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THÈSE PRÉSENTÉE
POUR OBTENIR LE GRADE DE

**DOCTEUR DE
L'UNIVERSITÉ DE BORDEAUX**

ÉCOLE DOCTORALE DES SCIENCES CHIMIQUES
SPÉCIALITÉ : CHIMIE ORGANIQUE

Par **ASHIQUE HUSSAIN JATOI**

**Some Recent Developments in Free-radical Additions to Olefins and
Heteroarenes**

Sous la direction du Prof. Yannick LANDAIS

Co-directeur : Dr. Frédéric ROBERT

Soutenue le 16 Avril 2019

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(Dr. Ashique Hussain Jatoi)

Dedication

This Dissertation is dedicated to:

MY BELOVED PARENTS

&

MY SON SHAHWAZ JATOI

List of Abbreviations

| | |
|-----------------------|---------------------------------------|
| Ac: | Acetyl |
| MeCN: | Acetonitrile |
| Atm: | Atmospheric pressure |
| AIBN: | Azobis(isobutyronitrile) |
| BDE: | Bond Dissociation Energy |
| Bn: | Benzyl |
| <i>i</i> Bu: | <i>iso</i> -Butyl |
| CAN: | Ceric Ammonium Nitrate |
| DBU: | 1,8-Diazobicyclo[5.4.0] undec-7-ene |
| DCM: | Dichloromethane |
| DCE: | 1,2-Dichloroethane |
| DMAP: | 4-Dimethylaminopyridine |
| DMF: | Dimethylformamide |
| DMSO: | Dimethylsulfoxide |
| DTBHN: | Di- <i>tert</i> -butylhyponitrite |
| DIBAL-H: | Diisobutylaluminium hydride |
| DFT: | Density Functional Theory |
| Eq.: | equivalent |
| E ⁺ : | Electrophile |
| EWG: | Electron Withdrawing Group |
| EDG: | Electron Donating Group |
| FMO: | Frontier Molecular Orbitals |
| g: | Gram |
| h: | Hour |
| s: | Second |
| IC ₅₀ : | Half-Maximal Inhibitory Concentration |
| IBX: | Iodobenzoic Acid |
| IR: | Infrared Spectroscopy |
| HOMO: | Highest Occupied Molecular Orbital |
| IBX | Iodobenzoic Acid |
| HIR: | Hypervalent Iodine Reagent |
| LUMO: | Lowest UnOccupied Molecular Orbital |
| Me: | Methyl |
| Ms: | Mesylate |
| MCRs: | Multicomponent reactions |
| <i>m</i> -CPBA: | <i>meta</i> -Chloro perbenzoic Acid |
| mg: | Milligram |
| MW: | Molecular Weight |
| NMR: | Nuclear Magnetic Resonance |
| Nu, Nu ⁻ : | Nucleophile |
| <i>o</i> : | Ortho |
| <i>p</i> : | Para |

| | |
|----------------|--|
| PTSA: | <i>p</i> -Toluene Sulfonic Acid |
| Ph: | Phenyl |
| Piv: | Pivalate |
| <i>i</i> -Pr: | <i>iso</i> -propyl |
| Py: | Pyridine |
| PC: | Photocatalyst |
| Rf: | Retention Factor |
| Rt: | Room Temperature |
| SOMO: | Singly Occupied Molecular Orbital |
| TBAF: | Tetra <i>n</i> -butyl ammonium fluoride |
| TEMPO: | 2,2,6,6-Tetramethyl Piperidine-N-oxy Radical |
| THF: | Tetrahydrofuran |
| TFA: | Trifluoroacetic acid |
| Ts: | Tosylate |
| <i>p</i> -Tol: | <i>p</i> -Tolyl |
| Tf: | Triflate |
| TMS: | Trimethylsilyl |

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CHAPTER 1
INTRODUCTION TO RADICAL CHEMISTRY

1. Introduction

The term radical, often referred as free-radicals can be defined as a species (atomic or molecular) containing unpaired electrons in their valence shell.^{1,2} Due to those reactive unpaired electrons, radicals take part in chemical reactions. There are several ways to generate free radicals, but the most common types are redox reactions. Besides this, ionizing radiation, electrical discharges, heat, and electrolysis are known methods by which free radicals can be produced (Scheme 1).

**Scheme 1**

The first radical species containing a carbon atom was discovered by Gay-Lussac who reported the formation of cyanogen (the dimer of $\bullet CN$), while heating mercuric cyanide.³ Later on in 1840s, Bunsen,⁴ Frankland⁵ and Wurtz⁶ performed numerous experiments involving pyrolysis of organometallic compounds. All these experiments reflected the existence of carbon radicals; on the contrary, there were no physical methods available to detect these radicals until 1900, when Gomberg reported the preparation of triphenylmethyl radical,⁷ the first stable and free trivalent carbon radical. Due to scientific doubts, scientists faced lot of challenges to prove the existence of carbon radicals.⁸ Finally, in 1929 Paneth and Hofeditz reported clearly the existence of alkyl radicals by thermolysis of vapour phase of $Pb(CH_3)_4$ and other organometallic compounds.⁹

The noticeable compatibility of free-radicals with many functional groups along with their broad chemoselectivity, prompted synthetic chemists to develop further radical chemistry. Radical processes are now part of the tools in the important armoury of organic chemists, which facilitates greatly the access to many important targets and complex natural products.¹⁰

¹ Carey and Sundberg "Advanced Organic Chemistry Part A", **1991**, 3rd Edition, Chap 12, p 651.

² Hayyan, M.; Hashim, M.A.; AlNashef, I.M. *Chem. Rev.* **2016**, *116*, 3029.

³ Gay-Lussac, H. L. *Ann. Chim.* **1815**, *95*, 172.

⁴ Bunsen, R. H. *Justus Liebigs Ann. Chim.* **1842**, *42*, 27.

⁵ Frankland, E. *Ann. Chem. Pharm.* **1849**, *71*, 213.

⁶ Wurtz, C. A. *Compt. Rend.* **1854**, *40*, 1285.

⁷ Gomberg, M. *J. Am. Chem. Soc.* **1900**, *22*, 757.

⁸ Forbes, M. D. E. in *Carbon Centered Free Radicals and Radical Cations*, John Wiley, **2010**, p. 1.

⁹ Paneth, F.; Hofeditz, W. *Chem. Ber.* **1929**, *62*, 1335.

¹⁰ Carey, F. A.; Sundberg, R. J. in *Advanced Organic Chemistry, Part A*, Springer, New-York, **2007**, p. 980.

2. Stability and Structure of Radicals

Being highly reactive, radicals are usually short-lived species. However, there are also long-lived radicals classified as stable and persistent radicals.

When radicals are not stable, they can undergo dimerization or disproportionate. In alkyl radicals, the disproportionation process involves a transfer of a β hydrogen to the radical site to form an alkane and an alkene (Figure 1). Short-lived radicals may also add to unsaturations.

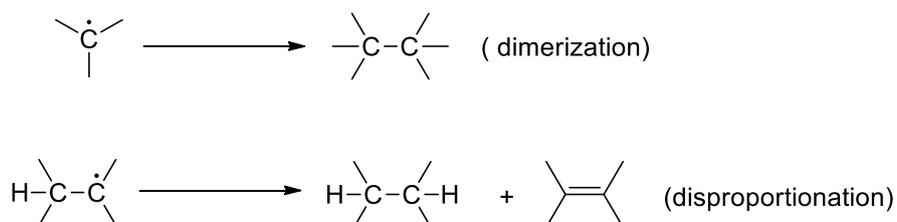


Figure 1. Dimerization and disproportionation in alkyl radical.

A few radicals are stable under ordinary conditions of temperature and pressure and are called indefinitely stable radicals. Solid **2** can thus exist indefinitely in the presence of air (Figure 2). Both **1** and **2**, show delocalization of unpaired electrons through aromatic rings, which provide a resistance toward dimerization or disproportionation. More rarely, functional groups having unpaired electron may be stable. The nitroxide group is one of the best example of such radicals, where the unpaired electron is delocalized over nitrogen and oxygen (N-O) as in **3**, which is stable to oxygen even above 100°C.

Molecular dioxygen (O₂) and nitric oxide (NO) constitute example of stable radicals. Steric crowding around the radical center increases radicals lifetime, as for instance in TEMPO **4**, which is a prototypical example of a persistent radical. The resonance in TEMPO is attributed to non-bonding electron on nitrogen which forms a 2-center 3-electron bond between nitrogen and oxygen. Its persistence results from the presence of the four methyl groups, which provide a steric protection to the aminoxyl group. Structure thus plays an important role in the stability of radicals.

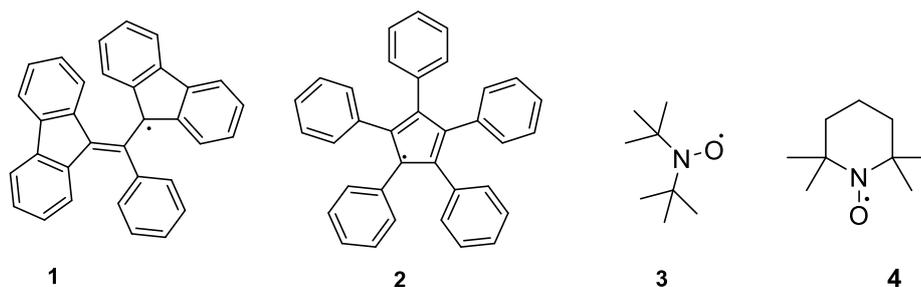


Figure 2

There are several geometrical configurations shown by carbon-centered radicals ($R_3C\cdot$). These trivalent radical goes through pyramidal to planar configuration, inverting rapidly as a function of the nature of substituents on the carbon bearing the radical. This trivalent radicals can thus change their hybridization from sp^3 to sp^2 . For instance, in methyl radical, the radical appears to be planar, although alkyl radicals are generally pyramidal (Figure 3).

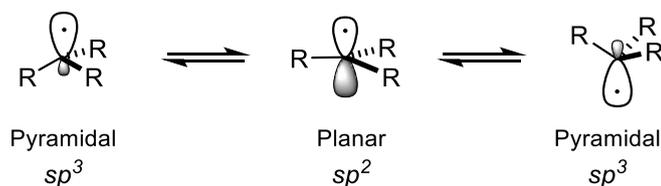


Figure 3

The order of stability of free-radical increases according to the following order: ethyl < *i*-propyl < *t*-butyl. Two effects have to be considered, one is the torsional strain resulting from repulsive interactions between the vicinal C-H bond and the SOMO in the planar configuration. The other results from an hyperconjugation between the SOMO and the σ orbital of the vicinal C-H bond stabilizing the pyramidal structure.¹¹ Stability of radicals based on their structure is described below (Figure 4) starting from least stable methyl radical to highly stable tertiary radical.

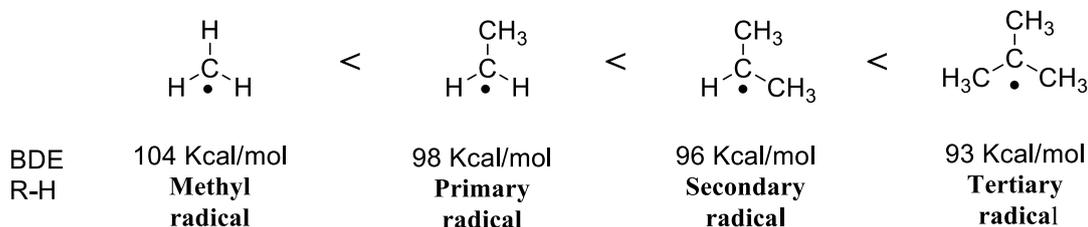


Figure 4. Stability of radical species

¹¹ Fleming, I. in *Frontier Orbitals and Organic Chemical Reactions*, 2009 John Wiley & Sons Ltd.

Thermodynamic and kinetics factors affect the stability of radicals. Hyperconjugation and delocalization of radical through mesomeric forms are part of thermodynamic factors (Figure 5).

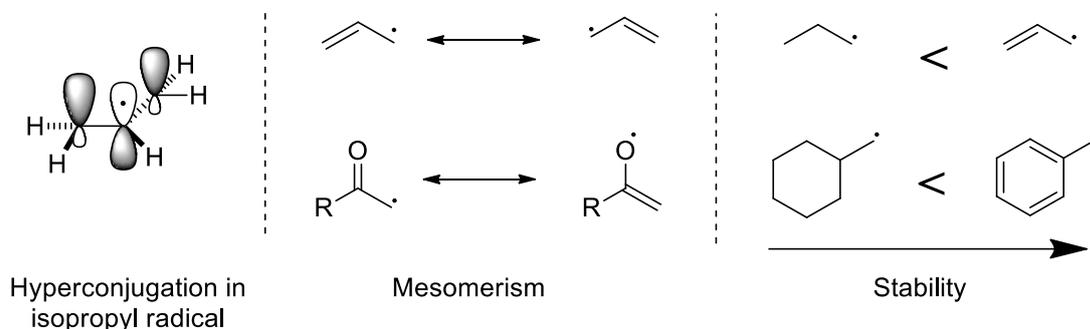


Figure 5

An important factor concerning the stability of radicals is the hybridization. The *s* character is inversely proportional to the stability. More *s* character in the SOMO makes the radical less stable. Therefore, alkyl radicals are more stable than vinyl and alkynyl radicals, as shown in (Figure 6).

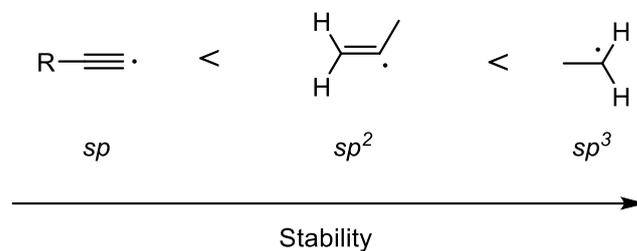


Figure 6. Hybridization effect on the stability of radical

Bond dissociation energies (BDE) are useful to estimate the thermodynamic stability of a radical R•. If bond dissociation energy of the broken bond is small, more readily the radical is formed (Figure 7).¹⁰

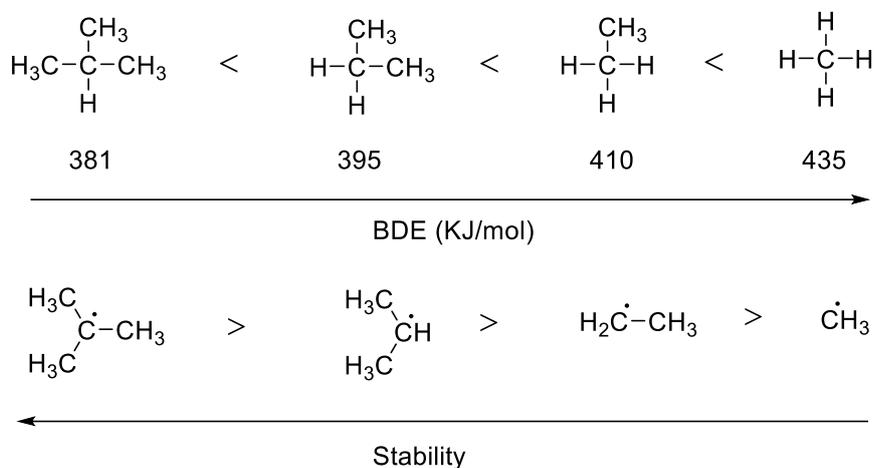


Figure 7. Bond dissociation energy vs radical stability

Kinetic factors also affect the stability of radicals and are controlled by the steric hindrance round the radical center (cf TEMPO **4**, Figure 2). Kinetic stability is directly proportional to steric hindrance.

3. Reactivity of Radicals

As already discussed, the reactivity of radicals depends mainly on two factors, *i.e.* the stability of the generated radicals and structural factors. Addition of a free-radical species onto an olefin is a favoured process and is thus exothermic. The transition state energy will thus resemble that of the reaction components (Hammond's postulate). On this basis, the Frontier Molecular Orbital theory (FMO) may be applied, providing a satisfying explanation of the radical reactivity.¹¹

By considering a reaction between a radical R• and an olefin, the electron in SOMO can interact with HOMO or LUMO orbitals of the olefin. Based on the difference of energy between these orbitals (SOMO and HOMO or LUMO of the olefin), the reactivity between the two molecules can be described. For instance, the rate at which a C-centered radical adds onto an olefin will depend on the energy difference between the SOMO orbital of the radical and the HOMO or LUMO orbitals of the olefin.

Considering above example there are two possibilities for this interaction:

(i) A carbon radical with electron donating groups (a nucleophilic radical) will have a high energy SOMO which will overlap readily with the low energy LUMO of an electron poor olefin (*i.e.* substituted by electron withdrawing groups) (Figure 8, left).

(ii) On the other hand, a C-centered radical having electron-withdrawing groups (*i.e.* an electrophilic radical) will add more favorably to an electron rich olefin through an interaction between a low energy SOMO orbital of the radical and a high energy HOMO orbital of the olefin (Figure 8, right).

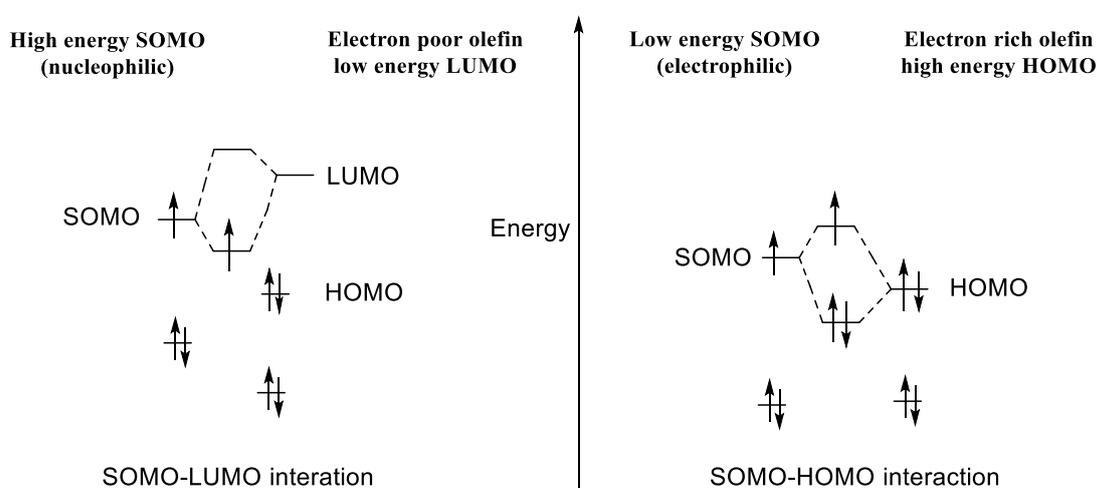


Figure 8. Orbital interaction between radicals and olefins

Polar effects are important in the reactivity of radical species. To understand the behavior of radicals, it is thus helpful to classify them according to their polarities. The same can be done for substrates reacting with radicals. In the scheme below (Figure 9), the different types of radicals and radical acceptors have been categorized according to their polarities.¹¹ This classification is a guideline to chemists when designing their radical reactions. Electrophilic radicals will thus react faster with electron-rich than electron-poor radical traps. It is however worth noticing that being highly reactive, a radical can react with either class of radical acceptors. For example, an electrophilic radical may well react with an electron-poor olefin, but this reaction will occur at a slow rate.

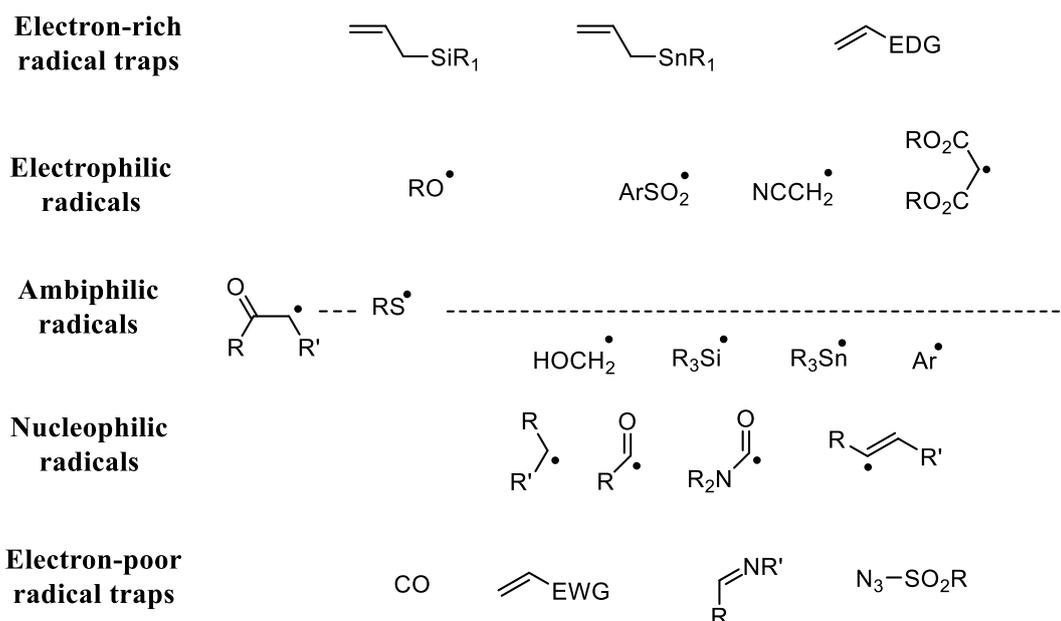


Figure 9. Polarities of radicals and radical traps.

4. Some useful radical species

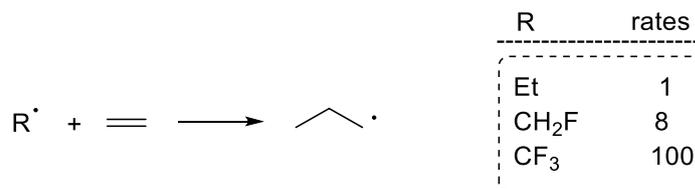
Various radical species have been generated and used along this PhD thesis which we will describe more precisely. A summary of their reactivity is given in this chapter.

4.1. Electrophilic radicals α to an electron-withdrawing group

Although electrically neutrals, carbon-centered radicals may exhibit electrophilic or nucleophilic character, depending on the nature of the substituents on the radical center. Their electrophilicity or nucleophilicity is apparent during their addition, for instance, onto unsaturated systems, including olefins, which occurs with various rates. Polarity of reacting substrates (*i.e* radicals and alkenes for instance) thus plays an important role in radical processes.¹² Therefore electron-deficient olefins will react faster with nucleophilic radicals and an electrophilic radical will react faster with an electron-rich olefin as shown above in Figure 8. The SOMO-HOMO interaction in addition of electrophilic radicals will be the dominant one, as electrophilic radicals possess low energy SOMO orbitals, leading to an efficient overlapping

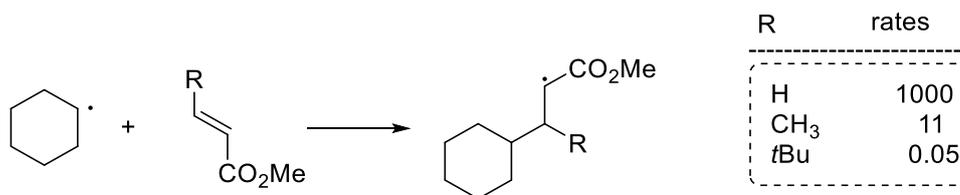
¹² a) Giese, B. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 753; b) Fischer, H.; Radom, L. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 1340; c) Godineau, E.; Landais, Y. *Chem. Eur. J.* **2009**, *15*, 3044.

with the high-lying HOMO orbital of the electron-rich olefins. For instance, electrophilic CF_3 radicals addition 100 times faster to ethylene as compared to the ethyl radical (Scheme 2).¹³



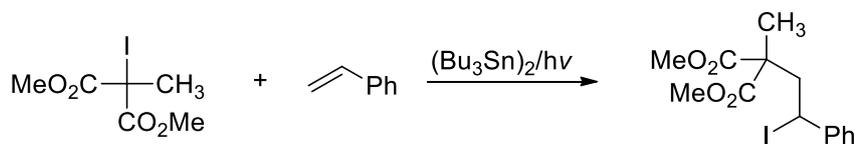
Scheme 2. Addition of electrophilic radicals to electron-rich alkenes.

The reaction rates are also slightly affected by the size of the radicals; for example, tertiary radicals add easily to form quaternary carbons. On the other hand, steric hindrance on the olefin may prevent additions. Substituted olefins exhibit lower rate for the radical additions. For instance, addition of cyclohexyl radicals is retarded by β -substitution on the acrylates (Scheme 3).



Scheme 3. Effect of substituents on rate of radical addition.

Iodomalonates are for instance good precursors of electrophilic malonyl radicals, which were added to various alkenes, as illustrated in this halogen atom-transfer reaction reported by Curran *et al.* (Scheme 4).^{14,15,16}



Scheme 4. Iodine-atom transfer to alkenes.

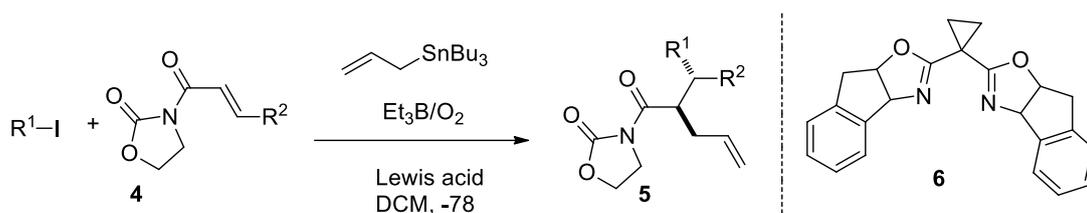
¹³ Tedder, J. M.; Walton, J. C. *Acc. Chem. Res.* **1976**, 9, 183.

¹⁴ Curran, D. P.; Seong, C. M. *J. Am. Chem. Soc.* **1990**, 112, 9401.

¹⁵ Curran, D. P.; Tamine, J. *J. Org. Chem.* **1991**, 56, 2746.

¹⁶ Curran, D. P.; Kim, D. *Tetrahedron* **1991**, 47, 6171.

The asymmetric radical addition in Scheme 5 reported by Sibi *et al.*¹⁷ is a good illustration of the importance of polar effects in radical chemistry. This reaction involves the addition of an electron-rich radical R^1 to an achiral amide, followed by the trapping of the resulting electrophilic radical intermediate by an electron-rich allyl-tin reagent. The reaction is catalyzed by a Lewis acid in the presence of a chiral ligand which controls the stereochemistry of the process (Scheme 5). They thus observed modest *syn* selectivities for alkyl and α -alkoxy radical additions (6:1), while less nucleophilic radicals led to excellent *anti* selectivity.

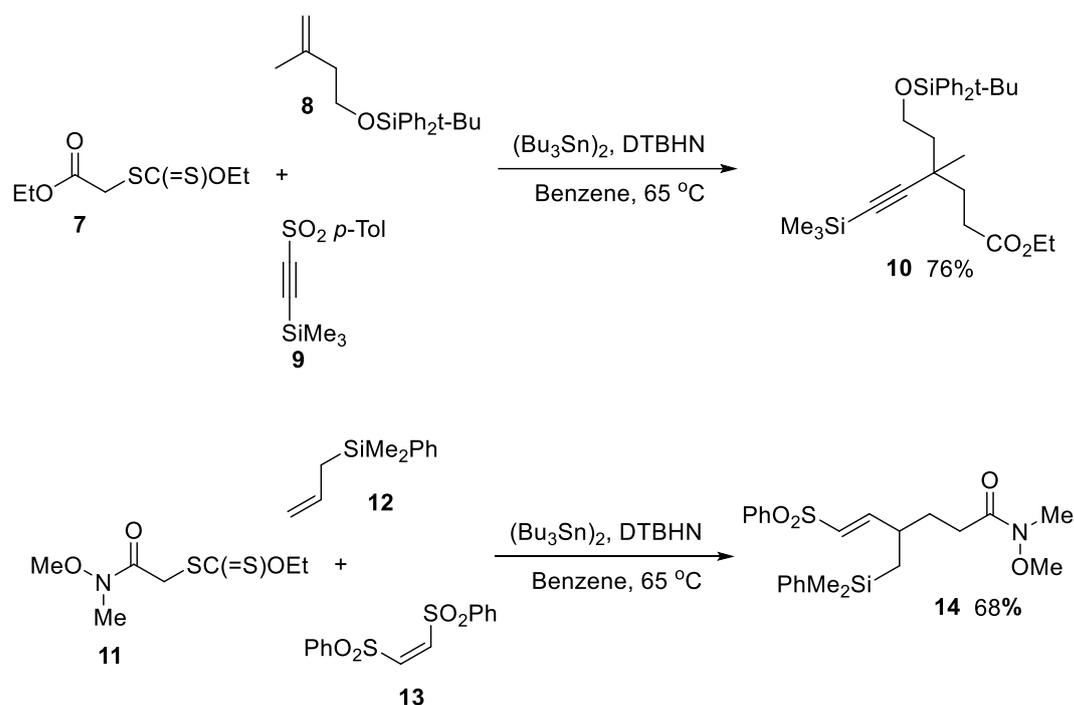


Scheme 5. Asymmetrical radical addition according to Sibi.

Following the same principles, our laboratory developed three-component vinylation and alkynylation processes, involving the intermediacy of a nucleophilic radical, generated by the addition of an electron-poor radical onto an olefin (Scheme 6).¹⁸ The desired carbo-vinylation, and carbo-alkynylation products were obtained in generally good yields, using vinyl and alkynylsulfones as radical traps. The electrophilic radical precursors were generally xanthates or halides α - to an electron-withdrawing group. Ketones, esters, amides and nitriles were successfully used in this context.

¹⁷ Sibi, M. P.; Miyabe, H. *Org. Lett.* **2002**, *4*, 3435.

¹⁸ Liautard, V.; Robert, F.; Landais, Y. *Org. Lett.* **2011**, *13*, 2658.



Scheme 6. Carbo-vinylation and alkynylation of olefins.

4.2. Cyclopropyl radical

During the course of recent studies within our laboratory and the present PhD work, cyclopropenes were used as olefins in our multicomponent reactions. These strained systems, rarely used in radical processes (*vide infra*) are very reactive, radical addition processes being very favoured due to the release of the ring strain. Addition of C-centered radical onto this peculiar olefin provides a cyclopropyl radical, which is itself very reactive. Some specific features of the cyclic radical are described below. The cyclopropyl radical in contrast to other cyclic or acyclic radicals, is a bent σ -radical.¹⁹ Its inversion barrier is only 3.0 kcal/mol with a pyramidal bending frequency of 713 cm^{-1} . The α -C-C bonds are stronger as compared to cyclopropane, whereas the β -C-C bond is weaker. When a substituent allowing delocalizing (π systems) is attached to the cyclopropyl radical, the σ -radical changes for a π -radical. In contrast, electronegative substituents (O, F) have the tendency to convert π to σ -radical. Such substituents reduce the rate of inversion by reinforcing the σ -character of the radical. The cyclopropyl radical inverts its configuration rapidly, passing through a π -radical transition state (Figure 10).

¹⁹ Fessenden, W.; Krusic, P.J.; Schuler, R. H. *J. Chem. Phys.* **1965**, *43*, 2704.

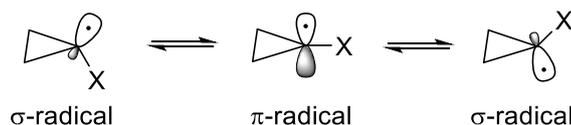


Figure 10. Structure of the cyclopropyl radical

Generally, σ -radicals are more reactive and less selective than π radicals. Hence, the cyclopropyl radical exhibits a high reactivity consistent with its σ -character. The cyclopropyl σ -radical, located in a sp^2 hybridized orbital, shows some resemblance with the phenyl σ -radical but is more selective and less reactive. From the relative reactivity data shown in Table 1, Shono²⁰ was able to conclude that the cyclopropyl radical reactivity more closely resembles that of the phenyl σ -radical than that of the cyclohexyl π -radical.

| Aromatic |  |  |  |
|---------------|---|---|---|
| C_6H_5Cl | 3.5 | 1.1 | 1.78 |
| $C_6H_5OCH_3$ | 2.3 | 1.7 | 1.95 |
| C_6H_5CN | 27 | 3.7 | 3.59 |
| $C_6H_5CH_3$ | 0.76 | 1.2 | 1.03 |
| C_6H_5tBu | 0.28 | 0.64 | 0.59 |

Table 1. Relative reactivity in homolytic aromatic substitution.

4.3. Carbamoyl radical

Acyl radicals have been categorized into three major classes namely alkanoyl radicals, alkoxy carbonyl radicals, and carbamoyl radicals (Figure 11).²¹ Alkanoyl radicals have been extensively studied used for synthetic purposes.²² They have a tendency to lose carbon monoxide to afford the corresponding alkyl radical, providing the latter is stabilized (tertiary, α -to heteroatoms, but not primary). Alkoxy carbonyl radicals have been less studied but, similarly, they can lose carbon dioxide to afford the corresponding alkyl radical. Although these species are valuable intermediates, their fragmentation somewhat limits their utility.

²⁰ Shono, T.; Nishiguchi, I. *Tetrahedron*, **1974**, *30*, 2183.

²¹ Chatgililoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991.

²² Herzon, S. B.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 5342.

Carbamoyl radicals, are comparatively long-lived species, because a decarbonylation would produce a highly energetic aminyl radical. These free-radicals have received less attention than the other two.²¹ Apparently, the rarity of appropriate methods to generate radicals such as **3** is the origin of this situation, although, inter- and intramolecular additions to unsaturated systems, including alkenes and alkynes,²³ arenes and heteroarenes²⁴ and oxime ethers have been reported. The potential of these radicals have been recently reported in the synthesis of the complex natural product stephacidin B.²² Loss of hydrogen under oxidative conditions also allow their conversion into useful isocyanates.²⁵

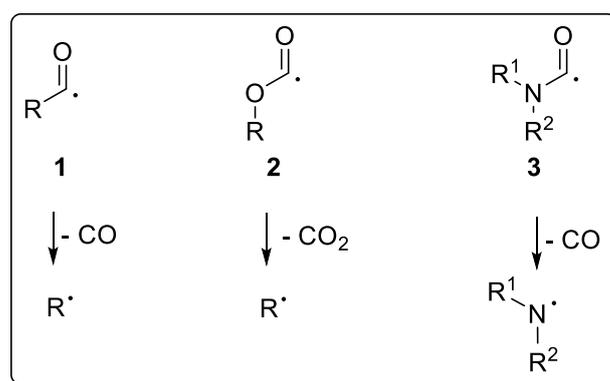


Figure 11. alkanoyl radicals and their decarbonylation

Carbamoyl radicals are accessible using essentially three main routes, *i.e.* through

- (i) the C-X bond cleavage in $R_2N(C=O)X$ precursors ($X = H$,^{26,25} xanthate,²⁷ SPh,²⁸ Co(salen),²⁹),
- (ii) The photoredox reductive decarboxylation of *N*-hydroxyphthalimido oxamides³ and,

²³ a) Yuan, L.; Chen, J.; Wang, S.; Chen, K.; Wang, Y.; Xue, G.; Yao, Z.; Luo, Y.; Zhang, Y. *Org. Lett.* **2015**, *17*, 346; b) Petersen, W. F.; Taylor, R. J. K.; Donald, J. R. *Org. Biomol. Chem.* **2017**, *15*, 5831; c) Minisci, F.; Citterio, A.; Vismara E.; Giordano, C. *Tetrahedron* **1985**, *41*, 4157.

²⁴ a) Minisci, F.; Recupero, F.; Punta, C.; Gambarotti, C.; Antonietti, F.; Fontana, F.; Gian, F. *Chem. Commun.* **2002**, 2496; b) Biyouki, M. A. A.; Smith, R. A. J.; Bedford, J. J.; Leader, J. P. *Synth. Commun.* **1998**, *28*, 3817; c) Nagata, K.; Itoh, T.; Okada, M.; Takahashi, O. A. *Heterocycles* **1991**, *32*, 2015; d) Minisci, F.; Gardini, G. P.; Galli, R.; Bertini, F. *Tetrahedron Lett.* **1970**, *1*, 15; (e) Minisci, F.; Fontana, F.; Coppa, F.; Yan, Y. M. *J. Org. Chem.* **1995**, *60*, 5430.

²⁵ a) Minisci, F.; Coppa, F.; Fontana, F. *Chem. Commun.* **1994**, 679; b) Minisci, F.; Fontana, F.; Coppa, F.; Yan, M. Y. *J. Org. Chem.* **1995**, *60*, 5430.

²⁶ Antonietti, F.; Fontana, F.; Gian, F. *Chem. Commun.* **2002**, 2496.

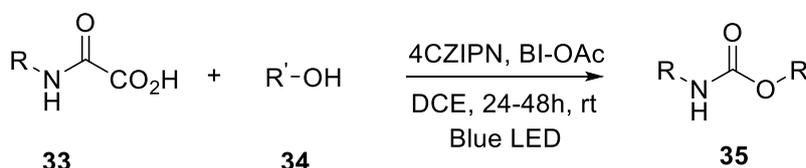
²⁷ a) Millan-Ortiz, A.; Lopez-Valdez, G.; Cortez-Guzman, F.; Miranda, L. D.; *Chem. Commun.*, **2015**, *51*, 8345; b) Betou, M.; Male, L.; Steed, J. W.; Grainger, R. S. *Chem. Eur. J.* **2014**, *20*, 6505.

²⁸ Sakamoto, M.; Takahashi, M.; Fujita, T.; Nishio, T.; Iida, I.; Watanabe, S. *J. Org. Chem.* **1995**, *60*, 4683.

²⁹ Gill, G. B.; Pattenden, G.; Reynolds, S. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 369.

(iii) The oxidative decarboxylation of oxamic acids.³⁰
 These methods will be described in more details later in chapter two.

Oxamic acids are readily available by combination of amines and oxalic acid derivatives³¹ and constitute potent precursors of carbamoyl radicals. The generation of carbamoyl radicals from oxamic acids is particularly useful as it circumvents the problem of regioselectivity encountered for instance during the C-H abstraction in formamides ($R_2N(C=O)H$), which occurs concurrently at CHO and α to nitrogen, leading to a mixture of products.²⁵ Oxidative decarboxylation of oxamic acids, to generate carbamoyl radicals, may be carried out in the presence of Ag(I) and Cu(II) salts and stoichiometric amount of $K_2S_2O_8$ as an oxidant in a biphasic medium, as originally proposed by Minisci and co-workers.^{25a} These conditions however suffer from the presence of large amount of metal catalysts, and water was shown to be detrimental to the process efficiency, as observed for instance during the preparation of isocyanates. Our group recently showed that the oxidative decarboxylation of oxamic acid could also be performed conveniently under metal-free conditions in an organic solvent, using an organo-photocatalyst under visible-light irradiation, leading to the corresponding isocyanates in good yields (Scheme 7).³² The chemistry of carbamoyl radical will be reported in more detail in the following chapter.



Scheme 7. Oxidative decarboxylation of oxamic acids.

³⁰ a) Guo, L. N.; Wang, H.; Duan, X.-H. *Org. Biomol. Chem.* **2016**, *14*, 7380; b) Petersen, W. F.; Taylor, R. J. K.; Donald, J. R. *Org. Lett.* **2017**, *19*, 874; c) Bai, Q.-F.; Jin, C.; He, J.-Y.; Feng, G. *Org. Lett.* **2018**, *20*, 2172.

³¹ a) Seki, Y.; Tanabe, K.; Sasaki, D.; Sohma, Y.; Oisaki, K.; Kanai, M. *Angew. Chem. Int. Ed.* **2004**, *53*, 6501; b) Mecinovic, J.; Loenarz, C.; Chowdhury R.; Schofield C. J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6192.

³² Pawar, G. G.; Robert, F.; Grau, E.; Cramail, H.; Landais, Y. *Chem. Commun.* **2018**, *54*, 9337.

5. Multicomponent Reactions or MCR

Multicomponent reactions are reactions in which more than two reactants are combined together to give a new product with the formation of several new bonds. A large number of organic compounds with diverse substitution patterns can be accessed in a straightforward manner using this approach. Looking 150 years back, one can see several major contributions in the field of multicomponent reactions including, the Strecker synthesis of α -amino nitriles (1850),³³ the Hantzsch pyridine synthesis (1881),³⁴ the Biginelli reaction (1891),³⁵ the Mannich reaction (1912)³⁶ and the Passerini α -acyloxy amide synthesis in 1921.³⁷ After the seminal contribution from Ugi (1959),³⁸ multicomponent reactions started to express their importance in the synthesis of library of compounds and became key to the development of combinatorial chemistry. Selectivity and efficiency, have also been associated to the mildness of radical processes and the compatibility of free-radical species with functional groups. In the next part of this chapter, we will highlight some of the developments of free radical multi-component reactions.

Multicomponent reactions involving radicals are highly efficient processes, from which complex structures can be obtained starting from simple and commercially available materials. In this context, polarities of the radical precursors and that of the generated radical intermediates play a significant role in the design of successful radical MCR. The data collected previously on radical kinetics and thermodynamics related to additions, abstractions or fragmentation processes helped predicting and designing radical MCRs. A few multicomponent radical processes are described below to illustrate the power of this approach for organic synthesis.

³³ a) Yamago, S.; Ejiri, S.; Nakamura, E. *Chem. Lett.* **1994**, *23*, 1889; b) Ferjancic, Z.; Cekovic, Z.; Saicic, R. N. *Tetrahedron Lett.* **2000**, *41*, 2979; c) Legrand, N.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **2000**, *41*, 9815; d) Ueda, M.; Doi, N.; Miyagawa, H.; Sugita, S.; Takeda, N.; Shinada, T.; Miyata, O. *Chem. Commun.* **2015**, *51*, 4204; e) Doi, N.; Takeda, N.; Miyata, O.; Ueda, M. J. *Org. Chem.* **2016**, *81*, 7855.

³⁴ Dange, N. S.; Robert, F.; Landais, Y. *Org. Lett.* **2016**, *18*, 6156.

³⁵ Godineau, E.; Landais, Y. *Chem. Eur. J.* **2009**, *15*, 3044.

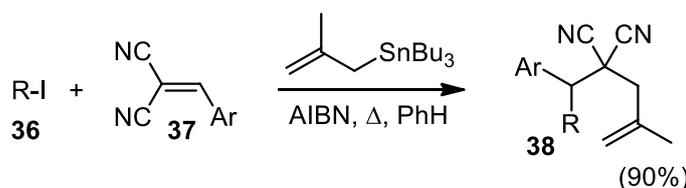
³⁶ a) Strecker, A. *Justus Liebigs Ann. Chem.* **1850**, *75*, 27; b) Strecker, A., *Ann. Chem. Pharm.* **1850**, *91*, 349.

³⁷ Mannich, C.; Krösche, W. *Arch. Pharm.* **1912**, *250*, 647.

³⁸ Hantzsch, A. *Justus Liebigs Ann. Chem.* **1882**, *215*, 1; a) Biginelli, P. *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 2962; b) Biginelli, P. *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 447.

5.1. Carbo-allylation reaction

Mizuno et al developed the first olefin carbo-allylation process in 1988.³⁹ This involves the addition of a nucleophilic radical species onto an electron-poor olefin. The nucleophilic radical is generated through abstraction of the iodine atom from the alkyl iodide with $\text{Bu}_3\text{Sn}\cdot$. The ensuing radical then adds onto the olefin, generating a new electrophilic radical which is finally trapped by the electron rich allylstannane to furnish the allylated product after β -elimination⁴⁰ (Scheme 8).



Scheme 8.

Later on, Porter and co-workers⁴¹ developed an asymmetric variant of this radical carbo-allylation by the addition of an alkyl radical, generated from the corresponding iodide, onto an oxazolidinone, using a chiral ligand in the presence of a Lewis acid.

5.2. Radical Mannich Reaction and related processes

The Mannich reaction is useful to access α -aminomethylated carbonyl compounds through the condensation of a non-enolizable aldehyde and an enolizable carbonyl compounds in the presence of primary or secondary amines.⁴² In a related addition of alkyl radicals to imines, Tomioka⁴³ came up with the idea of initiating the reaction by using dimethylzinc and oxygen. Abstraction of an hydrogen atom from THF by the methyl radical (generated from the reaction of Me_2Zn and oxygen), followed by the addition of the so-formed radical onto the imine

³⁹ Mizuno, K.; Ikeda, M.; Toda, S.; Otsuji, Y. *J. Am. Chem. Soc.* **1988**, *110*, 1288.

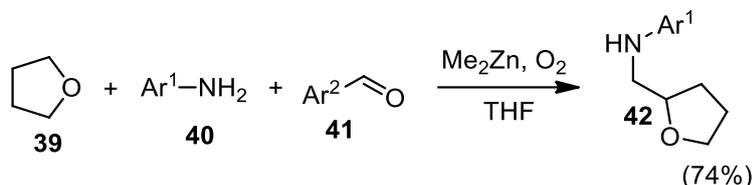
⁴⁰ a) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrucker, C. *Angew. Chem.* **1959**, *71*, 386; b) Ugi, I.; Steinbrucker, C.; *Angew. Chem.* **1960**, *72*, 267.

⁴¹ Wu, J H.; Radinov, R.; Porter, N. A. *J. Am. Chem. Soc.* **1995**, *117*, 11029.

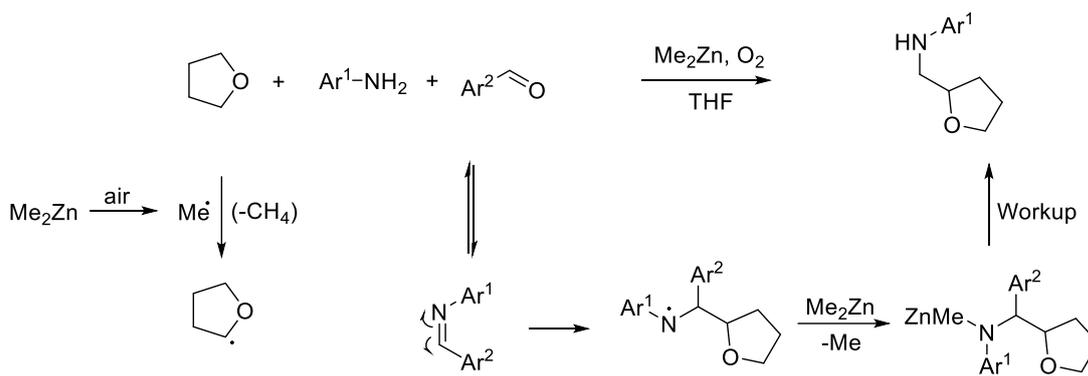
⁴² Canella, R.; Clerici, A.; Panzeri, W.; Pastori, N.; Punta, C.; Porta, O. *J. Am. Chem. Soc.* **2006**, *128*, 5358.

⁴³ Yamada, K.-I.; Yamamoto, Y.; Tomioka, K. *Org. Lett.* **2003**, *5*, 1797.

produced an aminyl radical, which reacted with dimethylzinc to form a zincate derivative, finally hydrolyzed, affording the β -aminoether (Scheme 9).

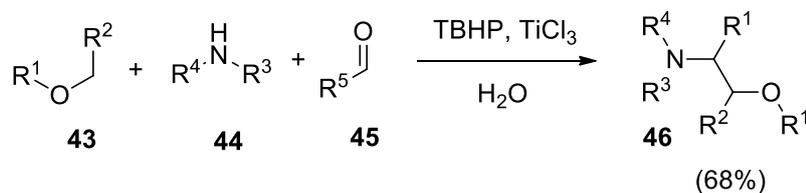


Scheme 9



Scheme 9. Mannich reaction.

Later, a related access to aminoalcohols or aminoethers was developed by Porta *et al*,⁴⁴ who generated the radical α - to oxygen using a *tert*-butoxy radical resulting from the reaction between *tert*-butyl hydroperoxide (TBHP) and Ti(III)/Ti(IV). As above, TBHP abstracts the hydrogen atom α - to the heteroatom to generate an α -alkoxyalkyl radical which adds onto the iminium intermediate to form the desired product (Scheme 10).



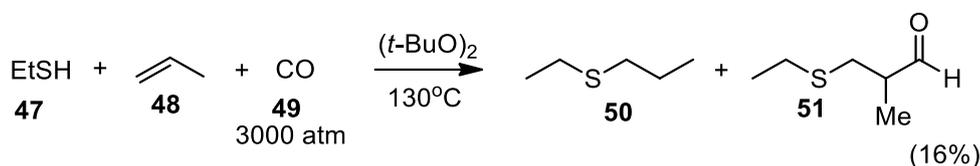
Scheme 10.

⁴⁴ a) Clerici, A.; Canella, R.; Pastori, N.; Panzeri, W.; Porta, O. *Tetrahedron* **2006**, *62*, 986; b) Clerici, A.; Ghilardi, A.; Pastori, N.; Punta, C.; Porta, O. *Org. Lett.* **2008**, *10*, 5063.

5.3. Carbonylation radical reaction

Carbon monoxide (CO) is abundant and a reasonably good radical acceptor (providing reactions are carried out under high pressure), which can easily be added to organic and inorganic substrates, in a process called carbonylation.

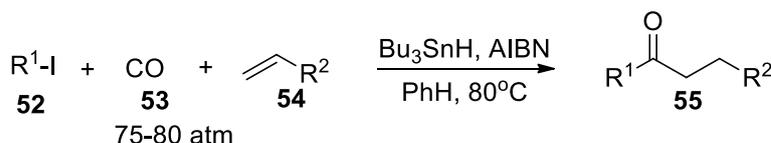
Lipscomb *et al.*⁴⁵ developed the first multicomponent radical reaction using high pressure of CO in 1956. Addition of the thiyl radical to propene led to the resulting C-centered-radical, upon which addition of CO generated an acyl radical. Abstraction by the latter of a hydrogen atom from the thiol finally afforded the desired aldehyde. However, yields were rather low as a result of the formation of sulfide side product (Scheme 11). Later, Tsuji managed to improve the yield using $\text{Co}_2(\text{CO})_8$ as a catalyst.⁴⁶



Scheme 11

Later on, Ryu and Sonoda developed an efficient synthesis of unsymmetrical ketones by using CO in presence of AIBN as an initiator (Scheme 12).⁴⁷

The alkyl radical generated from corresponding iodide, added to CO to form acyl radical which further reacted with olefin by generating another radical, finally, upon reduction with tin hydride to form the final product.

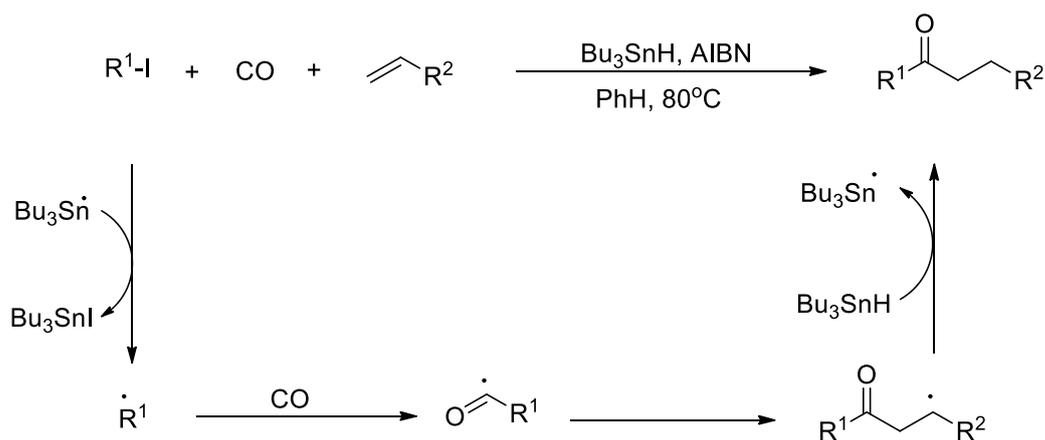


Scheme 12

⁴⁵ Foster, R. E.; Larchar, A. W.; Lipscomb, R. D.; McKusick, B. C. *J. Am. Chem. Soc.* **1956**, *78*, 5606.

⁴⁶ Susuki, T.; Tsuji, J. *J. Org. Chem.* **1970**, *35*, 2982.

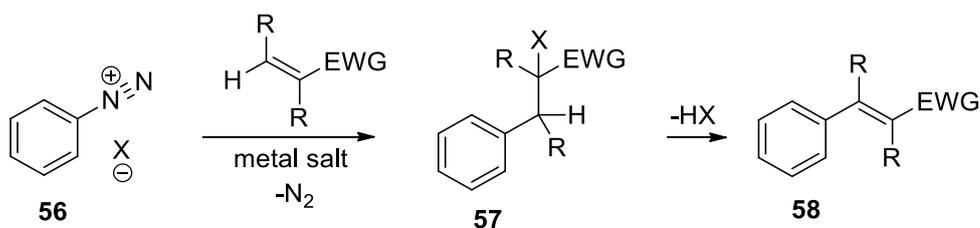
⁴⁷ a) Ryu, I.; Uehara, S.; Hirao, H.; Fukuyama, T. *Org. Lett.* **2008**, *10*, 1005; b) Kawamoto, T.; Uehara, S.; Hirao, H.; Fukuyama, T.; Matsubara, H.; Ryu, I. *J. Org. Chem.* **2014**, *79*, 3999.



Scheme 12. Carbonylation reaction by Ryu.

5.4. Multicomponent reactions based on aryl radicals

Aryl radicals can be easily generated from aryl diazonium salts. Aryl triazenes, aryl hydrazines, aryl bromides and iodides may also be used as alternative sources of aryl radicals. The Meerwein reaction (arylation) involves the addition of an aryl diazonium salt (ArN_2X) onto electron-poor or electron-rich alkenes in the presence of metal salts,⁴⁸ resulting in a neat addition of an arene onto an olefin backbone (Scheme 13).⁴⁹



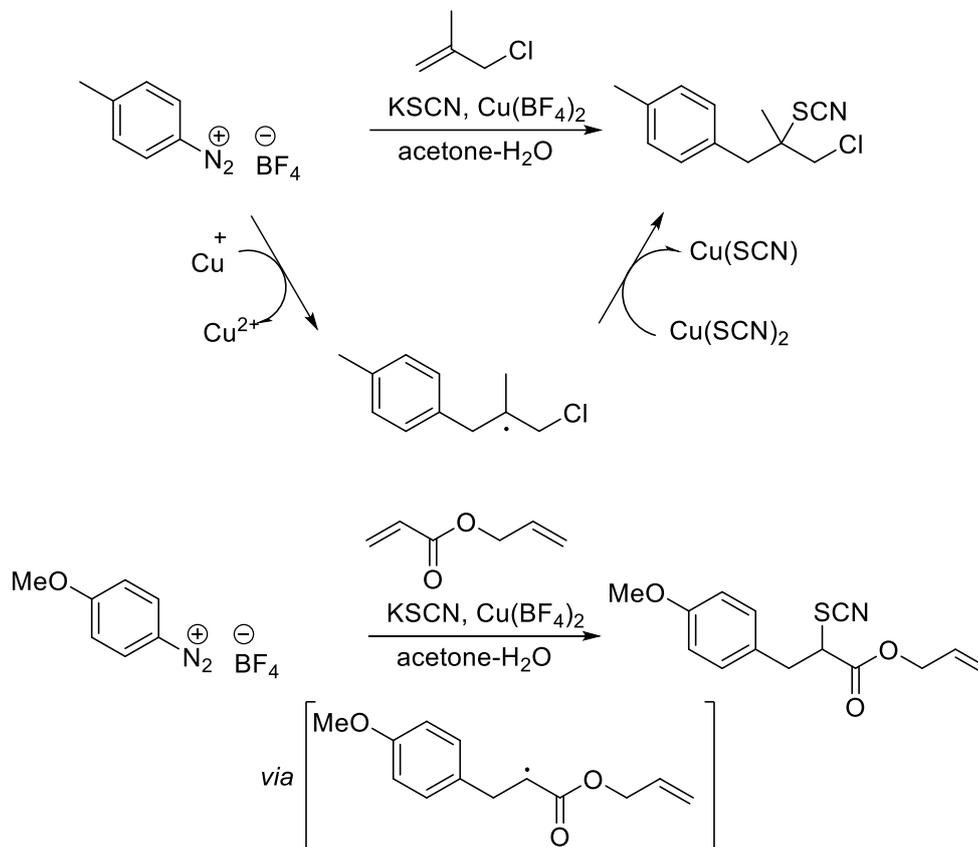
Scheme 13

Meerwein arylation constitute an important synthetic transformations of aryl radicals. 3-Component radical reactions between aryl radicals, olefins and a trapping reagent Y have also been described recently, as illustrated below with the radical aryl-thiocyanatation of olefins

⁴⁸ Hans, M.; Buchner, E. B.; Konrad, E. *J. Prakt. Chem.* **1939**, 152, 237.

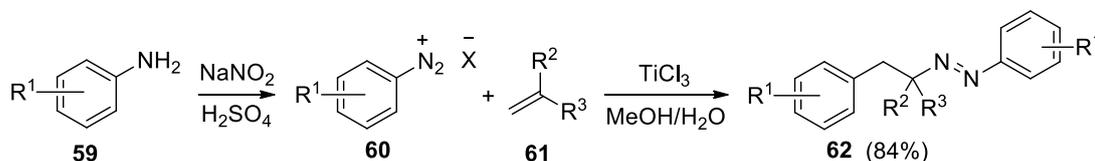
⁴⁹ Heinrich, M. R. *Chem. Eur. J.* **2009**, 15, 820.

(Scheme 14).^{50,51} It is worth noticing that the process is efficient with both electron-rich and poor olefins and that water used as a solvent does not interfere with the incorporation of the thiocyanate ion in the final step.



Scheme 14. Aryl-thiocyanatation of olefins

The development of a carbo-diazenylation reaction of olefins from aryl diazonium salts was established recently by Heinrich *et al*⁵² who used TiCl_3 to generate the aryl radical intermediate (Scheme 15).

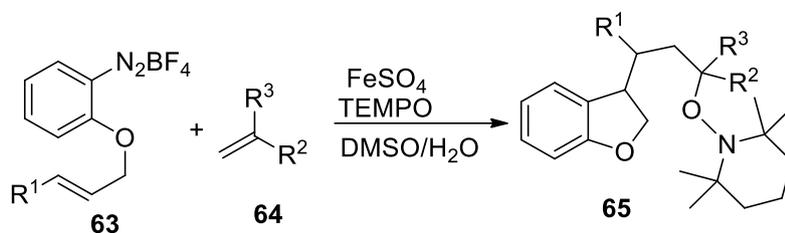


Scheme 15. Carbo-diazenylation reaction by Heinrich

⁵⁰ a) Zard, S. Z. *Angew. Chem.* **1997**, *109*, 724; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 672; b) B. Quiclet-Sire, Zard, S. Z. *Curr. Chem.* **2006**, *264*, 201; c) Quiclet-Sire, B.; Zard, S. Z. *Chem. Eur. J.* **2006**, *12*, 6002.

⁵¹ a) Grishchuk, B. D.; Gorbovoi, P. M.; Kudrik, E. Y.; Ganschak, N. I.; Kaspruk, B. I.; *Russ. J. Gen. Chem.* **1997**, *67*, 362.

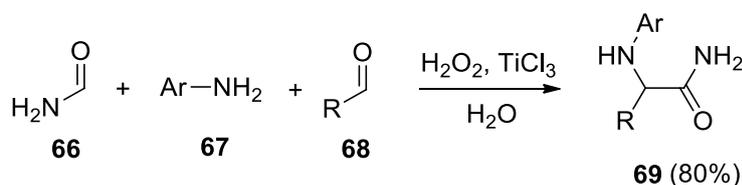
During a collaborative work, Landais and Heinrich groups successfully developed an intramolecular radical cyclization of diazonium-substituted allyl phenyl ethers, which was followed by a radical trapping via carbonitrosation, carbohydroxylation, allylation reactions and vinylation (Scheme 16).⁵²



Scheme 16.

5.5. Radical Strecker Reaction

The Strecker synthesis is commonly known as the Strecker amino acid synthesis, which relies on the addition of a cyanide ion onto an imine. A radical variant of this reaction was developed by Porta *et al* using a carbamoyl radical as a cyanide equivalent, which adds onto an imine, prepared *in situ* from an aldehyde and an aniline.⁴⁴ The reaction starts by the reduction of hydrogen peroxide with Ti(III) to form a hydroxyl radical. The latter then abstracts the CHO hydrogen atom from the formamide to produce the nucleophilic formamidyl radical, which adds onto the iminium intermediate. Finally, Ti(III) reduces the nitrogen-radical cation to give the α -amino amide (Scheme 17).

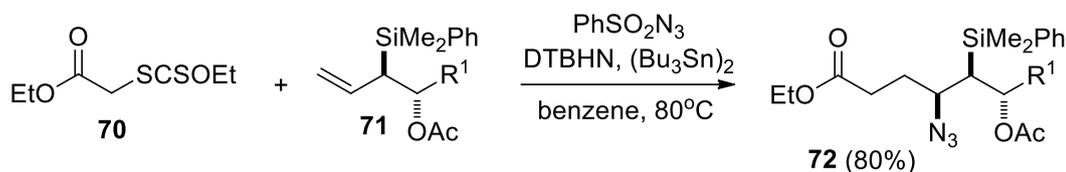


Scheme 17.

⁵² Heinrich, M. R.; Jasch, H.; Landais, Y. *Chem. Eur. J.* **2013**, *19*, 8411.

5.6. Carboazidation of olefins

Recently, a stereocontrolled carboazidation of acyclic chiral allylsilanes was examined by Renaud and Landais teams.⁵³ They reported the formation of β -azidosilanes with high level of diastereocontrol, after addition of the xanthate derivatives onto the electron rich chiral allylsilanes, followed by the trapping of the final nucleophilic radical by PhSO_2N_3 (Scheme 18).



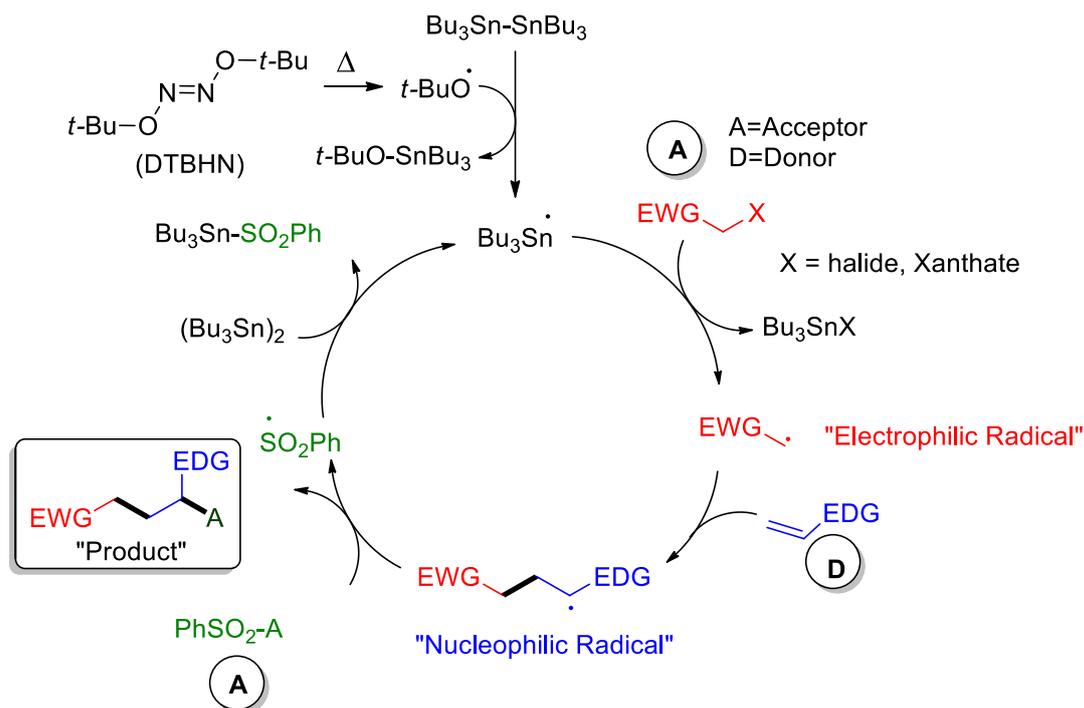
Scheme 18.

5.7. Carboalkenylation and alkynylation of olefins

A free radical three component carbo alkenylation and alkynylation of olefins have been developed by our group where two functional groups could be added across the π -system of unactivated olefins.⁵⁴ The reaction is initiated by generation of an electrophilic radical from the corresponding xanthates or alkyl halides by abstracting of halide or xanthate by tin radical, which then adds onto the less hindered end of an electron-rich olefin. The resultant nucleophilic radical can then be trapped by the electrophilic sulfone derivatives. Finally, the sulfonyl radical, generated by β -fragmentation, then propagates the chain by reacting with hexabutylditin (Scheme 19).

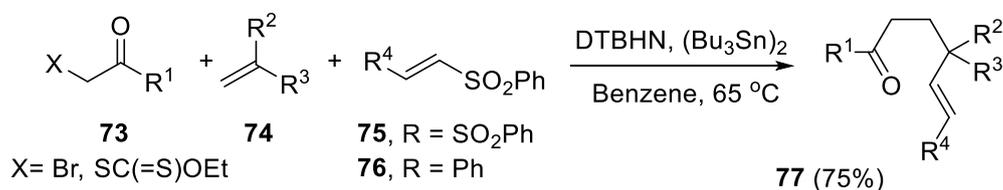
⁵³ Chabaud, L.; Landais, Y.; Renaud, P.; Robert, F.; Castet, F.; Lucarini, M.; Schenk, K. *Chem. Eur. J.* **2008**, *14*, 2744.

⁵⁴ Liautard, V.; Robert, F.; Landais, Y. *Org. Lett.* **2011**, *13*, 2658.



Scheme 19. Carboalkenylation and alkylation of olefins.

The use of ethylene bisphenylsulfone **3** as a sulfone acceptor produced the alkenylated products **77** in excellent yield (Scheme 20).



Scheme 20

6. Photoredox catalysis

Since last century sunlight has been used in the organic reactions but the scope was mostly limited to those molecules which could absorb UV light. Over the past decade, radical chemistry has experienced a renaissance of photochemistry.⁵⁵ The use of photocatalysts and visible light has contributed to the emergence of new reactivities that could not be attained using other catalytic techniques. Photoredox catalysis is thus one of the rapidly expanding area in radical

⁵⁵ Balzani, V.; Ceroni, P.; Juris, A. *Photochemistry and Photophysics, Concept, Research, Applications*, Wiley-VCH, Weinheim, **2014**.

chemistry nowadays. Organic photoredox catalysis also provides a metal-free alternative to metal catalyzed reactions, useful in the discovery and optimization of new synthetic methodologies. It is quite economical, mild, and environmental friendly method for promote radical based transformations in organic reactions.

6.1. Common Mechanistic pathways in photoredox catalysis.

Generally, a photo-active catalyst absorbs light from the visible region and participates with organic substrates by single electron transfer (SET) processes. Alternative energy transfer processes are also developed where homolytic cleavage of weak bonds occurs without transfer of electron. Photoredox catalytic reactions follow two mechanistic routes as described in Figure 12. One is known as “oxidative quenching” when the catalyst, in its excited state (Cat^*), is quenched by donating an electron to an oxidant [ox] present in the reaction mixture. The other is called a “reductive quenching”, when cat^* is quenched by accepting an electron from a reductant [red]. To allow the catalyst turnover, the oxidative cycle requires a reducing agent, involved in the reduction of $[\text{cat}]^{\bullet+}$ whereas, in the reductive cycle, an oxidant is needed to oxidize $[\text{cat}]^{\bullet-}$ these operations restoring the catalyst in its ground state.⁵⁵ Electron transfer thus carried out will serve as to generate new radical species ready for further transformation (cyclization, rearrangement).

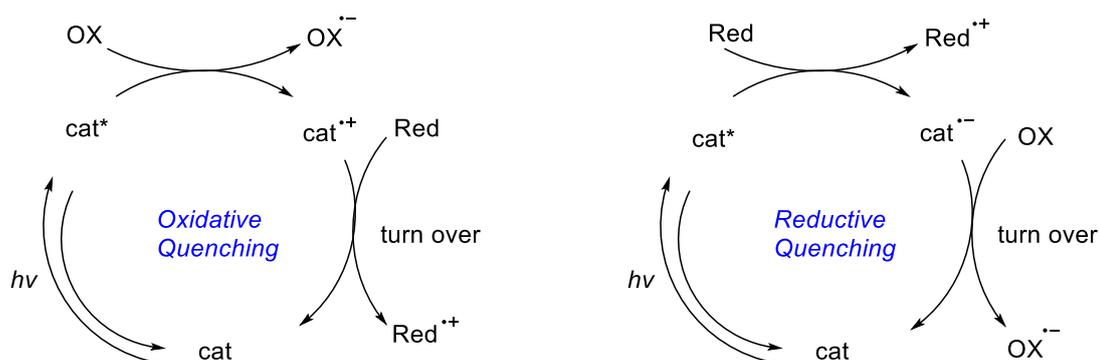


Figure 12. Oxidative and reductive quenching cycle of a photoredox catalyst.

The absorption of a photon promotes an organic molecule from the ground state S_0 to the electronically excited state S_1 as shown in the simple energy diagram known as the Jablonski diagram (Figure 13). Deactivation may then occur rapidly (within picoseconds) through various pathways, including radiative pathways with emission of light, or non-radiative pathways where energy is lost as heat. The Jablonski diagram describes the different events arising when a

molecule meets a photon. It is therefore most useful to construct such a diagram with measurable quantities, such as absorption, emission and excitation spectra, quantum yields etc... The molecule in its excited state S_1 may also, through an inter-crossing system, attain the triplet state T_1 which is usually longer-living. The molecule in this triplet state may then relax to return to the ground state through radiative and non-radiative pathways. Lifetime of these excited states varies with the nature of the photoactive species. Therefore, photocatalysts reacting through oxidative or reductive quenching cycles may do so in their singlet or triplet state.

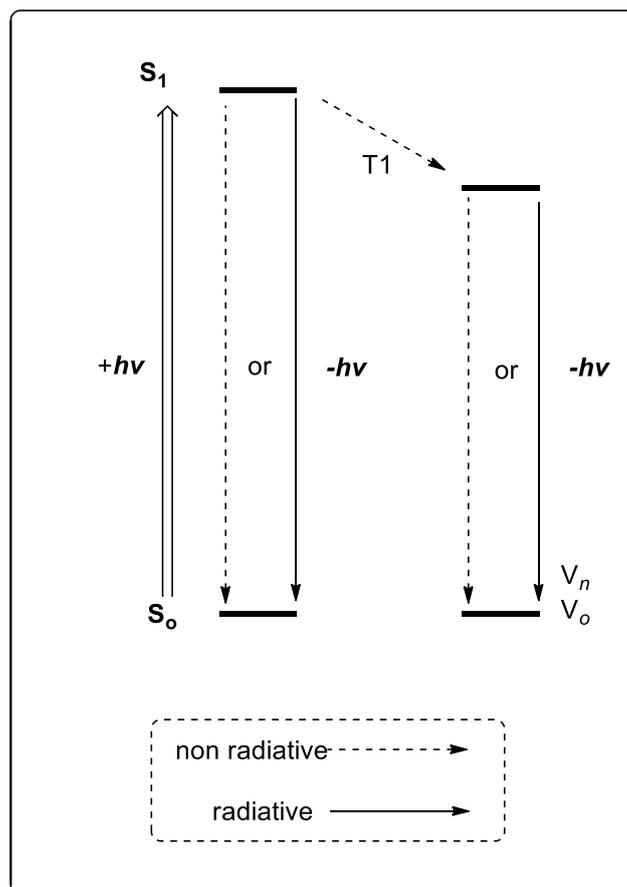


Figure 13. Jablonski diagram

The most well studied examples of photoredox catalysts are complexes of ruthenium tris(2,2'-bipyridine)ruthenium(II) and iridium tris[2-phenylpyridinato-C-2,N] iridium(III) (Figure 14).

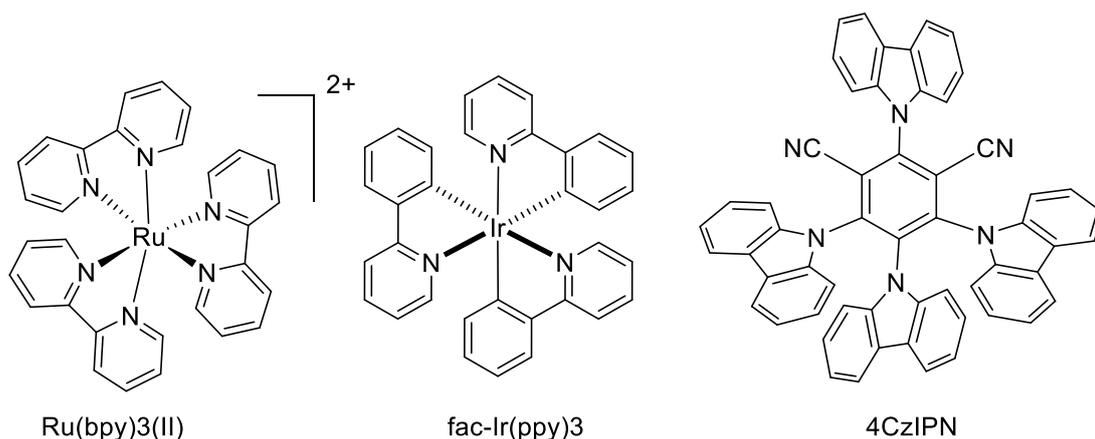


Figure 14. Organometallic photocatalysts

The expected rapid depletion of rare transition metals including iridium or ruthenium has prompted organic chemists to look for more readily accessible and sustainable alternatives. Organic photocatalysts have thus been developed, certain like eosin-Y being known for decades (Figure 15).

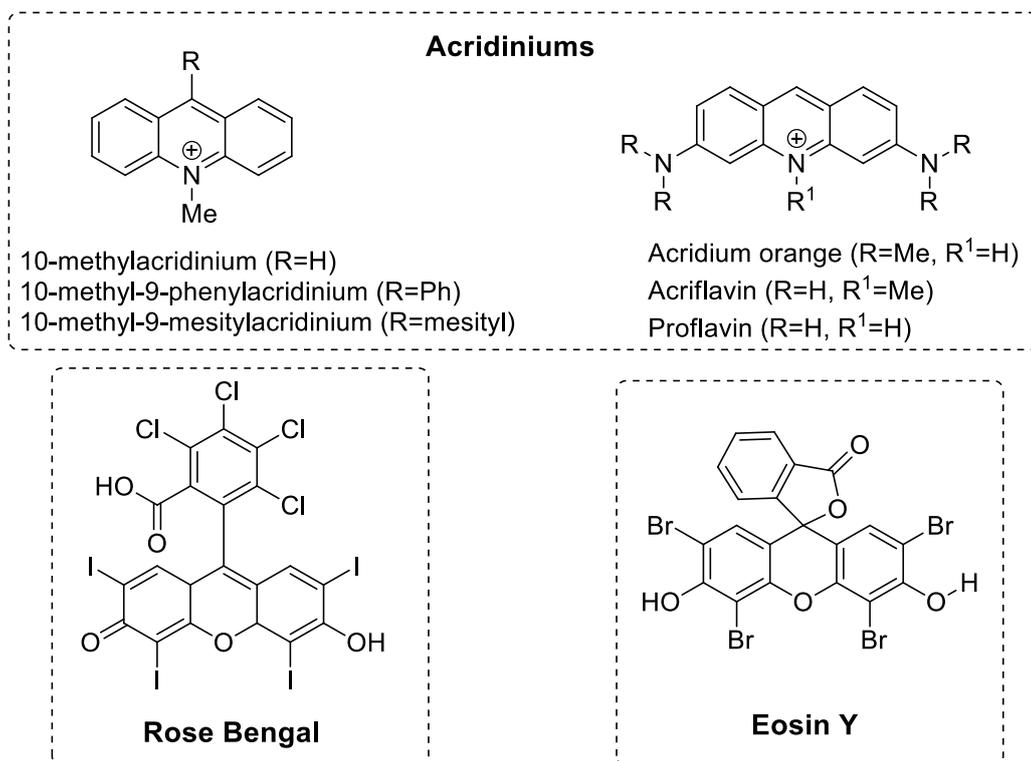
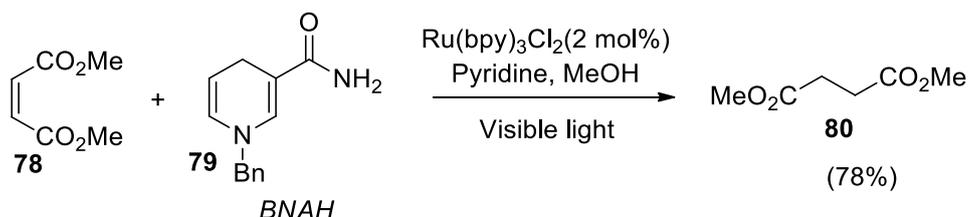


Figure 15. Organic photocatalysts

Photoredox catalysis is now used extensively in organic chemistry as illustrated with the examples below.

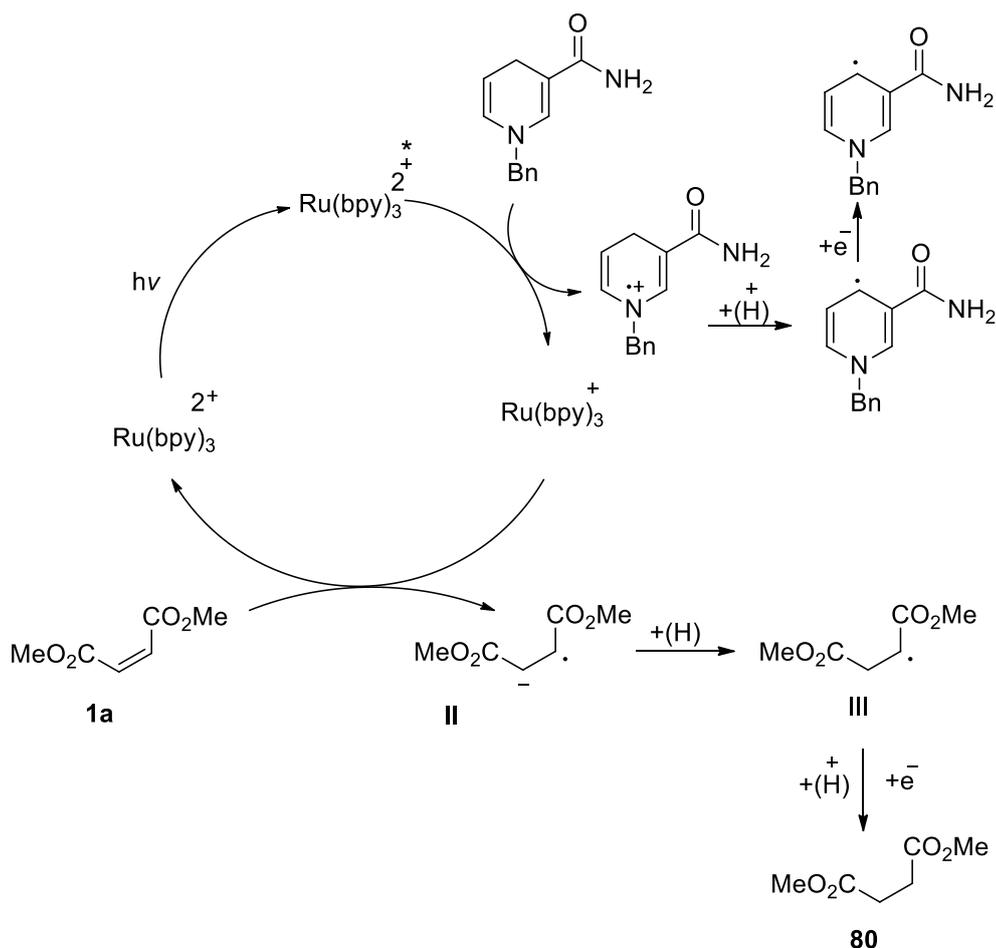
Chyongjin Pac *et al.*⁵⁶ thus described the reduction of electron-poor alkenes using BNAH as a stoichiometric reducing agent and Ru(bpy)₃Cl₂ as the catalyst to obtain desired products in excellent yields (Scheme 20).



Scheme 20.

They observed that the luminescence of Ru(bpy)₃²⁺ was quenched by BNAH but not by the olefins. This reveals that the initiation process depends on an electron transfer from BNAH to the excited ruthenium complex. Then, single-electron reduction Ru(bpy)₃²⁺ by the olefin led to the maleate radical-anion and returned Ru catalyst in its ground state. The anion radical rapidly protonated in protic media to afford a neutral radical, which second one electron reduction by BNAH led to an enolate protonated *in situ* to afford the final product **80** (Scheme 21).

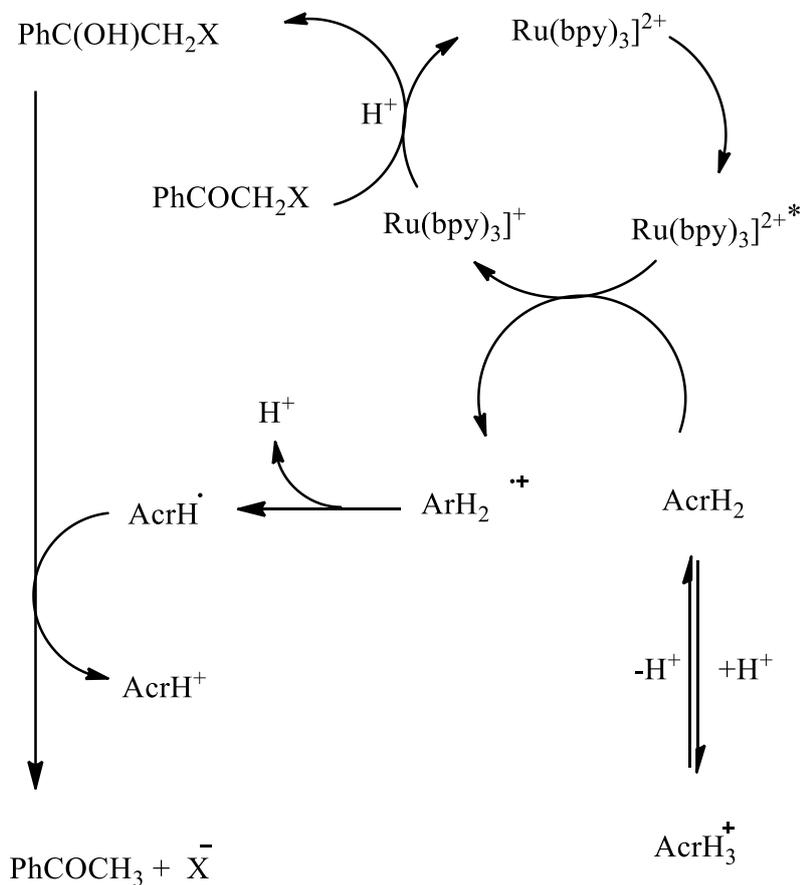
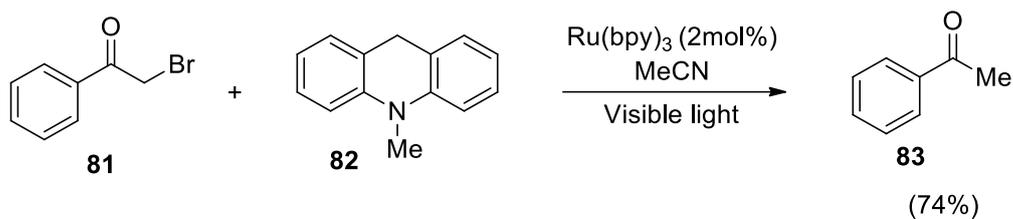
⁵⁶ Pac, C.; Ihama, M.; Yasuda, M.; Miyauchi, Y.; Sakurai, H. *J. Am. Chem. Soc.* **1981**, *103*, 6495.



Scheme 21.

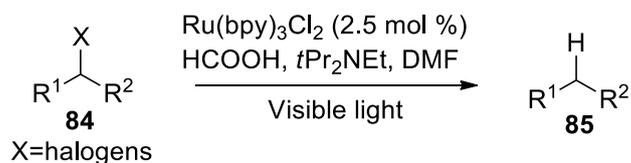
Few years later, Fukuzumi⁵⁷ and co-workers used $\text{Ru}(\text{bpy})_3\text{Cl}_2$ as a photocatalyst (as an electron donor and acceptor) to develop reductive dehalogenation of α -bromocarbonyl compounds in the presence of an acid (Scheme 22). $\text{Ru}(\text{bpy})_3$ is used as the photocatalyst for the reduction of the phenacyl halide. The reductive quenching of $[\text{Ru}(\text{bpy})]^{2+*}$ with AcrH is followed by the acid catalyzed transfer of electron from $\text{Ru}(\text{bpy})^+$ to PhCOCH_2X to produce $\text{PhC}(\text{OH})\text{CHX}$ along with the regeneration of $\text{Ru}(\text{bpy})_3^{2+}$. The AcrH_2^+ is deprotonated to produce AcrH^+ , which by reducing $\text{PhC}(\text{OH})\text{CHX}$ afford AcrH^+ and PhCOCH_3 (Scheme 22).

⁵⁷ Fukuzumi, S.; Mochizuki, S.; Tanaka, T. *J. Phys. Chem.* **1990**, *94*, 722.



Scheme 22.

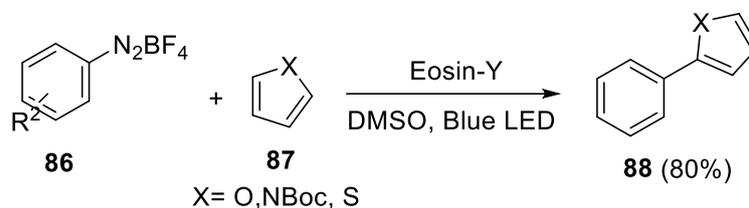
Recently, Stephenson *et al*⁵⁸ developed a reductive cleavage of aliphatic halides based on the photoredox catalysis. He thus found an alternative to toxic tin that is usually used for reductive dehalogenation (Scheme 23).



Scheme 23.

⁵⁸ Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2009**, *131*, 8756.

Kong *et al.*⁵⁹ used Eosin-Y as a photoredox catalyst for the direct C-H arylation of heteroaromatic compounds. The arylation of **87** with diazonium salt **86**, under blue LED irradiation and by using eosin-Y as a photoredox catalyst in DMSO as a solvent furnished the final product **88** in good yields (Scheme 23).



Scheme 23.

7. Conclusion

In this chapter, we introduced briefly radical chemistry, the various components which are able to enter into a radical process and finally elaborated free-radical multicomponent processes in which three and sometimes four or five components may combine together in a complex radical chain process. These reactions provide excellent pathways to access complex structures, with the incorporation of various functional groups and the formation of several new bonds (C-C, C-N, C-Cl etc.) in a single pot-operation. Photocatalysis has also been introduced at it now constitutes one of the most efficient method to initiate radical processes through electron or energy transfer.

⁵⁹ Hari, D. P.; Schroll, P.; König, B. *J. Am. Chem. Soc.* **2012**, *134*, 2958.

CHAPTER II
Visible-Light Mediated Carbamoyl Radical Addition to
Heteroarenes

1. Introduction

In this chapter, we intended to present the photocatalyzed carbamoylation of heterocycles and the formation of the amide linkage in the presence of hypervalent iodine (III). The formation of the amide bond still constitutes an important synthetic challenge, as this functional group is present in many commonly used products, for instance in artificial silks, nylon, hydrogels and many other biocompatible derivatives.⁶⁰ The amide linkage is also widely present in pharmacologically active substances,⁶¹ and 25% of marketed drugs. Many methodologies including novel coupling reagents have been reported to meet the challenging amide bond formation under mild conditions.⁶² Similarly, various natural products, pharmaceuticals, and bioactive molecules contain common N-heterocyclic structural motifs.⁶³ In organic chemistry, this class of compounds is very important in drug discovery, hence the development of novel and efficient methods for their modification still remains a very important research area in organic synthesis. In this regard, the Minisci reaction has recently attracted a great deal of interest for the C-H functionalization of heteroarenes and many modern version of Minisci reaction have been introduced by using photoredox chemistry. Recently, our group developed the decarboxylation of oxamic acids under metal-free conditions in an organic solvent, using an organo-photocatalyst under visible light irradiation, forming the corresponding isocyanates in good yields.⁶⁴ The present work is an extension of this study and will be described in more details later in this chapter.

1.1. Introduction to carbamoyl radicals.

In the last 30 years, carbamoyl radicals have been studied extensively. *N*-alkylcarbamoyl radicals exist in both *cis* and *trans*-configurations **1-2** (Figure 1),⁶⁵ with the dominating *trans*-form. The strong barrier of rotation around the N-C bond in amides (~20 kcal/mol) and formamides (~28 kcal/mol) is also found in the corresponding intermediate carbamoyl radicals. Therefore, abstraction of the formyl hydrogen in a *trans*-formamide **1** (major isomer) was shown

⁶⁰ Greenberg, A.; Breneman, C.; Liebman, J. *Wiley-Interscience, New York*. **2000**.

⁶¹ Ghose, A. K.; Viswanadhan, V. N.; Wendoloski, J. J. *J. Comb. Chem.* **1999**, *1*, 55.

⁶² a) de Figueiredo, R. M. S.; Suppo, J.; Campagne, J.-M. *Chem. Rev.* **2016**, *116*, 12029; b) Noda, H.; Furutachi, M.; Asada, Y.; Shibasaki, M.; Kumagai, N. *Nat. Chem.* **2017**, *9*, 571.

⁶³ Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. *Heterocycles*. **2011**, *18*.

⁶⁴ Pawar, G. G.; Robert, F.; Grau, E.; Cramail, H.; Landais, Y. *Chem. Commun.* **2018**, *54*, 9337.

⁶⁵ Sutcliffe, R.; Ingold, K. U. *J. Am. Chem. Soc.* **1981**, *103*, 7686.

to generate the corresponding *trans*- σ -carbamoyl radical **3** as the major isomer. With bulky alkyl groups, the percentage of *cis*-isomer increases. *N*-Arylcarbamoyl radicals (ArNHC(=O) \cdot), in which the aromatic ring is nearly coplanar along the amide plane, are known as transient species and subsequently produce the more persistent aminyl (ArNH \cdot) radical species by decarbonylation. Coplanarity is no longer found in *N*-aryl-*N*-alkyl-carbamoyl radicals, and cannot be detected directly by ESR.⁶⁶

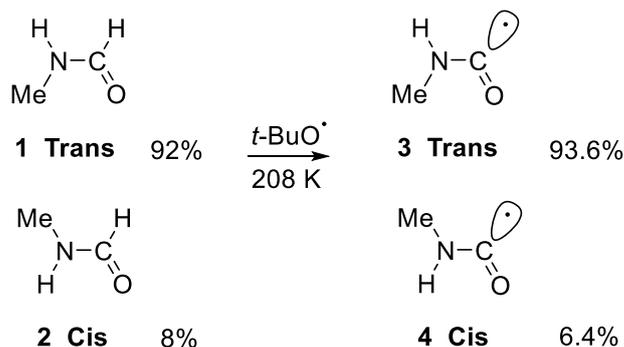


Figure 1.

The geometry of the carbamoyl radical has been calculated as for instance **5**, in which the N-C-O angle was estimated to be 142 $^\circ$ (Figure 2), which is intermediate between a linear geometry (*i.e.* with the unpaired electron in a pure p-orbital) and a trigonal geometry (*i.e.* with the unpaired electron in a formal sp² hybridized orbital).

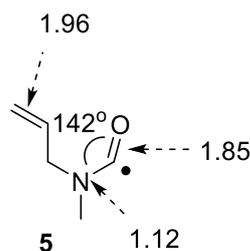


Figure 2. Geometry of the carbamoyl radical

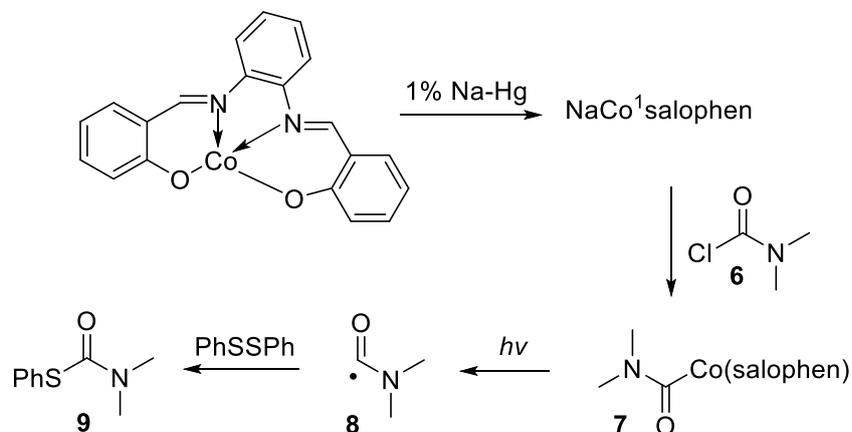
In the same study, Pattenden *et al*⁶⁷ reported that carbamoylcobalt(III) complexes are viable source of carbamoyl radicals, as shown for instance for carbamoyl radical **8**. Treatment of *N,N*-dimethylcarbamoyl chloride **6** with sodium cobalt(I) salophen,⁶⁸ afforded the

⁶⁶ Grossi, L. *Chem. Commun.* **1989**, 1248.

⁶⁷ Gill, G. B.; Pattenden, G.; Reynolds, S. J. *J. Chem. Soc.* **1994**, 369.

⁶⁸ Bigotto, A.; Costa, G.; Mestroni, G.; Pellizzer, G.; Puxeddu, G. A.; Reisenhofer, E.; Stefani, L.; Tazher, E. *Inorg. Chem. Acta Rev.* **1970**, 41.

carbamoylcobalt(III) compound **7**. Then the deoxygenated solution of **7** in dichloromethane containing diphenyl disulfide was irradiated, to afford, after reflux for 48 h, **9** in 46% yield, through the intermediate *N,N*-dimethylcarbamoyl radical **8** (Scheme 1).



Scheme 1.

As, we have already described types of acyl radicals in chapter one (Figure 3), in this chapter we will explain the chemistry of carbamoyl radical in more details. Appropriate methods to generate carbamoyl radicals remain scarce so far, although, the addition of this class of radicals to unsaturated systems, including double bonds,⁶⁹ arenes, or oxime ethers have been the subject of intense research. Some examples are provided below.

1.2. Methods of access to carbamoyl radical.

Carbamoyl radicals are accessible using essentially three main routes. These include: (1) the C-X bond cleavage in $R_2N(C=O)X$ precursors ($X=H$,⁷⁰ xanthate,⁷¹ SPh,⁷² Co(salen),); (2) the photoredox reductive decarboxylation of *N*-hydroxyphthalimido oxamides; and (3) the oxidative decarboxylation of oxamic acids.

⁶⁹ Herzon, S. B.; Myers, A.G. *J. Am. Chem. Soc.* **2005**, 127, 5342.

⁷⁰ a) Minisci, F.; Recupero, F.; Punta, C.; Gambarotti, C.; Antonietti, F.; Fontana, F.; Gian, F. *Chem. Commun.* **2002**, 2496; b) Biyouki, M. A. A.; Smith, R. A. J.; Bedford, J. J.; Leader, J. P. *Synth. Commun.* **1998**, 28, 3817; c) Minisci, F.; Gardini, G. P.; Galli, R.; Bertini, F. *Tetrahedron Lett.* **1970**, 1, 15.

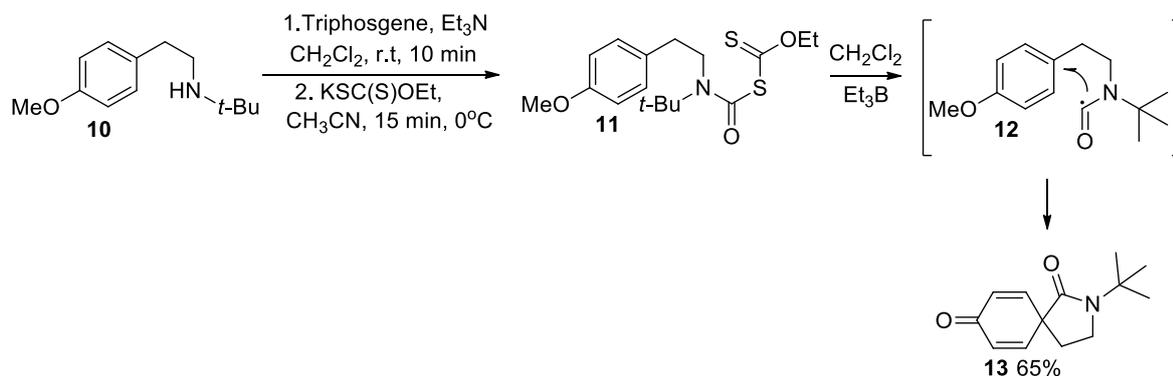
⁷¹ a) Millan-Ortiz A.; Lopez-Valdez G.; Cortez-Guzman F.; Miranda L. D. *Chem. Comm.* **2015**, 51, 8345; b) Betou, M.; Male, L.; Steed, J. W.; Grainger, R. S. *Chem. Eur. J.* **2014**, 20, 6505.

⁷² Sakamoto, M.; Takahashi, M.; Fujita, T.; Nishio, T.; Iida, I.; Watanabe, S. *J. Org. Chem.* **1995**, 60, 4683.

1.2.1. C-X bond cleavage in R₂N(C=O)X

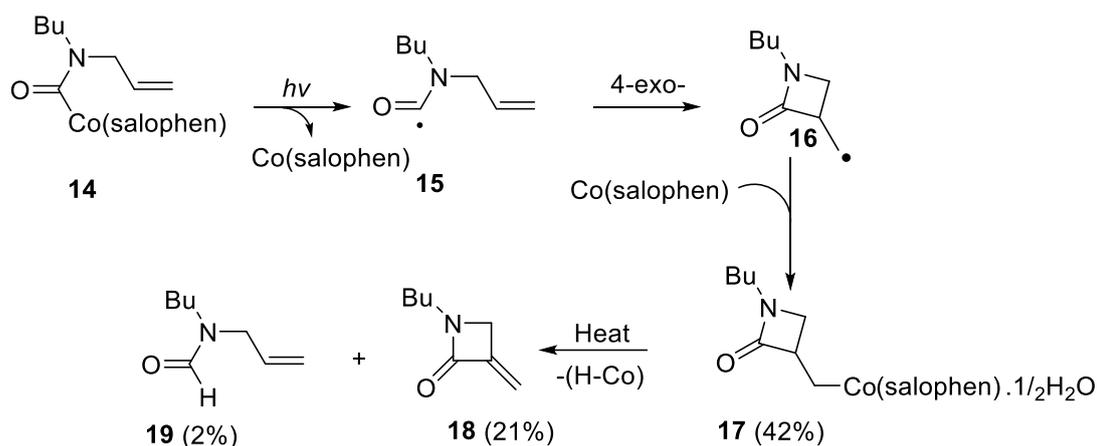
Several reports have been published to access carbamoyl radicals by this method and some of them are presented here, such as **13** in (Scheme 2).

Alejandra and co-workers⁷¹ were the first to describe a synthesis of spirodienonamides **13**, based on a de-aromatizing spiroacylation reaction proceeding through a carbamoyl radical intermediate. This approach was carried out treating carbamoylxanthate **11** with Et₃B as an initiator to generate the desired carbamoyl radical **12**, which cyclized onto the arene moiety to form the spirodienonamides **13** containing an acyl-functionalized all-carbon quaternary center. The stability of the carbamoyl xanthate **12** merely depends on the presence of an *N-t*-butyl group attached to the amine moiety. The carbamoyl xanthates **12** were obtained from the phenethylamines **10**, converted into the corresponding substituted xanthates in two steps and good yields (Scheme 2).



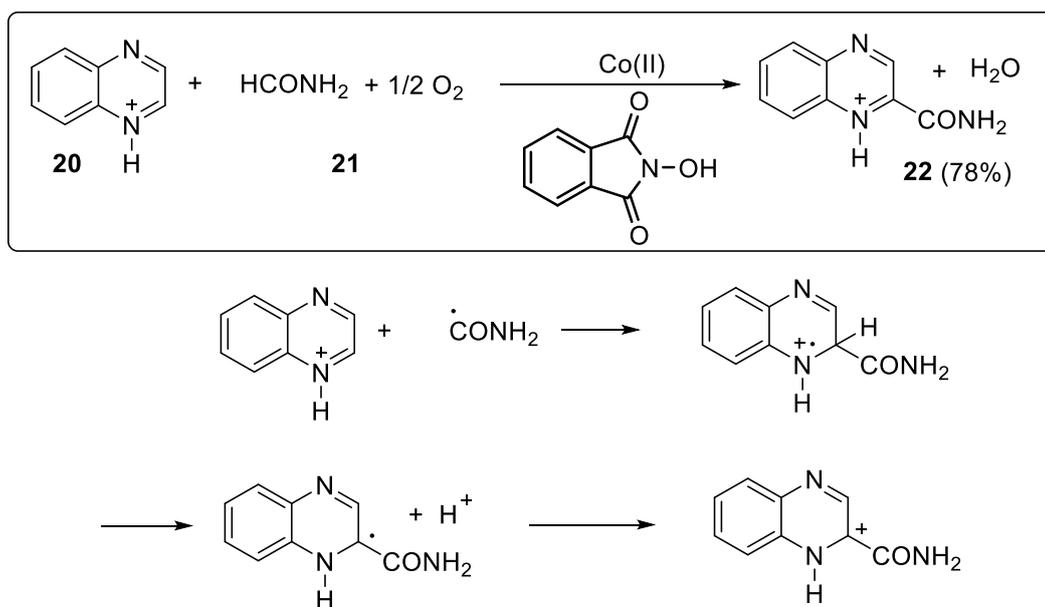
Scheme 2. Spirocyclization process through a carbamoyl radical.

Pattenden *et al.*⁶⁷ reported the intramolecular addition of carbamoyl radicals onto alkene for the synthesis of β -lactams. Irradiation of a deoxygenated solution of **14** in dichloromethane was expected to produce the formation of 3-methyleneazetidin-2-one **18**, but instead, 3-(azetidin-2-one)methylcobalt(III) salophen **17**, was obtained as a stable bright green solid in 42% yield. Cyclization of carbamoyl radical **15** generated the β -lactamidomethyl radical **16**, which was trapped by the cobalt(II)salophen species to afford **17**. By boiling **17** in toluene, **18** was obtained with 21% yield, while **19** was also formed in 2% yield (Scheme 3).



Scheme 3.

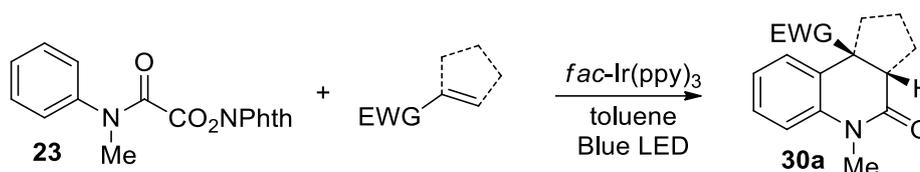
Minisci and co-workers⁷⁰ reported the carbamoylation of protonated quinoxaline by using atmospheric O_2 as an oxidant. They observed that reaction of carbamoyl radical, generated through hydrogen atom abstraction from formamide CHO , was faster with oxygen than with quinoxaline. Carbamoylation of the heteroaromatic base with protonated quinoxaline, took place during the aerobic oxidation of formamide, in the presence of NHPI and Co(II) salt as catalyst (Scheme 4). The absolute rate constant for hydrogen abstraction from NHPI by the peroxy radical was estimated at $7.4 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ at room temperature.



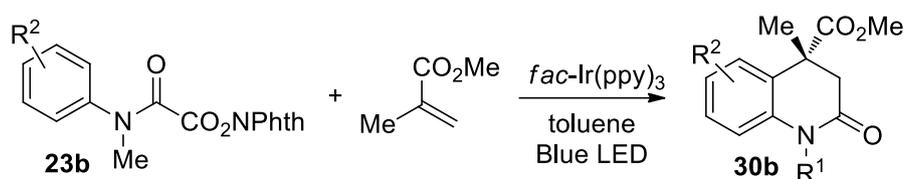
Scheme 4. Addition of carbamoyl radicals to heteroaromatic skeletons.

1.2.2. Photoredox reductive decarboxylation of N-hydroxyphthalimido oxamides

The photoredox reductive decarboxylation of *N*-hydroxyphthalimido oxamides constitutes a more recent and very attractive method to generate carbamoyl radicals.⁷³ Donald *et al.*^{73b} reported the formation of 3,4-dihydroquinolin-2-one **30a** in 70% yield, using oxamide **23** in the presence of Ru(bpy)₃Cl₂·6H₂O in toluene, after 24h of irradiation using blue LEDs (Scheme 7). Under the same reaction conditions, *p*-substituted *N*-methyl oxamides **30b** provided 3,4-dihydroquinolin-2-ones **30b** in 37% yield (Scheme 8).

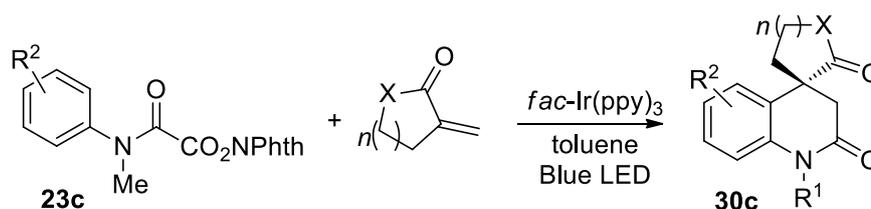


Scheme 7.



Scheme 8.

The same group also synthesized spirocyclic 3,4-dihydroquinolin-2-ones **30c** in 71% yield through the use of radical acceptors bearing exocyclic Alkenes (Scheme 9).

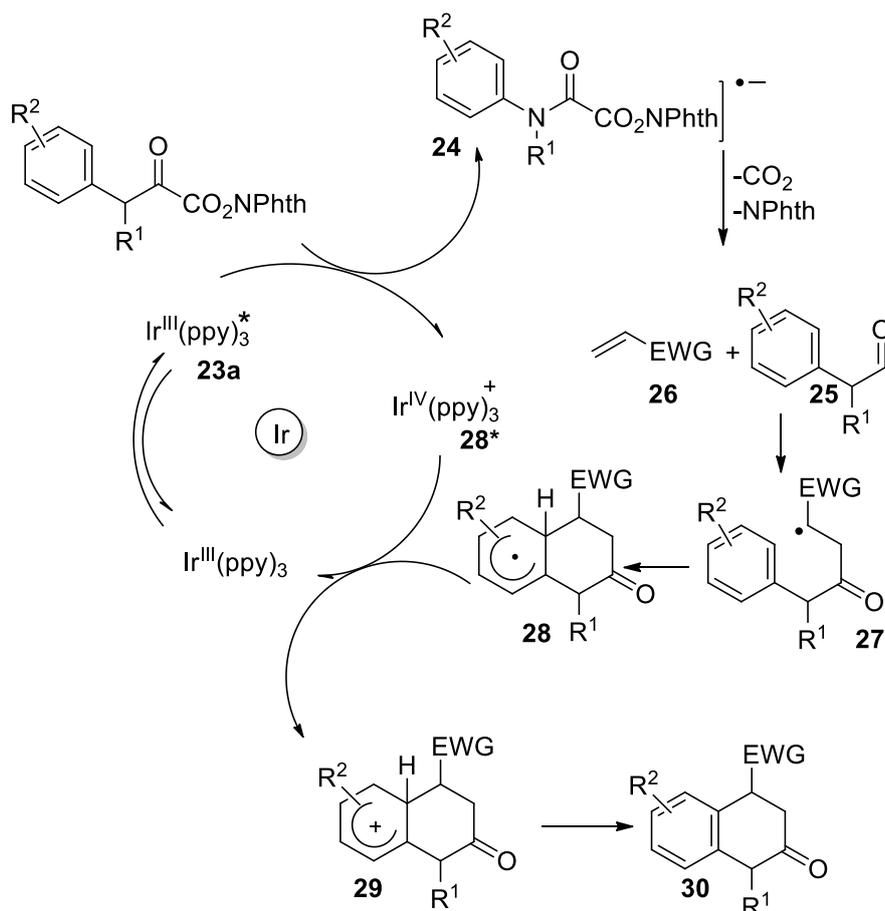


Scheme 9.

The mechanistic study for this reaction process is described in scheme 10. Through visible light irradiation, the Ir^{III} photocatalyst *fac*-Ir(ppy)₃ proceeds to the long-lived photo-excited state Ir^{III*} **23a** ($\tau = 1.9 \mu\text{s}$), which is a strong single electron reductant [$E_{1/2}(\text{Ir}^{\text{IV+}}/\text{Ir}^{\text{III*}}) = -1.73 \text{ V}$]. The latter thus reduces the *N*-hydroxyphthalimido oxamide to the transient radical anion **24**, which then

⁷³ a) Yuan, W.; Chen, L.; Wang, J.; Chen, S.; Wang, K.; Xue, Y.; Yao, G.; Luo, Z.; Zhang, Y. *Org. Lett.* **2015**, *17*, 346; b) Petersen, W. F.; Taylor, R. J. K.; Donald, J. R. *Org. Biomol. Chem.* **2017**, *15*, 583.

undergoes an homolytic cleavage with the loss of CO₂ and phthalimide anion to generate the carbamoyl radical intermediate **25**.⁷⁴ Radical **25** is then trapped by alkene **26**, leading to the cyclohexadienyl radical **27** by cyclizing onto the anilide. Being electron rich, **28** undergoes oxidation by Ir^{IV+} **29** ($E_{1/2}(\text{Ir}^{\text{IV}}/\text{Ir}^{\text{III}}) = +0.77$ V). **30** would thus regenerate Ir^{III} leading to cyclohexadienyl cation **32**, which upon rearomatization and loss of a proton affords the final 3,4-dihydroquinolin-2-one product.

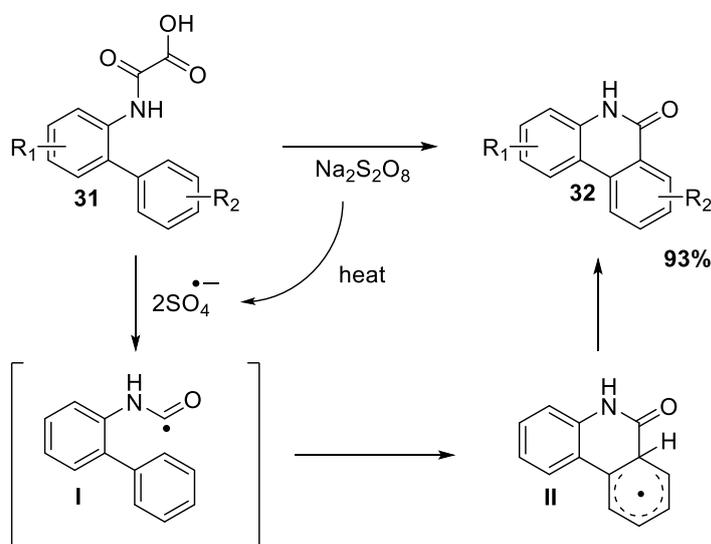


Scheme 10.

⁷⁴ Flamigni, L.; Barbieri, A.; Sabatini, C.; Ventura B.; Barigelletti, F. *Top. Curr. Chem.* **2007**, *281*, 43.

1.2.3. Oxidative decarboxylation of oxamic acids

The third method is an oxidative decarboxylation of oxamic acids.⁷⁵ These acids are readily available by combination of amines and oxalic acid derivatives⁷⁶ and constitute potent precursors of carbamoyl radicals. This strategy turned out to be an efficient and economical approach for the synthesis of phenanthridinones by decarboxylative cyclization of biaryl 2-oxamic acid such as **31** (Scheme 11). The novelty of this transition-metal free method is illustrated below, using Na₂S₂O₈ as the oxidant. In 2015, Ming Yuan, and co-workers⁷³ thus established the sodium persulfate-mediated intramolecular decarboxylative cyclization of oxamic acid **31** under these conditions, which led, after cyclization of the carbamoyl radical onto the aromatic ring, to phenanthridinones **32** in good yields (Scheme 11). The homolytic cleavage of the peroxydisulfate dianion generated the sulfate anion radical, which then abstracts a hydrogen from **31** to generate the carbamoyl radical **I** after decarboxylation. Intramolecular radical cyclization of radical **I** then formed intermediate **II**. Finally, another sulfate anion radical abstracts an H from intermediate **II** to produce **32**.

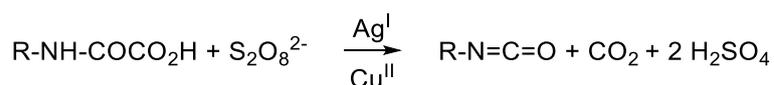


Scheme 11. Addition of carbamoyl radical to arenes.

⁷⁵ a) Guo, L. N.; Wang, H.; Duan, X.-H. *Org. Biomol. Chem.* **2016**, *14*, 7380; b) Petersen, F.; Taylor, R. J. K.; Donald, J. R. *Org. Lett.* **2017**, *19*, 874; c) Bai, Q.-F.; Jin, C.; He, J.-Y.; Feng, G. *Org. Lett.*, **2018**, *20*, 2172.

⁷⁶ a) Seki, Y.; Tanabe, K.; Sasaki, D.; Sohma, Y.; Oisaki, K.; Kanai, M. *Angew. Chem. Int. Ed.* **2004**, *53*, 6501; b) Mecinovic, J.; Loenarz, C.; Chowdhury, R.; Schofield, C. J.; *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6192.

Minisci and co-workers⁷⁷ reported a synthesis of isocyanates, involving carbamoyl radicals as intermediates. Their approach relied on the oxidation of oxamic acids in a two-phase system (water and an organic solvent such as dichloromethane or hexane) by $S_2O_8^{2-}$ catalyzed by silver iodide and copper salts (Scheme 12). The reaction leads to moderate yields in isocyanate, due to the presence of water reacting with the isocyanate, releasing the corresponding amine. The use of large quantities of costly metal salts constitutes another issue.



Scheme 12. Synthesis of isocyanates.

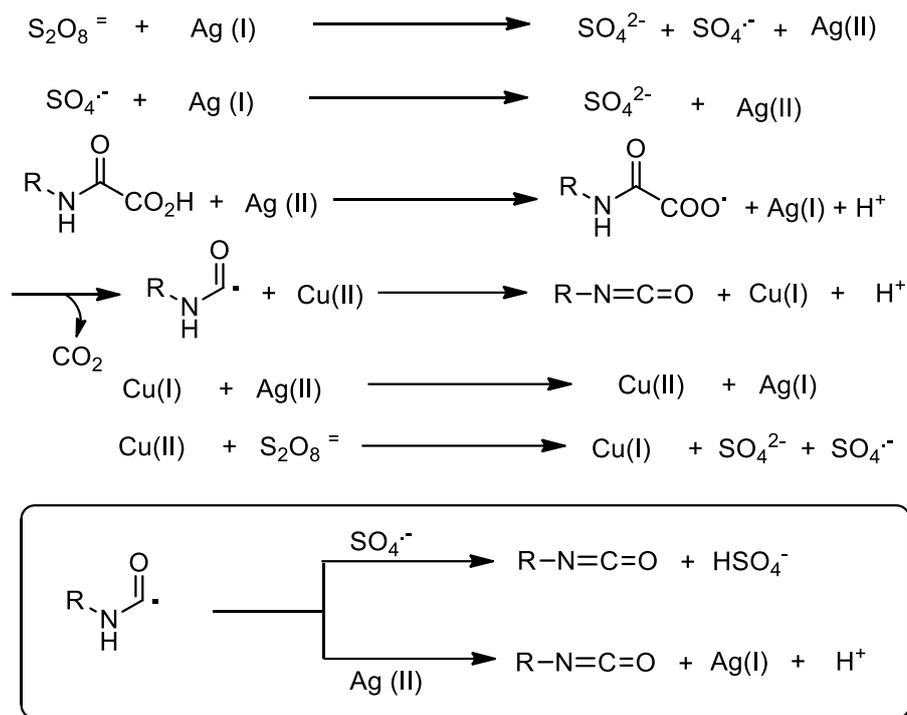
Generation of alkyl⁷⁸ and acyl⁷⁹ radicals *via* silver catalyzed-decarboxylation of carboxylic acids by $S_2O_8^{2-}$ salts is well described. The decomposition of the oxamic acid by $S_2O_8^{2-}$ is described below (Scheme 13), and involves first the decomposition by the silver salt of the persulfate to generate a SO_4 radical-anion and Ag(II). Inner-sphere oxidation of the carboxylate by Ag(II) leads to the corresponding carboxyl radical, which upon decarboxylation provides the carbamoyl radical intermediate. Further oxidation in the presence of the Cu(II) salt afford the final isocyanate. The latter may also be formed through oxidation of the carbamoyl radical by the SO_4 radical-anion or Ag(II). Minisci also showed that in the presence of a protonated heteroaromatic base (such as lepidine), under the same conditions, no isocyanate is observed, whereas the carbamoyl radical is trapped by the heteroaromatic base to form isocyanate (Scheme 13).⁸⁰

⁷⁷ Minisci, F.; Coppa, F.; Fontana, F. *J. Chem. Soc. Chem. Commun.* **1994**, 679.

⁷⁸ Fontana, F.; Minisci, F.; Nogueira Barbosa, M. C.; Vismara, E. *Tetrahedron.* **1990**, *46*, 2525.

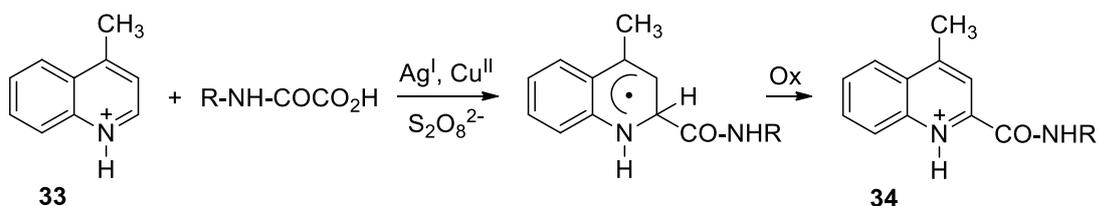
⁷⁹ Fontana, F.; Minisci, F.; Nogueira Barbosa M. C.; Vismara, E. *J. Org. Chem.* **1991**, *56*, 2866.

⁸⁰ Coppa, F.; Fontana, F.; Lazzarini, E.; Minisci, F. *Heterocycles* **1993**, *36*, 2687.



Scheme 13. Plausible Mechanism

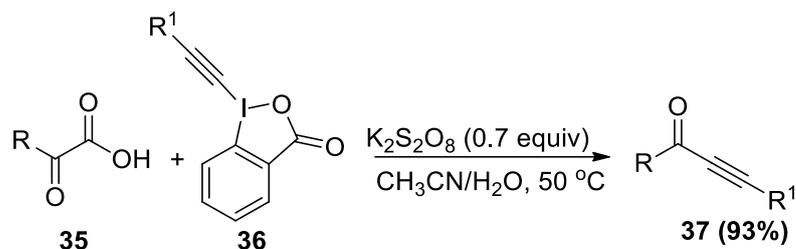
It was found that the slow oxidation to isocyanate was obtained in the presence of protonated Lepidine under the same conditions. There was no formation of isocyanate, only selective substitution of lepidine by carbamoyl radical was observed **34** (Scheme 14).



Scheme 14. Carbamoyl addition to Lepidine **33**.

Using this approach, Li-Na Guo and co-workers⁸¹ reported the synthesis of ynones **37**, via decarboxylative alkynylation of α -keto acids and oxamic acids using hypervalent iodine reagent **36** in the presence of $\text{K}_2\text{S}_2\text{O}_8$. This strategy is versatile and applicable to oxamic acids to produce the corresponding propiolamides (Scheme 15).

⁸¹ a) Guo, L. N.; Wang, H.; Duan, X.-H. *Org. Biomol. Chem.* **2016**, *14*, 7380; b) Petersen, W. F.; Taylor, R. J. K.; Donald, J. R. *Org. Lett.* **2017**, *19*, 874; c) Bai, Q.-F.; Jin, C.; He, J.-Y.; Feng, G. *Org. Lett.* **2018**, *20*, 2172.

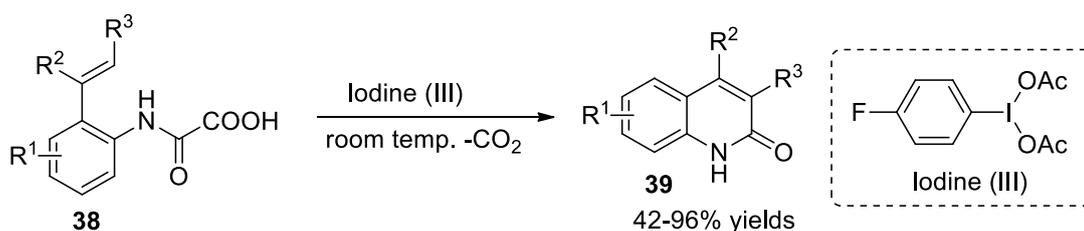


R = Aryl, Alkyl, NR²R³

R¹ = TIPS, TBS, Aryl, Alkyl

Scheme 15. Decarboxylative alkylation of α -keto acids

Recently, Wang and his co-workers⁸² envisioned the oxidative decarboxylative coupling reactions of oxamic acids with olefins, involving the formation of a carbamoyl radical intermediate.⁸³ They established that this readily accessible acid might thus participate in an intramolecular-decarboxylative Heck-type reaction, developing a novel method for the lactamization of 2-vinylanilines to produce 2-quinolinones in the presence of an iodine(III) reagent (Scheme 16). The reaction proceeds through the homolysis of the iodine oxygen bond, formed through the reaction of the oxamic acid and the hypervalent iodine species. The nitrogen of the phenyl oxamic acid was also shown to participate in the decarboxylative process, probably *via* the direct interaction with the hypervalent iodine reagent (III) (HIR).⁸⁴ Hence, they concluded that a macrocyclic iodine (III) trimer II with three directive secondary I···O bonds might be generated *in situ* in this process *via* the self-assembly of the highly distorted cyclic iodine (III) monomer I (scheme 16).



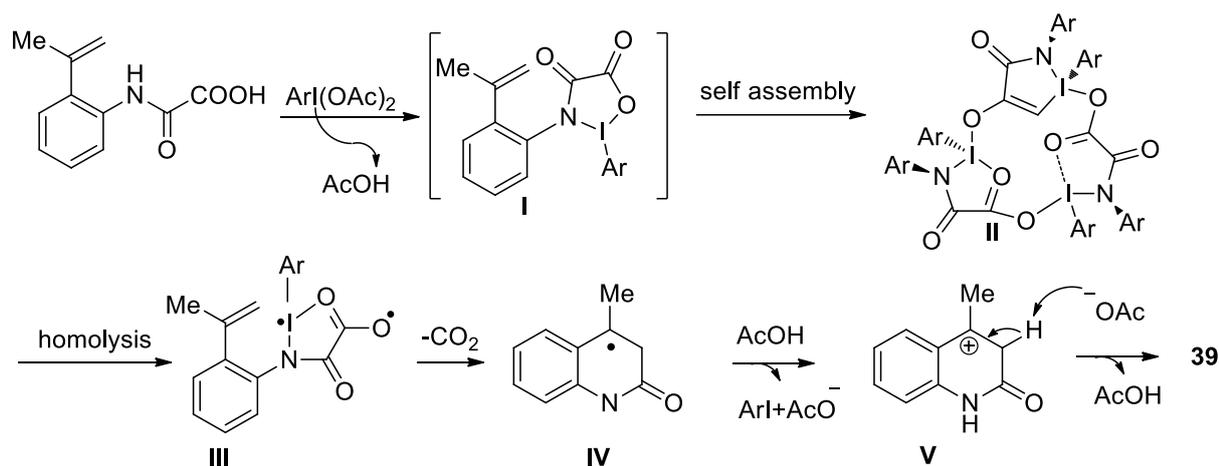
Scheme 16. Decarboxylative Heck-type Reaction of oxamic acids

⁸² Fan, H.; Pan, P.; Zhang, Y.; Wang, W. *Org. Lett.* **2018**, *20*, 638.

⁸³ a) Bai, Q.-F.; Jin, C.; He, J.-Y.; Feng, G. *Org. Lett.* **2018**, *20*, 2172; b) Cheng, W. M.; Shang, R.; Yu, H.-Z.; Fu, Y. *Chem. Eur. J.* **2015**, *21*, 13191. c) Huang, H.; Zhang, G.; Chen, Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 7872; d) Wang, H.; Guo, L.-N.; Wang, S.; Duan, X.-H. *Org. Lett.* **2015**, *17*, 3054; e) Yuan, M.; Chen, L.; Wang, J.-W.; Chen, S.-J.; Wang, K.-C.; Xue, Y.-B.; Luo, Z.-W.; Zhang, Y.-H. *Org. Lett.* **2015**, *17*, 346.

⁸⁴ Zhdankin, V. V.; Kuposov, A. E.; Smart, J. T.; Tykwinski, R. R.; McDonald, R.; Morales-Izquierdo, A. *J. Am. Chem. Soc.* **2001**, *123*, 4095.

The initiation of reaction took place through the formation of the cyclic iodine (III) monomer **I**, with subsequently self-assembled to afford a macrocyclic trimer **II**. The ring-strain induced homolysis of the newly formed iodine–oxygen bond led to the formation of the diradical intermediate **III**. The decarboxylation of **III**, along with radical addition onto the olefin led to radical **IV**, which oxidation generated the benzylic cation intermediate **V** with elimination of ArI. Lastly, in presence of a base, the E1 elimination from this intermediate afforded the final product **17** (Scheme 17).

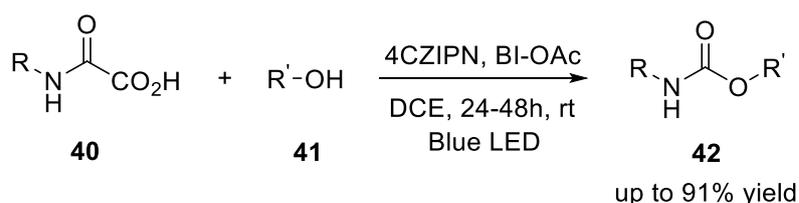


Scheme 17.

The generation of carbamoyl radicals from oxamic acids is particularly useful as it circumvents the problem of regioselectivity encountered for instance during the C-H abstraction in formamides ($\text{R}_2\text{N}(\text{C}=\text{O})\text{H}$), which occurs concurrently at CHO and α to nitrogen, leading to a mixture of products.

As shown above, oxidative decarboxylation of oxamic acids may be carried out in the presence of Ag(I) and Cu(II) salts and stoichiometric amount of $\text{K}_2\text{S}_2\text{O}_8$ as an oxidant in a biphasic medium, as originally proposed by Minisci and co-workers.¹² These conditions however suffer from the presence of large amount of metal catalysts, and water was shown to be detrimental to the process efficiency, as observed for instance during the preparation of isocyanates. Activation of organic molecules, by merging catalysis and visible light photoredox processes has attracted much interest recently and appeared particularly attractive to address these issues. As summarized in Chapter 1, this approach relies on the ability of metal complexes or organic dyes to participate in single-electron transfer (SET) or energy transfer processes with organic substrates in the presence of photoexcitation under visible light.

Our group recently showed that the oxidative decarboxylation of oxamic acid could be performed conveniently under metal-free conditions in an organic solvent, using an organo-photocatalyst under visible-light irradiation, leading to the corresponding isocyanates in good yields.⁶⁴ According to optimized reaction conditions, urethane **42** could be obtained in a one-pot process from oxamic acid **40**. The transformation was carried out in the presence of a photoredox catalyst (PC) 4CzIPN⁸⁵ and BI-OAc in DCE solvent at rt under visible light irradiation (blue LEDs, $\lambda_{\text{max}} = 452 \text{ nm}$) (Scheme 18).

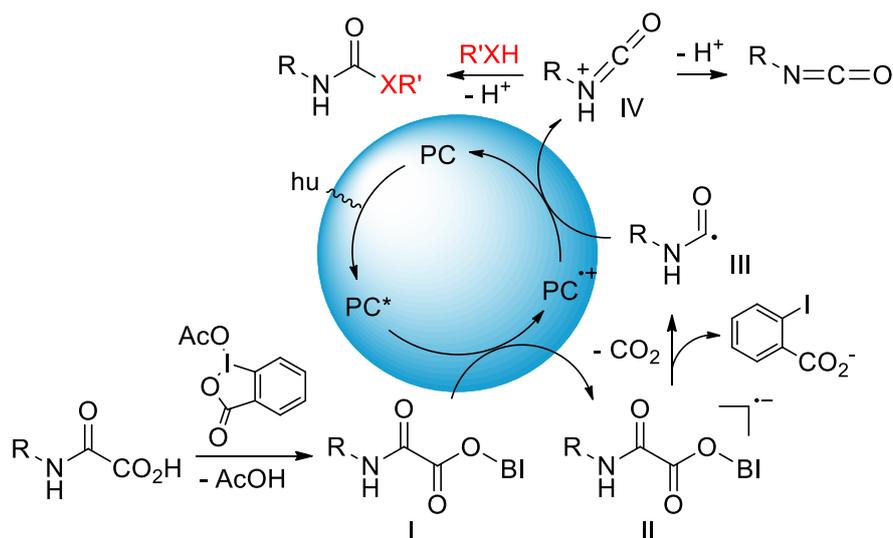


Scheme 18. Photo-organocatalyzed decarboxylation of oxamic acids to urethanes.

The reaction process starts by the quenching of photocatalyst (PC: 4CzIPN) in its excited state by an intermediate **I** which is formed through ligand exchange between BI-OAc and the oxamic acid (Scheme 19).⁸⁶ **I** then would generate the radical-anion **II**, and on collapsing lead to the corresponding amidocarboxyl radical, which on decarboxylation would form the carbamoyl radical **III**, and o-iodobenzoic acid anion. The photocatalyst radical cation PC^+ would then oxidize **III** into the corresponding protonated isocyanate **IV**. Finally, **IV** by losing a proton produces the desired isocyanate,⁶⁴ or react *in situ* with alcohols and amines to give urethanes and ureas respectively.

⁸⁵ Uoyama, H.; Goushi, K.; Shizu K.; Nomura, H.; Adachi, C. *Nature* **2012**, 492, 234.

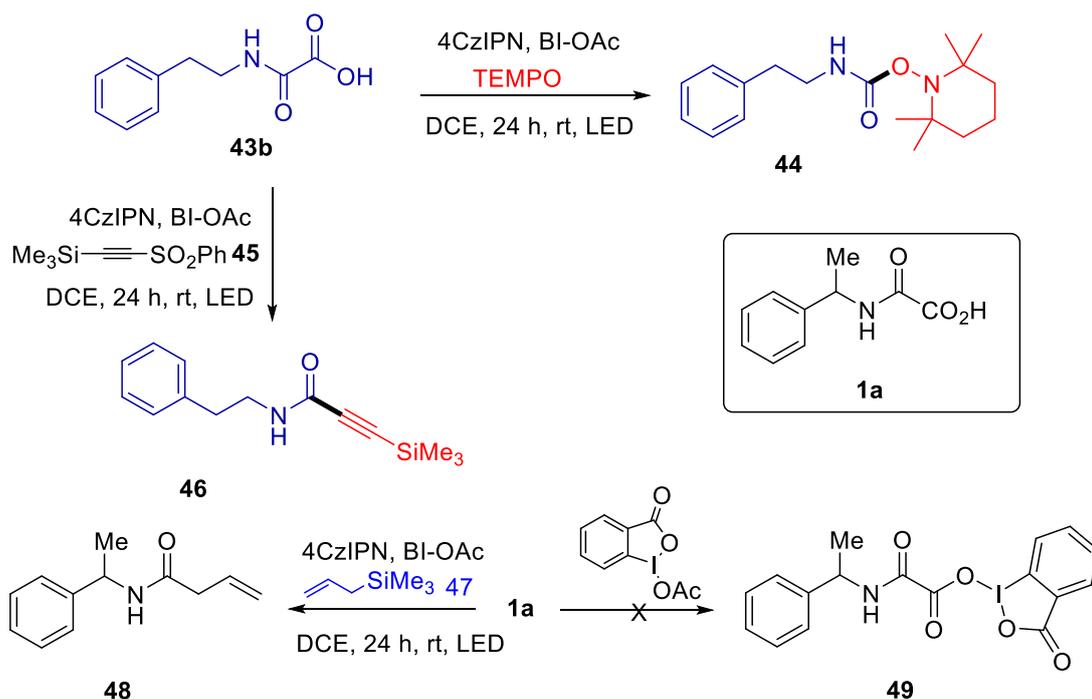
⁸⁶ Huang, H.; Jia, K.; Chen, Y. *Angew. Chem., Int. Ed.* **2015**, 54, 1881.



Scheme 19.

This protocol successfully avoids the isolation, purification and storage of the carcinogenic isocyanate intermediates and allows elaboration of urethanes and ureas in a one pot process from commercially available sources. When the reaction was carried out in the presence of alcohols, the corresponding urethanes were isolated in excellent yields in a one-pot process. The mechanistic studies unambiguously showed that a carbamoyl radical was generated under these conditions, which could be trapped by unsaturated substrates. For instance, **43b** was reacted under the standard conditions with TEMPO, providing **44**. When oxamic acid **43a** was treated under the same reaction conditions, replacing R'OH with alkynylsulfone **45**, amide **46** was observed which supports the presence of a carbamoyl radical intermediate radical that is reacting onto **45** to form **46** *via* an addition-elimination process (Scheme 20).⁸⁷ Repeating the same reaction using allylsilane **47**, produced amide **50**. Lastly, it was concluded that decarboxylation of oxamic acid would proceed through **49** (containing a weak O-I bond) resulting from the coupling between BIOAc and oxamic acid. However, efforts to prepare **49** through coupling between oxamic acid **1a** and BIOAc unfortunately met with failure.

⁸⁷ a) Nagatomo, M.; Yoshida, S.; Inoue, M. *Chem. Asian J.*, **2015**, *10*, 120; b) Zhou, S.; Song, T.; Chen, H.; Liu, Z.; Shen, H.; Li, C. *Org. Lett.*, **2017**, *19*, 698; c) Xiang, J.; Jiang, W.; P. Fuchs, L.; *Tetrahedron Lett.* **1997**, *38*, 6635; d) Schaffner, A.-P.; Darmency, V.; Renaud, P. *Angew. Chem., Int. Ed.*, **2006**, *45*, 5847; e) Lei, J.; Wu, X.; Zhu, Q. *Org. Lett.*, **2015**, *17*, 2322; f) Wang, H.; Guo, L.; Wang N S.; Duan, X.-H. *Org. Lett.*, **2015**, *17*, 3054.



Scheme 20.

During their mechanistic studies, Landais and co-workers were thus able to show that alkynylsulfones or allylsilanes were efficient traps for the carbamoyl radical species and that the latter could be efficiently generated through the intermediary of an oxamic hypiodite generated *in situ* and easily decomposed under mild conditions.

2. Present work. Visible-light mediated carbamoylation of N-heterocycles

2.1. Introduction

Based on the previous work in our laboratory and literature precedent, we anticipated that performing this photocatalyzed decarboxylation of oxamic acids in the presence of heteroaromatic bases (such as Lepidine **50a**) should allow the formation of the corresponding amides as first reported by Minisci. We thus report here our efforts on the development of the visible-light mediated addition of oxamic acids onto heteroaromatic bases using a visible-light photoredox catalysis in the presence of an hypervalent iodine reagent (Figure 4). This metal-free procedure enables the amidation of heteroarenes in generally good yields under mild conditions. The method was extended to the carbamoylation of heterocycles using α -aminoacids-derived oxamic acids, which occurred without racemization.

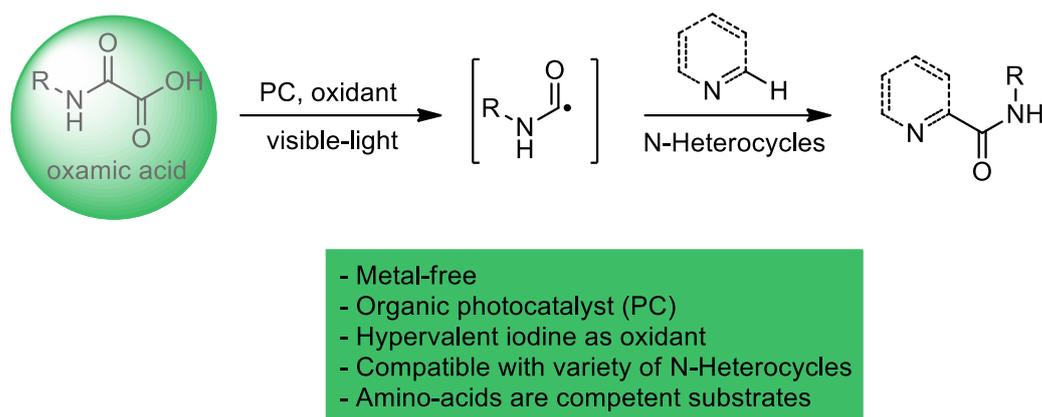


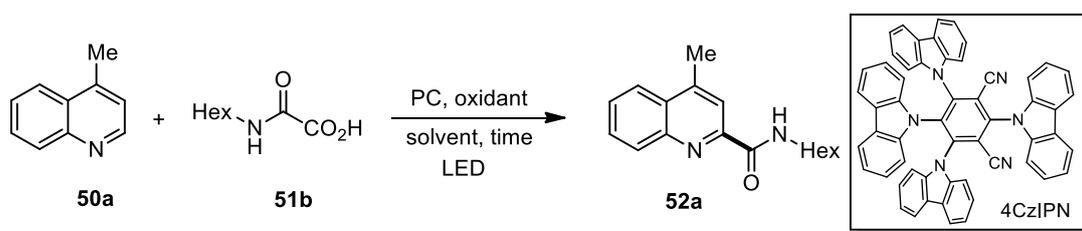
Figure 4. Visible-light mediated amidation of N-heterocycles

2.2. Optimization of reaction conditions

Reaction conditions were first optimized, as summarized in Table 1, to access carboxamides **52a** from oxamic acid **51b** and lepidine **50a** as a model heteroaromatic base. Photocatalyst 4CzIPN⁶⁴ was first tested considering its efficiency in our previous study. Blue LEDs were also designed regarding the maximum UV-vis absorption of 4CzIPN. Preliminary results using hypervalent iodine reagents such as PhI(OAc)₂ (PIDA), PhI(TFA)₂ (PIFA) and BI-OH afforded **38a** in good yields (entries 1-3). However, changing the oxidant to BI-OAc⁸⁸ remarkably improved the yield, as observed before,⁶⁴ likely due to the presence of a better leaving group (OAc) at the iodine center (entry 4). Eosin-Y and rose Bengal were also tested as photocatalysts, but led only to traces of **52a** (entries 6-7), while an acridinium salt⁸⁹ provided 70% conversion (entry 5). Thus, 1.0 mol % of 4CzIPN, 0.75 mmol of BI-OAc in dichloromethane for 12 h offered optimal conditions with 90% yield (entry 4).

⁸⁸ Li, Y.; Hari, D. P.; Vita, M. V.; Waser, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 44.

⁸⁹ Fukuzumi, S. S.; Kotani, H.; Ohkubo, K.; Ogo, S.; Tkachenko, N. V.; Lemmetyinen, H. *J. Am. Chem. Soc.* **2004**, *126*, 1600.

**Table 1.** Addition of oxamic acid **51b** to lepidine **50a**

| Entry | PC | Oxidant | Solvent | Time (h) | Yield (%) |
|-------|--------------------------------------|-----------------------|---------------------------------|----------|-----------|
| 1 | 4CzIPN | PhI(OAc) ₂ | CH ₂ Cl ₂ | 12 | 76 |
| 2 | 4CzIPN | PhI(TFA) ₂ | CH ₂ Cl ₂ | 12 | 65 |
| 3 | 4CzIPN | BI-OH | CH ₂ Cl ₂ | 12 | 69 |
| 4 | 4CzIPN | BI-OAc | CH ₂ Cl ₂ | 12 | 95 |
| 5 | AcrMes+ClO ₄ ⁻ | BI-OAc | CH ₂ Cl ₂ | 12 | 70 |
| 6 | Eosin Y | BI-OAc | CH ₂ Cl ₂ | 15 | Trace |
| 7 | Rose Bengal | BI-OAc | CH ₂ Cl ₂ | 12 | NA |
| 8 | 4CzIPN | BI-OAc | DCE | 12 | 85 |
| 9 | 4CzIPN | BI-OAc | THF | 12 | 33 |
| 10 | 4CzIPN | BI-OAc | MeCN | 12 | 58 |
| 11 | 4CzIPN | BI-OAc | DMF | 12 | 51 |
| 12 | 4CzIPN | BI-OAc | DMSO | 12 | NA |
| 13 | - | BI-OAc | CH ₂ Cl ₂ | 12 | NA |
| 14 | 4CzIPN | - | CH ₂ Cl ₂ | 12 | NA |
| 15 | 4CzIPN | BI-OAc | CH ₂ Cl ₂ | 12 | NA |

^a Unless otherwise mentioned, all reactions were performed with **50a** (1.0 eq.), **51b** (2.0 eq.), PC (1.0 mol%) and oxidant (1.5 eq.) in the indicated solvent (0.2 M), in a sealed tube. ^b Yields of **52a** determined by ¹H NMR with external standard 1,3,5-trimethylbenzene ^d Isolated yields of **52a**. ^c Absence of blue LED.

Solvents were also varied, indicating that CH₂Cl₂ and DCE were superior (entries 4 and 8), while THF, MeCN, DMF and DMSO led to lower yields (entries 9-12). Finally control experiments were carried out, showing that, photocatalyst, oxidant and light were all essential

for the transformation to occur (entries 13-15). Some commonly used hypervalent iodine reagents are described in (Figure 5) below.

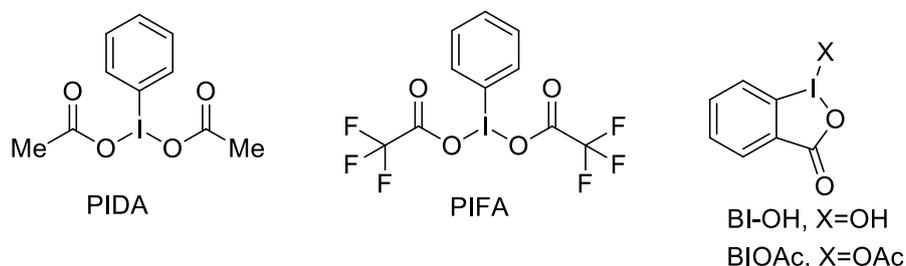
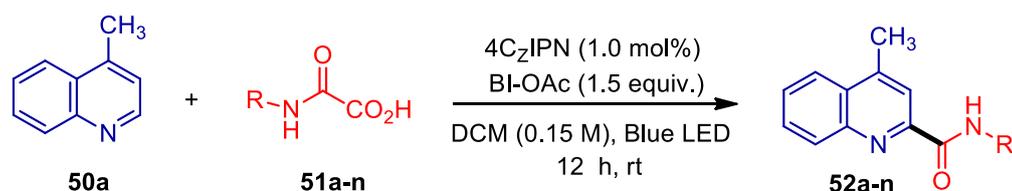


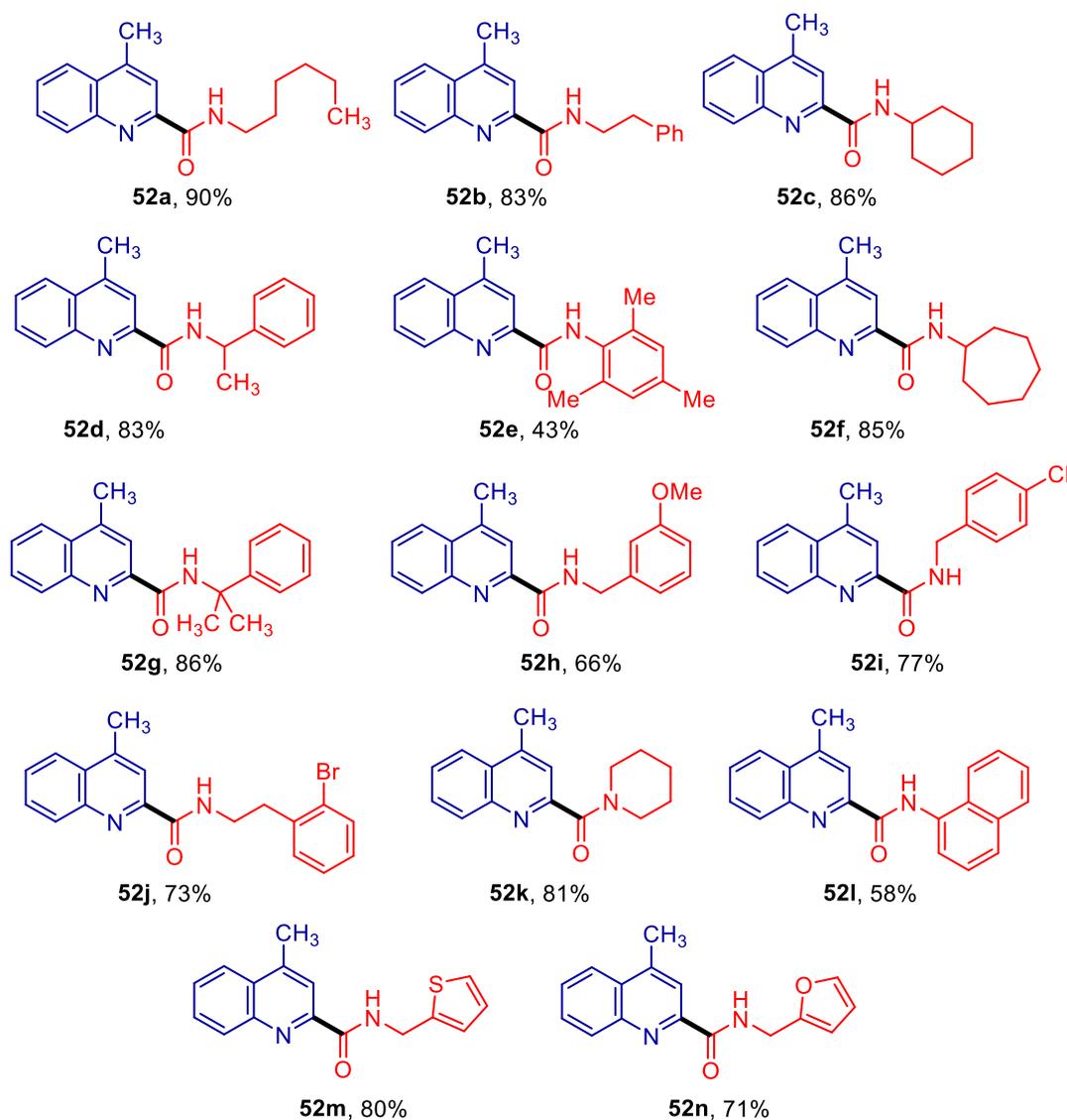
Figure 5.

2.3. Photocatalyzed decarboxylation of oxamic acids (Oxamic acid scope)

With these results, in hands, the substrate scope was extended varying the nature of oxamic acids **51** in the presence of Lepidine **50a** (Scheme 21). The mild reaction conditions allowed the formation of various amides **52a-n** in generally good yields. For oxamic acids bearing aromatic substituents, amides (e.g. **52e** and **52i**) were isolated in somewhat lower yields likely as result of the decarbonylation of carbamoyl radical which give in this case a rather aniliny radical. **52m-n**, having heteroarenes substituents sensitive to oxidations were also obtained in high yields (Scheme 21).



Scheme 21. Oxidative decarboxylation of oxamic



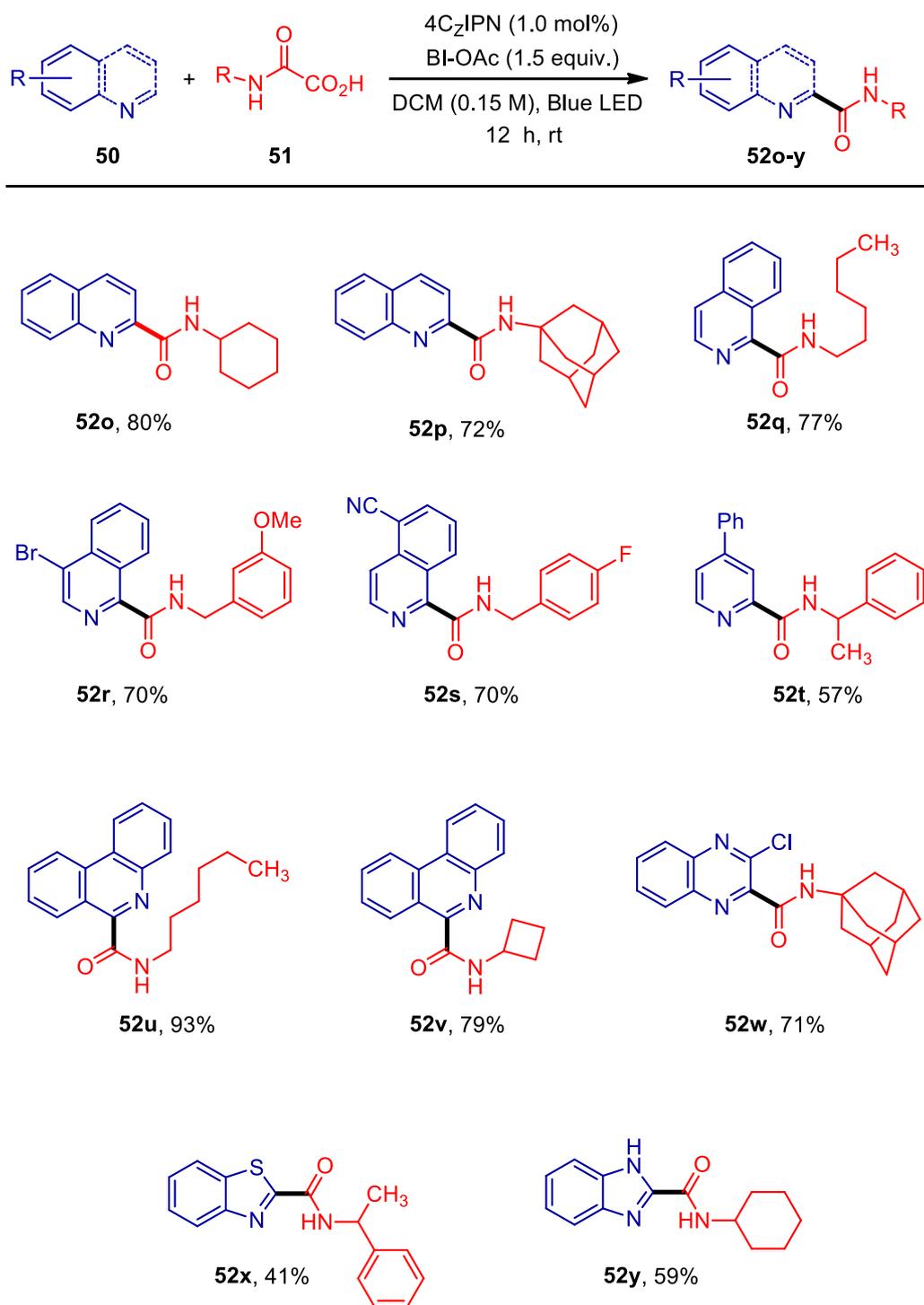
2.4. Photocatalyzed decarboxylation of oxamic acids in the presence of heteroarenes

Other heteroaromatic compounds were submitted to the optimal reaction conditions above, showing that the method is general, the addition occurring regioselectively α - to the nitrogen (Scheme 22).⁹⁰ Interestingly, in cases where two regioisomers may be formed as in **52q**, **52r** and

⁹⁰ a) Minisci, F.; Fontana, F.; Vismara, E. *J. Heterocycles, Chem.* **1990**, *27*, 79; b) O'Hara, F.; Blackmond, D.G.; Baran, P.S. *J. Am. Chem. Soc.* **2013**, *135*, 12122; c) Tauber, J.; Imbri, D.; Opatz,

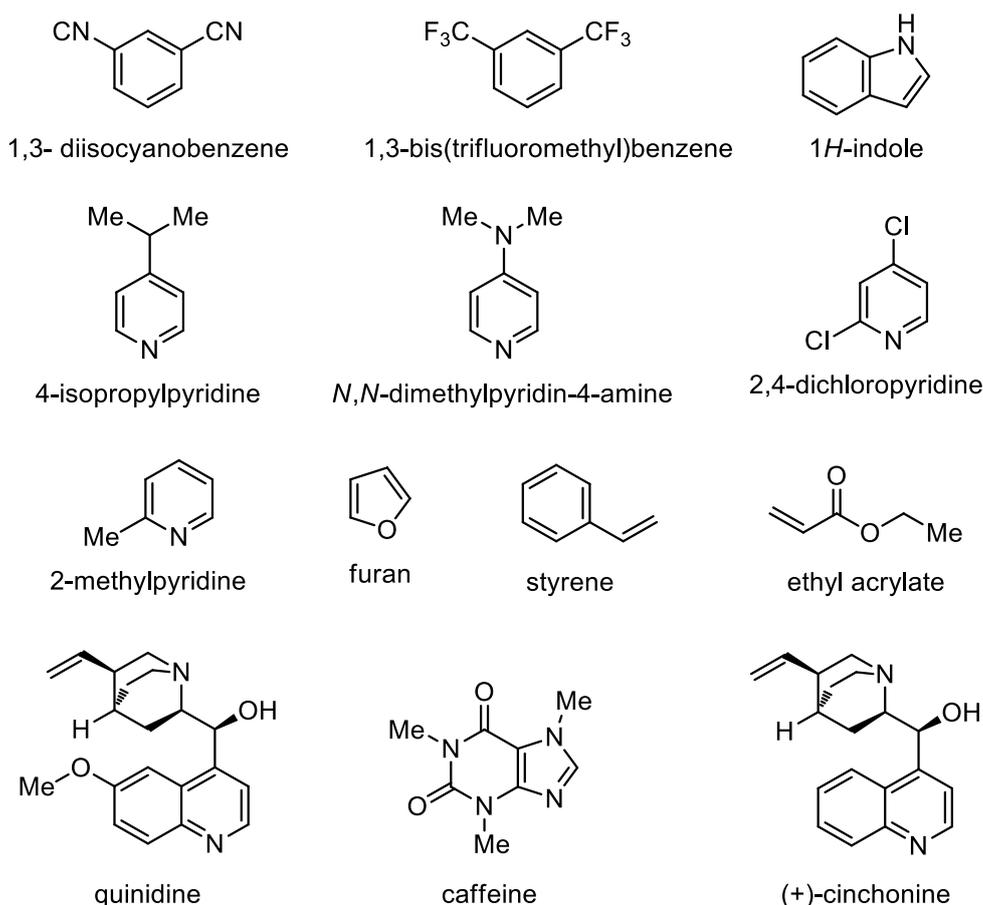
52s, only one was observed. Regioselectivity on substrate **52r** may be rationalized based on steric grounds, addition at the α' position being hindered by the Br substituent (Scheme 22). For **52q** and **52s**, DFT calculations indicate that the addition of the carbamoyl radical at the α -position is faster than the addition at the α' -site, also providing a more stable radical. Benzimidazole and benzothiazole were found competent substrates for the carbamoyl addition, albeit lower yields were observed. A similar reactivity was observed for 4-phenylpyridine, which led to amide **52t** in moderate yield. In these cases, the absence of extended aromatic systems probably explain the lower reactivity, the radical intermediate formed upon addition of the carbamoyl radical being less stabilized. This may also explain the failure of the addition encountered with several other heteroarenes including 4-*i*Pr-pyridine, 4-DMAP, indole, furane, (+)-cinchonine, caffeine or pyrrole. Considering that carbamoyl radicals are nucleophilic in nature, their addition was also attempted on electron-poor arenes such 1,3-dicyanobenzene or 1,3-(CF₃)₂benzene, but again no addition was observed under our conditions. Some examples of failure substrates are described in scheme 23.

T. *Molecules*, **2014**, *19*, 16190. d) Hara, F.O.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2013**, *135*, 12122; e) Tauber, J.; Imbri, D.; Opatz, T. *Molecules*, **2014**, *19*, 16190.



Scheme 22. Photocatalyzed decarboxylation of oxamic acids in the presence of heteroarenes

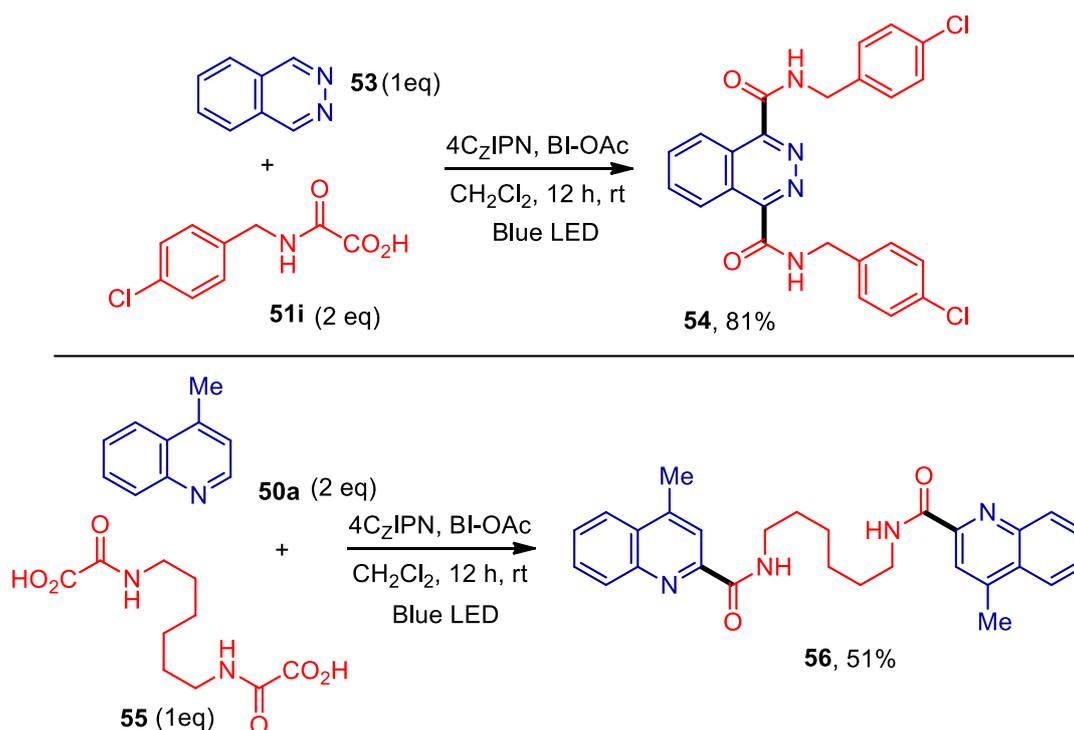
50a. Heteroarenes scope.



Scheme 23. Summary of failed substrates.

2.5. Double photocatalyzed decarboxylation of oxamic acids in the presence of heteroarenes.

Interestingly, double addition was observed using phthalazine **53** as a heteroaromatic base and oxamic acid **50i**, affording bis-amide **54** in excellent yield (Scheme 25). We were unable to detect mono-addition product, when using only one equivalent of **51i**, suggesting that the mono-amide was much more reactive than **53**, the first amidation increasing the electron-deficiency of the heteroarenes, thus accelerating the second addition.^{31c,e} In parallel, bis-amide **56** was prepared in moderate yield by coupling two equivalents of lepidine **50a** with bis-oxamic acid **55** (Scheme 25).

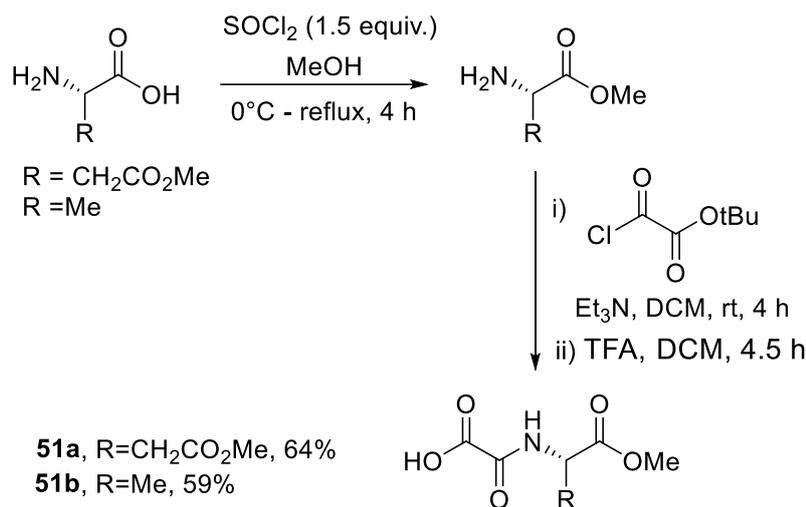


Scheme 25. Double photocatalyzed decarboxylation of oxamic acids in the presence of heteroarenes.

2.6. Photocatalyzed decarboxylation of amino acids derived oxamic acids

Finally, we prepared oxamic acids **51a-b** derived from (L)-amino acids through an efficient two-steps procedure involving the treatment of the amine-free amino-ester with $\text{ClCOCO}t\text{-Bu}$, followed by the removal of the *t*-Bu substituent using TFA (Scheme 26).⁹¹

⁹¹ a) Seki, Y.; Tanabe, K.; Sasaki, D.; Sohma, Y.; Oisaki, K.; Kanai, M. *Angew. Chem., Int. Ed.*, **2004**, *53*, 6501; b) Mecinovic, J.; Loenarz, C.; Chowdhury, R.; Schofield, C. J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6192.



Scheme 26.

51a-b were then submitted to the photocatalyzed decarboxylation in the presence of several heterocycles **50a-f**, leading to the corresponding chiral amides **56a-f** in excellent yields (Scheme 26). HPLC analysis showed unambiguously that the mild conditions of this photo-redox process ensured that no racemization, even partial has occurred.

Reaction was also carried out with *rac*-**51a**, and the HPLC signatures of *rac*-**56c** and homochiral **56c** were compared, showing unambiguously that no racemization has occurred during the process.

HPLC Data for (S)-Dimethyl 2-(4-phenanthridine-6-carboxamido) succinate **56c** and *rac*-**56c** are presented in Figure 6 and 7.

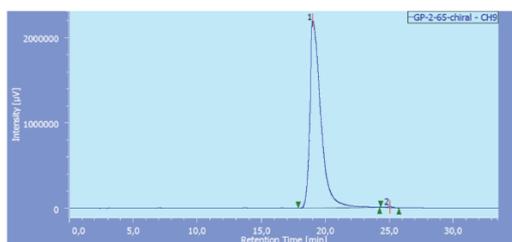


Figure 6. HPLC Data for (S)-**56c**

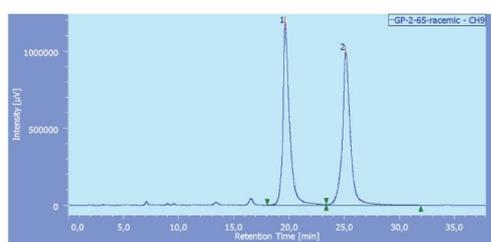
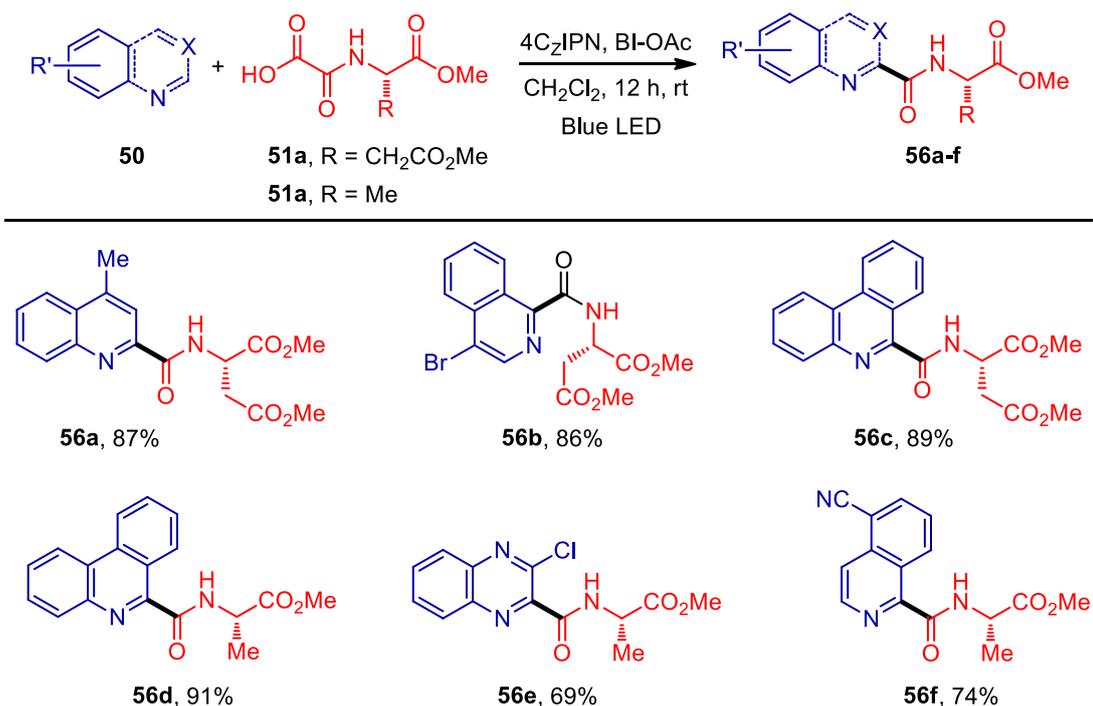


Figure 7. HPLC Data for *rac*-**56c**

It is also worth noticing that treatment of **56a** or **56d** for instance with Lewis acids such as $\text{Eu}(\text{hfc})_3$ led to no racemization, emphasizing on the poorly acidic nature of the proton on the stereogenic center and thus the high configurational stability of these compounds (Scheme 27).



Scheme 27. Photocatalyzed decarboxylation of amino-acids derived oxamic acids.

2.7. Mechanistic studies

A tentative mechanism for the carbamoylation of heteroarenes under photoredox conditions, based on our previous trapping experiments⁶⁴ is proposed in Figure 8 below. These studies have shown that the formation of the key carbamoyl radical species **III** likely results from the formation of a radical-anion **II**, itself issued from the hypoiodite species **I**, formed in situ through the coupling between the oxamic acid and BIOAc.⁹² **II** would in turn be formed through the quenching of the photocatalyst in its excited state by hypoiodite **I**, returning the semi-oxidized form of the photocatalyst (PC⁺). **II** would then collapse to afford the corresponding amidocarboxyl radical (not shown), which decarboxylation would generate **III** and *o*-

⁹² a) Tan, H.; Li, H.; Ji, W.; Wang, L. *Angew. Chem. Int. Ed.* **2015**, *54*, 8374; b) Huang, H.; Zhang, G.; Gong, L.; Zhang, S.; Chen, Y. *J. Am. Chem. Soc.* **2014**, *136*, 2280; c) Huang, H.; Jia, K.; Chen, Y. *Angew. Chem. Int. Ed.* **2015**, *54*, 1881; d) Huang, H.; Jia, K.; Chen, Y. *Acs Catal.*, **2016**, *6*, 4983; e) Genovino, J.; Lian, Y.; Zhang, Y.; Hope, T. O.; Juneau, A.; Gagné, Y.; Ingle, G.; Frenette, M. *Org. Lett.*, **2018**, *20*, 3229.

iodobenzoic acid. Radical addition of the carbamoyl radical **III** onto the heteroaromatic base would form intermediate **IV**, the oxidation of which, by the radical-cation PC^+ , generating cationic species **V**. Rearomatization of the latter after deprotonation would finally give the corresponding amide.^{70a,c} An alternative mechanism may also be proposed, considering the protonation of the heteroaromatic base under the reaction conditions (AcOH), as suggested by Minisci in his seminal studies on the addition of related formamide ($HC(=O)NH_2$) onto heteroarenes.⁹³ This would be followed by the addition of the carbamoyl radical forming N-protonated-**IV**. The ensuing loss of the α -C-H proton from N-protonated-**IV** would produce a rather stable allylic captodative radical species, which oxidation (by PC^+) would give the final amide under its protonated form. This mechanism cannot be formally ruled out, although our conditions are much less acidic than those reported in Minisci's work (H_2SO_4).

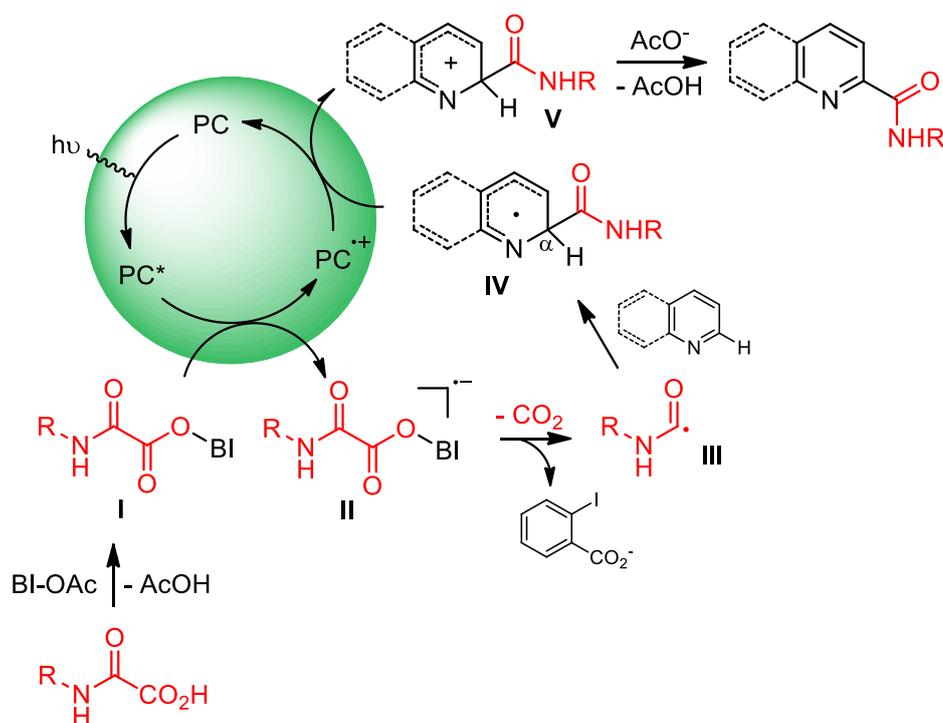


Figure 8. Mechanism of the photocatalyzed decarboxylative Amidation of oxamic acids.

⁹³ a) Minisci, F.; Citterio, A.; Vismara E.; Giordano, C. *Tetrahedron*, **1985**, *41*, 4157; b) Minisci, F.; Fontana, F.; Coppa, F.; Yan, Y. M. *J. Org. Chem.* **1995**, *60*, 5430.

3. Conclusion

In summary, we developed the addition, onto heteroaromatic bases, of carbamoyl radical species generated through a “metal-free” photocatalyzed decarboxylation of oxamic acids. This strategy allows a straightforward and environmentally benign carbamoylation of a variety of *N*-heterocycles. The methodology uses readily available starting material as well as a standard photocatalyst and hypervalent iodine sources. Reaction conditions are mild, offering an access to heteroaryl amides derived from amino-acids without racemization. This reaction however has some limitations as we were unable to perform the carbamoylation onto some electron-poor arenes, although the carbamoyl radical is known to be nucleophilic. Brønsted or Lewis acid activation of the heteroarenes might offer a solution in case where the carbamoylation is sluggish.

CHAPTER III
FREE-RADICAL CARBO-CYANATION OF OLEFIN.
A NEW STRATEGIES TOWARDS THE TOTAL SYNTHESIS
OF LEUCONOXINE

1. Introduction

The class of monoterpene indole alkaloids currently comprises over two thousand members with great diversity. Due to important bioactivities including anticancer, antimalarial, and antiarrhythmic properties, they remained the center of the attention of synthetic chemists for over a century.⁹⁴

Leuconoxine **1** is one of the monoterpene indole alkaloid, found in tropical regions of Malaysia and Indonesia and belongs to a subfamily of Aspidosperma alkaloids. It was first isolated by Abe and Yamauchi in 1994,⁹⁵ from methanolic extract of dried leaves of leuconotis eugenifolius. Leuconoxine consists on a tetracyclic ring skeleton fused at the aminal carbon and the adjacent quaternary carbon center as shown in (Figure 1). It belongs to the alkaloids family, a class of naturally existing compounds mostly containing nitrogen atoms and synthesized by a number of organisms such as fungi, bacteria, plants and animals.

Biogenically, it is a member of aspidosperma alkaloids⁹⁶ and is related to the antitumor agent Rhazinilam, possessing a pyrrole core, which has been used in the treatment of worm infections and bacterial disease yaws.⁹⁷ It stands out for its notable activity for inhibiting the growth of human pancreatic cancer cell lines⁹⁸ and Mycobacterium tuberculosis, for which patents have recently been filed. Furthermore, (-)-leuconoxine displays moderate activity in reversing resistant KB cells (IC₅₀ 12–18 µg/mL).⁹⁹

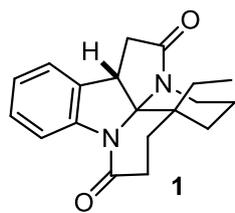


Figure 1. (-)- Leuconoxine natural product

Leuconotis eugenifolius

⁹⁴ a) Hajíček, J. *Collect. Czech. Chem. Commun.* **2011**, 76, 2023. b) Ishikura, M.; Abe, T.; Choshi, T.; Hibino, S. *Nat. Prod. Rep.* **2013**, 30, 694.

⁹⁵ Abe, F.; Yamauchi, T. *Phytochemistry* **1994**, 35, 169.

⁹⁶ David, B.; Sévenet, T.; Thoison, O.; Awang, K.; Pais, M.; Wright, M.; Guénard, D. *Bioorg. Med. Chem. Lett.* **1997**, 7, 2155.

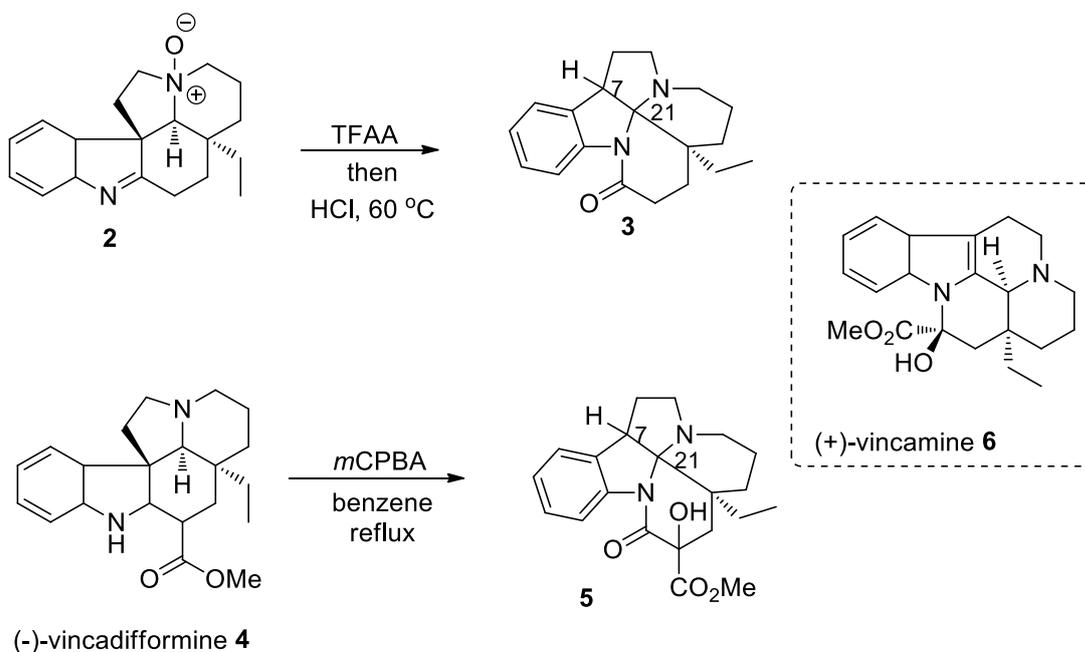
⁹⁷ Pfaffenbach, M., Gaich, T. *Chem. Eur. J.* **2016**, 22, 3600.

⁹⁸ Tian, L. Application of Leuconoxine in Preparation of Drug for Treating Pancreatic Cancer. CN 105311026 A, February 10, **2016**.

⁹⁹ Banerji, A.; Majumder, P. L.; Chatterjee, A. *Phytochemistry* **1970**, 9, 1491.

1.1. Biosynthetic pathway.

On the basis of their formation, complex skeletally diverse monoterpene indole alkaloids can be split into three categories such as 1) fragment coupling 2) cyclization, 3) postcyclization.¹⁰⁰ Moving towards the biosynthetic pathway of leuconoxine described by Wenkert *et al* in 1974,¹⁰¹ (-)-vincadifformine **4** and its derivatives were subjected to a number of oxidations to find a biosynthetic link between **4** and **6**. The treatment of the *N*-oxide **2** with TFAA under Polonovski-Potier conditions afforded the optical antipode of (-)-leuconodine D **3** (Scheme 1).¹⁰² However, the leuconoxine-type compound (+)-**5** was obtained by treatment of **4** with *m*CPBA in refluxing benzene.¹⁰³



Scheme 1. First descriptions of the leuconoxine skeleton in 1974.

The first total synthesis of Leuconoxine was published by Zhu *et al.* in 2013.¹⁰⁴ In their pioneering work, they defined an elegant way to access to the structurally distinct mersicarpine-

¹⁰⁰ a) Fischbach, M. A.; Clardy, J. *Nat. Chem. Biol.* **2007**, *3*, 353. b) Austin, M. B.; O'Maille, P. E.; Noel, J. P. *Nat. Chem. Biol.* **2008**, *4*, 217.

¹⁰¹ a) Wenkert, E. *J. Am. Chem. Soc.* **1962**, *84*, 98. b) Wenkert, E.; Wickberg, B. *J. Am. Chem. Soc.* **1965**, *87*, 1580.

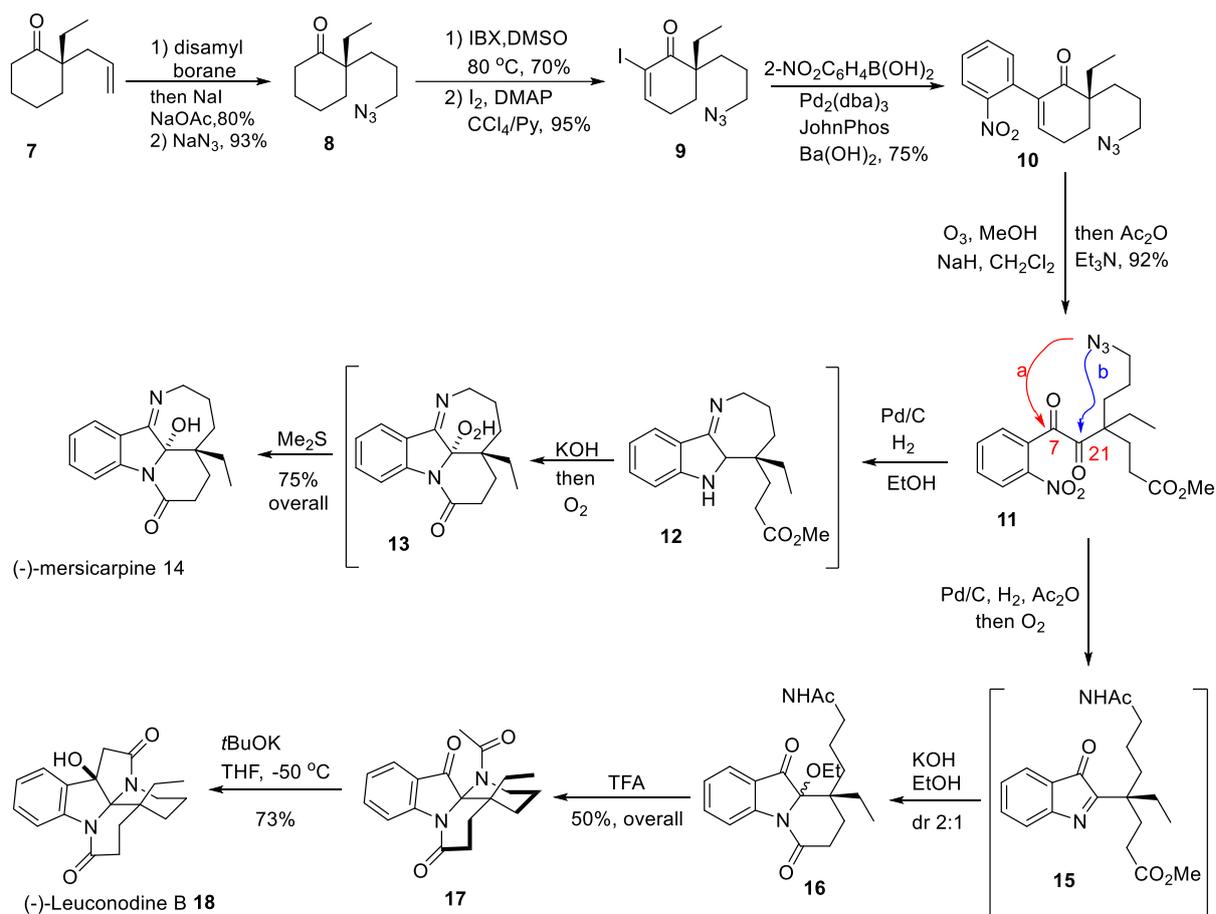
¹⁰² Hugel, G.; Lévy, J.; Le Men, J. *Tetrahedron Lett.* **1974**, *15*, 3109.

¹⁰³ Croquelois, G.; Kunesch, N.; Poisson, J. *Tetrahedron Lett.* **1974**, *15*, 4427.

¹⁰⁴ Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2013**, *135*, 19127.

Chapter III: Free-radical carbo-cyanation of olefin. A new strategies towards the total synthesis of Leuconoxine

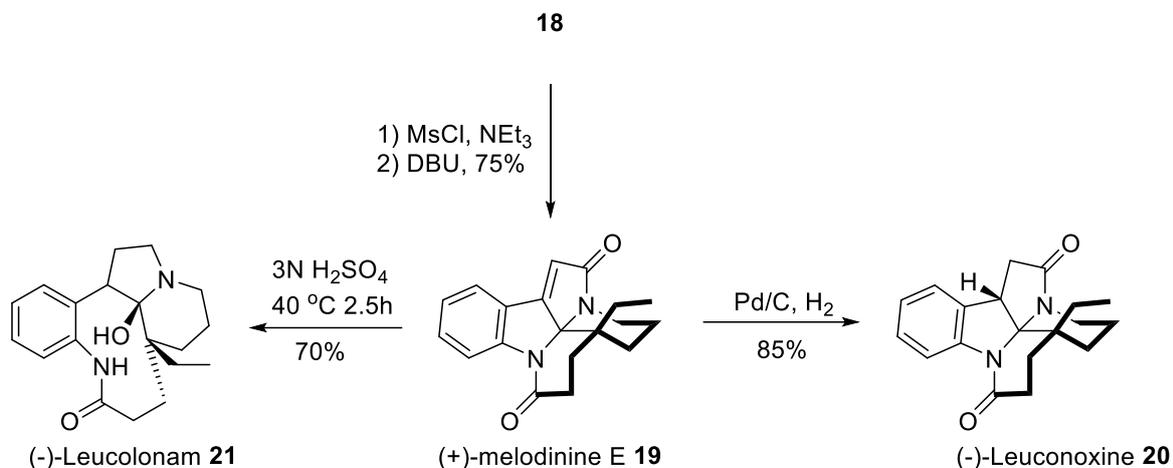
leuconoxine-leuconolam subfamily of *Aspidosperma* alkaloids in a maximum of 12 steps with 7% overall yield in a unified access (Scheme 2). Their strategy involves hydroboration and iodination of cyclohexanone **7**, followed by azidation to produce compound **8**. Then the compound **9** was obtained by using IBX in excess in DMSO and subsequent treatment with iodine in the presence of DMAP. A Suzuki-Miyaura coupling with 2-nitrophenyl boronic acid afford the cyclohexenone **10** which was transformed to diketone **11** by ozonolysis.



Scheme 2. First total synthesis of Leuconoxine alkaloids by Zhu in 2013.

Pd-catalyzed hydrogenation of **11** produced mescarpine **14**. Leuconoxine was also furnished from **11** by hydrogenation with Pd/C in the presence of acetic anhydride to give the corresponding indolin-3-one which was directly oxidized to unstable compound **15**. Then compound **16**, formed by adding potassium hydroxide, produced **17** on treatment with TFA. Then, by using excess *t*BuOK, leuconodine B **18** was obtained in 73% yield. Finally, mesylation of the tertiary hydroxyl group and subsequent elimination with DBU afforded (+)-melodinine E **19** (Scheme 2). A diastereoselective double bond reduction furnished (-)-leuconoxine **20** in 85%

yield. In a reverse biomimetic fashion and under acidic conditions, **19** was converted to (-)-leuconolam **21** in 70% yield.

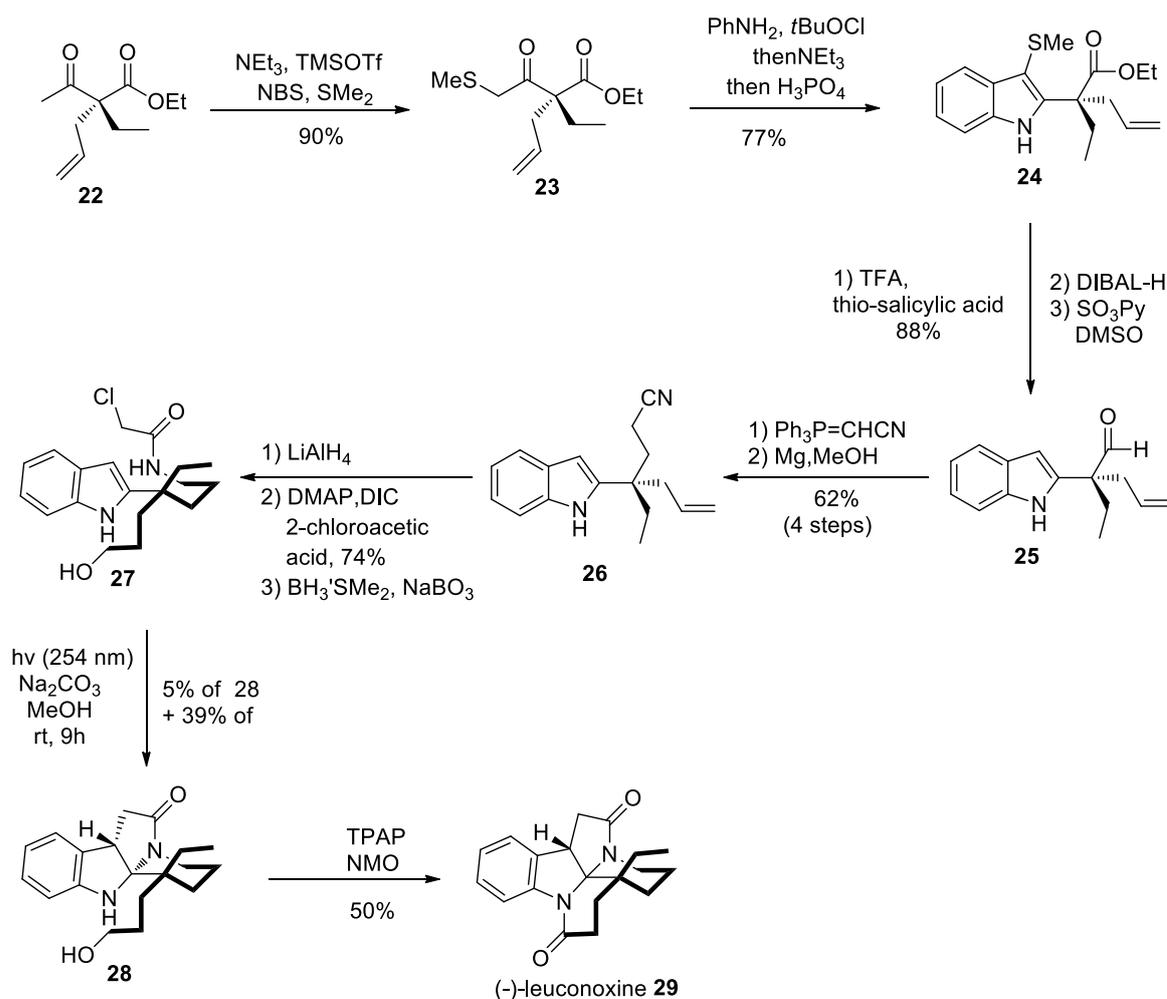


Scheme 3. Endgame for (+)-melodinine E **19** (-)-leuconolam **21**, and (-)-leuconoxine **20** by Zhu in 2013.

A recent synthesis of Leuconoxine was reported by Gaich and Pfaffenbach in 2015,¹⁰⁵ via a photoinduced domino Witkop macrocyclization/transannular cyclization in 12 steps (Scheme 4). They started the synthesis by converting β -ketoester **22** to the corresponding bromoketone with NBS then refluxed in Me₂S to furnished ketosulfide **23** in excellent yield. The compound **24** was formed by using tert-butyl hypochloride. Then, the sulfide group was removed selectively in the presence of the allyl double bond with thiosalicylic acid in TFA. **26** was then furnished through DIBAL-H reduction, Wittig olefination, and Mg reduction. The use of LAH as a reducing agent provided the corresponding amine, which on trapping with activated 2-chloroacetic acid produced the chloroacetamide moiety in good yield. Then, hydroboration-oxidation afforded the linear Witkop precursor **27**, which on UV-light directly generated the leuconoxine precursor **28** in 5% yield. Finally, oxidative ring closure of **28** with a mixture of TPAP and NMO afforded the (-)-leuconoxine **29**.

¹⁰⁵ Pfaffenbach, M.; Gaich, T. *Chem. Eur. J.* **2015**, *21*, 6355.

Chapter III: Free-radical carbo-cyanation of olefin. A new strategies towards the total synthesis of Leuconoxine



Scheme 4. Total synthesis of (-)-leuconoxine **29** by Gaich in 2015.

1.2. Background and literature review

For many years, medicinal chemists have restricted their research area to flat aromatic compounds, as they are simpler to prepare and accessible using a vast number of methods including coupling reactions, which also allow automatization. Synthesis of aromatic compounds circumvents the somewhat tedious and costly control of the stereochemistry and avoids contamination of the product with undesired stereoisomers. The two-dimensional nature of aromatic compounds however does not fully benefit from optimal interactions with three-dimensional biological targets such as proteins. Incorporation of chirality leads to bioactive molecules having improved binding with the chiral hosts, thus leading to improved biological effects. For this reason, chemists have also explored the chemical space, including compounds possessing stereogenic centers and more recently molecules bearing a quaternary stereocenter.

The latter may be ranged in two classes, those where the quaternary center is linked to carbon and heteroatoms (grey dot, Figure 2), and those where it is linked only to carbon substituents (blue dot). The control of the stereochemistry of the last class is still a daunting challenge, although important breakthroughs have been made recently.¹⁰⁶ As an illustration of this, it appears that only 12% of the 200 prescription drugs sold in US in 2012 contain a quaternary stereocenter but all are derived from natural products (e.g. **2-3**, Figure 2). In none of these compounds the quaternary center have been introduced through chemical synthesis.^{13c-d}

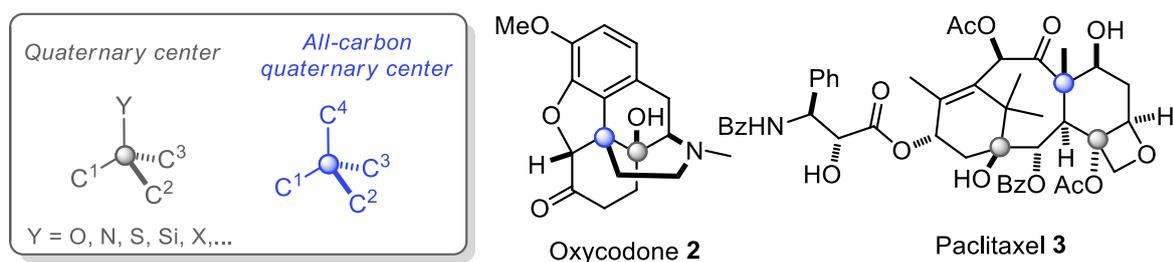
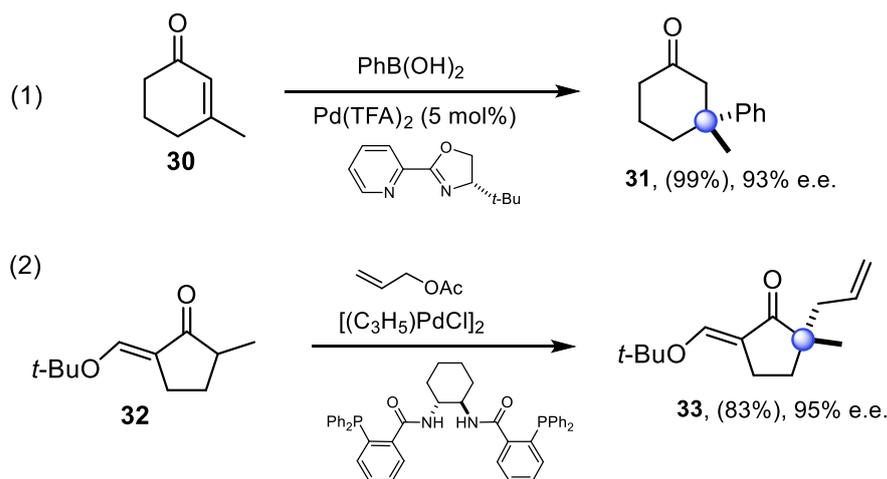


Figure 2. Quaternary stereocenters and their occurrence in bioactive compounds

It is only recently that organic chemists have shown interest in the development of methods to install all-carbon quaternary stereocenters.¹⁰⁶ Although for a long time, chemists have mainly relied on Claisen rearrangement or Diels-Alder reactions to perform this task, catalytic enantioselective methods have recently appeared using transition-metal and/or organocatalysts to control this stereochemical outcome. The progress in this area has been reviewed¹⁰⁶ and only some striking examples are provided here. Addition of carbon nucleophiles (e.g. boronic acids, Eq. (1), Scheme 5) to electrophiles has been described and constitutes an efficient mean to generate quaternary centers. Organocatalysis (using chiral urea in 1,4-addition) and phase-transfer catalysis have also been exploited. Chiral carbon electrophiles have also been used for this purpose, with seminal work by Trost^{106a} and Stoltz^{106c}, who established Pd-catalyzed asymmetric allylic alkylations on non-stabilized unbiased enolates (Eq. (2), Scheme 5).

¹⁰⁶ a) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. b) Minko, Y.; Marek, I. *Chem. Commun.*, **2014**, 50, 12597. c) Hong, A. Y.; Stoltz, B. M. *Eur. J. Org. Chem.* **2013**, 2745. d) Quasdorf, K. W.; Overman, L. E. *Nature* **2014**, 516, 181.



Scheme 5. Pd-catalyzed processes to install all-C quaternary stereocenters

2. Objectives and overview.

These few examples highlight progress made in the elaboration of compounds bearing all-carbon quaternary stereocenters. However, methods developed so far have mostly focused on the synthesis of cyclic systems and further developments are needed to get access to a larger variety of compounds including acyclic systems. We propose, in this project, a new approach to answer this demand, using a strategy relying on a carbo-functionalization of enantiopure cyclopropenes.¹⁰⁷ The tetrasubstituted cyclopropane could then be opened under basic conditions, relying on the suitable localization of two activating electron-withdrawing groups (EWG¹ and EWG²) at C1 and C2 (Figure 3). Control of the diastereoselectivity during the carbo-functionalization event should secure the enantioselectivity of the sequence and the optical purity of the final acyclic system bearing distinct carbon-substituents that may be functionalized further. A second objective will be to illustrate the power of the methodology with the total synthesis of Leuconoxine, which synthesis still constitutes a challenging task. As explained below, the incorporation of a nitrile functional group as the R' substituent onto the cyclopropane would offer a rapid entry toward the skeleton of the Leuconoxine.

¹⁰⁷ Rubin, M.; Rubina, M.; Gevorgyan, V. *Synthesis* **2006**, 1221.

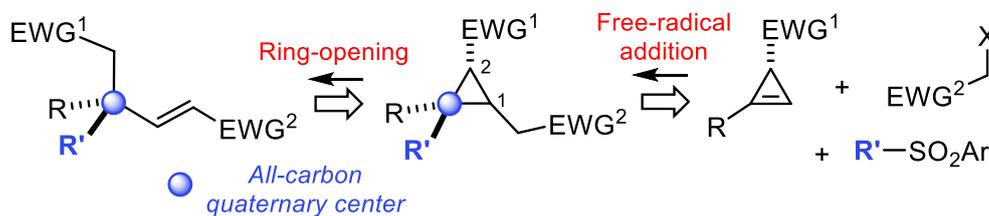


Figure 3. Installation of all-C quaternary stereocenters through cyclopropane ring opening

2.1. Retrosynthetic analysis.

The retrosynthesis analysis of Leuconoxine relies on the preparation of acyclic molecule **34** containing the quaternary center found in the natural alkaloid (Figure 4). This molecule can be synthesized by a carbocyanation process and this strategy could open an access not only to **1**, but also to other members of the Leuconotis alkaloids.

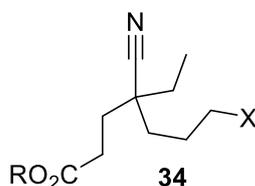


Figure 4. Acyclic intermediate **34**.

As mentioned above, our strategy would rely on the preparation of acyclic intermediate **34**, which can be obtained by a carbocyanation process. The coupling between **34** and **35** would provide an amide **36**, which upon basic treatment should provide an amidine **37**. The remaining two rings would then be formed relying on an organocatalyzed annulation process involving *N*-Heterocyclic carbene (NHC) as catalyst to access **29**. (Figure 2).

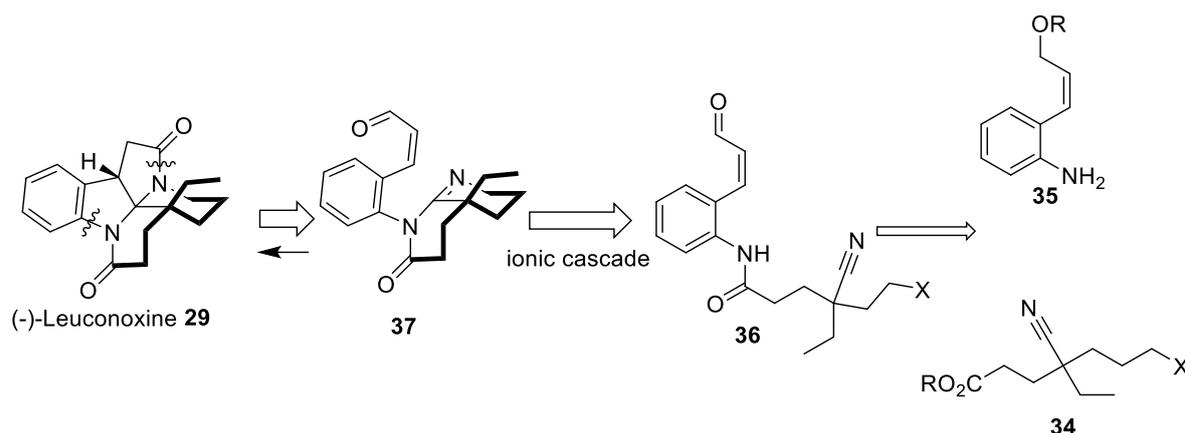
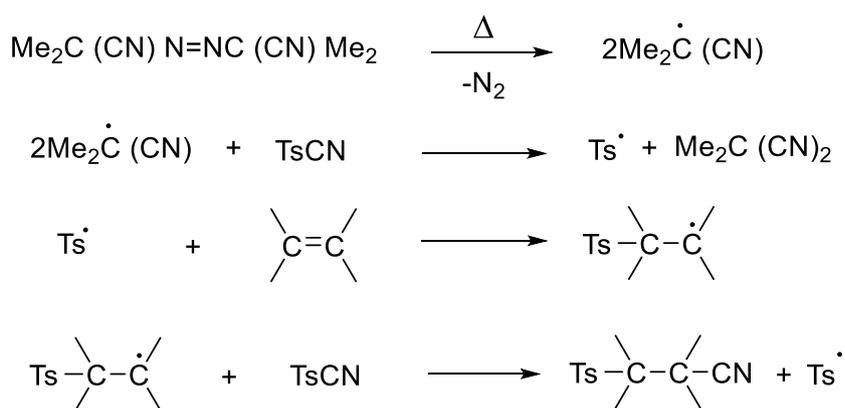


Figure 5. Retrosynthetic pathway

Following above strategy, we prepared a nitrile system by carbocyanation of alkenes with α -haloamides. These amides were obtained by reaction of aniline and phenylmethanamine with 2-bromoacetyl bromide. The resulting *N*-benzyl-2-bromoacetamide did not react effectively and was thus converted to *N*-benzyl-2-iodoacetamide in presence of sodium iodide. With these amides in hand, we established the scope of the carbocyanation reactions by varying olefins, as described in the following part of this chapter.

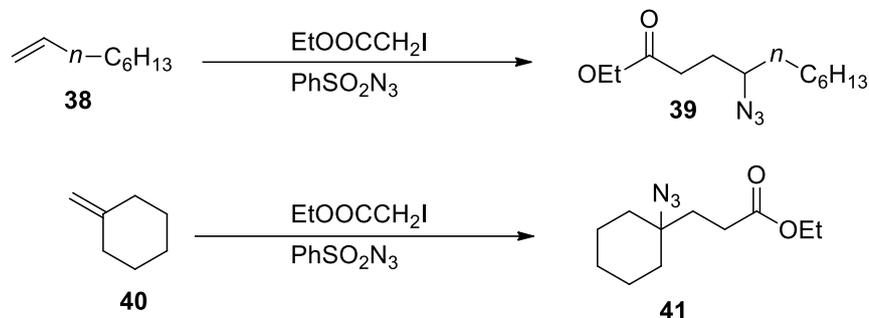
The addition *p*-TolSO₂CN across olefin π -bonds to produce the corresponding β -sulfonyl cyanides was first described by Fang *et al.*¹⁰⁸ The reaction was initiated by AIBN in benzene and dichlorobenzene to obtain the final products (Scheme 6).



Scheme 6. Addition of TsCN to unsaturated olefins.

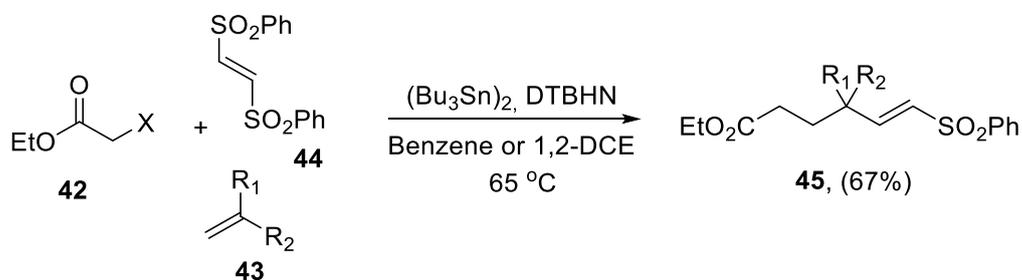
¹⁰⁸ Fang, M.; Chen, M.-Y. *Tetrahedron Lett.* **1987**, 28, 2853.

According to various reports, sulfonyl cyanides have been used as efficient cyanating agents in radical processes.¹⁰⁹ On the other hand, addition of a carbon fragment and a cyano substituent on an olefinic backbone was still unknown. Renaud and his co-workers¹¹⁰ reported the carboazidation of alkenes **8** and **10** to obtain azide **9** and **11** respectively (Scheme 7).



Scheme 7. Carboazidation of alkenes.

Recently, our group established a new radical carboalkenylation of olefins proceeding through a three-component process, in which the vinyl biphenylsulfone **44** was designed as the sulfone candidate. When reacted with **42** and **43** the desired vinyl sulfone **45** was obtained in excellent yield (Scheme 8).¹¹¹



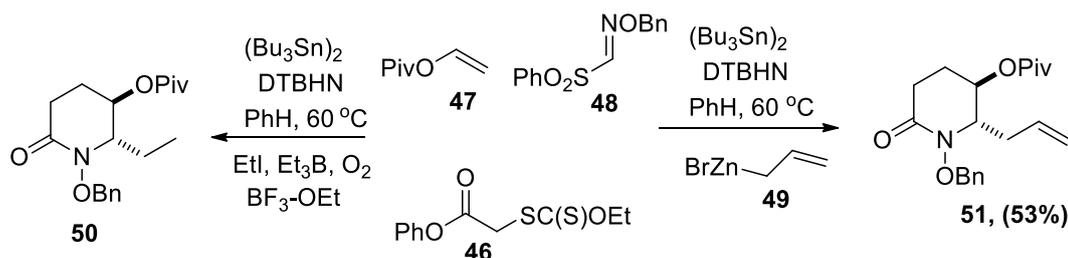
Scheme 8. Carboalkenylation reaction.

¹⁰⁹ a) Barton, D. H. R.; Jaszberenyi, J. S.; Theodorakis, E. A. *Tetrahedron* **1992**, *48*, 2613; b) Kim, S.; Song, H.-J. *Synlett* **2002**, 2110; c) Schaffner, A.-P.; Darmency, V.; Renaud, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 5847. d) Kim, S.; Kim, S.; Otsuka, N.; Ryu, I. *Angew. Chem. Int. Ed.* **2005**, *44*, 6183; *Angew. Chem.* **2005**, *117*, 6339; e) Kim, S.; Cho, C. H.; Kim, S.; Uenoyama, Y.; Ryu, I. *Synlett* **2005**, 3160. f) Kim, S.; Kim, S. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 809; g) Ren, R.; Wu, Z.; Xu, Y.; Zhu, C. *Angew. Chem. Int. Ed.* **2016**, *55*, 2866; *Angew. Chem.* **2016**, *128*, 2916.

¹¹⁰ a) Renaud, P.; Ollivier, C.; Panchaud, P. *Angew. Chem. Int. Ed.* **2002**, *41*, 460. b) Panchaud, P.; Renaud, P. *J. Org. Chem.* **2004**, *69*, 3205.

¹¹¹ a) Liautard, V.; Robert, F.; Landais, Y. *Org. Lett.* **2011**, *13*, 2658. b) Poittevin, C.; Liautard, V.; Beniazza, R.; Robert, F.; Landais, Y. *Org. Lett.* **2013**, *15*, 814.

Our group also established a sequential four-component carbo-oximation reaction to access highly substituted piperidinones in a one-pot operation, in which the oximated product was allowed to react with alkyl radicals or allylzinc reagent instead of hydrolyzing the oxime group.¹¹² Hence, the xanthate **46** generated electrophilic radical, which adds onto an electron rich olefin **47** to generate a radical intermediate. That nucleophilic radical is then trapped by the electrophilic sulfonyloxime **48**. Finally, reaction with an alkyl radical or an allylzinc reagent gives the lactamized products **50**, **51** in good yields and high diastereoselectivity (Scheme 9).



Scheme 9. Carbo-oximation cyclization sequence.

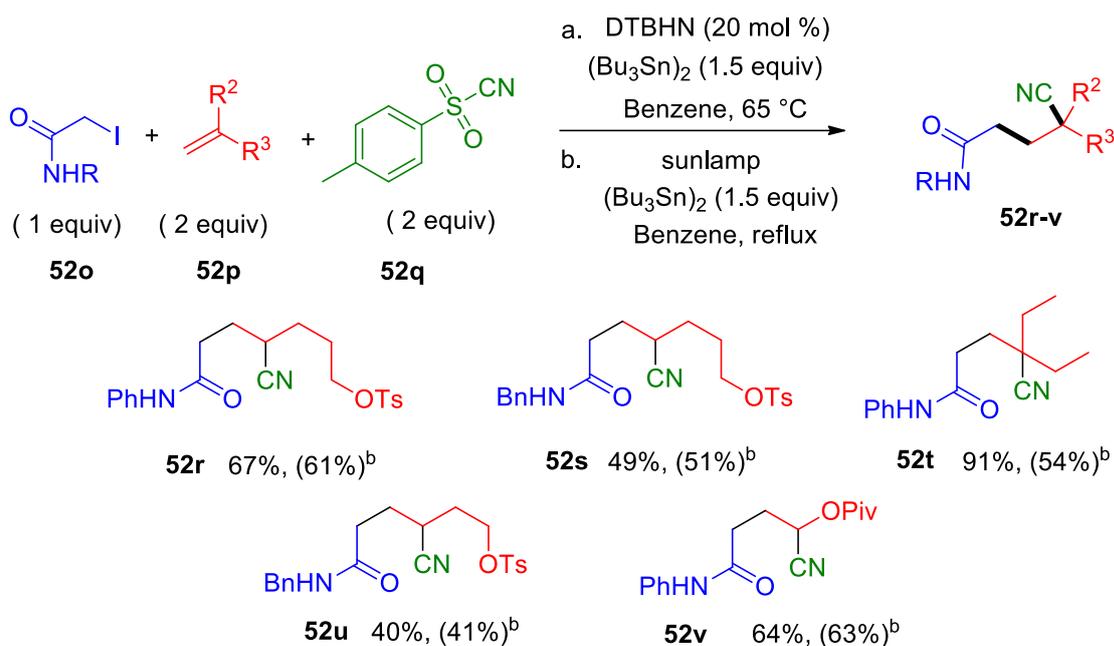
2.2. Radical Carbocyanation Reactions.

On the basis of above reported work, it is clear that the nitrile group would be an interesting function that could be introduced through a free radical process. *p*-TsCN is a commercially available and cheap starting material that could be used as a cyanating agent. Hence, considering these facts the group has described a three-component free-radical carbocyanation of electron-rich olefins, which works efficiently, and established a substrate scope.¹¹³ This scope is general as radical precursors, with electron withdrawing groups, add to various electron rich olefins, the generated radicals being trapped by the sulfonyl acceptor, leading from good to excellent yields (Scheme 10).¹¹⁴

¹¹² a) Godineau, E.; Landais, Y. *J. Am. Chem. Soc.* **2007**, *129*, 12662. b) Landais, Y.; Robert, F.; Godineau, E.; Huet, L.; Likhite, N. *Tetrahedron* **2013**, *69*, 10073.

¹¹³ Hassan, H.; Pirenne, V.; Wissing, M.; Khiar, C.; Jatoi, A. H.; Robert, F.; Landais, Y. *Chem. Eur. J.* **2017**, *23*, 4651.

¹¹⁴ Dange, N. S.; Robert, F.; Landais, Y. *Org. Lett.* **2016**, *18*, 6156.



Scheme 10. Carbocyanation of amides.

The three-component adducts **52r–v** were thus obtained by using amides as precursors, in moderate to good yields. Interestingly, useful O-protecting groups such as OPiv, but also OTs as in **52r, s** and **52v**, were also tolerated in these reactions. Finally, we also tested the efficiency of the photochemical initiation. For instance, three-component adducts **52r–v** were prepared under similar conditions, but using a sunlamp instead of DTBHN. Moderate to good yields were obtained, which suggest that this protocol may be suitable for reactions on a larger scale to avoid the use of costly DTBHN (Scheme 10).

2.3. Mechanistic pathway.

This free-radical three-component carbocyanation of olefins resulted in the addition of two functional groups across the π -system of unactivated olefins.¹¹³ This process relies on the addition of an electrophilic radical species, generated from the corresponding amides **52o** by abstraction of iodine with $\text{Bu}_3\text{Sn}\cdot$. The resultant nucleophilic radical is then trapped by the electrophilic vinyl or alkynylsulfone acceptor **52q**. The sulfonyl radical released during the addition β -elimination sequence, which does not fragment under the reaction conditions (e.g. 65 °C), serves as a radical chain propagator in the presence of a stoichiometric amount of hexabutylditin (Figure 6).¹¹⁵

¹¹⁵ Ovadia, B.; Robert, F.; Landais, Y. *Org. Lett.* **2015**, *17*, 1958.

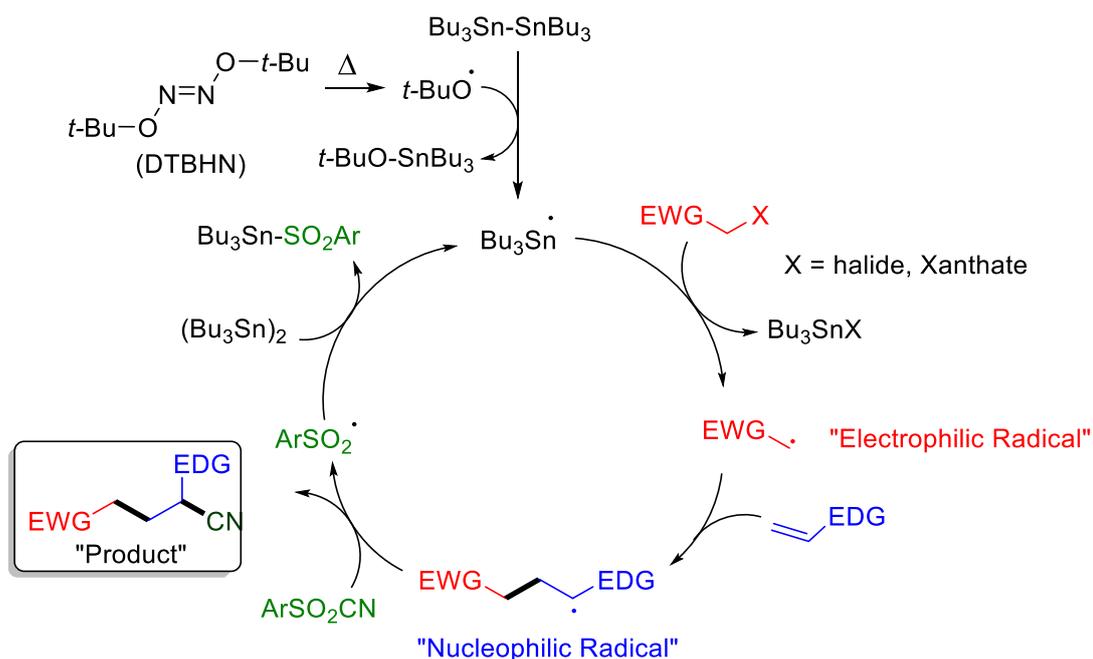


Figure 6. Mechanistic pathway of carbocyanation of amides.

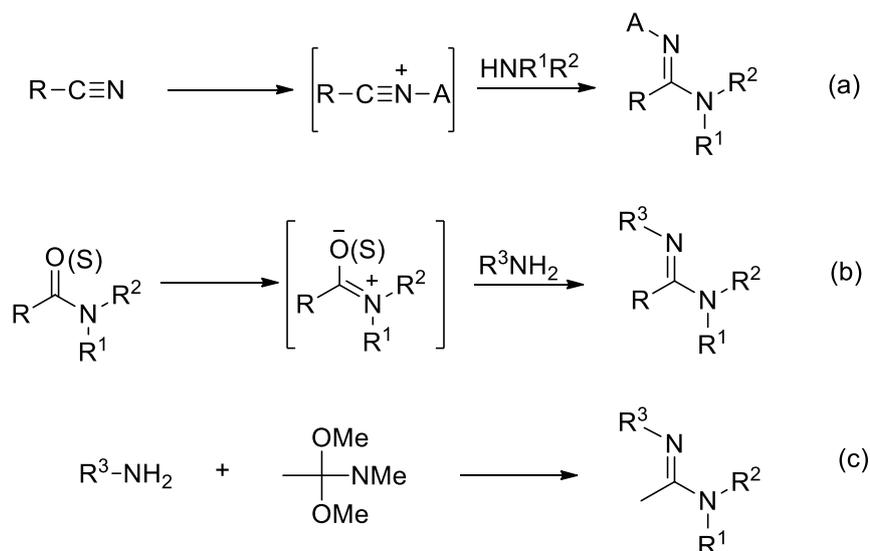
2.4. Transformation of cyano groups into amidines.

With an efficient synthesis of nitriles, some of them (*i.e.* **52t**) bearing an all-carbon stereocenter, the next step was the conversion of the CN functional group into an amidine as proposed in the retrosynthetic pathway in Figure 5, with the cyclization of nitrile **36** into amidine **37**.

Literature reveals that the nitriles and (thio) amides are the two most common building blocks for amidines synthesis.¹¹⁶ However, nitriles are used for the synthesis of amidines by making them electron-deficient (to activate the cyano group), with protic or Lewis acids or as nitrilium salts (Scheme 11, eq. a). Amidines can be obtained by using (thio) amides (Scheme 11, eq. b). Similarly, for the synthesis of both aryl and alkyl acetamidines, reaction of primary amine with modified ortho ester, the use of *N,N*-dimethylacetamide dimethyl acetal have been reported by Raczynska *et al.* (scheme 11, eq. c).¹¹⁷

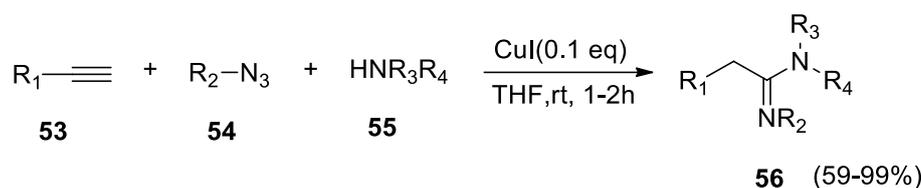
¹¹⁶ a) Dunn, P. J. *Comprehensive Organic Functional Group Transformations II*; Elsevier, Oxford, **2005**, 5, 655; b) Ostrowska, K.; Kolasa, A., *Science of Synthesis*; Georg Thieme Verlag, Germany. **2005**, 22, 379.

¹¹⁷ Oszczapowicz, J.; Raczynska, E. *J. Chem. Soc. Perkin Trans. 2* **1984**, 1643.



Scheme 11. General Methods for the Synthesis of Amidines.

Chang *et al.*¹¹⁸ developed a Cu-Catalyzed one-pot synthesis of *N*-Sulfonylamidines. The treatment of *p*-toluenesulfonyl azide and phenylacetylene with diisopropylamine in the presence of copper catalysts produced *N*-Sulfonylamidines in excellent yields (Scheme 12).



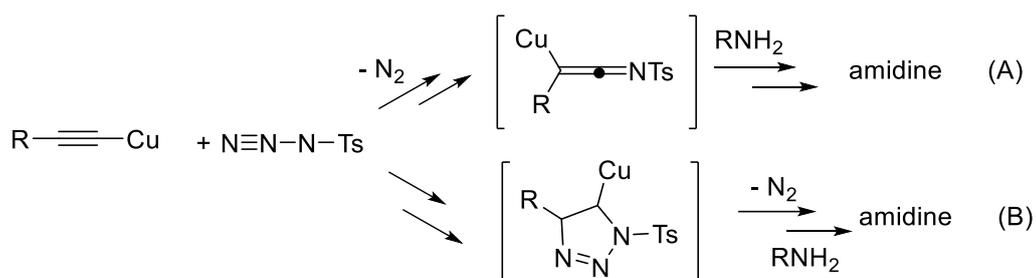
Scheme 12.

For this reaction two possible pathways were suggested. In pathway A, the reaction may go through a ketenimine intermediate generated by a nucleophilic attack of a Cu-acetylide to the azide nitrogen, followed by a rearrangement. The last step in pathway A relies on the amination on the Cu-N bond of the resulting ketenimine adduct and subsequent tautomerization.¹¹⁹ However, in the second possible pathway B: a triazole intermediate may be formed by a [3+2] cycloaddition between the azide and the Cu-acetylide, as in click chemistry, followed by an attack of the nitrogen atom and loss of N₂ (Scheme 13).¹²⁰

¹¹⁸ Bae, I.; Han, H.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 2038.

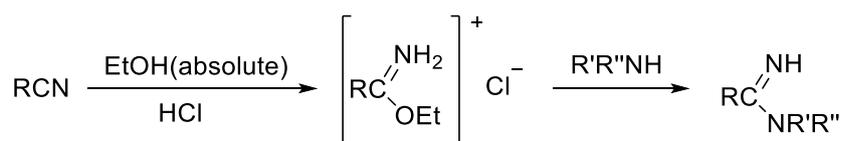
¹¹⁹ Sung, K.; Wu, S.-H.; Wu, R.-R.; Sun, S.-Y. *J. Org. Chem.* **2002**, *67*, 4298.

¹²⁰ Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210.



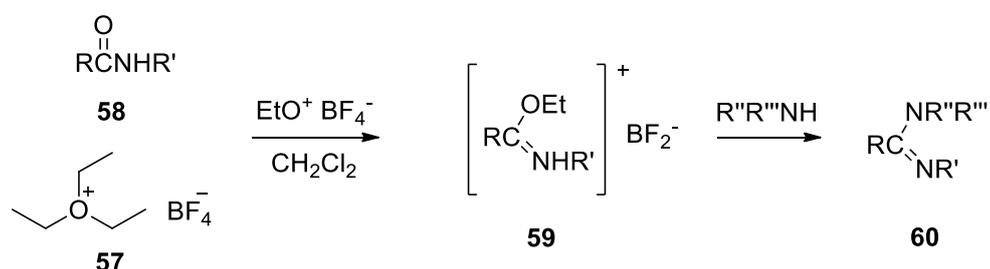
Scheme 13.

Until the end of last century, the Pinner method was one of the most commonly used procedure for the synthesis of amidines.¹²¹ This method involves the reaction of a nitrile with an anhydrous alcohol in the presence of an acid catalyst, commonly hydrogen chloride, through the *in-situ* preparation of an imidate salt, which is then reacted with ammonia or an amine to produce the amidine (Scheme 14).



Scheme 14.

Kalish *et al.*¹²² also converted imidates into amidines. Treatment of triethyloxonium tetrafluoroborate¹²³ with an amide **58** in dry CH_2Cl_2 resulted in the formation of imidate salt **59**, which on treatment with an amine produced the amidine **60** (Scheme 15).



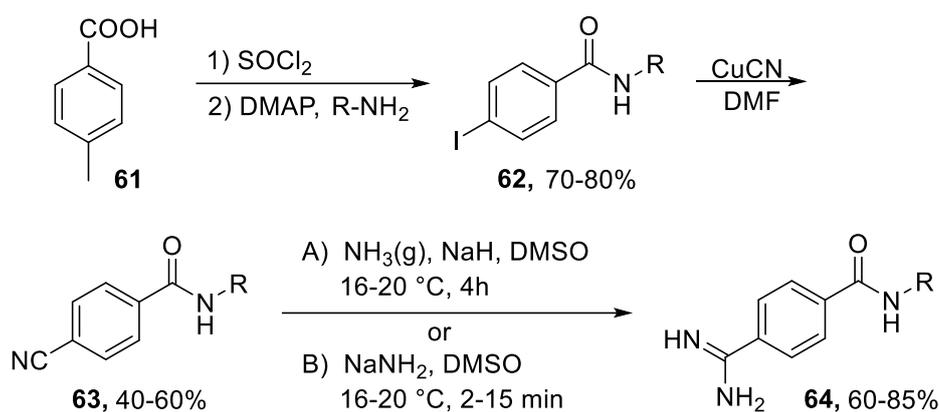
Scheme 15.

¹²¹ Pinner, A.; Klein, F. *Eur. J. Inorg. Chem.* **1877**, 10, 1889.

¹²² Weintraub, L.; Oles, S. R.; Kalish, N. *J. Org. Chem.* **1968**, 33, 1679.

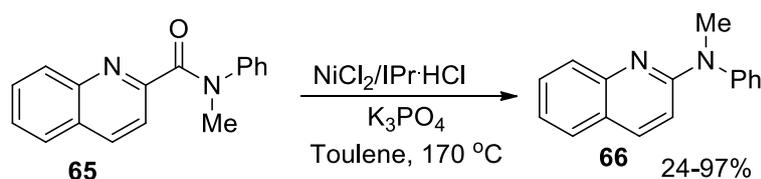
¹²³ For a description of current procedures for preparation and storage of triethyloxonium fluoroborate, see: Meerwein, H. *Org. Syn.* **1968**, 46, 113.

Recently, Begum *et al.*¹²⁴ reported an amidine formation by two methods, *i.e.* the *in situ* generation of dry NH₃(g) with sodium hydride in DMSO (method A) and *ex-situ* generation of sodium amide in DMSO (method B, Scheme 16). Both of these methods provided products in good yields at room temperature. The synthesis of compound **62** took place in two steps. In a first step **61** was treated with thionyl chloride, followed by the addition in second step, of DMAP/RNH₂. **62** then was treated with CuCN as a nitrile source in DMF to afford **63**. Finally, **64** was obtained by addition of ammonia to **63**.



Scheme 16.

Rueping *et al.*¹²⁵ developed the synthesis of amidines from amides by using a nickel catalyzed decarbonylative amination via CO extrusion and intramolecular recombination. They obtained the amidine **66**, by treatment of **65** with K₃PO₄ in presence of NiCl₂/IPr-HCl in toluene (Scheme 17).



Scheme 17.

3. Synthesis of amidines. Efforts towards the cyclization of amides onto nitriles.

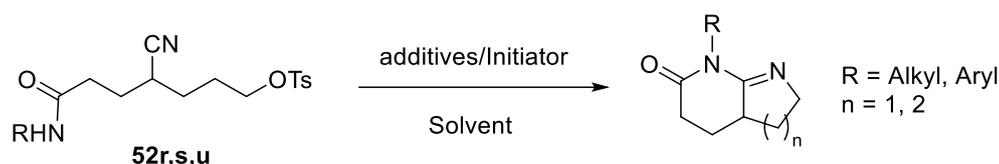
Based on literature about cyclization of amides, we turned our attention towards the cyclization of our nitrile products (Scheme 10). Our efforts were directed towards the cyclization of these

¹²⁴ Sahay, I. I.; Ghalsasi, P. S.; Singh, M.; Begum, R. *Synth. Commun.*, **2017**, *47*, 1400.

¹²⁵ Liu, X.; Yue, H.; Jia, J.; Guo, L.; Rueping, M. *Chem. A Eur. J.* **2017**, *23*, 11771.

amides as they would offer a rapid entry toward the bicyclic system present in leuconoxine, which could be functionalized further through simple manipulations to target the natural product. We thus envisaged that amides **52r-u** in hand could cyclize, in basic or acidic conditions, into the nitrile function and that the resulting imidate could displace the tosylate to form a bicyclic system. However, this model approach failed to afford the desired results, whatever the conditions. Our efforts to perform these experiments by varying initiators/additives and solvents at different temperatures are summarized in the following table (Table 1).

Table 1. Screening cyclization of amides under various conditions.

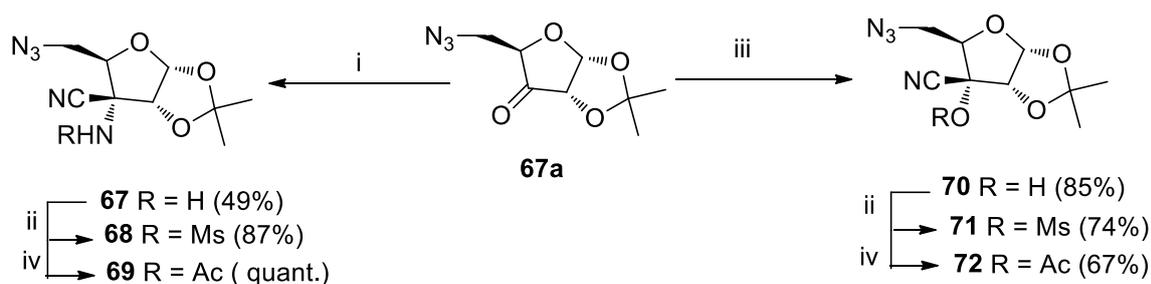


| Entry | additives/Initiator | Solvent | T(°C) | Time (h) | Yield (%) |
|-------|---|--------------------|-------|----------|-----------|
| 1 | NaH (1.5 eq) | THF (0.2M) | rt | 12-24 | N/A |
| 2 | NaH (1.5 eq) | THF (0.2M) | 40 | 12-24 | N/A |
| 3 | NaH (1.5 eq) | DMF (0.2M) | rt | 12-24 | N/A |
| 4 | NaH (1.5 eq) | DMF (0.2M) | 40 | 24-48 | N/A |
| 5 | NaH (1.5 eq) | DMF (0.2M) | 60 | 12-24 | N/A |
| 6 | LiHMDS (2 eq) | THF (0.2M) | rt | 24-48 | N/A |
| 7 | LiHMDS (2 eq) | THF (0.2M) | 50 | 24-48 | N/A |
| 8 | <i>t</i> BuOK (2 eq) | TBA (0.2M) | 90 | 24-48 | N/A |
| 9 | K ₂ CO ₃ (2 eq) | DMF (0.2M) | 120 | 24-48 | N/A |
| 10 | Cu(OAc).H ₂ O(0.1eq) | DMSO (0.1M) | 90 | 24-48 | N/A |
| 11 | K ₂ CO ₃ (1.3 eq) TMSOTf (3 eq), Et ₃ N (3 eq) | Benzene (0.1M) | rt | 24-48 | N/A |
| 12 | AlCl ₃ (1.5 eq) | DCM (0.5M) | rt | 24-48 | N/A |
| 13 | <i>p</i> -TSA (1.5 eq) | Toluene (0.1M) | 120 | 24-48 | N/A |
| 14 | K ₂ CO ₃ (2.8 eq), LiCl ₂ (2 eq) | DMA (0.1M) | 110 | 16 | N/A |
| 15 | IBX (4 eq) | THF/DMSO (10/1) | 90 | 16 | N/A |

Considering the failure of the above strategy, we then directed our efforts towards the preparation of azides and their cyclization.

3.1. Synthesis of amidines from azides

It was reasoned that azides might be good precursors to form amidines, through the cyclization of the N₃ group onto the nitrile using for instance a radical approach or the venerable Staudinger reaction. Ducatel and co-workers published the synthesis of amidines by treatment of various α -substituted γ -azido nitriles with either Ph₃P or Me₃P in THF.¹²⁶ The reaction of **75** with KCN and NaHCO₃ in biphasic H₂O–Et₂O afforded the ribo-cyanohydrine **69** in excellent yield, which on subsequent mesylation or acetylation furnished the corresponding derivatives **70** and **72** (Scheme 18).



Scheme 18. Reagents: (i) a. Ti(Oi-Pr)₄, MeOH-NH₃ 7 N. b. TMSCN, (ii) MsCl, DMAP, pyridine, (iii) NaHCO₃, KCN, H₂O-Et₂O, (iv) Ac₂O, pyridine.

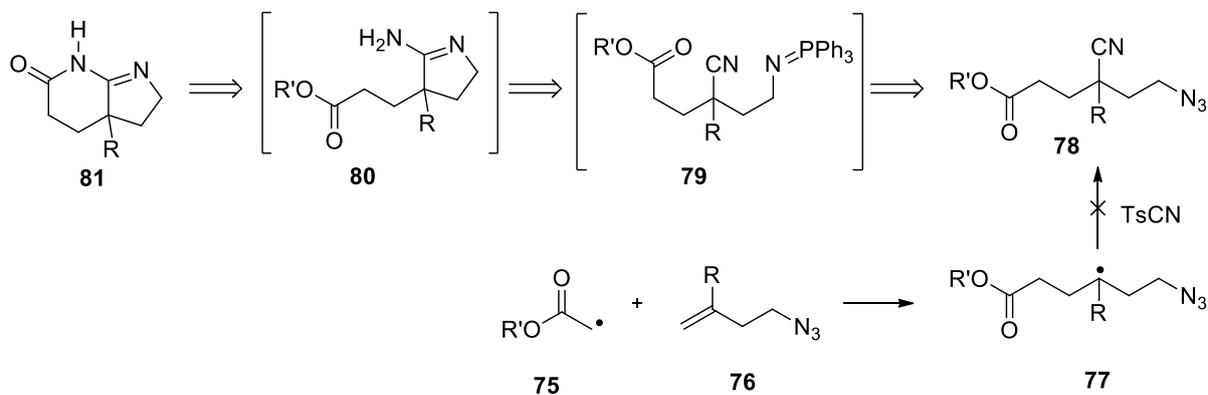
The reaction of **67a** with Me₃P–THF using classical Staudinger conditions afforded the heterocyclic iminopyrrolidine **73** and iminophosphorane intermediate **74** with traces of (Me)₃P=O (Figure 7). Longer treatment with NH₃–MeOH allowed quantitative conversion of **74** into the final compound **73** (Figure 7).



Figure 7.

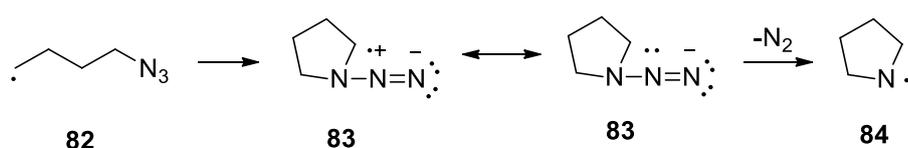
¹²⁶ Postel, D., Ducatel, H., Nguyen Van Nhien, A., Pilard, S. *Synlett*, **2006**, 12, 1875.

Following these premises, it was thus envisaged that a γ -azido nitrile such as **78**, when in presence of a phosphine, would form the iminophosphorane **79** that could attack the cyano group to generate the primary amidine **80**, then triggering a further cyclization onto an ester group to form the desired bicyclic amidinone **81** (Scheme 19).



Scheme 19.

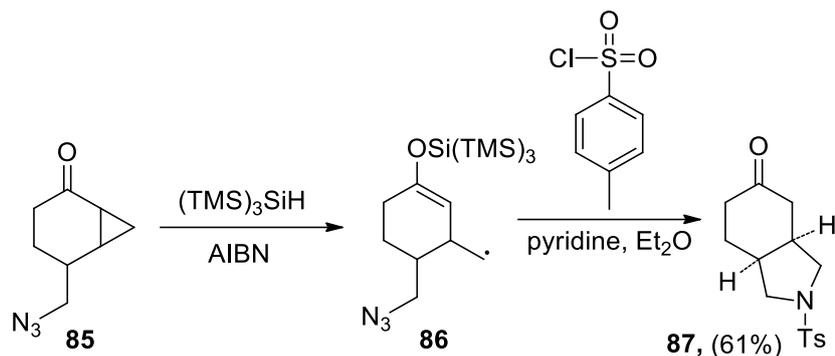
However, according to literature precedent, the synthesis of a cyano-azide such as **78** cannot be attained through a direct coupling between a radical precursor **75** and an azido-olefin **76**, due to the putative reaction of free-radical species with the N_3 functional group. Pioneering work by Kim and co-workers¹²⁷ effectively showed that an alkyl radical such as **82** was able to trigger an intramolecular addition onto an azido group to generate an aminyl radical **84** by loss of nitrogen, affording an access to nitrogen heterocycles (Scheme 20).



Scheme 20. Radical cyclization of azides.

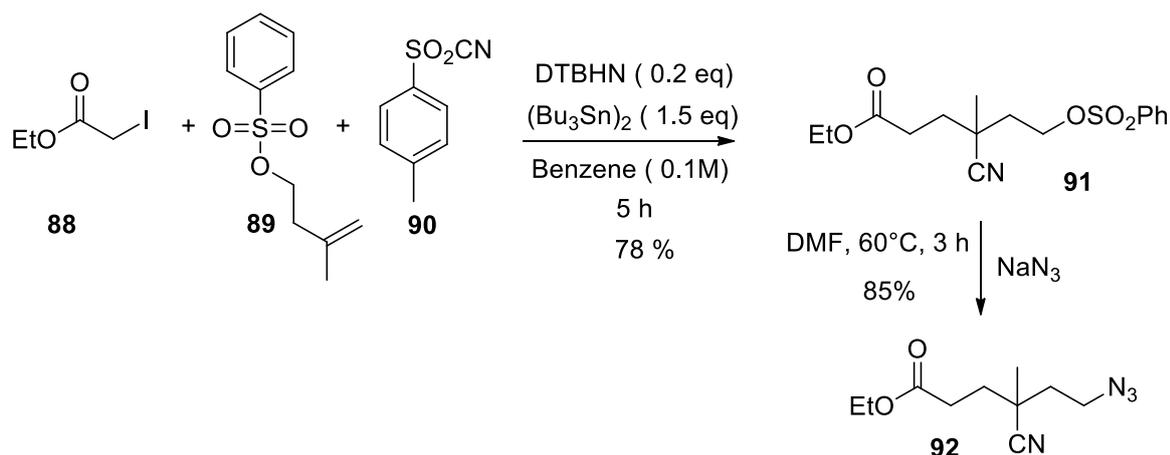
Application of this strategy was later reported to form bicyclic pyrrolidines (Scheme 21). For instance, the treatment of **85** in the presence of $(\text{TMS})_3\text{SiH}/\text{AIBN}$ in refluxing benzene for 1h generated the carbon-centered radical via fragmentation of the cyclopropyl ring **86**, which underwent an intramolecular addition onto the azido group, to afford **87** in 61% yield after tosylation (Scheme 21).

¹²⁷ Kim, S.; Joe, G. H.; Do, J. Y. *J. Am. Chem. Soc.* **1994**, *116*, 5521.



Scheme 21. Free-radical cyclization onto an azide

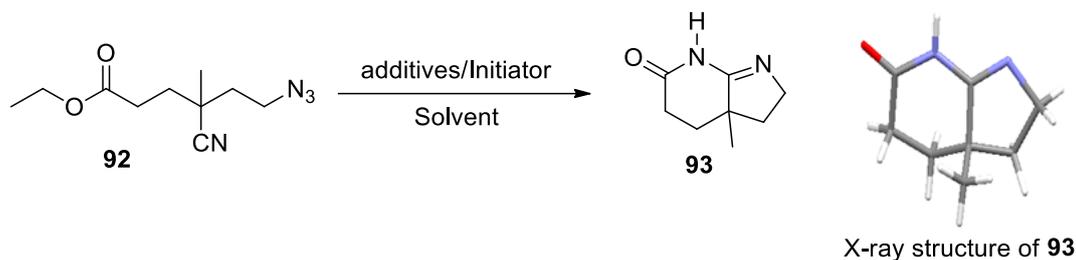
In the light of these examples, we turned our attention to the preparation of γ -azido nitrile **92** in two steps. First, the commercially available ethyl iodoacetate **88** was reacted with **89** and **90** to access acyclic nitrile system **91**. This compound was then transformed into azide **92** in a second step (Scheme 22).



Scheme 22. Carbocyanation of iodoacetates and azidation of nitriles.

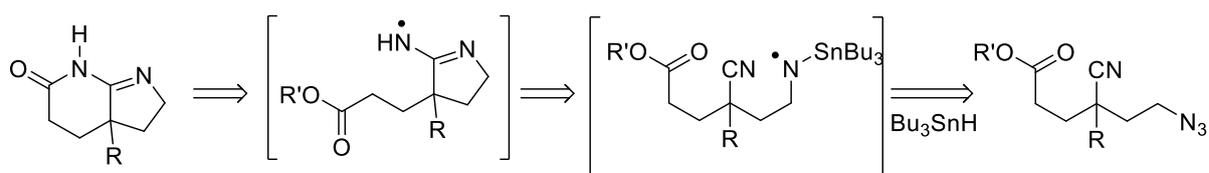
With the azide **92** in hand, we continued our efforts to obtain a bicyclic molecule. This model turned to be effective to obtain amidinone **93** with 41% yield by using PPh_3 in THF/H₂O (4:1) (entry 7 Table 2), the structure of which was confirmed by X-ray diffraction studies. However, a low 8% yield of **93** was obtained when only THF was used as a solvent with PPh_3 (entry 5 table 2). However, by using PPh_3 (resin) furnished 92% crude mixture of **93** which on filtration and purification did not provide the desired amidinone in pure form. Conditions were varied to increase the yields but unfortunately, the 41% yield were not improved.

Table 2. Cyclization of azides.



| Entry | Additives/Initiator | Solvent | T(°C) | Time (H) | Product Yield (%) |
|-------|--|----------------------------|-------|----------|-------------------|
| 1 | AIBN (0.1 equiv) Bu ₃ SnH (1.1 eq) | Benzene (0.1M) | 90 | 6-24 | N/A |
| 2 | AIBN (0.1 equiv) TTMSH (1.1 eq) | Benzene (0.1M) | 90 | 6-24 | N/A |
| 3 | Pd/C (0.1 eq) (hydrogenation) | EtOAc (0.2M) | R.T | 12-24 | N/A |
| 4 | PPh ₃ (1.2 eq) | THF/H ₂ O (4:1) | R.T | 24 | N/A |
| 5 | PPh ₃ (1.2 eq) | THF (0.1M) | 60 | 60 | 8 |
| 6 | PPh ₃ (resin) (1.2 eq) | THF/H ₂ O (4:1) | 60 | 60 | 92 crude |
| 7 | PPh ₃ (1.2 eq) | THF/H ₂ O (4:1) | 60 | 72 | 41 |

We also envisaged using the azide as a source of aminyl radical that could react with the cyano group to generate the bicyclic amidinone (Scheme 23).

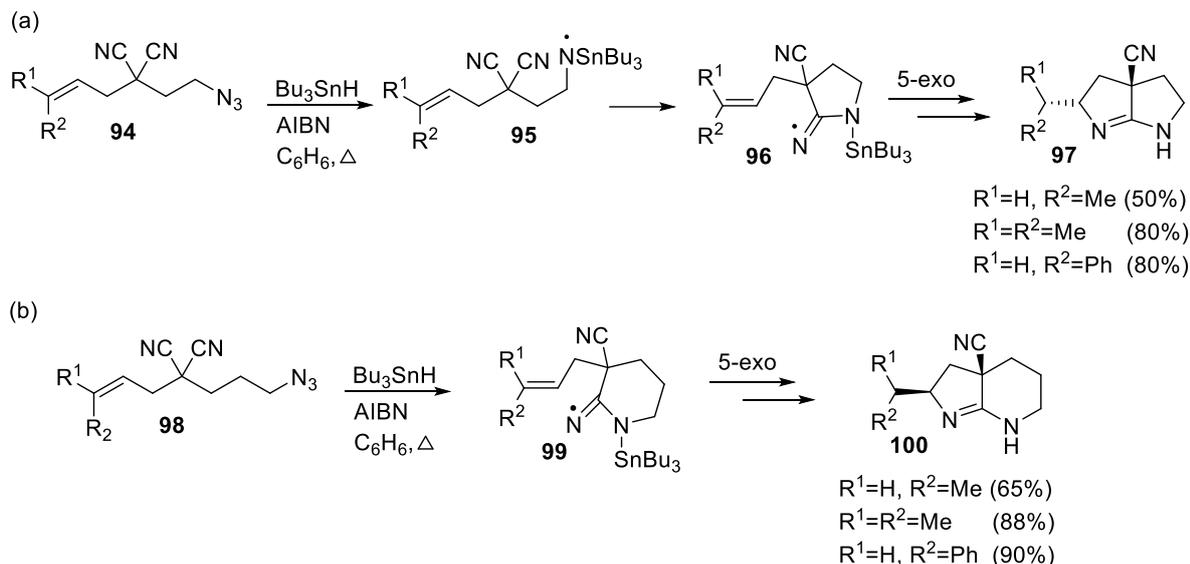


Scheme 23.

Spagnolo *et al.*¹²⁸ have indeed shown that the reaction of a tributyltin radical onto a cyano azide was able to generate efficiently the aminyl radical, after loss of N₂. The latter could then undergo an intramolecular addition onto an electrophilic cyano group in both 5-*exo* and 6-*exo* fashion, forming an amidinyl radical intermediate. They showed that the treatment of α -(2-azidoethyl) and α -(3-azidopropyl)-substituted malononitriles bearing an additional homoallylic substituent

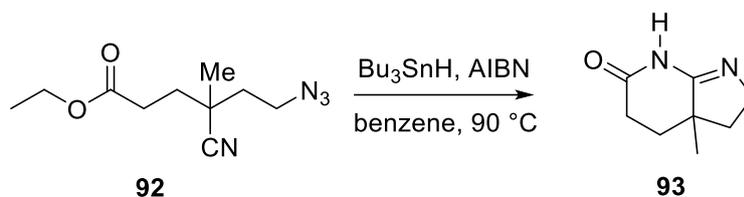
¹²⁸ Minozzi, M.; Nanni, D.; Spagnolo, P. *Chem. Eur. J.* **2009**, *15*, 7830.

produced good yields of fused hexahydropyrrolopyrroles and hexahydropyrrolopyridines using $\text{Bu}_3\text{SnH/AIBN}$ (Scheme 24, eq. a,b).



Scheme 24.

Hence, in the light of the above literature, we projected to react our azidonitrile **92** with Bu_3SnH and AIBN in benzene. However, extensive experimentations, varying the conditions only led to complex mixtures, where the final product **93** could not be extracted (Scheme 25, table 2). This approach was thus abandoned.

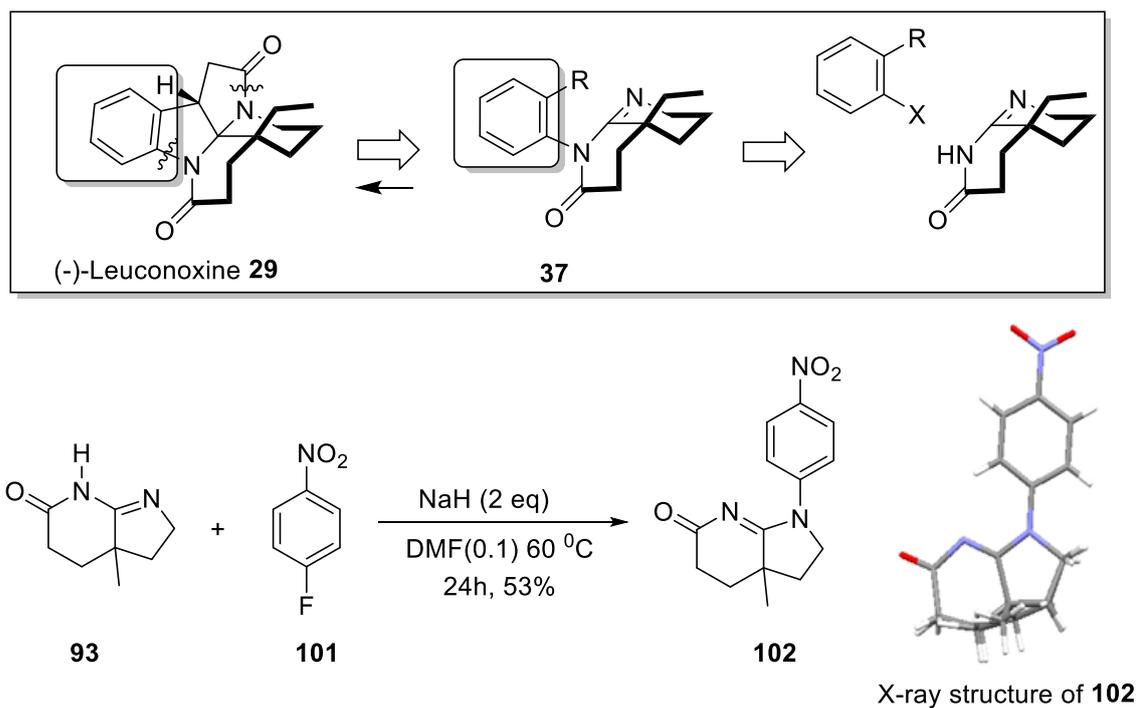


Scheme 25.

3.2. Functionalization of amidinones

Functionalization of the bicyclic amidinone **93** was then our next goal. Leuconoxine **29** containing an aromatic ring on one of the aminal nitrogen, our goal was to incorporate a simple arene through the coupling between our amidinone and a suitable aromatic partner (Scheme 25). This could be achieved through a standard C-N aryl coupling or following a $\text{S}_{\text{N}}\text{Ar}$ type reaction. The first approach leading to poor results, the second strategy was finally adopted.

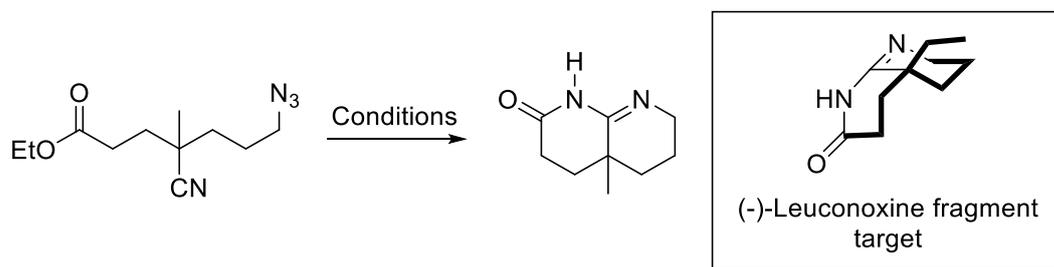
Hence, with the compound **93** in hand, we were able to install a *p*-nitrophenyl moiety on the bicyclic system through a nucleophilic aromatic substitution, leading, in moderate yield, to **102**, the structure of which was confirmed by X-ray structure diffraction studies (Scheme 25). This result, although noteworthy, is somewhat disappointing as it does not provide the required regioisomer. All our efforts to reverse the selectivity and get access to the Leuconoxine core were finally unsuccessful.



Scheme 25. Installation of aromatic ring on bicyclic molecule

4. Conclusion

In this chapter, we described an efficient free radical three-component carbocyanation of electron-rich olefins using *p*-tosyl cyanide as a cyanide source. The scope and limitations of the process were established by varying the nature of the alkene and the radical precursor. The process is compatible with many functional groups including ketones, esters, double bonds, amides, nitriles, phosphonates and sulfonates. In this thesis, we were particularly involved in expanding the scope using α -iodoamides as radical precursors as well as disubstituted olefins for a further use in total synthesis of leuconoxine alkaloid. The aim to obtain nitriles through carbocyanation was thus utilized to access the bicyclic core of Leuconoxine. While working on a model, we synthesized 6,5-bicyclic amidinone **93**. When the same strategy was applied to reach the 6,6-bicyclic system present in leuconoxine, under the same conditions, the strategy met with failure for currently unknown reasons (Scheme 26). This work could unfortunately not be continued because of a lack of time but efforts are pursued in our laboratory to access Leuconoxine natural product.



Scheme 26. Extension of the methodology to the 6,6-bicyclic system

CHAPTER IV
VISIBLE-LIGHT-MEDIATED ADDITION OF PHENACYL
BROMIDES ONTO CYCLOPROPENES

1. Introduction

1.1. Cyclopropenes – Reactivity and synthesis

Cyclopropenes are considered as important building blocks in organic synthetic chemistry.¹²⁹ They behave as both electrophilic and nucleophilic species.¹³⁰ For instance, they undergo ring-opening processes in the presence of gold(I) catalysts, to produce gold-stabilized allylic carbocations or vinyl gold carbenes.^{131,132} The highly acidic protons of olefins, due to ring strain, permits their easy deprotonation and further functionalization with electrophiles, while addition of organometallic species, including hydrides, Grignard reagents, organo-cuprates, zinc and indium reagents reveals their electrophilicity.

Cyclopropene is considered the most strained single ring organic molecule.^{133,134} In spite of that, its thermal stability is high as it does not decompose until temperatures approaching 200°C. The thermal stability of strained ring hydrocarbons, remained under intensive investigation during the period of 1930 to 1980. In that period the pyrolysis of cyclopropane, cyclobutane, cyclobutene and many of their derivatives were studied by physical organic chemists.^{135,136} The conclusions of these studies were that cyclopropane and cyclobutane rearrange and decompose *via* diradical intermediates (*via* C–C bond cleavage) and cyclobutene isomerizes *via* a concerted electrocyclic ring opening process (Scheme 1).

¹²⁹ Hashmi, A. S. K.; Nass, A. R.; Bats, J. W.; Bolte, M. *Angew. Chem. Int. Ed.* **1999**, *38*, 3370.

¹³⁰ a) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117; b) Zhu, Z.-B.; Wei, Y.; Shi, M. *Chem. Soc. Rev.* **2011**, *40*, 5534; c) Archambeau, A.; Miege, F.; Meyer, C.; Cossy, J. *Acc. Chem. Res.* **2015**, *48*, 1021; d) Vicente, R. *Synthesis* **2016**, *48*, 2343.

¹³¹ Hashmi A. S. K. *Angew. Chem. Int. Ed.* **2008**, *47*, 6754.

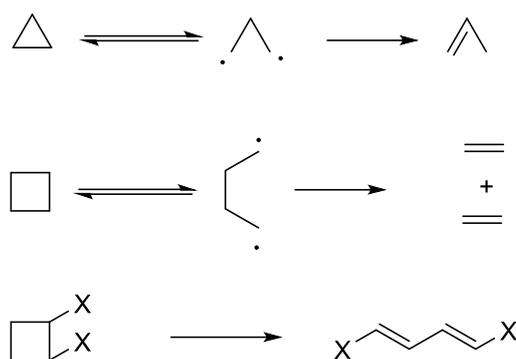
¹³² Seidel, G.; Mynott, R.; Fürstner, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 2510.

¹³³ Benson, S. W.; Cruickshank, F. R.; Golden, D. M.; Haugen, G. R.; O'Neal, H. E.; Rodgers, A. S.; Shaw, R.; Walsh, R. *Chem. Rev.* **1969**, *69*, 279.

¹³⁴ Benson, S. W., *Thermochemical Kinetics*, Wiley-Interscience, New, York, **1976**.

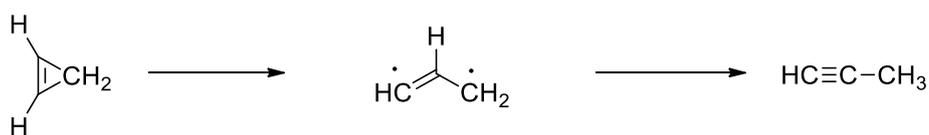
¹³⁵ Frey, H. M.; Walsh, R. *Chem. Rev.* **1969**, *69*, 103.

¹³⁶ Gajewski, J. J. *Hydrocarbon Thermal Isomerizations*, Academic Press, New York, **1981**.



Scheme 1.

Srinivasan¹³⁷ studied the kinetics of the pyrolysis of cyclopropene and 1-methylcyclopropene between 470–500°K, using low pressures of cyclopropene (1–3 Torr) under 50–60 Torr of CO₂. He found a first order kinetic with the following Arrhenius parameters: Cyclopropene: $\log (A/s^{-1}) = 12.13$; $E_a = 147 \pm 5 \text{ kJ mol}^{-1}$, 1-methylcyclopropene: $\log (A/s^{-1}) = 11.4$; $E_a = 145 \pm 5 \text{ kJ mol}^{-1}$. Whereas cyclopropene produced propyne as the sole product (100%) (Scheme 2), 1-methylcyclopropene gave a mixture of products consisting of 2-butyne (92%), 1,3-butadiene (5.5%) and 1,2-butadiene (2.5%). Based on these observations, Srinivasan proposed a mechanism involving a simple ring-opening, followed by a 1,2 H-shift from the diradical species (Scheme 2). While, in methyl cyclopropene, an analogous diradical affords all three products by parallel, but a distinct H-shift process.



Scheme 2.

Strained carbocycles can be involved in reactions that avoid the breaking of the three-membered ring to give highly substituted cyclopropenes, cyclopropanes, or alkylidene cyclopropanes or in transformations accompanied by ring cleavage.¹³⁸

Carbenoids **A** may be formed through reaction of cyclopropenes with metal complexes. Their resonance form corresponds to the metal-stabilized allylic carbocations **A'**.^{139,140} Ring opening

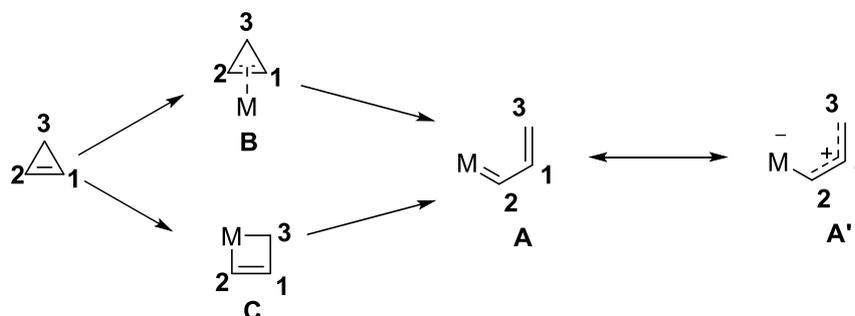
¹³⁷ Srinivasan, R. *J. Am. Chem. Soc.* **1969**, *91*, 6250.

¹³⁸ a) Binger, P.; Buch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77; b) Fox, J. M.; Yan, N. *Curr. Org. Chem.* **2005**, *9*, 719.

¹³⁹ Seidel, G.; Mynott, R.; Fu rstner, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 2510.

¹⁴⁰ Benitez, D.; Shapiro, N. D.; Tkatchouk, E.; Wang, Y.; Goddard, W. A.; Toste, F. D. A. *Nat. Chem.* **2009**, *1*, 482.

of cyclopropenes also relies on the oxidative addition of a transition metal into a σ -bond to produce metallacyclobutenes **C**. It is worth noting that metallacyclobutenes **C** can also generate carbenoids **A** by cycloreversion (Scheme 3).

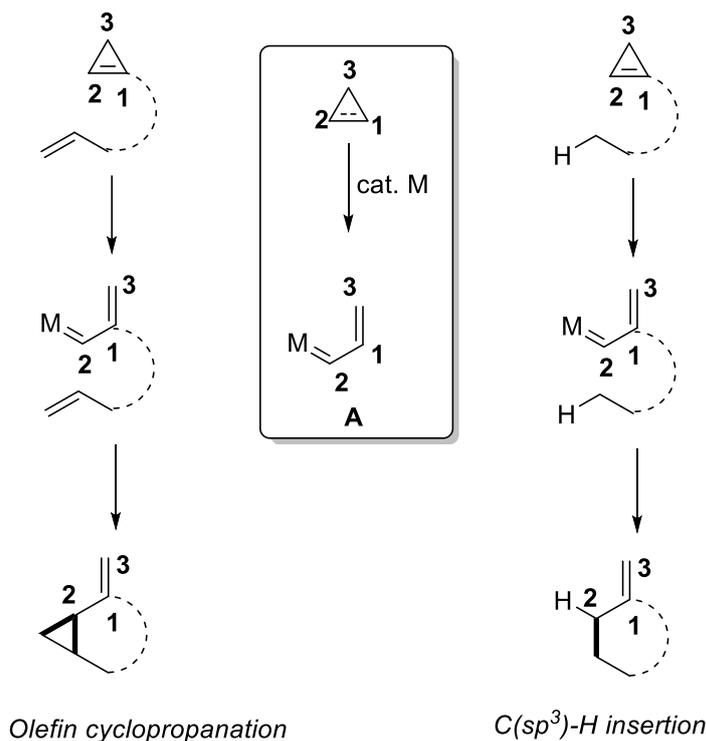


Scheme 3.

Cyclopropenes with a nucleophilic group at C3 have been extensively used as substrates in transition metal-catalyzed reactions, because the vinylcarbenoids **A** (intermediate) can be captured intramolecularly by a nucleophile. Recently, intermolecular nucleophilic addition to 3,3-disubstituted cyclopropenes proceeding with ring-opening with gold(I) complexes as catalysts have been reported.^{141,142} The reactivity of metal carbenoids **A** in cyclopropanation and C(sp³)-H insertion reactions are undoubtedly two of the most representative reactions triggered by metal carbenoids (Scheme 4).

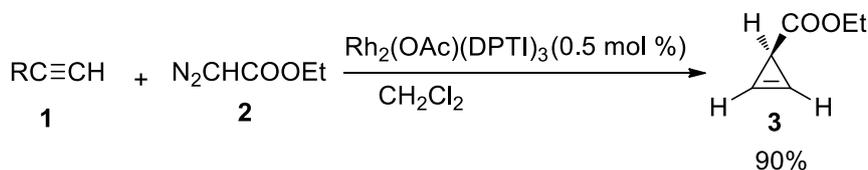
¹⁴¹ Bauer, J. T.; Hadfield, M. S.; Lee, A.-L. *Chem. Comm.* **2008**, 6405.

¹⁴² a) Hadfield, M. S.; Bauer, J. T.; Glen, P. E.; Lee, A.-L. *Org. Biomol. Chem.* **2010**, *8*, 4090; b) Mudd, R. J.; Young, P. C.; Jordan-Hore, J. A.; Rosair, G. M.; Lee, A.-L. *J. Org. Chem.* **2012**, *77*, 7633.



Scheme 4.

Cyclopropenes can easily be prepared by various methods and are available in enantiopure form through metal-catalyzed cyclopropanation of the corresponding alkynes.¹⁴³ The most efficient way to access cyclopropenyl esters, is thus the addition of alkyl diazoacetates to an excess of the appropriate alkyne in the presence of a catalytic amount of rhodium acetate.¹⁴⁴ Corey *et al.*^{15c} developed the addition of **2** to **1** in presence of 0.5 mol % of Rh₂(OAc)(DPTI)₃ as catalyst to obtain desired product **3** (Scheme 5). They found the catalyst so efficient in terms of selectivity, yield and scope of reaction.

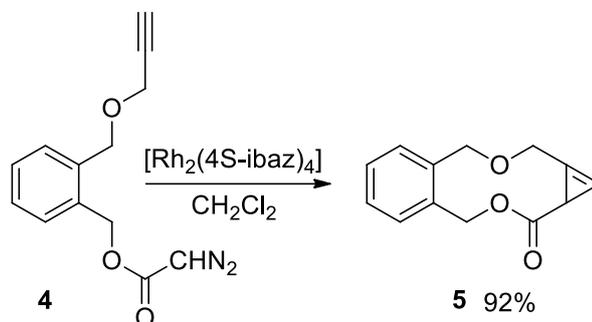


Scheme 5.

¹⁴³ a) Protopopova, M. N.; Doyle, M. P.; Müller, P.; Ene, D. *J. Am. Chem. Soc.* **1992**, *114*, 2755; b) Doyle, M. P.; Ene, D. G.; Peterson, C.S.; Lynch, V. *Angew. Chem., Int. Ed.* **1999**, *38*, 700; c) Lou, Y.; Horikawa, M.; Kloster, R. A.; Hawryluk, N. A.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 8916.

¹⁴⁴ Petiniot, N.; Anciaux, A. J.; Noels, A. F.; Hubert, A. J.; Teyssié, P. *Tetrahedron Lett.* **1978**, *14*, 1239.

Later on, Lynch *et al.*^{15b} reported that macrocyclic cyclopropanation of **4** in the presence of $[\text{Rh}_2(4\text{-}(S)\text{-ibaz})_4]$ as a catalyst in CH_2Cl_2 as a solvent. The catalytic diazo decomposition of **4** in CH_2Cl_2 resulted in the formation of **5** (Scheme 6).



Scheme 6.

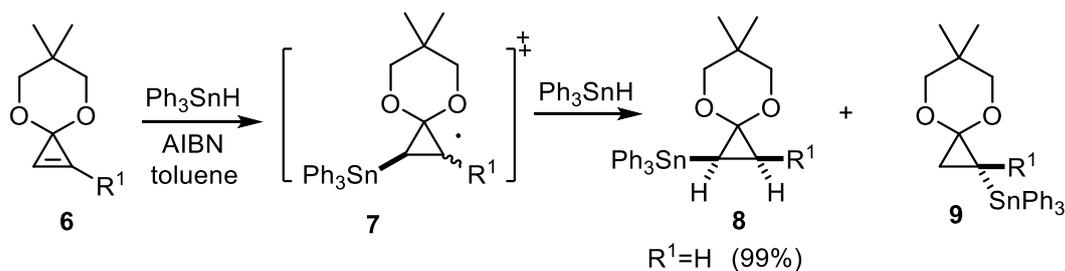
1.2. Reactivity of cyclopropenes under radical conditions

While cyclopropenes have been the subject of much work concerning their reactivity towards ionic and organometallic species, such is not the case with free radicals.¹⁴⁵

The first cyclopropene radical hydrostannation was reported by Nakamura *et al* in 1994.¹⁴⁶ They have shown the radical accepting ability of cyclopropene, where tin radical adds efficiently to the C=C bond of cyclopropene **6** to produce the stannyl alkyl radical **7**, which then reacts irreversibly with tin hydride to give the hydrostannation product **8**, along with the tin radical which is then responsible for chain propagation (Scheme 7).

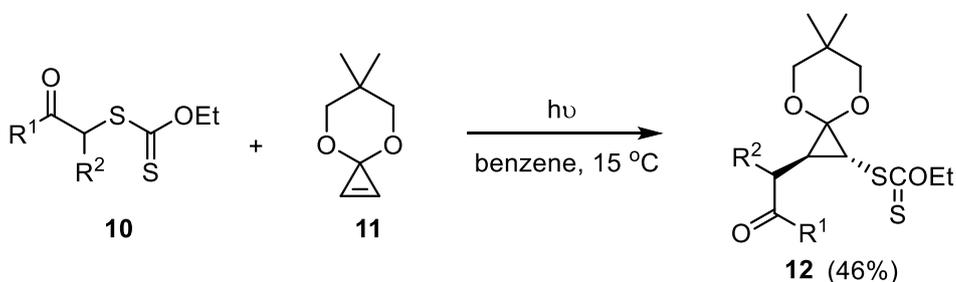
¹⁴⁵ a) Ferjancic, Z.; Cekovic, Z.; Saicic, R. N. *Tetrahedron Lett.* **2000**, *41*, 2979; b) Legrand, N.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **2000**, *41*, 9815. c) Ueda, M.; Doi, N.; Miyagawa, H.; Sugita, S.; Takeda, N.; Shinada, T.; Miyata, O. *Chem. Commun.* **2015**, *51*, 4204. d) Doi, N.; Takeda, N.; Miyata, O.; Ueda, M. *J. Org. Chem.* **2016**, *81*, 7855.

¹⁴⁶ Yamago, S.; Nakamura, E. *Chem. Lett.* **1994**, *23*, 1889.



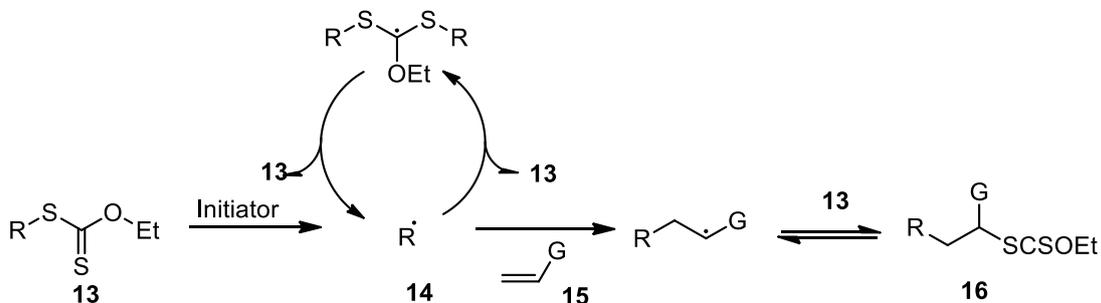
Scheme 7. Hydrostannation of cyclopropenes

Later on, xanthate atom transfer processes were described by Saicic and co-workers,^{18,147} who reported the synthesis of cyclopropanone acetal **12** by irradiation of **11** in the presence of **10** using a 250 W Xenofot sunlamp at 15°C in benzene (Scheme 8).



Scheme 8. Free radical addition to strained cyclopropene.

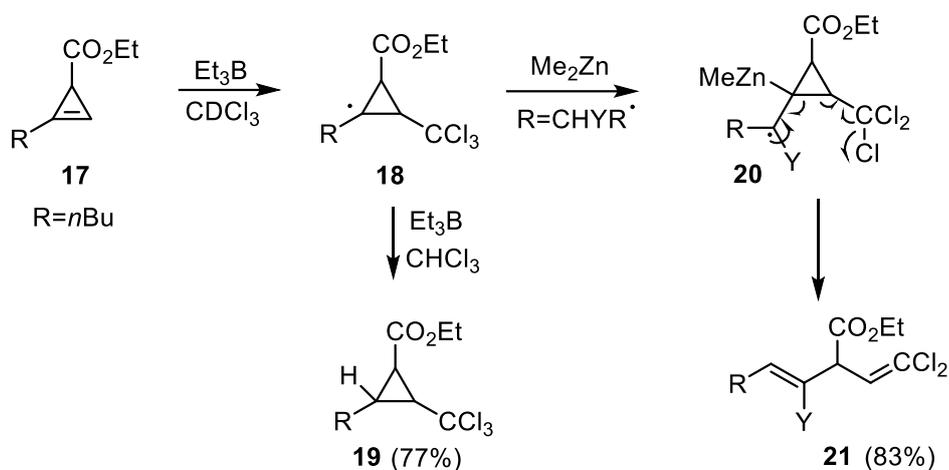
Zard and his team also described a radical xanthate transfer process slightly different from the work of Saicic by using lauroyl peroxide as an initiator.^{17b} They proposed that the reaction proceeds through radical **14** generated from **13**, the intermolecular addition of which to non-activated olefin **15** producing the final product **16** (Scheme 9).



Scheme 9. Radical xanthate transfer process

¹⁴⁷ Ferjancic, Z.; Cekovic, Z.; Saicic, R. N. *Tetrahedron Lett.* **2000**, *41*, 2979.

Similarly, Miyata and Ueda and co-workers respectively^{17c,d} came up with an idea of generating trichloromethyl radical from chloroform, which adds onto the cyclopropene **17**, and generates cyclopropyl radical **18**. The latter, then in presence of triethyl borane as an initiator, abstracts hydrogen from chloroform to produce the trichloromethylpropane carboxylate **19**. When radical initiator was changed to dimethyl zinc, resulted formation of cyclopropylzinc **20**, which then under goes ring opening and elimination produce unsaturated esters **21** (Scheme 10).^{17c,d}



Scheme 10. Addition of trichloromethyl radicals to cyclopropenes

2. Objectives and overview.

These few examples highlight the recent development of free-radical additions to cyclopropenes and show that such additions may represent a nice entry to access compounds bearing all-carbon quaternary stereocenters. Methods developed so far to answer this demand have mostly focused on the synthesis of cyclic systems bearing such all-carbon quaternary stereocenters, but further developments are needed to get access to a larger variety of compounds including acyclic systems. We propose, in this chapter, a new approach relying on a strategy using a carbonyl functionalization of enantiopure cyclopropenes, followed by the ring-opening of the resulting cyclopropanes.¹⁴⁸ Addition of two carbon fragments across the double bond of a dissymmetric cyclopropane should allow the formation of two new C-C bonds and the installation, in a stereocontrolled manner, of the all-carbon quaternary center.

¹⁴⁸ Rubin, M.; Rubina, M.; Gevorgyan, V. *Synthesis*, **2006**, 1221.

The tetrasubstituted cyclopropane could then be opened under basic conditions, relying on the suitable localization of two activating electron-withdrawing groups (EWG¹ and EWG²) at C1 and C2 (Figure 1). Control of the diastereoselectivity during the carbo-functionalization event should secure the enantioselectivity of the sequence and the optical purity of the final acyclic system bearing distinct carbon-substituents that may be functionalized further.

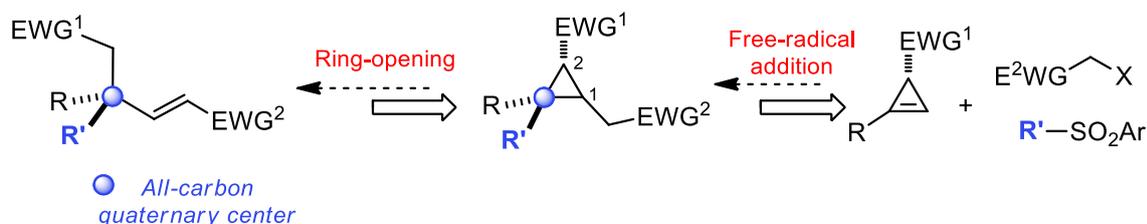


Figure 1. Installation of all-Carbon quaternary stereocenters

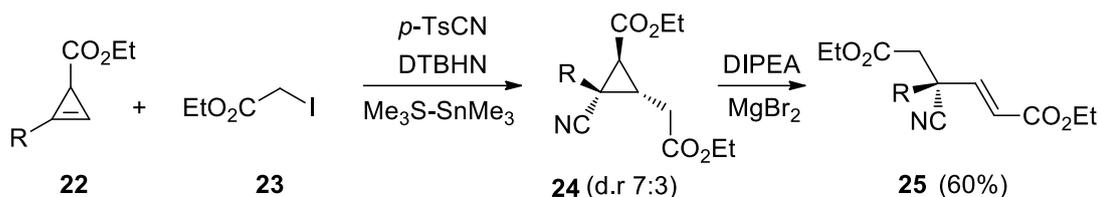
In this regard, our group has initiated the development of the carbocyanation¹⁴⁹ of cyclopropenes to access tetra-substituted cyclopropyl nitriles bearing a quaternary center.¹⁵⁰ After screening several combination of reagents, it was found that the reaction works efficiently with di-tert-butoxyhyponitrite (DTBHN) and (Me₃Sn)₂ as a chain carrier (Scheme 11). Preliminary experiments were carried out using iodoester **23** as a radical precursor, cyclopropene **22**, and commercially available *p*-tosyl cyanide as a cyanide source. Initiation of the process was performed using di-tert-butoxyhyponitrite (DTBHN) and (Bu₃Sn)₂ as a chain carrier.¹⁵¹ First reaction attempts by mixing the three components, DTBHN, and ditin produced less than 20% yield of the desired product and large amount of the iodine atom transfer product (not shown). The two diastereomers were easily separated through chromatography, and their structures assigned through ¹H NMR analysis. A slightly better yield was obtained by slow addition of a mixture of *p*-TsCN and DTBHN to the medium through a syringe pump. It was anticipated that Bu₃Sn radical might be too sterically hindered to abstract the iodine atom and regenerate the cyclopropyl radical for further cyanation. This proved to be the case, as the reaction using instead the smaller Me₃Sn radical led to a much improved yield of 60%. The best yield was observed when DTBHN and *p*-TsCN were added at a rate of 1 mL/h. Variation in the nature of

¹⁴⁹ a) Ovadia, B.; Robert, F.; Landais, Y. *Chimia* **2016**, *70*, 34 ; b) Liautard, V.; Robert, F.; Landais, Y. *Org. Lett.* **2011**, *13*, 2658; c) Hassan, H.; Pirenne, V.; Wissing, M.; Chahinaz, K.; Hussain, A.; Robert, F.; Landais, Y. *Chem. Eur. J.* **2017**, *23*, 4651.

¹⁵⁰ Dange, N. S.; Robert, F.; Landais, Y. *Org. Lett.* **2016**, *18*, 6156.

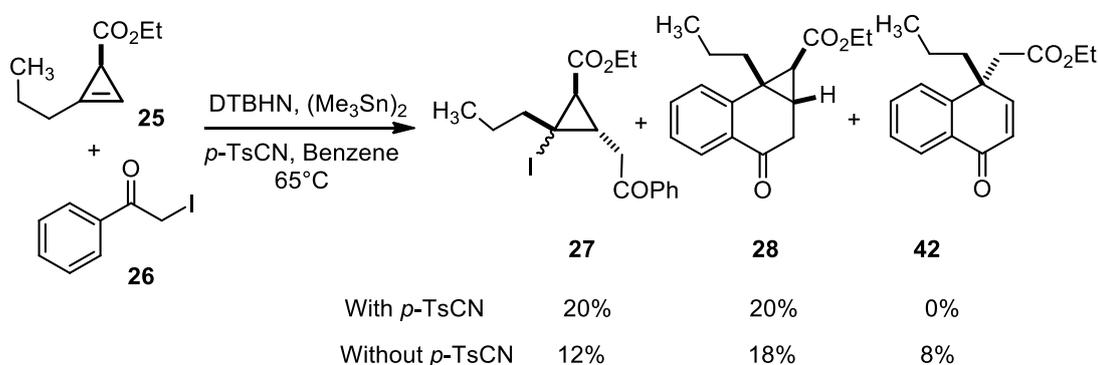
¹⁵¹ Fang, M.; Chen, M.-Y. *Tetrahedron Lett.* **1987**, *28*, 2853.

the solvent using DCE or CH₃CN led to a reduced yield compared with benzene or no conversion. Finally, an attempt with a lower reaction temperature of 45 °C (instead of 65 °C) to slow the decomposition of DTBHN also led to a lower yield. With cyclopropane nitriles **20** in hands, base-mediated ring opening was then performed affording the acyclic system **25** in generally good yield with complete retention of the stereochemistry of the diastereomerically pure cyclopropane **24**.



Scheme 11. Carbocyanation of cyclopropenes

During our studies on the carbocyanation of cyclopropanes, we observed contrasting results when using α -iodoacetophenone **26** instead of α -iodoester **23** (Scheme 12). The use of our previously reported conditions for carbocyanation of cyclopropane **25**,¹⁰ using α -iodoacetophenone **26** in the presence of *p*-TsCN, (Me₃Sn)₂ in benzene at 65 °C and di-tertbutylhyponitrite (DTBHN) as an initiator, did not provide the carbocyanation product, but instead the atom-transfer product **27**, and unexpectedly the cyclized product **28** in a 1:1 ratio (Scheme 12). Repeating the experiment without *p*-TsCN led to the same products along with the naphthalenone **29**, likely resulting from the cyclopropane ring opening of **28** under the reaction conditions.



Scheme 12. Addition of cyclopropane **25** of α -iodoacetophenone **26**.

The formation of **28** and **29** arise from the addition of the enoyl radical onto the cyclopropene, followed by the cyclization of the resulting highly reactive cyclopropyl radical onto the aromatic ring. Intramolecular carbonylation of olefins has precedent in the literature but to the best of our knowledge was not known with cyclopropenes.¹⁵²

With the above conditions in hand and the serendipitous discovery that naphthalenones such as **28** and **29** could be formed in a one-pot process from cyclopropenes, we started to investigate this unusual reaction, anticipating an extension of the strategy and further synthetic applications in organic synthesis. A careful literature survey indicated that the straightforward access to naphthalenones bearing a benzylic quaternary stereocenter was not known. Moreover, it was anticipated that the stereochemistry of the final product would be controlled during the well described enantioselective synthesis of the cyclopropene unit (Figure 2). The chiral naphthalene skeleton having a quaternary stereocenter is found in the structure of several natural products such as Labdane terpenoid (-)-Kujigamberol,¹⁵³ and the synthetic analgesic (-)-Eptazocine¹⁵⁴ (Figure 2).

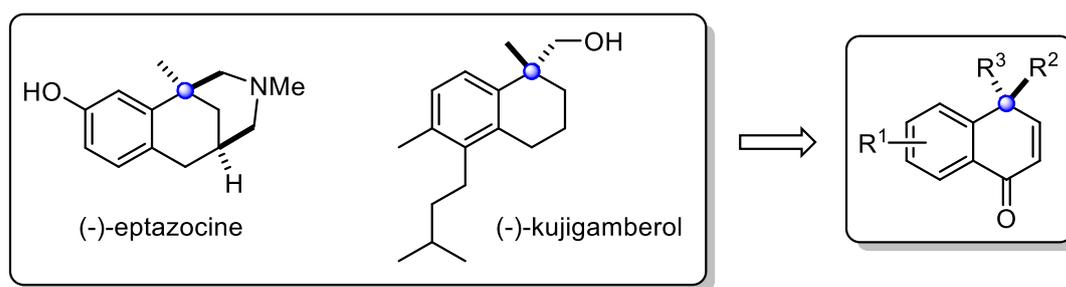


Figure 2. (-)-Eptazocine and (-)-Kujigamberol

Kujigamberol is found in fossilized tree resins called Ambers, which are formed under suitable conditions in soil, and sediments, where hardened resins can be preserved for hundreds of millions of years. There are many kinds of origins and geological ages reported in ambers such

¹⁵² a) Tucker, J. W.; Narayanam, J. M. R.; Krabbe, S. W.; Stephenson, C. R. J. *Org. Lett.* **2010**, *15*, 4884; b) Jiang, H.; Cheng, Y.; Zhang, Y.; Yu, S. *Org. Lett.* **2013**, *12*, 368; c) Fu, W.; Zhu, M.; Zou, G.; Xu, C.; Wang, Z.; Ji, B. *J. Org. Chem.* **2015**, *80*, 4766; d) Adouama, C.; Keyrouz, R.; Pilet, G.; Monnerau, C.; Gueyrard, D.; Noël, T.; Médebielle, M. *Chem. Commun.* **2017**, *53*, 5653; e) Cheng, J.; Deng, X.; Wang, G.; Li, Y.; Cheng, X.; Li, G. *Org. Lett.* **2016**, *18*, 4538; f) Liard, A.; Quiclet-Sire, B.; Saicic, R. N.; Zard, S. Z. *Tetrahedron Lett.* **1997**, *38*, 1759; g) Quiclet-Sire, B.; Zard, S. Z. *Top. Curr. Chem.* **2006**, *264*, 201 and references cited therein.

¹⁵³ a) Ye, Y. Q.; Koshino, H.; Hashizume, D.; Minamikawa, Y.; Kimura, K.-i.; Takahashi, S. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4259; b) Lim, H. J. L.; Rajanbabu, T. V. *Org. Lett.* **2011**, *13*, 6596.

¹⁵⁴ Maruyama, M.; Kobayashi, M.; Uchida, T.; Shimizu, E.; Higashio, H.; Ohno, M.; Kimura, K. *Fitoterapia*, **2018**, *127*, 263.

as Mexican (Mexico), Dominican (Dominican Republic), Cedar Lake (Canada), Baltic (Poland), New Jersey (USA), Lebanese (Lebanon), Dolomites (Italy) and Spain (Spain). Among them, Kuji (Iwate Prefecture in Japan) amber is one of the oldest types with a geological age dated at 85 million years.^{13a} It has been used as an ornament and in medicines for muscle pain, skin allergies and headaches. Kimura and co-workers^{13a} recently reported that kujigamberol showed growth restoring activity against the mutant yeast involving Ca^{2+} -signal transduction inhibited degranulation and Ca^{2+} influx in RBL-2H3 cells. It also suppresses the phosphorylation of ERK1/2 and generation of LTC_4 in the cells and improved nasal congestion against the rhinitis model about 5 times stronger than that of mometasone furoate. Kujigamberol is expected to provide the basis for the development of new types of anti-allergy drug. It has attracted considerable interest from synthetic chemists owing to its prominent or potential pharmacological activities. Several syntheses of this compound have been achieved.

Similarly, (-)-eptazocine is a modified form of the naturally occurring alkaloid (-)-morphine and is an important narcotic analgesic, used to avoid side effects such as addiction.^{14,155} As an example, we describe below an access to the decaline skeleton of (-)-eptazocine, which indicates that a strategy based on a rapid assembly of chiral enantiopure naphthalenones might shorten synthetic sequences and be of interest for the preparation of these morphine surrogates. She and co-workers¹⁵⁶ thus reported recently an efficient total synthesis of (-)-eptazocine starting with a diastereoselective Evans alkylation,¹⁵⁷ reacting oxazolidinone¹⁵⁸ with methallyl iodide. The cleavage of the chiral auxiliary¹⁵⁹ produced alcohol **30** as a single enantiomer in excellent yield (Scheme 13). Then, under Mitsunobu conditions, **31** was converted into azide **32**. Reduction of azide **32** with LiAlH_4 and subsequent protection of the amine with a tosyl group afforded **33**. On treatment with formaldehyde and CF_3COOH in CH_2Cl_2 , **33** provided a cyclic product, which was converted into **34** in the presence of AlCl_3 . Finally, (-)-eptazocine **35** was obtained after deprotection of the tosyl group, N-methylation with formaldehyde, and demethylation with BBr_3 . In summary, the synthesis of She encompasses 10 steps from oxazolidinone and provides

¹⁵⁵ a) Hudlicky, G.T.; Butora, S. P.; Fearnley, A. G.; Gum, M. R.; Stabile, S. *Nat. Prod. Chem.* **1995**, *18*, 43; b) Novak, B. H.; Hudlicky, T.; Reed, J. W.; Mulzer, J.; Trauner, D. *Curr. Org. Chem.* **2000**, *4*, 343; c) Blakemore, P. R.; White, J. D. *Chem. Commun.* **2002**, 11591.

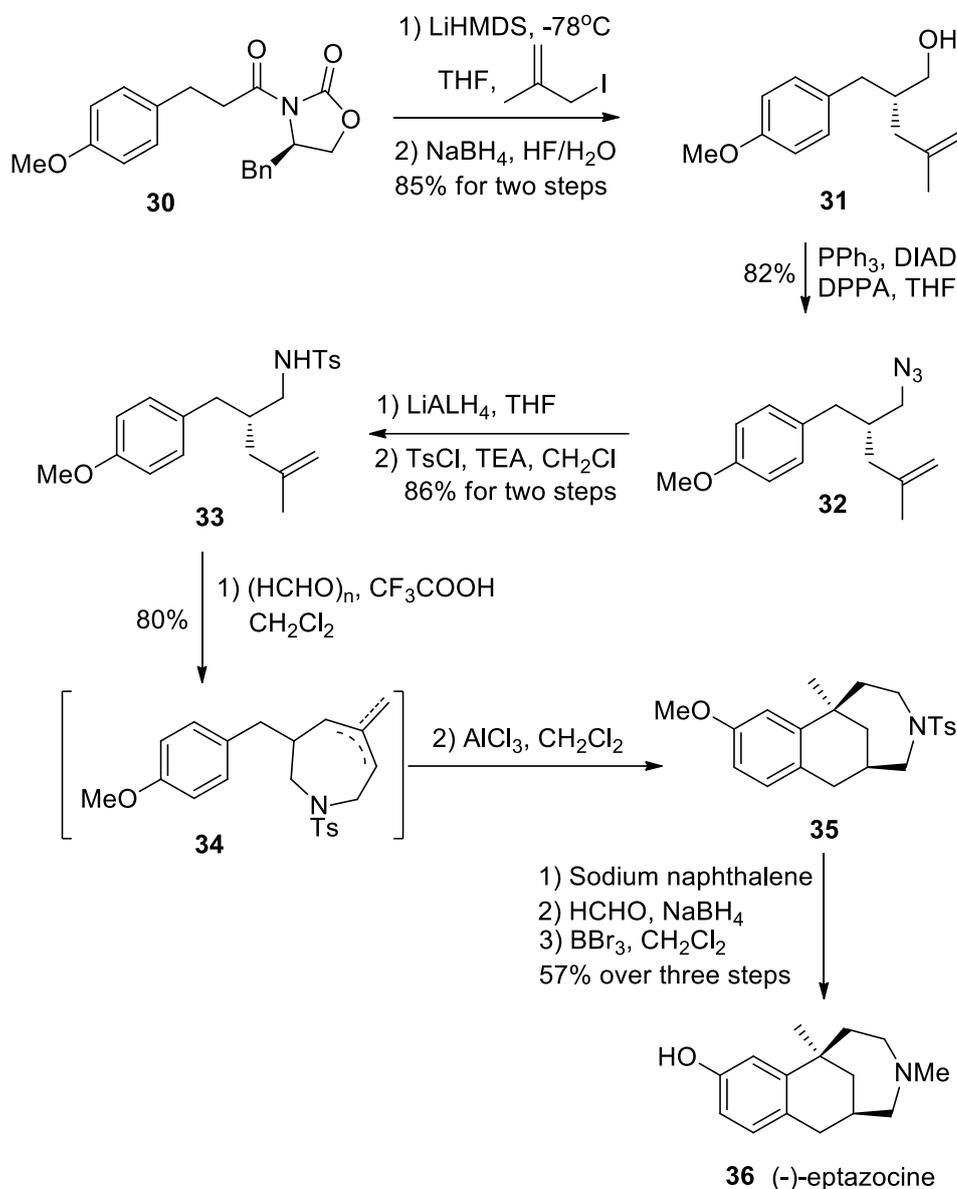
¹⁵⁶ Chen, Q.; Huo, X.; Yang, Z.; She, X. *Asian J. Chem.* **2012**, *7*, 2543.

¹⁵⁷ a) Smith, A. B.; Mesaros, E. F.; Meyer, E. A.; *J. Am. Chem. Soc.* **2006**, *128*, 5292; b) Heemstra, J. M.; Kerrigan, S. A.; Doerge, D. R.; Helferich, W. G.; Boulanger, W. A. *Org. Lett.* **2006**, *8*, 5441.

¹⁵⁸ Ugele, M.; Maier, M. E. *Tetrahedron*, **2010**, *66*, 2633.

¹⁵⁹ Prashad, M.; Kim, H.Y.; Lu, Y.; Liu, Y.; Har, D.; Repic, O.; Blacklock, T. J.; Giannousis, P. *J. Org. Chem.* **1999**, *64*, 1750.

(-)-eptazocine **36** in 27% overall yield, suggesting that a methodology, which would assemble the tricyclic core of **36** in a rapid manner would certainly raise interest.



Scheme 13. Synthesis of (-)-eptazocine; TEA=triethylamine, LiHMDS=lithium hexamethyldisilazide

Based on these premises and our previous experience in radical chemistry and inspired by photoredox catalysis,¹⁶⁰ we postulated that visible-light mediated cyclopropane ring opening

¹⁶⁰ For selected reviews on visible-light photoredox catalysis, see: a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322; b) Narayanam J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102; c) Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 1007; d) Marzo, L.; Pagire, S. K.; Reiser, O.; König, B. *Angew. Chem., Int. Ed.* **2018**, *57*, 10034.

with α -bromoacetophenones could provide a straightforward access to naphthalenones bearing a benzylic quaternary stereocenter, the stereochemistry of which being controlled early during the cyclopropene synthesis (Figure 3).

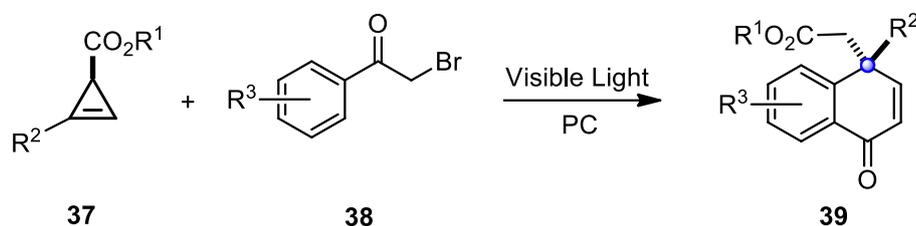
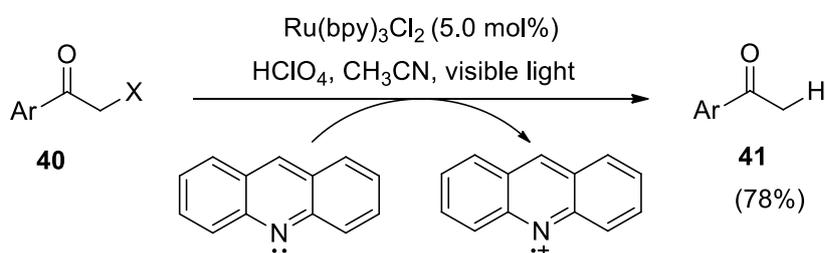


Figure 3. Visible-light mediated addition Phenacyl bromides to cyclopropenes.

3. Results. Carbocyanation of cyclopropenes using α -iodoacetophenones

Intramolecular carboarylation of olefins has precedent in the literature, but has not been reported with cyclopropenes. Therefore, considering the synthetic value of compounds such as **26** (*vide supra*), we focused our attention on the development of the one-pot preparation of naphthalenones from phenacyl halides and cyclopropenes, relying on an environmentally more benign initiation process than the one used above (Figure 3).

Pioneering studies by Stephenson *et al.*¹⁶¹ have established that photoredox-catalyzed atom transfer radical processes using α -haloacetophenones were efficiently performed under mild conditions using Ru or Ir catalysts and simple LED irradiation (Scheme 14).



Scheme 14. Reductive dehalogenation of phenacyl halides.

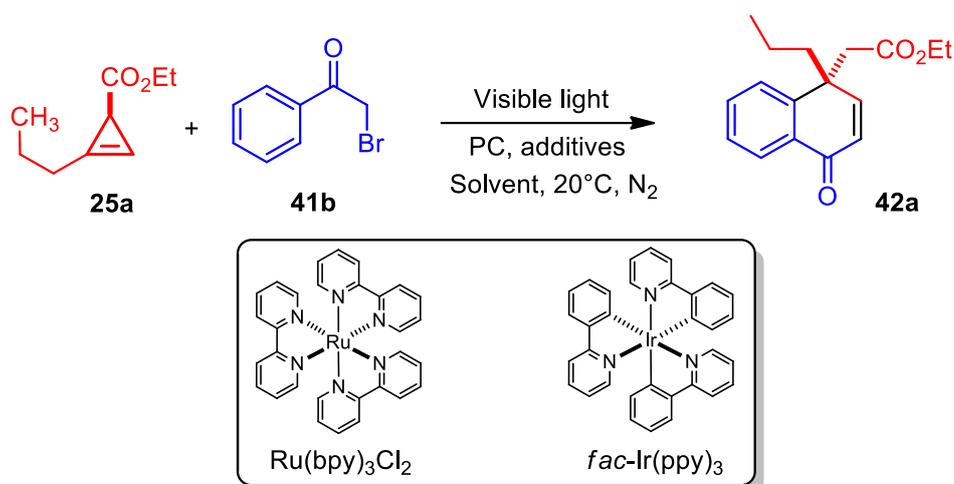
¹⁶¹ a) Tucker, J. W.; Narayanam, J. M. R.; Krabbe, S. W.; Stephenson, C. R. J. *Org. Lett.* **2010**, *15*, 4884; b) Jiang, H.; Cheng, Y.; Zhang, Y.; Yu, S. *Org. Lett.* **2013**, *12*, 368. c) Fu, W.; Zhu, M.; Zou, G.; Xu, C.; Wang, Z.; Ji, B. *J. Org. Chem.* **2015**, *80*, 4766.

3.1. Optimization of the carboarylation of cyclopropene

Inspired by these studies, we thus screened several photocatalysts for our reaction, varying the nature of the base and solvents (Table 1). α -Bromo acetophenone **41b** was used instead of its iodo analogue **26** to minimize the atom-transfer reaction.

The transformation was first carried out using cheaper $\text{Ru}(\text{bpy})_3\text{Cl}_2$ (2 mol %), Et_3N as a base, and LiBr as an additive (Table 1, entry 1).

Table 1. Optimization of the carboarylation of cyclopropene 25a.



| Entry | PC | Additive | Solvent | time (h) | Yield (%) ^b |
|-------|---------------------------|---------------------------------------|-------------------------------------|------------------|------------------------|
| 1 | $\text{Ru}^{\text{II a}}$ | Et_3N , LiBr | DMF | 72 | 10 |
| 2 | $\text{Ru}^{\text{II a}}$ | Et_3N , LiBr | $\text{DMF-H}_2\text{O}^{\text{c}}$ | 72 | 30 |
| 3 | $\text{Ru}^{\text{II a}}$ | LiBr | $\text{DMF-H}_2\text{O}^{\text{c}}$ | 72 | - ^d |
| 4 | Ir^{e} | Et_3N , LiBr | $\text{DMF-H}_2\text{O}^{\text{c}}$ | 72 | 15 |
| 5 | Ir^{e} | K_2CO_3 | DMF | 72 | 34 |
| 6 | Ir^{e} | $\text{K}_2\text{CO}_3, \text{LiBr}$ | DMF | 12 ^f | 40 |
| 7 | Ir^{e} | $\text{K}_2\text{CO}_3, \text{LiBr}$ | DMF^{g} | 12 ^f | 44 |
| 8 | Ir^{h} | $\text{K}_2\text{CO}_3, \text{LiBr}$ | DMF^{g} | 12 ^f | 22 |
| 9 | Ir^{i} | $\text{K}_2\text{CO}_3, \text{LiBr}$ | DMF^{g} | 12 ^f | 39 |
| 10 | Ir^{e} | $\text{K}_2\text{CO}_3, \text{LiBr}$ | DMF^{g} | 120 ^j | - |
| 11 | - ^k | $\text{K}_2\text{CO}_3, \text{LiBr}$ | DMF^{g} | 120 | - |

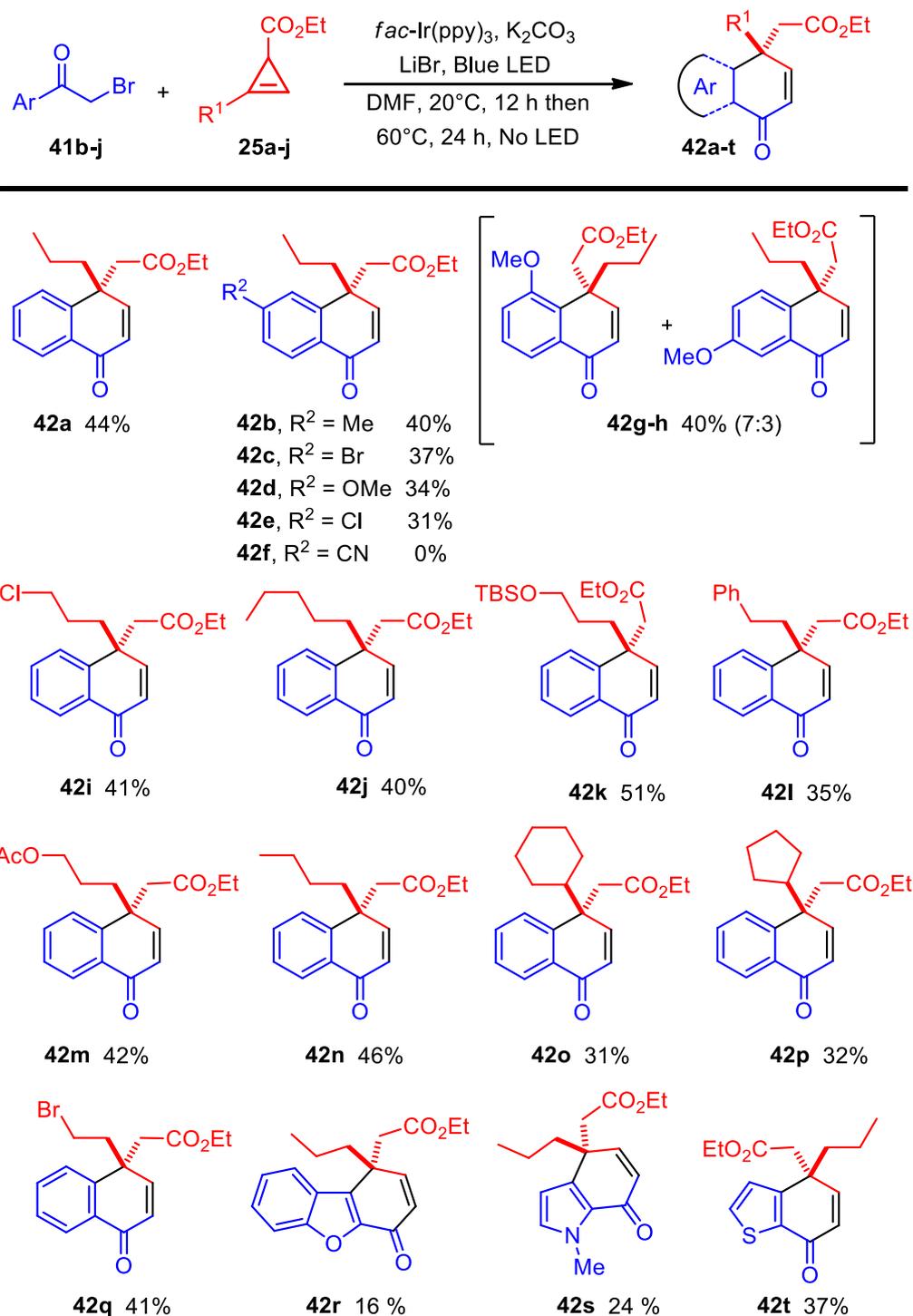
^a Ru^{II} : $\text{Ru}(\text{bpy})_3\text{Cl}_2$ (2 mol%). ^b Isolated yields. ^c $\text{DMF-H}_2\text{O}$ 4/1. ^d **31a** was isolated (28%). ^e Ir: $\text{fac-Ir}(\text{ppy})_3$ (2 mol%). ^f The reaction mixture was stirred 12h under LED irradiation then heated 24h at 60°C without irradiation. ^g DMF (0.2 M). ^h $\text{fac-Ir}(\text{ppy})_3$ (1 mol%). ⁱ $\text{fac-Ir}(\text{ppy})_3$ (4 mol%). ^j Without LED irradiation. ^k Without photocatalyst.

A better yield was observed when the reaction was performed in a DMF–H₂O mixture (Table 1, entry 2). This provided the desired naphthalenone **42a**, albeit in low yield.

In the absence of Et₃N, **28** was obtained without any trace of **42a**, indicating that the base was required for the ring opening, but not for the photocatalyst turnover (Table 1, entry 3) (*vide infra*). fac-Ir(ppy)₃ was then tested and displayed lower efficiency under these conditions (Table 1, entry 4). A higher amount of **42a** was however isolated with this catalyst, when K₂CO₃ was used as a base (Table 1, entry 5). Interestingly, we noticed that **42a** decomposed upon long exposure to the LED irradiation. Therefore, the carboarylation process was then performed for 12 h under irradiation, at which time **28a** was the major product formed. Then, the lamp was switched off, and the ring opening completed with gentle heating at 60 °C (Table 1, entry 6). Slightly higher yields were also obtained at higher concentration (0.2 M) (Table 1, entry 7). An increase of the concentration (0.4 M) or a decrease (0.05 M) led to lower yields. The catalyst loading was also varied, indicating that 2 mol % was optimal for this reaction (Table 1, entries 8–9). Finally, the reaction was carried out in the absence of light and photocatalyst, leading in both cases to no product, thus demonstrating the crucial and cooperative role of the Ir complex and visible-light irradiation (*vide infra*).

3.2. Scope of the intramolecular carbo-arylation of cyclopropenes

The scope of the reaction was then established using optimized conditions above (Table 1) on a series of α -bromoacetophenones **41b–k** and cyclopropenes **25a–j**, leading to naphthalenones **42a–t**, in moderate yields (Scheme 15).

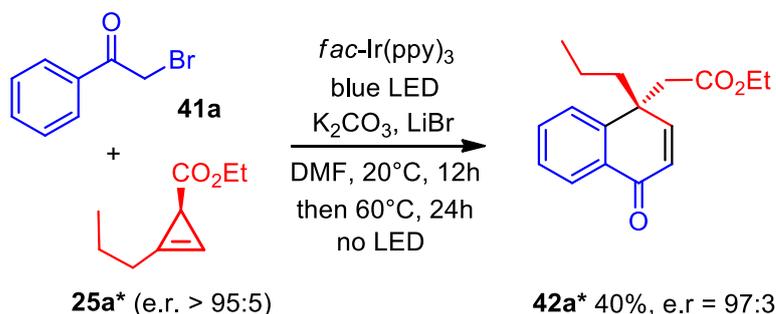
Scheme 15. Scope of the intramolecular carbo-arylation of cyclopropenes **25a-j**.

Higher yields are obtained with electron-donating substituents (R^2) on the phenacyl moiety, illustrating the influence of electronic effects in the process. For instance, when a *p*-CN substituent was present on the acetophenone, the corresponding unsaturated ketone **42f** was not formed, and a large amount of *p*-cyanoacetophenone was recovered instead, indicating that

reduction of the bromide was a competing pathway (vide infra).¹⁶² With *m*-substituted α -bromoacetophenones, a mixture of regioisomers was isolated (**42g–h** Scheme 15). The size of the substituents on the cyclopropene ring has a slight influence on the process efficiency, with lower yields observed with cyclic substituents (**42o–p** Scheme 15). The reaction was compatible with the presence of silyl ethers, esters, and halides as shown by the formation of **42i**, **42k**, and **42m**. Interestingly, naphthalenone **42q** was formed from cyclopropene **25j** having a mesylate substituent ($R^1 = (\text{CH}_2)_2\text{OMs}$), which was readily displaced in situ by LiBr. It is currently not established if the conversion of the mesylate into the bromide occurred before or after the photocatalyzed process. The reaction could also be performed with heteroarenes, leading to the desired compounds **42r–t**, with modest yields. Finally, it is worth noting that, although yields are generally moderate, final naphthalenones **42** are easily isolated through silica gel chromatography and obtained in only two synthetic operations from the corresponding commercially available alkynes.

3.3. Intramolecular carbo-arylation of enantioenriched cyclopropene

The stereochemical outcome of the carboarylation/cyclopropane ring-opening sequence was studied, by applying the reaction to enantioenriched cyclopropene **25a***, available through cyclopropanation of pent-1-yne using Corey's chiral rhodium catalyst (Scheme 16). **42a*** was obtained with the same enantiomeric excess as that of the starting **25a***, indicating that no erosion of the enantioselectivity occurred during the whole sequence.

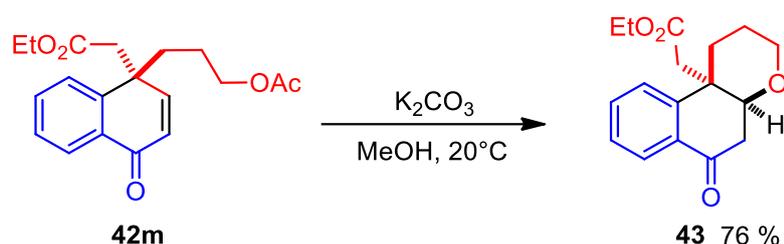


Scheme 16. Intramolecular carbo-arylation of enantioenriched cyclopropene **25a***.

¹⁶² Fukuzumi, S.; Mochizuki, S.; Tanaka, T. *J. Phys. Chem.* **1990**, 94, 722.

3.4. Further elaboration of Naphthalenones

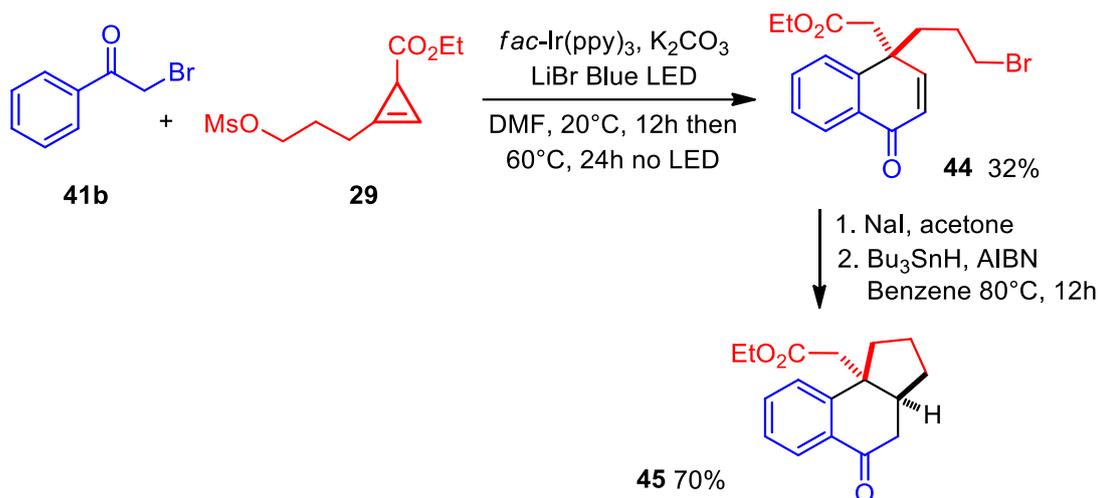
The naphthalenones obtained through this tandem process are useful precursors of polycyclic substrates, as demonstrated with the conversion of **42m** into the corresponding polysubstituted pyrane **43** through a simple treatment under basic conditions (Scheme 17). Saponification of the acetate under these conditions, followed by an oxa-Michael reaction provide a rapid access to tricyclic **43** in excellent yield.



Scheme 17. Functionalization of naphthalenones to pyrane.

Carbocycles such as **44** may also be reached in a straightforward manner starting from mesylcyclopropene **29** and **41b**, the conversion of which, under the optimized conditions mentioned above, led to the bromide **44**. Conversion of **44** into an iodide and then tin-mediated radical cyclization led to **45** as a single diastereomer (Scheme 18).¹⁶³ It is worth noticing that when the reaction was carried out directly on the bromide **44**, no radical cyclization was observed and **44** was recovered unchanged.

¹⁶³ Clive, D. L. J.; Sunasee, R.; Chen, Z. *Org. Biomol. Chem.* **2008**, *6*, 2434.



Scheme 18. Further elaboration of naphthalenones.

3.5. Mechanistic pathway

A mechanistic pathway was finally proposed to rationalize the course of the tandem process (Figure 4). This would involve, as a first step, a single electron transfer from the photocatalyst excited state ($fac\text{-Ir(ppy)}_3^*$) to the bromide **41b**, affording the α -phenacyl radical *i*. $fac\text{-Ir(ppy)}_3^*$ exhibits a sufficiently strong reduction potential ($E_{1/2} = -1.73$ V vs SCE)^{164a} to convert **41b** (-0.49 V vs SCE) into a radical-anion and then to *i*. The generation of the latter was shown by a radical trapping experiment using TEMPO, which led to the formation of **50** (Scheme 19). When the same reaction was performed in the presence of cyclopropene **25a**, **33** was also formed in 50% yield. *i* then adds onto the cyclopropene **25** to generate the highly reactive cyclopropyl radical *ii*,¹⁶⁵ which reacts intramolecularly with the arene moiety to afford the cyclohexadienyl radical *iii*. When using α -iodoacetophenone, the iodine atom transfer reaction was shown to compete with the intramolecular reaction (Scheme 16).¹⁶⁶

¹⁶⁴ a) Shih, H.-W.; VanderWal, M. N.; Grange, R. L.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 13600; b) Tanner, D. D.; Singh, H. K. *J. Org. Chem.* **1986**, *51*, 5182.

¹⁶⁵ Walborsky, H. M. *Tetrahedron* **1981**, *37*, 1625.

¹⁶⁶ Johnston, L. J.; Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1984**, *106*, 4877.

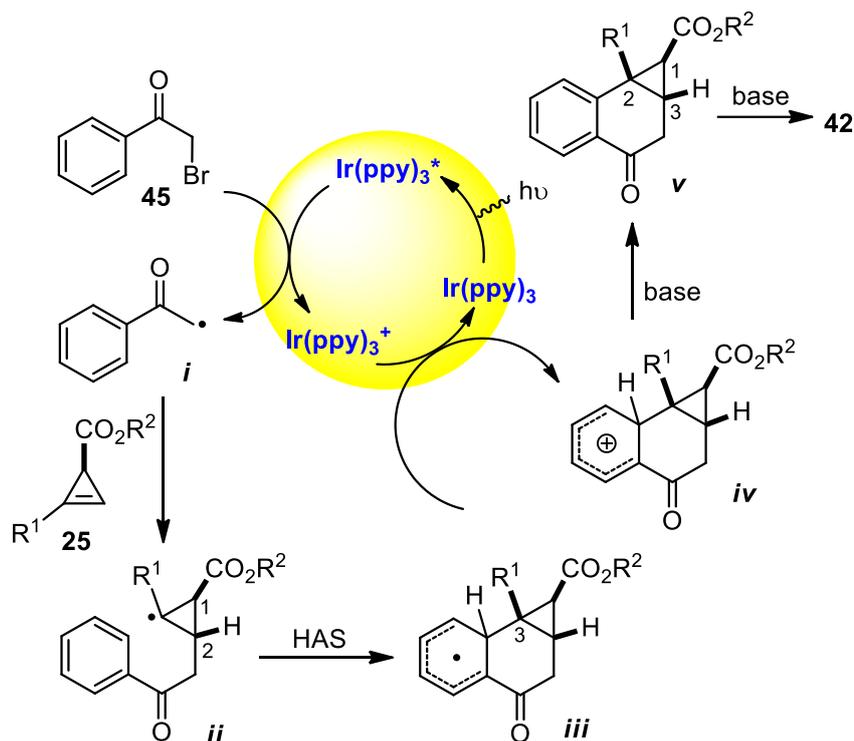
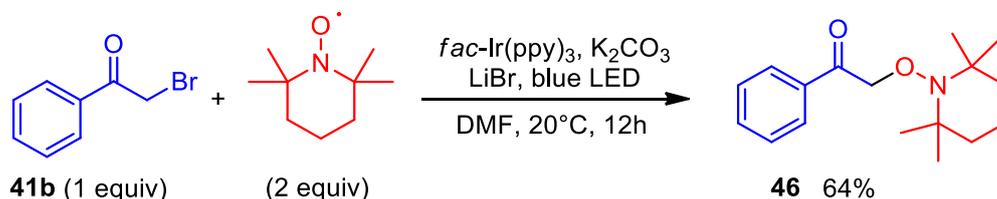


Figure 4. Proposed mechanism for the radical addition of Phenacyl bromide to cyclopropenes.



Scheme 19. Radical trapping by using TEMPO.

The homolytic aromatic substitution (HAS) is then completed through the oxidation of **iii** into **iv**, which rearomatizes through deprotonation under the basic conditions, to provide cyclopropane **27**. Oxidation of **iii** into **iv** is favored¹⁶⁷ due to the high oxidative power of Ir⁺ ($E_{1/2} = +0.77$ V vs SCE), **42a** which returns the iridium catalyst in its ground state. Single electron transfer from **iii** to **41** to generate **i** and **iv** is another option to sustain the radical chain (but not the Ir catalytic cycle).¹⁶⁸ **28** is finally converted in situ into naphthalenone **42** through deprotonation α to the ketone, followed by cyclopropane-ring opening. This mechanism is

¹⁶⁷ The redox potential for the cyclohexadienyl radical is $E = -0.1$ V (vs SCE); see: Bahtia, K.; Schuler, R. H. *J. Phys. Chem.* **1974**, *78*, 2335.

¹⁶⁸ Studer, A.; Curran, D. P. *Angew. Chem., Int. Ed.* **2016**, *55*, 58

consistent with the stereochemistry of **28**, resulting from an addition of radical **i** *anti* relative to the ester group as in **ii**, followed by the reaction of the cyclopropyl radical onto the arene from the same face. This *syn* addition (imposed by geometrical constraints) of the phenacyl radical across the cyclopropene π -system thus ensures a complete transfer of chirality from the stereocenter C1 to the newly created stereocenters at C2 and C3. Chirality at C3 is thus preserved upon base-promoted cyclopropane ring opening.

4. Conclusion

In conclusion, we reported a straightforward synthesis of substituted 1(4*H*)-naphthalenones, bearing a benzylic quaternary stereocenter, through a one-pot visible-light-mediated addition of α -bromoacetophenones to cyclopropenes. Although the overall yield is moderate but this methodology offers an access to useful intermediates, and constitutes a new way to generate synthons with a quaternary stereocenter, still a challenging task in organic synthesis.^{10,169} This methodology uses readily available enantioenriched cyclopropenes as starting material and the stereospecific *syn* carboarylation of the cyclopropene π -system allowing the formation of two new C–C bonds and ensuring control of the stereochemistry of the quaternary stereocenter.

¹⁶⁹ a) Quasdorf, K. W.; Overman, L. E. *Nature* **2014**, *516*, 181; b) Hong, A. Y.; Stoltz, B. M. *Eur. J. Org. Chem.* **2013**, 2745; c) Murphy, J. J.; Bastida, D.; Paria, S.; Fagnoni, M.; Melchiorre, P. *Nature* **2016**, *532*, 218. For reports on the use of cyclopropenes to set up all-carbon quaternary stereocenters, see: d) Zhang, F.-G.; Eppe, G.; Marek, I. *Angew. Chem., Int. Ed.* **2016**, *55*, 714; e) Müller, D. S.; Marek, I. *Chem. Soc. Rev.* **2016**, *45*, 4552.

EXPERIMENTAL PART

Experimental part for Chapter II

1. General Information

Reagents

All reagent-grade chemicals were obtained from commercial suppliers and were used as received unless otherwise noted. CH₂Cl₂ and THF were dried over activated alumina columns on MBraun Solvent Purification System (SPS-800). DCE and MeCN were distilled from CaH₂ and anhydrous dimethylformamide and dimethylsulfoxide was purchased from Sigma Aldrich. Triethylamine (reagent grade, ≥98%, Sigma Aldrich) and DMSO (anhydrous, ≥99.9%, Aldrich).

Reactions

All reactions for the Visible-Light Photocatalyzed Oxidation of Oxamic Acids were set up on bench-top in the open air and carried out in re-sealable test tubes with Teflon septa under an argon atmosphere. Unless otherwise noted, the reaction test tubes were cooled to room temperature prior to other operations. Unless otherwise noted, the solvents and the solutions of reagents/reactants were transferred *via* micro-syringe or plastic syringe (fitted with metal needle) into the reaction test tubes under a positive argon pressure.

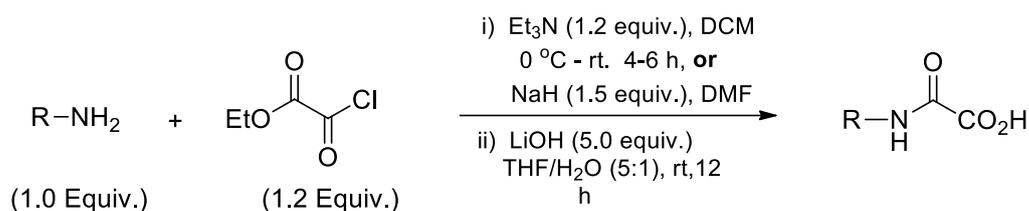
Photochemical reactions were performed with 455 nm (Castorama-blue LEDs ($\lambda = 455 \text{ nm} (\pm 15 \text{ nm})$), 12 V, 500 mA).

Analytical thin layer chromatography was performed using silica gel 60 F254 pre-coated plates (Merck) with visualization by ultraviolet light, Ceric Ammonium Molybdate and Ninhydrin. Flash chromatography was performed on silica gel (0.043-0.063 mm). Yields refer to chromatographically and spectroscopically (¹H-NMR) homogeneous materials, unless otherwise stated.

Instruments

¹H-NMR and ¹³C-NMR were recorded on various spectrometers: a Brüker DPX 200 (¹H: 200 MHz, ¹³C: 50.25 MHz), a Brüker Avance 300 (¹H: 300 MHz, ¹³C: 75.46 MHz), a using CDCl₃ as internal reference unless otherwise indicated. The chemical shifts (δ) and coupling constants (J) are expressed in ppm and Hz respectively. The following abbreviations were used to explain the multiplicities: bs = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplets. FTIR spectra were recorded on a Perkin-Elmer Spectrum 100 using a thin film between KBr plates. HRMS were recorded with a Waters Q-TOF 2 spectrometer in the electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI) mode.

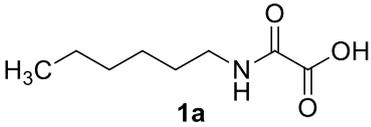
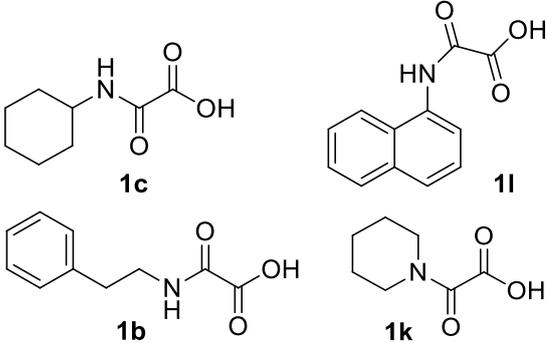
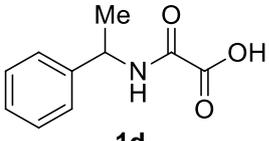
2. A. General procedure for the preparation of Oxamic Acids

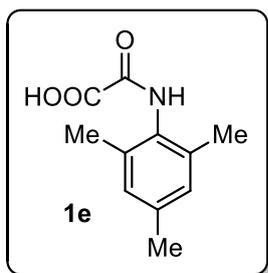


Scheme 1. Preparation of oxamic acids

To a solution of the corresponding aniline or amine (10 mmol) in CH_2Cl_2 (0.3 M) was added Et_3N (11 mmol), oxalyl chloride (11 mmol) was then added to the solution slowly at 0°C . The reaction mixture was warmed to room temperature and stirred for 4 - 6 h. The reaction mixture was then treated with 1 M HCl (20 mL) and extracted with dichloromethane (3 x 20 mL). The combined extracts were washed with brine, dried over Na_2SO_4 , filtered, and concentrated in vacuo, directly subjected to hydrolysis. The residue was dissolved in 15 mL THF and 5 mL H_2O , and LiOH (50 mmol) was added. After stirring for 6 - 8 h at room temperature, the basic reaction mixture was washed with dichloromethane (3 x 30 mL). The aqueous phase was separated and acidified with 1M aqueous HCl solution. The resulting mixture was extracted with ethyl acetate (3 x 30 mL) and the combined organic layers were washed with brine (30 mL) and dried over Na_2SO_4 . The solvent was evaporated and the residue was recrystallized by CH_2Cl_2 /hexanes.

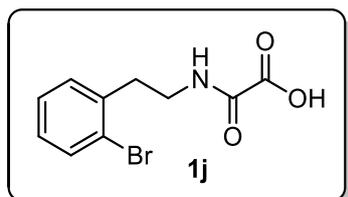
Table 1. Previously reported Oxamic acids

| Oxamic Acids | References |
|--|--|
|  <p style="text-align: center;">1a</p> | 1. Vujicic, N. S.; Glasovac, Z.; Zweep, N.; van Esch, J. H.; Vinkovic, M.; Popovic, J.; Zinic, M. <i>Chem. Eur. J.</i> 2013 , <i>19</i> , 8558. |
|  <p style="text-align: center;">1c 1l 1b 1k</p> | 2. Linton, S. D. <i>J. Med. Chem.</i> 2005 , <i>48</i> , 6779. |
|  <p style="text-align: center;">1d</p> | 3. Bálint, J.; Egri, G.; Czugler, Schindler, M. J.; Kiss, V.; Juvancz, Z.; Fogassy, E. <i>Tetrahedron: Asymmetry</i> 2001 , <i>12</i> , 1511. |



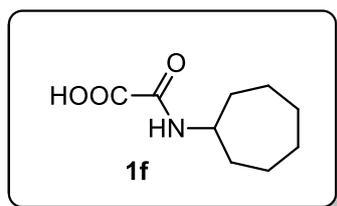
2-(Mesitylamino)-2-oxoacetic acid: 1e (1.2 g) was obtained through the general procedure A in 58 % yield as a white solid; mp 105-108 °C; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 8.49 (s, 1H), 6.94 (s, 2H), 2.29 (s, 3H), 2.19 (s, 6H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ (ppm) 160.0, 138.5, 134.6, 129.4, 128.9, 21.1, 18.4. **IR** (neat) ν_{max} (cm^{-1}) = 3250, 2922, 1883, 1668. **HRMS** (ESI): Calcd. For $\text{C}_{11}\text{H}_{11}\text{NO}_3$ $[\text{M}-\text{H}]^+$ 206.0817, found 206.0821.

2-((2-Bromophenethyl)amino)-2-oxoacetic acid: 1j (1.4 g) was obtained through the general



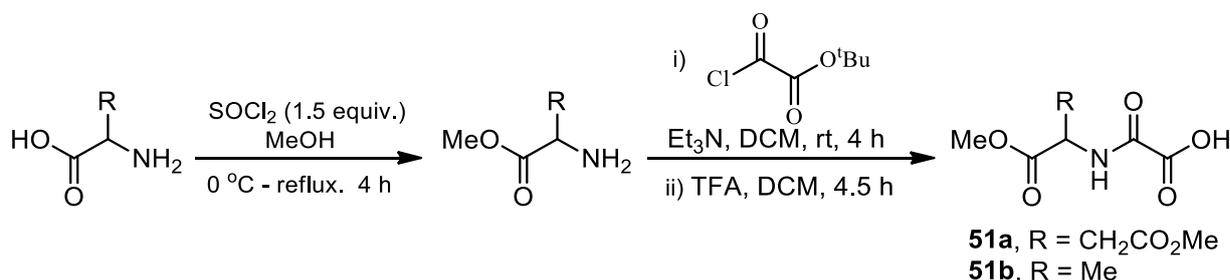
procedure A in 52 % yield as a white solid; mp 137-140 °C; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 7.59 (dd, $J = 8.0, 1.3$ Hz, 1H), 7.45 (s, 1H), 7.35 – 7.20 (m, 2H), 7.19 – 7.10 (m, 1H), 3.68 (q, $J = 7.2$ Hz, 1H), 3.07 (t, $J = 7.2$ Hz, 1H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ (ppm) 159.6, 157.5, 137.0, 133.2, 130.8, 128.8, 127.9, 124.5, 40.2, 35.3. **IR** (neat) ν_{max} (cm^{-1}) = 3282, 2938, 1769, 17672. **HRMS** (ESI): Calcd. For $\text{C}_{10}\text{H}_9\text{NO}_3\text{Br}$ $[\text{M}-\text{H}]^+$ 269.9771, found 269.9770.

2-(Cycloheptylamino)-2-oxoacetic acid: 1f (1.0 g) was obtained through the general procedure



A in 54 % yield as a white solid; mp 158-63 °C; $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 7.26 (s, 1H), 4.07-3.67 (m, 1H), 2.08 – 1.86 (m, 2H), 1.81 – 1.41 (m, 10H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ (ppm) 160.2, 156.3, 52.3, 34.6, 29.0, 24.0. **IR** (neat) ν_{max} (cm^{-1}) = 3293, 2923, 1767, 1674. **HRMS** (ESI): Calcd. For $\text{C}_9\text{H}_{14}\text{NO}_3$ $[\text{M}-\text{H}]^+$, 184.0979, found 184.0982.

2. B. General procedure for the preparation of Oxamic Acids¹⁷⁰

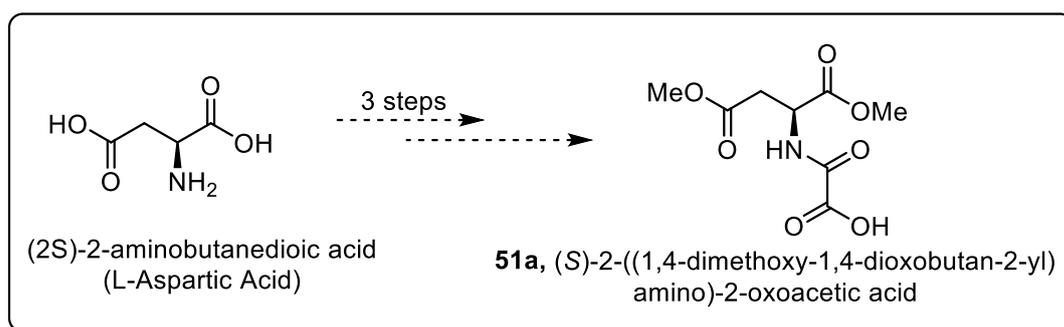


Scheme 2. Preparation of Oxamic acids

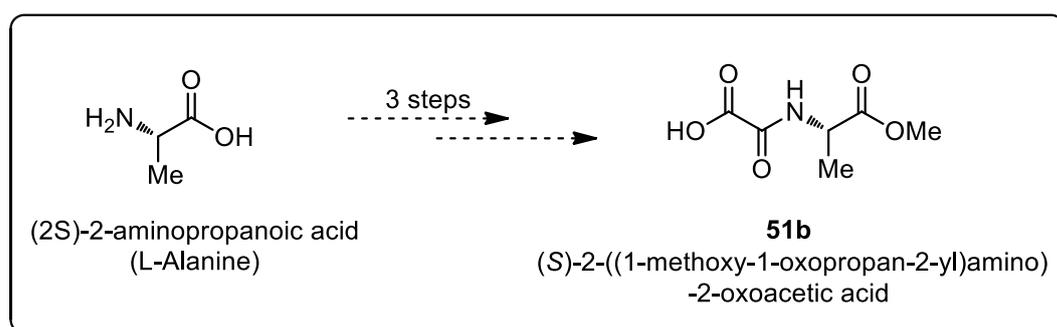
To a solution of the corresponding amino acid (30.07 mmol) in MeOH (25 mL) at 0 °C under nitrogen, thionyl chloride (3.2 mL, 45.11 mmol) was added dropwise over 15 mins. The reaction mixture was warmed to room temperature and then refluxed for 4 h. The solution was

¹⁷⁰ a) C. R. Reddy; M. D. Reddy; U. Dilipkumar. *Eur. J. Org. Chem.* **2014**, 6310-6313. b) Y. Seki, K. Tanabe, D. Sasaki, Y. Sohma, K. Oisaki, M. Kanai, *Angew. Chem. Int. Ed.* **2014**, 53, 6501-6505.

concentrated in vacuo to afford colorless oil. Hexane was added to this crude oil and was stirred for 10 min. Hexane was decanted and this procedure was repeated twice to obtain a solid compound.^{4a} This solid compound was dissolved in DCM (60 mL) and *tert*-butyl 2-chloro-2-oxoacetate was added dropwise at 0 °C under nitrogen. The reaction mixture was stirred at room temperature for 4 h. The resulting mixture was washed with water (100 mL), and brine (100 mL) then dried over sodium sulfate, concentrated under reduced pressure to obtain a crude solid compound.^{4b} The crude product was then treated with TFA in dichloromethane for 4 h at room temperature^{4b} and then mixture was concentrated under reduced pressure to give the desired oxamic acid product as a colorless oil.

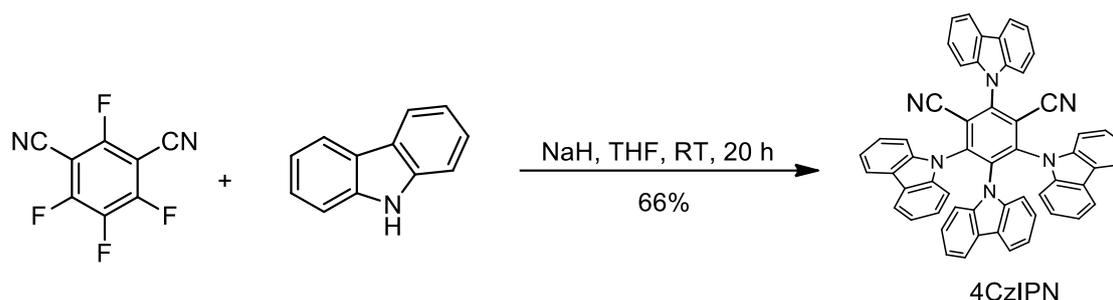


(S)-2-((1,4-Ddimethoxy-1,4-dioxobutan-2-yl)amino)-2-oxoacetic acid: 51a (4.5 g) was obtained through the general procedure B in 64 % yield as a colorless oil; ¹H NMR (300 MHz, CDCl₃) δ (ppm) 8.48 (s, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 4.94 – 4.78 (m, 1H), 3.80 (s, 3H), 3.72 (s, 3H), 3.11 (dd, *J* = 17.4, 5.0 Hz, 1H), 2.92 (dd, *J* = 17.4, 4.5 Hz, 1H). ¹³C NMR (76 MHz, CDCl₃) δ (ppm) 171.0, 169.7, 159.5, 157.5, 53.4, 52.5, 49.5, 35.6. IR (neat) *v*_{max} (cm⁻¹) = 3355, 2959, 1739, 1696. HRMS (ESI): Calcd. For C₈H₁₀NO₇ [M-H]⁺ 232.0457, found 232.0462. [α]_D²⁵ +80.76 (c 1.8, CHCl₃).



(S)-2-((1-Methoxy-1-oxopropan-2-yl) amino)-2-oxoacetic acid: 51b (3.1 g) was obtained through the general procedure B in 59 % yield as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ (ppm) 9.69 (s, 1H), 8.06 (d, *J* = 7.6 Hz, 1H), 4.57 (p, *J* = 7.2 Hz, 1H), 3.75 (s, 3H), 1.47 (d, *J* = 7.2 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 172.0, 160.1, 157.5, 52.9, 49.0, 17.5. IR (neat) *v*_{max} (cm⁻¹) = 3290, 2958, 1739, 1692. HRMS (ESI): Calcd. For C₆H₇NO₅ [M-H]⁺ 174.0402, found 174.0406. [α]_D²⁵ +9.32 (c 4.0, CHCl₃).

3. Synthesis of 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN):



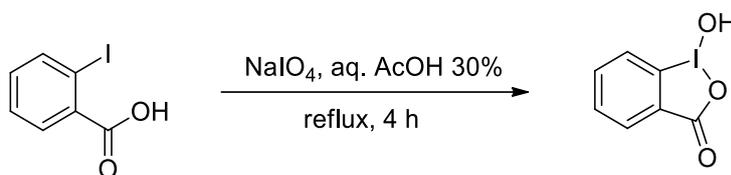
Scheme 3. Synthesis of 4CzIPN

The 4CzIPN was synthesized according to the following reported procedure.⁵ NaH (60% in oil, 1.4 g, 60 mmol) was added slowly to a stirred solution of carbazole (4.18 g, 25.0 mmol) in dry THF (100 mL) under a nitrogen atmosphere at room temperature. After 30 min, tetrafluoroisophthalonitrile (1.0 g, 5.0 mmol), was added. After stirring at room temperature for 12 h, 4-5 mL water was added to the reaction mixture to quench the excess NaH. The resulting mixture was then concentrated under reduced pressure and successively washed by water and EtOH to yield the crude yellow solid. The crude product was dissolved in a minimum quantity of CH₂Cl₂ and crystallized by addition of pentane to give the pure 4CzIPN (2.21 g, 66%) as a yellow solid; ¹H NMR (300 MHz, CDCl₃) δ (ppm) 8.25 (dt, *J* = 7.8, 1.0 Hz, 2H), 7.80 – 7.66 (m, 8H), 7.57 – 7.47 (m, 2H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.32 – 7.21 (m, 5H), 7.19 – 7.05 (m, 8H), 6.91 – 6.79 (m, 4H), 6.73 – 6.60 (m, 2H). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 145.2, 144.6, 140.0, 138.2, 137.0, 134.8, 127.0, 125.8, 125.0, 124.8, 124.5, 123.9, 122.4, 121.9, 121.4, 121.0, 120.4, 119.7, 116.4, 111.6, 110.0, 109.5, 109.4. Spectroscopic data were in good agreement with literature.¹⁷¹

¹⁷¹ Uoyama, H.; Goushi, K.; Shizu, K.; Nomura, H.; Adachi, C. *Nature* **2012**, 492, 234-238.

4. Hypervalent Iodine Reagents (HIR)

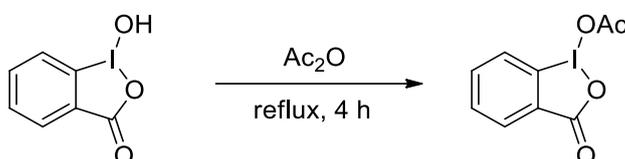
(a) 1-Hydroxy-1,2-benziodoxol-3(1H)-one (CAS: 131-62-4):



Scheme 4. Preparation of BI-OH

Following a reported procedure,¹⁷² NaIO₄ (6.7 g, 31.0 mmol, 1.00 equiv) and 2-iodobenzoic acid (7.4 g, 30.0 mmol, 1.00 equiv.) were suspended in 30% (v:v) aqueous AcOH (45 mL) under air. The mixture was vigorously stirred and refluxed for 4 h, protected from light. Cold water (120 mL) was added and the reaction mixture was allowed to cool to room temperature. After 1 h, the crude product was collected by filtration, washed with ice water (3 x 30 mL) and cold acetone (3 x 30 mL). After air dried in the dark overnight to give the pure compound **BI-OH** (6.8 g, 86%) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ (ppm) 8.09 – 7.91 (m, 3H), 7.85 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.70 (td, *J* = 7.3, 1.1 Hz, 1H). ¹³C NMR (75 MHz, DMSO-*d*₆) δ (ppm) 168.2, 134.9, 132.0, 131.6, 130.8, 126.7, 120.9. Spectroscopic data were in good agreement with literature.

(b) 1-Acetoxy-1,2-benziodoxol-3(1H)-one (CAS:1829-25-0):



Scheme 4. Preparation of BI-OAc

Following a reported procedure,¹⁷³ BI-OH (6.00 g, 22.7 mmol) was heated in Ac₂O (20 mL) to reflux until the solution turned clear (without suspension). The mixture was then left to cool down and white crystals started to form. The crystallization was continued at -20 °C. Crystals were then collected and dried overnight under high vacuum to give compound **BI-OAc** (6.1 g, 88%) as a white solid; ¹H NMR (300 MHz, CDCl₃) δ (ppm) 8.28 (dd, *J* = 7.6, 1.6 Hz, 1H), 8.07 – 8.01 (m, 1H), 8.00 – 7.92 (m, 1H), 7.79 – 7.71 (m, 1H), 2.29 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) 176.4, 168.2, 136.1, 133.2, 131.3, 129.3, 129.0, 118.3, 20.3. Spectroscopic data were in good agreement with literature.

¹⁷² Fernández González, D.; Brand, J. P.; Waser, J. *Chem. Eur. J.* **2010**, *16*, 9457.

¹⁷³ Eisenberger, P.; Gischig, S.; Togni, A. *Chem. Eur. J.* **2006**, *12*, 2579.

5. General procedure for the Visible-Light Mediated Carbamoyl Radical Addition to Heteroarenes

Reaction Setup:

Photochemical reactions were performed with 455 nm (Castorama-blue LEDs ($\lambda = 455 \text{ nm} (\pm 15 \text{ nm})$), 12 V, 500 mA).



Figure 1. Reaction Setup

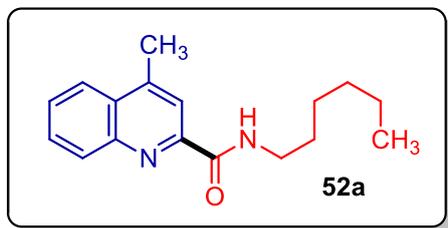


Scheme 5. Carbamoyl addition to Heteroarenes

The *N*-Heterocycle (1.0 equiv., 0.5 mmol), Oxamic Acid (1.5 equiv., 0.75 mmol), 4CzIPN (1.0 mol%, 0.005 mmol), and BIOAc (1.5 equiv., 0.75 mmol) were placed into a re-sealable test-tube with Teflon septa (10 mL) and a magnetic stir bar. Air was removed from the reaction vessel, which was then backfilled with argon three times, and DCM (0.2 M) was added afterwards (Note: for liquid substrates, they were added after the tube was backfilled with argon). The reaction mixture was stirred at room temperature under blue LED irradiation for 12 h. The reaction mixture was concentrated and purified directly by column chromatography to afford the product. (Eluting with ethyl acetate/hexanes).

6. ^1H and ^{13}C NMR Data

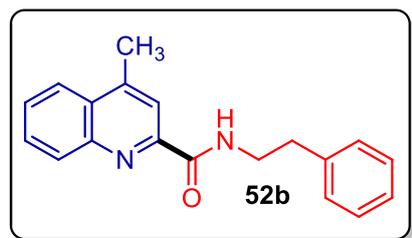
N-Hexyl-4-methylquinoline-3-carboxamide: 52a (122 mg) was obtained through the general



procedure in 90 % yield as a white solid, m.p. 60-63 °C. R_f = 0.84 (EtOAc-Hexane 10/90). ^1H NMR (300 MHz, CDCl_3) δ (ppm) 8.29 (s, 1H), 8.13 (d, J = 0.8 Hz, 1H), 8.10 – 8.02 (m, 1H), 7.98 (dd, J = 8.4, 1.0 Hz, 1H), 7.75 – 7.65 (m, 1H), 7.62 – 7.51 (m, 1H), 3.59 – 3.41 (m, 2H), 2.71 (d, J = 1.0 Hz, 3H), 1.72 – 1.56 (m, 2H), 1.48 – 1.22

(m, 6H), 0.96 – 0.77 (m, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ (ppm) 164.7, 149.6, 146.4, 146.0, 130.3, 129.6, 129.2, 127.5, 123.9, 119.5, 39.6, 31.6, 29.7, 26.8, 22.6, 18.9, 14.1. IR (neat) ν_{max} (cm^{-1}) = 3373, 2928, 1672, 1528. HRMS (ESI): Calcd. For $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}$, $[\text{M}+\text{H}]^+$ 271.1804, found 271.1809.

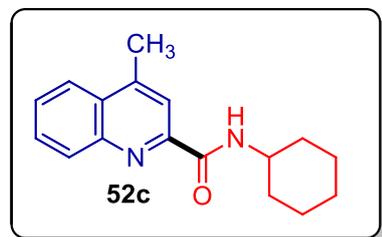
4-Methyl-N-phenethylquinoline-2-carboxamide: 52b (121 mg) was obtained through the



general procedure in 83 % yield as a yellow gel. R_f = 0.62 (EtOAc-Hexane 15/85). ^1H NMR (300 MHz, CDCl_3) δ (ppm) 8.42 (s, 1H), 8.19 – 8.12 (m, 1H), 8.09 – 7.95 (m, 3H), 7.73 (ddd, J = 8.4, 6.8, 1.4 Hz, 1H), 7.61 (ddd, J = 8.2, 6.8, 1.2 Hz, 1H), 7.42 – 7.26 (m, 5H), 3.88 – 3.73 (m, 2H), 3.01 (t, J = 7.3 Hz, 2H), 2.75 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3)

δ (ppm) 164.7, 149.4, 146.3, 146.0, 139.1, 130.3, 129.7, 129.2, 128.9, 128.6, 127.6, 126.5, 123.9, 119.4, 40.9, 36.1, 18.9. IR (neat) ν_{max} (cm^{-1}) = 3383, 2928, 1672, 1526. HRMS (APCI): Calcd. For $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}$, $[\text{M}+\text{H}]^+$ 291.1491, found 291.1493.

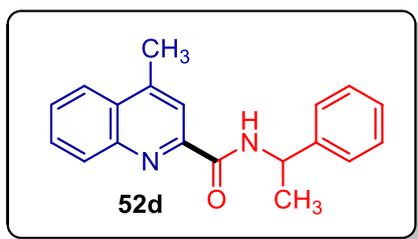
N-Cyclohexyl-4-methylquinoline-2-carboxamide: 52c (131 mg) was obtained through the



general procedure in 86 % yield as a yellow gel. R_f = 0.72 (EtOAc-Hexane 15/85). ^1H NMR (300 MHz, CDCl_3) δ (ppm) 8.13 (d, J = 0.8 Hz, 1H), 8.11 – 8.05 (m, 1H), 8.00 – 7.94 (m, 1H), 7.74 – 7.66 (m, 1H), 7.61 – 7.52 (m, 1H), 4.10 – 3.91 (m, 1H), 2.71 (d, J = 0.8 Hz, 3H), 2.12 – 1.96 (m, 2H), 1.86 – 1.71 (m, 2H), 1.72 – 1.57 (m, 1H), 1.51 – 1.13 (m, 5H). ^{13}C NMR

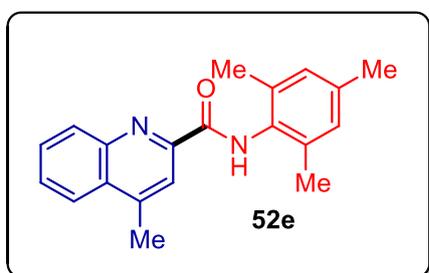
(75 MHz, CDCl_3) δ (ppm) 163.7, 149.7, 146.3, 146.0, 130.2, 129.6, 129.2, 127.5, 123.9, 119.5, 48.4, 33.2, 25.7, 25.0, 18.9. IR (neat) ν_{max} (cm^{-1}) = 3378, 2930, 1669, 1550. HRMS (APCI): Calcd. For $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}$, $[\text{M}+\text{H}]^+$ 269.1648, found 269.1641.

4-Methyl-N-(1-phenylethyl) quinoline-2-carboxamide: 52d (120 mg) was obtained through



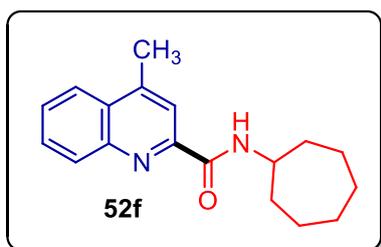
the general procedure in 83 % yield as a yellow gel. $R_f = 0.86$ (EtOAc-Hexane 10/90). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 8.62 (d, $J = 8.2$ Hz, 1H), 8.24 – 8.17 (m, 1H), 8.17 – 8.09 (m, 1H), 8.07 – 7.97 (m, 1H), 7.79 – 7.69 (m, 1H), 7.67 – 7.57 (m, 1H), 7.54 – 7.45 (m, 2H), 7.44 – 7.36 (m, 2H), 7.34 – 7.30 (m, 1H), 5.44 (p, $J = 7.0$ Hz, 1H), 2.75 (s, 3H), 1.71 (d, $J = 6.8$ Hz, 2H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ (ppm) 163.9, 149.3, 146.3, 146.1, 143.4, 130.3, 129.7, 129.2, 128.7, 127.6, 127.3, 126.3, 123.9, 119.5, 48.9, 22.1, 18.9. **IR** (neat) ν_{max} (cm^{-1}) = 3380, 2975, 1670, 1550. **HRMS** (APCI): Calcd. For $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}$, $[\text{M}+\text{H}]^+$ 291.1491, found, 291.1503.

N-Mesitylquinoline-2-carboxamide: 52e (65 mg) was obtained through the general procedure



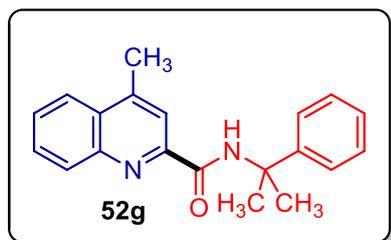
in 43 % yield as a brown solid; m.p., 198-201 °C. $R_f = 0.77$ (EtOAc-Hexane 10/90). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 9.66 (s, 1H), 8.25 (d, $J = 0.7$ Hz, 1H), 8.17 (s, $J = 8.4, 0.7$ Hz, 1H), 8.08 (m, $J = 8.4, 0.9$ Hz, 1H), 7.82 – 7.75 (m, 1H), 7.70 – 7.63 (m, 1H), 6.97 (s, 2H), 2.81 (d, $J = 0.8$ Hz, 3H), 2.31 (d, $J = 6.9$ Hz, 9H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ (ppm) 163.1, 149.4, 146.5, 136.9, 135.3, 131.4, 130.5, 129.9, 129.5, 129.1, 127.9, 124.1, 119.8, 21.1, 19.0, 18.7. **IR** (neat) ν_{max} (cm^{-1}) = 3348, 2920, 1686, 1559. **HRMS** (ESI): Calcd. For $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}$ $[\text{M}+\text{Na}]^+$, 327.1473, found 327.1469.

N-Cycloheptyl-4-methylquinoline-2-carboxamide: 52f (120 mg) was obtained through the



general procedure in 85 % yield as a white solid; m.p. 102-105 °C. $R_f = 0.88$ (EtOAc-Hexane 20/80). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 8.23 (d, $J = 8.4$ Hz, 1H), 8.14 – 8.03 (m, 2H), 7.95 (dd, $J = 1.0, 8.2$ Hz, 1H), 7.68 (dt, $J = 8.4, 6.8, 1.4$ Hz, 1H), 7.55 (dt, $J = 8.2, 6.8, 1.4$ Hz, 1H), 4.29 – 4.04 (m, 1H), 2.70 (d, $J = 1.0$ Hz, 3H), 2.14 – 1.93 (m, 2H), 1.80 – 1.40 (m, 10H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ (ppm) 163.4, 149.7, 146.3, 145.9, 130.2, 129.6, 129.1, 127.4, 123.8, 119.4, 50.6, 35.1, 28.1, 24.2, 18.8. **IR** (neat) ν_{max} (cm^{-1}) = 3380, 2926, 1669, 1522. **HRMS** (ESI): Calcd. For $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}$ $[\text{M}+\text{Na}]^+$, 305.1630, found 305.1624.

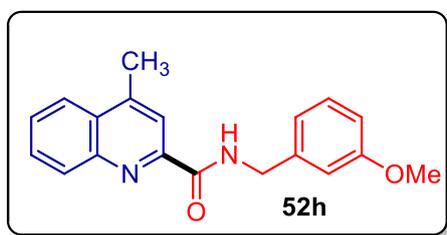
4-Methyl-N-(2-phenylpropan-2-yl) quinoline-2-carboxamide: 52g (131 mg) was obtained



through the general procedure in 86 % yield as a yellow gel. $R_f = 0.85$ (EtOAc-Hexane 10/90). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 8.79 (s, 1H), 8.24 – 8.13 (m, 2H), 8.05 (dd, $J = 8.2, 1.4$ Hz, 1H), 7.78 (ddd, $J = 8.4, 6.8, 1.4$ Hz, 1H), 7.71 – 7.54 (m, 3H), 7.45 – 7.36 (m, 2H), 7.34 – 7.24 (m, 1H), 2.75 (d, $J = 0.8$ Hz, 3H), 1.95 (s, 6H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3)

δ (ppm) 163.7, 149.9, 147.0, 146.3, 146.0, 130.3, 129.7, 129.2, 128.8, 128.5, 127.6, 126.7, 124.9, 123.9, 119.3, 55.8, 29.3, 18.9. **IR (neat)** ν_{max} (cm^{-1}) = 3372, 2976, 1677, 1503. **HRMS (ESI):** Calcd. For $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}$ $[\text{M}+\text{Na}]^+$, 327.1467, found 327.1474.

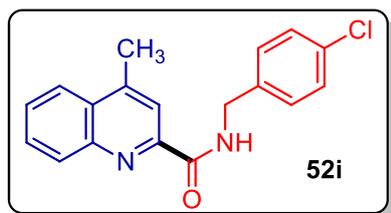
N-(3-Methoxybenzyl)-4-methylquinoline-2-carboxamide: 52h (115 mg) was obtained



through the general procedure in 66 % yield as a brown gel. $R_f = 0.88$ (EtOAc-Hexane 10/90). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 8.67 (s, 1H), 8.25 – 8.17 (m, 1H), 8.13 – 7.98 (m, 2H), 7.80 – 7.68 (m, 1H), 7.68 – 7.57 (m, 1H), 7.34 – 7.24 (m, 1H), 7.06 – 6.94 (m, 2H), 6.85 (dd, $J = 8.0, 2.2$ Hz, 1H), 4.73 (d, $J = 6.2$ Hz, 2H), 3.81 (s, 3H),

2.78 (d, $J = 0.8$ Hz, 3H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ (ppm) 164.7, 160.0, 149.2, 146.3, 146.3, 140.0, 130.3, 129.8, 129.3, 127.7, 123.9, 120.2, 119.6, 113.5, 113.0, 55.3, 43.6, 19.0. **IR (neat)** ν_{max} (cm^{-1}) = 3381, 2936, 1672, 1527. **HRMS (ESI):** Calcd. For $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_2$ $[\text{M}+\text{Na}]^+$, 329.1260, found 329.1267.

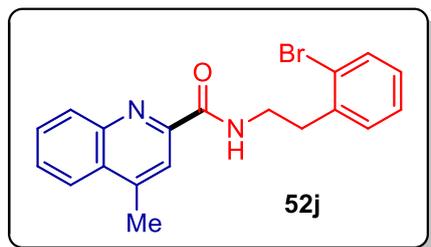
N-(4-Chlorobenzyl)-4-methylquinoline-2-carboxamide: 52i (132 mg) was obtained through



the general procedure in 77 % yield as a yellow gel. $R_f = 0.61$ (EtOAc-Hexane 15/85). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 8.68 (s, 1H), 8.24 – 8.16 (m, 1H), 8.13 – 8.01 (m, 1H), 7.82 – 7.59 (m, 3H), 7.39 – 7.30 (m, 4H), 7.16 – 7.05 (m, 1H), 4.71 (d, $J = 6.2$ Hz, 1H), 2.80 (d, $J = 0.8$ Hz, 3H). $^{13}\text{C NMR}$ (75

MHz, CDCl_3) δ (ppm) 164.8, 149.0, 146.3, 136.9, 133.1, 130.2, 129.7, 129.2, 128.7, 127.7, 123.9, 119.5, 42.8, 18.9. **IR (neat)** ν_{max} (cm^{-1}) = 3379, 2924, 1685, 1526. **HRMS (ESI):** Calcd. For $\text{C}_{18}\text{H}_{15}\text{N}_2\text{OCl}$, $[\text{M}+\text{H}]^+$, 311.0945, found 311.0939.

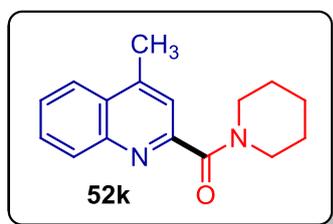
N-(2-Bromophenethyl)-4-methylquinoline-2-carboxamide: 52j (135 mg) was obtained



through the general procedure in 73 % yield as a yellow solid; m.p. 245-249 °C. $R_f = 0.69$ (EtOAc-Hexane 15/85). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 8.45 (s, 1H), 8.19 (d, $J = 0.8$ Hz, 1H), 8.12 – 8.03 (m, 2H), 7.80 – 7.74 (m, 1H), 7.69 – 7.58 (m, 2H), 7.35 (dd, $J = 7.6, 1.8$ Hz, 1H), 7.31 – 7.28 (m, 1H), 7.17 – 7.11 (m, 1H), 3.84 (dt, $J = 7.4, 6.5$ Hz,

2H), 3.18 (t, $J = 7.3$ Hz, 2H), 2.79 (d, $J = 0.9$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ (ppm) 164.9, 149.3, 146.4, 146.1, 138.4, 133.0, 131.1, 130.3, 129.7, 129.3, 128.3, 127.7, 124.7, 123.96, 119.4, 39.4, 36.2, 19.0. IR (neat) ν_{max} (cm^{-1}) = 3379, 2930, 1672, 1525. HRMS (ESI): Calcd. For $\text{C}_{19}\text{H}_{17}\text{N}_2\text{OBr}$, $[\text{M}+\text{H}]^+$, 369.0597, found 369.0594.

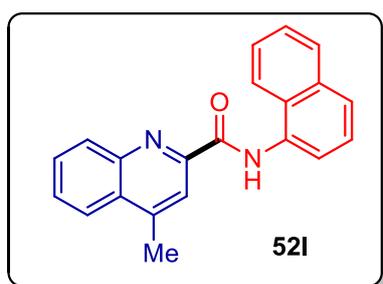
(4-Methylquinoline-2-yl)(piperidin-1-yl)methanone: 52k (103 mg) was obtained through the



general procedure in 81 % yield as a brown gel, $R_f = 0.74$ (EtOAc-Hexane 10/90). ^1H NMR (300 MHz, CDCl_3) δ (ppm) 8.16 – 8.09 (m, 1H), 8.00 (dd, $J = 8.4, 1.2$ Hz, 1H), 7.77-7.70 (m, 1H), 7.64-7.57 (m, 1H), 7.51 – 7.45 (m, 1H), 3.78 (t, $J = 4.8$ Hz, 2H), 3.55 – 3.39 (m, 2H), 2.73 (d, $J = 0.8$ Hz, 3H), 1.82 – 1.46 (m, 6H). ^{13}C NMR (75 MHz, CDCl_3) δ (ppm) 167.5, 153.8, 146.6, 146.1,

130.1, 129.8, 128.1, 127.4, 123.8, 121.0, 48.4, 43.4, 26.6, 25.6, 24.6, 19.0. IR (neat) ν_{max} (cm^{-1}) = 3344, 2937, 1669, 1557. HRMS (APCI): Calcd. For $\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}$, $[\text{M}+\text{H}]^+$, 255.1491, found 255.1492.

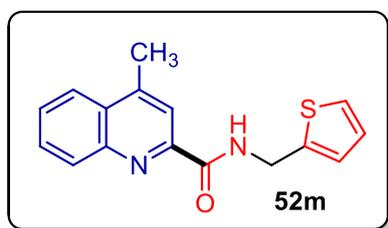
4-Methyl-N-(naphthalen-1-yl) quinolone-2-carboxamide: 52l (91 mg) was obtained through



the general procedure in 58 % yield as a brown gel. $R_f = 0.66$ (EtOAc-Hexane 15/85). ^1H NMR (300 MHz, CDCl_3) δ (ppm) 11.01 (s, 1H), 8.47 (dd, $J = 7.5, 1.0$ Hz, 1H), 8.33 – 8.26 (m, 2H), 8.24 – 8.18 (m, 1H), 8.11 (dd, $J = 8.4, 0.9$ Hz, 1H), 7.93 (dd, $J = 8.4, 1.0$ Hz, 1H), 7.84 (ddd, $J = 8.4, 6.9, 1.4$ Hz, 1H), 7.77 – 7.53 (m, 6H), 2.85 (d, $J = 0.9$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ (ppm) 162.8, 149.5, 146.8, 146.3, 134.3,

132.7, 130.6, 130.1, 129.6, 129.0, 128.0, 126.3, 125.1, 124.1, 120.7, 119.5, 118.76, 19.2. IR (neat) ν_{max} (cm^{-1}) = 3331, 2926, 1691, 1542. HRMS (ESI): Calcd. For $\text{C}_{21}\text{H}_{16}\text{N}_2\text{O}$, $[\text{M}+\text{H}]^+$, 313.1335, found 313.1345.

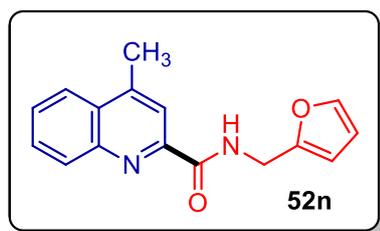
4-Methyl-N-(thiophen-2-ylmethyl) quinoline-2-carboxamide: 52m (113 mg) was obtained



through the general procedure in 80 % yield as a white solid, m.p. 145-148 °C. $R_f = 0.41$ (EtOAc-Hexane 20/80). ^1H NMR (300 MHz, CDCl_3) δ (ppm) 8.71 (s, 1H), 8.19 (d, $J = 0.9$ Hz, 1H), 8.12 – 7.97 (m, 2H), 7.77 – 7.67 (m, 1H), 7.66 – 7.56 (m, 1H), 7.25 (dd, $J = 5.2, 1.2$ Hz, 1H), 7.14 – 7.05 (m, 1H), 6.99 (dd, $J = 5.2, 3.4$ Hz, 1H), 4.91 (dd, $J = 6.0, 0.8$ Hz, 2H), 2.75

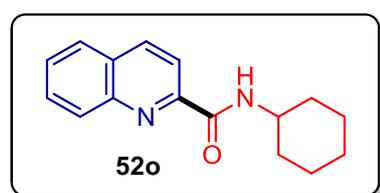
(d, $J = 0.8$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ (ppm) 164.5, 149.0, 146.3, 146.2, 141.0, 130.2, 129.7, 129.3, 127.7, 126.9, 126.1, 125.2, 123.9, 119.5, 38.3, 18.9. IR (neat) ν_{max} (cm^{-1}) = 3381, 2924, 1671, 1596. HRMS (ESI): Calcd. For $\text{C}_{16}\text{H}_{14}\text{N}_2\text{OS}$ $[\text{M}+\text{Na}]^+$, 305.0719, found 305.0714.

N-(Furan-2-ylmethyl)-4-methylquinoline-2-carboxamide: 52n (111 mg) was obtained



through the general procedure in 71 % yield as a white solid; m.p. 145-148 °C. R_f = 0.40 (EtOAc-Hexane 20/80). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 8.59 (s, 1H), 8.18 (d, J = 1.0 Hz, 1H), 8.13 – 8.01 (m, 2H), 7.80-7.72 (m, 1H), 7.68-7.61 (m, 1H), 7.42 (dd, J = 1.8, 1.0 Hz, 1H), 6.41 – 6.32 (m, 2H), 4.74 (d, J = 6.0 Hz, 2H), 2.79 (d, J = 1.0 Hz, 3H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ (ppm) 164.6, 151.4, 149.0, 146.4, 146.1, 142.3, 130.3, 129.7, 127.7, 123.9, 119.5, 110.4, 107.5, 36.5, 18.9. IR (neat) ν_{max} (cm^{-1}) = 3382, 2923, 1673, 1596.

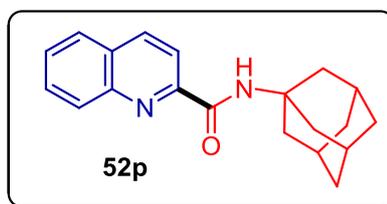
N-Cyclohexylquinoline-2-carboxamide: 52o (101 mg) was obtained through the general



procedure in 80 % yield as a yellow solid; m.p. 92-94 °C. R_f = 0.57 (EtOAc-Hexane 15/85). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 8.34 – 8.22 (m, 2H), 8.17 (d, J = 8.0 Hz, 1H), 8.12 – 8.05 (m, 1H), 7.83 (dd, J = 8.2, 1.0 Hz, 1H), 7.72 (ddd, J = 8.4, 6.8, 1.4 Hz, 1H), 7.57 (ddd, J = 8.0, 6.8, 1.2 Hz, 1H), 4.12 – 3.89

(m, 1H), 2.12 – 1.95 (m, 2H), 1.85 – 1.58 (m, 3H), 1.52 – 1.30 (m, 5H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ (ppm) 163.5, 150.2, 146.5, 137.4, 130.0, 129.7, 129.3, 127.8, 127.8, 118.9, 48.4, 33.2, 25.7, 25.0. IR (neat) ν_{max} (cm^{-1}) = 3381, 2931, 1671, 1526. HRMS (ESI): Calcd. For $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}$, $[\text{M}+\text{H}]^+$, 255.1491, found 255.1499.

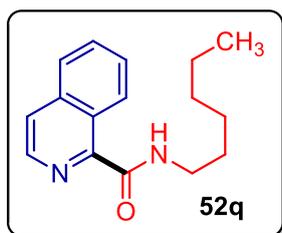
N-((1s, 3s)-Adamantan-1-yl) quinoline-2-carboxamide: 52p (111 mg) was obtained through



the general procedure in 72 % yield as a white gel. R_f = 0.56 (EtOAc-Hexane 15/85). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 8.30 (s, 2H), 8.20 – 8.07 (m, 2H), 7.87 (dd, J = 8.2, 1.4 Hz, 1H), 7.75 (dtd, J = 8.4, 6.8, 1.4 Hz, 1H), 7.61 (ddd, J = 8.2, 6.8, 1.2 Hz, 1H), 2.33 – 2.10 (m, 9H), 1.87 – 1.67 (m, 6H). ^{13}C

NMR (75 MHz, CDCl_3) δ (ppm) 163.4, 150.9, 146.4, 137.5, 130.0, 129.7, 129.2, 127.8, 127.7, 118.6, 51.8, 41.6, 36.6, 29.6. IR (neat) ν_{max} (cm^{-1}) = 3364, 2908, 1676, 1527. HRMS (ESI): Calcd. For $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}$ $[\text{M}+\text{Na}]^+$, 329.1624, found 329.1625.

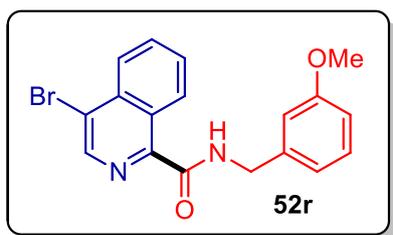
N-Hexylisoquinoline-3-carboxamide: 52q (99 mg) was obtained through the general



procedure in 77 % yield as a yellow gel. R_f = 0.60 (EtOAc-Hexane 15/85). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 9.65 – 9.52 (m, 1H), 8.41 (d, J = 5.5 Hz, 1H), 8.21 (s, 1H), 7.86 – 7.55 (m, 4H), 3.58 – 3.39 (m, 2H), 1.64 (q, J = 7.8 Hz, 2H), 1.50 – 1.23 (m, 6H), 0.96 – 0.80 (m, 3H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ (ppm) 166.1, 148.6, 140.2, 137.4, 130.5, 128.6, 128.0, 127.0, 126.8, 124.2, 39.6, 31.6, 29.7, 26.8, 22.6, 14.1. IR

(neat) ν_{max} (cm^{-1}) = 3381, 2929, 1666, 1518. HRMS (ESI): Calcd. $\text{C}_{16}\text{H}_{21}\text{N}_2\text{O}$, $[\text{M}+\text{H}]^+$, 257.1648, found, 257.1651.

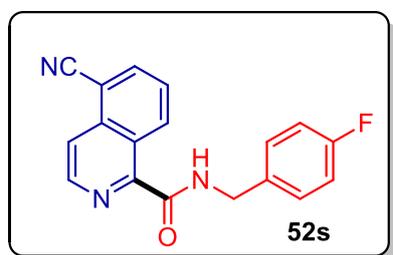
4-Bromo-N-(3-methoxybenzyl) isoquinoline-1-carboxamide: 52r (131 mg) was obtained



through the general procedure in 70 % yield as a yellow gel. $R_f = 0.61$ (EtOAc-Hexane 15/85). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 9.68 (d, $J = 8.4$ Hz, 1H), 8.61 (bs, 1H), 8.49 (bs, 1H), 8.19 (d, $J = 8.4$ Hz, 1H), 7.90 – 7.66 (m, 2H), 7.27 (t, $J = 7.0$ Hz, 1H), 7.07 – 6.92 (m, 2H), 6.84 (d, $J = 8.2$ Hz, 1H), 4.70 (d, $J = 6.0$ Hz, 2H), 3.81 (s, 3H). $^{13}\text{C NMR}$ (75

MHz, CDCl_3) δ (ppm) 165.4, 159.9, 147.4, 142.1, 139.8, 135.9, 131.8, 129.8, 129.5, 128.4, 126.1, 123.5, 123.3, 120.1, 113.5, 113.0, 55.5, 55.3, 43.6. **IR (neat)** ν_{max} (cm^{-1}) = 3378, 2929, 1668, 1516. **HRMS (ESI):** Calcd. For, $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_2\text{Br}$, $[\text{M}+\text{H}]^+$, 371.0389, found 371.0392.

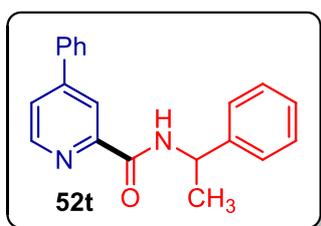
Cyano-N-(4-fluorobenzyl)isoquinoline-1-carboxamide : 52s (107 mg) was obtained through



the general procedure in 70 % yield as a yellow gel. $R_f = 0.30$ (EtOAc-Hexane 30/70). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 10.06 (dt, $J = 8.9, 1.1$ Hz, 1H), 8.78 – 8.55 (m, 2H), 8.29 – 8.11 (m, 2H), 7.79 (dd, $J = 8.8, 7.2$ Hz, 1H), 7.46 – 7.36 (m, 2H), 7.15 – 7.00 (m, 2H), 4.71 (d, $J = 6.1$ Hz, 2H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ (ppm) 165.2, 164.0, 148.6, 142.7,

137.0, 133.7, 129.7, 129.6, 127.9, 126.7, 121.6, 116.7, 115.9, 115.6, 109.9, 43.1. **IR (neat)** ν_{max} (cm^{-1}) = 3381, 2929, 1666, 1518. **HRMS (ESI):** Calcd. For $\text{C}_{16}\text{H}_{21}\text{N}_2\text{O}$, $[\text{M}+\text{Na}]^+$, 328.0856, found, 328.0855.

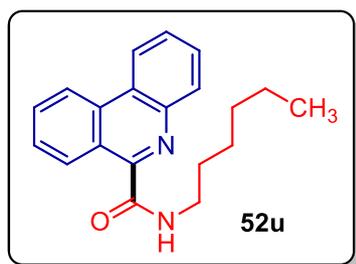
4-Phenyl-N (1-phenylethyl) picolinamide: 52t (86 mg) was obtained through the general



procedure in 57 % yield as a yellow gel. $R_f = 0.53$ (EtOAc-Hexane 20/80). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 8.58 (dd, $J = 5.1, 0.7$ Hz, 1H), 8.52 – 8.30 (m, 2H), 7.73 – 7.68 (m, 2H), 7.64 (dd, $J = 5.1, 1.9$ Hz, 1H), 7.54 – 7.42 (m, 5H), 7.40 – 7.33 (m, 2H), 7.31 – 7.27 (m, 1H), 5.45 – 5.25 (m, 1H), 1.65 (d, $J = 6.9$ Hz, 3H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ (ppm) 163.6, 150.6, 150.0, 148.7, 143.4, 137.5,

129.4, 128.8, 127.3, 126.4, 123.9, 120.3, 49.0, 22.2. **IR (neat)** ν_{max} (cm^{-1}) = 3378, 2974, 1670, 1515. **HRMS (ESI):** Calcd. For, $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}$ $[\text{M}+\text{Na}]^+$, 325.1311, found 325.1325.

N-Hexylphenanthridine-6-carboxamide: 52u (142 mg) was obtained through the general

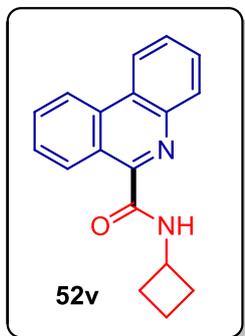


procedure in 93 % yield as a yellow solid; m.p. 91-95 °C. $R_f = 0.61$ (EtOAc-Hexane 10/90). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 9.59 – 9.48 (m, 1H), 8.55 – 8.39 (m, 2H), 8.20 (s, 1H), 8.12 – 8.03 (m, 1H), 7.81 – 7.72 (m, 1H), 7.71 – 7.57 (m, 3H), 3.61 – 3.45 (m, 2H), 1.79 – 1.60 (m, 2H), 1.51 – 1.24 (m, 6H), 0.99 – 0.79 (m, 3H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ (ppm) 166.1, 149.8, 141.8,

133.6, 130.8, 130.3, 129.0, 128.7, 128.3, 127.8, 125.3, 124.2, 122.0, 121.7, 39.8, 31.6, 29.6,

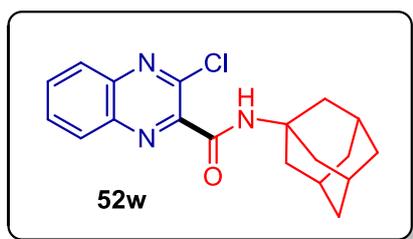
26.8, 22.6, 14.1. **IR (neat)** ν_{\max} (cm^{-1}) = 3295, 2928, 1653, 1522. **HRMS (ESI):** Calcd. For, $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}$, $[\text{M}+\text{H}]^+$, 307.1804, found 307.1810.

N-Cyclobutylphenanthridine-6-carboxamide: 52v (110 mg) was obtained through the



general procedure in 79 % yield as a yellow gel. $R_f = 0.53$ (EtOAc-Hexane 10/90). **^1H NMR (300 MHz, CDCl_3)** δ (ppm) 9.66 – 9.49 (m, 1H), 8.65 – 8.55 (m, 2H), 8.31 (d, $J = 7.4$ Hz, 1H), 8.22 – 8.12 (m, 1H), 7.85 (td, $J = 7.0, 3.5$ Hz, 1H), 7.80 – 7.69 (m, 3H), 4.67 (dd, $J = 16.4, 8.1$ Hz, 1H), 2.59 – 2.43 (m, 2H), 2.19 – 2.09 (m, 2H), 1.89 – 1.79 (m, 2H). **^{13}C NMR (75 MHz, CDCl_3)** δ (ppm) 165.2, 149.5, 141.9, 133.8, 131.1, 130.5, 129.2, 128.9, 128.5, 128.0, 125.6, 124.4, 122.2, 121.9, 45.06, 31.3, 15.5, 8.8. **IR (neat)** ν_{\max} (cm^{-1}) = 3372, 2976, 1678, 1520. **HRMS (ESI):** Calcd. For, $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}$, $[\text{M}+\text{H}]^+$, 277.1335, found 277.1340.

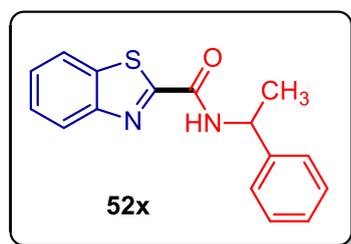
N-((3s, 5s, 7s)-Adamantan-1-yl)-3-chloroquinoline-2-carboxamide: 52w (120 mg) was



obtained through the general procedure in 71 % yield as a yellow solid; m.p. 198-203 °C. $R_f = 0.30$ (EtOAc-Hexane 30/70). **^1H NMR (300 MHz, CDCl_3)** δ (ppm) 8.11 – 7.96 (m, 2H), 7.89 – 7.72 (m, 2H), 7.15 (s, 1H), 2.28 – 2.07 (m, 9H), 1.73 (s, 6H). **^{13}C NMR (75 MHz, CDCl_3)** δ (ppm) 161.8, 145.1, 144.2, 142.4, 138.9, 132.4, 130.9, 129.2, 128.3, 52.8,

41.6, 41.4, 36.4, 29.7, 29.6. **IR (neat)** ν_{\max} (cm^{-1}) = 3294, 2909, 1665, 1563. **HRMS (ESI):** Calcd. For, $\text{C}_{19}\text{H}_{21}\text{N}_3\text{OCl}$, $[\text{M}+\text{H}]^+$, 342.1367, found 342.1362.

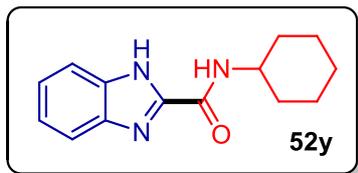
N-(1-Phenylethyl) benzo[d]thiazole-2-carboxamide: 52x (58 mg) was obtained through the



general procedure in 41 % yield as a yellow solid; m.p. 145-148 °C. $R_f = 0.50$ (EtOAc-Hexane 20/80). **^1H NMR (300 MHz, CDCl_3)** δ (ppm) 8.11 – 8.04 (m, 1H), 8.02 – 7.94 (m, 1H), 7.74 (d, $J = 8.4$ Hz, 1H), 7.61 – 7.29 (m, 6H), 5.48 – 5.27 (m, 1H), 1.70 (d, $J = 6.8$ Hz, 3H). **^{13}C NMR (75 MHz, CDCl_3)** δ (ppm) 164.1, 159.1, 152.9, 142.5, 137.2, 128.9, 127.7, 126.9, 126.8, 126.4,

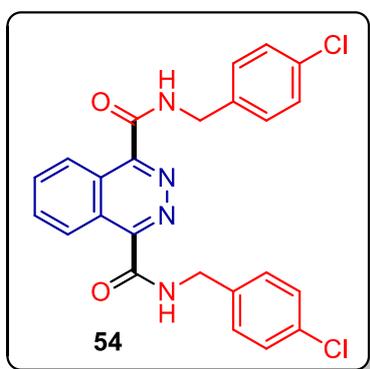
124.3, 122.5, 49.6, 21.9. **IR (neat)** ν_{\max} (cm^{-1}) = 3392, 2976, 1667, 1524. **HRMS (ESI):** Calcd. For $\text{C}_{16}\text{H}_{14}\text{N}_2\text{OS}$ $[\text{M}+\text{Na}]^+$, 305.0719, found 305.0717.

N-Cyclohexyl-1H-benzo[d]thiazole-2-carboxamide: 52y (71 mg) was obtained through the



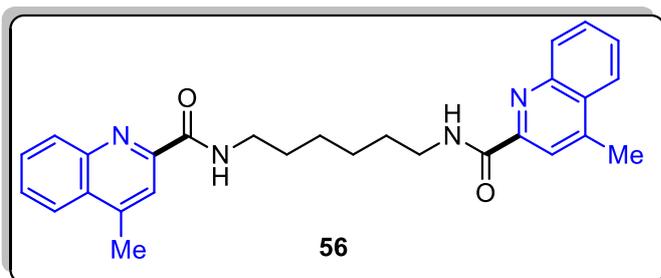
general procedure in 59 % yield as a white solid; m.p. 153-156 °C. $R_f = 0.50$ (EtOAc-Hexane 20/80). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 7.71 (s, 3H), 7.41 – 7.31 (m, 2H), 4.17 – 3.92 (m, 1H), 2.08 (d, $J = 9.9$ Hz, 2H), 1.83 (dd, $J = 9.2, 3.5$ Hz, 2H), 1.69 (d, $J = 12.6$ Hz, 1H), 1.51 – 1.35 (m, 4H), 1.33 – 1.14 (m, 2H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ (ppm) 159.1, 158.3, 145.3, 142.9, 134.1, 124.9, 123.3, 120.4, 112.2, 48.9, 32.9, 32.6, 25.4, 24.8. **IR (neat)** ν_{max} (cm^{-1}) = 3379, 2971, 1658, 1541. **HRMS (ESI):** Calcd. For $\text{C}_{14}\text{H}_{17}\text{N}_3\text{O}$ $[\text{M}+\text{Na}]^+$, 266.1263, found 266.1270.

N1,N4-Bis(4-chlorobenzyl)phthalazine-1,4-dicarboxamide: 54 (188 mg) was obtained



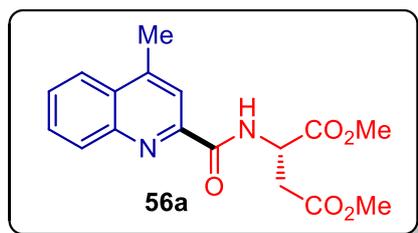
through the general procedure in 81 % yield as a yellow solid, m.p. 170-73 °C. $R_f = 0.31$ (EtOAc-Hexane 30/70). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 9.65 – 9.42 (m, 2H), 8.46 (s, 2H), 8.14 – 7.91 (m, 2H), 7.40 – 7.28 (m, 8H), 4.71 (dd, $J = 6.2, 1.8$ Hz, 4H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ (ppm) 163.8, 150.4, 136.1, 134.0, 133.5, 129.2, 129.0, 126.8, 126.4, 43.1. **IR (neat)** ν_{max} (cm^{-1}) = 3288, 2922, 1640, 1530. **HRMS (ESI):** Calcd. For, $\text{C}_{24}\text{H}_{18}\text{N}_4\text{O}_2\text{Cl}_2$ $[\text{M}+\text{Na}]^+$, 487.0699, found 487.0713.

N, N'-(Hexane-1,6-diyl)bis(4-methylquinoline-2-carboxamide) : 7 (115 mg) was obtained



through the general procedure, in 51 % yield as a yellow gel. $R_f = 0.51$ (EtOAc-Hexane 30/70). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 8.31 (t, $J = 5.2$ Hz, 2H), 8.15 (d, $J = 0.8$ Hz, 2H), 8.09 (dd, $J = 8.4, 0.8$ Hz, 2H), 8.02 (dd, $J = 8.4, 0.8$ Hz, 2H), 7.77-7.70 (m, 2H), 7.65 – 7.56 (m, 2H), 3.58 – 3.49 (m, 4H), 2.76 (d, $J = 0.8$ Hz, 6H), 1.78 – 1.67 (m, 4H), 1.57 – 1.48 (m, 4H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ (ppm) 164.7, 149.5, 146.3, 146.0, 130.3, 129.6, 129.2, 127.5, 123.9, 119.4, 39.5, 29.7, 26.8, 18.9. **IR (neat)** ν_{max} (cm^{-1}) = 3380, 2929, 1667, 1531. **HRMS (ESI):** Calcd. For $\text{C}_{28}\text{H}_{30}\text{N}_4\text{O}_2$ $[\text{M}+\text{Na}]^+$, 477.2266, found 477.2260.

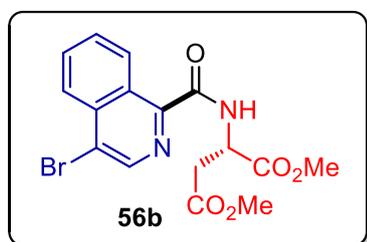
(S)-Dimethyl 2-(4-methylquinoline-2-carboxamido) succinate: 56a (144 mg) was obtained



through the general procedure, in 87 % yield as a yellow gel. $R_f = 0.43$ (EtOAc-Hexane 30/70). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 9.04 (d, $J = 8.4$ Hz, 1H), 8.14 – 8.06 (m, 2H), 7.97 (d, $J = 8.4, 0.9$ Hz, 1H), 7.76 – 7.67 (m, 1H), 7.61 – 7.45 (m, 1H), 5.16 – 5.08 (m, 1H), 3.78 (s, 3H), 3.70 (s, 3H), 3.15 (dd, $J = 17.0, 4.8$ Hz, 1H), 3.01 (dd, $J = 17.0, 4.8$

Hz, 1H), 2.71 (d, $J = 0.8$ Hz, 3H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ (ppm) 171.3, 164.7, 148.5, 146.4, 146.0, 130.6, 129.7, 129.3, 127.8, 123.8, 119.3, 52.9, 52.1, 48.8, 36.4, 18.9. **IR** (neat) ν_{max} (cm^{-1}) = 3383, 2954, 1677, 1504. **HRMS** (ESI): Calcd. For $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_5$ $[\text{M}+\text{Na}]^+$, 353.1113, found 353.1111. $[\alpha]_{\text{D}}^{25} +31.75$ (c 1.8, CHCl_3).

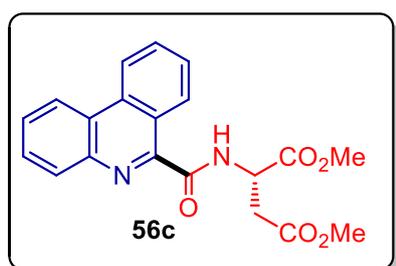
(S)-Dimethyl 2-(4-bromoisoquinoline-1-carboxamido) succinate: 56b (169 mg) was



obtained through the general procedure, in 86 % yield as a yellow gel. $R_f = 0.41$ (EtOAc-Hexane 30/70). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 9.56 – 9.51 (m, 1H), 8.95 (d, $J = 8.2$ Hz, 1H), 8.65 (s, 1H), 8.21 – 8.08 (m, 1H), 7.81 – 7.74 (m, 1H), 7.72 – 7.65 (m, 1H), 5.14 – 5.06 (m, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 3.16 (dd, $J = 17.0, 4.8$ Hz, 1H), 3.02 (dd, $J = 17.0, 4.8$ Hz, 1H).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ (ppm) 171.2, 165.2, 146.5, 142.4, 135.8, 131.8, 129.6, 128.1, 126.1, 123.8, 53.0, 52.2, 48.8, 36.3. **IR** (neat) ν_{max} (cm^{-1}) = 3383, 2953, 1673, 1507. **HRMS** (ESI): Calcd. For $\text{C}_{16}\text{H}_{15}\text{BrN}_2\text{O}_5$ $[\text{M}+\text{Na}]^+$, 417.0062, found 417.0057. $[\alpha]_{\text{D}}^{25} +29.38$ (c 2.0, CHCl_3).

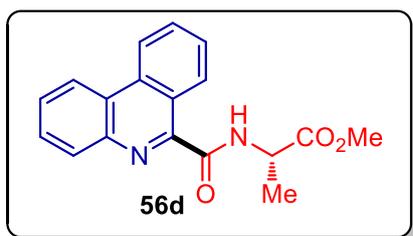
(S)-Dimethyl 2-(4-phenanthridine-6-carboxamido) succinate: 56c (163 mg) was obtained



through the general procedure, in 89 % yield as a yellow gel. $R_f = 0.44$ (EtOAc-Hexane 30/70). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 9.57 – 5.52 (m, 1H), 9.09 (d, $J = 8.2$ Hz, 1H), 8.55 – 8.43 (m, 2H), 8.17 – 8.12 (m, 1H), 7.78 (m, 1H), 7.73 – 7.65 (s, 3H), 5.22 – 5.15 (m, 1H), 3.83 (s, 3H), 3.72 (s, 3H), 3.21 (dd, $J = 17.0, 4.8$ Hz, 1H), 3.09 (dd, $J = 17.0, 4.8$ Hz, 1H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ (ppm) 171.3, 165.8,

148.1, 141.7, 133.6, 130.8, 128.7, 127.9, 125.4, 124.2, 121.9, 52.9, 52.1, 48.9, 36.4. **IR** (neat) ν_{max} (cm^{-1}) = 3379, 2954, 1674, 1505. $[\alpha]_{\text{D}}^{25} +71.80$ (c 1.8, CHCl_3).

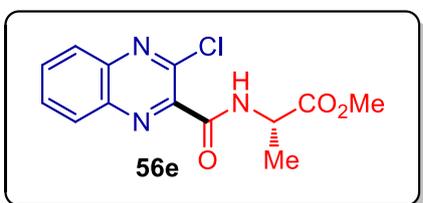
(S)-Methyl 2-(phenanthridine-6-carboxamido) propanoate: 56d (140 mg) was obtained



through the general procedure, in 91 % yield as a white solid. m.p. 149-152 °C. $R_f = 0.47$ (EtOAc-Hexane 30/70). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 9.54 (dd, $J = 8.4, 0.8$ Hz, 1H), 8.73 (d, $J = 7.4$ Hz, 1H), 8.60 – 8.37 (m, 2H), 8.22 – 8.06 (m, 1H), 7.86 – 7.59 (m, 4H), 4.92 - 4.81 (m, 1H), 3.84 (s, 3H), 1.66 (d, $J = 7.2$ Hz, 3H). $^{13}\text{C NMR}$ (75 MHz,

CDCl_3) δ (ppm) 173.4, 165.6, 153.2, 148.5, 141.7, 133.6, 130.8, 130.5, 128.8, 128.5, 127.9, 125.4, 124.1, 122.0, 121.7, 52.5, 48.4, 18.3. **IR (neat)** ν_{max} (cm^{-1}) = 3328, 2924, 1743, 1525. **HRMS (ESI):** Calcd. For $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_3$ $[\text{M}+\text{Na}]^+$, 331.1058, found 331.1054. $[\alpha]_{\text{D}}^{25} +94.70$ (c 2.3, CHCl_3).

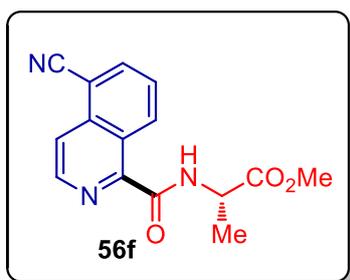
(S)-Methyl 2-(3-chloroquinoline-2-carboxamido) propanoate: 56e (102 mg) was obtained



through the general procedure, in 69 % yield as a yellow gel. $R_f = 0.39$ (EtOAc-Hexane 30/70). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 8.22 – 8.16 (m, 1H), 8.13 – 8.08 (m, 1H), 7.98 – 7.83 (m, 2H), 4.94 – 4.80 (m, 1H), 3.85 (s, 3H), 1.64 (d, $J = 7.2$ Hz, 3H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ (ppm)

173.1, 161.9, 145.2, 142.7, 142.2, 138.9, 132.9, 131.0, 129.4, 128.3, 52.7, 48.5, 18.4. **IR (neat)** ν_{max} (cm^{-1}) = 3331, 2924, 1741, 1680, 1530. **HRMS (ESI):** Calcd. For $\text{C}_{13}\text{H}_{12}\text{ClN}_3\text{O}_3$ $[\text{M}+\text{Na}]^+$, 316.0464, found 316.0458. $[\alpha]_{\text{D}}^{25} +39.33$ (c 1.7, CHCl_3).

(S)-Methyl 2-(5-cyanoisoquinoline-1-carboxamido) propanoate: 56f (104 mg) was obtained

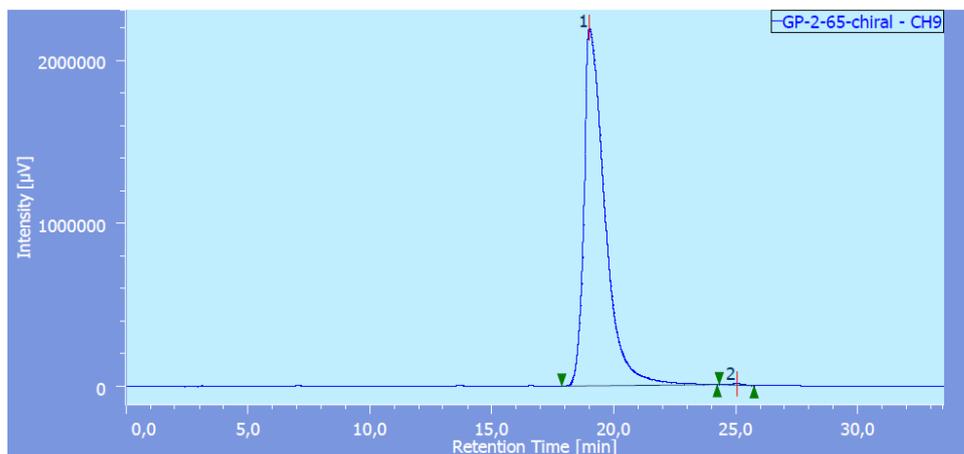


through the general procedure, in 74 % yield as a white solid; m.p. 123-126 °C. $R_f = 0.51$ (EtOAc-Hexane 30/70). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ (ppm) 9.94 (dt, $J = 8.8, 1.2$ Hz, 1H), 8.74 (s, 1H), 8.72 (d, $J = 5.6$ Hz, 2H), 8.23 (dd, $J = 5.6, 1.2$ Hz, 1H), 8.16 (dd, $J = 7.2, 1.2$ Hz, 1H), 7.75 (dd, $J = 8.8, 7.2$ Hz, 1H), 4.90 – 4.77 (m, 1H), 3.83 (s, 3H), 1.62 (d, $J = 7.2$ Hz, 3H). $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ (ppm) 173.1, 164.7, 148.1, 142.7, 136.8,

133.3, 127.8, 126.5, 121.5, 116.5, 109.8, 52.6, 48.3, 27.7, 18.3. **IR (neat)** ν_{max} (cm^{-1}) = 3377, 2929, 1743, 1671, 1513. **HRMS (ESI):** Calcd. For $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}_3$ $[\text{M}+\text{Na}]^+$, 306.0854, found 306.0849. $[\alpha]_{\text{D}}^{25} +167.66$ (c 1.4, CHCl_3).

8. HPLC Data for (S)-Dimethyl 2-(4-phenanthridine-6-carboxamido) succinate (52c)

Chromatogram



Chromatogram Information

User Name Administrator
 Date Modified 05/10/2018 15:53:15
 Description
 HPLC System Name Orga
 Injection Date 05/10/2018 15:19:40
 Volume 20.00 [µL]
 Sample Number 32
 Project Name Test
 Acquisition Time 59.0 [min]
 Acquisition Sequence GP-2-65-Chiral-85-Hx-15-EtOH 1mL-min 20° C IA
 Control Method 85A-Hx 15D-EtOH 60Min-1ml-min 20° C
 Peak ID Table
 Calibration Method
 Additional Information

Channel & Peak Information Table

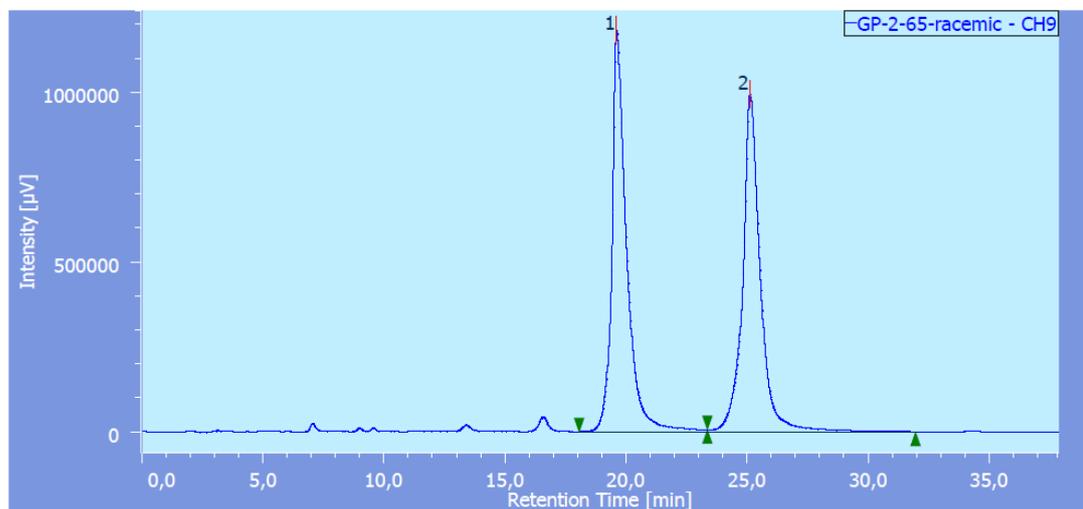
Chromatogram Name GP-2-65-chiral-CH9
 Sample Name
 Channel Name 252,5nm
 Sampling Interval 100 [msec]
 Peak Method IT (Manual)

Decision

| # | Peak Name | CH | tR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|-----------|----|----------|---------------|-------------|--------|---------|----------|-------|------------|-----------------|---------|
| 1 | Unknown | 9 | 18.993 | 131633855 | 2193708 | 99.762 | 99.599 | N/A | 2838 | 5.103 | 1.928 | |
| 2 | Unknown | 9 | 25.023 | 313987 | 8828 | 0.238 | 0.401 | N/A | 11256 | N/A | 0.945 | |

HPLC Data for Dimethyl 2-(4-phenanthridine-6-carboxamido) succinate (rac-52c)

Chromatogram



Chromatogram Information

User Name Administrator
 Date Modified 05/10/2018 12:21:01
 Description
 HPLC System Name Orga
 Injection Date 05/10/2018 11:43:07
 Volume 20,00 [µL]
 Sample Number 31
 Project Name Test
 Acquisition Time 59,0 [min]
 Acquisition Sequence GP-2-65-Racemic-85-Hx-15-EtOH 1mL-min 20° C IA
 Control Method 85A-Hx 15D-EtOH 60Min-1ml-min 20° C
 Peak ID Table
 Calibration Method
 Additional Information

Channel & Peak Information Table

Chromatogram Name GP-2-65-racemic-CH9
 Sample Name
 Channel Name 252,5nm
 Sampling Interval 100 [msec]
 Peak Method IT (Manual)
 Formula
 Decision

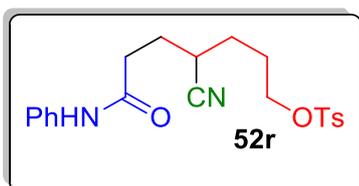
| # | Peak Name | CH | tR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|-----------|----|----------|---------------|-------------|--------|---------|----------|------|------------|-----------------|---------|
| 1 | Unknown | 9 | 19,608 | 49926380 | 1179801 | 49,688 | 54,319 | N/A | 7055 | 5,384 | 1,455 | |
| 2 | Unknown | 9 | 25,113 | 50554084 | 992200 | 50,312 | 45,681 | N/A | 8094 | N/A | 1,093 | |

Experimental part for Chapter III

General Procedure (A) for the photochemical initiation.

A dried round bottom flask containing a magnetic bar was charged with the α -iodo secondary amide **1e-f** (1.0 eq.), but-3-en-1-yl benzenesulfonate (2.0 eq.), *p*-toluenesulfonyl cyanide **5** (2.0 equiv), $(\text{Bu}_3\text{Sn})_2$ (1.5 eq.) in distilled dry benzene (0.1 M), then the reaction mixture was degassed (for 10-15 min) and stirred under light (UV sunlamp) till consumption of starting material. The solvent was then evaporated in vacuo and the residue purified by column chromatography to afford the desired amide.

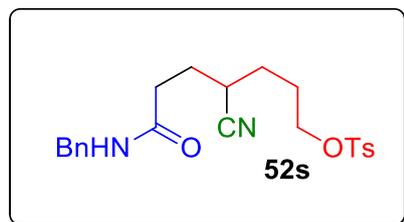
4-cyano-7-oxo-7-(phenyl amino) heptyl benzenesulfonate: 52r (99 mg) was obtained



through the general procedure **A**, in 67 % yield as a yellow oil. **52r** (91 mg) was also obtained through the general procedure **B**, in 61 % yield as yellow oil. $R_f = 0.28$ (EtOAc/Pentane 80/20). **IR** (ATR) $\nu_{\text{max}} (\text{cm}^{-1}) = 3322, 2929, 2870, 2240, 1668, 1445, 1359, 1187, 756, 587$. **^1H NMR (300 MHz, CDCl_3):** δ (ppm) = 7.95 (bs, 1H), 7.90 (ddd, $J = 7.0, 3.2, 1.8$ Hz, 2H), 7.72 – 7.61 (m, 1H), 7.60 – 7.45 (m, 4H), 7.30 (d, $J = 7.6$ Hz, 2H), 7.08 (dd, $J = 7.4, 7.4$ Hz, 1H), 4.06 (t, $J = 5.9$ Hz, 2H), 2.74 – 2.40 (m, 3H), 2.10 – 1.95 (m, 1H), 1.94 – 1.72 (m, 3H), 1.71 – 1.58 (m, 2H).

^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 169.6, 137.8, 134.0, 129.4, 129.0, 127.8, 124.4, 121.3, 120.1, 120.0, 69.7, 34.0, 30.5, 28.3, 27.5, 26.5. **HRMS (ESI):** $[\text{M}+\text{Na}]^+ \text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_4\text{NaS}$: calcd. 409.1192, found 409.1189.

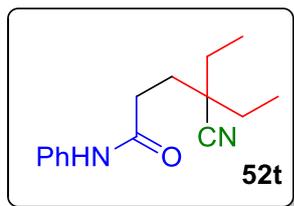
7-(benzyl amino)-4-cyano-7-oxoheptyl benzenesulfonate: 52s (71 mg) was obtained through



the general procedure **A**, in 49 % yield as a yellow oil. **52s** (93 mg) was also obtained through the general procedure **B**, in 64 % yield as a yellow oil. $R_f = 0.26$ (EtOAc/Pentane 80/20). **IR** (ATR) $\nu_{\text{max}} (\text{cm}^{-1}) = 3307, 2934, 2239, 1651, 1359, 1445, 1176, 1097, 925, 588$. **^1H NMR (300 MHz, CDCl_3):** δ (ppm) = 7.92 (d, $J = 7.0$ Hz, 2H), 7.69 (s, 1H), 7.61 – 7.57 (m, 2H), 7.35 – 7.27 (m, 6H), 5.98 (s, 1H), 4.44 (dd, $J = 5.7, 2.1$ Hz, 2H), 4.10 (d, $J = 6.2$ Hz, 1H), 2.67 (d, $J = 4.6$ Hz, 1H), 2.46 – 2.35 (m, 2H), 2.02 (d, $J = 8.5$ Hz, 1H), 1.85 (dd, $J = 10.9, 4.8$ Hz, 3H), 1.69 (s, 2H).

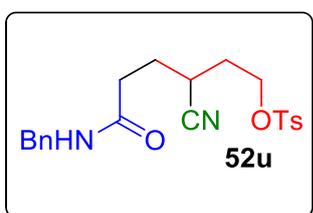
^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 170.7, 138.0, 135.9, 134.0, 129.4, 128.8, 127.9, 127.9, 127.7, 121.2, 69.6, 43.8, 33.2, 30.6, 28.4, 27.7, 26.6. **HRMS (ESI):** $[\text{M}+\text{Na}]^+ \text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_4\text{NaS}$: calcd. 423.1350, found 423.1354.

4-cyano-4-Ethyl-N-phenylhexanamide: 52t (85 mg) was obtained through the general



procedure **A**, in 91 % yield as a yellow oil. **52t** (46.6 mg) was also obtained through the general procedure **B**, in 54 % yield as a yellow oil. $R_f = 0.59$ (EtOAc/Pentane 60/40). **IR (ATR)** ν_{\max} (cm^{-1}) = 3313, 2972, 2232, 1666, 1546, 1443, 1329, 1251, 756, 506. **$^1\text{H NMR}$ (300 MHz, CDCl_3):** δ (ppm) = 7.64 (d, $J = 7.6$, Hz, 2H), 7.47 (s, 2H), 7.39 (s, 1H), 2.66 (d, $J = 8.0$, 8.0 Hz, 2H), 2.10 (s, 2H), 1.88 – 1.73 (m, 4H), 1.42 (s, 2H), 1.18 (s, 6H). **$^{13}\text{C NMR}$ (75 MHz, CDCl_3):** δ (ppm) = 169.9, 137.9, 129.1, 124.5, 123.6, 119.9, 41.5, 33.0, 30.8, 28.5, 8.7. **HRMS (ESI):** $[\text{M}+\text{Na}]^+$ $\text{C}_{15}\text{H}_{20}\text{N}_2\text{ONa}$: calcd. 267.1189, found 267.1192.

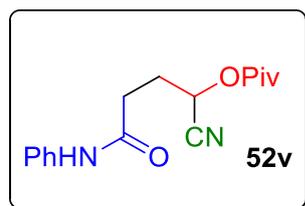
6-(benzylamino)-3-cyano-6-oxohexyl benzenesulfonate: 52u (56 mg) was obtained through



the general procedure **A**, in 40 % yield as a light green oil. (56 mg) was also obtained through the general procedure **B**, in 40 % yield as a yellow oil. $R_f = 0.28$ (EtOAc/Pentane 80/20). **IR (ATR)** ν_{\max} (cm^{-1}) = 3304, 2925, 2240, 1649, 1542, 1361, 1187, 1096, 754, 586. **$^1\text{H NMR}$ (300 MHz, CDCl_3):** δ (ppm) = 7.96 – 7.88 (m, 2H), 7.75 – 7.54 (m, 3H), 7.39 – 7.26 (m, 5H), 5.94 (s, 1H), 4.44 (d, $J = 5.7$, Hz,

2H), 4.20 (ddd, $J = 13.3$, 9.2, 5.2 Hz, 2H), 2.86 (s, 1H), 2.39 (dd, $J = 10.8$, 4.8 Hz, 2H), 2.07 – 1.85 (m, 4H), 1.45 – 1.19 (m, 5H), 0.89 (dd, $J = 9.3$, 4.6 Hz, 2H). **$^{13}\text{C NMR}$ (75 MHz, CDCl_3):** δ (ppm) = 134.2, 129.5, 128.9, 128.0, 127.9, 127.7, 76.7, 67.1, 43.8, 33.2, 31.7, 27.7, 27.5, 27.1, 13.7. **HRMS (ESI):** $[\text{M}+\text{Na}]^+$ $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_4\text{NaS}$: calcd. 409.1193, found 409.1192.

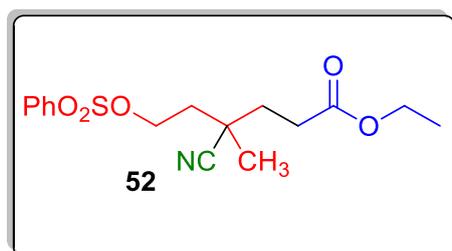
1-cyano-4-oxo-4-(phenyl amino) butyl pivalate: 52v (71 mg) was obtained through the general



procedure **A**, in 64 % yield as a yellow oil. (70 mg) was also obtained through the general procedure **B**, in 63 % yield as a yellow oil. $R_f = 0.37$ (EtOAc/Pentane 70/30). **IR (ATR)** ν_{\max} (cm^{-1}) = 3316, 2960, 1745, 1600, 1544, 1443, 1131, 1052, 756. **$^1\text{H NMR}$ (300 MHz, CDCl_3):** δ (ppm) = 7.84 (s, 1H), 7.68 (d, $J = 7.7$, Hz, 2H), 7.47 (dd,

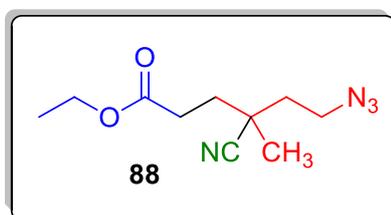
$J = 21.9$, 13.7 Hz, 2H), 7.29 (d, $J = 7.4$, 7.4 Hz, 1H), 5.62 (s, $J = 6.5$ Hz, 1H), 2.74 (dd, $J = 7.2$, 1.8 Hz, 2H), 2.61 – 2.51 (m, 2H), 1.39 (d, $J = 3.7$ Hz, 9H). **$^{13}\text{C NMR}$ (75 MHz, CDCl_3):** δ (ppm) = 176.7, 168.7, 137.7, 129.4, 129.1, 124.7, 124.6, 120.0, 116.8, 60.6, 31.8, 27.8, 26.9, 13.6. **HRMS (ESI):** $[\text{M}+\text{Na}]^+$ $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_3\text{Na}$: calcd. 311.1377, found 311.1366.

Ethyl 4-cyano-4-methyl-6-((phenyl sulfonyl) oxy) hexanoate: 52 (340 mg) was obtained



through the general procedure, in 90 % yield as a yellow oil. $R_f = 0.52$ (EtOAc/Pentane 30/70); **IR (ATR) ν_{max} (cm^{-1})** = 2981, 2872, 2235, 1732, 1645. **1H NMR (300 MHz, $CDCl_3$)**: δ 7.64 – 7.56 (m, 2H), 7.40 – 7.32 (m, 1H), 7.26 (s, 2H), 3.92 (t, $J = 6.6$ Hz, 2H), 3.81 (q, $J = 7.1$ Hz, 2H), 2.13 (t, $J = 8.1$ Hz, 2H), 1.76 – 1.47 (m, 4H), 0.99 (s, 3H), 0.94-0.88 (m, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ 188.13, 151.76, 150.37, 145.68, 144.11, 138.50, 93.89, 93.47, 93.04, 82.60, 53.85, 50.86, 50.41, 46.04, 39.97, 30.38. **HRMS (ESI)**: Calcd. For $C_{16}H_{21}NO_5S$ $[M+Na]^+$, 362.3032 found 362.3036.

Ethyl 6-azido-4-cyano-4-methylhexanoate (88): A 10 mL oven dry one-neck round-bottom

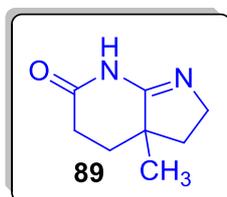


flask was equipped with a magnetic stir bar was charged sequentially with Ethyl 4-cyano-4-methyl-6-((phenyl sulfonyl) oxy) hexanoate (200 mg, 0.589 mmol, 1 equiv), in anhydrous dimethylformamide (0.2M) sodium azide (115 mg, 1.769 mmol, 3 equiv). Then the reaction mixture heated at 60

$^{\circ}C$ for 3h. Finally, reaction mixture quenched by addition of water (2 ml) and aqueous layer extracted 3-4 times with ethyl acetate (50 ml). Organic layer washed with brine, dried over sodium sulphate. Then the solvent was removed in vacuo, and the residue was purified by flash column chromatography over silica gel using EtOAc/pentane (10/90 to 60/40) afforded the title compound (280 mg, 84 %).

. $R_f = 0.44$ (EtOAc/Pentane 60/40); **IR (ATR) ν_{max} (cm^{-1})** = 2978, 2881, 2241, 1729, 1453. **1H NMR (300 MHz, $CDCl_3$)**: δ 4.17 (q, $J = 7.2$ Hz, 2H), 3.58 – 3.47 (m, 2H), 2.52 (dd, $J = 8.6$ Hz, 2H), 2.14 – 1.58 (m, 5H), 1.38 (s, 3H), 1.34 – 1.23 (m, 4H), 0.93 (t, $J = 7.4$ Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$)**: δ 172.01, 121.00, 60.73, 50.64, 31.33, 30.59, 29.37, 27.28, 26.49, 14.11.

3a-methyl-3, 3a, 4, 5-tetrahydro-2H-pyrrolo [2, 3-b] pyridin-6(7H)-one (89): A 10 mL oven

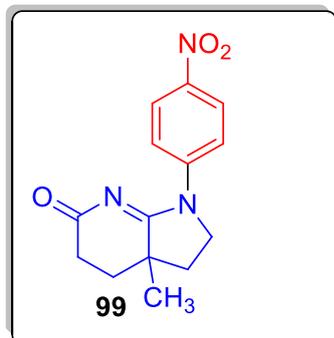


dry one-neck round-bottom flask was equipped with a magnetic stir bar then charged sequentially with ethyl 6-azido-4-cyano-4-methylhexanoate (100 mg, 0.420 mmol, 1 equiv), in a solution of tetrahydrofuran and water (3:1, 0.2 M), and triphenylphosphine (220 mg, 0.840 mmol, 1.2 equiv). Then the reaction mixture was heated at 60 $^{\circ}C$ for 24h. The solvent was removed

in vacuo, and the residue dissolved in ethyl acetate. The organic layer was dried over sodium sulphate, purified by flash column chromatography over silica gel using MeOH/DCM (0/100 to 15/85) affording **89** (25 mg, 53 %). $R_f = 0.23$ (MeOH/DCM 10/90); **IR (ATR) ν_{max} (cm^{-1})** = 3246, 2928, 2232, 1662. **1H NMR (300 MHz, $CDCl_3$)**: δ 9.41 (s, 1H), 3.83 – 3.64 (m, 2H), 2.55 (ddd, $J = 16.5, 12.5, 8.0$ Hz, 2H), 1.99 – 1.89 (m, 2H), 1.85 – 1.66 (m, 2H), 1.18 (s, 3H).

^{13}C NMR (75 MHz, CDCl_3): δ 173.6, 167.1, 53.07, 44.0, 35.41, 26.8, 18.06. HRMS (ESI): Calcd. For $\text{C}_8\text{H}_{12}\text{N}_2\text{O}_1$ $[\text{M}+\text{Na}]^+$, 175.0950 found 175.1013.

3a-methyl-7-(4-nitrophenyl)-3, 3a, 4, 5-tetrahydro-2H-pyrrolo [2, 3-b] pyridin-6(7H)-one



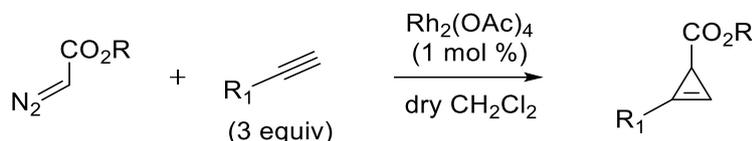
(99): A 10 mL oven dry one-neck round-bottom flask equipped with a magnetic stir bar was charged sequentially with 3a-methyl-3, 3a, 4, 5-tetrahydro-2H-pyrrolo [2, 3-b] pyridin-6(7H)-one (20 mg, 0.131 mmol, 1 equiv), 1-fluoro-4-nitrobenzene (28 mg, 0.196 mmol, 1.5 equiv), sodium hydride (6 mg, 0.262 mmol, 2 equiv), in anhydrous dimethylformamide (0.2M). Then the reaction mixture was stirred at room temperature for 24h. The reaction mixture was quenched by addition of water (1 mL) and the aqueous layer

extracted 4 times with ethyl acetate (50 mL). The organic layer was washed with brine, dried over sodium sulphate. Then the solvent was removed in vacuo, and the residue purified by flash column chromatography over silica gel using MeOH/DCM (0/100 to 10/90), affording compound **99** (23 mg, 66 %). R_f = 0.20 (MeOH/DCM 10/90). IR (ATR) ν_{max} (cm^{-1}) = 3426, 1605, 1550, 1299. ^1H NMR (300 MHz, CDCl_3): δ 8.34 – 8.23 (m, 2H), 8.17 – 8.06 (m, 2H), 4.31 – 4.14 (m, 1H), 4.08 – 3.95 (m, 1H), 2.77 – 2.63 (m, 2H), 2.25 – 1.95 (m, 4H), 1.36 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 182.49, 125.12, 122.08, 50.07, 40.98, 35.48, 33.48, 28.49, 21.44. HRMS (ESI): Calcd. For $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}_3$ $[\text{M}+\text{Na}]^+$, 296.1011.

Experimental part for Chapter IV

General procedure for the synthesis of cyclopropene derivatives

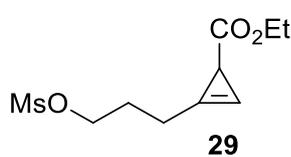
Cyclopropenes were prepared according to a previously described procedure using alkynes, rhodium acetate dimer and ethyl diazoacetate in CH₂Cl₂.



An oven dry 50 mL two-neck round-bottom flask was charged with alkynes (3.0 equiv) and Rh₂(OAc)₄ (0.01 equiv). A solution of ethyl diazoacetate (1 equiv) in DCM (0.5 M) was added via a syringe pump over 12 h. The solvent was then removed in vacuo, and the residue was purified by flash column chromatography to afford the desired cyclopropene derivatives.

Cyclopropenes **25a**¹⁷⁴, **25b**¹, **25c**¹⁷⁵, **25d**¹, **25e**¹⁷⁶, **25f**¹⁷⁷, **25g**¹⁷⁸, **25h**⁴, **25i**⁴ and **225j**¹ were reported and synthesized using general procedure A.

Ethyl 2-(3-((methyl sulfonyl) oxy) propyl) cycloprop-2-enecarboxylate (**29**):



An oven dry 10 mL round-bottom flask was charged with pent-4-yn-1-yl methane sulfonate (1.278 g, 7.83 mmol, 3 equiv), Rh₂(OAc)₄ (5.8 mg, 0.013 mmol, 0.005 equiv). A solution of ethyl diazoacetate (200 mg, 1.754 mmol, 1 equiv) in DCM (3.5 mL, 0.5M) was added via a syringe pump over 12 h. The solvent was then removed in vacuo, and the residue was purified by flash column chromatography over silica gel (EtOAc-pentane 10/90) to afford compound **29** as a yellow oil (414 mg, 95 %). R_f = 0.6 (EtOAc-Pentane 10/90). **IR (ATR)** ν_{max} (cm⁻¹) = 2974, 1714, 1349, 1255, 1173, 961, 925, 834, 733. **¹H NMR (300 MHz, CDCl₃)** δ (ppm) = 6.45 (q, *J* = 1.4 Hz, 1H), 4.29 (td, *J* = 6.3, 1.2 Hz, 2H), 4.12 (qd, *J* = 7.1, 2.1 Hz, 2H), 3.01 (s, 3H), 2.67 (dd, *J* = 4.8, 1.3 Hz, 2H), 2.16 (d, *J* = 1.5 Hz, 1H), 2.05 (dd, *J* = 7.0, 6.2 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H). **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) = 176.36, 113.93, 96.11, 68.77, 60.50, 37.44, 26.58, 21.39, 19.83, 14.48. **HRMS (ESI):** Calcd. For C₁₀H₁₆O₅NaS [M+ Na]⁺, 271.0610 found 271.0603.

¹⁷⁴ Dange, N.S.; Robert, F.; Landais, Y. *Org. Lett.* **2016**, *18*, 6156.

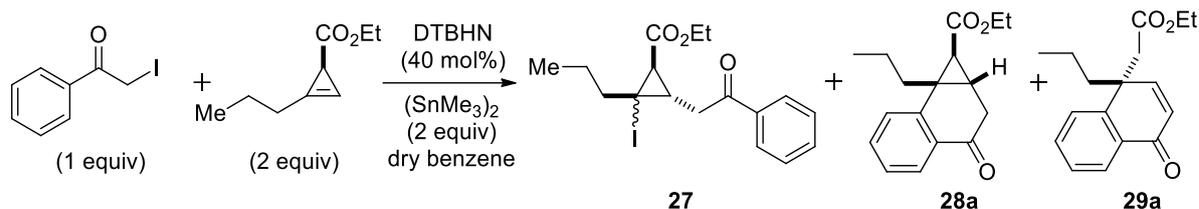
¹⁷⁵ Zhang, F.-G.; Eppe, G.; Marek, I. *Angew. Chem. Int. Ed.* **2016**, *55*, 714.

¹⁷⁶ Cho, S.H.; Liebeskind, L.S. *J. Org. Chem.* **1987**, *52*, 2631.

¹⁷⁷ Araki, S.; Shiraki, F.; Tanaka, T.; Nakano, H.; Subburaj, K.; Hirashita, T.; Yamamura, H.; Kawai, M. *Chem. Eur. J.* **2001**, *7*, 2784.

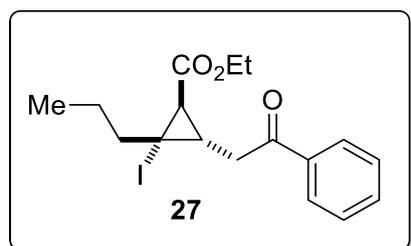
¹⁷⁸ Ueda, M.; Doi, N.; Miyagawa, H.; Sugita, S.; Takeda, N.; Shinada, T.; Miyata, O. *Chem. Comm.*, **2015**, *51*, 4204.

General procedure for the radical carbocyclization reaction



In an oven dry 25 mL two-neck round-bottom flask connected to a reflux condenser, 2-iodo-1-phenylethanone **50a** (100 mg, 0.406 mmol, 1 equiv), ethyl 2-propylcycloprop-2-enecarboxylate **51a** (250 mg, 1.624 mmol, 4 equiv) and $(\text{SnMe}_3)_2$ (159.6 mg, 0.487 mmol, 1.2 equiv) were dissolved in benzene (4 mL, 0.1 M) and the reaction mixture was degassed (argon bubbling for 10 min). To this solution was added DTBHN (14 mg, 0.081 mmol, 0.2 equiv) and the reaction mixture was allowed to warm to 65 °C for 2 h. Then the solvent was removed in vacuo, and the residue purified by flash column chromatography over silica gel (Et_2O -pentane 5/95 to 30/70), affording the title compounds as colorless oils (**27** = 20 mg, 12%, **28a** = 20 mg, 18% and **29a** = 9 mg, 8%).

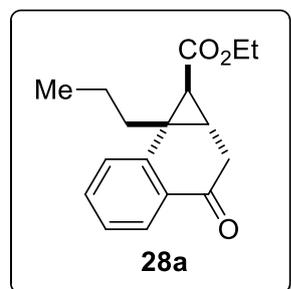
Ethyl 2-iodo-3-(2-oxo-2-phenylethyl)-2-propylcyclopropanecarboxylate 27: $R_f = 0.5$ (Et_2O -



pentane 10/90 developed two times). **IR (ATR)** ν_{max} (cm^{-1}) = 2959, 1711, 1682, 1446, 1398, 1318, 1305, 1188, 1122, 1036, 751, 689. **$^1\text{H-NMR}$ (600 MHz, CDCl_3)** δ (ppm) = 7.97 (dd, $J = 8.4, 1.3$ Hz, 2H), 7.60 – 7.56 (m, 1H), 7.50 – 7.46 (m, 2H), 4.17 (q, $J = 7.1$ Hz, 2H), 3.34 (d, $J = 6.7$ Hz, 2H), 2.09 – 2.04 (m, 1H), 2.03 (d, $J = 7.0$ Hz, 1H), 1.94 – 1.87 (m, 1H),

1.73 – 1.65 (m, 1H), 1.48 – 1.40 (m, 1H), 1.35 (q, $J = 6.8$ Hz, 1H), 1.29 (t, $J = 7.1$ Hz, 3H), 0.94 (t, $J = 7.4$ Hz, 3H). **$^{13}\text{C-NMR}$ (150 MHz, CDCl_3)** δ (ppm) = 197.49, 170.33, 136.77, 133.45, 128.84, 128.14, 61.28, 45.58, 41.28, 36.18, 28.16, 26.27, 23.28, 14.39, 13.25. **HRMS (ESI):** Calcd. For $\text{C}_{17}\text{H}_{21}\text{NaIO}_3$ $[\text{M}+\text{Na}]^+$ 423.0427, found 423.0421.

Ethyl 3-oxo-7b-propyl-1a,2,3,7b-tetrahydro-1H-cyclopropa[a]naphthalene-1-carboxylate

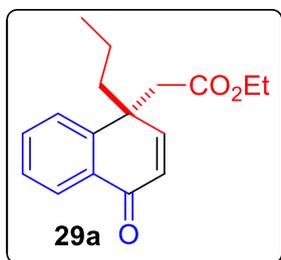


(**28a**): $R_f = 0.6$ (Et_2O /pentane 10/90 developed two times). **IR (ATR)** ν_{max} (cm^{-1}) = 2961, 1722, 1683, 1600, 1283, 1178, 1024, 754. **$^1\text{H-NMR}$ (400 MHz, CDCl_3)** δ (ppm) = 8.01 – 7.96 (m, 1H), 7.59 – 7.54 (m, 2H), 7.31 (ddd, $J = 7.9, 6.1, 2.4$ Hz, 1H), 4.20 – 4.08 (m, 2H), 3.05 (d, $J = 18.7$ Hz, 1H), 2.94 (dd, $J = 18.7, 5.5$ Hz, 1H), 2.37 – 2.24 (m, 2H), 1.84 (ddd, $J = 14.4, 10.4, 6.6$ Hz, 1H), 1.56 (dddd, $J = 14.7, 10.4, 6.1, 2.8$ Hz, 1H), 1.48 (d, $J = 6.1$ Hz, 1H), 1.46 – 1.36 (m, 1H), 1.24 (t,

$J = 7.1$ Hz, 3H), 0.95 (t, $J = 7.4$ Hz, 3H). **$^{13}\text{C-NMR}$ (100 MHz, CDCl_3)** δ (ppm) = 195.23, 170.40, 144.93, 133.84, 131.00, 128.16, 127.18, 126.56, 61.01, 39.10, 35.51, 32.10, 30.24,

25.48, 20.63, 14.39, 14.19. **HRMS (ESI):** Calcd. For $C_{17}H_{20}NaO_3$ $[M+Na]^+$ 295.1310, found 295.1307.

Ethyl 2-(4-oxo-1-propyl-1,4-dihydronaphthalen-1-yl)acetate (29a): $R_f = 0.1$ (Et₂O/pentane



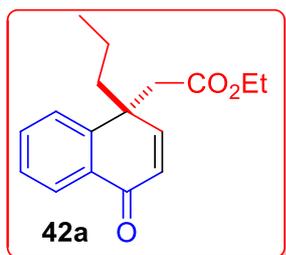
10/90 developed two times). **IR (ATR)** ν_{max} (cm⁻¹) = 2960, 1732, 1665, 1602, 1456, 1303, 1179, 1159, 1035, 767. **¹H-NMR (600 MHz, CDCl₃)** δ (ppm) = 8.17 (d, $J = 7.5$ Hz, 1H), 7.61 – 7.55 (m, 1H), 7.46 (d, $J = 7.9$ Hz, 1H), 7.39 (dd, $J = 7.5, 7.5$ Hz, 1H), 6.94 (d, $J = 10.3$ Hz, 1H), 6.54 (d, $J = 10.3$ Hz, 1H), 3.89 – 3.79 (m, 2H), 2.97 (d, $J = 14.5$ Hz, 1H), 2.83 (d, $J = 14.5$ Hz, 1H), 1.98 (td, $J = 12.8, 4.4$ Hz, 1H), 1.83 (td, $J = 12.8, 4.4$ Hz, 1H), 1.04 (ddd, $J = 17.8, 12.2, 5.5$ Hz, 1H), 0.92 (t, $J = 7.1$ Hz, 3H), 0.75 (t, $J = 7.1$ Hz, 3H), 0.68 (ddd, $J = 20.8, 12.8, 6.9$ Hz, 1H). **¹³C-NMR (150 MHz, CDCl₃)** δ (ppm) = 185.20, 169.67, 153.80, 145.65, 132.78, 132.67, 129.60, 127.18, 126.97, 125.83, 60.56, 46.93, 44.28, 44.04, 17.50, 14.19, 13.95. **HRMS (ESI):** Calcd. For $C_{17}H_{20}NaO_3$ $[M+Na]^+$ 295.1304, found 295.1300.

General Procedure C for Carboarylation of Cyclopropene

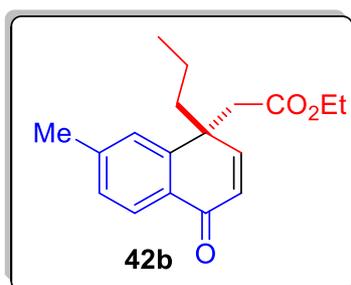


A 25 mL oven dry one-neck round-bottom flask, equipped with a magnetic stirring bar, was charged sequentially with the photocatalyst *fac*-Ir(ppy)₃ (0.02 equiv), the cyclopropene derivative (2 equiv), lithium bromide (2 equiv), potassium carbonate (2 equiv) and 2-bromo-1-arylethanone (1 equiv) under air and then anhydrous DMF (0.2 M) was added under argon. The reaction mixture was carefully degassed (freeze-pump thaw three times using liquid N₂) and refilled with argon, then stirred at room temperature under blue LED irradiation for 12 hours. Blue LED was then switched off and the reaction mixture heated at 60°C for 24h. Finally, the reaction mixture was quenched by addition of water (10 mL) and the aqueous layer extracted 3-4 times with ethyl acetate. The organic layer was then washed with brine and dried over sodium sulfate. Then the solvent was removed in vacuo, and the residue purified by flash column chromatography to afford the desired products.

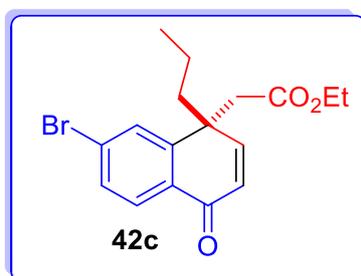
Ethyl 2-(4-oxo-1-propyl-1,4-dihydronaphthalen-1-yl)acetate: 42a (60 mg) was obtained through general procedure C in 44% yield as a yellow oil. **(R)-Ethyl 2-(4-oxo-1-propyl-1,4-dihydronaphthalen-1-yl)acetate: 42a*** (27mg) was obtained through general procedure C in 40% yield as a yellow oil (e.r. = 95:5). $[\alpha]_D^{25} = -56.9$ (*c* 0.42, CHCl₃).



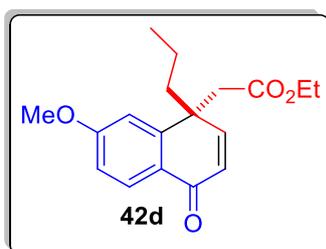
Ethyl 2-(7-methyl-4-oxo-1-propyl-1,4-dihydronaphthalen-1-yl)acetate: 42b (58 mg) was obtained through general procedure C in 40% yield as a yellow oil. $R_f = 0.3$ (EtOAc-Pentane 20/80). **IR (ATR) ν_{\max} (cm⁻¹)** = 2959, 1731, 1661, 1608, 1297, 1160, 815. **¹H-NMR (300 MHz, CDCl₃) δ (ppm)** = 8.05 (d, *J* = 8.0 Hz, 1H), 7.24 – 7.13 (m, 2H), 6.89 (d, *J* = 10.3 Hz, 1H), 6.49 (d, *J* = 10.3 Hz, 1H), 3.92 – 3.78 (m, 2H), 2.87 (dd, *J* = 41.3, 14.5 Hz, 2H), 2.43 (s, 3H), 2.01 – 1.75 (m, 2H), 1.11 – 0.98 (m, 1H), 0.93 (t, *J* = 7.1 Hz, 3H), 0.82 – 0.59 (m, 4H). **¹³C-NMR (75 MHz, CDCl₃) δ (ppm)** = 185.05, 169.68, 153.41, 145.71, 143.31, 130.38, 129.55, 128.26, 126.97, 126.13, 60.47, 46.88, 44.20, 43.88, 22.13, 17.46, 14.18, 13.94. **HRMS (ESI):** Calcd. For C₁₈H₂₂NaO₃ [M+Na]⁺ 309.1461, found 309.1464.



Ethyl 2-(7-bromo-4-oxo-1-propyl-1,4-dihydronaphthalen-1-yl)acetate: 42c (65 mg) was obtained through general procedure C in 37% yield as a yellow oil. $R_f = 0.19$ (EtOAc-Pentane 20/80). **IR (ATR) ν_{\max} (cm⁻¹)** = 2960, 1732, 1664, 1588, 1416, 1293, 1179, 1161, 812. **¹H-NMR (300 MHz, CDCl₃) δ (ppm)** = 8.03 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 1.8 Hz, 1H), 7.53 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.90 (d, *J* = 10.3 Hz, 1H), 6.53 (d, *J* = 10.3 Hz, 1H), 3.88 (qd, *J* = 7.1, 2.1 Hz, 2H), 2.95 (d, *J* = 14.7 Hz, 1H), 2.81 (d, *J* = 14.7 Hz, 1H), 2.02 – 1.75 (m, 2H), 1.12 – 1.01 (m, 1H), 0.97 (t, *J* = 7.1 Hz, 3H), 0.82 – 0.63 (m, 4H). **¹³C-NMR (75 MHz, CDCl₃) δ (ppm)** = 184.27, 169.29, 153.32, 147.55, 131.56, 130.74, 129.51, 128.97, 128.77, 128.17, 60.69, 46.67, 44.15, 44.03, 17.51, 14.16, 13.99. **HRMS (ESI):** Calcd. For C₁₇H₁₉BrNaO₃ [M+Na]⁺ 373.0409, found 373.0422.

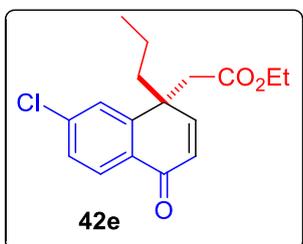


Ethyl 2-(7-methoxy-4-oxo-1-propyl-1,4-dihydronaphthalen-1-yl)acetate: 42d (52 mg) was obtained through general procedure C in 34% yield as a yellow oil. $R_f = 0.5$ (EtOAc-Pentane 20/80 developed two times). **IR (ATR) ν_{\max} (cm⁻¹)** = 2960, 1731, 1659, 1600, 1268, 1241, 1175, 1028, 818. **¹H-NMR (300 MHz, CDCl₃) δ (ppm)** = 8.14 (d, *J* = 8.7 Hz, 1H), 6.97 – 6.80 (m, 3H), 6.48 (d, *J* = 10.3 Hz, 1H), 3.96 – 3.79 (m, 5H), 2.85 (dd, *J* = 37.3, 14.5 Hz, 2H), 1.97 – 1.77 (m, 2H), 1.11 –



1.00 (m, 1H), 0.95 (t, $J = 7.1$ Hz, 3H), 0.77 – 0.73 (m, 4H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ (ppm) = 184.36, 169.62, 163.19, 152.87, 148.01, 129.59, 129.36, 126.43, 112.84, 110.98, 60.54, 55.58, 47.05, 44.44, 44.06, 17.45, 14.20, 13.98. **HRMS (ESI)**: Calcd. For $\text{C}_{18}\text{H}_{22}\text{NaO}_4$ $[\text{M}+\text{Na}]^+$ 325.1410, found 325.1415.

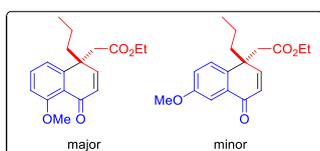
Ethyl 2-(7-chloro-4-oxo-1-propyl-1,4-dihydronaphthalen-1-yl)acetate: 42e (48 mg) was obtained through general procedure C in 31% yield as a yellow oil. **IR**



(ATR) ν_{max} (cm^{-1}) = 2960, 1732, 1665, 1593, 1418, 1338, 1293, 1163, 1098, 819. $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ (ppm) = 8.11 (d, $J = 8.4$ Hz, 1H), 7.43 (d, $J = 2.0$ Hz, 1H), 7.37 (dd, $J = 8.4, 2.0$ Hz, 1H), 6.90 (d, $J = 10.3$ Hz, 1H), 6.52 (d, $J = 10.3$ Hz, 1H), 3.87 (qd, $J = 7.1, 2.0$ Hz, 2H), 2.95 (d, $J = 14.7$ Hz, 1H), 2.81 (d, $J = 14.7$ Hz, 1H), 2.02 – 1.76 (m, 2H), 1.12 – 1.00 (m, 1H), 0.96 (t, $J = 7.1$ Hz, 3H), 0.82 – 0.63

(m, 4H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ (ppm) = 184.11, 169.29, 153.34, 147.44, 139.39, 131.19, 129.52, 128.71, 127.82, 125.95, 60.68, 46.69, 44.18, 44.07, 17.50, 14.15, 13.98. **HRMS (ESI)**: Calcd. For $\text{C}_{17}\text{H}_{19}\text{ClNaO}_3$ $[\text{M}+\text{Na}]^+$ 329.0914, found 329.0925.

Ethyl 2-(8-methoxy-4-oxo-1-propyl-1,4-dihydronaphthalen-1-yl)acetate: 42g (60 mg) was obtained through general procedure C in 40 % yield as a yellow oil

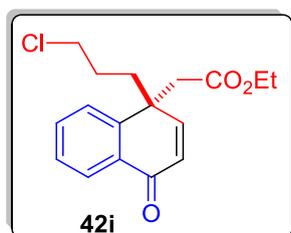


as a yellow oil (r.r. 70:30). **Major**: $R_f = 0.24$ (EtOAc-Pentane20/80 developed two times); **IR** (ATR) ν_{max} (cm^{-1}) = 2961, 1730, 1665, 1595, 1433, 1310, 1298, 1257, 1179, 1051, 803. $^1\text{H-NMR}$ (600 MHz, CDCl_3) δ (ppm)

= 7.85 (dd, $J = 8.0, 1.2$ Hz, 1H), 7.39 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.10 (dd, $J = 8.0, 1.2$ Hz, 1H), 6.83 (d, $J = 10.2$ Hz, 1H), 6.50 (d, $J = 10.2$ Hz, 1H), 3.93 (s, 3H), 3.82 – 3.74 (m, 2H), 3.63 (d, $J = 14.1$ Hz, 1H), 2.69 (d, $J = 14.1$ Hz, 1H), 2.60 (td, $J = 12.8, 4.8$ Hz, 1H), 1.58 (dd, $J = 25.3, 4.5$ Hz, 1H), 1.02 – 0.94 (m, 1H), 0.86 (t, $J = 7.1$ Hz, 3H), 0.74 (t, $J = 7.2$ Hz, 3H), 0.69 – 0.60 (m, 1H). $^{13}\text{C-NMR}$ (150 MHz, CDCl_3) δ (ppm) = 185.44, 170.46, 157.43, 156.41, 134.32, 133.07, 128.39, 128.15, 119.49, 115.07, 60.21, 55.86, 44.51, 43.33, 39.91, 17.97, 14.32, 13.94.

HRMS (ESI): Calcd. For $\text{C}_{18}\text{H}_{22}\text{NaO}_4$ $[\text{M}+\text{Na}]^+$ 325.1410, found 325.1406.

Ethyl 2-(1-(3-chloropropyl)-4-oxo-1,4-dihydronaphthalen-1-yl)acetate: 42i (63 mg) was obtained through general procedure C in 41 % yield as a yellow oil.

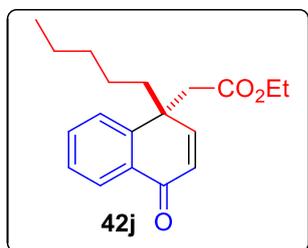


IR (ATR) ν_{max} (cm^{-1}) = 2958, 2927, 1729, 1664, 1601, 1455, 1302, 1177, 1033, 767. $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ (ppm) = 8.18 (dd, $J = 7.8, 1.3$ Hz, 1H), 7.65 – 7.57 (m, 1H), 7.50 – 7.38 (m, 2H), 6.97 – 6.91 (m, 1H), 6.57 (d, $J = 10.3$ Hz, 1H), 3.99 – 3.75 (m, 2H), 3.46 – 3.19 (m, 2H), 2.92 (dd, $J = 39.3, 14.6$ Hz, 2H), 2.29 – 1.97 (m, 2H),

1.59 – 1.36 (m, 1H), 1.22 – 1.01 (m, 1H), 0.94 (t, $J = 7.1$ Hz, 3H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ (ppm) = 184.81, 169.36, 152.87, 144.85, 133.06, 132.63, 130.12, 127.54, 127.15, 125.79,

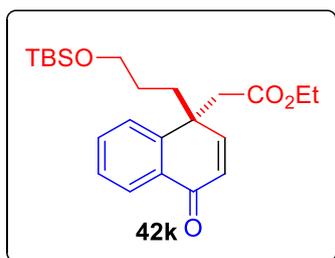
60.68, 46.96, 44.78, 43.41, 38.81, 27.24, 13.97. **HRMS (ESI):** Calcd. For $C_{17}H_{19}NaClO_3$ [$M+Na$]⁺, 329.0914 found 329.0917

Ethyl 2-(4-oxo-1-pentyl-1,4-dihydronaphthalen-1-yl)acetate: 42j (61 mg) was obtained



through general procedure C in 41 % yield as a yellow oil. R_f = 0.36 (EtOAc-Pentane 20/80); **IR (ATR)** ν_{max} (cm^{-1}) = 2932, 1731, 1664, 1602, 1456, 1393, 1301, 1164, 1034, 767. **1H NMR (300 MHz, $CDCl_3$)** δ (ppm) = 8.30 – 8.03 (m, 1H), 7.63 – 7.53 (m, 1H), 7.49 – 7.35 (m, 2H), 6.93 (d, J = 10.3 Hz, 1H), 6.54 (d, J = 10.3 Hz, 1H), 3.97 – 3.73 (m, 2H), 2.89 (dd, J = 43.8, 14.4 Hz, 2H), 2.00 (ddd, J = 13.3, 11.8, 4.8 Hz, 1H), 1.84 (td, J = 12.8, 4.1 Hz, 1H), 1.11 (ddd, J = 5.9, 4.0, 2.3 Hz, 5H), 0.92 (t, J = 7.1 Hz, 3H), 0.79 – 0.71 (m, 3H), 0.71 – 0.58 (m, 1H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ (ppm) = 185.18, 169.64, 153.78, 145.64, 132.76, 132.68, 129.63, 127.16, 126.95, 125.80, 60.54, 46.97, 43.97, 41.99, 31.87, 23.75, 22.36, 14.00, 13.95. **HRMS (ESI):** Calcd. For $C_{19}H_{24}NaO_3$ [$M+Na$]⁺, 323.1606, found 323.1617.

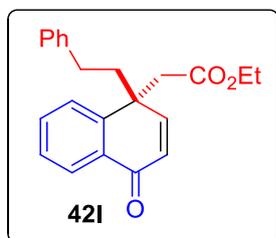
Ethyl 2-(1-(3-((tert-butyldimethylsilyloxy)propyl)-4-oxo-1,4-dihydronaphthalen-1-yl)acetate: 42k (103 mg) was obtained through general procedure



C in 51 % yield as a yellow oil. R_f = 0.27 (EtOAc-Pentane 20/80); **IR (ATR)** ν_{max} (cm^{-1}) = 2929, 2857, 1732, 1666, 1458, 1391, 1301, 1256, 1165, 1098, 836, 773. **1H -NMR (300 MHz, $CDCl_3$)** δ (ppm) = 8.18 (dd, J = 7.9, 1.2 Hz, 1H), 7.63 – 7.54 (m, 1H), 7.54 – 7.35 (m, 2H), 6.94 (d, J = 10.3 Hz, 1H), 6.55 (d, J = 10.3 Hz, 1H), 3.85 (tt, J = 7.1, 3.5 Hz, 2H), 3.42 (t, J = 6.3 Hz, 2H), 2.92

(dd, J = 43.2, 14.4 Hz, 2H), 2.16 – 2.04 (m, 1H), 2.03 – 1.87 (m, 1H), 1.33 – 1.12 (m, 2H), 0.93 (t, J = 7.1 Hz, 3H), 0.84 (s, 9H), -0.04 (s, 3H), -0.05 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ (ppm) = 185.06, 169.55, 153.57, 145.39, 132.81, 132.68, 129.74, 127.23, 126.96, 125.89, 62.53, 60.54, 47.08, 43.64, 38.25, 31.04, 27.47, 26.01, 18.36, 13.95, -5.26. **HRMS (ESI):** Calcd. For $C_{23}H_{34}NaO_4Si$ [$M+Na$]⁺, 425.2118 found 425.2125

Ethyl 2-(4-oxo-1-phenethyl-1,4-dihydronaphthalen-1-yl)acetate: 42l (59 mg) was obtained

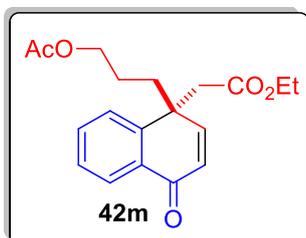


through general procedure C in 35 % yield as a yellow oil. R_f = 0.38 (EtOAc-Pentane 10/90); **IR (ATR)** ν_{max} (cm^{-1}) = 2929, 1729, 1662, 1601, 1455, 1392, 1301, 1265, 1156, 1030, 843. **1H -NMR (300 MHz, $CDCl_3$)** δ (ppm) = 8.23 (dd, J = 7.8, 1.3 Hz, 1H), 7.70 – 7.61 (m, 1H), 7.54 (s, 1H), 7.50 – 7.42 (m, 1H), 7.29 – 7.14 (m, 3H), 7.02 (d, J = 10.3 Hz, 1H), 7.00 – 6.94 (m, 2H), 6.62 (d, J = 10.3 Hz, 1H), 3.86 (qd, J =

7.1, 1.8 Hz, 2H), 3.00 (d, J = 14.5 Hz, 1H), 2.86 (d, J = 14.5 Hz, 1H), 2.39 – 2.15 (m, 3H), 2.00 – 1.91 (m, 1H), 0.94 (t, J = 7.1 Hz, 3H). **^{13}C -NMR (75 MHz, $CDCl_3$)** δ (ppm) = 185.00, 169.45, 153.10, 145.08, 141.12, 133.01, 132.79, 130.05, 128.54, 128.24, 127.46, 127.15, 126.19,

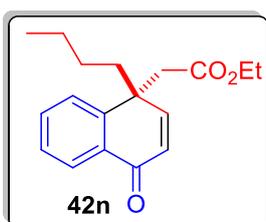
125.74, 60.64, 46.94, 43.95, 43.64, 30.55, 13.96. **HRMS (ESI):** Calcd. For $C_{22}H_{22}NaO_3$ $[M+Na]^+$ 357.1461 found 357.1457.

Ethyl 2-(1-(3-acetoxypropyl)-4-oxo-1,4-dihydronaphthalen-1-yl)acetate: 42m (70 mg) was



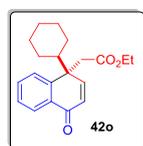
obtained through general procedure C in 42 % yield as a yellow oil. R_f = 0.15 (EtOAc-Pentane 40/60); **IR (ATR)** ν_{max} (cm^{-1}) = 2960, 1734, 1739, 1664, 1456, 1369, 1302, 1242, 1179, 1038, 770. **1H NMR (300 MHz, $CDCl_3$)** δ (ppm) = 8.17 (dd, J = 7.9, 1.2 Hz, 1H), 7.67 – 7.54 (m, 1H), 7.51 – 7.38 (m, 2H), 6.92 (d, J = 10.3 Hz, 1H), 6.56 (d, J = 10.3 Hz, 1H), 3.93 – 3.78 (m, 4H), 2.91 (dd, J = 41.4, 14.5 Hz, 2H), 2.12 – 1.90 (m, 4H), 1.41 – 1.21 (m, 2H), 1.01 – 0.85 (m, 4H). **^{13}C -NMR (75 MHz, $CDCl_3$)** δ (ppm) = 184.80, 170.95, 169.34, 152.87, 144.86, 132.95, 132.62, 130.03, 127.43, 127.06, 125.67, 63.87, 60.58, 46.82, 43.46, 37.97, 23.54, 20.95, 13.91. **HRMS (ESI)** Calcd. For $C_{19}H_{22}NaO_5$ $[M+Na]^+$, 353.1359, found 353.1357.

Ethyl 2-(1-butyl-4-oxo-1,4-dihydronaphthalen-1-yl)acetate: 42n (66 mg) was obtained



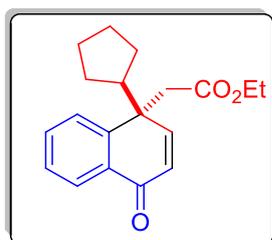
through general procedure C in 46 % yield as a yellow oil. R_f = 0.52 (EtOAc-Pentane 10/90); **IR (ATR)** ν_{max} (cm^{-1}) = 2932, 2865, 1731, 1664, 1602, 1457, 1370, 1301, 1157, 1031, 766. **1H NMR (300 MHz, $CDCl_3$)** δ (ppm) = 8.17 (dd, J = 7.9, 1.2 Hz, 1H), 7.57 (ddd, J = 8.1, 7.2, 1.5 Hz, 1H), 7.49 – 7.34 (m, 2H), 6.93 (d, J = 10.3 Hz, 1H), 6.53 (d, J = 10.3 Hz, 1H), 3.83 (qd, J = 7.1, 1.3 Hz, 2H), 2.89 (dd, J = 44.2, 14.5 Hz, 2H), 2.08 – 1.93 (m, 1H), 1.86 (dd, J = 12.2, 4.5 Hz, 1H), 1.20 – 1.06 (m, 2H), 1.06 – 0.96 (m, 1H), 0.92 (dd, J = 9.4, 4.9 Hz, 3H), 0.72 (t, J = 7.3 Hz, 3H), 0.68 – 0.53 (m, 1H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ (ppm) = 185.14, 169.60, 153.78, 145.61, 132.74, 132.65, 129.60, 127.13, 126.91, 125.79, 60.50, 46.94, 43.91, 41.75, 26.21, 22.78, 13.93, 13.84. **HRMS (ESI):** Calcd. For $C_{18}H_{22}NaO_3$ $[M + Na]^+$ 309.1461, found 309.1464

Ethyl 2-(1-cyclohexyl-4-oxo-1,4-dihydronaphthalen-1-yl)acetate: 42o (49 mg) was obtained



through general procedure C in 31 % yield as a yellow oil. R_f = 0.32 (EtOAc-Pentane 10/90); **IR (ATR)** ν_{max} (cm^{-1}) = 2930, 2853, 1731, 1600, 1452, 1368, 1302, 1037, 840, 764. **1H NMR (300 MHz, $CDCl_3$)** δ (ppm) = 8.16 (dd, J = 7.8, 1.2 Hz, 1H), 7.61 – 7.53 (m, 1H), 7.49 – 7.35 (m, 2H), 6.99 (d, J = 10.4 Hz, 1H), 6.57 (d, J = 10.4 Hz, 1H), 3.75 (q, J = 7.1 Hz, 2H), 3.02 (s, 2H), 2.07 – 1.98 (m, 1H), 1.90 – 1.75 (m, 2H), 1.65 – 1.48 (m, 2H), 1.28 – 0.93 (m, 6H), 0.82 (t, J = 7.1 Hz, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ (ppm) = 185.11, 170.28, 152.14, 146.12, 133.09, 132.56, 130.06, 127.02, 126.68, 125.84, 60.42, 50.15, 47.00, 43.92, 28.15, 27.70, 27.12, 26.59, 26.27, 13.84. **HRMS (ESI):** Calcd. For $C_{20}H_{24}NaO_3$ $[M]^+$ 335.1617, found 335.1620.

Ethyl 2-(1-cyclopentyl-4-oxo-1,4-dihydronaphthalen-1-yl)acetate: 42p (48 mg) was obtained through general procedure C in 32 % yield as a yellow oil. R_f



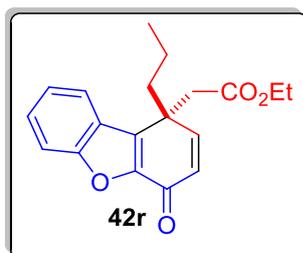
= 0.31 (EtOAc-Pentane 10/90); **IR (ATR)** ν_{\max} (cm^{-1}) = 2953, 2868, 1731, 1663, 1600, 1455, 1302, 1157, 1028, 840, 766. **^1H NMR (300 MHz, CDCl_3)** δ (ppm) = 8.25 – 8.16 (m, 1H), 7.64 – 7.49 (m, 2H), 7.41 (dd, J = 6.7, 1.2 Hz, 1H), 7.05 (d, J = 10.4 Hz, 1H), 6.63 (d, J = 10.4 Hz, 1H), 3.80 (qd, J = 7.1, 0.6 Hz, 2H), 3.16 (d, J = 14.6 Hz, 1H), 3.00 (d, J = 14.6 Hz, 1H), 2.46 (dt, J = 17.4, 4.8 Hz, 1H), 1.95 – 1.80 (m, 1H), 1.65 – 1.31 (m, 5H), 1.18 – 1.03 (m, 1H), 1.00 – 0.91 (m, 1H), 0.87 (t, J = 7.1 Hz, 3H). **^{13}C -NMR (75 MHz, CDCl_3)** δ (ppm) = 185.03, 169.92, 151.28, 146.47, 132.54, 132.42, 130.59, 126.98, 126.81, 125.94, 60.46, 52.06, 45.64, 44.98, 27.62, 27.54, 25.59, 24.93, 13.88. **HRMS (ESI):** Calcd. For $\text{C}_{19}\text{H}_{22}\text{NaO}_3$ $[\text{M} + \text{Na}]^+$, 321.1461 found 321.1458.

Ethyl 2-(1-(2-bromoethyl)-4-oxo-1,4-dihydronaphthalen-1-yl)acetate: 42q (70 mg) was obtained through general procedure C in 41 % yield as a yellow oil. R_f



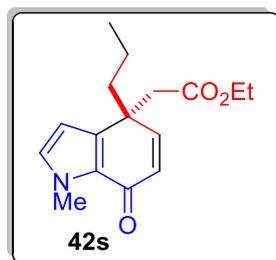
= 0.625 (EtOAc-Pentane 15/85); **IR (ATR)** ν_{\max} (cm^{-1}) = 2979, 1727, 1664, 1601, 1457, 1370, 1301, 1177, 1033, 842, 768. **^1H -NMR (300 MHz, CDCl_3)** δ (ppm) = 8.21 (dd, J = 7.8, 1.2 Hz, 1H), 7.71 – 7.63 (m, 1H), 7.55 – 7.40 (m, 2H), 6.99 (d, J = 10.3 Hz, 1H), 6.61 (d, J = 10.3 Hz, 1H), 3.98 – 3.81 (m, 2H), 3.06 – 2.84 (m, 3H), 2.73 – 2.59 (m, 2H), 2.58 – 2.44 (m, 1H), 0.97 (t, J = 7.1 Hz, 3H). **^{13}C NMR (75 MHz, CDCl_3)** δ (ppm) = 184.38, 168.93, 151.49, 143.56, 133.33, 132.50, 130.52, 127.90, 127.37, 125.69, 60.81, 46.68, 44.41, 44.16, 26.39, 13.96. **HRMS (ESI):** Calcd. For $\text{C}_{16}\text{H}_{17}\text{BrNaO}_3$ $[\text{M} + \text{Na}]^+$ 359.0253 found 359.0268

Ethyl 2-(4-oxo-1-propyl-1,4-dihydrodibenzo[b,d]furan-1-yl)acetate: 42r (25 mg) was obtained through general procedure C in 16 % yield as a yellow oil. R_f

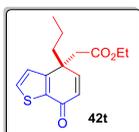


= 0.25 (EtOAc-Pentane 20/80); **IR (ATR)** ν_{\max} (cm^{-1}) = 2960, 1731, 1667, 1575, 1447, 1171, 1108, 752. **^1H NMR (300 MHz, CDCl_3)** δ (ppm) = 7.81 – 7.75 (m, 1H), 7.67 (dt, J = 8.4, 0.8 Hz, 1H), 7.53 (ddd, J = 8.4, 7.2, 1.3 Hz, 1H), 7.38 (ddd, J = 8.1, 7.3, 1.0 Hz, 1H), 7.06 (d, J = 10.2 Hz, 1H), 6.54 (d, J = 10.2 Hz, 1H), 3.97 – 3.82 (m, 2H), 3.02 (s, 2H), 2.29 – 2.15 (m, 1H), 2.10 – 1.96 (m, 1H), 1.14 – 0.98 (m, 1H), 0.94 (t, J = 7.1 Hz, 3H), 0.83 – 0.71 (m, 4H). **^{13}C NMR (75 MHz, CDCl_3)** δ (ppm) = 176.42, 169.16, 155.80, 153.53, 148.43, 134.59, 130.66, 128.62, 124.88, 123.98, 121.97, 113.47, 60.80, 45.01, 44.69, 41.20, 17.83, 14.19, 13.96. **HRMS (ESI):** Calcd. For $\text{C}_{19}\text{H}_{20}\text{NaO}_4$ $[\text{M} + \text{Na}]^+$ 335.1253, found 335.1263.

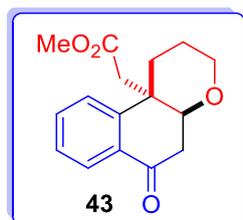
Ethyl 2-(1-methyl-7-oxo-4-propyl-4,7-dihydro-1H-indol-4-yl)acetate: 42s (33 mg) was obtained through general procedure C in 24 % yield as a yellow oil. $R_f = 0.19$ (EtOAc-Pentane 20/80 developed two times). **IR (ATR)** ν_{\max} (cm^{-1}) = 2958, 1730, 1649, 1604, 1509, 1434, 1416, 1173, 1030, 830. **$^1\text{H-NMR}$ (300 MHz, CDCl_3)** δ (ppm) = 6.81 (d, $J = 2.6$ Hz, 1H), 6.77 (d, $J = 10.1$ Hz, 1H), 6.26 (d, $J = 10.1$ Hz, 1H), 6.08 (d, $J = 2.6$ Hz, 1H), 4.03 – 3.93 (m, 5H), 2.71 (d, $J = 6.2$ Hz, 2H), 1.87 – 1.75 (m, 2H), 1.08 (t, $J = 7.1$ Hz, 3H), 1.05 – 0.97 (m, 1H), 0.91 – 0.80 (m, 1H), 0.77 (t, $J = 6.4$ Hz, 3H). **$^{13}\text{C NMR}$ (75 MHz, CDCl_3)** δ (ppm) = 177.59, 170.18, 151.28, 139.41, 130.68, 129.93, 126.60, 104.92, 60.42, 46.24, 43.09, 43.02, 36.44, 17.66, 14.30, 14.15. **HRMS (ESI):** Calcd. For $\text{C}_{16}\text{H}_{21}\text{NaNO}_3$ $[\text{M}+\text{Na}]^+$ 298.1413, found 298.1411.



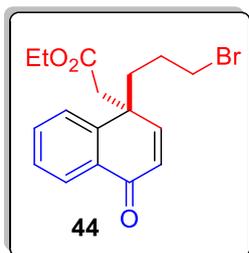
Ethyl 2-(7-oxo-4-propyl-4,7-dihydrobenzo[b]thiophen-4-yl)acetate: 42t (51 mg) was obtained through general procedure C in 37 % yield as a yellow oil. $R_f = 0.161$ (EtOAc-Pentane 15/85); **IR (ATR)** ν_{\max} (cm^{-1}) = 2933, 2872, 1729, 1651, 1426, 1308, 1262, 1171, 1035, 830, 706. **$^1\text{H NMR}$ (300 MHz, CDCl_3)** δ (ppm) = 7.67 (d, $J = 5.1$ Hz, 1H), 7.12 (d, $J = 5.1$ Hz, 1H), 6.94 (d, $J = 10.1$ Hz, 1H), 6.46 (d, $J = 10.1$ Hz, 1H), 3.91 (qd, $J = 7.1, 2.7$ Hz, 2H), 2.82 (s, 2H), 1.99 – 1.76 (m, 2H), 1.12 – 1.04 (m, 1H), 1.00 (t, $J = 7.1$ Hz, 3H), 0.82 – 0.65 (m, 4H). **$^{13}\text{C NMR}$ (75 MHz, CDCl_3)** δ (ppm) = 180.39, 169.40, 153.71, 153.15, 137.69, 133.11, 129.50, 125.79, 60.68, 45.84, 45.23, 42.94, 17.63, 14.16, 14.03. **HRMS (ESI):** Calcd. For $\text{C}_{15}\text{H}_{18}\text{O}_3\text{S}$ $[\text{M}+\text{Na}]^+$, 301.0868 found 301.0870.



Methyl 2-(6-oxo-2,3,4a,5,6,10b-hexahydro-1H-benzo[f]chromen-10b-yl) acetate (43): In a 5 mL oven dry one-neck round-bottom flask, equipped with a magnetic stirring bar, was dissolved in methanol (0.6 mL, 0.2 M), ethyl 2-(1-(3-acetoxypentyl)-4-oxo-1,4-dihydronaphthalen-1-yl)acetate **42m** (35 mg, 0.106 mmol, 1 equiv) and potassium carbonate (29 mg, 0.212 mmol, 2 equiv). The reaction mixture was then stirred at room temperature for 12 h. Ethyl acetate (10 mL) was then added and the organic layer washed with water (3 x 5 mL), with brine and dried over sodium sulfate. Then the solvent was removed in vacuo and the residue purified by flash chromatography over silica gel (EtOAc-pentane 20/80 to 30/70) affording the title compound as a yellow oil (22 mg, 76 %). $R_f = 0.5$ (EtOAc-Pentane 30/70); **IR (ATR)** ν_{\max} (cm^{-1}) = 2936, 2851, 1731, 1687, 1598, 1452, 1285, 1195, 1098, 768. **$^1\text{H NMR}$ (300 MHz, CDCl_3)** δ (ppm) = 8.11 (dd, $J = 8.0, 1.5$ Hz, 1H), 7.62 – 7.53 (m, 1H), 7.43 – 7.33 (m, 2H), 4.08 (t, $J = 3.2$ Hz, 1H), 3.89 – 3.79 (m, 1H), 3.63 (s, 3H), 3.49 (tt, $J = 11.7, 5.9$ Hz, 1H), 3.10 (dd, $J = 17.9, 3.1$ Hz, 1H), 2.88 – 2.78 (m, 1H), 2.67 (dd, $J = 14.2, 1.7$ Hz, 1H), 2.57 (d, $J = 1.5$ Hz, 2H), 1.98 (ddd, $J = 14.1, 12.8, 4.4$ Hz, 1H), 1.61 – 1.44 (m, 2H). **$^{13}\text{C NMR}$ (75 MHz, CDCl_3)** δ (ppm) = 195.50, 170.70, 144.58, 134.18, 132.34, 127.92, 127.26, 126.49, 79.05, 68.56, 51.84, 46.15, 41.28, 40.08, 32.22, 22.48. **HRMS (ESI):** Calcd. For $\text{C}_{16}\text{H}_{18}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$, 297.1097 found 297.1092.



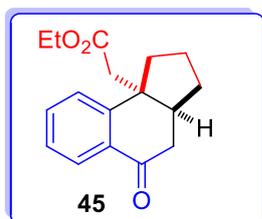
Ethyl 2-(1-(3-bromopropyl)-4-oxo-1,4-dihydronaphthalen-1-yl) acetate (44). Following the



general procedure C, using photocatalyst *fac*-Ir(ppy)₃ (6.6 mg, 0.010 mmol, 0.02 equiv), ethyl 2-(3-((methyl sulfonyl)oxy)propyl)cycloprop-2-enecarboxylate **7** (189 mg, 1 mmol, 2 equiv), lithium bromide (87 mg, 1 mmol, 2 equiv), potassium carbonate (138 mg, 1 mmol, 2 equiv) and 2-bromo-1-phenylethanone **1b** (100 mg, 0.5 mmol, 1 equiv) in anhydrous DMF (2.5 mL, 0.2 M) under argon. After stirring at 20°C under blue LED irradiation for 12 hours, then heating at 60°C for 24h *without blue LED*, the reaction mixture was quenched with water (10 mL) then extracted with ethyl acetate (50 mL). The residue was purified by flash column chromatography over silica gel (EtOAc-pentane 5/95 to 20/80) affording the title compound as a yellow oil (57 mg, 32 %).

$R_f = 0.1$ (EtOAc-Pentane 10/90); **IR (ATR)** ν_{\max} (cm⁻¹) = 2925, 1728, 1600, 1453, 1370, 1301, 1178, 1030, 913, 745. **¹H NMR (300 MHz, CDCl₃)** δ 8.20 – 8.17 (m, 1H), 7.61 (ddd, $J = 8.0, 7.2, 1.5$ Hz, 1H), 7.50 – 7.46 (m, 1H), 7.45 – 7.39 (m, 1H), 6.94 (d, $J = 10.3$ Hz, 1H), 6.57 (d, $J = 10.3$ Hz, 1H), 3.87 (qd, $J = 7.1, 0.8$ Hz, 2H), 2.99 (d, $J = 14.5$ Hz, 1H), 2.86 (d, $J = 14.6$ Hz, 1H), 2.22 (ddd, $J = 13.3, 11.8, 4.7$ Hz, 1H), 2.06 (ddd, $J = 13.4, 11.7, 4.5$ Hz, 1H), 1.63 – 1.49 (m, 2H), 1.27 – 1.20 (m, 2H), 0.95 (t, $J = 7.1$ Hz, 3H). **¹³C NMR (75 MHz, CDCl₃)** δ (ppm) = 184.79, 169.36, 152.85, 144.83, 133.08, 132.60, 130.12, 127.56, 127.15, 125.80, 60.69, 46.94, 43.38, 40.00, 33.41, 27.32, 13.98. **HRMS (ESI):** Calcd. For C₁₇H₁₉BrNaO₃ [M + Na]⁺, 373.0409 found 373.0409.

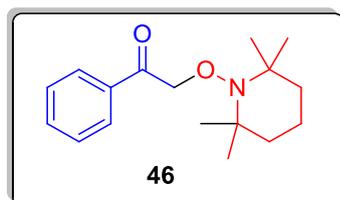
Ethyl 2-(5-oxo-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[a]naphthalen-9b-yl) acetate: 45



A 5 mL oven dry one-neck round-bottom flask was equipped with a magnetic stirring bar, then charged sequentially with ethyl 2-(1-(3-bromopropyl)-4-oxo-1,4-dihydronaphthalen-1-yl)acetate **44** (20 mg, 0.056 mmol, 1 equiv), sodium iodide (16 mg, 0.112 mmol, 2 equiv) and acetone (0.3 mL, 0.2M). The reaction mixture was then refluxed 5 h and the solvent removed in vacuo. The reaction mixture was quenched with aqueous saturated solution of sodium thiosulfate (5 mL). Then the aqueous layer was extracted with Et₂O (3 x 10 mL). The organic layer was then washed with brine and dried over sodium sulfate, filtered, concentrated to afford the desired product as a yellow oil (20 mg, 91 %), which was subjected to the next step without further purification. A solution of Bu₃SnH (0.02 mL, 0.1 mmol, 2 equiv), and AIBN (3 mg, 0.02 mmol, 0.4 equiv) in dry benzene (0.5 mL, 0.1M) was added over 5 h by syringe pump to a stirred and heated (85 °C) solution of the ethyl 2-(1-(3-iodopropyl)-4-oxo-1,4-dihydronaphthalen-1-yl)acetate (20 mg, 0.05 mmol, 1 equiv) in dry benzene (0.5 mL, 0.1M). Heating was continued for 12 hours after the addition. Evaporation of the solvent and flash chromatography of the residue over KF-flash chromatography silica gel (10% w/w KF) (EtOAc-pentane 10/90 to 30/70) afforded the cyclized product **45** (10 mg, 77 %). **IR (ATR)** ν_{\max} (cm⁻¹) = 2923, 1729, 1686, 1600, 1450, 1368, 1286, 1181, 1031, 769. **¹H NMR**

(300 MHz, CDCl₃) δ (ppm) = 8.01 (dd, J = 7.8, 1.2 Hz, 1H), 7.59 – 7.51 (m, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.36 – 7.28 (m, 1H), 4.02 (qd, J = 7.1, 2.3 Hz, 2H), 2.92 (dd, J = 17.1, 5.3 Hz, 1H), 2.75 (s, 2H), 2.69 (dd, J = 17.1, 3.8 Hz, 1H), 2.57 (dt, J = 9.2, 7.1 Hz, 1H), 2.45 – 2.34 (m, 1H), 2.11 – 1.94 (m, 2H), 1.46 – 1.32 (m, 3H), 1.12 (t, J = 7.1 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) = 198.04, 171.29, 134.18, 132.21, 127.62, 126.96, 126.90, 60.53, 47.15, 45.43, 42.81, 39.93, 38.91, 30.10, 29.86, 21.79, 14.22. HRMS (ESI): Calcd. For C₁₇H₂₀NaO₃ [M + Na]⁺, 295.1304 found 295.1292.

1-phenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy) ethanone (46): A 25 mL oven dry one-

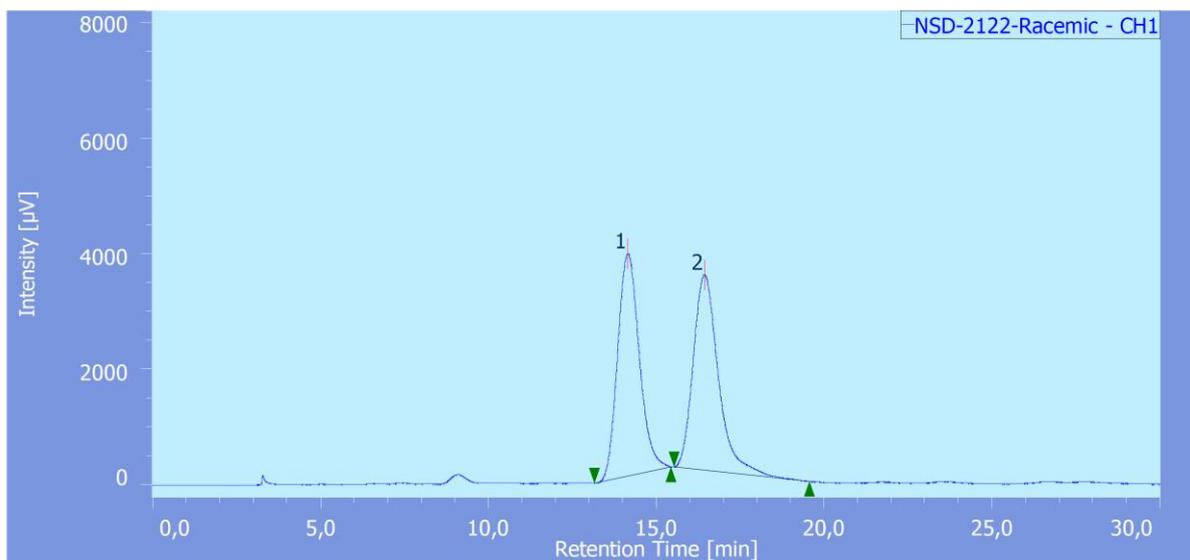


neck round-bottom flask was equipped with a magnetic stirring bar, then charged sequentially with the photocatalyst *fac*-Ir(ppy)₃ (6.6 mg, 0.010 mmol, 0.02 equiv), (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO) (156 mg, 1 mmol, 2 equiv), lithium bromide (87 mg, 1 mmol, 2 equiv), potassium carbonate (138 mg,

1 mmol, 2 equiv) 2-bromo-1-phenylethanone (100 mg, 0.5 mmol, 1 equiv), and anhydrous DMF (2.5 mL, 0.2 M) under argon. The reaction mixture was carefully degassed (freeze-pump thaw three times using liquid N₂) and refilled with argon, then stirred at room temperature under blue LED irradiation for 12 h. The solvent was removed in vacuo and the residue purified directly by flash chromatography over silica gel (Et₂O-pentane 10/90), affording the title compound as a yellow oil (88 mg, 64 %). R_f = 0.66 (Et₂O-Pentane 10/90). ¹H NMR (300 MHz, CDCl₃) δ (ppm) = 7.98 – 7.88 (m, 2H), 7.56 (ddd, J = 6.6, 3.9, 1.4 Hz, 1H), 7.51 – 7.40 (m, 2H), 5.11 (s, 2H), 1.49 – 1.46 (m, 6H), 1.17 (s, 12H). ¹³C NMR (75 MHz, CDCl₃) δ (ppm) = 195.88, 135.56, 133.35, 128.70, 128.10, 81.46, 60.28, 39.87, 32.95, 20.39, 17.19. HRMS (ESI): Calcd. For C₁₇H₂₅NNaO₂ [M + Na]⁺, 298.1777 found 298.1786.

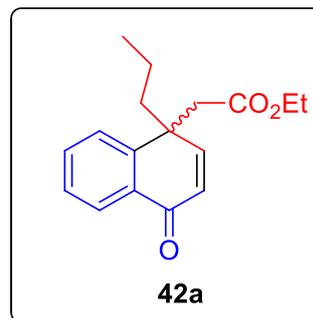
HPLC data-42a:

Chromatogram



Chromatogram Information

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 Date Modified 17/02/2017 13:23:41
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 Injection Date 17/02/2017 12:16:03
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 Sample Number 1
 Project Name Test
 Acquisition Time 30,0 [min]
 Acquisition Sequence NSD-2122-Racemic-3
 Control Method 97Hx 3IPA COL-IA 35min
 Peak ID Table
 Calibration Method
 Additional Information



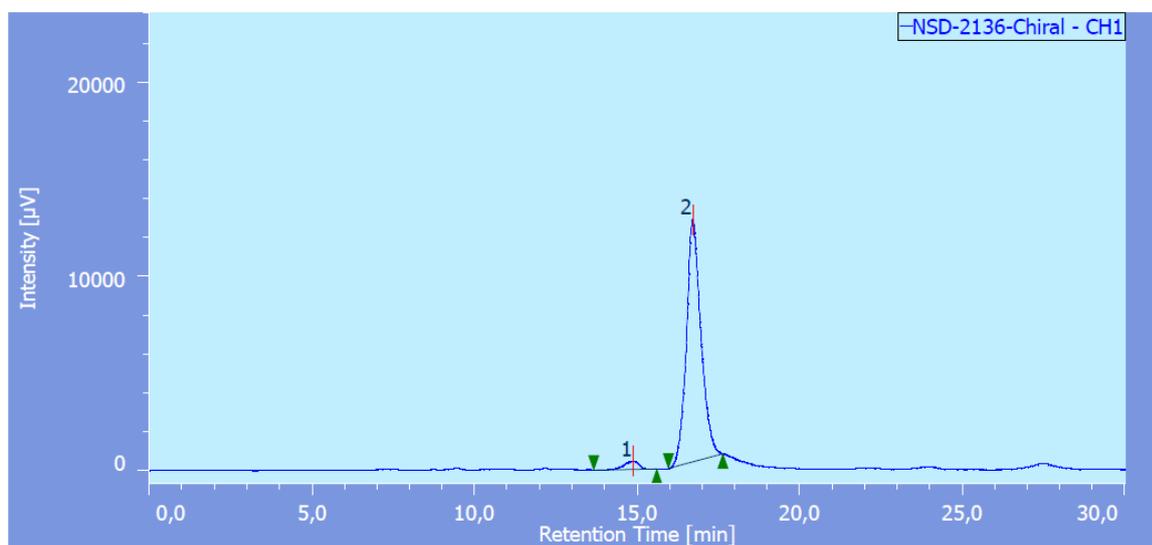
Channel & Peak Information Table

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 Sample Name
 Channel Name CH1
 Sampling Interval 500 [msec]
 Peak Method (Manual)
 Formula
 Decision

| # | Peak Name | CH | tR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|-----------|----|----------|---------------|-------------|--------|---------|----------|------|------------|-----------------|---------|
| 1 | Unknown | 1 | 14,158 | 173004 | 3849 | 49,558 | 53,248 | N/A | 2330 | 1,838 | 1,168 | |
| 2 | Unknown | 1 | 16,425 | 176091 | 3379 | 50,442 | 46,752 | N/A | 2553 | N/A | 1,396 | |

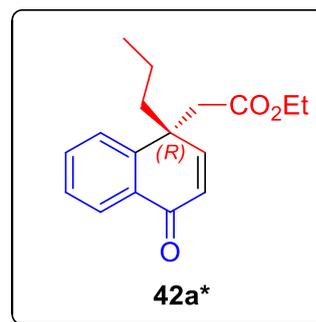
HPLC data-42a*:

Chromatogram



Chromatogram Information

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 Injection Date 17/02/2017 11:11:36
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 Sample Number 2
 Project Name Test
 Acquisition Time 30,0 [min]
 Acquisition Sequence NSD-2136-Chiral
 Control Method 97Hx 3IPA COL-IA 35min
 Peak ID Table
 Calibration Method
 Additional Information



Channel & Peak Information Table

Chromatogram Name NSD-2136-Chiral-CH1
 Sample Name
 Channel Name CH1
 Sampling Interval 500 [msec]
 Peak Method (Manual)

Formula
 Decision

| # | Peak Name | CH | tR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|-----------|----|----------|---------------|-------------|--------|---------|----------|------|------------|-----------------|---------|
| 1 | Unknown | 1 | 14.892 | 13809 | 423 | 3.441 | 3.280 | N/A | 4592 | 2.206 | 0.795 | |
| 2 | Unknown | 1 | 16.708 | 387544 | 12474 | 96.559 | 96.720 | N/A | 7486 | N/A | 1.157 | |