5 mol%), and solvent (0.5 M), 38 W Kessil blue LED lamp (455 nm, 38 W), room temperature for 16 h. ^b Conversions were determined by ¹H NMR analysis of the crude mixture. ^c Isolated yield. ^d Without light.

2) Scope of the reaction.

With the optimised conditions in hand, we started to investigate the scope of this alkylation reaction with various ketones and prenol as allylic alcohol (Scheme 5.21). Various substituted ketones bearing electron-donating (methoxy, methyl, acetal) or electron-withdrawing groups (halide, -CF₃) can be engaged in this alkylation reaction and led to the alkylated products **21a-i** and **21l** in good yields (50-97 %, Scheme 5.21). Heteroaryl groups are also tolerated and compounds **21j** and **21k** were isolated in 50 and 10 % yield, respectively. The low yield for **21k** may be attributed to a possible polymerisation of this substrate under photoirradiation as already observed.²⁹⁵ However, in contrast to our previous

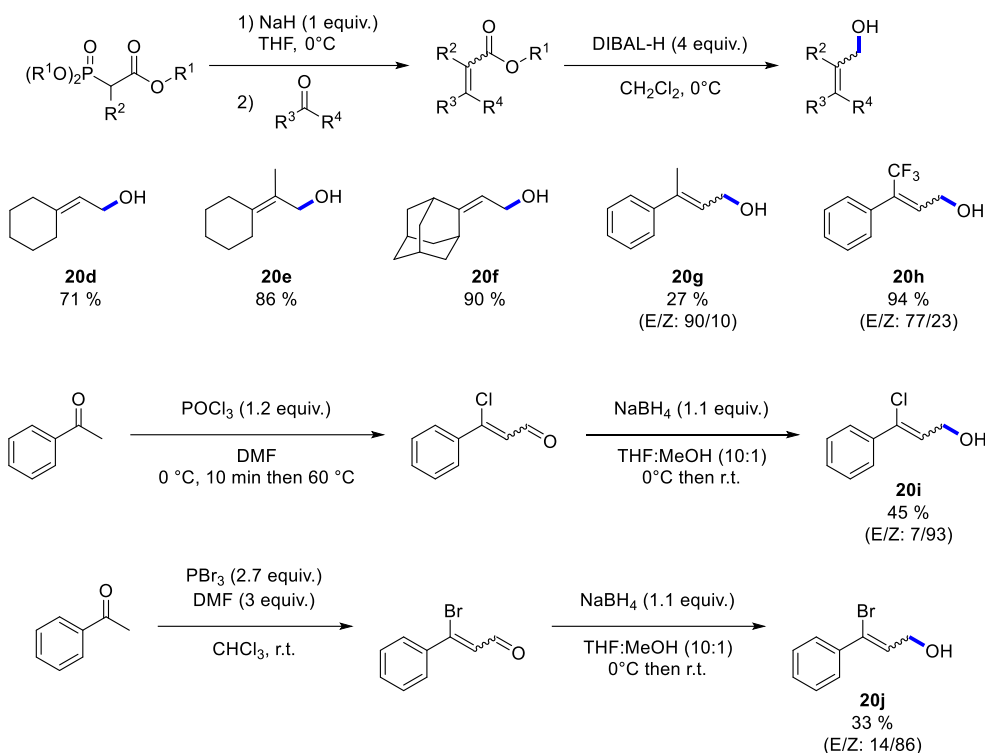
²⁹⁵ Chapter V, part III.2.

work with saturated alcohols, the use of green light (525 nm, 18 W) did not improve the yield of this reaction.



Scheme 5.21: Iron-catalysed alkylation of ketones with prenyl.

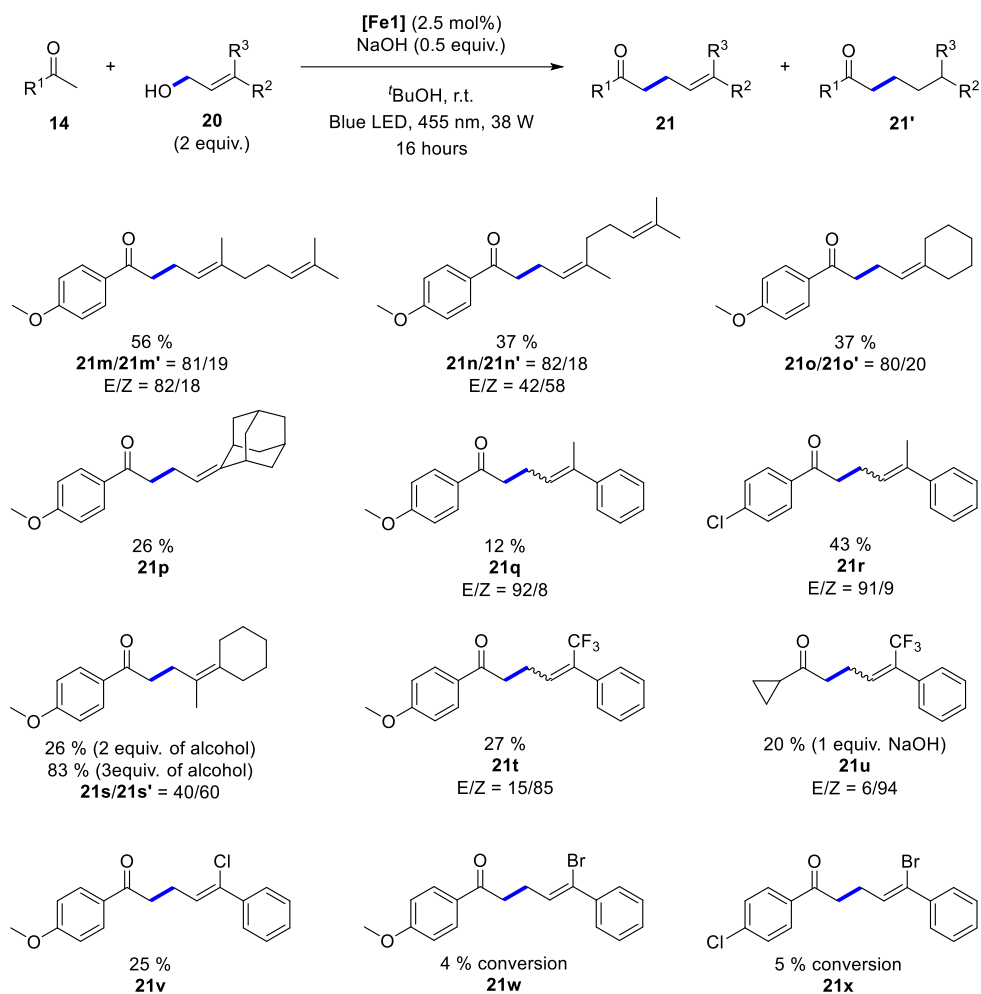
To extend the scope of this reaction, various allylic alcohols were synthesised (Scheme 5.22). Allylic alcohols **20d-h** were obtained in two steps from aliphatic and aromatic ketones *via* a sequence involving a Horner-Wadsworth-Emmons reaction to give a α,β -unsaturated ester, followed by a reduction with DIBAL to give the corresponding allylic alcohols. Halogen derivatives **20i-j** were prepared by treatment of acetophenone with either POCl₃ or PBr₃ to give the α,β -unsaturated aldehyde, followed by a reduction in the presence of NaBH₄.



Scheme 5.22: Synthesis of substituted allylic alcohols.

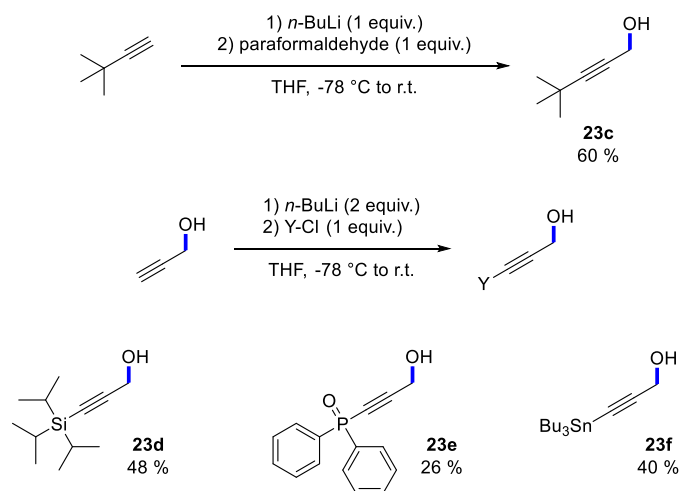
We investigated next our alkylation reaction using these different allylic alcohols (Scheme 5.23). Compounds **21m** and **21n** were obtained from geraniol and nerol in 56 and 37 % yield, respectively. In both cases, the product was isolated as a mixture of E/Z isomers. We hypothesized that the isomerisation may come from a photoinduced *cis-trans* isomerisation, as already reported in literature with similar products.²⁹⁶ The steric hindrance was also a key parameter as compound **21p** bearing an adamantylidene moiety was the only product of the reaction. Increasing the amount of allylic alcohol **20f** up to 4.5 equiv. did not improve the conversion with this pro-electrophile. Tetra-substituted allylic alcohols can also be engaged in this reaction and compound **21s** was isolated in 26 % yield. Increasing the amount of allylic alcohol **20e** to 3 equiv. led to a better yield (83 %). Surprisingly, in this example, the reduced compound **21s'** was the major product. Allylic alcohols bearing an aromatic ring were also tolerated in this reaction as compounds **21t-v** were isolated in 12 to 43 % yield and the saturated product was not observed. We suppose, once again, that both the steric hindrance and the electronic richness of the allylic alcohol are the two key parameters to avoid the reduction of the allylic moiety. Aliphatic ketones can also be engaged in this process and product **21u** was isolated in a modest 20 % yield with 1 equiv. of NaOH. Allylic alcohol **20i** led to the alkylated product **21v** in 25 % yield, however, the bromine derivative **20j** gave the alkylated product **21w-x** with only 4 and 5 % conversion.

²⁹⁶ Kozukue, N.; Park, M.-S.; Choi, S.-H.; Lee, S.-U.; Ohnishi-Kameyama, M.; Levin, C. E.; Friedman, M. J. *Agric. Food Chem.* **2007**, *55*, 7131-7139.



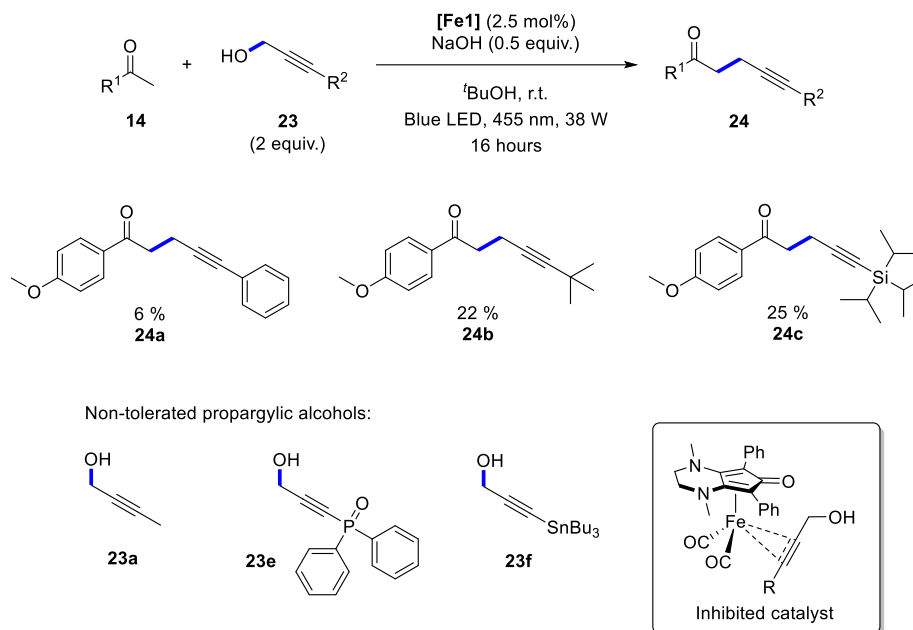
Scheme 5.23: Iron-catalysed alkylation of ketones with allylic alcohols.

Finally, this alkylation reaction was extended to propargylic alcohols as pro-electrophiles. The substituted propargylic alcohol **23c** was obtained in one step from 3,3-dimethylbut-1-yn and paraformaldehyde in 60 % yield (Scheme 5.24). The lithium anion of propargyl alcohol reacted with either TIPS-Cl, (Ph)₂P(O)-Cl or (Bu)₃Sn-Cl to provide the propargyl alcohols **23d-f** in 26 to 48 % yields (Scheme 5.24).



Scheme 5.24: Synthesis of substituted propargylic alcohols.

These pro-electrophiles were then engaged in the alkylation reaction (Scheme 5.25). The use of but-2-yn-1-ol **23a** as pro-electrophile led to no conversion. When 3-phenylpropargyl alcohol **23b** was engaged, the alkylated product was isolated in a low 6 % yield. Variation of the amount of alcohol **23b** from 1 to 5 equiv. did not change the conversion. We supposed that the coordination of the C≡C bond to the vacant site of the 16-electron deficient iron intermediate might inhibit the reaction. This hypothesis was confirmed when propargyl alcohol **23c** was engaged in this process, giving the alkylated product **24b** in 22 % yield. TIPS-protected alkyne **23d** was also suitable for this reaction and compound **24c** was obtained in 25 % yield. In the case of propargyl alcohol **23e**, we supposed that either the phosphine oxide was inhibiting the catalyst by coordination to the iron, or this substituent was not bulky enough to protect the alkyne, while the stannane derivative **23f** was degraded by NaOH during the reaction.

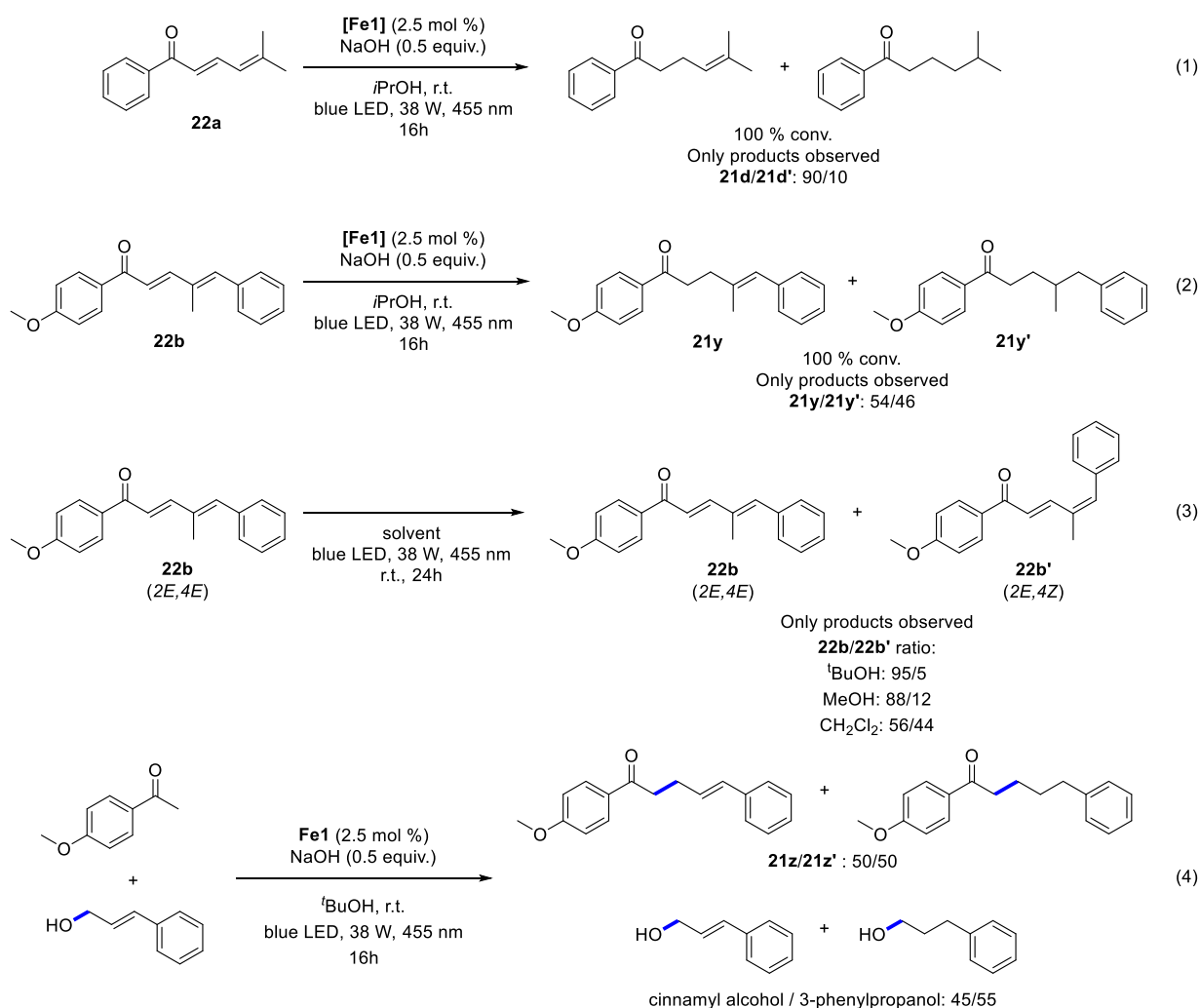


Scheme 5.25: Iron-catalysed alkylation of ketones with propargyl alcohols.

3) Mechanistic investigations.

To gain more insights on the mechanism of this alkylation reaction, several experiments were performed (Scheme 5.26). It was initially supposed that the saturated products **21'** were obtained *via* initial 1,4-reduction of the α,β -unsaturated aldehyde intermediate, followed by the alkylation with this latter. To verify this hypothesis, the dienone intermediate **22a** was reacted in the presence of NaOH (0.5 equiv.) and the iron complex **Fe1** (2.5 mol %) in isopropanol as solvent and hydride source under photoirradiation (Scheme 5.26, Eq. 1). A complete conversion was observed into the products **21d** and **21d'** in a 90/10 ratio (*versus* 86/14 for the alkylation reaction). This experiment highlighted the possible 1,6-reduction followed by a 1,4-reduction of the dienone intermediate by the iron complex. Therefore, the saturated product could be obtained either by a 1,4-reduction of the α,β -unsaturated aldehyde intermediate followed by an alkylation with this latter, or a 1,6-reduction of the dienone intermediate. In a second experiment, the dienone intermediate **22b** was reacted in the same conditions (Scheme 5.26, Eq. 2). In this case, products **21y** and **21y'** were obtained in a 54/46 ratio, confirming the role of the di-substitution of the allylic alcohols in C3-position, which generates steric hindrance and therefore avoid the double bond reduction. In a third experiment, dienone **22b** was placed under light for 24 hours to check the effect of light regarding the isomerisation of the dienone intermediate (Scheme 5.26, Eq. 3).

Due to the presence of two double bonds, four isomers can be obtained. However, only two products were observed after photoirradiation, whatever the solvent used, and one of them being the starting dienone **22b**. Selective NOESY experiments allowed to identify **22b'** as the only isomerisation product of this reaction. The different ratios obtained depend on the solubility of the dienone in the solvent: a poor solubility in ^tBuOH and MeOH did not favour the isomerisation (**22b/22b'**: 95/5 and 88/12, respectively) while CH₂Cl₂, as solvent, allowed a total solubility of the product facilitating the isomerisation of the dienone **22b** and led to a 56/44 ratio. Finally, the alkylation of 4-methoxyacetophenone with cinnamyl alcohol was performed (Scheme 5.26, Eq. 4). Analysis of the crude mixture by ¹H NMR showed the alkylated products **21z** and **21z'** in a 50/50 ratio along with the 3-phenylpropanol in an almost equimolar ratio with cinnamyl alcohol. This last experiment highlights the non-desired 1,4-reduction of the α,β -unsaturated aldehyde intermediate and the difficulty to use mono- or non-substituted allyl alcohols in such reactions.



Scheme 5.26: Mechanistic investigation.

VII. Conclusion.

A novel light-induced iron-catalysed α -alkylation of ketones at room temperature was described using alcohols as alkylating agents. These results demonstrate the versatility of cyclopentadienone iron complexes in a variety of reaction conditions using the borrowing hydrogen methodology. This new strategy highlights the potential of these complexes in organic synthesis and catalysis, and could extend the scope of such reactions in terms of substrates and functional tolerance. As demonstrated in this chapter, the alkylation reaction between two aliphatic substrates is now possible, as well as the use of allylic and propargylic alcohols as pro-electrophiles. The development of an efficient asymmetric version could also be envisioned thanks to these mild reaction conditions.

VIII. Experimental part.

1) General considerations.

All air- and moisture-sensitive manipulations were carried out using standard vacuum line Schlenk tubes techniques. The photocatalysed reactions were run in an Hepatochem HCK1006-01-025 PhotoredoxBox or PhotoredoxBox Duo irradiated with (1) a 38 W A 160WE Tuna Blue Kessil lamp (455 nm); (2) a 5 W Diall Blue LED lamp; (3) a 23 W E27 220-240V CDL 865 Phillips cold white lamp; (4) a 32 W E27 230-240V WW 827 Philips warm white lamp; (5) a 18 W Green EvoluChem P203-18-1 (525 nm); or (6) a 18 W Blue EvoluChem 425PF lamp (425 nm). Solvents were degazed prior to use by bubbling argon gas directly in the solvent. Silica was purchased from Carlo Erba (60Å 40-63µ). Deuterated solvents for NMR spectroscopy were purchased from Eurisotope and used as received. NMR spectra were recorded on a 500 MHz or 600 MHz Brücker spectrometer. Proton (¹H) NMR information is given in the following format: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet), coupling constant(s) (*J*) in Hertz (Hz), number of protons, type. Carbon (¹³C) NMR spectra are reported in ppm (δ) relative to CDCl₃ unless noted otherwise. Infrared spectra were recorded over a PerkinElmer Spectrum 100 FT-IR Spectrometer using neat conditions. HRMS (ESI-TOF) *m/z* analyses were performed by Laboratoire de Chimie Moléculaire et Thioorganique analytical Facilities. Emission spectra were measured at room temperature in liquid state on a Perkin Elmer LS 55 spectrofluorometer. UV-visible absorption spectrum in solution was measured at room temperature on a Perkin Elmer Lambda 40 UV-visible spectrometer.

2) Blue-light induced iron-catalysed α-alkylation of ketones.

a) Alkylation reactions.

General procedure A:

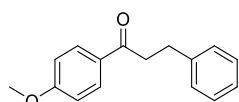
In a 10 mL vial, the desired ketone (0.5 mmol, 1.0 equiv.), aryl alcohol (1.3 mmol, 2.5 equiv.), NaOH (40 mol%, 19.22 mg, 0.2 mmol), **Fe1** (2.5 mol%, 5.892 mg, 0.0125 mmol), ^tBuOH (1.0 mL) were poured in under an argon atmosphere. The reaction tube was sealed. The mixture was stirred at room temperature and exposed to blue light (455 nm, 40 W) for 16 hours. The mixture was filtrated on celite, eluted with diethyl ether and concentrated under reduced pressure. The conversion was determined by ¹H NMR spectroscopy. The residue was purified by silica gel chromatography using pentane/diethyl ether as eluent to afford the desired product.

General procedure B:

In a 10 mL vial, the desired ketone (0.5 mmol, 1.0 equiv.), aryl alcohol (1.3 mmol, 2.5 equiv.), NaOH (40 mol%, 19.22 mg, 0.2 mmol), **Fe1** (2.5 mol%, 5.892 mg, 0.0125 mmol), ^tBuOH (1.0 mL) were poured in under an argon atmosphere. The reaction tube was sealed. The mixture was stirred at room temperature and exposed to green light (525 nm, 18 W) for 16 hours. The mixture was filtrated on celite, eluted with diethyl ether and concentrated under reduced pressure. The conversion was determined by ¹H NMR spectroscopy. The residue was purified by silica gel chromatography using pentane-diethyl ether as eluent to afford the desired product.

General Procedure C:

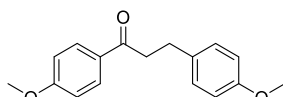
In a 10 mL vial, the desired ketone (0.5 mmol, 1.0 equiv.), aryl alcohol (1.3 mmol, 2.5 equiv.), NaOH (2 equiv., 40.00 mg, 1.0 mmol), **Fe1** (2.5 mol%, 5.892 mg, 0.0125 mmol), ^tBuOH (1.0 mL) were poured in under an argon atmosphere. The reaction tube was sealed. The mixture was stirred at room temperature and exposed to blue light (455 nm, 40 W) for 16 hours. The mixture was filtrated on celite, eluted with diethyl ether and concentrated under reduced pressure. The conversion was determined by ¹H NMR spectroscopy. The residue was purified by silica gel chromatography using pentane-diethyl ether as eluent to afford the desired product.



Chemical Formula: C₁₆H₁₆O₂

- **1-(4-methoxyphenyl)-3-phenylpropan-1-one (15a)**^{23a}

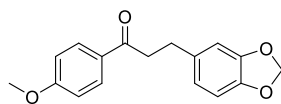
According to general procedure A, using 1-(4-methoxyphenyl)ethan-1-one (75.58 mg, 0.5 mmol, 1.0 equiv.), benzyl alcohol (103.0 μL, 1.3 mmol, 2.5 equiv.), NaOH (40 mol%, 7.994 mg, 0.2 mmol), **Fe1** (2.5 mol%, 5.892 mg, 0.0125 mmol), ^tBuOH (1.0 mL), the product was obtained as a white solid (0.077 g, 65 % yield) after purification by silica gel column chromatography (pentane/ether (9:1)). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.97 – 7.92 (m, 2H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.25 (s, 1H), 7.21 (t, *J* = 7.1 Hz, 2H), 6.94 – 6.90 (m, 2H), 3.87 (s, 3H), 3.25 (dd, *J* = 8.6, 6.9 Hz, 2H), 3.08 – 3.03 (m, 2H). ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 197.9, 163.5, 141.6, 130.4, 130.1, 128.6, 128.5, 126.2, 113.8, 55.6, 40.2, 30.4.



Chemical Formula: C₁₇H₁₈O₃

- **1,3-bis(4-methoxyphenyl)propan-1-one (15b)**^{23a}

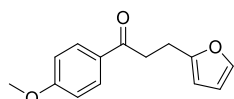
According to general procedure A, using 1-(4-methoxyphenyl)ethan-1-one (75.58 mg, 0.5 mmol, 1.0 equiv.), NaOH (40 mol%, 7.994 mg, 0.2 mmol), (4-methoxyphenyl)methanol (179.613 mg, 1.3 mmol, 2.5 equiv.), **Fe1** (2.5 mol%, 5.892 mg, 0.0125 mmol), ^tBuOH (1.0 mL), the product was obtained as a yellow oil (0.115 g, 85 % yield) after purification by silica gel column chromatography (pentane/ether (95:5)). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.96 – 7.92 (m, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 6.94 – 6.90 (m, 2H), 6.86 – 6.82 (m, 2H), 3.87 (s, 3H), 3.79 (s, 3H), 3.21 (dd, *J* = 8.5, 6.9 Hz, 2H), 3.02 – 2.97 (m, 2H). ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 198.1, 163.5, 158.0, 133.6, 130.4, 130.1, 129.4, 114.0, 113.8, 55.6, 55.4, 40.5, 29.6.



Chemical Formula: C₁₇H₁₆O₄

- **3-(benzo[d][1,3]dioxol-5-yl)-1-(4-methoxyphenyl)propan-1-one (15c)**^{23a}

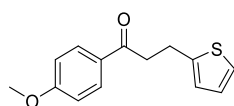
According to general procedure A, using 1-(4-methoxyphenyl)ethan-1-one (75.58 mg, 0.5 mmol, 1.0 equiv.), benzo(d)(1,3)dioxo-5-ylmethanol (197.795 mg, 1.3 mmol, 2.5 equiv.), NaOH (40 mol%, 7.994 mg, 0.2 mmol), **Fe1** (2.5 mol%, 5.892 mg, 0.0125 mmol), ^tBuOH (1.0 mL), the product was obtained as a white solid (0.104 g, 74 % yield) after purification by silica gel column chromatography (pentane/ether (9:1)). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.94 (d, *J* = 8.9 Hz, 2H), 6.92 (dd, *J* = 9.3, 2.3 Hz, 2H), 6.74 (d, *J* = 1.3 Hz, 1H), 6.73 (s, 1H), 6.69 (dd, *J* = 7.9, 1.4 Hz, 1H), 5.92 (s, 2H), 3.87 (s, 3H), 3.23 – 3.18 (m, 2H), 3.00 – 2.95 (m, 2H). ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 197.9, 163.5, 147.7, 145.9, 135.4, 130.4, 130.1, 121.3, 113.8, 109.0, 108.4, 100.9, 55.6, 40.4, 30.2.



Chemical Formula: C₁₄H₁₄O₃

- **3-(furan-2-yl)-1-(4-methoxyphenyl)propan-1-one (15d)**^{23a}

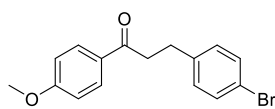
According to general procedure A, using 1-(4-methoxyphenyl)ethan-1-one (75.58 mg, 0.5 mmol, 1.0 equiv.), NaOH (40 mol%, 7.994 mg, 0.2 mmol), furan-2-yl-methanol (113.0 μL, 1.3 mmol, 2.5 equiv.), **Fe1** (2.5 mol%, 5.892 mg, 0.0125 mmol), ^tBuOH (1.0 mL), the product was obtained as a white solid (0.071 g, 62 % yield) after purification by silica gel column chromatography (pentane/ether (9:1)). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.98 – 7.93 (m, 2H), 7.32 – 7.29 (m, 1H), 6.93 (d, *J* = 8.9 Hz, 2H), 6.28 (dd, *J* = 3.0, 1.9 Hz, 1H), 6.04 (dd, *J* = 3.1, 0.6 Hz, 1H), 3.87 (s, 3H), 3.28 (dd, *J* = 8.4, 6.7 Hz, 2H), 3.10 – 3.05 (m, 2H). ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 197.3, 163.6, 155.0, 141.1, 130.4, 129.9, 113.8, 110.3, 105.3, 55.6, 36.6, 22.7.



Chemical Formula: C₁₄H₁₄O₂S

- **1-(4-methoxyphenyl)-3-(thiophen-2-yl)propan-1-one (15e)**^{23a}

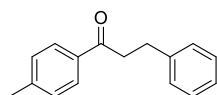
According to general procedure B, using 1-(4-methoxyphenyl)ethan-1-one (75.58 mg, 0.5 mmol, 1.0 equiv.), thiophen-2-ylmethanol (141.0 μL, 1.3 mmol, 2.5 equiv.), NaOH (40 mol%, 7.994 mg, 0.2 mmol), **Fe1** (2.5 mol%, 5.892 mg, 0.0125 mmol), ^tBuOH (1.0 mL), the product was obtained as a white solid (0.068 g, 55 % yield) after purification by silica gel column chromatography (pentane/ether (9:1)). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.98 – 7.93 (m, 2H), 7.12 (dd, *J* = 5.1, 1.1 Hz, 1H), 6.95 – 6.92 (m, 2H), 6.92 (d, *J* = 3.4 Hz, 1H), 6.87 – 6.84 (m, 1H), 3.87 (s, 3H), 3.35 – 3.23 (m, 4H). ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 197.2, 163.6, 144.2, 130.4, 129.9, 126.9, 124.7, 123.4, 113.8, 55.5, 40.2, 24.4.



Chemical Formula: C₁₆H₁₅BrO₂

- **3-(4-bromophenyl)-1-(4-methoxyphenyl)propan-1-one (15f)**^{23a}

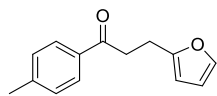
According to general procedure A, using 1-(4-methoxyphenyl)ethan-1-one (75.58 mg, 0.5 mmol, 1.0 equiv.), NaOH (40 mol%, 7.994 mg, 0.2 mmol), (4-bromoxyphenyl)methanol (243.152 mg, 1.3 mmol, 2.5 equiv.), **Fe1** (2.5 mol%, 5.892 mg, 0.0125 mmol), ^tBuOH (1.0 mL), the product was obtained as a white solid (0.108 g, 50 % yield) after purification by silica gel column chromatography (pentane/ether (9:1)). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.92 (d, *J* = 8.8 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.12 (d, *J* = 8.2 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 3.22 (t, *J* = 7.6 Hz, 2H), 3.00 (t, *J* = 7.5 Hz, 2H). ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 197.5, 163.6, 140.5, 131.6, 130.4, 130.3, 129.9, 119.9, 113.9, 55.6, 39.8, 29.7.



Chemical Formula:
C₁₆H₁₆O

- **3-phenyl-1-(p-toyl)propan-1-one (15g)**^{23a}

According to general procedure A, using 1-(4-methylphenyl)ethan-1-one (67.0 μL, 0.5 mmol, 1.0 equiv.), benzyl alcohol (135.0 μL, 1.3 mmol, 2.5 equiv.), NaOH (40 mol%, 7.994 mg, 0.2 mmol), **Fe1** (2.5 mol%, 5.892 mg, 0.0125 mmol), ^tBuOH (1.0 mL), the product was obtained as a white solid (0.112 g, 99 % yield) after purification by silica gel column chromatography (pentane/ether (95:5)). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.85 – 7.82 (m, 2H), 7.30 – 7.25 (m, 2H), 7.24 – 7.21 (m, 4H), 7.18 (ddd, *J* = 6.5, 2.8, 1.4 Hz, 1H), 3.27 – 3.23 (m, 2H), 3.06 – 3.01 (m, 2H), 2.38 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 199.0, 143.9, 141.5, 134.5, 129.4, 128.6, 128.5, 128.3, 126.2, 40.4, 30.3, 21.7.



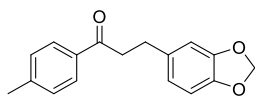
Chemical Formula: C₁₄H₁₄O₂

- **3-(furan-2-yl)-1-(p-tolyl)propan-1-one (15h)**²⁹⁷

According to general procedure A, using 1-(4-methylphenyl)ethan-1-one (67.0 μL, 0.5 mmol, 1.0 equiv.), furan-2-yl-methanol (113.0 μL, 1.3 mmol, 2.5 equiv.), NaOH (40 mol%, 7.994 mg, 0.2 mmol), **Fe1** (2.5 mol%, 5.892 mg, 0.0125 mmol), ^tBuOH (1.0 mL), the product was obtained as a white solid (0.082 g, 49 % yield) after purification by silica gel column chromatography (pentane/ether (9:1)). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.90 – 7.86 (m, 2H), 7.31 (dd, *J* = 1.8, 0.6 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 6.28 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.05 (dd, *J* = 3.1, 0.7 Hz, 1H), 3.33 – 3.28 (m, 2H), 3.11 – 3.06

²⁹⁷ Shimizu, K.-I.; Sato, R.; Satsuma, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 3982-3986.

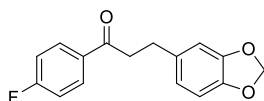
(m, 2H), 2.41 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 198.4, 154.9, 144.0, 141.1, 134.3, 129.4, 128.2, 110.3, 105.3, 36.9, 22.6, 21.7.



Chemical Formula: $\text{C}_{17}\text{H}_{16}\text{O}_3$

- **3-(benzo[d][1,3]dioxol-5-yl)-1-(p-tolyl)propan-1-one (15i)**

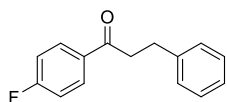
According to general procedure A, using 1-(4-methylphenyl)ethan-1-one (67.0 μL , 0.5 mmol, 1.0 equiv.), benzo(d)(1,3)dioxo-5-ylmethanol (197.795 mg, 1.3 mmol, 2.5 equiv.), NaOH (40 mol%, 7.994 mg, 0.2 mmol), **Fe1** (2.5 mol%, 5.892 mg, 0.0125 mmol), $^t\text{BuOH}$ (1.0 mL), the product was obtained as a colorless oil (0.031 g, 23 % yield) after purification by silica gel column chromatography (pentane/ether (95:5)). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.88 – 7.83 (m, 2H), 7.25 (d, $J = 8.1$ Hz, 2H), 6.75 – 6.72 (m, 2H), 6.71 – 6.68 (m, 1H), 5.92 (s, 2H), 3.23 (dd, $J = 8.3, 7.0$ Hz, 2H), 3.01 – 2.95 (m, 2H), 2.41 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 199.0, 147.7, 145.9, 144.0, 135.3, 134.5, 129.4, 128.3, 121.3, 109.0, 108.4, 100.9, 40.7, 30.1, 21.7. IR (neat): ν 2895, 2159, 2030, 1678, 1606, 1487, 1442, 1242, 1201, 1036, 927, 804 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{17}\text{O}_3$: 269.1178; found 269.1176.



Chemical Formula: $\text{C}_{16}\text{H}_{13}\text{FO}_3$

- **3-(benzo[d][1,3]dioxol-5-yl)-1-(4-fluorophenyl)propan-1-one (15j)**

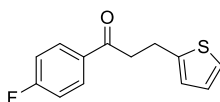
According to general procedure A, using 1-(4-fluorophenyl)ethan-1-one (70.0 μL , 0.5 mmol, 1.0 equiv.), benzo(d)(1,3)dioxo-5-ylmethanol (197.795 mg, 1.3 mmol, 2.5 equiv.), NaOH (40 mol%, 7.994 mg, 0.2 mmol), **Fe1** (2.5 mol%, 5.892 mg, 0.0125 mmol), $^t\text{BuOH}$ (1.0 mL), the product was obtained as a yellow oil (0.112 g, 83 % yield) after purification by silica gel column chromatography (pentane/ether (9:1)). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 8.00 – 7.95 (m, 2H), 7.15 – 7.09 (m, 2H), 6.75 – 6.72 (m, 2H), 6.69 (dd, $J = 7.9, 1.5$ Hz, 1H), 5.92 (s, 2H), 3.25 – 3.20 (m, 2H), 2.98 (t, $J = 7.6$ Hz, 2H). ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 197.7, 166.8, 164.8, 147.8, 146.0, 135.0, 133.4 (d, $J = 3.0$ Hz), 130.8, 130.7, 121.3, 115.9, 115.7, 109.0, 108.4, 100.9, 40.7, 29.9. ^{19}F NMR (471 MHz, CDCl_3) δ (ppm): -105.2. IR (neat): ν 2905, 2786, 1681, 1598, 1499, 1486, 1435, 1407, 1358, 1224, 1201, 1148, 1036, 988, 920, 842, 801, 586, 531, 491 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{13}\text{O}_3\text{FNa}$: 295.0746; found 295.0744.



Chemical Formula: C₁₅H₁₃FO

- **1-(4-fluorophenyl)-3-phenylpropan-1-one (15k)**^{23a}

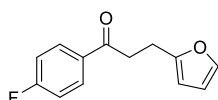
According to general procedure A, using 1-(4-fluorophenyl)ethan-1-one (70.0 μ L, 0.5 mmol, 1.0 equiv.), benzyl alcohol (135.0 μ L, 1.3 mmol, 2.5 equiv.), NaOH (40 mol%, 7.994 mg, 0.2 mmol), **Fe1** (2.5 mol%, 5.892 mg, 0.0125 mmol), ^tBuOH (1.0 mL), the product was obtained as a white solid (0.086 g, 75 % yield) after purification by silical gel column chromatography (pentane/ether (9:1)). **¹H NMR (500 MHz, CDCl₃) δ (ppm):** 7.97 – 7.92 (m, 2H), 7.30 – 7.25 (m, 2H), 7.24 – 7.20 (m, 2H), 7.20 – 7.16 (m, 1H), 7.10 – 7.05 (m, 2H), 3.26 – 3.21 (m, 2H), 3.06 – 3.01 (m, 2H). **¹³C NMR (125 MHz, CDCl₃) δ (ppm):** 197.6, 166.7, 164.7, 141.2, 133.34 (d, *J* = 3.0 Hz), 130.7, 130.6, 128.6, 128.4, 126.2, 115.8, 115.6, 40.4, 30.1.



Chemical Formula: C₁₃H₁₁FOS

- **1-(4-fluorophenyl)-3-(thiophen-2-yl)propan-1-one (15l)**²⁹⁸

According to general procedure B, using 1-(4-fluorophenyl)ethan-1-one (70.0 μ L, 0.5 mmol, 1.0 equiv.), thiophen-2-ylmethanol (141.0 μ L, 1.3 mmol, 2.5 equiv.), NaOH (40 mol%, 7.994 mg, 0.2 mmol), **Fe1** (2.5 mol%, 5.892 mg, 0.0125 mmol), ^tBuOH (1.0 mL), the product was obtained as a colorless oil (0.085 g, 73 % yield) after purification by silica gel column chromatography (pentane/ether (9:1)). **¹H NMR (500 MHz, CDCl₃) δ (ppm):** 8.02 – 7.97 (m, 2H), 7.16 – 7.10 (m, 3H), 6.92 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.87 – 6.85 (m, 1H), 3.36 – 3.32 (m, 2H), 3.31 – 3.27 (m, 2H). **¹³C NMR (125 MHz, CDCl₃) δ (ppm):** 197.1, 166.9, 164.9, 143.8, 133.30 (d, *J* = 3.0 Hz), 130.80 (d, *J* = 9.3 Hz), 127.0, 124.8, 123.5, 115.9, 115.7, 40.6, 24.3.



Chemical Formula:
C₁₃H₁₁FO₂

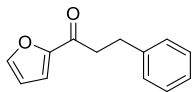
- **1-(4-fluorophenyl)-3-(furan-2-yl)propan-1-one (15m)**²⁹⁹

According to general procedure A, using 1-(4-fluorophenyl)ethan-1-one (70.0 μ L, 0.5 mmol, 1.0 equiv.), furan-2-yl-methanol (113.0 μ L, 1.3 mmol, 2.5 equiv.), NaOH (40 mol%, 7.994 mg, 0.2 mmol), **Fe1** (2.5 mol%, 5.892 mg, 0.0125 mmol), ^tBuOH (1.0 mL), the product was obtained as a colorless oil (0.043 g, 40 % yield) after purification by silica gel column chromatography (pentane/ether (9:1)). **¹H NMR (500 MHz, CDCl₃) δ (ppm):** 8.03 – 7.97 (m, 2H), 7.31 (dd, *J* = 1.7, 0.6 Hz, 1H), 7.16 – 7.10 (m, 2H), 6.28

²⁹⁸ Patent number WO2004/011410A1.

²⁹⁹ Patent number WO98/25896A1.

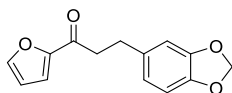
(dd, $J = 3.1, 1.9$ Hz, 1H), 6.05 (dd, $J = 3.1, 0.8$ Hz, 1H), 3.31 (dd, $J = 8.2, 6.8$ Hz, 2H), 3.09 (t, $J = 7.4$ Hz, 2H). ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 197.2, 166.9, 164.9, 154.7, 141.2, 133.3 (d, $J = 3.0$ Hz), 130.8 (d, $J = 9.3$ Hz), 115.8 (d, $J = 21.9$ Hz), 110.4, 105.5, 37.0, 22.6.



Chemical Formula: $\text{C}_{13}\text{H}_{12}\text{O}_2$

- **1-(2-Furyl)-3-phenyl-1-propanone (15n)**^{23a}

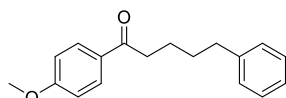
According to general procedure A, using (2-furyl)ethan-1-one (55.06 mg, 0.5 mmol, 1.0 equiv.), benzyl alcohol (135.0 μL , 1.3 mmol, 2.5 equiv.), NaOH (40 mol%, 7.994 mg, 0.2 mmol), **Fe1** (5 mol%, 11.78 mg, 0.025 mmol), $^t\text{BuOH}$ (1.0 mL), the product was obtained as a colorless oil (0.076 g, 76 % yield) after purification by silica gel column chromatography (pentane/ether (9:1)). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.57 (dd, $J = 1.7, 0.7$ Hz, 1H), 7.29 (d, $J = 7.2$ Hz, 2H), 7.25 (t, $J = 4.1$ Hz, 2H), 7.20 (t, $J = 7.2$ Hz, 1H), 7.17 (dd, $J = 3.6, 0.7$ Hz, 1H), 6.52 (dd, $J = 3.5, 1.7$ Hz, 1H), 3.18 – 3.13 (m, 2H), 3.07 – 3.02 (m, 2H). ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 188.6, 152.8, 146.4, 141.1, 128.6, 128.5, 126.3, 117.1, 112.3, 40.3, 30.1.



Chemical Formula: $\text{C}_{14}\text{H}_{12}\text{O}_4$

- **1-(2-Furyl)-3-(benzo[d][1,3]dioxol-5-yl)-1-propanone (15o)**^{23a}

According to general procedure A, using (2-furyl)ethan-1-one (55.06 mg, 0.5 mmol, 1.0 equiv.), benzo(d)(1,3)dioxo-5-ylmethanol (197.8 mg, 1.3 mmol, 2.5 equiv.), NaOH (40 mol%, 7.994 mg, 0.2 mmol), **Fe1** (5 mol%, 11.78 mg, 0.025 mmol), $^t\text{BuOH}$ (1.0 mL), the product was obtained as a colorless oil (0.067 g, 55 % yield) after purification by silica gel column chromatography (pentane/ether (9:1)). ^1H NMR (500 MHz, CDCl_3) δ (ppm): 7.57 (dd, $J = 1.5, 0.5$ Hz, 1H), 7.17 (dd, $J = 3.5, 0.5$ Hz, 1H), 6.73 (d, $J = 2.1$ Hz, 1H), 6.72 (s, 1H), 6.68 (dd, $J = 7.9, 1.5$ Hz, 1H), 6.52 (dd, $J = 3.6, 1.7$ Hz, 1H), 5.91 (s, 2H), 3.13 – 3.08 (m, 2H), 2.96 (t, $J = 7.7$ Hz, 2H). ^{13}C NMR (125 MHz, CDCl_3) δ (ppm): 188.5, 152.8, 147.7, 146.4, 146.0, 134.9, 121.3, 117.1, 112.3, 109.0, 108.4, 100.9, 40.5, 29.8.



Chemical Formula: $\text{C}_{18}\text{H}_{20}\text{O}_2$

- **1-(4-methoxyphenyl)-5-phenylpentan-1-one (15p)**³⁰⁰

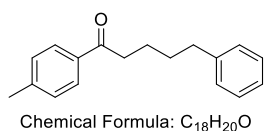
According to general procedure A, using 1-(4-methoxyphenyl)ethan-1-one (75.58 mg, 0.5 mmol, 1.0 equiv.), NaOH (19.985 mg, 0.5 mmol, 1.0 equiv.), 3-phenyl-1-propanol (177.0 μL , 1.3 mmol, 2.5

³⁰⁰ Patent number CN103330701A.

equiv.), **Fe1** (2.5 mol%, 5.892 mg, 0.0125 mmol), ^tBuOH (1.0 mL), the product was obtained as a colorless oil (0.098 g, 73 % yield) after purification by silica gel column chromatography (pentane/ether (9:1)). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.93 (d, *J* = 8.9 Hz, 2H), 7.30 – 7.25 (m, 2H), 7.20 – 7.15 (m, 3H), 6.95 – 6.90 (m, 2H), 3.87 (s, 3H), 2.96 – 2.91 (m, 2H), 2.66 (t, *J* = 7.5 Hz, 2H), 1.78 (dd, *J* = 14.8, 7.8 Hz, 2H), 1.75 – 1.67 (m, 2H). ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 199.0, 163.4, 142.4, 130.4, 128.5, 128.4, 125.8, 125.8, 113.8, 55.5, 38.2, 35.9, 31.3, 24.3.

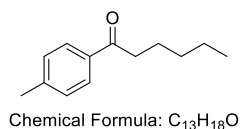
- **Scale-up to 2.5 mmol scale reaction:**

According to general procedure A, using 1-(4-methoxyphenyl)ethan-1-one (188.95 mg, 2.5 mmol, 1.0 equiv.), NaOH (49.96 mg, 2.5 mmol, 1.0 equiv.), 3-phenyl-1-propanol (443.0 μL, 3.25 mmol, 2.5 equiv.), **Fe1** (5 mol%, 57.05 mg, 0.125 mmol), ^tBuOH (5.0 mL), the product was obtained as a colorless oil (0.363 g, 54 % yield) after purification by silica gel column chromatography (pentane/ether (9:1)). ¹H NMR data was comparable with previous NMR data.



- **5-phenyl-1-(*p*-tolyl)pentan-1-one (15q)**³⁰¹

According to general procedure A, using 1-(4-methylphenyl)ethan-1-one (67.0 μL, 0.5 mmol, 1.0 equiv.), 4-phenylbutan-1-ol (177.0 μL, 1.3 mmol, 2.5 equiv.), NaOH (19.985 mg, 0.5 mmol, 1.0 equiv.), **Fe1** (2.5 mol%, 5.892 mg, 0.0125 mmol), ^tBuOH (1.0 mL), the product was obtained as a colorless oil (0.097 g, 77 % yield) after purification by silica gel column chromatography (pentane/ether (95:5)). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.86 – 7.83 (m, 2H), 7.30 – 7.23 (m, 4H), 7.21 – 7.15 (m, 3H), 2.99 – 2.94 (m, 2H), 2.70 – 2.64 (m, 2H), 2.41 (s, 3H), 1.83 – 1.76 (m, 2H), 1.72 (ddd, *J* = 8.9, 7.6, 5.6 Hz, 2H). ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 200.1, 143.8, 142.4, 134.7, 129.3, 128.5, 128.4, 128.3, 125.8, 38.4, 35.9, 31.2, 24.2, 21.7.

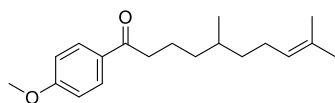


- **1-(4-Methylphenyl)-1-hexanone (15r)**

According to general procedure A, using 1-(4-methylphenyl)ethan-1-one (67.0 μL, 0.5 mmol, 1.0 equiv.), 1-butanol (119.0 μL, 1.3 mmol, 2.5 equiv.), NaOH (19.985 mg, 0.5 mmol, 1.0 equiv.), **Fe1** (2.5 mol%, 5.892 mg, 0.0125 mmol), ^tBuOH (1.0 mL), the product was obtained as a colorless oil (0.043 g, 45 % yield) after purification by silica gel column chromatography (pentane/ether (95:5)). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.89 – 7.82 (m, 2H), 7.24 (d, *J* = 7.9 Hz, 2H), 2.95 – 2.88 (m, 2H), 2.40 (s, 3H), 1.76 – 1.68 (m, 2H), 1.39 – 1.31 (m, 4H), 0.93 – 0.87 (m, 3H). ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 200.3, 143.6, 134.7, 129.3, 128.2, 38.5, 31.6, 24.2, 22.6, 21.6, 14.0. IR (neat): ν 2987, 2159,

³⁰¹ Crawley, M. L.; Phipps, K. M.; Goljer, I.; Mehlmann, J. F.; Lundquist, J. T.; Ullrich, J. W.; Yang, C.; Mahaney, P. E. *Org. Lett.* **2009**, *11*, 5, 1183-1185.

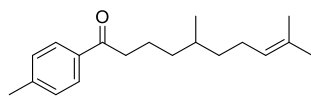
2029, 1977, 1393, 1242, 1065 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{13}\text{H}_{19}\text{O}$: 191.1436; found 191.1432.



Chemical Formula: $\text{C}_{19}\text{H}_{28}\text{O}_2$

• **1-(4-methoxyphenyl)-5,9-dimethyldec-8-en-1-one (15s)**

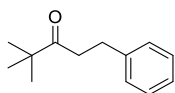
According to general procedure A, using 1-(4-methoxyphenyl)ethan-1-one (75.58 mg, 0.5 mmol, 1.0 equiv.), NaOH (19.985 mg, 0.5 mmol, 1.0 equiv.), citronellol (237.0 μL , 1.3 mmol, 2.5 equiv.), **Fe1** (2.5 mol%, 5.892 mg, 0.0125 mmol), $t\text{BuOH}$ (1.0 mL), the product was obtained as a yellow oil (0.053 g, 37 % yield) after purification by silica gel column chromatography (pentane/ether (9:1)). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ (ppm): 7.96 – 7.92 (m, 2H), 6.95 – 6.91 (m, 2H), 5.09 (tdd, $J = 5.8, 2.7, 1.4$ Hz, 1H), 3.87 (s, 3H), 2.91 – 2.87 (m, 2H), 1.96 (dt, $J = 21.6, 14.4, 7.1$ Hz, 2H), 1.81 – 1.69 (m, 2H), 1.68 (d, $J = 0.9$ Hz, 3H), 1.60 (s, 3H), 1.45 (ddd, $J = 16.2, 11.0, 5.0$ Hz, 1H), 1.40 – 1.30 (m, 2H), 1.24 – 1.10 (m, 2H), 0.89 (d, $J = 6.6$ Hz, 3H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ (ppm): 199.3, 163.4, 131.2, 130.4, 130.3, 125.0, 113.8, 55.5, 38.7, 37.1, 36.8, 32.5, 25.8, 25.6, 22.3, 19.6, 17.7. IR (neat): ν 2955, 2913, 2851, 1675, 1599, 1509, 1458, 1256, 1169, 1031, 909, 828, 731, 568 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{29}\text{O}_2$: 289.2168; found 289.2162.



Chemical Formula: $\text{C}_{19}\text{H}_{28}\text{O}$

• **5,9-dimethyl-1-(p-tolyl)dec-8-en-1-one (15t)**

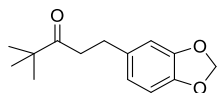
According to general procedure A, using 1-(4-methylphenyl)ethan-1-one (67.0 μL , 0.5 mmol, 1.0 equiv.), NaOH (19.985 mg, 0.5 mmol, 1.0 equiv.), citronellol (237.0 μL , 1.3 mmol, 2.5 equiv.), **Fe1** (2.5 mol%, 5.892 mg, 0.0125 mmol), $t\text{BuOH}$ (1.0 mL), the product was obtained as a yellow oil (0.024 g, 25 % yield) after purification by silica gel column chromatography (pentane/ether (9:1)). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ (ppm): 7.88 – 7.84 (m, 2H), 7.25 (d, $J = 7.7$ Hz, 2H), 5.11 – 5.07 (m, 1H), 2.94 – 2.88 (m, 2H), 2.41 (s, 3H), 2.03 – 1.88 (m, 2H), 1.81 – 1.72 (m, 1H), 1.73 – 1.69 (m, 1H), 1.68 (d, $J = 0.9$ Hz, 3H), 1.60 (s, 3H), 1.49 – 1.41 (m, 1H), 1.36 (dddd, $J = 13.3, 11.8, 8.6, 5.4$ Hz, 2H), 1.24 – 1.10 (m, 2H), 0.89 (d, $J = 6.6$ Hz, 3H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ (ppm): 200.4, 143.7, 134.7, 131.2, 129.3, 128.3, 125.0, 38.9, 37.1, 36.8, 32.4, 25.8, 25.6, 22.1, 21.7, 19.6, 17.7. IR (neat): ν 2957, 2922, 2865, 1682, 1607, 1453, 1376, 1263, 1180, 974, 806, 749, 699, 597 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{19}\text{H}_{29}\text{O}$: 273.2218; found 273.2228.



Chemical Formula: C₁₃H₁₈O

- **4,4-dimethyl-1-phenylpentan-3-one (15u)**^{23a}

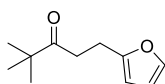
According to general procedure A, using pivalone (63.0 μ L, 0.5 mmol, 1.0 equiv.), NaOH (19.985 mg, 0.5 mmol, 1.0 equiv.), benzyl alcohol (135.0 μ L, 1.3 mmol, 2.5 equiv.), **Fe1** (2.5 mol%, 5.892 mg, 0.0125 mmol), ^tBuOH (1.0 mL), the product was obtained as a colorless oil (0.068 g, 72 % yield) after purification by silica gel column chromatography (pentane/ether (9:1)). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.30 – 7.26 (m, 2H), 7.21 – 7.17 (m, 3H), 2.90 – 2.85 (m, 2H), 2.80 (ddd, *J* = 8.4, 5.6, 1.9 Hz, 2H), 1.11 (s, 9H). ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 215.1, 141.7, 128.5, 128.5, 126.1, 44.2, 38.6, 30.2, 26.4.



Chemical Formula: C₁₄H₁₈O₃

- **1-(benzo[*d*][1,3]dioxol-5-yl)-4,4-dimethylpentan-3-one (15v)**³⁰²

According to general procedure A, using pivalone (63.0 μ L, 0.5 mmol, 1.0 equiv.), NaOH (19.985 mg, 0.5 mmol, 1.0 equiv.), benzo(*d*)(1,3)dioxo-5-ylmethanol (197.795 mg, 1.3 mmol, 2.5 equiv.), **Fe1** (2.5 mol%, 5.892 mg, 0.0125 mmol), ^tBuOH (1.0 mL), the product was obtained as a colorless oil (0.071 g, 61 % yield) after purification by silica gel column chromatography (pentane/ether (9:1)). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 6.72 (d, *J* = 7.9 Hz, 1H), 6.67 (d, *J* = 1.6 Hz, 1H), 6.63 (dd, *J* = 7.9, 1.8 Hz, 1H), 5.91 (s, 2H), 2.81 – 2.77 (m, 2H), 2.76 – 2.72 (m, 2H), 1.10 (s, 9H). ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 215.06, 147.7, 145.8, 135.5, 121.2, 109.0, 108.3, 100.9, 44.2, 38.8, 29.9, 26.4.



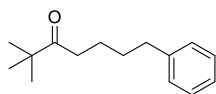
Chemical Formula:
C₁₁H₁₆O₂

- **1-(furan-2-yl)-4,4-dimethylpentan-3-one (15w)**

According to general procedure A, using pivalone (63.0 μ L, 0.5 mmol, 1.0 equiv.), NaOH (19.985 mg, 0.5 mmol, 1.0 equiv.), furan-2-yl-methanol (113.0 μ L, 1.3 mmol, 2.5 equiv.), **Fe1** (2.5 mol%, 5.892 mg, 0.0125 mmol), ^tBuOH (1.0 mL), the product was obtained as a colorless oil (0.038 g, 43 % yield) after purification by silica gel column chromatography (pentane/ether (9:1)). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.29 (d, *J* = 1.1 Hz, 1H), 6.26 (dd, *J* = 3.0, 1.9 Hz, 1H), 5.98 (d, *J* = 2.5 Hz, 1H), 2.90 (dd, *J* = 11.1, 4.1 Hz, 2H), 2.83 (ddd, *J* = 8.4, 5.4, 1.5 Hz, 2H), 1.13 (s, 9H). ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 214.5, 155.1, 141.1, 110.3, 105.2, 44.2, 35.1, 26.4, 22.6. IR (neat): ν 2968, 2871, 1705, 1608,

³⁰² Murphy, W. S.; Wattanasin, S. *Tetrahedron Lett.* **1981**, 22, 695-698.

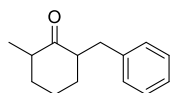
1478, 1366, 1149, 1083, 1072, 1008, 981, 804, 728, 599 cm^{-1} . HRMS (ESI-TOF) m/z : $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{11}\text{H}_{16}\text{O}_2\text{Na}$: 203.1048; found 203.1046.



Chemical Formula: $\text{C}_{15}\text{H}_{22}\text{O}$

- **2,2-dimethyl-7-phenylheptan-3-one (15x)**³⁰³

According to general procedure A, using pivalone (63.0 μL , 0.5 mmol, 1.0 equiv.), NaOH (19.985 mg, 0.5 mmol, 1.0 equiv.), 3-phenyl-1-propanol (177.0 μL , 1.3 mmol, 2.5 equiv.), **Fe1** (2.5 mol%, 5.892 mg, 0.0125 mmol), $^t\text{BuOH}$ (1.0 mL), the product was obtained as a colorless oil (0.045 g, 41 % yield) after purification by silica gel column chromatography (pentane/ether (9:1)). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ (ppm): 7.29 – 7.24 (m, 2H), 7.17 (d, $J = 6.2$ Hz, 2H), 7.14 (ddd, $J = 13.2, 5.5, 4.1$ Hz, 1H), 2.62 (t, $J = 7.1$ Hz, 2H), 2.49 (t, $J = 6.9$ Hz, 2H), 1.66 – 1.55 (m, 4H), 1.12 (s, $J = 20.3$ Hz, 9H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ (ppm): 215.9, 142.4, 128.4, 128.3, 125.8, 44.1, 36.3, 36.0, 31.2, 26.5, 23.7.



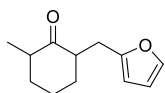
Chemical Formula: $\text{C}_{14}\text{H}_{18}\text{O}$

- **2-benzyl-6-methylcyclohexanone (15y)**³⁰⁴

According to general procedure C, using 2-methylcyclohexanone (60.0 μL , 0.5 mmol, 1.0 equiv.), NaOH (40.0 mg, 1.0 mmol, 2.0 equiv.), benzyl alcohol (135.0 μL , 1.3 mmol, 2.5 equiv.), **Fe1** (2.5 mol%, 5.892 mg, 0.0125 mmol), $^t\text{BuOH}$ (1.0 mL), the product was obtained as a colorless oil (0.070 g, 69 % yield, d.r. 91:9) after purification by silica gel column chromatography (pentane/ether (9:1)). Major isomer: $^1\text{H NMR}$ (500 MHz, CDCl_3) δ (ppm): 7.27 (t, $J = 7.4$ Hz, 2H), 7.20 – 7.14 (m, 3H), 3.23 (dd, $J = 14.0, 5.0$ Hz, 1H), 2.59 – 2.52 (m, 1H), 2.44 (ddd, $J = 12.8, 6.4, 1.7$ Hz, 1H), 2.42 – 2.37 (m, 1H), 2.13 – 2.03 (m, 2H), 1.83 – 1.77 (m, 1H), 1.71 – 1.61 (m, 1H), 1.35 (dq, $J = 20.2, 13.0, 3.9$ Hz, 2H), 1.03 (d, $J = 6.5$ Hz, 3H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ (ppm): 213.8, 140.9, 129.3, 128.3, 125.9, 52.7, 45.8, 37.5, 35.6, 34.8, 25.6, 14.7. Minor isomer: $^1\text{H NMR}$ (500 MHz, CDCl_3) δ (ppm): 7.27 (t, $J = 7.4$ Hz, 2H), 7.20 – 7.14 (m, $J = 14.0, 7.1$ Hz, 3H), 3.08 (dd, $J = 13.6, 5.2$ Hz, 1H), 2.65 – 2.60 (m, 1H), 2.44 (ddd, $J = 12.8, 6.4, 1.7$ Hz, 1H), 2.42 – 2.37 (m, 1H), 2.13 – 2.03 (m, 2H), 1.83 – 1.77 (m, 1H), 1.71 – 1.61 (m, 1H), 1.35 (dq, $J = 20.2, 13.0, 3.9$ Hz, 2H), 1.11 (d, $J = 6.9$ Hz, 3H). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ (ppm): 216.0, 139.8, 129.1, 128.5, 126.3, 50.2, 43.3, 36.4, 34.9, 31.5, 20.3, 15.9.

³⁰³ Patent number DE3321422A1.

³⁰⁴ Schleppehorst, C.; Maji, B.; Glorius, F. *ACS Catal.* **2016**, *6*, 4184-4188.

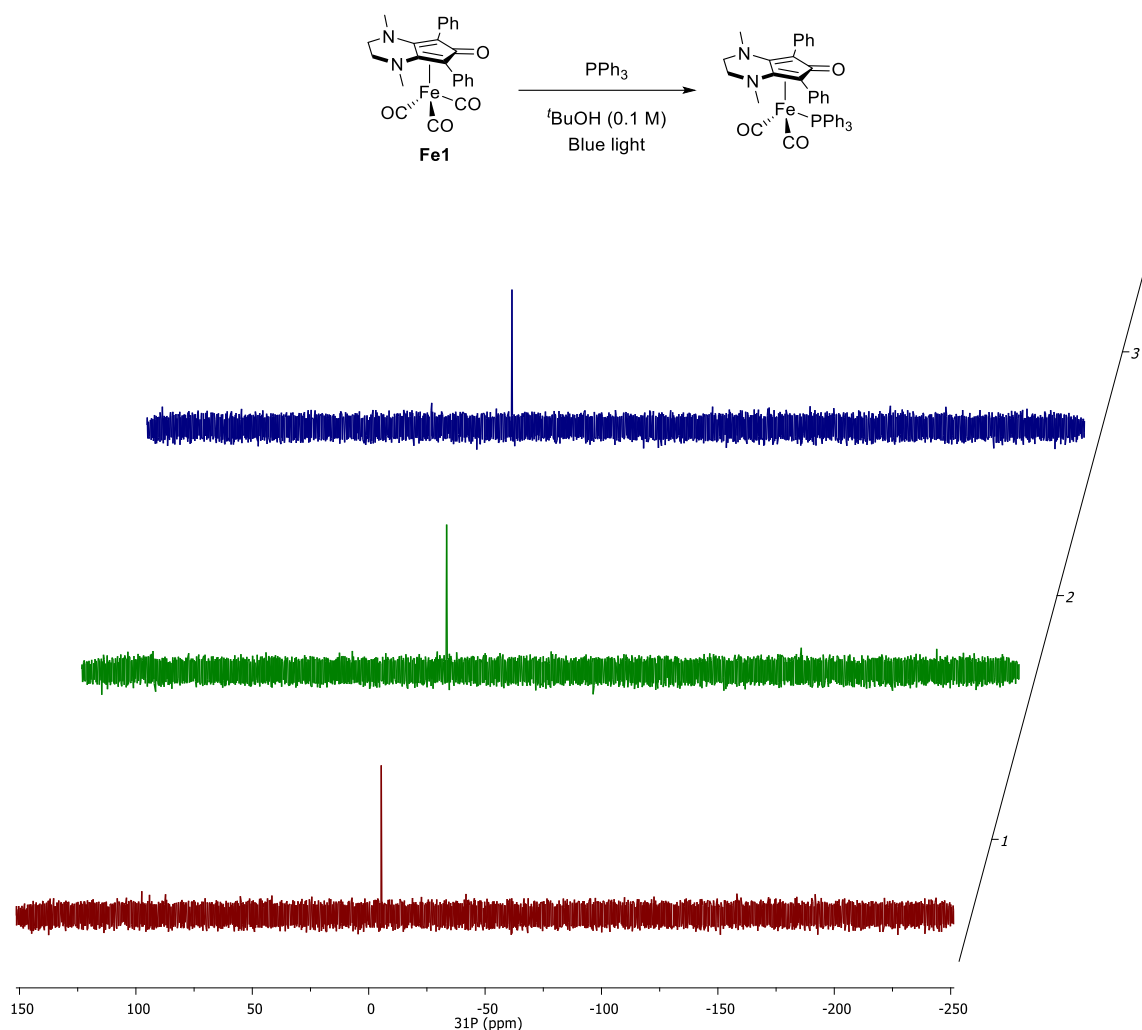


Chemical Formula: C₁₂H₁₆O₂

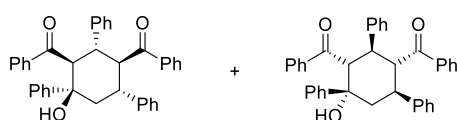
- **2-(furan-2-yl)-6-methylcyclohexanone (15z)**

According to general procedure C, using 2-methylcyclohexanone (60.0 μ L, 0.5 mmol, 1.0 equiv.), NaOH (40.0 mg, 1.0 mmol, 2.0 equiv.), furan-2-yl-methanol (113.0 μ L, 1.3 mmol, 2.5 equiv.), **Fe1** (2.5 mol%, 5.892 mg, 0.0125 mmol), ^tBuOH (1.0 mL), the product was obtained as a colorless oil (0.067 g, 70 % yield, d.r. 90:10) after purification by silica gel column chromatography (pentane/ether (9:1)). **Major isomer:** ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.28 (dd, $J = 1.8, 0.7$ Hz, 1H), 6.26 (dd, $J = 3.1, 1.9$ Hz, 1H), 6.00 (dd, $J = 3.1, 0.7$ Hz, 1H), 3.17 (dd, $J = 15.3, 4.9$ Hz, 1H), 2.68 (dq, $J = 8.4, 5.3, 1.3$ Hz, 1H), 2.50 (dd, $J = 15.4, 8.4$ Hz, 1H), 2.43 (dtd, $J = 7.8, 6.5, 1.2$ Hz, 1H), 2.15 – 2.08 (m, 2H), 1.86 – 1.79 (m, 1H), 1.77 – 1.67 (m, 1H), 1.41 – 1.27 (m, 2H), 1.03 (d, $J = 6.4$ Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 213.2, 154.5, 141.0, 110.3, 106.3, 49.9, 45.7, 37.4, 34.9, 27.9, 25.5, 14.6. **Minor isomer:** ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.29 (dd, $J = 1.8, 0.8$ Hz, 1H), 6.26 (dd, $J = 3.1, 1.9$ Hz, 1H), 6.02 (d, $J = 0.6$ Hz, 1H), 3.08 (dd, $J = 15.2, 5.8$ Hz, 1H), 2.83 (tt, $J = 8.5, 5.6$ Hz, 1H), 2.50 (dd, $J = 15.4, 8.4$ Hz, 1H), 2.43 (dtd, $J = 7.8, 6.5, 1.2$ Hz, 1H), 2.15 – 2.08 (m, 2H), 1.99 – 1.89 (m, 1H), 1.64 – 1.52 (m, 1H), 1.41 – 1.27 (m, 2H), 1.13 (d, $J = 7.0$ Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 213.2, 153.7, 141.3, 110.3, 106.5, 47.2, 43.5, 34.7, 32.4, 28.7, 20.3, 16.1. **IR (neat):** ν 2930, 2857, 1708, 1597, 1507, 1448, 1376, 1148, 1129, 1008, 935, 729, 599 cm⁻¹. **HRMS (ESI-TOF) m/z:** [M + H]⁺ calcd for C₁₂H₁₇O₂: 193.1229; found 193.1225.

b) Mechanistic investigations.



Stacked ^{31}P -NMR spectra (202 MHz, CDCl_3) of the crude reaction mixture after 1 hour (bottom, red), 2 hours (middle, green) and 5 hours (top, blue).



Chemical Formula: $\text{C}_{38}\text{H}_{32}\text{O}_3$

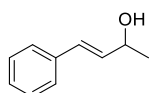
- **[(1*R*,2*S*,3*R*,4*S*,6*S*)-4-Hydroxy-2,4,6-triphenylcyclohexane-1,3-diyl]bis(phenylmethanone)³⁰⁵**

To a solution of chalcone (104 mg, 0.5 mmol, 1 equiv.) in $t\text{BuOH}$ (5 mL) was added NaOH (200 mg, 5 mmol, 10 equiv.) and the mixture was stirred at 30 °C for 24 hours. Water was added and the product was extracted with Et_2O , washed with brine, dried over MgSO_4 and concentrated under reduced pressure. The crude solid was recrystallised in $i\text{PrOH}/\text{CHCl}_3$ 1/1. White solid (71 mg, 79 %). ^1H NMR

³⁰⁵ Palamarchuka, I. V.; Shulgaub, Z. T.; Sergazyb, Sh, D.; Zhulikeevab, A. M.; Gatilovc, Yu. V.; Kulakov, I. V. *Russ. J. Gen. Chem.* **2021**, *91*, 2462-2468.

(600 MHz, CDCl₃) δ (ppm): 7.55 (dd, J = 8.3, 1.0 Hz, 2H), 7.27 (d, J = 7.2 Hz, 2H), 7.25 – 7.20 (m, 5H), 7.18 (t, J = 7.8 Hz, 3H), 7.14 (s, 2H), 7.09 (t, J = 7.7 Hz, 2H), 7.06 – 7.00 (m, 5H), 6.98 (t, J = 7.4 Hz, 1H), 6.83 (t, J = 7.9 Hz, 2H), 6.72 (t, J = 7.4 Hz, 1H), 5.39 (d, J = 2.5 Hz, 1H), 4.49 (d, J = 11.3 Hz, 1H), 4.20 (dt, J = 31.1, 11.1 Hz, 2H), 4.06 (td, J = 12.5, 3.5 Hz, 1H), 2.54 – 2.48 (m, 1H), 2.25 (dd, J = 14.1, 3.6 Hz, 1H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 207.3, 203.7, 146.0, 142.2, 139.1, 138.7, 138.2, 132.8, 131.9, 128.5, 128.3, 128.2, 128.1, 127.8, 127.8, 127.7, 127.5, 127.1, 127.0, 126.8, 124.9, 75.4, 56.8, 56.8, 48.2, 45.9, 43.4. HRMS (m/z): [M+Na]⁺ calculated for C₃₈H₃₂O₃Na: 559.2249; found: 559.2255.

3) Blue light induced iron-catalysed β -alkylation of allylic alcohols.



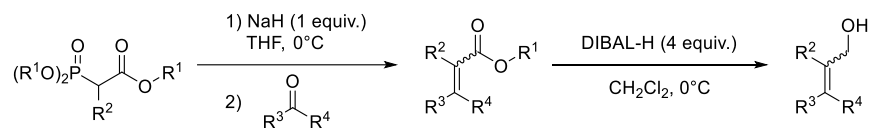
Chemical Formula: C₁₀H₁₂O

- **4-phenylbut-3-en-2-ol (18)**³⁰⁶

To a solution of *trans*-cinnamaldehyde (1.26 mL, 10 mmol, 1 equiv.) in dry Et₂O (5 mL) at 0°C under argon, a solution of methyl lithium (1.6 M in Et₂O) (9.4 mL, 15 mmol, 1.5 equiv.) was added dropwise. The solution was warmed to room temperature and stirred overnight. The reaction was quenched by a saturated aqueous solution of NH₄Cl and the product was extracted with Et₂O, washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The pure enough product was used without further purifications. Yellow oil (1.463 g, 98 %). ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.39 (dd, J = 8.2, 1.0 Hz, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.24 (t, J = 7.3 Hz, 1H), 6.57 (d, J = 15.9 Hz, 1H), 6.27 (dd, J = 15.9, 6.4 Hz, 1H), 4.50 (pd, J = 6.4, 1.0 Hz, 1H), 1.38 (d, J = 6.4 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 136.8, 133.6, 129.5, 128.7, 127.7, 126.5, 69.1, 23.5.

4) Blue light induced alkylation of ketones with allylic and propargylic alcohols.

a) Synthesis of starting materials.

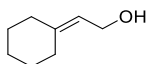


General Procedure D:

Step 1: To a suspension of NaH (60 %w in mineral oil, 1 equiv.) in dry THF (0.1 M) under argon was added the desired phosphonoacetate (1 equiv.) dropwise at 0°C. The mixture was stirred for 15 minutes and the desired carbonyl (0.8 equiv.) was added portionwise at 0°C. The mixture was warmed to room temperature and stirred for 48 hours. The reaction was quenched by adding saturated aqueous NH₄Cl solution, the aqueous layer was extracted with Et₂O, organics were combined, washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure to give the crude α,β -unsaturated ester.

³⁰⁶ Langlois, J.-B.; Alexakis, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 1877-1881.

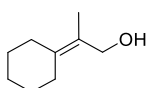
Step 2³⁰⁷: The crude α,β -unsaturated ester was dissolved in dry CH_2Cl_2 (0.3 M) under argon and placed at 0°C . Diisobutylaluminium hydride (1.2 M in toluene) (4 equiv.) was added dropwise to the solution. The mixture was warmed to room temperature and stirred for 2 hours. The reaction was quenched with saturated aqueous Na_2SO_4 solution and stirred overnight. Water was added, the aqueous phase was extracted with EtOAc, the combined organic layers were washed with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure to give the desired allyl alcohol.



Chemical Formula: $\text{C}_8\text{H}_{14}\text{O}$

- **2-cyclohexylideneethan-1-ol (20d)**³⁰⁸

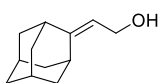
According to general procedure D starting from trimethyl phosphonoacetate (1.618 mL, 10.0 mmol, 1 equiv.) and cyclohexanone (0.828 mL, 8.0 mmol, 0.8 equiv.), the desired allyl alcohol was obtained as a colorless oil (653 mg, 71 % overall yield). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ (ppm): 5.36 (t, $J = 7.1$ Hz, 1H), 4.14 (d, $J = 6.5$ Hz, 2H), 2.23 – 2.16 (m, 2H), 2.13 – 2.08 (m, 2H), 1.63 – 1.49 (m, 6H). $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ (ppm): 144.7, 120.3, 58.7, 37.1, 28.9, 28.5, 28.0, 26.8.



Chemical Formula: $\text{C}_9\text{H}_{16}\text{O}$

- **2-cyclohexylidenepropan-1-ol (20e)**³⁰⁹

According to general procedure D starting from triethyl 2-phosphonopropionate (2.2 mL, 10.0 mmol, 1 equiv.) and cyclohexanone (0.828 mL, 8.0 mmol, 0.8 equiv.), the desired allyl alcohol was obtained as a colorless oil (963 mg, 86 % overall yield). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ (ppm): 4.12 (s, 2H), 2.23 (m, 2H), 2.17 (m, 2H), 1.76 (s, 3H), 1.59 – 1.48 (m, 6H). $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ (ppm): 138.0, 124.4, 63.5, 30.9, 30.3, 28.6, 27.9, 26.9, 16.3.



Chemical Formula: $\text{C}_{12}\text{H}_{18}\text{O}$

- **2-adamantylideneethanol (20f)**³¹⁰

According to general procedure D starting from trimethyl phosphonoacetate (809 μL , 5.0 mmol, 1 equiv.) and 2-adamantanone (601 mg, 4.0 mmol, 0.8 equiv.), the desired allyl alcohol was obtained as a colorless oil (802 mg, 90 % overall yield). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ (ppm): 5.34 (t, $J = 7.2$ Hz,

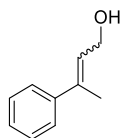
³⁰⁷ Kim, S. W.; Wurm, T.; Brito, G. A.; Jung, W.-O.; Zbieg, J. R.; Stivala, C. E.; Krische, M. J. *J. Am. Chem. Soc.* **2018**, *140*, 9087-9090.

³⁰⁸ Chavan, S. P.; Pawara, K. P.; Garaia, S. *RSC Adv.* **2014**, *4*, 14468-14470.

³⁰⁹ Koy, M.; Bellotti, P.; Katzenburg, F.; Daniliuc, C. G.; Glorius, F. *Angew. Chem. Int. Ed.* **2020**, *59*, 2375-2379.

³¹⁰ Mukherjee, A.; Wu, O.; le Noble, W. J. *J. Org. Chem.* **1994**, *59*, 3270-3274.

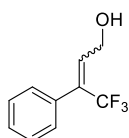
1H), 4.13 (dd, $J = 7.1, 5.5$ Hz, 2H), 2.88 (s, 1H), 2.38 (s, 1H), 1.96 (s, 2H), 1.92 – 1.86 (m, 4H), 1.83 (s, 2H), 1.80 (s, 1H), 1.78 (s, 1H), 1.73 (s, 1H), 1.71 (s, 1H). ^{13}C NMR (150 MHz, CDCl_3) δ (ppm): 153.0, 115.5, 58.3, 40.5, 39.8, 39.3, 37.2, 32.5, 28.5.



Chemical Formula: $\text{C}_{10}\text{H}_{12}\text{O}$

- **3-phenylbut-2-en-1-ol (20g)**³¹¹

According to general procedure D starting from trimethyl phosphonoacetate (809 μL , 5.0 mmol, 1 equiv.) and acetophenone (470 μL , 4.0 mmol, 0.8 equiv.), the desired allyl alcohol was obtained as a colorless oil (160 mg, 27 % overall yield, E/Z: 90/10). E isomer: ^1H NMR (600 MHz, CDCl_3) δ (ppm): 7.41 (d, $J = 7.2$ Hz, 2H), 7.33 (t, $J = 7.6$ Hz, 2H), 7.27 (t, $J = 7.3$ Hz, 1H), 5.98 (tq, $J = 6.7, 1.2$ Hz, 1H), 4.37 (d, $J = 6.7$ Hz, 2H), 2.09 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ (ppm): 142.9, 138.0, 128.4, 127.4, 126.5, 125.9, 60.0, 16.1. Z isomer: ^1H NMR (600 MHz, CDCl_3) δ (ppm): 7.41 (d, $J = 7.2$ Hz, 2H), 7.33 (t, $J = 7.6$ Hz, 2H), 7.27 (t, $J = 7.3$ Hz, 1H), 5.72 (td, $J = 7.0, 1.4$ Hz, 1H), 4.08 (dd, $J = 7.0, 1.0$ Hz, 2H), 2.09 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ (ppm): 140.8, 128.8, 128.2, 127.8, 127.3, 126.4, 60.4, 25.4.



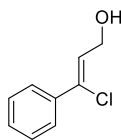
Chemical Formula: $\text{C}_{10}\text{H}_9\text{F}_3\text{O}$

- **4,4,4-trifluoro-3-phenylbut-2-en-1-ol (20h)**³¹²

According to general procedure D starting from trimethyl phosphonoacetate (809 μL , 5.0 mmol, 1 equiv.) and 2,2,2-trifluoro-1-phenylethan-1-one (562 μL , 4.0 mmol, 0.8 equiv.), the desired allyl alcohol was obtained as a colorless oil (948 mg, 94 % overall yield, E/Z: 77/23). E isomer: ^1H NMR (600 MHz, CDCl_3) δ (ppm): 7.42 – 7.22 (m, 5H), 6.57 (tq, $J = 6.3, 1.5$ Hz, 1H), 4.16 (d, $J = 1.1$ Hz, 2H), 1.47 (t, $J = 5.6$ Hz, 1H). ^{19}F NMR (565 MHz, CDCl_3) δ (ppm): -66.1. ^{13}C NMR (150 MHz, CDCl_3) δ (ppm): 134.82 (q, $J = 5.4$ Hz), 132.6 (q, $J = 30.2$ Hz), 131.4, 129.4, 129.1, 128.7, 123.1 (q, $J = 273.3$ Hz), 59.4. Z isomer: ^1H NMR (600 MHz, CDCl_3) δ (ppm): 7.42 – 7.22 (m, 5H), 6.21 (t, $J = 5.7$ Hz, 1H), 4.60 (dt, $J = 8.0, 2.7$ Hz, 2H), 1.72 (t, $J = 5.6$ Hz, 1H). ^{19}F NMR (565 MHz, CDCl_3) δ (ppm): -58.1. ^{13}C NMR (150 MHz, CDCl_3) δ (ppm): 140.70 (q, $J = 2.8$ Hz), 135.40 (q, $J = 1.8$ Hz), 131.36 (q, $J = 31.0$ Hz), 128.6, 128.5, 128.09 (q, $J = 0.8$ Hz), 123.76 (q, $J = 275.5$ Hz), 59.75 (q, $J = 3.7$ Hz).

³¹¹ (a) Jacob, J.; Espenson, J. H.; Jensen, J. H.; Gordon, M. S. *Organometallics* **1998**, *17*, 1835-1840. (b) Li, H.; Chen, H.; Zhou, Y.; Huang, J.; Yi, J.; Zhao, H.; Wang, W.; Jing, L. *Chem. Asian J.* **2020**, *15*, 555-559.

³¹² Kimura, M.; Yamazaki, T.; Kitazume, T.; Kubota, T. *Org. Lett.* **2004**, *6*, 4651-4654.

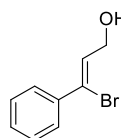


Chemical Formula: C₉H₉ClO

- **(Z)-3-chloro-3-phenylprop-2-en-1-ol (20i)**³¹³

Step 1³¹⁴: POCl₃ (1.12 mL, 12 mmol, 1.2 equiv.) was added dropwise to 2.6 mL of DMF at 0°C under argon. The mixture was stirred for 10 minutes and a solution of acetophenone (1.17 mL, 10 mmol, 1 equiv.) in 10 mL of DMF was added dropwise while stirring. The mixture was stirred at 60°C for 3 hours. After cooling to room temperature, the reaction was poured into a solution of sodium acetate (10% in water), the product was extracted with CH₂Cl₂, washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure to give the crude α,β -unsaturated aldehyde (yellow oil, 1.110 g).

Step 2: The crude α,β -unsaturated aldehyde (1 equiv.) was dissolved in THF:MeOH (10:1, 0.2 M). Sodium borohydride (1.1 equiv.) was added portionwise at 0°C and the mixture was stirred at room temperature for 2 hours. The reaction was quenched with water, the product was extracted with EtOAc, washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified on silica gel column chromatography (pentane/EtOAc: 90/10 to pentane/EtOAc 50/50). Yellow oil (758 mg, 45 % overall yield, E/Z: 7/93). Z isomer: ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.60 (dd, $J = 8.1, 1.5$ Hz, 2H), 7.39 – 7.34 (m, 3H), 6.35 (t, $J = 6.0$ Hz, 1H), 4.52 (t, $J = 5.6$ Hz, 2H), 1.69 (t, $J = 5.4$ Hz, 1H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 137.4, 134.3, 129.1, 128.5, 126.5, 126.4, 60.8. E isomer: ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.62 – 7.57 (m, 2H), 7.41 – 7.32 (m, 3H), 6.19 (t, $J = 7.3$ Hz, 1H), 4.16 (dd, $J = 7.2, 5.3$ Hz, 2H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 136.4, 135.1, 129.3, 128.7, 128.4, 125.5, 60.1.



Chemical Formula: C₉H₉BrO

- **(Z)-3-bromo-3-phenylprop-2-en-1-ol (20j)**³¹⁵

Step 1³¹⁶: To a mixture of DMF (4.8 mL, 60 mmol, 3.0 eq) and chloroform (0.1 M) was added PBr₃ (5.2 mL, 54.0 mmol, 2.7 eq) dropwise at 0 °C and the mixture was stirred for 1 hour. Acetophenone (2.4 mL, 20 mmol, 1.0 eq) was added dropwise to the mixture and the reaction was stirred at room temperature overnight. The reaction mixture was poured into iced water and neutralised to pH=8 by adding K₂CO₃. The product was extracted with Et₂O, washed with brine, the organic phase was dried over MgSO₄, filtered and concentrated under reduced pressure to give the crude the crude α,β -unsaturated aldehyde (orange oil, 2.157 g).

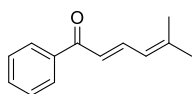
³¹³ Zhou, X.; Zhang, G.; Huang, R.; Huan, H. *Org. Lett.* **2021**, *23*, 365-369.

³¹⁴ Herbivo, C.; Comel, A.; Kirsch, G.; Raposo, M. M. *Tetrahedron* **2009**, *65*, 2079-2086.

³¹⁵ Limberger, J.; Claudino, T. S.; Monteiro, A. L. *RSC Adv.* **2014**, *4*, 45558-45565.

³¹⁶ Wang, G.; Chen, X.; Miao, G.; Yao, W.; Ma, C. *J. Org. Chem.* **2013**, *78*, 6223-6232.

Step 2: The crude α,β -unsaturated aldehyde (1 equiv.) was dissolved in THF:MeOH (10:1, 0.2 M). Sodium borohydride (1.1 equiv.) was added portionwise at 0°C and the mixture was stirred at room temperature for 2 hours. The reaction was quenched with water, the product was extracted with EtOAc, washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified on silica gel column chromatography (pentane/EtOAc: 90/10 to pentane/EtOAc 50/50). Orange oil (1.392 g, 33 % overall yield, E/Z: 14/86). Z isomer: ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.55 (dd, J = 8.1, 1.5 Hz, 2H), 7.37 – 7.32 (m, 3H), 6.47 (t, J = 5.8 Hz, 1H), 4.47 (d, J = 5.8 Hz, 2H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 139.0, 130.2, 129.0, 128.5, 127.6, 126.4, 63.4. E isomer: ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.57 – 7.54 (m, 2H), 7.37 – 7.32 (m, 3H), 6.43 (t, J = 7.2 Hz, 1H), 4.08 (d, J = 7.2 Hz, 2H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 137.9, 132.7, 129.2, 128.9, 128.4, 125.0, 60.8.

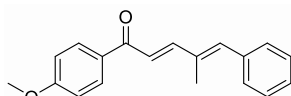


Chemical Formula: C₁₃H₁₄O

- **(E)-5-methyl-1-phenylhexa-2,4-dien-1-one (22a)**³¹⁷

To a solution of diisopropylamine (1.8 mL, 12.8 mmol, 1.3 equiv.) in dry THF (15 mL) under argon was added n-butyllithium (2.5 M in hexane) (5.2 mL, 13.0 mmol, 1.3 equiv.) dropwise at -20 °C. The mixture was stirred for 30 minutes and cooled to -78 °C. Acetophenone (1.17 mL, 10 mmol, 1 equiv.) was added dropwise and the mixture was stirred for 30 minutes. 3-methylcrotonaldehyde (1.06 mL, 11.0 mmol, 1.1 equiv.) was added to the mixture and the reaction was stirred for 30 minutes at -78 °C. Saturated aqueous NaHCO₃ solution was added and the mixture was allowed to warm room temperature. The aqueous layer was extracted with Et₂O, organics were combined, washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The yellow oil residue was dissolved in pyridine (1.21 mL, 15.0 mmol, 1.5 equiv.) under argon, methane sulfonyl chloride (1.0 mL, 13.0 mmol, 1.3 equiv.) was added at 0 °C and the mixture was stirred at room temperature overnight. Water was added, the product was extracted with Et₂O, washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Purification on silica gel column chromatography (pentane/EtOAc: 98/2 to pentane/EtOAc 95/5) afforded the desired product. Orange oil (906 mg, 49 %). ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.95 (dd, J = 8.4, 1.3 Hz, 2H), 7.75 (dd, J = 14.8, 11.7 Hz, 1H), 7.54 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 6.88 (d, J = 14.8 Hz, 1H), 6.15 (ddd, J = 11.7, 2.0, 1.3 Hz, 1H), 1.95 (s, 3H), 1.93 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 191.0, 148.7, 141.4, 138.6, 132.5, 128.6, 128.4, 124.8, 123.0, 26.9, 19.3.

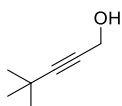
³¹⁷ Sim, H.-S.; Feng, X.; Yun, J. *Chem. Eur. J.* **2009**, *15*, 1939-1943.



Chemical Formula: C₁₉H₁₈O₂

- **(2E,4E)-1-(4-methoxyphenyl)-4-methyl-5-phenylpenta-2,4-dien-1-one (22b)**

To a solution of 4-methoxyacetophenone (1.503 g, 10 mmol, 1 equiv.) and α -methyl-trans-cinnamaldehyde (1.7 mL, 12 mmol, 1.2 equiv.) in absolute ethanol (4 mL) was added a solution of NaOH (400 mg, 10 mmol, 1 equiv.) in absolute ethanol (6 mL) dropwise at 0 °C. The mixture was stirred at room temperature and monitored by TLC. After total consumption of the starting material, the product was isolated by filtration and washing with ethanol as a pale-yellow solid (2.785 g, 99 %). **¹H NMR (600 MHz, CDCl₃) δ (ppm):** 8.02 (d, J = 8.9 Hz, 2H), 7.63 (dd, J = 15.3, 0.7 Hz, 1H), 7.42 – 7.37 (m, 4H), 7.32 – 7.28 (m, 1H), 7.07 (d, J = 15.2 Hz, 1H), 6.98 (d, J = 8.9 Hz, 2H), 6.97 (s, 1H), 3.89 (s, 3H), 2.17 (d, J = 1.2 Hz, 3H). **¹³C NMR (150 MHz, CDCl₃) δ (ppm):** 189.2, 163.4, 149.5, 140.1, 137.0, 134.8, 131.4, 130.8, 129.6, 128.4, 127.9, 121.4, 113.9, 55.6, 14.1. **IR (neat) ν** 2963, 1652, 1587, 1507, 1411, 1293, 1248, 1217, 1176, 1038, 1021, 977, 834, 818, 695, 521 cm⁻¹. **HRMS (m/z): [M+H]⁺** calculated for C₁₉H₁₉O₂: 279.1385; found: 279.1385.

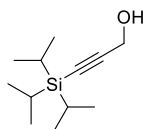


Chemical Formula: C₇H₁₂O

- **4,4-dimethylpent-2-yn-1-ol (23c)**³¹⁸

To a solution of 3,3-dimethylbut-1-yne (616 μ L, 5 mmol, 1 equiv.) in dry THF (50 mL, 0.1 M) under argon was added *n*-butyllithium (2.5 M in hexane) (2.0 mL, 5 mmol, 1 equiv.) dropwise at –78 °C. The mixture was stirred at this temperature for 15 minutes before paraformaldehyde (151 mg, 5 mmol, 1 equiv.) was added in one portion. The mixture was warmed to room temperature and stirred overnight. The reaction was quenched with saturated aqueous NH₄Cl solution and the product was extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure to give the pure propargylic alcohol as a colorless oil (337 mg, 60 %). **¹H NMR (600 MHz, CDCl₃) δ (ppm):** 4.25 (s, 2H), 1.22 (s, 9H). **¹³C NMR (150 MHz, CDCl₃) δ (ppm):** 94.9, 76.9, 51.5, 31.0, 27.5.

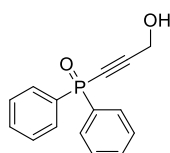
³¹⁸ Brown, H. C.; Molander, G. A.; Singh, S. M.; Racherla, U. S. *J. Org. Chem.* **1985**, *50*, 1577-1582.



Chemical Formula: C₁₂H₂₄OSi

- **3-triisopropylsilylprop-2-yn-1-ol (23d)**³¹⁹

To a solution of propargyl alcohol (288 μ L, 5 mmol, 1 equiv.) in dry THF (50 mL, 0.1 M) under argon was added *n*-butyllithium (2.5 M in hexane) (4.0 mL, 10 mmol, 2 equiv.) dropwise at -78°C . The mixture was stirred at this temperature for 15 minutes before triisopropylsilyl chloride (1.1 mL, 5 mmol, 1 equiv.) was added dropwise. The mixture was warmed to room temperature and stirred overnight. The reaction was quenched with water and the product was extracted with Et₂O. The organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The product was purified on silica gel column chromatography (pentane/EtOAc: 90/10) to give the pure product as a colorless oil (509 mg, 48 %). **¹H NMR (600 MHz, CDCl₃) δ (ppm):** 4.30 (d, J = 6.2 Hz, 2H), 1.53 (t, J = 6.1 Hz, 1H), 1.08 (s, 3H), 1.07 (s, 18H). **¹³C NMR (150 MHz, CDCl₃) δ (ppm):** 105.7, 87.0, 51.9, 18.6, 11.2.

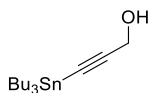


Chemical Formula: C₁₅H₁₃O₂P

- **(3-hydroxyprop-1-yn-1-yl)diphenylphosphine oxide (23e)**

To a solution of propargyl alcohol (288 μ L, 5 mmol, 1 equiv.) in dry THF (50 mL, 0.1 M) under argon was added *n*-butyllithium (2.5 M in hexane) (4.0 mL, 10 mmol, 2 equiv.) dropwise at -78°C . The mixture was stirred at this temperature for 15 minutes before diphenylphosphinic chloride (0.954 mL, 5 mmol, 1 equiv.) was added dropwise. The mixture was warmed to room temperature and stirred overnight. The reaction was quenched with saturated aqueous NH₄Cl solution and the product was extracted with Et₂O. The organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The product was purified on silica gel column chromatography (CH₂Cl₂/EtOAc: 95/5) to give the pure product as a colorless oil (331 mg, 26 %). **¹H NMR (600 MHz, CDCl₃) δ (ppm):** 7.85 – 7.81 (m, 4H), 7.53 (td, J = 7.4, 1.3 Hz, 2H), 7.45 (td, J = 7.6, 3.6 Hz, 4H), 4.69 (dd, J = 8.4, 2.4 Hz, 2H), 2.47 (t, J = 2.5 Hz, 1H). **³¹P NMR (243 MHz, CDCl₃) δ (ppm):** 34.2. **¹³C NMR (150 MHz, CDCl₃) δ (ppm):** 132.5 (d, J = 2.9 Hz), 131.8 (d, J = 10.4 Hz), 130.8 (d, J = 136.7 Hz), 128.7 (d, J = 13.3 Hz), 78.1 (d, J = 8.9 Hz), 75.8, 52.5 (d, J = 4.6 Hz). **IR (neat) ν** 3450, 3292, 3200, 2122, 1438, 1217, 1129, 1020, 988, 942, 728, 692, 539 cm⁻¹. **HRMS (m/z):** [M+H]⁺ calculated for C₁₅H₁₄O₂P: 257.0731; found: 257.0728.

³¹⁹ Sinka, V.; Cruz, D. A.; Martín, V. S.; Padrón, J. I. *Org. Lett.* **2022**, *24*, 5271-5275.



Chemical Formula: C₁₅H₃₀OSn

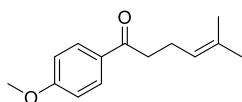
- **3-(tributylstannyl)prop-2-yn-1-ol (23f)**

To a solution of propargyl alcohol (288 μ L, 5 mmol, 1 equiv.) in dry THF (50 mL, 0.1 M) under argon was added *n*-butyllithium (2.5 M in hexane) (4.0 mL, 10 mmol, 2 equiv.) dropwise at -78°C . The mixture was stirred at this temperature for 15 minutes before tributyltin chloride (1.4 mL, 5 mmol, 1 equiv.) was added dropwise. The mixture was warmed to room temperature and stirred overnight. The reaction was quenched with saturated aqueous NH₄Cl solution and the product was extracted with Et₂O. The organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The product was purified on silica gel column chromatography (pentane/EtOAc: 90/10) to give the pure product as a colorless oil (683 mg, 40 %). ¹H NMR (600 MHz, CDCl₃) δ (ppm): 4.27 (d, $J = 6.1$ Hz, 2H), 1.58 – 1.52 (m, 6H), 1.37 – 1.30 (m, 6H), 1.06 – 0.93 (m, 6H), 0.90 (t, $J = 7.3$ Hz, 9H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 108.5, 89.3, 52.0, 28.9, 27.1, 13.79 (s), 11.1. IR (neat) ν 3312, 2955, 2921, 2851, 1464, 1044, 957, 765, 750, 655, 601, 494 cm⁻¹.

b) Alkylation reactions.

General Procedure E:

In a 10 mL vial, ketone **1** (0.5 mmol, 1.0 equiv.), the desired alcohol (1.0 mmol, 2 equiv.), NaOH (10 mg, 0.25 mmol, 0.5 equiv.), **Fe1** (2.5 mol%, 5.8 mg, 0.0125 mmol), ^tBuOH (1.0 mL) were poured in under an argon atmosphere. The reaction tube was sealed. The mixture was stirred at room temperature and exposed to blue light for 16 hours. The mixture was filtrated on celite, eluted with diethyl ether and concentrated under reduced pressure. The conversion was determined by ¹H NMR spectroscopy. The residue was purified by silica gel chromatography using pentane/ethyl acetate as eluent to afford the desired product.



Chemical Formula: C₁₄H₁₈O₂

- **1-(4-methoxyphenyl)-5-methylhex-4-en-1-one (21a)**

According to general procedure E, using 1-(4-methoxyphenyl)ethan-1-one (75.58 mg, 0.5 mmol, 1.0 equiv.), prenol (102.0 μ L, 1.0 mmol, 2 equiv.), NaOH (10 mg, 0.25 mmol, 0.5 equiv.), **Fe1** (2.5 mol%, 5.8 mg, 0.0125 mmol), and ^tBuOH (1.0 mL), the title compound **21a** was obtained in a mixture of unsaturated (**21a**) and saturated compound (**21a'**) in a 74:26 ratio after purification by silica gel column chromatography (pentane/ethyl acetate (95:5)). Colorless oil (77 mg, 70 % yield).

21a³²⁰: ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.94 (d, $J = 8.9$ Hz, 2H), 6.93 (d, $J = 8.9$ Hz, 2H), 5.17 (t, $J = 7.2$ Hz, 1H), 3.87 (s, 3H), 2.97 – 2.91 (m, 2H), 2.40 (q, $J = 7.4$ Hz, 2H), 1.69 (s, 3H), 1.63 (s, 3H).

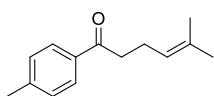
³²⁰ Narender, T.; Sarkar, S.; Rajendar, K.; Tiwari, S. *Org. Lett.* **2011**, *13*, 6140-6143.

¹³C NMR (125 MHz, CDCl₃) δ (ppm): 198.8, 163.4, 132.8, 130.4, 130.2, 123.2, 113.7, 55.5, 38.5, 25.8, 23.2, 17.8.

21a³²¹: ¹H NMR (500 MHz, CDCl₃) δ (ppm): 7.94 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 3.87 (s, 3H), 2.91 – 2.85 (m, 2H), 1.76 – 1.69 (m, 2H), 1.62 – 1.54 (m, 1H), 1.28 – 1.23 (m, 2H), 0.90 (d, *J* = 6.6 Hz, 6H). ¹³C NMR (125 MHz, CDCl₃) δ (ppm): 199.3, 163.4, 130.4, 130.2, 113.7, 55.5, 38.8, 38.6, 28.0, 22.6, 22.6.

- **Scale-up of the reaction to 5 mmol starting material**

According to general procedure E, using 1-(4-methoxyphenyl)ethan-1-one (760 mg, 5 mmol, 1.0 equiv.), prenol (1.02 mL, 10 mmol, 2 equiv.), NaOH (100 mg, 2.5 mmol, 0.5 equiv.), **Fe1** (2.5 mol%, 58 mg, 0.125 mmol), and ^tBuOH (10 mL), the title compound **21a** was obtained in a mixture of unsaturated (**21a**) and saturated compound (**21a'**) in a 75:25 ratio after purification by silica gel column chromatography (pentane/ethyl acetate (95:5)). Colorless oil (776 mg, 71 % yield). ¹H-NMR data was comparable with the previous NMR data.



Chemical Formula: C₁₄H₁₈O

- **5-methyl-1-(p-tolyl)hex-4-en-1-one (21b)**

According to general procedure E, using 1-(4-methylphenyl)ethan-1-one (67 μL, 0.5 mmol, 1.0 equiv.), prenol (102 μL, 1.0 mmol, 2 equiv.), NaOH (10 mg, 0.25 mmol, 0.5 equiv.), **Fe1** (2.5 mol%, 5.8 mg, 0.0125 mmol), and ^tBuOH (1.0 mL), the title compound **21b** was obtained in a mixture of unsaturated (**21b**) and saturated compound (**21b'**) in a 73:27 ratio after purification by silica gel column chromatography (pentane/ethyl acetate (95:5)). Colorless oil (76 mg, 75 % yield).

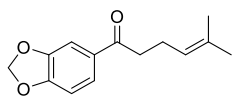
21b³²²: ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.86 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 7.9 Hz, 2H), 5.17 (t, *J* = 7.2 Hz, 1H), 2.98 – 2.95 (m, 2H), 2.44 – 2.37 (m, 2H), 2.41 (s, 3H), 1.69 (s, 3H), 1.63 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 199.9, 143.7, 134.6, 132.8, 129.3, 128.3, 123.1, 38.7, 25.8, 23.1, 21.7, 17.8.

21b³²³: ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.86 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 7.9 Hz, 2H), 2.94 – 2.90 (m, 2H), 2.41 (s, 3H), 1.73 (dt, *J* = 15.1, 7.7 Hz, 2H), 1.61 – 1.56 (m, 1H), 1.26 (dd, *J* = 15.5, 7.4 Hz, 2H), 0.90 (d, *J* = 6.6 Hz, 6H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 200.4, 143.7, 134.7, 129.3, 128.3, 38.8, 38.7, 28.0, 22.6, 22.5, 21.7.

³²¹ Shen, D.; Pool, D. L.; Shotton, C. C.; Kornahrens, A. F.; Healy, M. P.; Donohoe, T. J. *Angew. Chem. Int. Ed.* **2014**, *54*, 1642-1645.

³²² Sankar, R. V.; Manikpuri, D.; Gunanathan, C. *Org. Biomol. Chem.* **2023**, *21*, 273-278.

³²³ Wu, C.-L.; Chen, W.-Y.; Chu, C.-S. *Nat. Prod. Commun.* **2007**, *2*(4), 361-365.



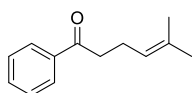
Chemical Formula: C₁₄H₁₆O₃

- **5-methyl-3',4'-(methylenedioxy)phenylhex-4-en-1-one (21c)**

According to general procedure E, using 3',4'-(methylenedioxy)acetophenone (82 mg, 0.5 mmol, 1.0 equiv.), prenol (102 μ L, 1.0 mmol, 2 equiv.), NaOH (10 mg, 0.25 mmol, 0.5 equiv.), **Fe1** (2.5 mol%, 5.8 mg, 0.0125 mmol), and ^tBuOH (1.0 mL), the title compound **21c** was obtained in a mixture of unsaturated (**21c**) and saturated compound (**21c'**) in a 78:22 ratio after purification by silica gel column chromatography (pentane/ethyl acetate (95:5)). Colorless oil (71 mg, 61 % yield).

21c: ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.56 (dd, J = 8.2, 1.7 Hz, 1H), 7.44 (d, J = 1.7 Hz, 1H), 6.84 (d, J = 8.1 Hz, 1H), 6.04 (s, 2H), 5.16 (t, J = 7.2 Hz, 1H), 2.93 – 2.89 (m, 2H), 2.39 (q, J = 7.3 Hz, 2H), 1.69 (s, 3H), 1.63 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 198.2, 151.7, 148.2, 132.8, 132.0, 124.3, 123.1, 108.0, 107.9, 101.9, 38.6, 25.8, 23.2, 17.8. IR (neat) ν 2965, 2903, 1674, 1603, 1439, 1352, 1242, 1036, 933, 806 cm⁻¹. HRMS (m/z): [M+H]⁺ calculated for C₁₄H₁₇O₃: 233.1178; found: 233.1176.

21c': ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.56 (dd, J = 8.2, 1.7 Hz, 6H), 7.44 (d, J = 1.7 Hz, 1H), 6.84 (d, J = 8.1 Hz, 1H), 6.04 (s, 2H), 2.88 – 2.83 (m, 2H), 1.75 – 1.69 (m, 2H), 1.61 – 1.55 (m, 1H), 1.28 – 1.22 (m, 2H), 0.89 (d, J = 6.6 Hz, 6H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 198.8, 151.6, 148.2, 132.1, 124.3, 108.0, 107.9, 101.9, 38.7, 38.7, 28.0, 22.6, 22.6. HRMS (m/z): [M+H]⁺ calculated for C₁₄H₁₉O₃: 235.1334; found: 235.1336.



Chemical Formula: C₁₃H₁₆O

- **5-methyl-1-phenylhex-4-en-1-one (21d)**

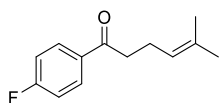
According to general procedure E, using acetophenone (58 μ L, 0.5 mmol, 1.0 equiv.), prenol (102 μ L, 1.0 mmol, 2 equiv.), NaOH (10 mg, 0.25 mmol, 0.5 equiv.), **Fe1** (2.5 mol%, 5.8 mg, 0.0125 mmol), and ^tBuOH (1.0 mL), the title compound **21d** was obtained in a mixture of unsaturated (**21d**) and saturated compound (**21d'**) in a 86:14 ratio after purification by silica gel column chromatography (pentane/ethyl acetate (95:5)). Colorless oil (50 mg, 53 % yield).

21d³²²: ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.96 (dd, J = 8.3, 1.2 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.7 Hz, 2H), 5.17 (t, J = 7.2 Hz, 1H), 3.01 – 2.98 (m, 2H), 2.42 (q, J = 7.3 Hz, 2H), 1.69 (d, J = 1.0 Hz, 3H), 1.64 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 200.2, 137.1, 133.0, 132.9, 128.6, 128.1, 123.0, 38.9, 25.8, 23.0, 17.8.

21d'³²⁴: ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.96 (dd, J = 8.3, 1.2 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.7 Hz, 2H), 2.97 – 2.93 (m, 2H), 1.76 – 1.71 (m, 2H), 1.62 – 1.56 (m, 1H), 1.27 (dd, J =

³²⁴ Cao, J. -J.; Zhou, F.; Zhou, J. *Angew. Chem. Int. Ed.* **2010**, *49*, 4976-4980.

16.1, 6.8 Hz, 2H), 0.90 (d, $J = 6.6$ Hz, 6H). ^{13}C NMR (150 MHz, CDCl_3) δ (ppm): 200.7, 137.2, 133.0, 128.6, 128.1, 38.9, 38.7, 28.0, 22.6, 22.3.



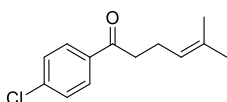
Chemical Formula: $\text{C}_{13}\text{H}_{15}\text{FO}$

- **1-(4-fluorophenyl)-5-methylhex-4-en-1-one (21e)**

According to general procedure E, using 1-(4-fluorophenyl)ethan-1-one (61 μL , 0.5 mmol, 1.0 equiv.), prenol (102 μL , 1.0 mmol, 2 equiv.), NaOH (10 mg, 0.25 mmol, 0.5 equiv.), **Fe1** (2.5 mol%, 5.8 mg, 0.0125 mmol), and $^t\text{BuOH}$ (1.0 mL), the title compound **21e** was obtained in a mixture of unsaturated (**21e**) and saturated compound (**21e'**) in a 87:13 ratio after purification by silica gel column chromatography (pentane/ethyl acetate (95:5)). White solid (65 mg, 63 % yield).

21e³²²: ^1H NMR (600 MHz, CDCl_3) δ (ppm): 7.99 (dd, $J = 8.9, 5.4$ Hz, 2H), 7.12 (t, $J = 8.7$ Hz, 2H), 5.16 (t, $J = 7.2$ Hz, 1H), 2.98 – 2.94 (m, 2H), 2.41 (q, $J = 7.3$ Hz, 2H), 1.69 (s, 3H), 1.63 (s, 3H). $^{19}\text{F}\{\text{H}\}$ NMR (470 MHz, CDCl_3) δ (ppm): -105.6. ^{13}C NMR (150 MHz, CDCl_3) δ (ppm): 198.6, 165.7 (d, $J = 254.3$ Hz), 133.6 (d, $J = 3.0$ Hz), 133.0, 130.8 (d, $J = 9.3$ Hz), 122.9, 115.7 (d, $J = 21.8$ Hz), 38.8, 25.8, 23.0, 17.8.

21e': ^1H NMR (600 MHz, CDCl_3) δ (ppm): 7.99 (dd, $J = 8.9, 5.4$ Hz, 2H), 7.12 (t, $J = 8.7$ Hz, 2H), 2.94 – 2.90 (m, 2H), 1.73 (dt, $J = 15.1, 7.6$ Hz, 2H), 1.60 – 1.54 (m, 1H), 1.28 – 1.23 (m, 2H), 0.90 (d, $J = 6.6$ Hz, 6H). $^{19}\text{F}\{\text{H}\}$ NMR (470 MHz, CDCl_3) δ (ppm): -105.7. ^{13}C NMR (150 MHz, CDCl_3) δ (ppm): 199.1, 165.7 (d, $J = 254.3$ Hz), 133.6 (d, $J = 3.0$ Hz), 130.7 (d, $J = 9.3$ Hz), 115.7 (d, $J = 21.8$ Hz), 38.9, 38.7, 28.0, 22.6, 22.3.



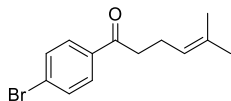
Chemical Formula: $\text{C}_{13}\text{H}_{15}\text{ClO}$

- **1-(4-chlorophenyl)-5-methylhex-4-en-1-one (21f)**

According to general procedure E, using 1-(4-chlorophenyl)ethan-1-one (65 μL , 0.5 mmol, 1.0 equiv.), prenol (102 μL , 1.0 mmol, 2 equiv.), NaOH (10 mg, 0.25 mmol, 0.5 equiv.), **Fe1** (2.5 mol%, 5.8 mg, 0.0125 mmol), and $^t\text{BuOH}$ (1.0 mL), the title compound **21f** was obtained in a mixture of unsaturated (**21f**) and saturated compound (**21f'**) in a 92:8 ratio after purification by silica gel column chromatography (pentane/ethyl acetate (95:5)). White solid (108 mg, 97 % yield).

21f³²²: ^1H NMR (600 MHz, CDCl_3) δ (ppm): 7.90 (d, $J = 8.7$ Hz, 2H), 7.43 (d, $J = 8.7$ Hz, 2H), 5.15 (t, $J = 7.2$ Hz, 1H), 2.98 – 2.94 (m, 2H), 2.41 (q, $J = 7.3$ Hz, 2H), 1.69 (s, 3H), 1.63 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ (ppm): 198.9, 139.4, 135.4, 133.1, 129.6, 129.0, 122.8, 38.8, 25.8, 22.9, 17.8.

21f³²⁵: ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.90 (d, *J* = 8.7 Hz, 2H), 7.43 (d, *J* = 8.7 Hz, 2H), 2.94 – 2.89 (m, 2H), 1.76 – 1.70 (m, 2H), 1.60 – 1.54 (m, 1H), 1.29 – 1.23 (m, 2H), 0.90 (d, *J* = 6.6 Hz, 6H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 198.9, 139.4, 135.5, 129.5, 128.6, 38.9, 38.7, 28.0, 22.6, 22.2.



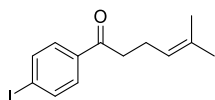
Chemical Formula: C₁₃H₁₅BrO

- **1-(4-bromophenyl)-5-methylhex-4-en-1-one (21g)**

According to general procedure E, using 1-(4-bromophenyl)ethan-1-one (100 mg, 0.5 mmol, 1.0 equiv.), prenol (102 μL, 1.0 mmol, 2 equiv.), NaOH (10 mg, 0.25 mmol, 0.5 equiv.), **Fe1** (2.5 mol%, 5.8 mg, 0.0125 mmol), and ^tBuOH (1.0 mL), the title compound **21g** was obtained in a mixture of unsaturated (**21g**) and saturated compound (**21g'**) in a 88:12 ratio after purification by silica gel column chromatography (pentane/ethyl acetate (95:5)). Yellow solid (110 mg, 83 % yield).

21g³²²: ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.82 (d, *J* = 8.7 Hz, 2H), 7.60 (d, *J* = 8.7 Hz, 2H), 5.15 (t, *J* = 7.2 Hz, 1H), 2.99 – 2.93 (m, 2H), 2.41 (q, *J* = 7.3 Hz, 2H), 1.69 (s, 3H), 1.63 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 199.1, 135.8, 133.1, 132.0, 129.7, 128.1, 122.8, 38.8, 25.8, 22.9, 17.8.

21g³²⁶: ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.82 (d, *J* = 8.7 Hz, 2H), 7.60 (d, *J* = 8.7 Hz, 2H), 2.92 – 2.89 (m, 2H), 1.75 – 1.70 (m, 2H), 1.60 – 1.52 (m, 1H), 1.27 – 1.23 (m, 2H), 0.90 (d, *J* = 6.6 Hz, 6H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 199.6, 135.9, 131.9, 129.6, 128.2, 38.9, 38.7, 28.0, 22.6, 22.2.



Chemical Formula: C₁₃H₁₅IO

- **1-(4-iodophenyl)-5-methylhex-4-en-1-one (21h)**

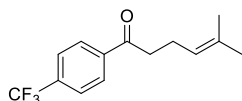
According to general procedure E, using 1-(4-iodophenyl)ethan-1-one (123 mg, 0.5 mmol, 1.0 equiv.), prenol (102 μL, 1.0 mmol, 2 equiv.), NaOH (10 mg, 0.25 mmol, 0.5 equiv.), **Fe1** (2.5 mol%, 5.8 mg, 0.0125 mmol), and ^tBuOH (1.0 mL), the title compound **21h** was obtained in a mixture of unsaturated (**21h**) and saturated compound (**21h'**) in a 91:9 ratio after purification by silica gel column chromatography (pentane/ethyl acetate (95:5)). Yellow oil (82 mg, 52 % yield).

21h: ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.82 (d, *J* = 8.6 Hz, 2H), 7.66 (d, *J* = 8.6 Hz, 2H), 5.15 (t, *J* = 7.2 Hz, 1H), 2.96 – 2.92 (m, 2H), 2.40 (q, *J* = 7.3 Hz, 2H), 1.68 (s, 3H), 1.63 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 199.4, 138.0, 136.3, 133.1, 129.6, 122.8, 100.9, 38.8, 25.8, 22.9, 17.8. IR (neat) ν 2963, 2924, 1738, 1674, 1579, 1447, 1390, 1274, 1057, 1004, 975, 836, 749, 536 cm⁻¹. HRMS (m/z): [M+H]⁺ calculated for C₁₃H₁₆IO: 315.0246; found: 315.0247.

³²⁵ Kalutharage, N.; Yi, C. S. *Angew. Chem. Int. Ed.* **2013**, *52*, 13651-13655.

³²⁶ Wang, J.; Pang, Y.-B.; Tao, N.; Zeng, R.-S. *J. Org. Chem.* **2019**, *84*, 15315-15322.

21h': ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.82 (d, *J* = 8.6 Hz, 2H), 7.66 (d, *J* = 8.6 Hz, 2H), 2.91 – 2.86 (m, 2H), 1.76 – 1.70 (m, 2H), 1.61 – 1.55 (m, 1H), 1.25 (ddd, *J* = 14.8, 8.8, 6.2 Hz, 2H), 0.89 (d, *J* = 6.6 Hz, 6H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 200.2, 138.0, 136.3, 129.6, 100.9, 38.9, 38.6, 28.0, 23.0, 22.6. HRMS (m/z): [M+H]⁺ calculated for C₁₃H₁₈IO: 317.0402; found: 317.0389.



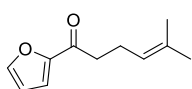
Chemical Formula: C₁₄H₁₅F₃O

- **5-methyl-1-(4-(trifluoromethyl)phenyl)hex-4-en-1-one (21i)**

According to general procedure E, using 1-(4-(trifluoromethyl)phenyl)ethan-1-one (94 mg, 0.5 mmol, 1.0 equiv.), prenol (102 μL, 1.0 mmol, 2 equiv.), NaOH (10 mg, 0.25 mmol, 0.5 equiv.), **Fe1** (2.5 mol%, 5.8 mg, 0.0125 mmol), and ^tBuOH (1.0 mL), the title compound **21i** was obtained in a mixture of unsaturated (**21i**) and saturated compound (**21i'**) in a 83:17 ratio after purification by silica gel column chromatography (pentane/ethyl acetate (95:5)). Colorless oil (67 mg, 52 % yield).

21i³²⁷: ¹H NMR (600 MHz, CDCl₃) δ (ppm): 8.06 (d, *J* = 8.1 Hz, 2H), 7.73 (d, *J* = 8.2 Hz, 2H), 5.16 (dddd, *J* = 7.2, 5.8, 2.8, 1.4 Hz, 1H), 3.04 – 3.00 (m, 2H), 2.43 (q, *J* = 7.3 Hz, 2H), 1.69 (s, 3H), 1.64 (s, 3H). ¹⁹F NMR (565 MHz, CDCl₃) δ (ppm): -63.0. ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 199.1, 139.7 (dd, *J* = 2.3, 1.2 Hz), 134.3 (q, *J* = 32.7 Hz), 133.3, 128.5, 125.7 (q, *J* = 3.8 Hz), 123.7 (d, *J* = 272.6 Hz), 122.6, 39.2, 25.8, 22.8, 17.8.

21i³²⁸: ¹H NMR (600 MHz, CDCl₃) δ (ppm): 8.06 (d, *J* = 8.1 Hz, 2H), 7.73 (d, *J* = 8.2 Hz, 2H), 2.99 – 2.95 (m, 2H), 1.74 – 1.71 (m, 2H), 1.62 – 1.56 (m, 1H), 1.26 – 1.25 (m, 2H), 0.91 (d, *J* = 6.6 Hz, 6H). ¹⁹F NMR (565 MHz, CDCl₃) δ (ppm): -63.0. ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 199.6, 139.7, 134.3 (q, *J* = 32.7 Hz), 128.5, 125.7 (q, *J* = 3.8 Hz), 123.7 (d, *J* = 272.6 Hz), 39.2, 38.6, 28.0, 22.6, 22.1.



Chemical Formula: C₁₁H₁₄O₂

- **1-(furan-2-yl)-5-methylhex-4-en-1-one (21j)**

According to general procedure E, using 2-acetylfuran (55 mg, 0.5 mmol, 1.0 equiv.), prenol (102 μL, 1.0 mmol, 2 equiv.), NaOH (10 mg, 0.25 mmol, 0.5 equiv.), **Fe1** (2.5 mol%, 5.8 mg, 0.0125 mmol), and ^tBuOH (1.0 mL), the title compound **21j** was obtained in a mixture of unsaturated (**21j**) and saturated compound (**21j'**) in a 91:9 ratio after purification by silica gel column chromatography (pentane/ethyl acetate (95:5)). Yellow oil (45 mg, 50 % yield).

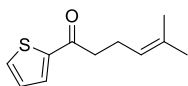
21j: ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.57 (dd, *J* = 1.6, 0.6 Hz, 1H), 7.17 (dd, *J* = 3.5, 0.6 Hz, 1H), 6.52 (dd, *J* = 3.5, 1.7 Hz, 1H), 5.14 (t, *J* = 7.2 Hz, 1H), 2.86 – 2.82 (m, 2H), 2.40 (q, *J* = 7.4 Hz, 2H), 1.68 (s, 3H), 1.63 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 189.4, 152.9, 146.3, 133.1,

³²⁷ Patent number WO2022160637A1.

³²⁸ Patent Number WO2016029021A1.

122.7, 117.0, 112.2, 38.7, 25.8, 23.0, 17.8. **IR (neat)** ν 2967, 2926, 1672, 1568, 1467, 1394, 1156, 1011, 883, 759, 595 cm^{-1} . **HRMS (m/z):** $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{11}\text{H}_{15}\text{O}_2$: 179.1072; found: 179.1073.

21j': **^1H NMR (600 MHz, CDCl_3) δ (ppm):** 7.57 (dd, $J = 1.6, 0.6$ Hz, 1H), 7.17 (dd, $J = 3.5, 0.6$ Hz, 1H), 6.52 (dd, $J = 3.5, 1.7$ Hz, 1H), 2.81 – 2.77 (m, 2H), 1.75 – 1.69 (m, 2H), 1.60 – 1.56 (m, 1H), 1.27 – 1.22 (m, 2H), 0.89 (d, $J = 6.6$ Hz, 6H). **^{13}C NMR (150 MHz, CDCl_3) δ (ppm):** 190.0, 152.9, 146.3, 116.9, 112.3, 38.8, 38.6, 28.0, 22.6, 22.3. **HRMS (m/z):** $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{11}\text{H}_{17}\text{O}_2$: 181.1229; found: 181.1224.



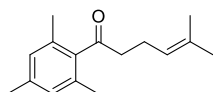
Chemical Formula: $\text{C}_{11}\text{H}_{14}\text{OS}$

- **1-(thiophen-2-yl)-5-methylhex-4-en-1-one (21k)**

According to general procedure E, using 2-acetylthiophene (54 μL , 0.5 mmol, 1.0 equiv.), prenol (102 μL , 1.0 mmol, 2 equiv.), NaOH (10 mg, 0.25 mmol, 0.5 equiv.), **Fe1** (2.5 mol%, 5.8 mg, 0.0125 mmol), and $^t\text{BuOH}$ (1.0 mL), the title compound **21k** was obtained in a mixture of unsaturated (**21k**) and saturated compound (**21k'**) in a 86:14 ratio after purification by silica gel column chromatography (pentane/ethyl acetate (95:5)). Yellow oil (10 mg, 10 % yield).

21k³²²: **^1H NMR (600 MHz, CDCl_3) δ (ppm):** 7.70 (dd, $J = 3.8, 1.1$ Hz, 1H), 7.62 (dd, $J = 4.9, 1.1$ Hz, 1H), 7.12 (dd, $J = 4.9, 3.8$ Hz, 1H), 5.16 (t, $J = 7.2$ Hz, 1H), 2.95 – 2.90 (m, 2H), 2.43 (q, $J = 7.4$ Hz, 2H), 1.69 (s, $J = 1.0$ Hz, 3H), 1.63 (s, 3H). **^{13}C NMR (150 MHz, CDCl_3) δ (ppm):** 193.1, 144.5, 133.5, 133.1, 131.8, 128.1, 122.8, 39.6, 25.8, 23.4, 17.8.

21k': **^1H NMR (600 MHz, CDCl_3) δ (ppm):** 7.70 (dd, $J = 3.8, 1.1$ Hz, 1H), 7.62 (dd, $J = 4.9, 1.1$ Hz, 1H), 7.12 (dd, $J = 4.9, 3.8$ Hz, 1H), 2.89 – 2.86 (m, 2H), 1.78 – 1.71 (m, 2H), 1.61 – 1.52 (m, 1H), 1.28 – 1.22 (m, 2H), 0.90 (d, $J = 6.6$ Hz, 6H). **^{13}C NMR (150 MHz, CDCl_3) δ (ppm):** 193.7, 144.6, 133.4, 131.7, 128.2, 39.8, 38.7, 28.0, 22.8, 22.6, 17.8. **HRMS (m/z):** $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{11}\text{H}_{17}\text{OS}$: 197.1000; found: 197.1000.



Chemical Formula: $\text{C}_{16}\text{H}_{22}\text{O}$

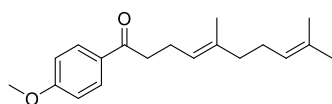
- **5-methyl-1-(2',4',6'-trimethylphenyl)hex-4-en-1-one (21l)**

According to general procedure E, using 2',4',6'-trimethylacetophenone (83 μL , 0.5 mmol, 1.0 equiv.), prenol (102 μL , 1.0 mmol, 2 equiv.), NaOH (10 mg, 0.25 mmol, 0.5 equiv.), **Fe1** (2.5 mol%, 5.8 mg, 0.0125 mmol), and $^t\text{BuOH}$ (1.0 mL), the title compound **21l** was obtained in a mixture of unsaturated (**21l**) and saturated compound (**21l'**) in a 54:46 ratio after purification by silica gel column chromatography (pentane/ethyl acetate (95:5)). Yellow oil (58 mg, 50 % yield).

21l³²²: **^1H NMR (600 MHz, CDCl_3) δ (ppm):** 6.82 (s, 2H), 5.14 (t, $J = 7.2$ Hz, 1H), 2.71 (t, $J = 7.4$ Hz, 2H), 2.39 (q, $J = 7.3$ Hz, 2H), 2.27 (s, 3H), 2.19 (s, 3H), 2.18 (s, 3H), 1.68 (s, 3H), 1.63 (s, 3H). **^{13}C**

NMR (150 MHz, CDCl₃) δ (ppm): 210.7, 139.8, 138.3, 133.0, 132.6, 128.6, 122.9, 44.9, 25.8, 22.2, 21.1, 19.2, 17.8.

211³²⁹: ¹H NMR (600 MHz, CDCl₃) δ (ppm): 6.83 (s, 2H), 2.69 – 2.65 (m, 2H), 2.27 (s, 3H), 2.19 (s, 3H), 2.18 (s, 3H), 1.73 – 1.69 (m, 2H), 1.60 – 1.55 (m, 1H), 1.26 – 1.21 (m, 2H), 0.90 (d, J = 6.6 Hz, 6H). **¹³C NMR (150 MHz, CDCl₃) δ (ppm):** 211.1, 140.0, 138.3, 132.6, 128.5, 45.2, 38.6, 28.1, 22.6, 22.2, 21.4, 19.2.



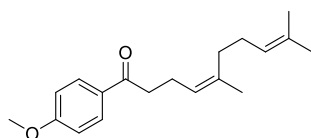
Chemical Formula: C₁₉H₂₆O₂

- **(E)-1-(4-methoxyphenyl)-5,9-dimethyldeca-4,8-dien-1-one (21m(E))**

According to general procedure E, using 1-(4-methoxyphenyl)ethan-1-one (75.58 mg, 0.5 mmol, 1.0 equiv.), geraniol (173.0 μ L, 1.0 mmol, 2 equiv.), NaOH (10 mg, 0.25 mmol, 0.5 equiv.), **Fe1** (2.5 mol%, 5.8 mg, 0.0125 mmol), and ^tBuOH (1.0 mL), the title compound **21m** was obtained in a mixture of unsaturated (**21m**) and saturated compound (**21m'**) in a 81:19 ratio after purification by silica gel column chromatography (pentane/ethyl acetate (95:5)) (E/Z = 82/18). Colorless oil (80 mg, 56 % yield).

21m(E): ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.95 (d, J = 9.0 Hz, 2H), 6.93 (d, J = 8.9 Hz, 2H), 5.18 (dd, J = 7.2, 5.9 Hz, 1H), 5.08 (t, J = 7.0 Hz, 1H), 3.87 (s, 3H), 2.96 – 2.93 (m, 2H), 2.42 (q, J = 7.1 Hz, 2H), 2.08 – 2.03 (m, 2H), 2.00 – 1.96 (m, 2H), 1.67 (s, 3H), 1.63 (s, 3H), 1.59 (s, 3H). **¹³C NMR (150 MHz, CDCl₃) δ (ppm):** 198.8, 163.4, 136.4, 131.5, 130.4, 130.3, 124.3, 123.0, 113.8, 55.5, 39.8, 38.5, 26.8, 25.8, 23.2, 17.8, 16.1. **IR (neat) ν** 2965, 2913, 1676, 1599, 1255, 1168, 1030, 977, 831, 568 cm⁻¹. **HRMS (m/z):** [M+H]⁺ calculated for C₁₉H₂₇O₂: 287.2011; found: 287.2012.

21m³³⁰: ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.95 (d, J = 9.0 Hz, 2H), 6.93 (d, J = 8.9 Hz, 2H), 5.11 (dd, J = 3.2, 1.5 Hz, 1H), 3.87 (s, 3H), 2.91 – 2.87 (m, 2H), 2.08 – 2.03 (m, 2H), 2.00 – 1.96 (m, 2H), 1.67 (s, J = 1.0 Hz, 3H), 1.60 (s, 3H), 1.45 (dt, J = 13.1, 6.5 Hz, 1H), 1.41 – 1.31 (m, 2H), 1.24 – 1.11 (m, 2H), 0.89 (d, J = 6.6 Hz, 3H). **¹³C NMR (150 MHz, CDCl₃) δ (ppm):** 199.3, 163.4, 131.2, 130.4, 130.3, 125.0, 113.8, 55.5, 38.7, 37.1, 36.8, 32.4, 25.8, 25.6, 22.2, 19.6, 17.7.



Chemical Formula: C₁₉H₂₆O₂

- **(Z)-1-(4-methoxyphenyl)-5,9-dimethyldeca-4,8-dien-1-one (21n(Z))**

According to general procedure E, using 1-(4-methoxyphenyl)ethan-1-one (75.58 mg, 0.5 mmol, 1.0 equiv.), nerol (175.0 μ L, 1.0 mmol, 2 equiv.), NaOH (10 mg, 0.25 mmol, 0.5 equiv.), **Fe1** (2.5 mol%,

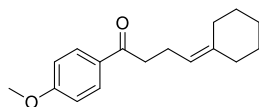
³²⁹ Frost, J. R.; Cheong, C. B.; Akhtar, W. M.; Caputo, D. F. J.; Stevenson, N. G.; Donohoe, T. J. *J. Am. Chem. Soc.* **2015**, *137*, 15664-15667.

³³⁰ Abdallah, M.-S.; Joly, N.; Gaillard, S.; Poater, A.; Renaud, J.-L. *Org. Lett.* **2022**, *24*, 5584-5589.

5.8 mg, 0.0125 mmol), and ^tBuOH (1.0 mL), the title compound **21n** was obtained in a mixture of unsaturated (**21n**) and saturated compound (**21n'**) in a 82:18 ratio after purification by silica gel column chromatography (pentane/ethyl acetate (95:5)). (E/Z = 42/58). Colorless oil (53 mg, 37 % yield).

21n(Z): ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.94 (d, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 5.21 – 5.17 (m, 1H), 5.10 – 5.06 (m, 1H), 3.87 (s, 3H), 2.94 (dd, *J* = 15.3, 7.9 Hz, 2H), 2.44 – 2.38 (m, 2H), 2.08 – 2.02 (m, 4H), 1.69 (d, *J* = 1.2 Hz, 3H), 1.67 (s, 3H), 1.60 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 198.7, 163.4, 136.5, 131.8, 130.4, 130.2, 124.3, 123.9, 113.7, 55.5, 39.8, 38.8, 26.6, 25.8, 23.5, 17.8, 16.1. IR (neat) ν 2964, 2914, 2854, 1676, 1599, 1509, 1442, 1255, 1168, 1030, 977, 831, 568 cm⁻¹. HRMS (m/z): [M+H]⁺ calculated for C₁₉H₂₇O₂: 287.2011; found: 287.2011.

21n³³⁰: ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.95 (d, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 5.11 (dd, *J* = 3.2, 1.5 Hz, 1H), 3.87 (s, 3H), 2.91 – 2.87 (m, 2H), 2.08 – 2.03 (m, 2H), 2.00 – 1.96 (m, 2H), 1.67 (s, *J* = 1.0 Hz, 3H), 1.60 (s, 3H), 1.45 (dt, *J* = 13.1, 6.5 Hz, 1H), 1.41 – 1.31 (m, 2H), 1.24 – 1.11 (m, 2H), 0.89 (d, *J* = 6.6 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 199.3, 163.4, 131.2, 130.4, 130.3, 125.0, 113.8, 55.5, 38.7, 37.1, 36.8, 32.4, 25.8, 25.6, 22.2, 19.6, 17.7.



Chemical Formula: C₁₇H₂₂O₂

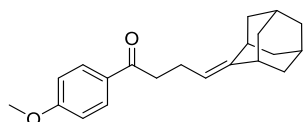
- **4-cyclohexylidene-1-(4-methoxyphenyl)butan-1-one (21o)**

According to general procedure E, using 1-(4-methoxyphenyl)ethan-1-one (75.58 mg, 0.5 mmol, 1.0 equiv.), cyclohexylideneethan-1-ol **20d** (126 mg, 1.0 mmol, 2 equiv.), NaOH (10 mg, 0.25 mmol, 0.5 equiv.), **Fe1** (2.5 mol%, 5.8 mg, 0.0125 mmol), and ^tBuOH (1.0 mL), the title compound **21o** was obtained in a mixture of unsaturated (**21o**) and saturated compound (**21o'**) in a 80:20 ratio after purification by silica gel column chromatography (pentane/ethyl acetate (95:5)). Colorless oil (48 mg, 37 % yield).

21o: ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.94 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 5.13 (t, *J* = 7.3 Hz, 1H), 3.87 (s, 3H), 2.96 – 2.91 (m, 2H), 2.41 (dd, *J* = 15.0, 7.4 Hz, 2H), 2.15 – 2.11 (m, 2H), 2.07 – 2.03 (m, 2H), 1.55 – 1.44 (m, 6H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 198.8, 163.4, 141.0, 130.4, 130.3, 119.7, 113.7, 55.6, 38.9, 37.2, 28.8, 28.7, 27.9, 27.0, 22.4. IR (neat) ν 2923, 2850, 1675, 1599, 1509, 1445, 1418, 1358, 1310, 1254, 1168, 1028, 978, 842, 828, 604, 568 cm⁻¹. HRMS (m/z): [M+H]⁺ calculated for C₁₇H₂₃O₂: 259.1698; found: 259.1695.

21o³³¹: ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.94 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 3.87 (s, 3H), 2.90 – 2.86 (m, 2H), 1.75 – 1.55 (m, 7H), 1.29 – 1.11 (m, 6H), 0.92 – 0.83 (m, 2H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 199.4, 163.4, 130.4, 130.3, 113.7, 55.6, 38.7, 37.7, 37.2, 33.4, 26.8, 26.5, 22.1.

³³¹ Yuan, B.; Ding, D.; Wang, C. *ACS Catal.* **2022**, *12*, 4261-4267.

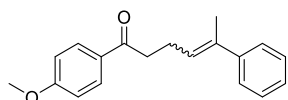


Chemical Formula: C₂₁H₂₆O₂

- **4-((1r,3r,5R,7S)-adamantan-2-ylidene)-1-(4-methoxyphenyl)butan-1-one (21p)**

According to general procedure E, using 1-(4-methoxyphenyl)ethan-1-one (75.58 mg, 0.5 mmol, 1.0 equiv.), 2-adamantylideneethanol **20f** (178 mg, 1.0 mmol, 2 equiv.), NaOH (10 mg, 0.25 mmol, 0.5 equiv.), **Fe1** (2.5 mol%, 5.8 mg, 0.0125 mmol), and ¹BuOH (1.0 mL), the title compound **21p** was obtained after purification by silica gel column chromatography (pentane/ethyl acetate (95:5)). White solid (41 mg, 26 % yield).

21p: ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.95 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 5.09 (t, *J* = 7.4 Hz, 1H), 3.87 (s, 3H), 2.96 – 2.90 (m, 2H), 2.83 (s, 1H), 2.40 (dd, *J* = 15.0, 7.4 Hz, 2H), 2.31 (s, 1H), 1.93 (s, 1H), 1.88 – 1.81 (m, 4H), 1.80 (s, 2H), 1.74 (s, 1H), 1.72 (s, 1H), 1.68 (s, 1H), 1.66 (s, 1H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 199.0, 163.4, 148.9, 130.5, 130.3, 114.7, 113.7, 55.6, 40.6, 39.9, 39.2, 39.0, 37.4, 32.2, 28.7, 22.1. IR (neat) ν 2899, 2845, 1666, 1605, 1578, 1507, 1422, 1362, 1276, 1255, 1200, 1179, 1108, 1033, 975, 773, 714, 604 cm⁻¹. HRMS (m/z): [M+H]⁺ calculated for C₂₁H₂₇O₂: 311.2011; found: 311.2011.

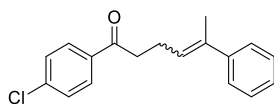


Chemical Formula: C₁₉H₂₀O₂

- **1-(4-methoxyphenyl)-5-phenylhex-4-en-1-one (21q)**

According to general procedure E, using 1-(4-methoxyphenyl)ethan-1-one (75.58 mg, 0.5 mmol, 1.0 equiv.), 3-phenylbut-2-en-1-ol **20g** (148 mg, 1.0 mmol, 2 equiv.), NaOH (10 mg, 0.25 mmol, 0.5 equiv.), **Fe1** (2.5 mol%, 5.8 mg, 0.0125 mmol), and ¹BuOH (1.0 mL), the title compound **21q** was obtained after purification by silica gel column chromatography (pentane/ethyl acetate (95:5)). Colorless oil (17 mg, 12 % yield, E:Z = 92:8).

21q: Major isomer: ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.97 (d, *J* = 9.0 Hz, 2H), 7.37 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.30 (t, *J* = 7.7 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 6.93 (d, *J* = 2.1 Hz, 2H), 5.82 (td, *J* = 7.3, 1.3 Hz, 1H), 3.87 (s, 3H), 3.10 – 3.05 (m, 2H), 2.64 (q, *J* = 7.5 Hz, 2H), 2.07 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 198.4, 163.5, 143.8, 135.9, 130.4, 130.2, 128.3, 126.9, 126.7, 125.7, 113.8, 55.6, 38.1, 23.8, 15.9. Minor isomer: ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.97 (d, *J* = 9.0 Hz, 2H), 7.37 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.30 (t, *J* = 7.7 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 6.93 (d, *J* = 2.1 Hz, 2H), 5.53 (td, *J* = 7.4, 1.4 Hz, 1H), 3.87 (s, 3H), 2.95 – 2.88 (m, 2H), 2.40 (dd, *J* = 14.3, 6.9 Hz, 2H), 2.03 (d, *J* = 1.2 Hz, 3H). IR (neat) ν 2931, 1674, 1598, 1509, 1418, 1361, 1307, 1254, 1167, 1026, 978, 831, 756, 696, 569 cm⁻¹. HRMS (m/z): [M+H]⁺ calculated for C₁₉H₂₁O₂: 281.1542; found: 281.1546.

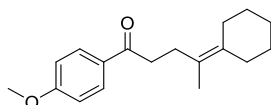


Chemical Formula: C₁₈H₁₇ClO

- **1-(4-chlorophenyl)-5-phenylhex-4-en-1-one (21r)**

According to general procedure E, using 1-(4-chlorophenyl)ethan-1-one (65 μ L, 0.5 mmol, 1.0 equiv.), 3-phenylbut-2-en-1-ol **20g** (148 mg, 1.0 mmol, 2 equiv.), NaOH (10 mg, 0.25 mmol, 0.5 equiv.), **Fe1** (2.5 mol%, 5.8 mg, 0.0125 mmol), and ^tBuOH (1.0 mL), the title compound **21r** was obtained after purification by silica gel column chromatography (pentane/ethyl acetate (95:5)). Yellow oil (61 mg, 43 % yield, E:Z = 91:9).

21r: Major isomer: ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.92 (d, J = 8.7 Hz, 2H), 7.44 (d, J = 8.7 Hz, 2H), 7.36 (dd, J = 8.3, 1.2 Hz, 2H), 7.30 (t, J = 7.7 Hz, 2H), 7.22 (t, J = 7.3 Hz, 1H), 5.80 (td, J = 7.3, 1.3 Hz, 1H), 3.12 – 3.08 (m, 2H), 2.64 (q, J = 7.4 Hz, 2H), 2.07 (d, J = 1.1 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 198.5, 143.7, 139.6, 136.2, 135.3, 129.6, 129.0, 128.3, 126.8, 126.4, 125.7, 38.5, 23.5, 16.0. Minor isomer: ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.92 (d, J = 8.7 Hz, 2H), 7.44 (d, J = 8.7 Hz, 2H), 7.36 (dd, J = 8.3, 1.2 Hz, 2H), 7.30 (t, J = 7.7 Hz, 2H), 7.22 (t, J = 7.3 Hz, 1H), 5.51 (td, J = 7.4, 1.5 Hz, 1H), 2.95 – 2.90 (m, 2H), 2.40 (dd, J = 15.1, 7.7 Hz, 2H), 2.05 (s, 3H). IR (neat) ν 2922, 1684, 1588, 1491, 1399, 1200, 1091, 1012, 824, 757, 695, 526 cm⁻¹. HRMS (m/z): [M+H]⁺ calculated for C₁₈H₁₈O₂Cl: 285.1046; found: 285.1045.



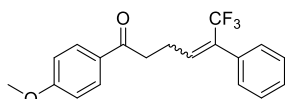
Chemical Formula: C₁₈H₂₄O₂

- **4-cyclohexylidene-1-(4-methoxyphenyl)pentan-1-one (21s)**

According to general procedure E, using 1-(4-methoxyphenyl)ethan-1-one (75.58 mg, 0.5 mmol, 1.0 equiv.), cyclohexylideneopropan-1-ol **20e** (420 mg, 1.5 mmol, 3 equiv.), NaOH (10 mg, 0.25 mmol, 0.5 equiv.), **Fe1** (2.5 mol%, 5.8 mg, 0.0125 mmol), and ^tBuOH (1.0 mL), the title compound **21s** was obtained in a mixture of unsaturated (**21s**) and saturated compound (**21s'**) in a 40:60 ratio after purification by silica gel column chromatography (pentane/ethyl acetate (95:5)). Colorless oil (113 mg, 83 % yield).

21s: ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.94 (d, J = 8.9 Hz, 2H), 6.93 (dd, J = 8.9, 1.0 Hz, 2H), 3.87 (s, 3H), 2.94 – 2.90 (m, 2H), 2.46 – 2.41 (m, 2H), 2.16 – 2.11 (m, 2H), 1.75 – 1.71 (m, 2H), 1.70 (s, 3H), 1.56 – 1.44 (m, 6H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 199.2, 163.4, 134.1, 130.4, 130.4, 123.2, 113.7, 55.5, 37.7, 30.7, 30.4, 29.3, 28.5, 27.0, 26.9, 18.1. HRMS (m/z): [M+H]⁺ calculated for C₁₈H₂₅O₂: 273.1855; found: 273.1856.

21s': ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.94 (d, J = 8.9 Hz, 2H), 6.93 (dd, J = 8.9, 1.0 Hz, 2H), 3.87 (s, 3H), 2.97 – 2.90 (m, 1H), 2.88 – 2.79 (m, 1H), 1.84 – 1.70 (m, 2H), 1.56 – 1.44 (m, 6H), 1.40 – 1.33 (m, 1H), 1.26 – 0.95 (m, 5H), 0.88 (d, J = 6.8 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 199.7, 163.4, 130.4, 130.4, 113.7, 55.5, 42.8, 38.1, 36.7, 30.7, 29.0, 28.7, 28.1, 27.0, 26.9, 16.1. HRMS (m/z): [M+H]⁺ calculated for C₁₈H₂₇O₂: 275.2011; found: 275.2014.

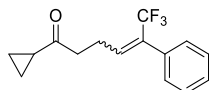


Chemical Formula: C₁₉H₁₇F₃O₂

- **6,6,6-trifluoro-1-(4-methoxyphenyl)-5-phenylhex-4-en-1-one (21t)**

According to general procedure E, using 1-(4-methoxyphenyl)ethan-1-one (75.58 mg, 0.5 mmol, 1.0 equiv.), 4,4,4-trifluoro-3-phenylbut-2-en-1-ol **20h** (202 mg, 1.0 mmol, 2 equiv.), NaOH (10 mg, 0.25 mmol, 0.5 equiv.), **Fe1** (2.5 mol%, 5.8 mg, 0.0125 mmol), and ^tBuOH (1.0 mL), the title compound **21t** was obtained after purification by silica gel column chromatography (pentane/ethyl acetate (95:5)). White solid (45 mg, 27 % yield, E:Z = 15:85).

21t: Major isomer: ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.88 (d, *J* = 8.9 Hz, 2H), 7.42 – 7.26 (m, 5H), 6.92 (d, *J* = 8.9 Hz, 2H), 6.50 (td, *J* = 7.5, 1.6 Hz, 1H), 3.87 (s, 3H), 2.99 (t, *J* = 7.3 Hz, 2H), 2.44 (qd, *J* = 7.5, 2.1 Hz, 2H). ¹⁹F NMR (565 MHz, CDCl₃) δ (ppm): -65.9. ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 196.9, 163.7, 135.41 (q, *J* = 5.4 Hz), 132.2, 132.2 (q, *J* = 29.7 Hz), 130.4, 129.7, 128.6, 128.6, 128.3, 123.52 (q, *J* = 272.9 Hz), 113.9, 55.6, 37.1, 23.1. **Minor isomer:** ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.96 (d, *J* = 8.9 Hz, 2H), 7.42 – 7.26 (m, 5H), 6.95 (d, *J* = 8.9 Hz, 2H), 6.14 (t, *J* = 7.8 Hz, 1H), 3.88 (s, 3H), 3.14 (t, *J* = 7.2 Hz, 2H), 2.87 (ddd, *J* = 14.9, 7.4, 2.4 Hz, 2H). ¹⁹F NMR (565 MHz, CDCl₃) δ (ppm): -57.2. ¹³C NMR (150 MHz, CDCl₃) δ (ppm): (Observed peaks) 197.1, 163.8, 140.6, 131.0, 130.4, 129.7, 128.8, 128.3, 128.2, 113.9, 55.6, 37.6, 24.4. **IR (neat)** ν 2971, 1662, 1599, 1574, 1508, 1364, 1312, 1276, 1259, 1151, 1113, 1021, 980, 843, 762, 695 cm⁻¹. **HRMS (m/z):** [M+H]⁺ calculated for C₁₉H₁₈O₂F₃: 335.1259; found: 335.1261.



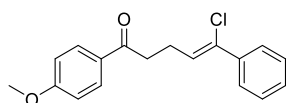
Chemical Formula: C₁₅H₁₅F₃O

- **1-cyclopropyl-6,6,6-trifluoro-5-phenylhex-4-en-1-one (21u)**

According to general procedure E, using cyclopropyl-methyl ketone (50 μL, 0.5 mmol, 1.0 equiv.), 4,4,4-trifluoro-3-phenylbut-2-en-1-ol **20h** (202 mg, 1.0 mmol, 2 equiv.), NaOH (20 mg, 0.5 mmol, 1 equiv.), **Fe1** (2.5 mol%, 5.8 mg, 0.0125 mmol), and ^tBuOH (1.0 mL), the title compound **21u** was obtained after purification by silica gel column chromatography (pentane/ethyl acetate (95:5)). Colorless oil (27 mg, 20 % yield, E:Z = 6:94).

21u: Major isomer: ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.41 – 7.35 (m, 3H), 7.24 (d, *J* = 7.7 Hz, 2H), 6.40 (td, *J* = 7.5, 1.6 Hz, 1H), 2.64 (t, *J* = 7.3 Hz, 2H), 2.32 – 2.27 (m, 2H), 1.86 (tt, *J* = 7.8, 4.6 Hz, 1H), 1.02 – 0.99 (m, 2H), 0.88 – 0.85 (m, 2H). ¹⁹F NMR (565 MHz, CDCl₃) δ (ppm): -65.9. ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 209.1, 135.1 (q, *J* = 5.6 Hz), 132.1, 132.1 (q, *J* = 29.4 Hz), 129.7, 128.6, 128.6, 123.5 (q, *J* = 272.9 Hz), 42.0 (d, *J* = 1.1 Hz), 22.7, 20.5, 11.0. **Minor isomer:** ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.41 – 7.35 (m, 3H), 7.24 (d, *J* = 7.7 Hz, 2H), 6.03 (t, *J* = 7.9 Hz, 1H), 2.54 – 2.51 (m, 2H), 2.33 – 2.27 (m, 2H), 1.86 (tt, *J* = 7.8, 4.6 Hz, 1H), 0.99 – 0.97 (m, 2H), 0.85 – 0.82 (m, 2H). ¹⁹F NMR (565 MHz, CDCl₃) δ (ppm): -69.8. ¹³C NMR (150 MHz, CDCl₃) δ (ppm): (Observed peaks) 210.2, 140.3, 135.2, 131.1, 129.8, 128.8, 128.8, 42.9, 22.8, 20.5, 11.0. **IR (neat)** ν

2925, 1700, 1385, 1301, 1167, 1113, 908, 763, 701, 515 cm^{-1} . **HRMS (m/z):** $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{15}\text{H}_{16}\text{OF}_3$: 269.1153; found: 269.1152.

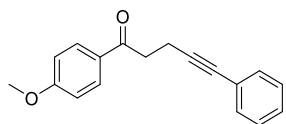


Chemical Formula: $\text{C}_{18}\text{H}_{17}\text{ClO}_2$

- **(Z)-5-chloro-1-(4-methoxyphenyl)-5-phenylpent-4-en-1-one (21v)**

According to general procedure E, using 1-(4-methoxyphenyl)ethan-1-one (75.58 mg, 0.5 mmol, 1.0 equiv.), (Z)-3-chloro-3-phenylprop-2-en-1-ol **20i** (169 mg, 1.0 mmol, 2 equiv.), NaOH (10 mg, 0.25 mmol, 0.5 equiv.), **Fe1** (2.5 mol%, 5.8 mg, 0.0125 mmol), and $^t\text{BuOH}$ (1.0 mL), the title compound **21v** was obtained after purification by silica gel column chromatography (pentane/ethyl acetate (95:5)). Yellow solid (38 mg, 25 % yield).

21v: $^1\text{H NMR}$ (600 MHz, CDCl_3) δ (ppm): 7.97 (d, $J = 9.0$ Hz, 2H), 7.56 (d, $J = 7.0$ Hz, 2H), 7.33 (t, $J = 7.3$ Hz, 2H), 7.29 (t, $J = 7.2$ Hz, 1H), 6.94 (d, $J = 9.0$ Hz, 2H), 6.28 (t, $J = 7.2$ Hz, 1H), 3.87 (s, 3H), 3.15 (t, $J = 7.2$ Hz, 2H), 2.81 (q, $J = 7.2$ Hz, 2H). $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ (ppm): 197.8, 163.6, 138.1, 133.8, 130.4, 130.0, 128.5, 128.4, 126.5, 126.5, 113.9, 55.6, 37.0, 24.5. **IR** (neat) ν 3003, 2964, 2929, 2836, 1670, 1598, 1572, 1506, 1415, 1368, 1309, 1253, 1169, 1029, 984, 889, 841, 738, 692, 605, 561, 495 cm^{-1} . **HRMS (m/z):** $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{18}\text{H}_{18}\text{O}_2\text{Cl}$: 301.0995; found: 301.0990.

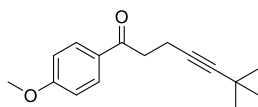


Chemical Formula: $\text{C}_{18}\text{H}_{16}\text{O}_2$

- **1-(4-methoxyphenyl)-5-(phenyl)pent-4-yn-1-one (24a)**³³²

According to general procedure E, using 1-(4-methoxyphenyl)ethan-1-one (75.58 mg, 0.5 mmol, 1.0 equiv.), 3-phenylprop-2-yn-1-ol (125 μL , 1.0 mmol, 2 equiv.), NaOH (10 mg, 0.25 mmol, 0.5 equiv.), **Fe1** (2.5 mol%, 5.8 mg, 0.0125 mmol), and $^t\text{BuOH}$ (1.0 mL), the title compound **24a** was obtained after purification by silica gel column chromatography (pentane/ethyl acetate (95:5)). Colorless oil (8 mg, 6 % yield). $^1\text{H NMR}$ (600 MHz, CDCl_3) δ (ppm): 7.99 (d, $J = 8.9$ Hz, 2H), 7.38 (dd, $J = 6.5, 3.2$ Hz, 2H), 7.29 – 7.26 (m, 3H), 6.95 (d, $J = 8.9$ Hz, 2H), 3.88 (s, 3H), 3.30 – 3.26 (m, 2H), 2.86 – 2.82 (m, 2H). $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ (ppm): 196.7, 163.7, 131.7, 130.5, 129.8, 128.3, 127.8, 123.8, 113.9, 89.2, 81.1, 55.6, 37.6, 14.5.

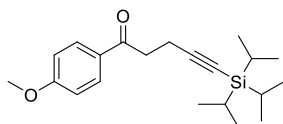
³³² Zheng, H.; Felix, R. J.; Gagné, M. R. *Org. Lett.* **2014**, *16*, 2272-2275.



Chemical Formula: C₁₆H₂₀O₂

- **1-(4-methoxyphenyl)-6,6-dimethylhept-4-yn-1-one (24b)**³³³

According to general procedure E, using 1-(4-methoxyphenyl)ethan-1-one (75.58 mg, 0.5 mmol, 1.0 equiv.), 4,4-dimethylpent-2-yn-1-ol (112 μ L, 1.0 mmol, 2 equiv.), NaOH (10 mg, 0.25 mmol, 0.5 equiv.), **Fe1** (2.5 mol%, 5.8 mg, 0.0125 mmol), and ^tBuOH (1.0 mL), the title compound **24b** was obtained after purification by silica gel column chromatography (pentane/ethyl acetate (95:5)). White solid (27 mg, 22 % yield). ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.96 (d, *J* = 8.9 Hz, 2H), 6.94 (d, *J* = 8.9 Hz, 2H), 3.87 (s, 3H), 3.14 – 3.10 (m, 2H), 2.58 – 2.55 (m, 2H), 1.17 (s, 9H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 197.3, 163.6, 130.5, 130.0, 113.8, 89.6, 77.4, 55.6, 38.1, 31.4, 27.4, 14.1.



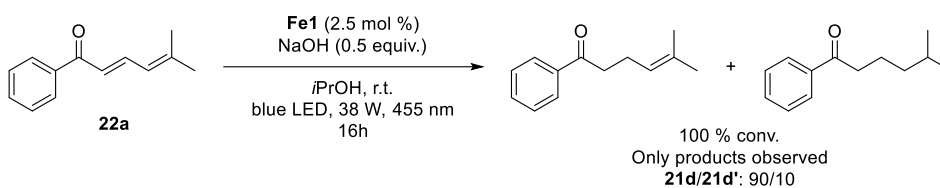
Chemical Formula: C₂₁H₃₂O₂Si

- **1-(4-methoxyphenyl)-5-(triisopropylsilyl)pent-4-yn-1-one (24c)**

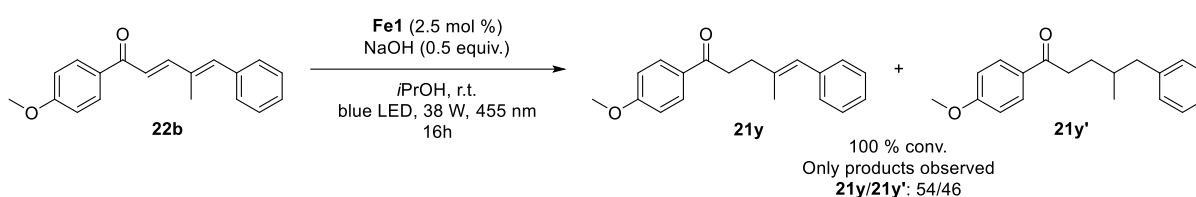
According to general procedure E, using 1-(4-methoxyphenyl)ethan-1-one (75.58 mg, 0.5 mmol, 1.0 equiv.), 3-triisopropylsilylprop-2-yn-1-ol (212 mg, 1.0 mmol, 2 equiv.), NaOH (10 mg, 0.25 mmol, 0.5 equiv.), **Fe1** (2.5 mol%, 5.8 mg, 0.0125 mmol), and ^tBuOH (1.0 mL), the title compound **24c** was obtained after purification by silica gel column chromatography (pentane/ethyl acetate (95:5)). Yellowish oil (45 mg, 25 % yield). ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.95 (d, *J* = 9.0 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 3.87 (s, 3H), 3.20 – 3.16 (m, 2H), 2.70 – 2.66 (m, 2H), 1.06 – 1.02 (m, 21H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 196.8, 163.6, 130.5, 129.9, 113.8, 107.8, 81.0, 55.6, 37.8, 18.7, 15.2, 11.3. IR (neat) ν 2941, 2864, 2173, 1679, 1600, 1510, 1462, 1360, 1257, 1208, 1168, 1031, 969, 882, 676, 660, 624, 457 cm⁻¹. HRMS (m/z): [M+H]⁺ calculated for C₂₁H₃₃O₂Si: 345.2250; found: 345.2244.

³³³ Wang, C.-Y.; Song, R.-J.; Xie, Y.-X.; Li, J.-H. *Synthesis* **2016**, *48*, 223-230.

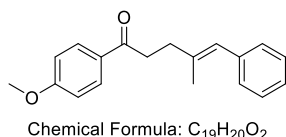
c) Mechanistic investigations.



In a 10 mL vial, dienone **22a** (139 mg, 0.5 mmol, 1.0 equiv.), **NaOH** (10 mg, 0.25 mmol, 0.5 equiv.), **Fe1** (2.5 mol%, 5.8 mg, 0.0125 mmol), *i*PrOH (1.0 mL) were poured in under an argon atmosphere. The reaction tube was sealed. The mixture was stirred at room temperature and exposed to blue light for 16 hours. The mixture was filtrated on celite, eluted with diethyl ether and concentrated under reduced pressure. The conversion was determined by ¹H NMR spectroscopy.



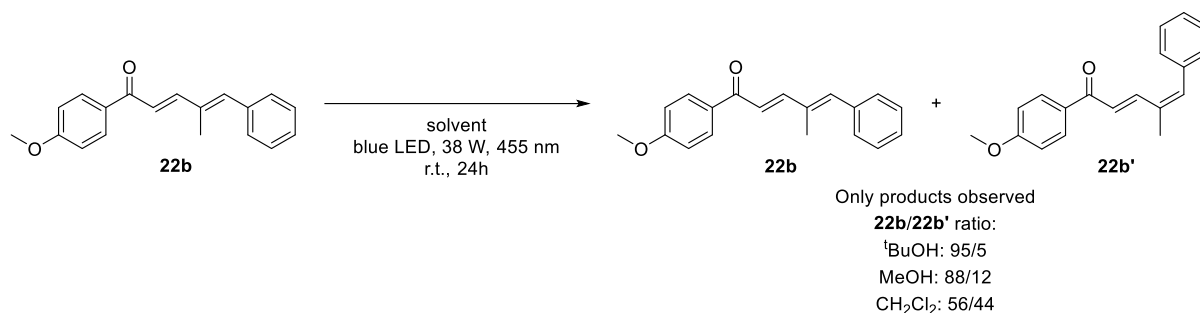
In a 10 mL vial, dienone **22b** (139 mg, 0.5 mmol, 1.0 equiv.), **NaOH** (10 mg, 0.25 mmol, 0.5 equiv.), **Fe1** (2.5 mol%, 5.8 mg, 0.0125 mmol), *i*PrOH (1.0 mL) were poured in under an argon atmosphere. The reaction tube was sealed. The mixture was stirred at room temperature and exposed to blue light for 16 hours. The mixture was filtrated on celite, eluted with diethyl ether and concentrated under reduced pressure. The conversion was determined by ¹H NMR spectroscopy.



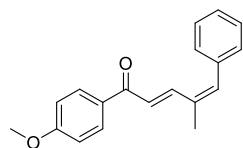
• **(E)-1-(4-methoxyphenyl)-4-methyl-5-phenylpent-4-en-1-one (21y)**

21y: ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.98 (d, *J* = 8.9 Hz, 2H), 7.31 (t, *J* = 7.7 Hz, 2H), 7.26 (t, *J* = 7.5 Hz, 1H), 7.22 (d, *J* = 7.3 Hz, 2H), 6.95 (d, *J* = 8.9 Hz, 2H), 6.33 (s, 1H), 3.88 (s, 3H), 3.17 – 3.12 (m, 2H), 2.62 – 2.57 (m, 2H), 1.91 (d, *J* = 1.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 198.5, 163.5, 141.2, 137.9, 130.5, 130.2, 128.9, 128.1, 126.1, 125.5, 113.8, 55.6, 37.1, 34.9, 18.1.

21y': ¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.91 (d, *J* = 8.9 Hz, 2H), 7.26 (t, *J* = 7.5 Hz, 1H), 7.19 (t, *J* = 7.0 Hz, 2H), 7.15 (d, *J* = 7.0 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 3.87 (s, 3H), 3.01 – 2.94 (m, 1H), 2.92 – 2.86 (m, 1H), 2.69 (dd, *J* = 13.7, 5.6 Hz, 1H), 2.44 (dd, *J* = 13.5, 7.9 Hz, 1H), 1.85 – 1.78 (m, 2H), 1.63 – 1.57 (m, 1H), 0.91 (d, *J* = 6.5 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ (ppm): 199.3, 163.4, 138.4, 130.4, 130.2, 129.3, 128.3, 125.9, 113.8, 55.6, 43.7, 36.2, 35.3, 31.5, 19.4.



In a 10 mL vial, dienone **22b** (139 mg, 0.5 mmol, 1.0 equiv.) and the appropriate solvent (1.0 mL) were poured in under an argon atmosphere. The reaction tube was sealed. The mixture was stirred at room temperature and exposed to blue light for 24 hours. The mixture was concentrated under reduced pressure. The conversion was determined by ¹H NMR spectroscopy.

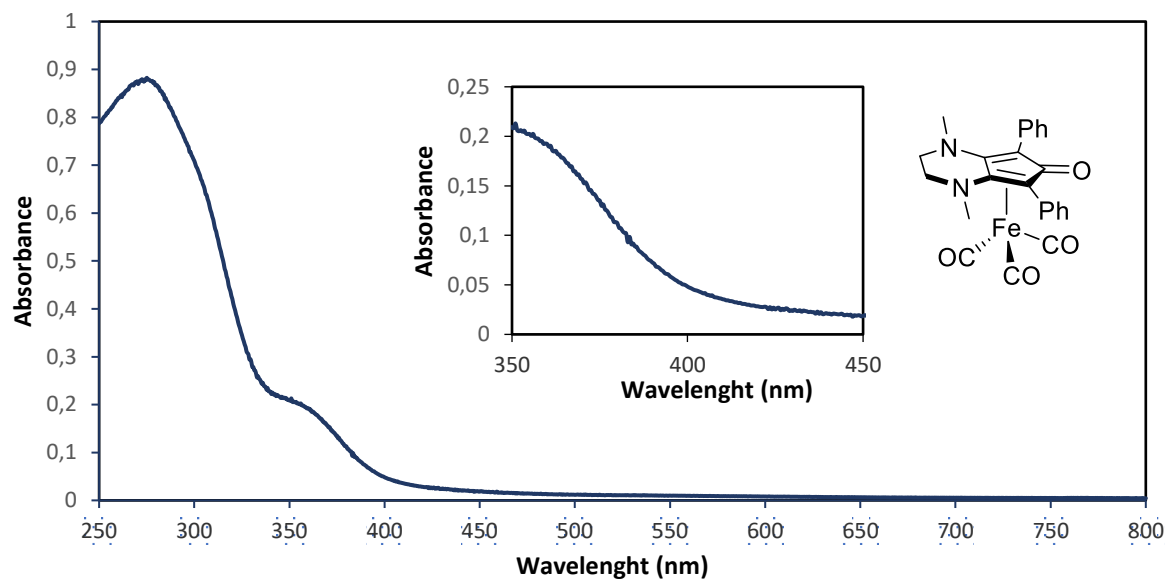


Chemical Formula: C₁₉H₁₈O₂

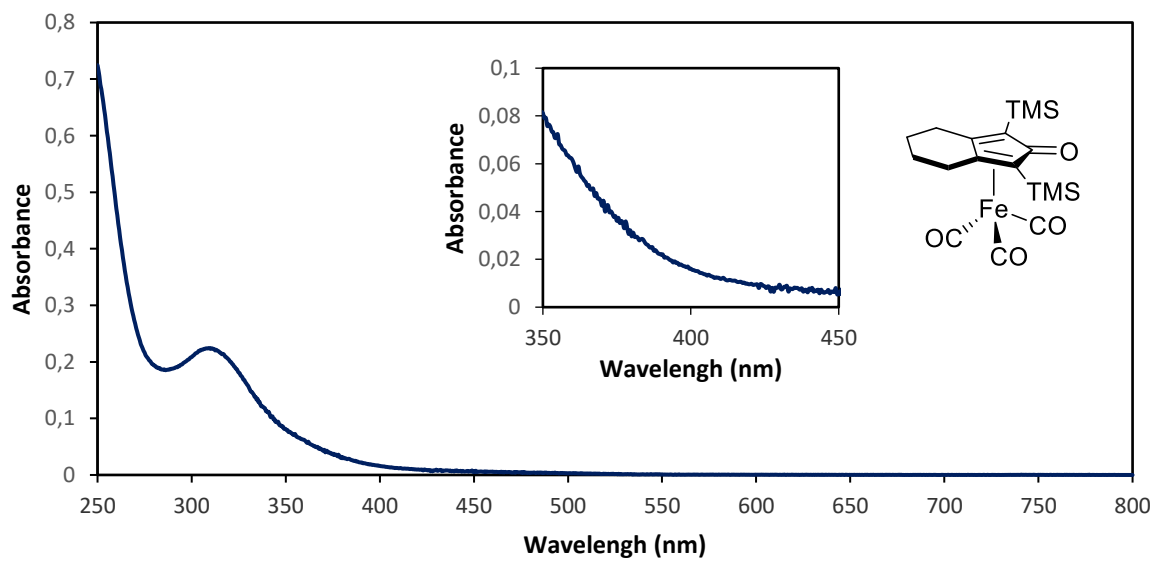
- **(2E,4Z)-1-(4-methoxyphenyl)-4-methyl-5-phenylpenta-2,4-dien-1-one (22b')**

¹H NMR (600 MHz, CDCl₃) δ (ppm): 7.99 (d, *J* = 8.9 Hz, 2H), 7.94 (dd, *J* = 15.4, 0.6 Hz, 1H), 7.38 – 7.34 (m, 2H), 7.32 – 7.29 (m, 1H), 7.30 – 7.27 (m, 2H), 7.11 (d, *J* = 15.4 Hz, 1H), 6.96 (d, *J* = 8.9 Hz, 2H), 6.89 (s, 1H), 3.88 (s, 3H), 2.16 (d, *J* = 1.4 Hz, 3H). **¹³C NMR (150 MHz, CDCl₃) δ (ppm):** 189.3, 163.4, 142.1, 138.1, 136.7, 133.4, 131.3, 130.8, 129.7, 128.5, 127.7, 123.7, 113.9, 55.6, 21.0.

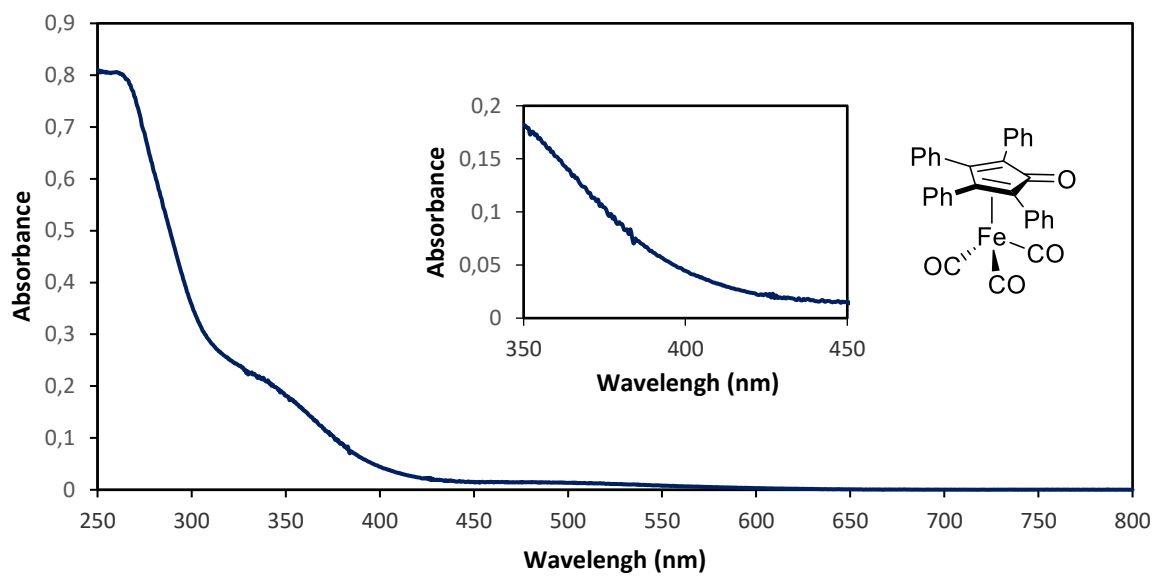
5) UV-Vis spectra of iron complexes.



Absorbance spectrum of complex Fe1 (100 μM in MeOH).



Absorbance spectrum of complex Fe2 (100 μM in MeOH).



Absorbance spectrum of complex Fe3 (100 μM in MeOH).

GENERAL CONCLUSION

The objectives of this thesis were the development of new methodologies for C-N and C-C bonds formation through the hydrogen autotransfer strategy, the investigation of the reaction mechanisms involved and the improvement of Knölker-type complexes in these reactions.

An efficient alkylation of hydrazide derivatives was described using the cyclopentadienone ruthenium tricarbonyl complex **Ru1** (Chapter II.). This ruthenium complex showed a greater performance than the iron analogues. A deep mechanistic understanding of the reaction unveiled the selectivity for the mono- or di-alkylation of these substrates. With the calculation of the %V_{Bur} it is now possible to predict whether the mono- or di-alkylated product will be obtained with our system. Further exploration of this reaction allowed the synthesis of non-symmetric dialkylated hydrazides using methanol or ethanol as a coupling partner. The order of alkylation was demonstrated both theoretically and experimentally.

Pursuing our investigation on nitrogen containing compounds, the synthesis of 3-arylquinolin-2-(1*H*)-ones was developed (Chapter III.). The Knölker complex **Fe3** was used as a catalyst. This work represents the first example of a dehydrogenative coupling approach to such heterocycles. This strategy allowed the obtention of functionalised heterocycles with substitution in any position of the quinolinone product. Even though this methodology was limited to arylacetamides, it paves the way for the synthesis of cyclic and non-cyclic enamides.

As the diaminocyclopentadienone iron complex **Fe1** showed, in general, a higher activity than the other Knölker-type complexes in alkylation or reductive amination reactions, a theoretical study of this complex was performed aiming to improve its efficiency (Chapter IV.). This study showed the key role of electronic effects in the catalytic activity of the complex and more specifically for the activation step. EWGs substituted catalysts were predicted to be more active in the studied reductive amination reaction. The theoretical observations were confirmed afterwards experimentally with a shorter reaction time for the CF₃-substituted iron complexes **Fe15** and **Fe16**.

The iron complex **Fe1** was also found to be active at room temperature under light irradiation (Chapter V.). The mild conditions used to perform the alkylation of carbonyl compounds with aliphatic, benzylic, allylic and propargylic alcohols highlights the potential of this new methodology. The functional groups tolerance was therefore improved as temperature-sensitive molecules can now be engaged. Some limitations were found (ethers, substituted allylic alcohols, bulky propargyl alcohols), but the scope of such a reaction has to be re-evaluated more deeply to delineate the limits of this new methodology.

The works performed along this thesis is framed within the topics developed by Renaud and Poater in the last decade concerning the development of more efficient catalysts based on cheap Earth-abundant metals. Exploration of hydrogen autotransfer reactions with new partners could extend the applicability of this strategy and catalysts. Another continuation of this thesis is the design of a chromophoric Knölker-type catalyst able to harvest a larger band of visible light. Such modifications could make the alkylation reaction possible using harmless white lamps rather than powerful blue LEDs. The development of a stereoselective alkylation reaction can also be targeted with the improved mild reaction conditions presented. Finally, the combination of two different catalysts in a dual system could enable the formation of complex molecules in a one-pot approach.

Résumé.

I. Introduction.

Durant les dernières décennies, de nouvelles méthodologies ont été développées pour la formation de liaisons C-N et C-C utilisant les réactions d'autotransfer d'hydrogène. Ces réactions ont été définies pour la première fois par Williams en 2004 sous le nom de « Borrowing Hydrogen »,¹ bien que plusieurs exemples aient déjà été décrits précédemment dans la littérature.² Cette stratégie consiste en l'utilisation d'alcools en tant qu'agents alkylants à la place de dérivés halogénés, ces derniers étant préparés à partir d'alcools, menant donc à des étapes de synthèse supplémentaires et à la génération de déchets.³ C'est pourquoi l'utilisation d'alcools pour la synthèse de produits carbonés et azotés présente un grand intérêt, notamment grâce à leur présence dans les milieux naturels et leur disponibilité directe à partir de la biomasse.⁴ De cette manière, les réactions par autotransfer d'hydrogène font partie du domaine de la chimie verte et durable. Le mécanisme général de ces réactions est le suivant : un alcool est déshydrogéné en présence d'un complexe organométallique pour générer la fonction carbonyle correspondante et un complexe de type métal-hydrure (Schéma 6.1). La présence d'un nucléophile dans le milieu réactionnel engendre une étape de condensation avec le dérivé carbonyle générant une espèce insaturée qui est finalement réduite par le complexe métal-hydrure.

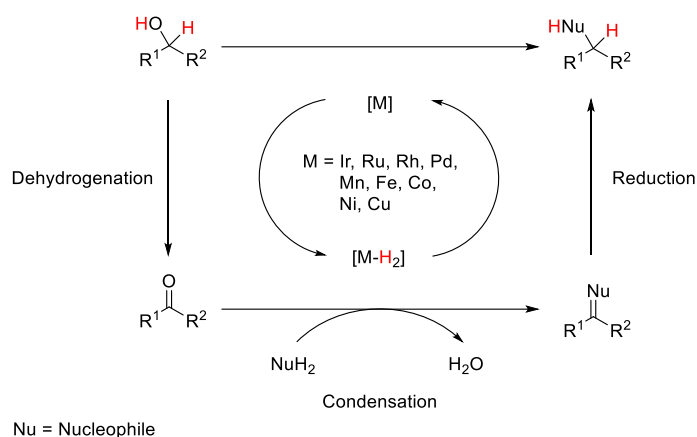


Schéma 6.1 : Mécanisme général des réactions par autotransfer d'hydrogène.

De nombreux métaux nobles tels que l'iridium,⁵ le rhodium⁶ ou le ruthenium⁷ ont été décrits comme catalysant de telles réactions. L'alkylation de nucléophiles variés tels que les cétones,⁸ les amides ou esters,⁹ les amines,¹⁰ les nitriles¹¹ ou les dérivés nitros¹² a été décrite (Figure 6.1). Les réactions d'alkylation ou de synthèse d'hétérocycles ont aussi été décrites.^{13,14}

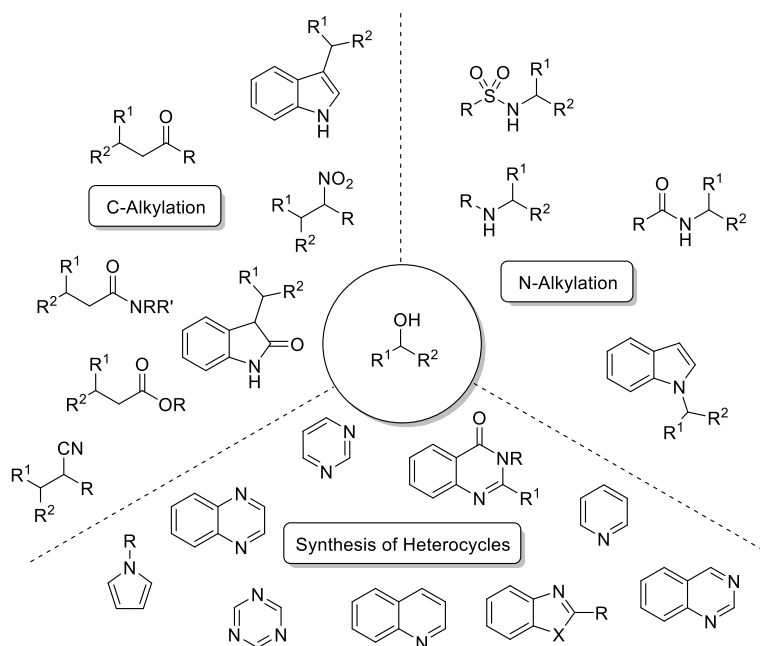


Figure 6.1 : Exemples de produits d'alkylation et de synthèse d'hétérocycles.

Néanmoins, la rareté de ces métaux et leur demande toujours croissante rend leur utilisation de plus en plus coûteuse. Ces dernières années, les complexes de métaux abondants tels que le manganèse, le fer ou le cobalt, ont prouvé leur efficacité, comparé aux métaux nobles et leur compétitivité dans les réactions d'alkylation.¹⁵ Notre groupe s'est plus particulièrement intéressé au fer qui est, parmi tous les métaux de transition, le plus abondant de la croûte terrestre et par conséquent le moins cher (quelques dizaines de centimes par kilogramme). Grâce à l'utilisation de ligands organophosphorés, la chimie du fer s'est bien établie ces dernières années.¹⁶ Toutefois, ces ligands sont souvent coûteux, sensibles à l'air et à l'humidité. Le développement de ligands moins chers tels que les cyclopentadiénones a pour but de pallier à ces problèmes. Basés sur les travaux de Knölker (**Fe3**, Figure 6.2),¹⁷ notre groupe a développé différents complexes de fer portant des ligands cyclopentadiénones (**Fe1** et **Fe2**, parmi d'autres) et a contribué à l'utilisation de ces complexes en catalyse homogène, plus particulièrement pour la réduction de composés carbonyles¹⁸ et les aminations réductrices.¹⁹ Le complexe de fer **Fe1** a démontré une plus grande activité et sélectivité que le complexe de Knölker **Fe3** et a été engagé dans diverses réactions d'alkylation avec des composés de type anilines,²⁰ indoles,²¹ alcools²² ou cétones.²³

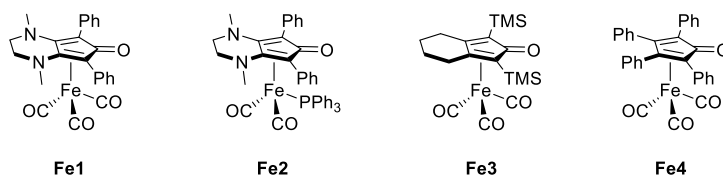


Figure 6.2 : Complexes de fer utilisés durant cette thèse.

Dans la continuité de ces travaux, les principaux objectifs de cette thèse portent sur le développement de nouvelles méthodologies pour la formation de liaisons C-N et C-C, la détermination des mécanismes réactionnels et l'amélioration des complexes de type Knölker. Dans certains cas, l'utilisation de complexes de ruthénium analogues a été étudiée, permettant de pallier au manque de réactivité des complexes de fer (Figure 6.3).

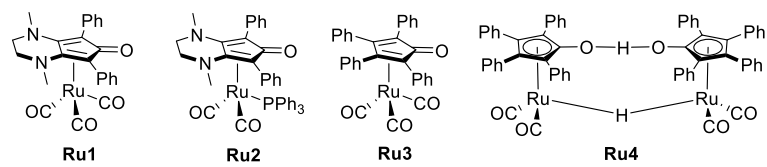


Figure 6.3 : Complexes de ruthénium utilisés durant cette thèse.

II. Alkylation d'hydrazides à partir d'alcools.

Les hydrazides sont des molécules azotées portant une fonction acyle sur l'un des deux atomes d'azote du motif hydrazine. Ces dérivés sont d'importants synthons puisqu'ils trouvent des applications dans la synthèse de médicaments, de produits phytosanitaires ou encore la fabrication de polymères.¹³⁴ L'approche la plus connue pour obtenir des hydrazides substituées repose sur l'utilisation de dérivés halogénés en conditions basiques, ou bien sur la condensation d'une fonction carbonyle suivie de la réduction de la liaison C=N par un agent réducteur en proportion équimolaire. Nous nous sommes donc intéressés à l'alkylation de ce type de substrats par réaction d'autotransfer d'hydrogène à partir d'alcools.

La première réaction d'alkylation d'hydrazide par autotransfer d'hydrogène a été décrite par Zhou en 2017 (Schéma 6.2).¹³⁶ De nombreux alcools benzyliques ont pu être engagés en présence d'un sel de nickel et d'une diphosphine en conditions acides. L'utilisation d'un ligand chiral ((S)-Binapine) a permis d'obtenir des excès énantiomériques allant de 72 à 96 %. Plus récemment, Gunanathan a décrit la dialkylation d'hydrazides à partir d'alcools catalysée par un complexe de ruthénium de type Macho, cette fois-ci en conditions basiques (Schéma 6.2).¹³⁸

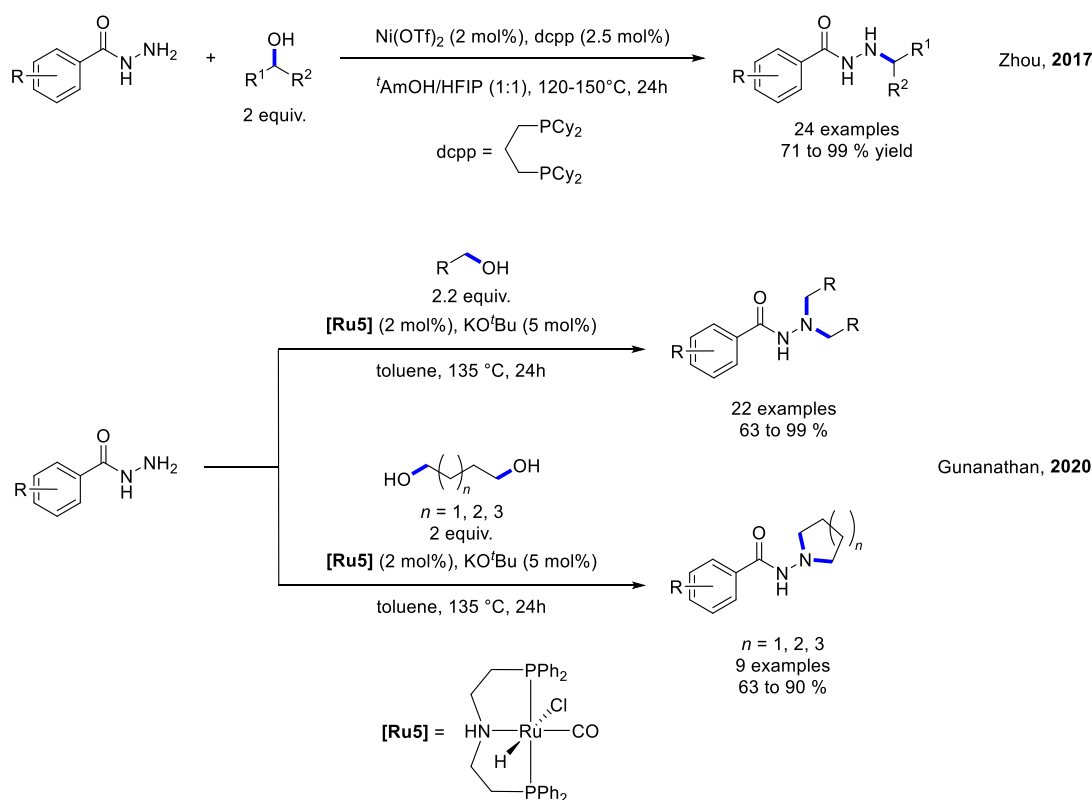


Schéma 6.2 : Alkylation d'hydrazides par autotransfer d'hydrogène précédemment décrites.

Basé sur ces précédents travaux, nous nous sommes intéressés à l'alkylation d'hydrazides par des alcools catalysée par un complexe de fer tricarbonyle à ligand cyclopentadiénone. Malheureusement, aucun de ces complexes n'a permis d'obtenir les produits désirés. Toutefois, l'utilisation des analogues au ruthénium a ouvert la voie aux produits d'alkylation, et le complexe **Ru1** a montré la plus grande activité dans cette réaction. Différents alcools primaires ont pu être engagés dans cette réaction, donnant les produits dialkylés avec des rendements allant de 54 à 93 % (Schéma 6.3).¹⁴⁶ De façon surprenante,

les alcools primaires α -substitués, encombrés ou les alcools secondaires n'ont permis d'obtenir que le produit de mono-alkylation avec des rendements allant de 47 à 71 % (Schéma 6.3).

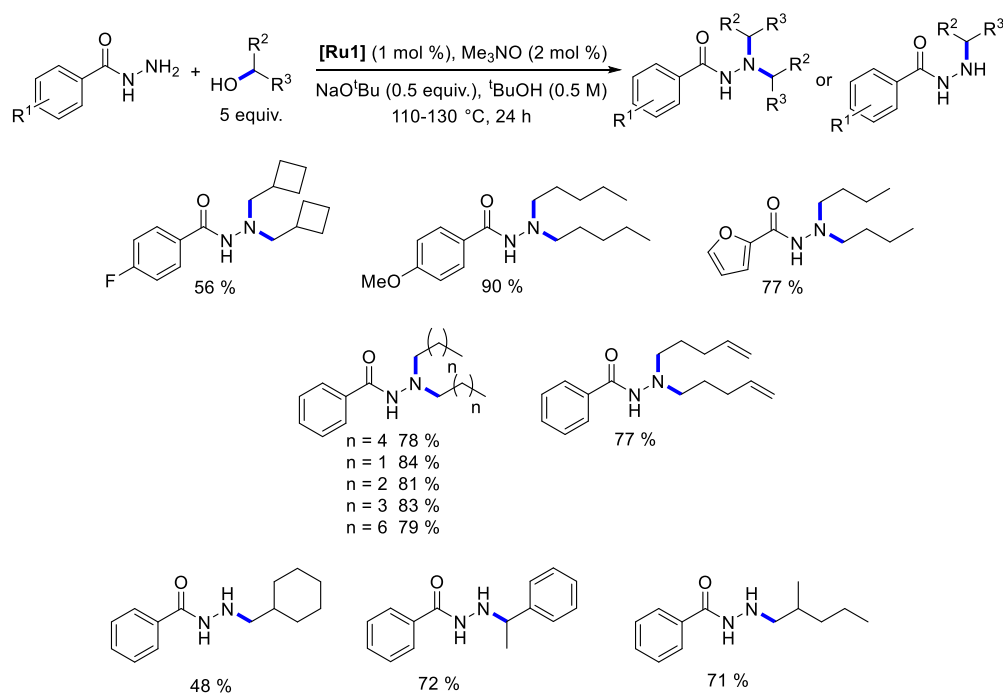


Schéma 6.3 : Mono- et di-alkylation d'acyl hydrazides catalysés par **Ru1**.

Pour comprendre cette différence de sélectivité, une étude DFT a été réalisée. Dans cette réaction, l'étape de condensation de l'hydrazide sur la fonction carbonyle semble être l'étape cinétiquement déterminante. Plus précisément, lors de la seconde étape d'alkylation, la formation de l'iminium intermédiaire est l'étape cinétiquement déterminante (Figure 6.4). Le calcul de la barrière énergétique correspondant à cette étape de condensation a montré que la formation de l'intermédiaire iminium était limitée par l'encombrement stérique autour de l'atome de carbone portant la fonction alcool, les alcools encombrés donnant des barrières énergétiques beaucoup plus élevées. Pour éviter de calculer les niveaux d'énergie pour chaque alcool, il a été proposé de calculer l'encombrement stérique autour de l'atome de carbone porteur de la fonction alcool pour chacun des pro-électrophiles utilisés. Le calcul de cet encombrement (% V_{Bur}) introduit pour la première fois par Cavallo *et al*¹⁴⁷ a permis de déterminer une limite d'encombrement située entre 45 et 48 % pour laquelle, sous cette limite le produit de dialkylation est obtenu alors qu'au-dessus de cette limite le produit de monoalkylation sera obtenu (Table 6.1).

Table 6.1 : % V_{Bur} des alcools étudiés (rayon de la sphère : 3,5 Å, le carbone en alpha de l'alcool est à l'origine de la sphère).

Alcool (menant à la dialkylation)	% V_{Bur}	Alcool (menant à la monoalkylation)	% V_{Bur}
Methanol	25.6	Citronellol	45.4
Ethanol	36.9	Cyclohexylmethanol	47.7
Propan-1-ol	42.3	2-methylpentan-1-ol	47.9
Butan-1-ol	42.3	2,2-dimethylpropan-1-ol	53.1

Pent-4-en-1-ol	42.3	Cyclopentanol	53.9
3-phenylethan-1-ol	42.4	1-(thiophen-2-yl)ethan-1-ol	55.5
Cyclopropylmethanol	43.9	1-phenylethan-1-ol	55.8
Cyclobutylmethanol	44.6	1-(benzo[d][1,3]dioxol-5-yl)ethan-1-ol	57.3
Benzyl alcohol	44.7	1-(naphthalen-2-yl)ethan-1-ol	59.0
2-phenylethan-1-ol	45.2		

Basé sur ces résultats et des travaux précédents sur l'alkylation tandem de cétones, nous avons proposé de développer une réaction d'alkylation multi composants permettant d'accéder à des hydrazides dialkylés non-symétriques en utilisant deux alcools différents en un seul pot.¹⁴⁸ La réalisation d'une telle réaction repose sur la différence d'énergie d'oxydation des deux alcools de départ. Le méthanol a été choisi pour démarrer cette étude car il présente l'énergie d'oxydation la plus haute (84 kJ/mol *versus* 68 kJ/mol pour éthanol par exemple). Après optimisation des conditions réactionnelles, divers alcools primaires et secondaires ont été engagés dans cette réaction, permettant la préparation de produits dialkylés non-symétriques avec des rendements allant de 35 à 79 % (Schéma 6.4). Des rendements plus faibles ont été obtenus avec les alcools aliphatiques dus à leurs énergies d'oxydation plus proches de celle du méthanol, rendant cette réaction plus complexe. Les alcools primaires encombrés ou secondaires ont aussi mené à des rendements plus faibles en raison de leur encombrement stérique, favorisant la formation du produit diméthylé.

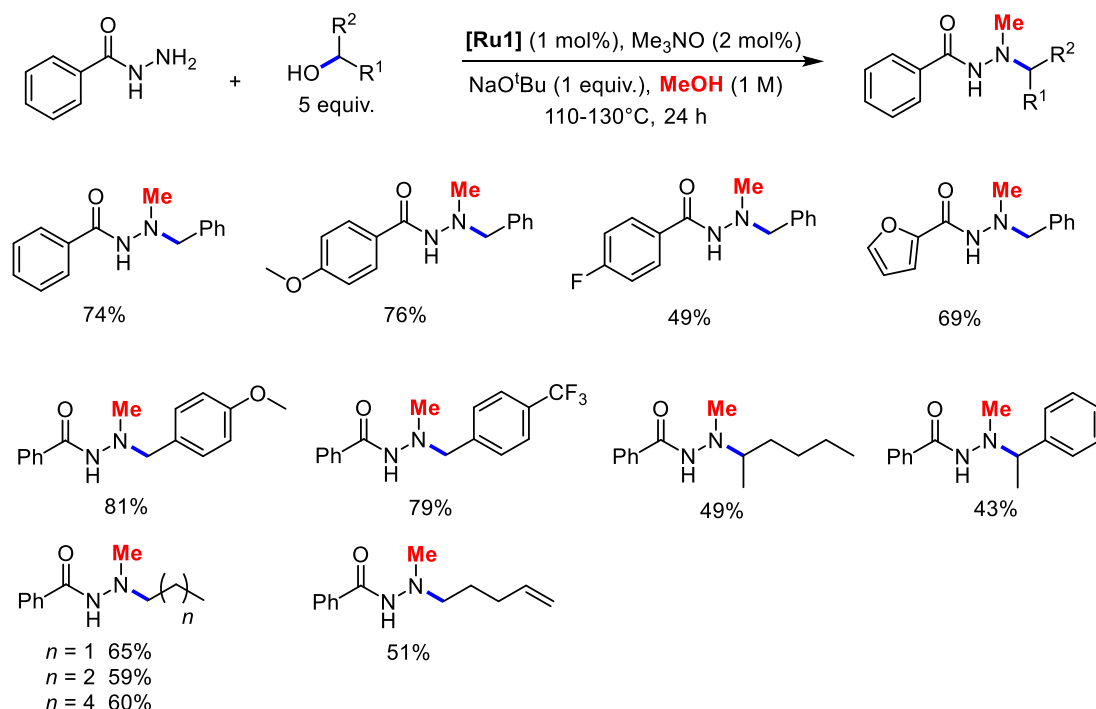


Schéma 6.4 : Dialkylation non-symétrique d'hydrazides avec le méthanol.

Pour aller plus loin, le méthanol a été remplacé par l'éthanol (Schéma 6.5). Ce dernier rend cette réaction d'autant plus complexe puisque son énergie d'oxydation est beaucoup plus proche de celle des autres alcools. Par conséquent, il devient plus difficile de faire la différence entre l'éthanol et le second

alcool. Après une optimisation des conditions réactionnelles, des produits de dialkylation non-symétriques ont été obtenus avec des rendements allant de 48 à 71 %.

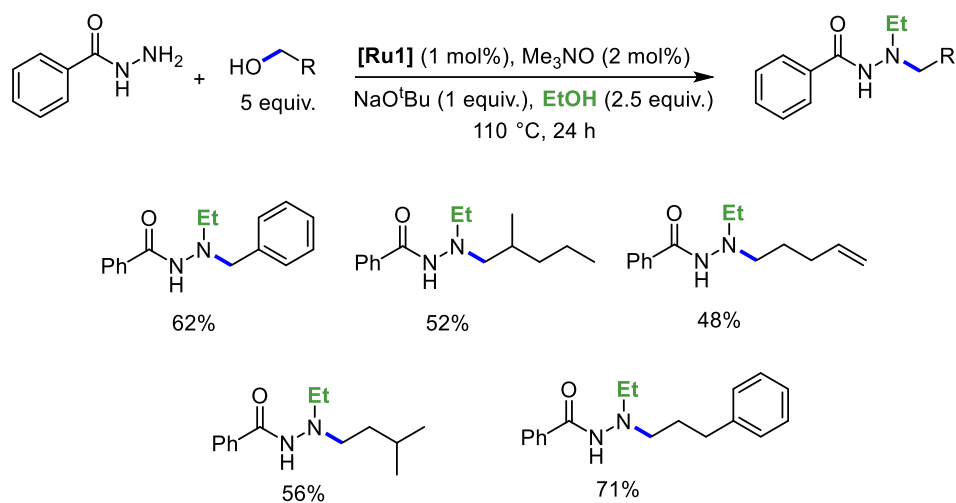


Schéma 6.5 : Alkylation non-symétrique d'hydrazides avec l'éthanol.

Afin de déterminer l'ordre d'alkylation permettant d'obtenir le produit non-symétrique, une étude DFT a été réalisée. Une fois la première alkylation réalisée avec différents alcools (méthanol, alcool benzylique, ...), une seconde alkylation par le méthanol présente une barrière énergétique d'environ 32 kcal/mol, peu importe le premier alcool ayant été alkylé. En revanche, l'alkylation par l'alcool benzylique du méthyl hydrazide présente une barrière énergétique plus élevée, d'environ 36 kcal/mol, rendant cette étape plus difficile à réaliser. Ainsi, le produit non-symétrique est obtenu par une première alkylation avec l'alcool le plus encombré, puis une seconde alkylation avec le méthanol. Cette étude a pu être confirmée expérimentalement en réalisant la réaction d'alkylation non-symétrique de façon séquentielle.

III. Synthèse de quinolin-2(1H)-ones par couplage déshydrogénant d'amido-alcools.

Les quinolin-2(1H)-ones sont des hétérocycles azotés pouvant être assimilés à des amides cycliques. De telles structures peuvent être rencontrées dans une grande diversité de produits présentant des activités biologiques.¹⁶⁴ Ces motifs sont traditionnellement préparés via des réactions de type Vilsmeier-Haak¹⁶⁸ ou Friedlander,¹⁶⁹ mais des synthèses alternatives utilisant la catalyse par des métaux de transition ont été développées ces dernières années.^{171,173,175,177,178} Toutefois, ces synthèses nécessitent l'utilisation de dérivés halogénés permettant de réaliser les réactions de couplages correspondantes. Les synthèses d'hétérocycles par réactions de couplage déshydrogénant catalysées par des métaux de transition se sont alors développées permettant des approches plus durables de ces motifs.^{180,14} Le mécanisme général de ces réactions est décrit sur le schéma 6.6. Dans une première étape, le catalyseur métallique oxyde un alcool par déshydrogénation pour générer le dérivé carbonyle correspondant et une espèce métal-hydrure. Contrairement aux réactions d'alkylation, ce dernier va libérer une molécule d'hydrogène assisté ou non par un oxydant pour régénérer l'espèce catalytique. Le dérivé carbonyle subit alors une étape de condensation intramoléculaire menant à un produit insaturé cyclique.

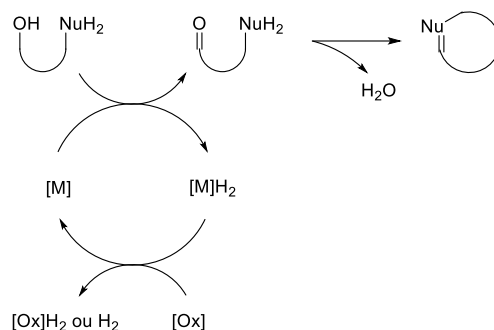


Schéma 6.6 : Mécanisme général du couplage déshydrogénant.

Ce type de couplage déshydrogénant a été appliqué à la synthèse de nombreux hétérocycles aromatiques. Cependant, à l'heure actuelle, aucune synthèse de quinolin-2(1H)-ones n'a été décrite par cette méthodologie. L'approche que nous avons proposée repose sur la condensation/cyclisation intramoléculaire d'amido-alcools. Pour ce faire, divers amido-alcools ont été préparés suivant différentes méthodes. Une première approche a permis la synthèse en deux étapes de *N*-(2-(hydroxyméthyl)phényl)-2-arylacétamides à partir d'acides 2-arylacétiques avec des rendements allant de 37 à 91 % (Schéma 6.7).

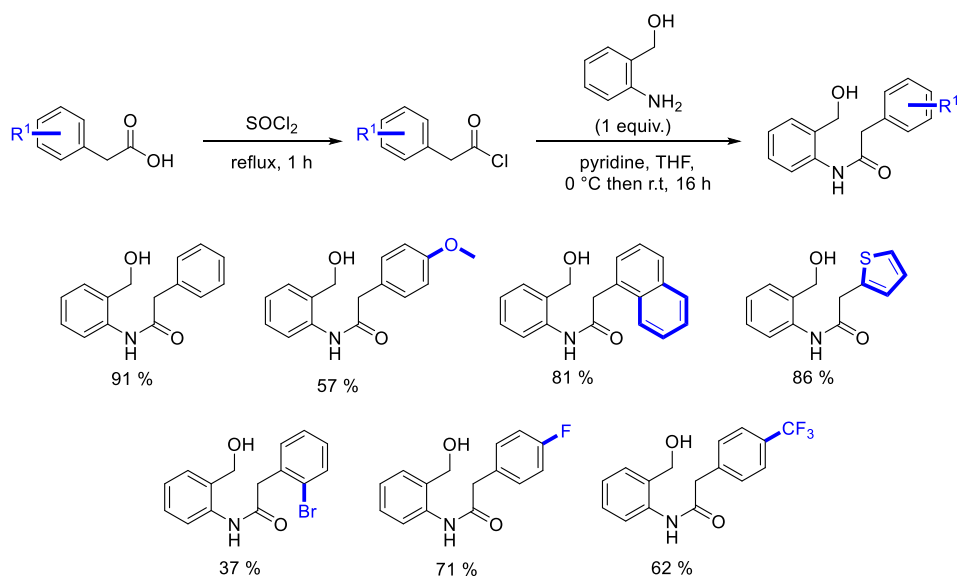


Schéma 6.7 : Synthèse d'amido-alcools à partir d'acides 2-arylacétiques.

Une seconde approche permettant la substitution sur le motif aniline des amido-alcools a ensuite été étudiée. A partir d'anilines substituées, une synthèse en cinq étapes a permis l'obtention d'amido-alcools fonctionnalisés avec des rendements globaux allant de 26 à 35 % (Schéma 6.8).

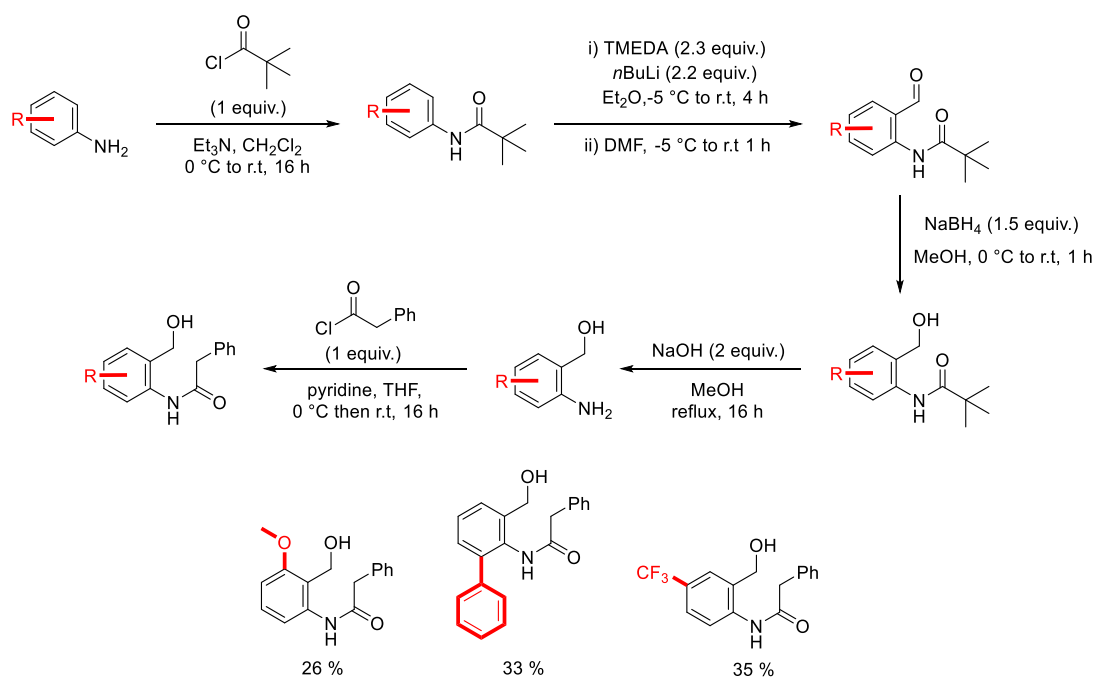


Schéma 6.8 : Synthèse d'amido-alcools à partir d'anilines substituées.

Enfin, une dernière stratégie de synthèse à partir d'halogénures d'aryles a permis de synthétiser en trois étapes des amido-alcools secondaires avec des rendements compris entre 47 et 55 % (Schéma 6.9).

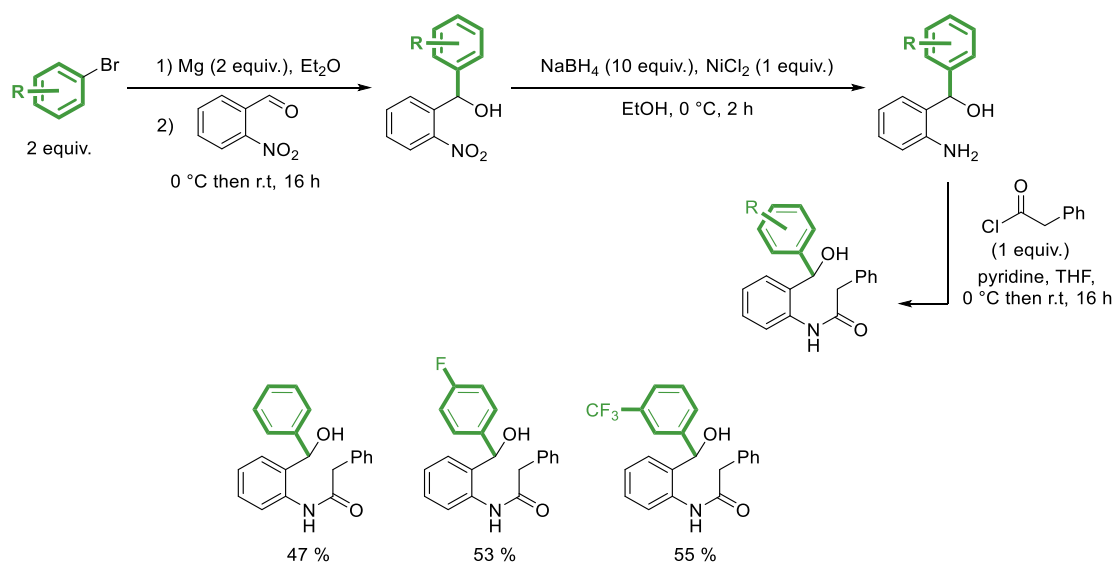


Schéma 6.9 : Synthèse d'amido-alcools secondaires à partir d'alogénures d'aryles.

Avec ces nouveaux amido-alcools fonctionnalisés, la synthèse de quinolin-2(1*H*)-ones par couplage déshydrogénant a été étudié. Une première optimisation des conditions réactionnelles avec le complexe de ruthénium **Ru1** a permis d'obtenir le produit désiré avec un taux de conversion de 96 %. Afin de rendre cette réaction encore plus compétitive, les complexes de fer ont aussi été engagés dans cette réaction. Après optimisation des conditions réactionnelles, le complexe de Knölker **Fe3** a montré l'activité la plus élevée et le produit désiré a été obtenu avec une conversion de 92 % et un rendement isolé de 78 %. L'étendue de cette réaction a ainsi pu être explorée à partir des amido-alcools préparés précédemment. Des quinolinones portant divers groupements aryles en position 3 ont été isolées avec des rendements allant de 48 à 83 % (Schéma 6.10). La substitution sur le motif aniline a permis l'obtention de 3-phenylquinolin-2(1*H*)-ones fonctionnalisées avec des groupements donneurs et attracteurs. Enfin, l'utilisation d'alcools secondaires a aussi permis l'obtention des quinolinones substituées en position 4 avec des rendements compris entre 58 et 79 %. L'utilisation du *N*-méthylamido alcool a mené à l'obtention du produit *N*-substitué avec un rendement plus élevé (89 %). Cette amélioration du rendement peut s'expliquer par l'absence du proton labile de l'amide, favorisant la formation de l'énol et donc la condensation.

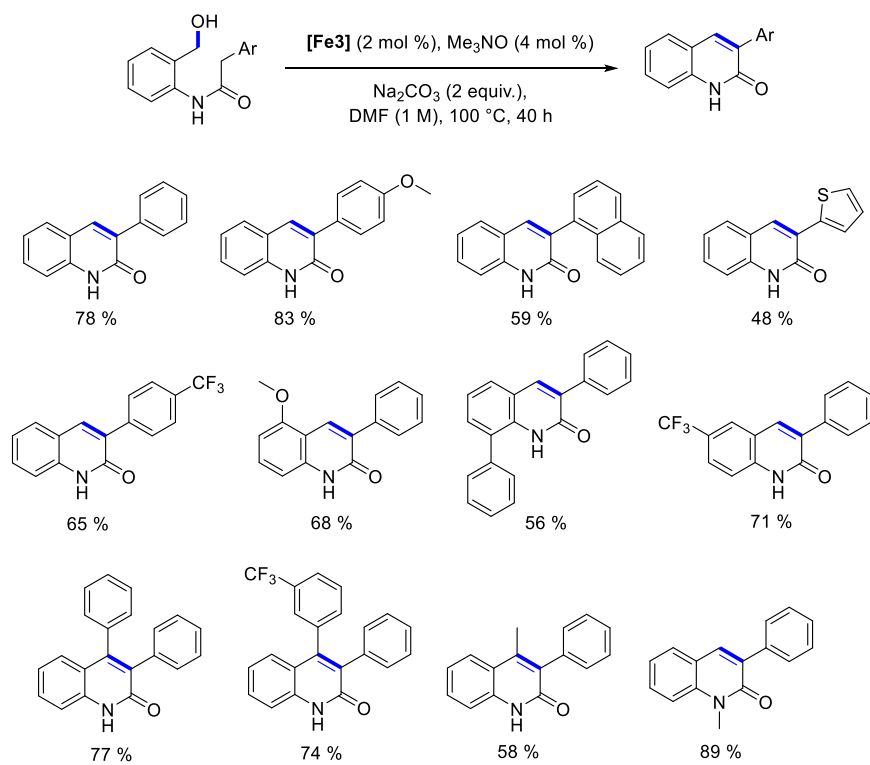


Schéma 6.10 : Synthèse de 3-arylquinolin-2(1H)-ones par couplage déshydrogénant.

IV. Modification des complexes de fer à ligand cyclopentadiénone.

Durant les dernières décennies, le remplacement des métaux nobles par des métaux abondants est devenu un sujet de recherche important. Les complexes de fer à ligand cyclopentadiénone ont montré de bonnes activités dans différentes réactions d'autotransfer d'hydrogène, pourtant, leur efficacité doit encore être améliorée pour rendre ces complexes compétitifs comparés aux complexes de métaux nobles utilisés en milieu industriel. Des premières études sur la modification du complexe de Knölker **Fe3** par Renaud et Poater ont montré que l'activité des complexes de fer à ligand cyclopentadiénone résultait en l'association d'une forte richesse électronique sur le ligand, permettant de rendre l'oxygène plus basique, avec un encombrement important sur les carbones 2 et 5 de la cyclopentadiénone, évitant la dimérisation du complexe et par conséquent son inactivité en catalyse.^{21a,53,55} Ces études ont permis le développement du complexe **Fe1** et son utilisation dans diverses réactions de réduction ou d'autotransfer d'hydrogène (Schéma 6.11).

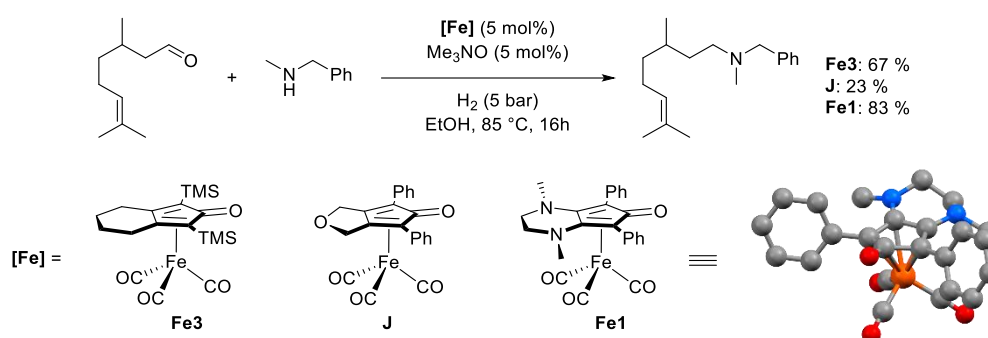


Schéma 6.11 : Amination réductrice catalysée par différents complexes de fer.

Pour continuer cette étude sur l'amélioration des complexes de type Knölker, il a été proposé de modifier la substitution sur le ligand du complexe **Fe1**.²⁵⁶ Afin d'éviter la synthèse de nombreux complexes, les effets de la substitution du ligand sur la réactivité du catalyseur ont été étudiés par DFT. Les différents complexes ont été évalués au long d'une réaction d'amination réductrice, pour laquelle deux étapes cinétiquement déterminantes peuvent être observées : la première étant l'étape d'activation du catalyseur (TS I-II, Schéma 6.12), la seconde étant l'étape cinétiquement déterminante au sein du cycle catalytique et correspondant à l'étape de fractionnement de l'hydrogène (TS III-IV, Schéma 6.12). Ce dernier peut être assisté par une molécule de solvant servant de navette à proton et facilitant la migration d'un atome hydrogène sur la fonction carbonyle du ligand (TS III-IV^a, Schéma 6.12).

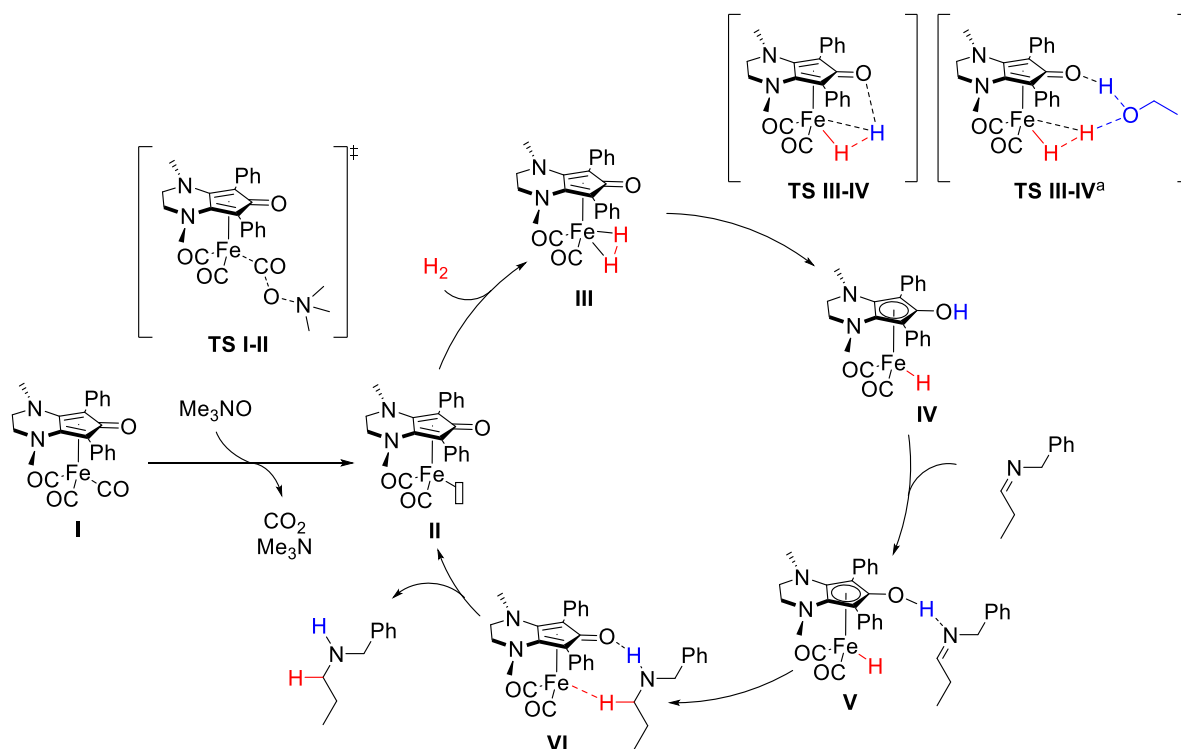
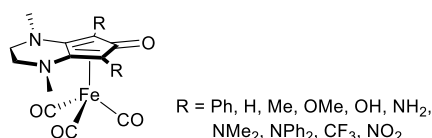


Schéma 6.12 : Mécanisme de la réaction d'amination réductrice catalysée par FeI (a = transfert de proton assisté par une molécule d'éthanol).

La chimie computationnelle permettant d'étudier une seule espèce à la fois, le rôle des substituants en position 2- et 5- de la cyclopentadiénone a tout d'abord été évalué, sans se préoccuper de la dimérisation potentielle du catalyseur. Les noyaux aromatiques du complexe de fer **FeI** ont été remplacés par différents groupements électrodonneurs ou électroattracteurs, les barrières énergétiques pour les deux étapes cinétiquement déterminantes citées précédemment sont présentées dans la Table 6.2. Concernant l'étape d'activation du catalyseur, un effet bénéfique des groupements électroattracteurs est observé alors que les groupements donneurs tendent à augmenter cette barrière énergétique ($\Delta G(\text{I-II})$). Pour l'étape de fractionnement de l'hydrogène, les groupements phényles initiaux donnent une barrière énergétique minimale. Aussi, pour cette étape, l'assistance du solvant permet de diminuer la barrière énergétique d'environ 10 kcal/mol pour tous les substituants et rend leurs barrières énergétiques proches les unes des autres.

Table 6.2 : Barrières énergétiques pour les étapes limitantes de l'amination réductrice catalysée par des complexes de fer avec les substituants directement sur la cyclopentadiénone.

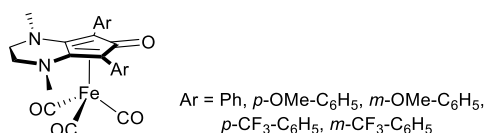


	Neutre		EDG						EWG	
	Ph	H	Me	OMe	OH	NH ₂	NMe ₂	NPh ₂	CF ₃	NO ₂
$\Delta G(\text{I-II})$	19.6	21.7	20.7	23.5	23.2	23.1	27.0	21.0	15.2	12.2
$\Delta G(\text{III-IV})$	24.4	26.9	26.8	30.5	31.9	26.9	29.2	31.8	32.4	32.0
$\Delta G(\text{III-IV}^a)$	14.7	17.5	17.7	19.8	20.1	18.9	20.6	21.9	18.5	14.8

Energies libres de Gibbs en kcal/mol (M06/TZVP~SDD(pcm-EtOH)//BP86/SVP~SDD) niveau de théorie. (a = calculé avec une molécule d'éthanol assistant le transfert de proton).

Nous avons poursuivi cette étude en ajoutant cette fois les substituants sur les noyaux aromatiques (Table 6.3). Pour des raisons synthétiques, seuls les groupements trifluorométhyl et méthoxy ont été introduits dans le travail expérimental. Comme précédemment, l'activation du catalyseur est favorisée pour les complexes portant des groupements électroattracteurs. Concernant l'étape de fractionnement de l'hydrogène, les barrières énergétiques sont relativement similaires. Par conséquent, la substitution des noyaux aromatiques n'a pas de réel effet sur cette seconde étape limitante.

Table 6.3 : Barrières énergétiques pour les étapes limitantes de l'amination réductrice catalysée par des complexes de fer avec les substituants sur les phényles de la cyclopentadiénone.



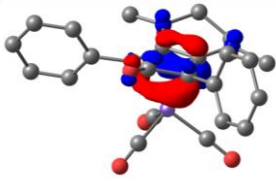
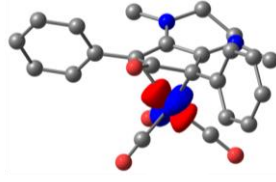
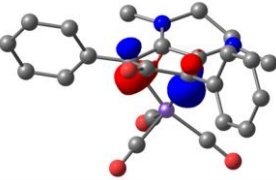
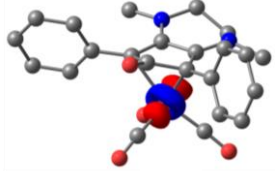
	Ph	<i>p</i> -OMe-C ₆ H ₄	<i>m</i> -OMe-C ₆ H ₄	<i>p</i> -CF ₃ -C ₆ H ₄	<i>m</i> -CF ₃ -C ₆ H ₄
$\Delta G(\text{I-II})$	19.6	20.9	21.3	19.8	16.7
$\Delta G(\text{III-IV}^a)$	14.7	16.7	15.7	15.9	16.0

Energies libres de Gibbs en kcal/mol (M06/TZVP~SDD(pcm-EtOH)//BP86/SVP~SDD) niveau de théorie. (a = calculé avec une molécule d'éthanol assistant le transfert de proton).

Au vu de ces résultats, la question d'un tel effet des substituants sur l'étape d'activation du catalyseur s'est posée. L'occupation effective des orbitales (EFOs)²⁵⁹ des deux fragments ligand/fer tricarbonyl a été évaluée (Table 6.4). Cette analyse a montré deux canaux de transfert de charges lors de la formation du complexe. Un premier canal concerne la donation de la HOMO du ligand vers la LUMO du métal et, dans le même temps, un second canal prend place entre la HOMO du métal et la LUMO du ligand. En regardant plus en détail la forme des orbitales, et plus particulièrement la HOMO du métal, nous pouvons nous apercevoir qu'elle est liée à la liaison Fe-C, ce qui signifie que lors de la formation du complexe, cette liaison Fe-C perd de la densité électronique, elle est alors plus facile à rompre. Par

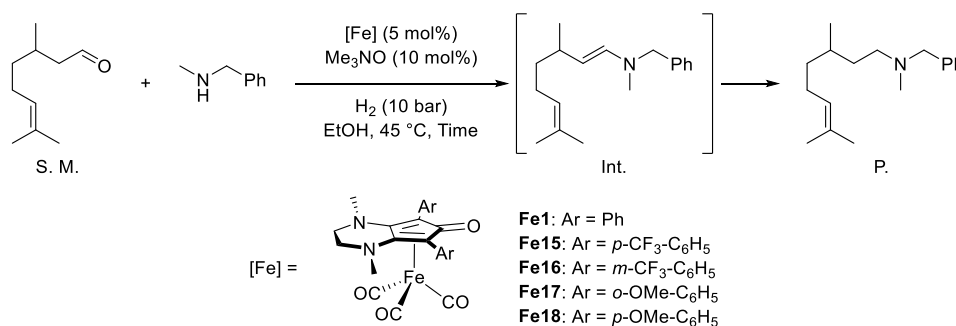
conséquent, l'introduction de substituants électroattracteurs sur la cyclopentadiénone renforce la donation du métal au ligand et appauvrit d'avantage la liaison Fe-C. Le catalyseur est ainsi plus facile à activer. L'effet inverse est obtenu avec les groupements électrodonneurs.

Table 6.4 : EFOs des fragments cyclopentadiénone et fer tricarbonyl.

	cyclopentadiénone	Fer tricarbonyl
LUMO		
HOMO		

Pour évaluer cette étude par DFT, des réactions d'amination réductrice avec différents complexes de fer portant des groupements trifluorométhyles ou méthoxy sur les noyaux aromatiques ont été réalisées. Ces expériences ont montré une plus grande activité des complexes portant les groupements -CF₃, alors que les groupements -OMe ont mené à des activités plus faibles que le complexe initial (Table 6.5). La tendance générale déterminée par l'étude théorique a donc pu être confirmée expérimentalement.

Table 6.5 : Sélectivités obtenue pour la réaction d'amination réductrice catalysée par différents complexes de fer.



Time (h)	Fe1			Fe2			Fe3			Fe4			Fe5		
	S.M.	Int.	P.	S.M.	Int.	P.	S.M.	Int.	P.	S.M.	Int.	P.	S.M.	Int.	P.
1	24	71	5	32	63	5	47	47	4	56	44	0	75	25	0
2	9	73	18	18	47	35	35	40	25	43	57	0	48	47	5
5	27	38	36	0	0	100	0	0	100	0	100	0	8	70	22

Conditions générales: Citronellal (1 mmol), *N*-methyl benzylamine (2 mmol), [Fe] (5 mol%), Me₃NO (10 mol%), ethanol (2 mL), H₂ (10 bar), 45 °C. Conversions déterminées par RMN ¹H du brut réactionnel.

V. Alkylation de cétones en conditions photochimiques.

Les réactions d'alkylation par autotransfer d'hydrogène ont été très largement étudiées durant les dernières décennies. Les métaux abondants tels que le manganèse, le fer, le cobalt ou le nickel ont montré leur efficacité dans ces réactions d'alkylation.¹⁵ Une grande variété de complexes et de ligands ont été conçus pour améliorer l'efficacité des catalyseurs métalliques, permettant de travailler dans des conditions plus douces ou de réduire les temps de réaction. Néanmoins, des températures élevées sont souvent toujours requises pour réaliser ces transformations. Récemment, l'association de la catalyse par des métaux de transition avec la chimie photoredox a ouvert la voie à la fois à de nouvelles réactions mais aussi à de nouvelles réactivités, utilisant la lumière comme source d'énergie plutôt qu'un chauffage à température élevée.²⁸⁴ Toutefois, le photocatalyseur peut être incompatible pour la réaction envisagée. Aussi, cette stratégie montre parfois des problèmes de transfert d'énergie ou d'électrons entre le photocatalyseur et le complexe organométallique. C'est pourquoi, l'application de catalyseurs chromophoriques à base de métaux de transition permet l'utilisation d'une seule espèce catalytique dans la réaction, surpassant alors ces différentes limitations.

Sundararaju a décrit en 2022 une réaction de méthylation de cétones catalysée par le complexe de fer **Fe3** à température ambiante sous irradiation lumineuse.²⁸⁵ Les cétones α -méthylées ont été isolées avec des rendements compris entre 37 et 99 % (Schéma 6.13).

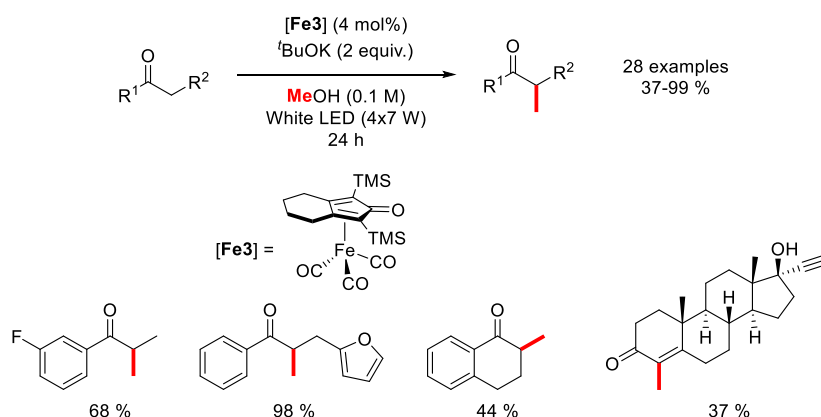


Schéma 6.13 : Méthylation de cétones sous irradiation lumineuse catalysée par **Fe3**.

De façon simultanée, nous nous sommes intéressés à la réaction d'alkylation de cétones en conditions photochimiques.²⁸⁸ Dans ces conditions, seul le complexe **Fe1** a montré une activité et a permis d'obtenir les produits désirés. Une exemplification de la réaction a montré que les cétones aromatiques et aliphatiques peuvent être alkylées par des alcools benzyliques et aliphatiques avec des rendements allant de 23 à 99 % (Schéma 6.14).

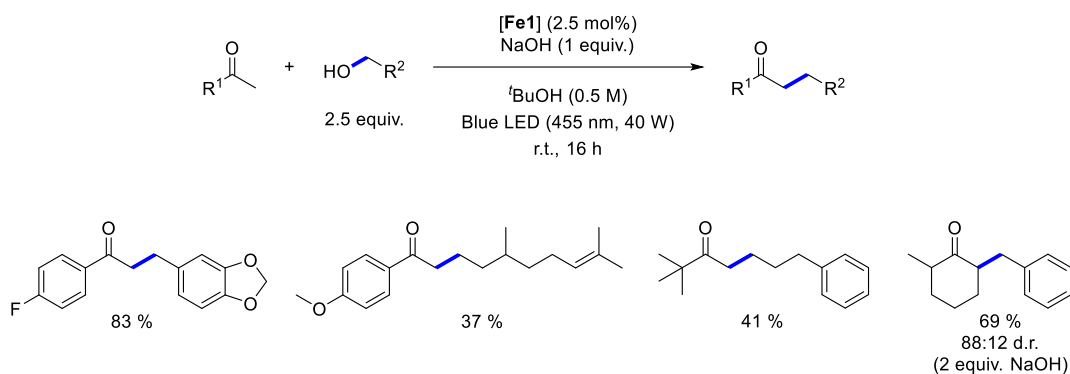


Schéma 6.14 : Alkylation de cétones en conditions photochimiques catalysées par **Fe1**.

Une étude mécanistique a été réalisée afin de déterminer le rôle de la lumière dans cette réaction. Dans un premier temps, la décooordination d'un ligand CO par la lumière permettant l'activation du catalyseur a été étudiée. Le complexe **Fe1** a été mis en présence de triphénylphosphine et la réaction a été suivie par RMN ^{31}P (Schéma 6.15, Eq. 1). Cette réaction n'a pas montré la formation du complexe **Fe2**. Une seconde expérience a montré que l'étape d'oxydation de l'alcool en carbonyle n'était réalisable que sous irradiation lumineuse (Schéma 6.15, Eq. 2). Enfin, la réduction de l'espèce α,β -insaturée intermédiaire ne s'effectue qu'en présence de lumière (Schéma 6.15, Eq. 3). Ainsi, le rôle de la lumière le long de ce mécanisme a pu être clairement identifié : celle-ci intervient uniquement lors des étapes d'oxydation et de réduction.

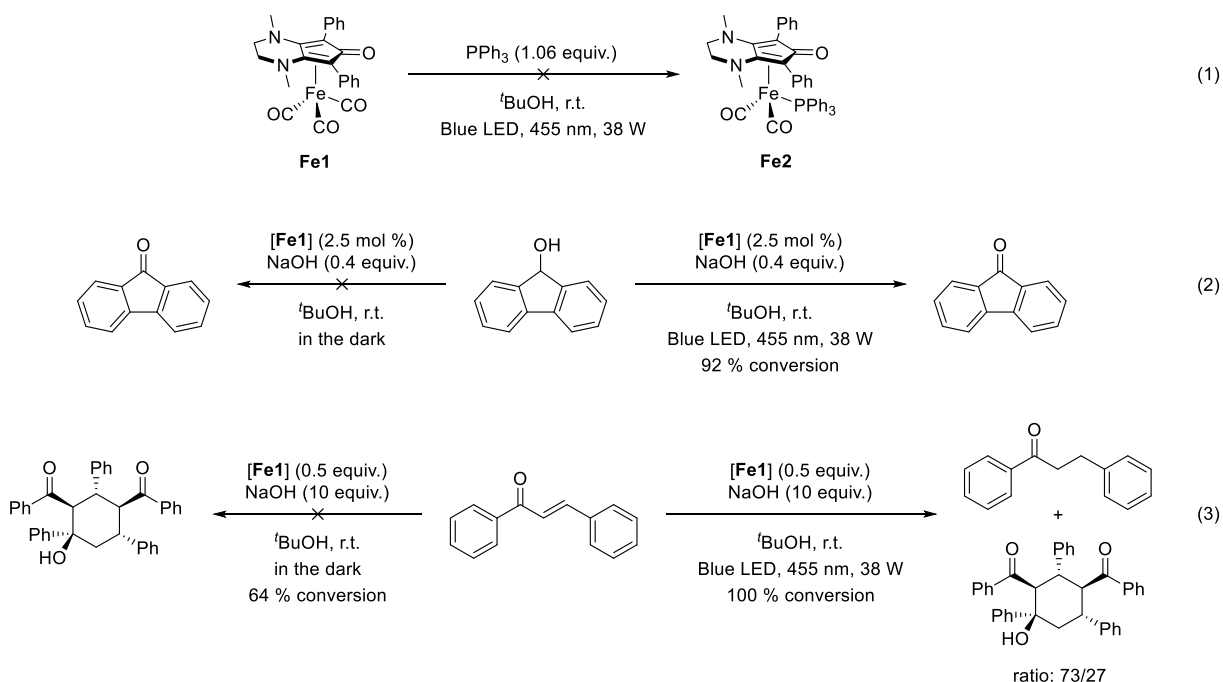


Schéma 6.15 : Etude mécanistique permettant de déterminer le rôle de la lumière.

Pour aller plus loin, nous nous sommes intéressés à l'utilisation d'alcools allyliques et propargyliques en tant que pro-électrophiles. Seuls deux exemples récents décrivent des réactions d'alkylation utilisant des alcools allyliques comme pro électrophiles. Gunanathan a d'abord décrit en 2023 l'alkylation de cétones par des terpenols catalysée par un complexe de ruthénium-Macho à 100 °C.²⁹³ Les produits d'alkylation ont pu être obtenus avec des rendements compris entre 28 et 95 % (Schéma 6.16). Sundararaju a ensuite décrit en 2023 l'alkylation d'oxindoles par des alcools allyliques

catalysés par le complexe de fer **Fe1** à 100 °C,²⁹⁴ permettant d'obtenir les produits correspondant avec des rendements allant de 30 à 95 % (Schéma 6.16). Cependant, ces méthodologies restent limitées à des substrats non fonctionnalisés.

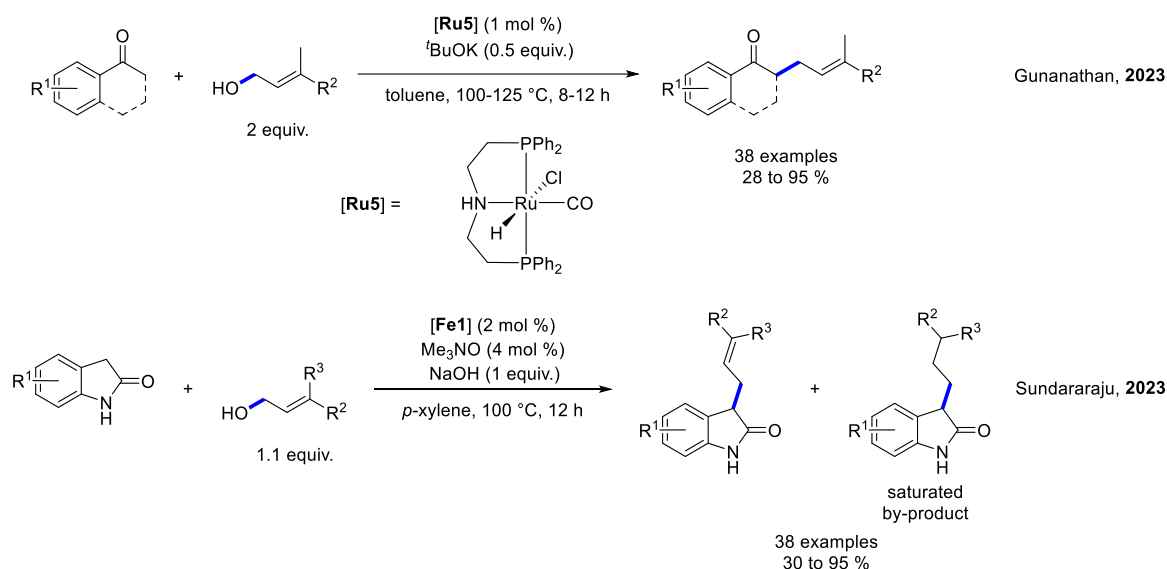


Schéma 6.16 : Précédentes alkylations utilisant les alcools allyliques comme pro-électrophiles.

Dans des conditions très similaires à celles décrites pour l'alkylation de cétones par les alcools primaires, l'alkylation de cétones par des alcools allyliques a pu être réalisée, permettant l'obtention des produits insaturés correspondants avec des rendements allant de 10 à 97 % (Schéma 6.17). Le coproduit saturé obtenu est issu de la réduction de l'espèce diénone intermédiaire et n'a pu être séparé du produit désiré. Il a été observé que l'obtention du produit saturé n'était effective qu'avec les alcools allyliques peu encombrés. De plus, une plus grande tolérance vis-à-vis des groupements fonctionnels a été notée.

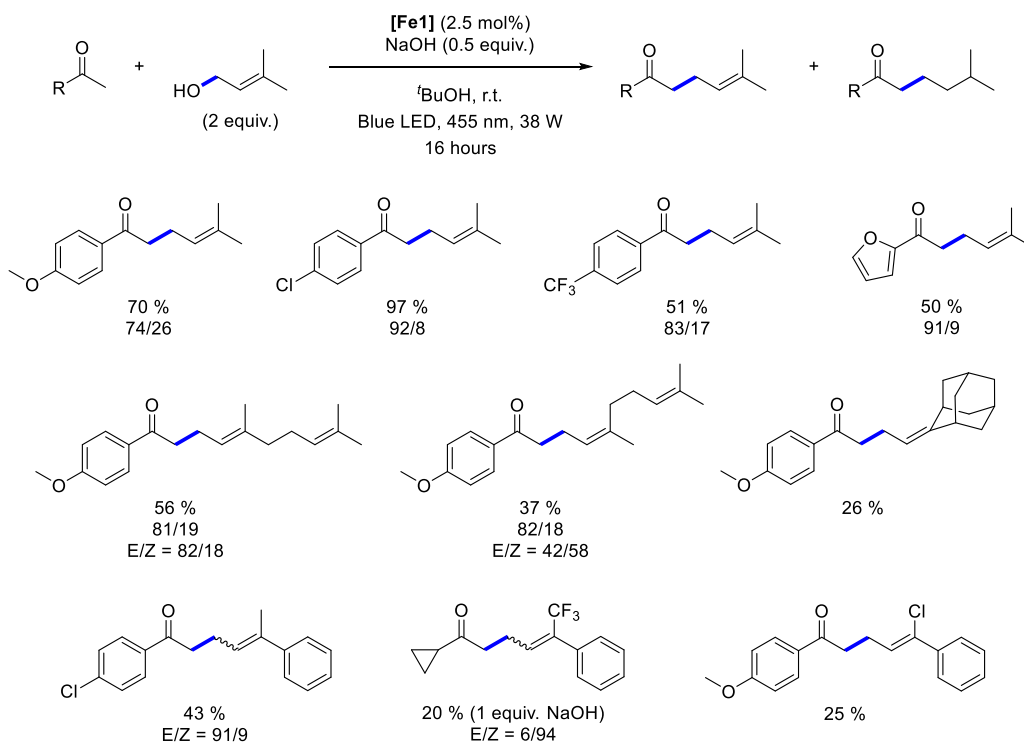


Schéma 6.17 : Alkylation de cétones par des alcools allyliques en conditions photochimiques.

Nous nous sommes ensuite intéressés à l'utilisation d'alcools propargyliques en tant que pro-électrophiles. Dans les mêmes conditions réactionnelles, différents alcools ont pu être engagés dans cette réaction, les produits d'alkylation ayant pu être obtenu avec des rendements modestes compris entre 6 et 25 % (Schéma 6.18). Cependant, cette réaction reste limitée aux alcools propargyliques portant des groupements encombrants sur la position terminale.

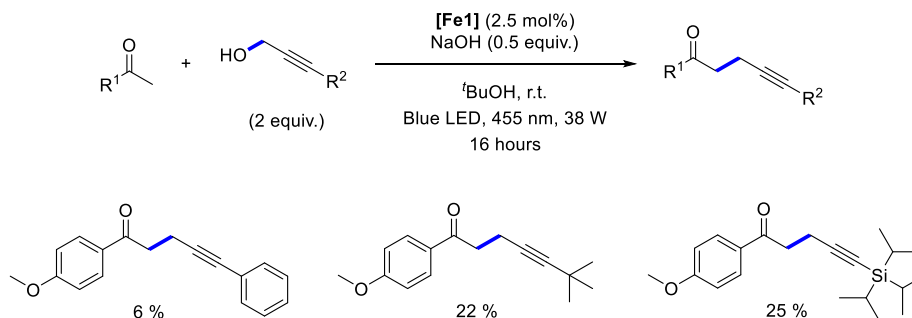


Schéma 6.18 : Alkylation de cétones par des alcools propargyliques en conditions photochimiques.

VI. Conclusion.

Les objectifs de cette thèse portaient sur le développement de nouvelles méthodologies pour la formation de liaisons C-N et C-C par autotransfer d'hydrogène, l'étude des mécanismes réactionnels impliqués et l'amélioration des complexes de fer de type Knölker pour ce type de réactions.

Une méthode efficace d'alkylation d'hydrazides a été décrite utilisant le complexe de ruthénium à ligand cyclopentadiénone **Ru1** (Chapitre II.). Ce complexe de ruthénium a montré une meilleure activité que les complexes de fer analogues. Une étude mécanistique approfondie a mis en lumière une sélectivité pour le produit de mono- ou de di-alkylation pour ces substrats. Le calcul du taux d'encombrement ($\%V_{\text{Bur}}$) permet désormais de prédire lequel de ces deux produits sera obtenu avec notre système catalytique. L'extension de cette réaction aux réactions tandem a été réalisée utilisant le méthanol et l'éthanol comme partenaire de couplage. L'ordre d'alkylation entre les deux alcools mis en jeu a été déterminé à la fois par DFT et expérimentalement.

Pour poursuivre notre étude sur les composés azotés, la synthèse de 3-arylquinoli-2(1*H*)-ones a été développée (Chapitre III.). Le complexe de Knölker **Fe3** a été utilisé comme catalyseur de cette réaction. Ce travail représente le premier exemple de couplage déshydrogénant permettant la synthèse de tels hétérocycles. Cette stratégie a permis l'obtention de molécules fonctionnalisées portant une substitution sur n'importe laquelle des positions de la quinolinone. Même si cette méthodologie reste limitée aux acétamides aromatiques, elle ouvre la voie à la synthèse d'énamides cycliques et non-cycliques.

De manière générale, le complexe de fer **Fe1** a montré une plus grande activité dans les réactions d'alkylation ou d'amination réductrice que les autres complexes de type Knölker. Une étude théorique a été réalisée sur ce complexe dans le but d'améliorer encore son efficacité (Chapitre IV.). Cette étude a montré le rôle clé des effets électroniques dans l'activité catalytique du complexe et plus particulièrement sur l'étape d'activation. Les groupements électroattracteurs sont apparus comme étant bénéfiques pour la réaction d'amination réductrice étudiée. Ces observations théoriques ont pu être confirmées expérimentalement *a posteriori* avec des temps de réaction plus courts pour les complexes **Fe15** et **Fe16** portant des groupements CF_3 .

Le complexe **Fe1** a montré une activité catalytique à température ambiante sous irradiation lumineuse (Chapitre V.). Les conditions douces utilisées pour réaliser l'alkylation de cétones avec des alcools aliphatiques, benzyliques, allyliques et propargyliques montre le potentiel de cette nouvelle méthodologie. La tolérance de groupements fonctionnels est, de fait, améliorée puis que des molécules thermosensibles peuvent maintenant être engagées dans ces réactions. Quelques limitations subsistent (les éthers, alcools allyliques substitués, alcools propargyliques encombrés), toutefois l'étendue de telles réactions doit être réévalué plus en détails pour déterminer les limites de cette nouvelle méthodologie.

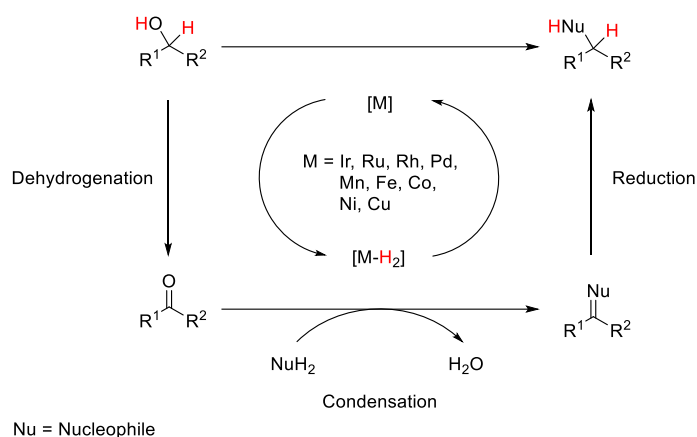
Les travaux réalisés durant cette thèse font partie des sujets développés par Renaud et Poater durant la dernière décennie concernant le développement de catalyseurs plus efficaces basés sur les métaux abondants. L'exploration des réactions d'autotransfer d'hydrogène avec de nouveaux partenaires permettra d'étendre encore l'application de cette stratégie et de ces catalyseurs. Une autre continuité de cette thèse porterait sur la conception d'un complexe chromophorique de type Knölker capable d'absorber une bande plus large du spectre visible. De telles modifications pourraient rendre les réactions d'alkylation possible en utilisant des sources lumineuses moins dangereuses. Le développement d'une réaction d'alkylation stéréosélective peut aussi être étudiée grâce aux nouvelles

conditions réactionnelles plus douces. Enfin, la combinaison de deux catalyseurs différents en un système dual pourrait permettre la formation de molécules complexes par une approche one-pot.

Resumen.

I. Introducción.

En las últimas décadas, se han desarrollado nuevas metodologías para la formación de enlaces C-N y C-C utilizando las reacciones de Autotransfer de hidrógeno. Estas reacciones fueron definidas por primera vez por Williams en 2004 como «Borrowing Hydrogen»,¹ aunque ya se han descrito varios ejemplos en la bibliografía.² Esta estrategia consiste en utilizar alcoholes como agentes alquilantes en lugar de derivados halogenados, estos últimos preparados a partir de alcoholes, que conduzcan a fases de síntesis suplementarias y a la generación de residuos.³ Además, la utilización de alcoholes para la síntesis de productos carbonosos y nitrogenados presenta un gran interés, especialmente debido a su presencia en los ambientes naturales y su disponibilidad directa a partir de la biomasa.⁴ De esta manera, las reacciones por autotransfer de hidrógeno son parte del campo de la química verde y sostenible. El mecanismo general de estas reacciones es el siguiente: un alcohol se deshidrata en presencia de un complejo organometálico para generar el carbonilo correspondiente y un complejo de tipo metal-hidrógeno (Esquema 6.1). La presencia de un nucleófilo en el medio reactivo genera una etapa de condensación con el carbonilo generando una especie insaturada que es finalmente reducida por el complejo metal-hidrógeno.



Esquema 6.1: Mecanismo general de reacciones por Autotransfer de hidrógeno.

Muchos metales nobles, como el iridio,⁵ el rodio⁶ o el rutenio,⁷ han sido descritos como catalizadores de tales reacciones. Se ha descrito la alquilación de varios nucleófilos como cetonas,⁸ amidas o ésteres,⁹ aminas,¹⁰ nitriles¹¹ o nitratos¹² (Figura 6.1). También se describieron las reacciones de alquilación o síntesis de heterociclos.^{13,14}

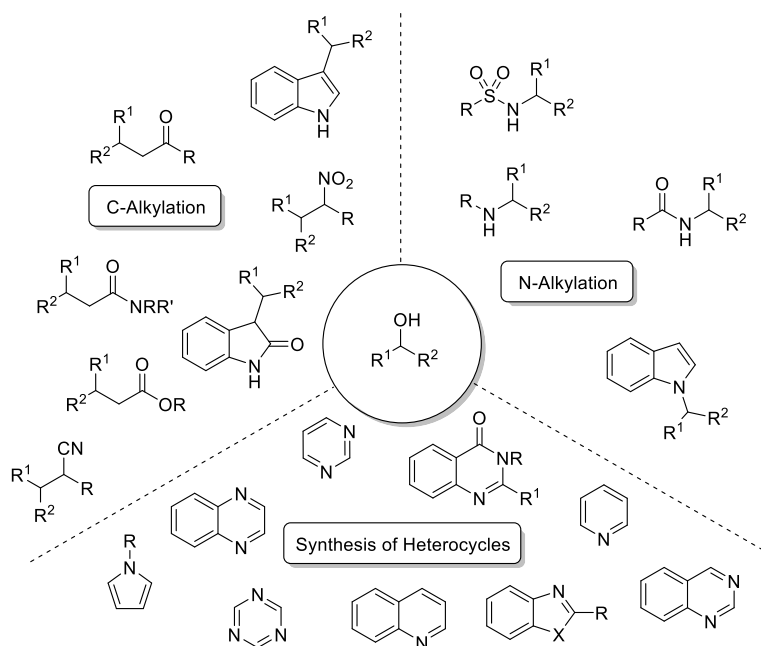


Figura 6.1: Ejemplos de productos de alquilación y síntesis de heterociclos.

Sin embargo, la escasez de estos metales y su creciente demanda hacen que su uso sea cada vez más costoso. En los últimos años, los complejos de metales abundantes como el manganeso, el hierro o el cobalto han demostrado su eficacia y competitividad en las reacciones de alquilación, en comparación con los metales nobles.¹⁵ Nuestro grupo se ha interesado especialmente en el hierro, que es, entre todos los metales de transición, el más abundante de la corteza terrestre y por lo tanto el más barato (algunas decenas de centavos por kilogramo). Gracias al uso de ligandos organofosforados, la química del hierro se ha establecido bien en los últimos años.¹⁶ Sin embargo, estos ligandos son a menudo costosos, sensibles al aire y a la humedad. El desarrollo de ligandos más baratos como los ciclopentadienonas tiene como objetivo paliar estos problemas. Basados en el trabajo de Knölker (**Fe3**, Figura 6.2),¹⁷ nuestro grupo ha desarrollado varios complejos de hierro que portan ligandos ciclopentadienonas (**Fe1** y **Fe2**, entre otros) y ha contribuido al uso de estos complejos como catalizadores homogéneos, especialmente para la reducción de compuestos carbonilos¹⁸ y las aminaciones reductoras.¹⁹ El complejo de hierro **Fe1** ha demostrado una mayor actividad y selectividad que el complejo de Knölker **Fe3** y ha participado en diversas reacciones de alquilación con compuestos de tipo anilina,²⁰ indoles,²¹ alcohol²² o cetonas.²³

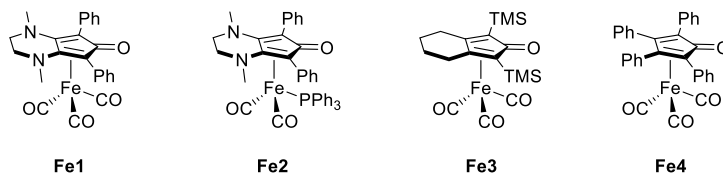


Figura 6.2: Complejos de hierro utilizados en esta tesis.

Como continuación de estos trabajos, los principales objetivos de esta tesis son el desarrollo de nuevas metodologías para la formación de enlaces C-N y C-C, la determinación de los mecanismos reactivos y la mejora de los complejos de tipo Knölker. En algunos casos, se ha estudiado el uso de complejos de rutenio análogos, lo que permite paliar la falta de reactividad de los complejos de hierro (Figura 6.3).

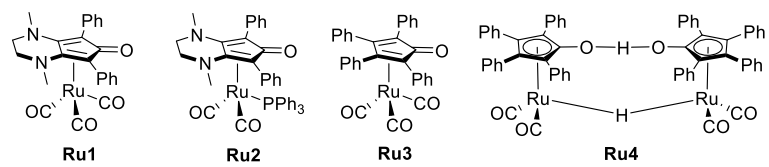
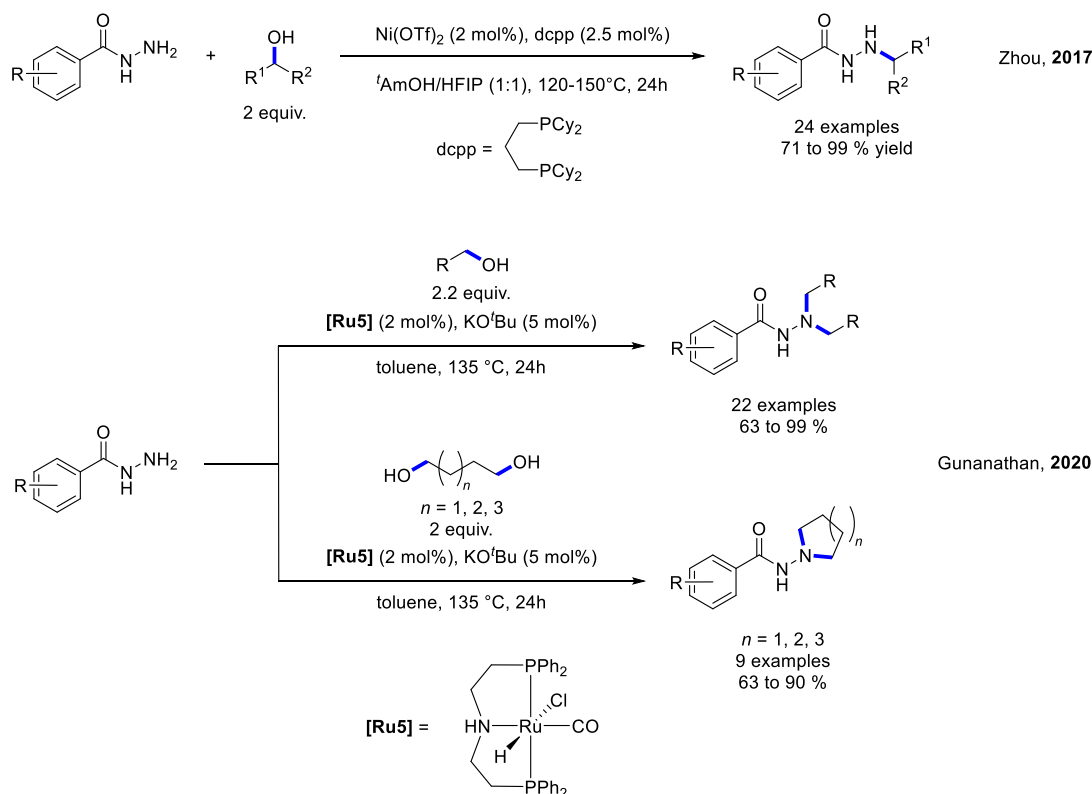


Figura 6.3: *Complejos de rutenio utilizados en esta tesis.*

II. Alquilación de hidracidas de Alcoholes.

Las hidracidas son moléculas nitrogenadas con una función acílica en uno de los dos átomos de nitrógeno del motivo hidracina. Estos derivados son importantes sintones ya que encuentran aplicaciones en la síntesis de medicamentos, productos fitosanitarios o la fabricación de polímeros.¹³⁴ El enfoque más conocido para obtener hidracidas sustituidas se basa en la utilización de derivados halogenados en condiciones básicas, o bien la condensación de un carbonilo seguida de la reducción del enlace C=N por un agente reductor en proporción equimolar. Por lo tanto, nos interesamos en la alquilación de este tipo de substratos por reacción de autotransferencia de hidrógeno a partir de alcoholes.

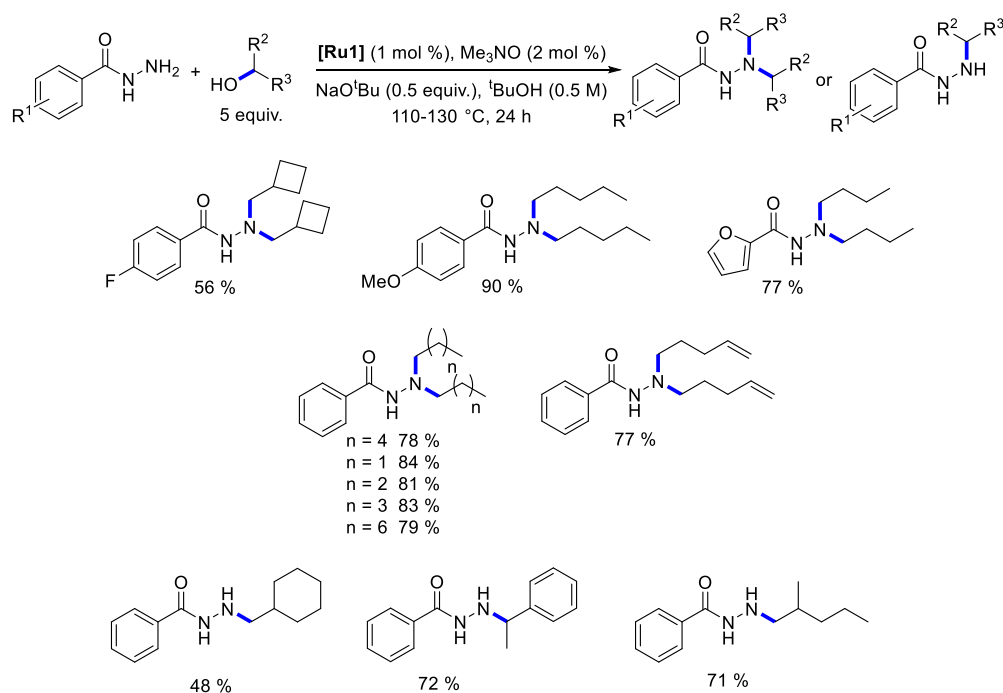
La primera reacción de alquilación de hidracida por autotransferencia del hidrógeno fue descrita por Zhou en 2017 (Figura 6.2).¹³⁶ Muchos alcoholes bencílicos se pudieron emplear en presencia de una sal de níquel y de una difosfina en condiciones ácidas. La utilización de un ligando quirral ((S)-Binapina) permitió obtener excesos enantioméricos que oscilaban entre el 72 y el 96 %. Más recientemente, Gunanathan describió la dialquilación de hidracidas a partir de alcoholes catalizada por un complejo de rutenio de tipo Macho, esta vez en condiciones básicas (Figura 6.2).¹³⁸



Esquema 6.2: Alquilaciones de hidracidas por autotransferencia de hidrógeno descritas anteriormente.

Basado en estos trabajos anteriores, nos interesamos en la alquilación de hidracidas por alcoholes catalizado por un complejo de hierro tricarbonilo con ligando ciclopentadienona. Desafortunadamente, ninguno de estos complejos ha permitido obtener los productos deseados. Sin embargo, el uso de análogos de rutenio allanó el camino para los productos de alquilación, y el complejo **Ru1** mostró la mayor actividad en esta reacción. Diferentes alcoholes primarios se han podido comprometer en esta reacción, dando los productos dialquilados con rendimientos que van del 54 al 93% (Esquema 6.3).¹⁴⁶ Sorprendentemente, los alcoholes primarios α -sustituidos, saturados o

secundarios solo han permitido obtener el producto de monoalquilación con rendimientos que van del 47 al 71 % (Esquema 6.3).



Esquema 6.3: Mono- y di-alquilación de acil hidracidas catalizadas por **Ru1**.

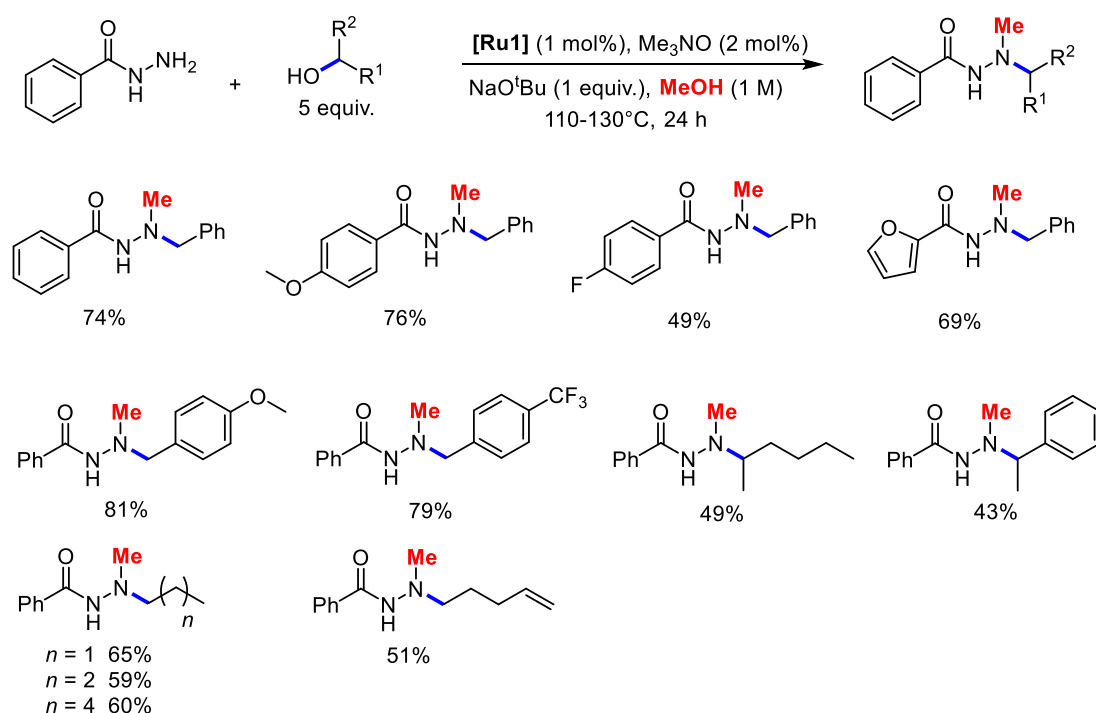
Para comprender esta diferencia de selectividad, se realizó un estudio DFT. En esta reacción, la etapa de condensación de hidracida en carbonilo parece ser la etapa cinéticamente determinante. Más concretamente, en la segunda etapa de la alquilación, la formación de la imina media es la etapa cinéticamente determinante (Esquema 6.4). El cálculo de la barrera de energía correspondiente a esta etapa de condensación mostró que la formación del intermediario imina estaba limitada por la saturación estérica alrededor del carbono que llevaba la función alcohol, los alcoholes saturados que dan barreras energéticas mucho más altas. Para evitar el cálculo de los niveles de energía para cada alcohol, se propuso calcular el tamaño estérico alrededor del carbono portador de la función alcohol para cada uno de los pro-electrofílicos utilizados. El cálculo de esta dimensión (% V_{Bur}) introducido por primera vez por Cavallo *et al*¹⁴⁷ permitió determinar un límite de capacidad comprendido entre el 45 % y el 48 % para el cual, por debajo de este límite, se obtiene el producto de diálisis, mientras que, por encima de este límite se obtendrá el producto de monoalquilación (Tabla 6.1).

Tabla 6.1: % V_{Bur} de los alcoholes estudiados (radio de la esfera: 3,5 Å, el carbono alfa del alcohol es el origen de la esfera).

Alcohol (que conducen a la dialquilación)	% V_{Bur}	Alcohol (que conducen a la monoalquilación)	% V_{Bur}
Metanol	25.6	Citronellol	45.4
Ehanol	36.9	Ciclohexilmetanol	47.7
Propan-1-ol	42.3	2-metilpentan-1-ol	47.9
Butan-1-ol	42.3	2,2-dimetilpropan-1-ol	53.1

Pent-4-en-1-ol	42.3	Ciclopentanol	53.9
3-fenyletan-1-ol	42.4	1-(tiofen-2-yl)etan-1-ol	55.5
Cyclopropilmetanol	43.9	1-fenyletan-1-ol	55.8
Cyclobutilmetanol	44.6	1-(benzo[d][1,3]dioxol-5-yl)etan-1-ol	57.3
Alcohol bencílico	44.7	1-(naftalen-2-yl)etan-1-ol	59.0
2-feniletan-1-ol	45.2		

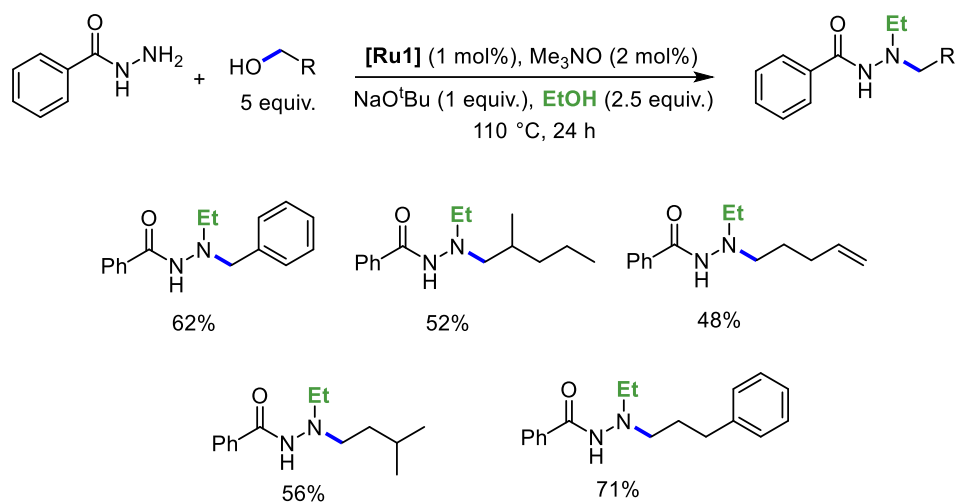
Sobre la base de estos resultados y de trabajos anteriores sobre la alquilación tándem de cetonas, hemos propuesto desarrollar una reacción de alquilación de componentes múltiples que permite acceder a hidracidas dialquiladas no-simétricas utilizando dos alcoholes diferentes en una sola olla.¹⁴⁸ La realización de tal reacción se basa en la diferencia de energía de oxidación de los dos alcoholes de partida. El metanol se eligió para iniciar este estudio porque tiene la energía de oxidación más alta (por ejemplo, 84 kJ/mol frente a 68 kJ/mol para etanol). Tras la optimización de las condiciones de reacción, se emplearon diversos alcoholes primarios y secundarios, lo que permitió la preparación de productos dialquílicos no simétricos con rendimientos comprendidos entre el 35 y el 79 % (Esquema 6.4). Con alcoholes alifáticos se obtuvieron rendimientos más bajos debido a sus energías de oxidación más cercanas a la del metanol, haciendo esta reacción más compleja. Los alcoholes primarios congestionados o secundarios también han llevado a rendimientos más bajos debido a su desorden estérico, favoreciendo la formación del producto dimetilado.



Esquema 6.4: Dialquilación no simétrica de hidracidas con metanol.

Para ir más lejos, el metanol fue reemplazado por etanol (Esquema 6.5). Este último hace que esta reacción sea aún más compleja ya que su energía de oxidación está mucho más próxima a la de otros alcoholes. Por lo tanto, se hace más difícil distinguir entre etanol y segundo alcohol. Tras una

optimización de las condiciones de reacción, se obtuvieron productos de dialquilación no simétricos con rendimientos que oscilaban entre el 48 y el 71 %.

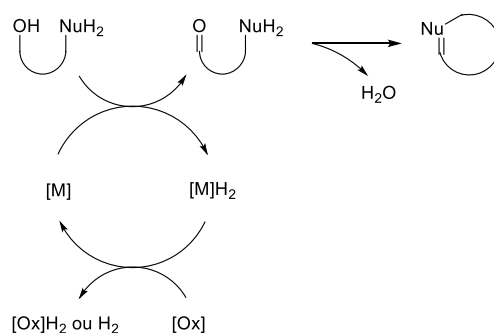


Esquema 6.5: Alquilación no simétrica de hidracidas con etanol.

Con el fin de determinar el orden de alquilación que permite obtener el producto no simétrico, se realizó un estudio DFT. Una vez realizada la primera alquilación con diferentes alcoholes (metanol, alcohol bencílico...), una segunda alquilación por metanol presenta una barrera energética de aproximadamente 32 kcal/mol, independientemente del primer alcohol alquilado. En cambio, la alquilación por alcohol bencílico de la metilhidracida presenta una barrera energética más elevada, de alrededor de 36 kcal/mol, lo que hace que este paso sea más difícil de realizar. Así, el producto no simétrico se obtiene mediante una primera alquilación con el alcohol más congestionado y, a continuación, una segunda alquilación con metanol. Este estudio pudo confirmarse experimentalmente realizando la reacción de alquilación no simétrica de forma secuencial.

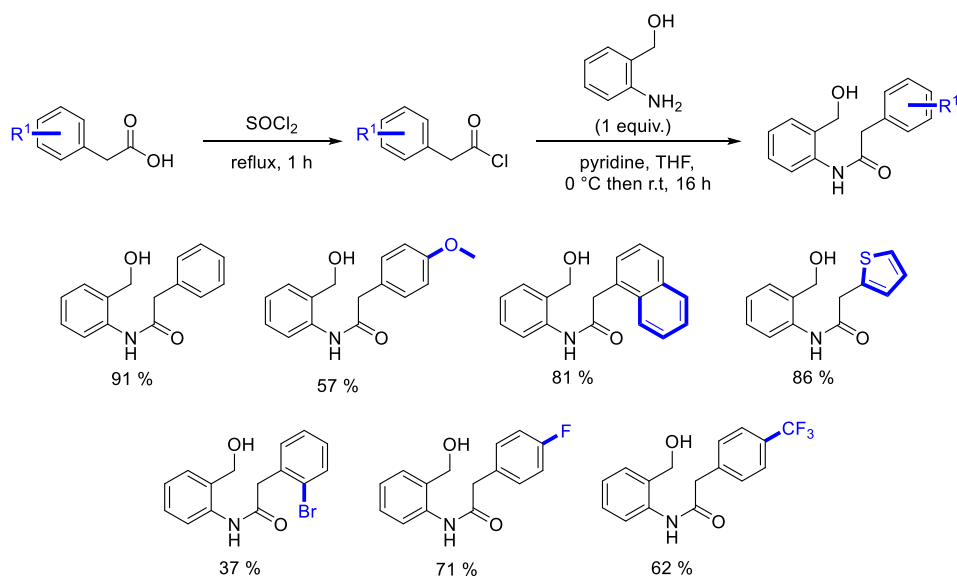
III. Síntesis del quinolin-2(1H)-ones por acoplamiento deshidrogenante del amido-alcoholes.

Los quinolin-2(1H)-onas son heterociclos nitrogenados que pueden asimilarse a las amidas cíclicas. Tales estructuras pueden encontrarse en una gran variedad de productos con actividades biológicas.¹⁶⁸ Estos motivos se preparan tradicionalmente mediante reacciones de tipo Vilsmeier-Haak¹⁶⁸ o Friedlander,¹⁶⁹ pero las síntesis alternativas que utilizan la catálisis por los metales de transición se han desarrollado en los últimos años.^{171,173,175,177,178} Sin embargo, estas síntesis requieren el uso de derivados halogenados que permitan realizar las reacciones de acoplamiento correspondientes. Las síntesis de heterociclos por reacciones de acoplamientos deshidrogenantes catalizadas por metales de transición se desarrollaron permitiendo síntesis más duraderas de estos motivos.^{180,14} El mecanismo general de estas reacciones se describe en el esquema 6.6. En una primera etapa, el catalizador metálico deshidrogeniza un alcohol para generar el carbonilo correspondiente y una especie de metal-hidrógeno. A diferencia de las reacciones de alquilación, este último liberará una molécula de hidrógeno asistida o no por un oxidante para regenerar la especie catalítica. El carbonilo sufre entonces una etapa de condensación intramolecular que conduce a un producto insaturado cíclico.



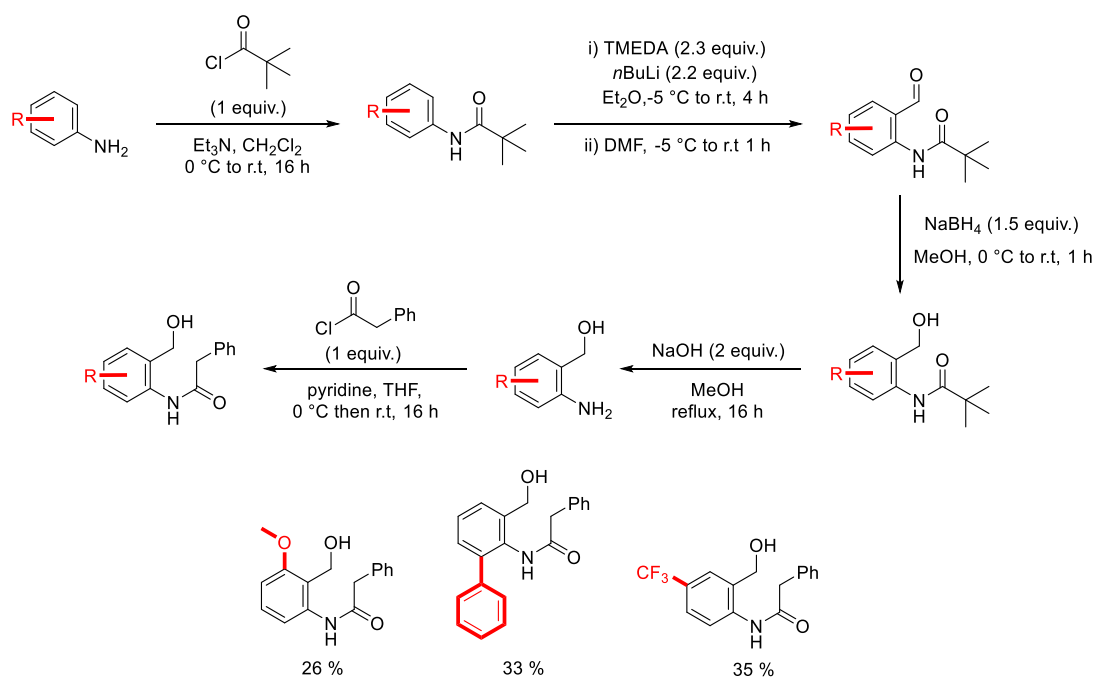
Esquema 6.6: Mecanismo general del acoplamiento deshidrogenante.

Este tipo de acoplamiento deshidrogenante se ha aplicado a la síntesis de muchos heterociclos aromáticos. Sin embargo, en la actualidad, esta metodología no describe ninguna síntesis de quinolin-2(1H)-ones. El enfoque que hemos propuesto se basa en la condensación/ciclación intramolecular de amido-alcoholes. Para ello, se han preparado diversos amido-alcoholes siguiendo diferentes métodos. Un primer enfoque permitió la síntesis en dos etapas de *N*-(2-(hidroximetil)fenil)-2-aracetamidas a partir de ácidos 2-arilcésicos con rendimientos que oscilaban entre el 37 y el 91% (Esquema 6.7).



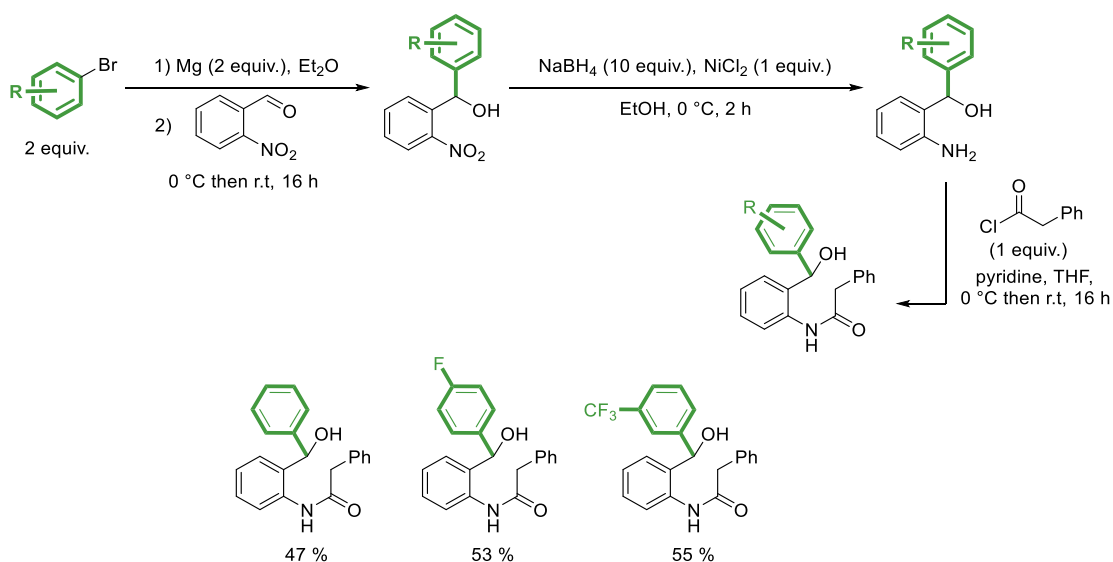
Esquema 6.7: Síntesis de amido-alcoholes a partir de ácidos 2-ariláceos.

A continuación, se estudió un segundo enfoque que permite la sustitución de amido-alcoholes por anilina. A partir de anilinas sustituidas, una síntesis en cinco etapas permitió la obtención de amido-alcoholes funcionalizados con rendimientos globales que oscilaban entre el 26 y el 35 % (Esquema 6.8).



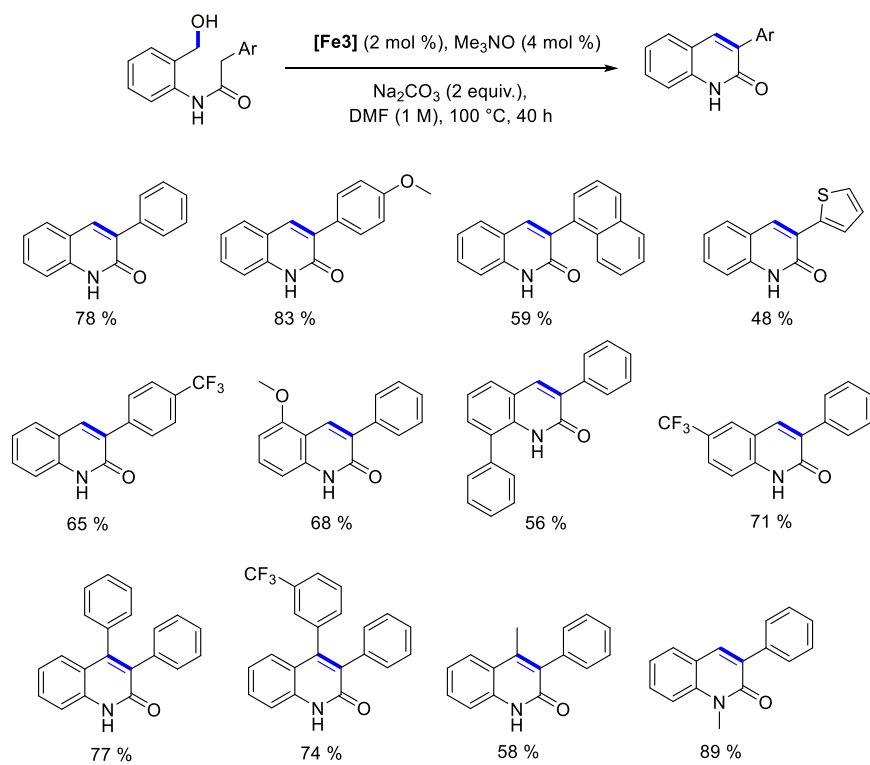
Esquema 6.8: Síntesis de amido-alcoholes a partir de anilinas sustituidas.

Finalmente, una última estrategia de síntesis a partir de halogenuros de arilos permitió sintetizar en tres etapas amido-alcoholes secundarios con rendimientos comprendidos entre el 47 y el 55 % (Esquema 6.9).



Esquema 6.9: Síntesis de amido-alcoholes secundarios a partir de alogenuros de arilos.

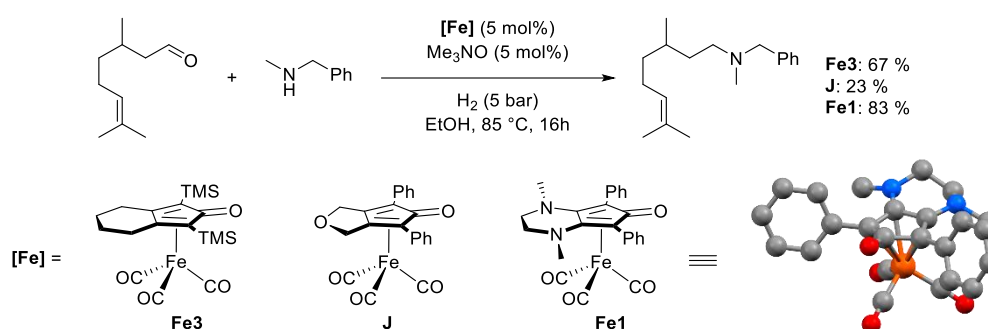
Con estos nuevos amido-alcoholes funcionalizados, se ha estudiado la síntesis de quinolin-2(1*H*)-onas por acoplamiento deshidrogenante. Una primera optimización de las condiciones de reacción con el complejo de rutenio **Ru1** permitió obtener el producto deseado con una tasa de conversión del 96%. Con el fin de hacer esta reacción aún más competitiva, Los complejos de hierro también participaron en esta reacción. Después de optimizar las condiciones de reacción, el complejo de Knölker **Fe3** mostró la actividad más alta y el producto deseado se obtuvo con una conversión del 92 % y un rendimiento aislado del 78 %. La amplitud de esta reacción se pudo explorar a partir de las amido-alcoholes preparados previamente. Se han aislado quinolinonas con diversos grupos arílicos en la posición 3, con rendimientos que oscilan entre el 48% y el 83% (Esquema 6.10). La sustitución en el motivo anilina permitió la obtención de 3-fenilquinolin-2(1*H*)-Onas funcionalizadas con grupos donadores y atractores. Por último, la utilización de alcoholes secundarios permitió también la obtención de quinolinonas sustituidas en la posición 4 con rendimientos comprendidos entre el 58 y el 79 %. La utilización del *N*-metilamido alcohol condujo a la obtención del producto *N*-sustituido con un rendimiento más elevado (89 %). Esta mejora del rendimiento puede explicarse por la ausencia del protón lábil de la amida, favoreciendo la formación del enol y por tanto la condensación.



Esquema 6.10: Síntesis de 3-arylquinolin-2(1H)-ones por acoplamiento deshidrogenante.

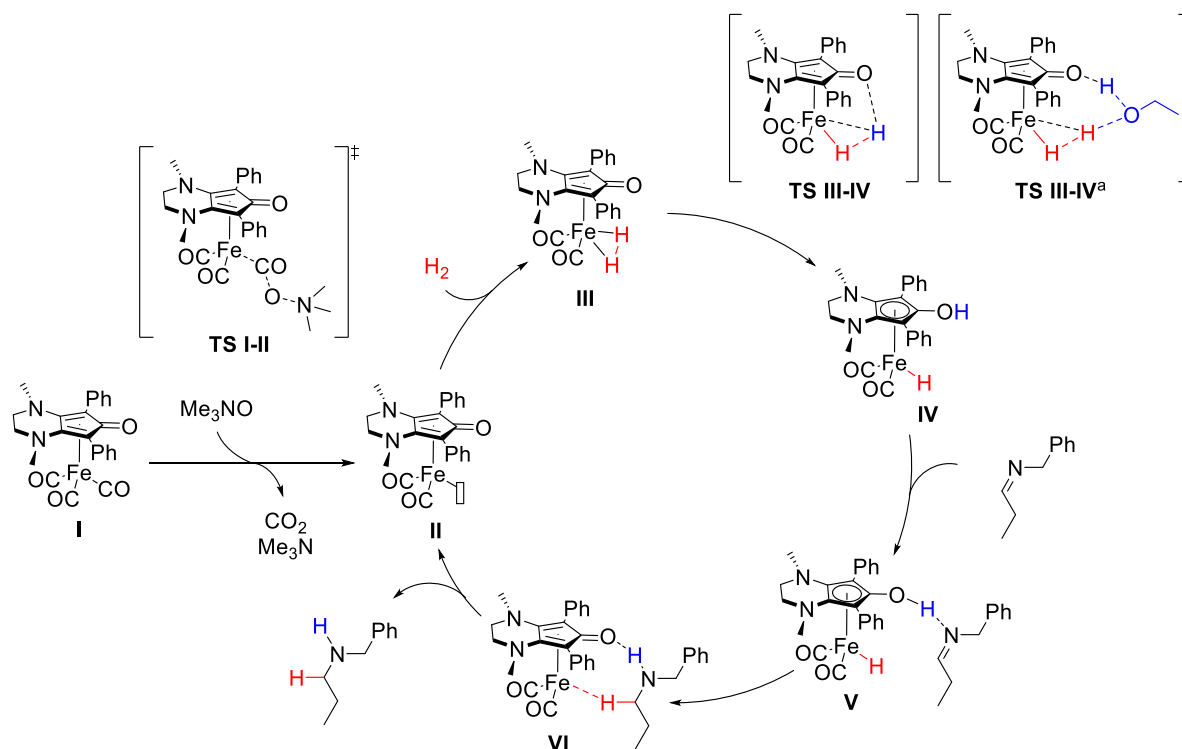
IV. Modificación de los complejos de hierro con el ligand ciclopentadienona.

En las últimas décadas, la sustitución de metales nobles por metales abundantes se ha convertido en un tema importante de investigación. Los complejos del hierro del ligand ciclopentadienona demostraron sus buenas actividades en diversas reacciones de la autotransferencia del hidrógeno, Sin embargo, su eficacia debe mejorarse para que estos complejos sean competitivos en comparación con los complejos de metales nobles utilizados en el medio industrial. Los primeros estudios sobre la modificación del complejo de Knölker **Fe3** por Renaud y Poater mostraron que la actividad de los complejos de hierro con ligando ciclopentadienona resultó en la asociación de una gran riqueza electrónica en el ligando, permitiendo hacer el oxígeno más básico, con un espacio considerable en los carbonos 2 y 5 de la ciclopentadienona, evitando la dimerización del complejo y por consiguiente su inactividad en catálisis.^{21a,53,55} Estos estudios han permitido el desarrollo del complejo **Fe1** y su utilización en diversas reacciones de reducción o autotransferencia de hidrógeno (Esquema 6.11).



Esquema 6.11: Aminación reductiva catalizada por diferentes complejos de hierro.

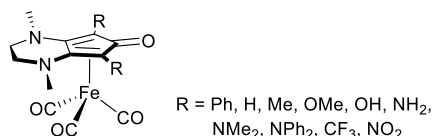
Para continuar este estudio sobre la mejora de los complejos de tipo Knölker, se propuso modificar la sustitución en el ligando del complejo **Fe1**.²⁵⁶ Para evitar la síntesis de numerosos complejos, DFT ha estudiado los efectos de la sustitución del ligando sobre la reactividad del catalizador. Los diferentes complejos fueron evaluados a lo largo de una reacción de aminación reductora, para la cual se pueden observar dos etapas cinéticamente determinantes: la primera es la etapa de activación del catalizador (TS I-II, Esquema 6.12) siendo la segunda la etapa cinéticamente determinante dentro del ciclo catalítico y correspondiente a la etapa de fraccionamiento del hidrógeno (TS III-IV, Esquema 6.12). Este último puede ser asistido por una molécula de disolvente que actúa como transbordador de protones y facilita la migración de un hidrógeno sobre el carbonilo del ligando (TS III-Iva, Esquema 6.12).



Esquema 6.12: Mecanismo de la reacción de aminación reductiva catalizada por **FeI** ($a =$ transferencia de protones asistida por una molécula de etanol).

La química computacional que permite estudiar una sola especie a la vez, en un primer momento se estudió el papel de los sustituyentes en posición 2- y 5- de la ciclopentadienona, sin ocuparse de la dimerización del catalizador. Los núcleos aromáticos del complejo de hierro **FeI** han sido sustituidos por diferentes grupos electrodonadores o electroattractores, las barreras energéticas para las dos etapas cinéticamente determinantes presentadas anteriormente se presentan en la tabla 6.2. En cuanto a la fase de activación del catalizador, se observa un efecto beneficioso de los grupos electroattractores, mientras que los grupos donantes tienden a aumentar esta barrera energética ($\Delta G(I-II)$). Para la etapa de fraccionamiento del hidrógeno, las agrupaciones fenilos iniciales proporcionan una barrera energética mínima. Además, para esta etapa, la asistencia del disolvente permite reducir la barrera energética en unas 10 kcal/mol para todos los sustitutos y hace que sus barreras energéticas estén cerca unas de otras.

Tabla 6.2: Barreras energéticas para las etapas limitantes de la aminación reductora catalizada por complejos de hierro con los sustitutos directamente sobre la ciclopentadienona.

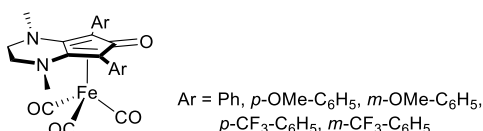


	Neutre		EDG						EWG	
	Ph	H	Me	OMe	OH	NH ₂	NMe ₂	NPh ₂	CF ₃	NO ₂
$\Delta G(\text{I-II})$	19.6	21.7	20.7	23.5	23.2	23.1	27.0	21.0	15.2	12.2
$\Delta G(\text{III-IV})$	24.4	26.9	26.8	30.5	31.9	26.9	29.2	31.8	32.4	32.0
$\Delta G(\text{III-IV}^a)$	14.7	17.5	17.7	19.8	20.1	18.9	20.6	21.9	18.5	14.8

Energías libres de Gibbs en kcal/mol (M06/TZVP~SDD(pcm-EtOH)//BP86/SVP~SDD) nivel de la teoría. (a = calculado con una molécula de etanol que ayuda a la transferencia del protón).

Hemos continuado este estudio añadiendo los sustituyentes en los núcleos aromáticos (Tabla 6.3). Por razones sintéticas, sólo se han introducido en el trabajo experimental los grupos trifluorometil y metoxi. Como antes, se favorece la activación del catalizador para los complejos que llevan grupos electroattractores. En cuanto a la etapa de fraccionamiento del hidrógeno, las barreras energéticas son relativamente similares. Por lo tanto, la sustitución de los núcleos aromáticos no tiene un efecto real sobre esta segunda etapa limitante.

Tabla 6.3: Barreras energéticas para las etapas limitantes de la aminación reductora catalizada por complejos de hierro con los sustitutos en los fenilos de la ciclopentadienona.



	Ph	<i>p</i> -OMe-C ₆ H ₄	<i>m</i> -OMe-C ₆ H ₄	<i>p</i> -CF ₃ -C ₆ H ₄	<i>m</i> -CF ₃ -C ₆ H ₄
$\Delta G(\text{I-II})$	19.6	20.9	21.3	19.8	16.7
$\Delta G(\text{III-IV}^a)$	14.7	16.7	15.7	15.9	16.0

Energías libres de Gibbs en kcal/mol (M06/TZVP~SDD(pcm-EtOH)//BP86/SVP~SDD) nivel de la teoría. (a = calculado con una molécula de etanol que ayuda a la transferencia del protón).

A la vista de estos resultados, se planteó la cuestión de tal efecto de los sustitutos en la etapa de activación del catalizador. Se ha evaluado la ocupación real de los orbitales (EFOs)²⁵⁹ de los dos fragmentos ligando/hierro tricarbonyl (tabla 6.4). Este análisis mostró dos canales de transferencia de carga durante la formación del complejo. Un primer canal se refiere a la donación de la HOMO del ligando a la LUMO del metal y, al mismo tiempo, un segundo canal toma lugar entre la HOMO del metal y la LUMO del ligando. Mirando más en detalle la forma de los orbitales, es más particularmente la HOMO del metal, se puede ver que está relacionada con el enlace Fe-C, lo que significa que durante la formación del complejo, este enlace Fe-C pierde densidad electrónica lo que hace que sea más fácil de romper. Por lo tanto, la introducción de sustitutos electroattractores en la ciclopentadienona refuerza

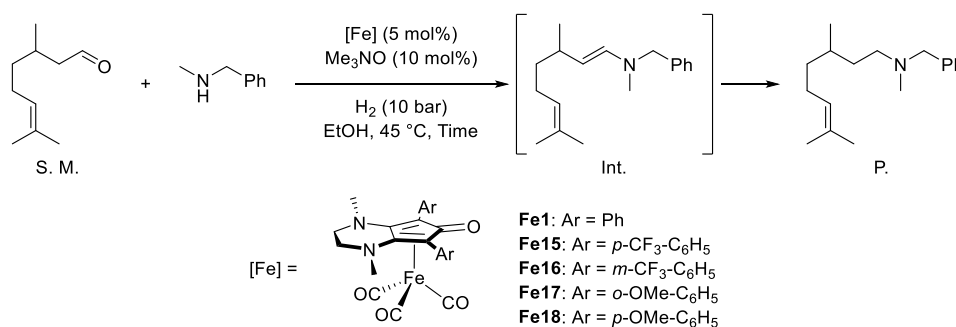
la donación del metal al ligando y empobrece aún más el enlace Fe-C. El catalizador es así más fácil de activar. El efecto contrario se obtiene con los grupos electrodonadores.

Tabla 6.4: EFOs de fragmentos de ciclopentadienona y tricarbonil.

	cyclopentadienone	Fer tricarbonyl
LUMO		
HOMO		

Para evaluar este estudio con DFT, se realizaron reacciones de aminación reductora con diferentes complejos de hierro que contienen grupos trifluorometil o metoxi en los núcleos aromáticos. Estas experiencias mostraron una mayor actividad de los complejos que llevan las agrupaciones -CF₃, mientras que las agrupaciones -OMe llevaron a actividades más débiles que el complejo inicial (Tabla 6.5). Así pues, la tendencia general determinada por el estudio teórico pudo confirmarse experimentalmente.

Tabla 6.5: Selectividad obtenida para la reacción de aminación reductora catalizada por diferentes complejos de hierro.



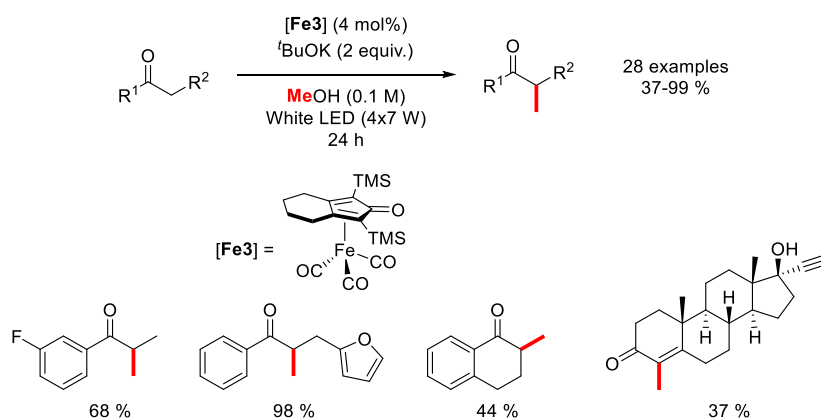
Time (h)	Fe1			Fe2			Fe3			Fe4			Fe5		
	S.M.	Int.	P.	S.M.	Int.	P.	S.M.	Int.	P.	S.M.	Int.	P.	S.M.	Int.	P.
1	24	71	5	32	63	5	47	47	4	56	44	0	75	25	0
2	9	73	18	18	47	35	35	40	25	43	57	0	48	47	5
5	27	38	36	0	0	100	0	0	100	0	100	0	8	70	22

Condiciones general: Citronelal (1 mmol), *N*-metil bencilamina (2 mmol), [Fe] (5 mol%), Me₃NO (10 mol%), etanol (2 mL), H₂ (10 bar), 45 °C. Conversión fue determinada por ¹H NMR de la mezclaz del crudo.

V. Alquilación de cetonas en condiciones fotoquímicas.

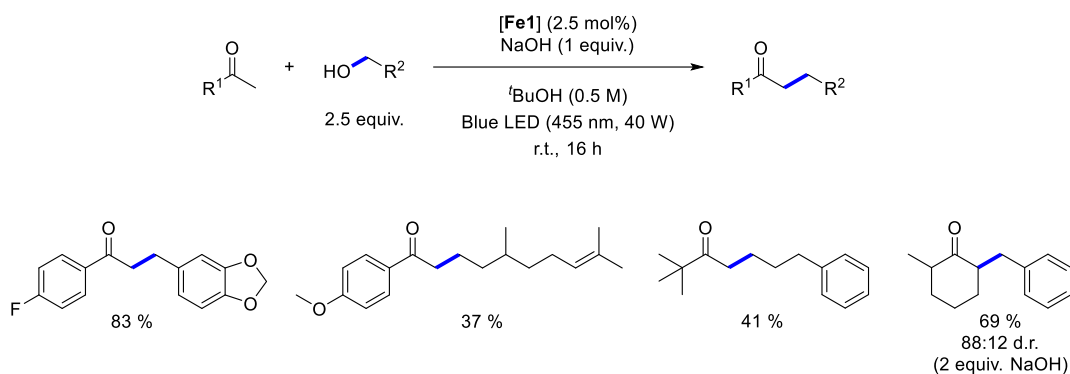
Las reacciones de alquilación por autotransferencia de hidrógeno han sido ampliamente estudiadas en las últimas décadas. Los metales abundantes tales como manganeso, hierro, cobalto o níquel han mostrado su eficacia en estas reacciones de la alquilación.¹⁵ Una amplia variedad de complejos y de ligandos se han diseñado para mejorar la eficacia de los catalizadores metálicos, para trabajar en condiciones más suaves o reducir los tiempos de reacción. Sin embargo, a menudo se requieren altas temperaturas para realizar estas transformaciones. Recientemente, la asociación de la catálisis por metales de transición con la química fotoredox ha abierto el camino a nuevas reacciones, pero también a nuevas reactividades. Utilizando la luz como fuente de energía en lugar de un calentamiento a temperatura elevada.²⁸⁴ Sin embargo, el fotocatalizador puede ser incompatible para la reacción prevista. Además, esta estrategia a veces muestra problemas de transferencia de energía o electrones entre el fotocatalizador y el complejo organometálico. Por lo tanto, la aplicación de catalizadores cromóforos a base de metales de transición permite el uso de una sola especie catalítica en la reacción, superando estas diferentes limitaciones.

Sundararaju describió en 2022 una reacción de metilación de cetonas catalizada por el complejo de hierro **Fe3** a temperatura ambiente bajo irradiación luminosa.²⁸⁵ Las cetonas α -metiladas se aislaron con rendimientos comprendidos entre el 37 y el 99% (Esquema 6.13).



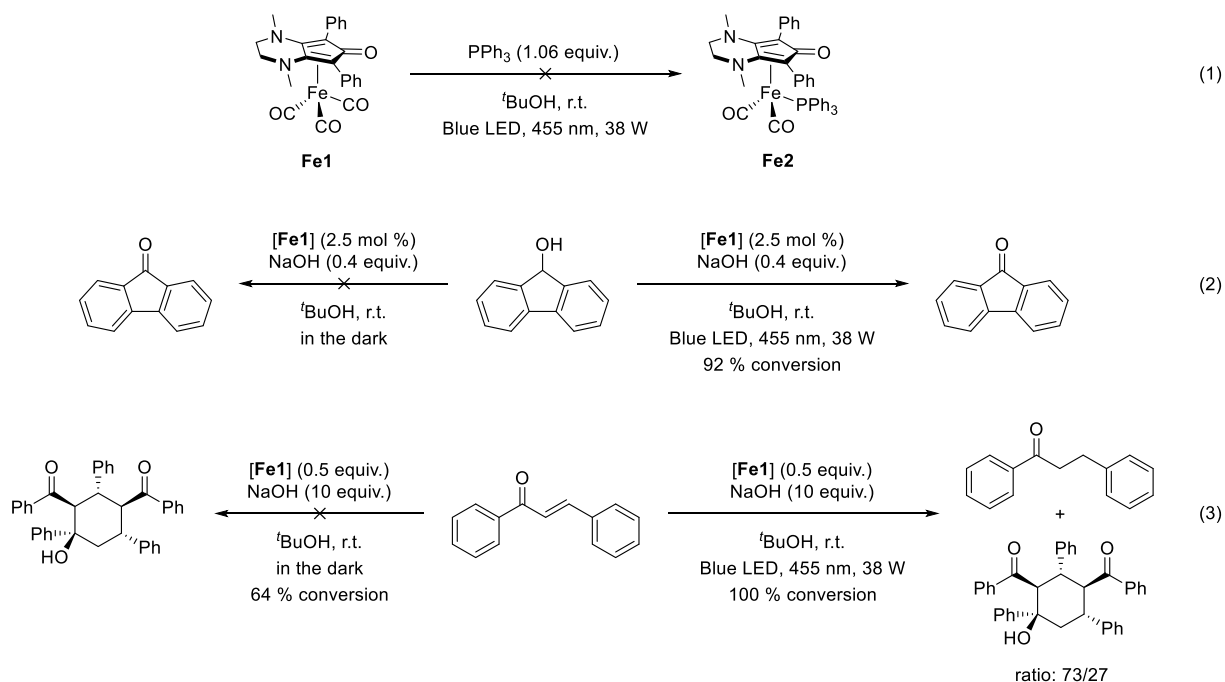
Esquema 6.13: Metilación de cetonas bajo irradiación luminosa catalizada por **Fe3**.

Simultáneamente, nos interesamos por la reacción de alquilación de cetonas en condiciones fotoquímicas.²⁸⁸ En estas condiciones, solo el complejo **Fe1** mostró actividad y permitió obtener los productos deseados. Una ejemplificación de la reacción mostró que las cetonas aromáticas y alifáticas pueden ser alquiladas por alcoholes bencílicos y alifáticos con rendimientos que van del 23 al 99% (Esquema 6.14).



Esquema 6.14: Alquilación de cetonas en condiciones fotoquímicas catalizadas por **Fe1**.

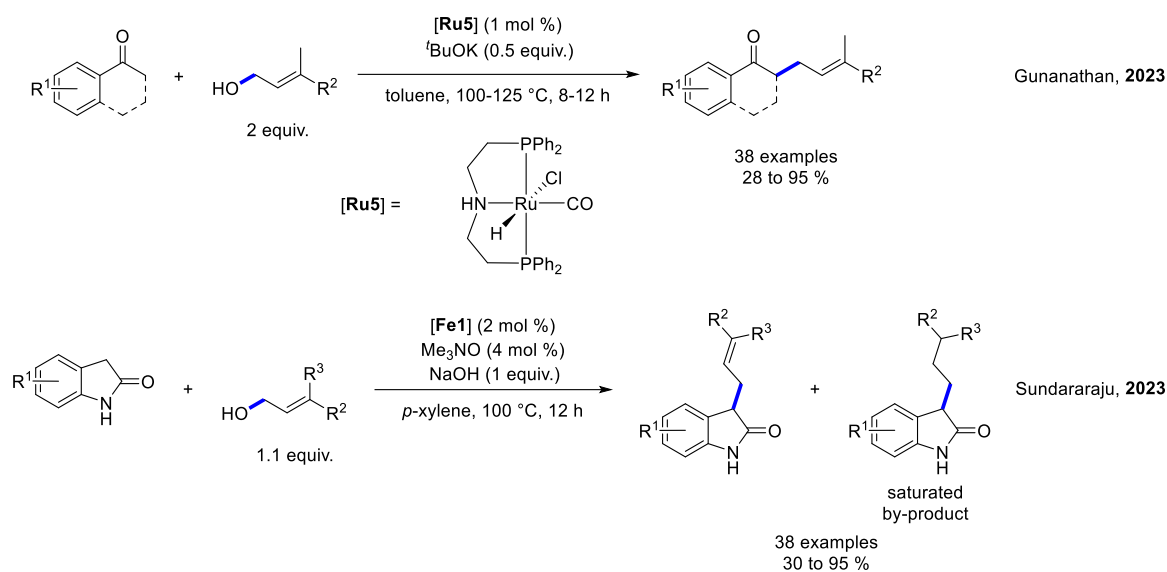
Se realizó un estudio mecánico para determinar el papel de la luz en esta reacción. En un primer momento, se estudió la decoordinación de un ligando CO por la luz que permite la activación del catalizador. El complejo **Fe1** se colocó en presencia de trifenilfosfina y la reacción fue seguida por RMN ^{31}P (Esquema 6.15, Ec. 1). Esta reacción no mostró la formación del complejo **Fe2**. Un segundo experimento mostró que la etapa de oxidación del alcohol en carbonilo solo era posible con radiación luminosa (Esquema 6.15, Ec. 2). Por último, la reducción de la especie α,β -insaturada intermedia solo se produjo en presencia de luz (Esquema 6.15, Ec. 3). Así, el papel de la luz a lo largo de este mecanismo se ha podido identificar claramente: ésta interviene únicamente en las etapas de oxidación y reducción.



Esquema 6.15: Estudio mecánico para determinar el papel de la luz.

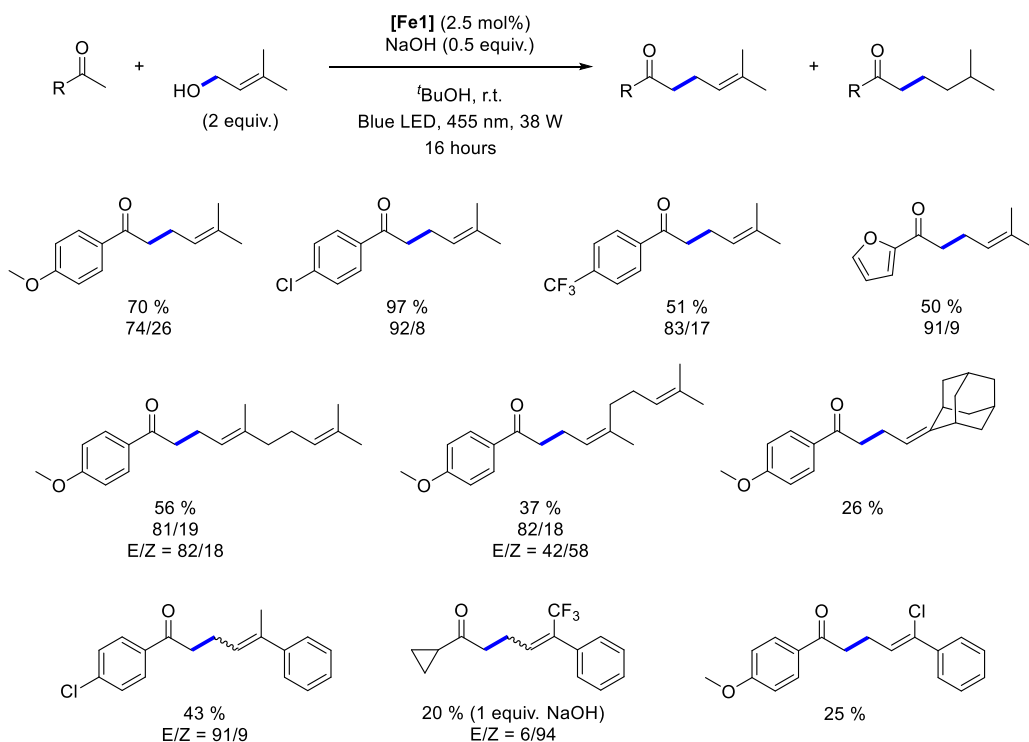
Para ir más allá, nos interesó el uso de alcoholes alélicos y propargílicos como proelectrofilicos. Solo dos ejemplos recientes describen reacciones de alquilación utilizando alcoholes alélicos como electrofilicos. Gunanathan describió por primera vez en 2023 la alquilación de cetonas por terpenoles catalizada por un complejo de rutenio-Macho de 100 °C.²⁹³ Los productos de alquilación pudieron obtenerse con rendimientos comprendidos entre el 28 y el 95 % (Esquema 6.16). A continuación, Sundararaju describió la alquilación de oxindolas por alcoholes alélicos catalizados por el complejo de hierro **Fe1** a 100 °C,²⁹⁴ que permiten obtener los productos correspondientes con

rendimientos que van del 30 al 95 % (Esquema 6.16). Sin embargo, estas metodologías se limitan a sustratos no funcionalizados.



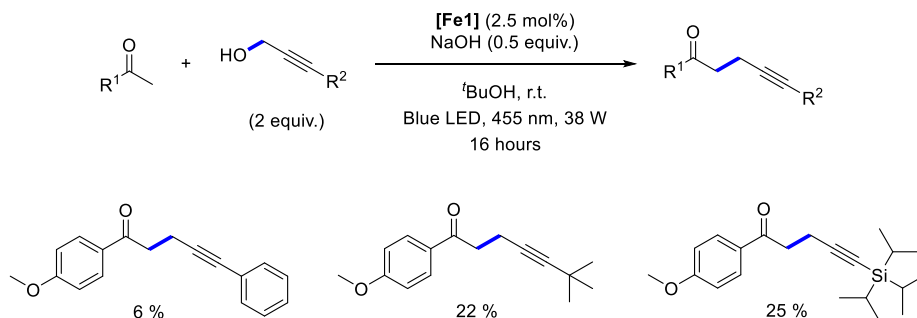
Esquema 6.16: Alquilaciones anteriores utilizando alcoholes alílicos como pro-electrofílicos.

En condiciones muy similares a las descritas para la alquilación de cetonas por los alcoholes primarios, pudo realizarse la alquilación de cetonas por alcoholes alílicos, lo que permitió obtener los productos insaturados correspondientes con rendimientos que oscilaban entre el 10 y el 97 % (Esquema 6.17). El coproducto saturado resultante procede de la reducción de la especie dienona intermedia y no puede separarse del producto deseado. Se observó que la obtención del producto saturado sólo era efectiva con los alcoholes aliílicos poco saturados. Por lo tanto, se ha logrado una mayor tolerancia hacia las agrupaciones funcionales.



Esquema 6.17: Alquilación de cetonas por alcoholes alílicos en condiciones fotoquímicas.

Luego nos interesó el uso de alcoholes propargílicos como pro-electrófilos. En las mismas condiciones reactivas, diferentes alcoholes pudieron participar en esta reacción, ya que los productos de alquilación pudieron obtenerse con rendimientos modestos comprendidos entre el 6 y el 25 % (Esquema 6.18). Sin embargo, esta reacción se limita a los alcoholes propargílicos que llevan agrupaciones voluminosas en la posición terminal.



Esquema 6.18: Alquilación de cetonas por alcoholes propargílicos en condiciones fotoquímicas.

VI. Conclusión

Los objetivos de esta tesis eran el desarrollo de nuevas metodologías para la formación de enlaces C-N y C-C por autotransferencia de hidrógeno, el estudio de los mecanismos reactivos implicados y la mejora de los complejos de hierro de tipo Knölker para este tipo de reacciones.

Se ha descrito un método eficaz de alquilación de hidracidas utilizando el complejo de rutenio de ligando ciclopentadienona **Ru1** (Capítulo II). Este complejo de rutenio mostró una mejor actividad que los complejos de hierro análogos. Un minucioso estudio mecánico ha puesto de manifiesto la selectividad del producto de mono- o di-alquilación para estos sustratos. El cálculo de la tasa de congestión (% V_{Bur}) permite ahora predecir cuál de estos dos productos se obtendrá con nuestro sistema catalítico. La extensión de esta reacción a las reacciones tándem se realizó utilizando metanol y etanol como socio de acoplamiento. El orden de alquilación entre los dos alcoholes involucrados fue determinado tanto por DFT y experimentalmente.

Para continuar nuestro estudio sobre los compuestos nitrogenados, se desarrolló la síntesis de 3-arylquinoli-2(1*H*)-Ones (Capítulo III). El complejo de Knölker **Fe3** se utilizó como catalizador de esta reacción. Este trabajo representa el primer ejemplo de acoplamiento deshidrogenante que permite la síntesis de tales heterociclos. Esta estrategia permitió obtener moléculas funcionalizadas que llevaban una sustitución en cualquiera de las posiciones de la quinolinona. Aunque esta metodología se limita a las acetamidas aromáticas, abre el camino a la síntesis de enamidas cíclicas y no cíclicas.

En general, el complejo de hierro **Fe1** mostró una mayor actividad en las reacciones de alquilación o aminación reductora que otros complejos de tipo Knölker. Se ha realizado un estudio teórico sobre este complejo con el fin de mejorar aún más su eficacia (Capítulo IV). Este estudio mostró el papel clave de los efectos electrónicos en la actividad catalítica del complejo y más particularmente en la etapa de activación. Los grupos electroattractores se consideraron beneficiosos para la reacción de aminación reductora estudiada. Estas observaciones teóricas pudieron confirmarse experimentalmente a posteriori con tiempos de reacción más cortos para los complejos **Fe15** y **Fe16** con agrupaciones CF_3 .

El complejo **Fe1** mostró actividad catalítica a temperatura ambiente bajo irradiación luminosa (Capítulo V). Las condiciones suaves utilizadas para realizar la alquilación de cetonas con alcoholes alifáticos, bencílicos, alílicos y propargílicos muestra el potencial de esta nueva metodología. La tolerancia de las agrupaciones funcionales es, de hecho, mejorada entonces que las moléculas termosensibles pueden ahora ser implicadas en estas reacciones. Subsisten algunas limitaciones (los éteres, alcoholes alílicos sustituidos, alcoholes propargílicos estorbados), sin embargo la amplitud de tales reacciones debe reevaluarse con más detalle para determinar los límites de esta nueva metodología.

Los trabajos realizados durante esta tesis forman parte de los temas desarrollados por Renaud y Poater durante la última década sobre el desarrollo de catalizadores más eficaces basados en los metales abundantes. La exploración de las reacciones de autotransferencia de hidrógeno con nuevos socios permitirá ampliar aún más la aplicación de esta estrategia y de estos catalizadores. Otra continuidad de esta tesis sería la concepción de un complejo cromóforo de tipo Knölker capaz de absorber una banda más amplia del espectro visible. Tales cambios podrían hacer posible la reacción de alquilación utilizando fuentes de luz menos peligrosas. El desarrollo de una reacción de alquilación estereoselectiva también se puede estudiar gracias a las nuevas condiciones reactivas más suaves. Finalmente, la combinación de dos catalizadores diferentes en un sistema dual podría permitir la formación de moléculas complejas mediante un enfoque de una sola olla.

Resumen.

El empleo de complejos organometálicos en síntesis orgánica permitió realizar nuevas transformaciones, pero también superar algunas limitaciones como la generación de residuos o la economía atómica. Sin embargo, aparecieron algunos inconvenientes, principalmente debido al costo del metal y/o del ligando. Durante las últimas décadas, la sustitución de metales nobles por otros abundantes en la Tierra como el manganeso, el hierro, el cobalto o el níquel, hizo que estos enfoques fueran más relevantes desde el punto de vista económico por su abundancia y bajo coste. Basándonos en trabajos previos, nuestro grupo desarrolló diferentes complejos de hierro y rutenio con un ligando ciclopentadienona que presentaba excelentes actividades para la reducción de enlaces polarizados ($C=C$ o $C=N$), o para reacciones de alquilación utilizando alcoholes como proelectrófilos. Este proyecto de doctorado se enmarca dentro de trabajos previos realizados en nuestro grupo: el desarrollo de nuevas metodologías de alquilación mediante hidrazidas o cetonas, nuevas reacciones de acoplamiento deshidrogenativo que dan acceso a estructuras altamente funcionalizadas, o la mejora de reacciones catalizadas por metales modificando los complejos organometálicos.

Resum.

L'ocupació de complexos organometàl·lics en la síntesi orgànica va permetre realitzar noves transformacions, però també superar algunes limitacions com la generació de residus o l'economia atòmica. Tanmateix, van aparèixer alguns inconvenients, sobretot pel cost del metall i/o del lligand. Durant les últimes dècades, la substitució de metalls nobles per altres d'abundància terrestre com ara manganès, ferro, cobalt o níquel, va fer que aquests enfocaments fossin més rellevants des del punt de vista econòmic per la seva abundància i baix cost. A partir de treballs anteriors, el nostre grup va desenvolupar diferents complexos de ferro i ruteni que portaven un lligand de ciclopentadienona que van mostrar excel·lents activitats per a la reducció d'enllaços polaritzats ($C=C$ o $C=N$), o per a reaccions d'alquilació utilitzant alcohols com a proelectròfils. Aquest projecte de doctorat s'emmarca dins de treballs anteriors realitzats al nostre grup: el desenvolupament de noves metodologies d'alquilació mitjançant hidrazides o cetones, noves reaccions d'acoblament deshidrogenants que donen accés a estructures altament funcionalitzades, o la millora de reaccions catalitzades per metalls mitjançant la modificació dels complexos organometàl·lics.

Summary.

The employment of organometallic complexes in organic synthesis allowed to perform new transformations, but also to overcome some constraints such as the waste generation or the atom economy. However, some drawbacks appeared, mostly due to the cost of the metal and/or the ligand. During the last decades, the replacement of noble metals by Earth-abundant ones such as manganese, iron, cobalt or nickel, made these approaches more relevant on the economical point of view due to their abundance and low cost. Based on previous works, our group developed different iron and ruthenium complexes bearing a cyclopentadienone ligand which showed excellent activities for the reduction of polarized bonds ($C = C$ or $C = N$), or for alkylation reactions using alcohols as pro-electrophiles. This PhD project is framed within previous works carried out in our group: the development of new alkylation methodologies using hydrazides or ketones, new dehydrogenative coupling reactions giving access to highly functionalised structures, or the improvement of metal-catalysed reactions by modifying the organometallic complexes.

Résumé.

L'emploi de complexes organométalliques dans la synthèse organique a permis d'effectuer de nouvelles transformations, mais aussi de surmonter certaines contraintes telles que la production de déchets ou encore l'économie d'atomes. Cependant, certains inconvénients sont apparus, principalement en raison du coût du métal et/ou du ligand. Au cours des dernières décennies, le remplacement des métaux nobles par des métaux abondants comme le manganèse, le fer, le cobalt ou le nickel, a rendu ces approches plus pertinentes du point de vue économique en raison de leur abondance et de leur faible coût. Sur la base de travaux antérieurs, notre groupe a développé différents complexes de fer et de ruthénium portant un ligand cyclopentadienone qui ont montré d'excellentes activités pour la réduction des liaisons polarisées ($C = C$ ou $C = N$), ou des réactions d'alkylation utilisant des alcools comme pro-électrophiles. Ce projet de doctorat s'inscrit dans le cadre de travaux antérieurs réalisés au sein de notre groupe : le développement de nouvelles méthodologies d'alkylations utilisant des hydrazides ou des cétones comme pro-nucléophiles, de nouvelles réactions de couplage déshydrogénant donnant accès à des structures hautement fonctionnalisées, ou l'amélioration de réactions catalytiques par modification des complexes organométalliques utilisés.

Keywords.

Organic Chemistry

Organometallic Chemistry

Homogeneous Catalysis

Borrowing Hydrogen

Alkylation Reactions