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Fluorinated Alcohols : A Perfect Medium for Direct Functionalization of Aromatics

Renjin Tang

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NNT: 2018SACLS324

Fluorinated Alcohols: A Perfect Medium for the Direct Functionalization of Aromatics

Thèse de doctorat de l'Université Paris-Saclay

préparée à l'Université Paris-Sud

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Thèse de doctorat

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Last my thanks should to my lovely girl-friend Can Peng, for the patiently waiting and support me over the years.

List of Abbreviations

Ac-Gly-OH	N-acetylglycine
Ac-Phe-OH	N-acetylphenylalanine
AcCl	acetyl chloride
bipy	2, 2'-bipyridine
BODIPYs	boron dipyrromethenes
Boc	*tert*-butyloxycarbonyl
Cbz	benzyloxycarbonyl
18-crown-6	1, 4, 7, 10, 13, 16-hexaoxacyclooctadecane
Cp*	pentamethylcyclopentadienyl
DFT	density functional theory
DMPU	*N, N*-dimethylpropyleneurea
dba	dibenzylideneacetone
DIPEA	*N, N*-diisopropylethylamine
DME	1, 2-dimethoxyethane
DEAD	diethyl azodicarboxylate
DG	directing group
EDC	ethylcarbodiimide hydrochloride
ee	enantiomeric excess
eh	1, 2-diaminoethane
FC	Friedel-Crafts
HBD	hydrogen-bond-donator
HBA	hydrogen-bond-acceptor
HFIP	1, 1, 1, 3, 3, 3-hexafluoroisopropanol
m-CPBA	3-chloroperbenzoic acid
MOF	metal-organic framework
MFE	2-fluoroethanol
NHPI	N-hydroxyphthalimide
NBE-CO_2Me	2-carbomethoxynorbornene
NFSI	N-fluorobenzenesulfonimide
NXS	N-halosuccinimides
NBS	N-bromosuccinimide
NIS	N-iodosuccinimide
NCS	N-chlorosuccinimide

Oxone	potassium peroxymonosulfate
PFTB	perfluoro-*tert*-butanol,
PB	$KHSO_4$
PTSA	*p*-toluenesulfonic acid
PhI=NNs	[*N*-(p-Toluenesulfonyl)imino]phenyliodinane
Ph_4PBF_4	tetraphenylphosphonium tetrafluoroborate
$PhI(OAc)_2$	(diacetoxyiodo)benzene
$PhI(OPiv)_2$	di-(pivaloyloxy)iodobenzene
Piv-Leu-OH	N-pivaloylleucine
TfOH	trifluoromethanesulfonic acid
TFE	2, 2, 2-trifluoroethanol
$TMSN_3$	azidotrimethylsilane
TFA	trifluoroacetic acid
TIPP	2, 4, 6-triisopropylphenyl
TMP	trimethylolpropane
Δ	heating

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General Conclusion

General Introduction

Due to the aromatic ring's great impression in drug's discovery and biological science, how to modify aromatic rings directly and effectively is one of the hot points of modern chemistry. Over the last years, fluorinated alcohols such as trifluoroethanol (TFE) and hexafluoro-2-propanol (HFIP) have been shown to display unique features as solvents, cosolvents and additives in organic synthesis due to its nearly unique set of properties that include high ionizing power, strong hydrogen-bond donating ability, mild acidity and low nucleophilicity. All of these properties are favorable for electrophilic aromatic substitution reactions. During my Ph.D., I focused on aromatic functionalization in fluorinated alcohols. Such work includes:

1. C-H Amination of Arenes with Azodicarboxylates

The amination of anilines always needs protecting groups due to the high nucleophilicity of the free amino group. However, the introduction and subsequent removal of protecting groups not only requires additional operations but also significantly decreases functional group compatibility. We reported our efforts to develop an effective, mild, and clean method for the C-H amination of free anilines with azodicarboxylates in HFIP without the need for any additional catalysts or reagents. The reaction was found to be highly regioselective and provided a series of *p*-aminophenylhydrazine derivatives in excellent yields. Meanwhile, the amination of less active arenes was realized by using catalytic amount of green, inexpensive and readily available inorganic salt potassium bisulfate ($KHSO_4$) as catalyst in HFIP. This protocol is shown to efficiently aminate a broad range of arenes, including arenes with certain electron-withdrawing groups, generating the corresponding hydrazides in good to excellent yields. An additional advantage of $KHSO_4$ is its low cost, ready availability and easy removal in aqueous workup.

2. Friedel-Crafts (FC) Alkylation with β-Nitroalkenes and with Benzylic Alcohols

The development of general and more atom-economical catalytic processes for FC alkylation is an important objective of interest for the production of pharmaceuticals and commodity chemicals. In the first part, we described an effective and clean FC alkylation of indoles and electron-rich arenes with β-nitroalkenes in HFIP. The desired products are formed rapidly in excellent yields under mild conditions without the need for any additional catalysts or reagents. This methodology can also be applied to one-pot synthesis of biologically active tryptamine derivatives. In the second part, a method for direct FC benzylation of simple arenes with benzylic alcohols using the mild and green system of $KHSO_4$/HFIP was developed. The catalytic system was powerful with large diversity of slightly activated and neutral arenes and

benzyl alcohols including modestly electronically deactivated benzylic alcohols and secondary benzylic alcohols. These mild conditions provided a straightforward synthesis of a variety of unsymmetrical diarylmethanes in high yield with good to high regioselectivity. Though stereochemical studies, a S_N1 mechanism involving activation of the hydroxy group through hydrogen-bond-network system was proposed.

3. C-H Halogenation of Arenes and Heterocycles with NXS.

Aryl halides are very important compounds as the key precursors for metal-catalyzed cross-couplings and widely employed in natural products, pharmaceuticals, and materials science. The development of efficient and mild halogenation of aromatic compounds is an intensively investigated area of great significance. Herein, fluorinated alcohols have been found to be a particularly efficient solvent system for the halogenation of arenes and heterocycles. A wide diversity of halogenated arenes and heterocycles were obtained using commercially available N-halosuccinimides including NCS and NIS, with good to excellent yields and with very high selectivity. Additionally, the versatility of the method was demonstrated by the development of one-pot sequential halogenation and halogenation-Suzuki cross-coupling reactions.

Introduction Générale

En raison de la présence du cycle aromatique dans les médicaments, la modification directe et efficace des cycles aromatiques est l'un des points important de la chimie moderne. Au cours des dernières années, des alcools fluorés tels que le trifluoroéthanol (TFE) et l'hexafluoro-2-propanol (HFIP) ont montré des caractéristiques uniques en tant que solvants, cosolvants et additifs de synthèse organique en raison de leurs propriétés uniques : capacité à former des liaisons hydrogène, Ph acide et peu nucléophile. Toutes ces propriétés sont favorables aux réactions de substitution électrophiles aromatiques. Au cours de mon doctorat, je me suis concentré sur la fonctionnalisation aromatique des alcools fluorés. Ce travail comprend:

1. Amination des Arènes par C-H avec des Azodicarboxylates

L'amination des anilines a toujours besoin de groupes protecteurs en raison de la forte nucléophilie du groupe amino libre. Cependant, l'introduction et la suppression de groupes protecteurs nécessitent non seulement des réactions supplémentaires, mais également une diminution significative de la compatibilité des groupes fonctionnels. Nous avons focalisé nos efforts pour mettre au point une méthode efficace, douce et propre d'amination d'anilines non protégées avec des azodicarboxylates dans l'HFIP sans catalyseurs. La réaction s'est révélée hautement régiosélective et a fourni une série de dérivés de *p*-aminophénylhydrazines avec d'excellents rendements. L'amination d'arènes moins actives a été réalisée en utilisant une quantité catalytique de bisulfate de potassium ($KHSO_4$), sel inorganique, peu coûteux et facilement disponible dans l'HFIP. Il a été démontré que ce protocole était efficacement avec une large gamme d'arènes, y compris des arènes avec certains groupes électro-attracteurs d'électrons, conduisant aux hydrazides avec des rendements bons à excellents. Un avantage supplémentaire de $KHSO_4$ est son faible coût, sa disponibilité immédiate et son retrait facile en traitement aqueux.

2. Alkylation de Friedel-Crafts (FC) avec des β-Nitroalcènes et des Alcools Benzyliques

Le développement de procédés catalytiques et plus économiques en atomes pour l'alkylation de FC est un objectif important pour la production de produits pharmaceutiques et de produits chimiques de base. Dans la première partie, nous avons décrit une alkylation FC propre et efficace d'indoles et d'arènes riches en électrons avec des β-nitroalcènes dans l'HFIP. Les produits désirés se forment rapidement avec d'excellents rendements dans des conditions douces sans catalyseurs. Cette méthodologie peut également être appliquée à la synthèse one-pot de dérivés de tryptamine biologiquement actifs. Dans la deuxième partie, une méthode de

benzylation directe de FC d'arènes simples avec des alcools benzyliques en utilisant le système $KHSO_4$/HFIP a été développée. Le système catalytique était efficace avec une grande diversité d'arènes et d'alcools benzyliques activés et neutres, y compris des alcools benzyliques légèrement désactivés électroniquement et des alcools benzyliques secondaires. Ces conditions douces ont fourni une synthèse directe d'une variété de diarylméthanes non symétriques avec de bons rendements et une régiosélectivité bonne à élevée. Bien que des études stéréochimiques aient été proposées, un mécanisme S_N1 impliquant l'activation du groupe hydroxy via un système de réseau de liaisons hydrogène a été proposé.

3. Halogénation C-H des Arènes et des Hétérocycles avec NXS.

Les halogénures d'aryle sont des composés très importants en tant que précurseurs clés des couplages croisés catalysés par des métaux et largement utilisés dans la construction de produits naturels, de produits pharmaceutiques et de matériaux. Le développement d'une halogénation efficace et douce des composés aromatiques est un domaine de grande importance à approfondir. Les alcools fluorés se sont révélés particulièrement efficace pour l'halogénation des arènes et des hétérocycles. Une grande diversité d'arènes et d'hétérocycles halogénés a été obtenue en utilisant des *N*-halosuccinimides disponibles dans le commerce, avec de bons rendements et une très grande sélectivité. De plus, la polyvalence de la méthode a été démontrée par le développement de réactions de couplage croisé d'halogénation et de réactions séquentielles d'halogénation-Suzuki en un pot.

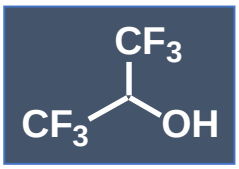
Chapter I

Fluorinated Alcohols as Highly Versatile Solvents in Organic Chemistry

I. Introduction

Over the last years, fluorinated alcohols have been shown to display unique properties as solvents, co-solvents, and additives in synthetic chemistry.[1-3] Due to the strong electron-withdrawing character of fluoroalkyl groups, the presence of one or more fluoroalkyl groups brings specific properties to fluorinated alcohols compared to common solvents and non-fluorinated analogues, which were expected to dramatically modify the course of reactions and to offer a new interesting aspect to fluorinated solvents in organic synthesis. The most commonly used and cheapest fluorinated alcohols are 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), which are available on a commercial scale. Other fluorinated alcohols, such as perfluoro-*tert*-butanol (PFTB), 1,3-bis(1,1,1,3,3,3-hexafluoro-2-hydroxypropyl)benzene, and 2-fluoroethanol (MFE) are also available, but the high price often limits their broad application.

TFE



HFIP

Scheme 1. 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP)

II. Properties of Fluorinated Alcohols

To understand the role of fluorinated alcohols in organic synthesis, we first summarized some properties of fluorinated alcohols as well as the non-fluorinated analogues and selected solvents, which are commonly used in organic synthesis, are given for comparison.

Table 1. Properties of Fluorinated Alcohols and Common Solvents

Solvent	B.p. (^{o}C)	M.p. (^{o}C)	p*K*a	Nucleophilicity (N)	Polarity (E^{N}_{T})	Ionizing power (Y)	HBD (α)	HBA (β)
CH_2Cl_2	39.6	- 97	-	-	0.309	-	0.13	0.10
PhMe	110.6	- 95	41	-	0.099	-	0	0.11
EtOH	78	- 117	15.9	0	0.654	- 1.75	0.83	0.77
TFE	73.8	- 44	12.4	- 2.78	0.898	1.8	1.51	0.18

HFIP	58.6	- 5	9.3	- 4.23	1.068	3.82	1.96	0.03

As you can see from **Table 1**, compared to common solvents and non-fluorinated alcohols, fluorinated alcohols exhibit unique properties in the following areas:

Lower boiling points: Fluorinated alcohols exhibit lower boiling points and higher melting points than do their non-fluorinated counterparts. This means that TFE (b.p. 74 °C) and HFIP (b.p. 59 °C) can be easily removed from the reaction mixture by distillation, resulting in reduced solvent waste and offsetting the initial expense.

Enhanced acidity: Because of their strong negative inductive effect, fluorine substituents increase the acidity of the hydroxyl group. The acidity of alcohols increases with the number of fluorine atoms in the molecule with p*K*a values of 12.4 for TFE compared with 15.9 for EtOH and 9.3 for HFIP compared with 17.1 for ^{i}PrOH.[4]

High hydrogen-bond donating (HBD) ability: Fluorinated alcohols possess a very strong hydrogen bond donor power. Moreover, it was also demonstrated that aggregation of HFIP could also enhance this property.[5] The solvating power of HFIP through hydrogen bonds is so strong that it forms a discrete complex with THF and other basic solvents.[6]

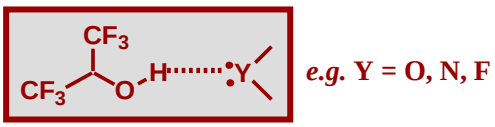
High polarity and ionizing power: Fluorinated alcohols are highly polar solvents, as shown in solvatochromic investigations, HFIP was the most polar solvent among 360 compounds investigated.[7] They also possess a high ionizing power.

Low nucleophilicity and hydrogen-bond accepting (HBA) ability: Despite the presence of the hydroxyl group, fluorinated alcohols distinctly differ from non-fluorinated alcohols and other protic solvents in the fact that they are poor hydrogen-bond acceptors and nucleophiles.

These unique properties, in particular, their mild acidity and hydrogen-bond donating ability characters have been exploited in many reactions. Fluorinated alcohols are ideal solvents in which to generate and study cations. Besides these important applications, fluorinated alcohols are used from time to time as solvents or co-solvents in transition metal-catalyzed C-H activation, although the role of fluorinated alcohols was not so clear. In this chapter, we focused on contributions made in the past decade, with a particular emphasis on works published in the past five years.

III. Activation of Functional Groups

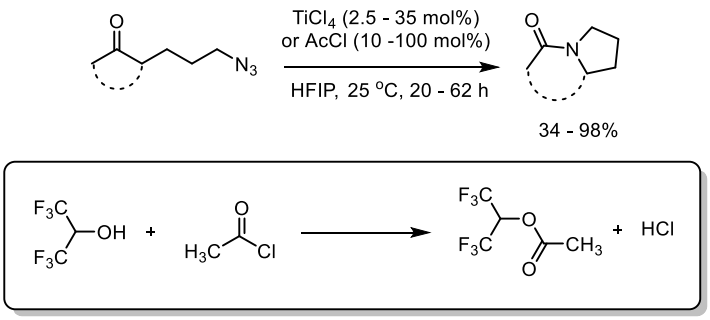
Due to the high hydrogen-bond donating ability, fluorinated alcohols can form hydrogen-bond with functional groups such as carbonyl, epoxide, and halides etc.



Scheme 2. Hydrogen Bonding between Fluorinated Alcohols and Functional Groups

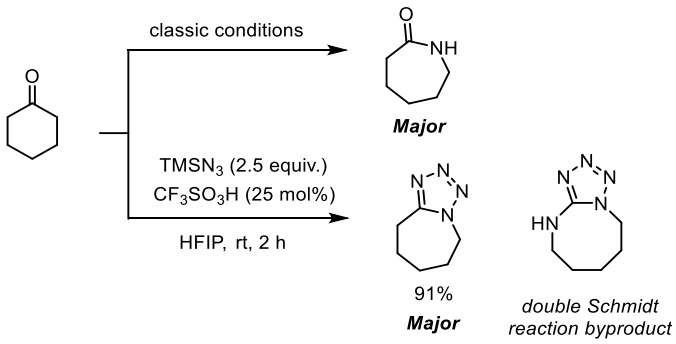
III. 1. Activation of Carbonyl Group

In 2013, Aubé and co-workers reported the intramolecular Schmidt reaction using 2.5 - 25 mol% of $TiCl_4$ or 10 - 100 mol% of AcCl as catalysts.[8] The use of HFIP as solvent was critical to these reactions that overcomes one of the previous limitations of the reaction which required for excess Lewis or Brønsted acid to achieve complete conversion.[9] Meanwhile, the discovery of conditions employing AcCl as a pro-catalyst in the presence of HFIP provided evidence that HCl is an active catalytic species as well as providing a metal-free catalytic reaction.



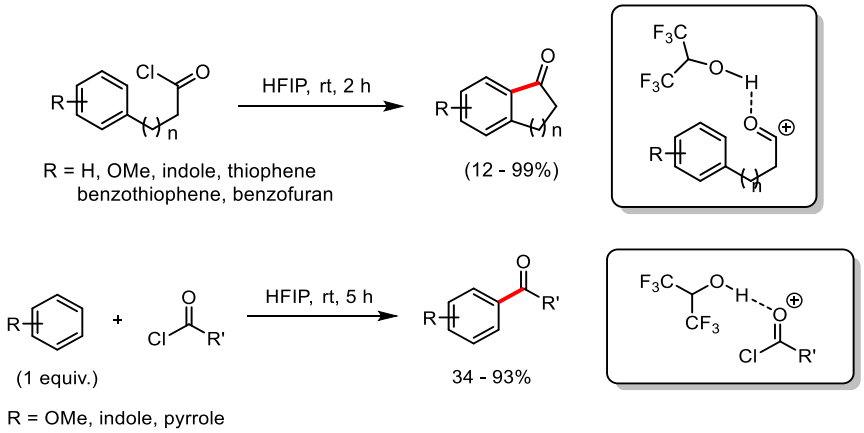
Scheme 3. Intramolecular Schmidt Reaction in HFIP

More recently, this methodology has been extended to an intermolecular Schmidt reaction.[10] When $TMSN_3$ was reacted with ketones in the presence of TfOH as the catalyst in HFIP, tetrazoles were obtained as the major products. This observation was in contrast to classic conditions, which usually led to amides or lactams arising from formal NH insertion as the major products.[11]



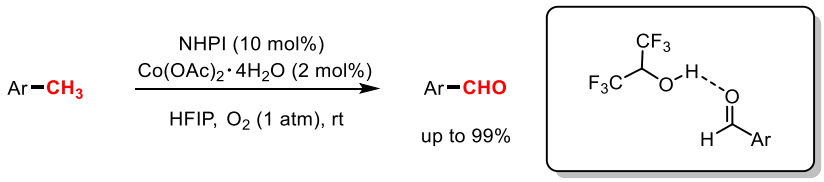
Scheme 4. Intermolecular Schmidt Reaction in HFIP

Meanwhile, both HFIP-promoted intramolecular[12] and intermolecular[13] Friedel-Crafts acylation with acyl chlorides without any additional catalyst or reagent have also been reported by Aubé and co-workers. Mechanistic experiments were consistent with the activation of the acyl chloride through hydrogen bonding to HFIP.



Scheme 5. HFIP-Promoted Friedel-Crafts Acylation Reaction

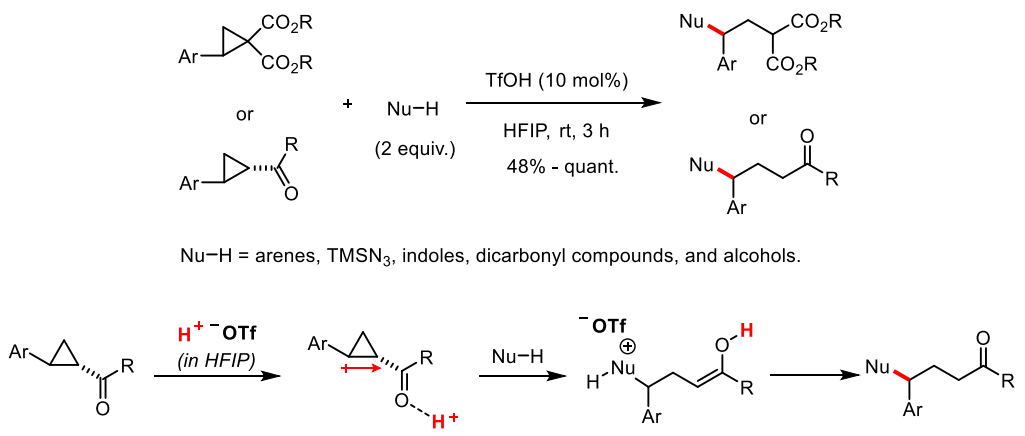
In 2017, Pappo and co-workers developed an efficient and highly selective catalytic condition for the aerobic auto-oxidation of both electron-deficient and electron-efficient methylenes to benzaldehydes, using the combination of N-hydroxyphthalimide (NHPI) and cobalt(II) acetate in HFIP.[14] Based on mechanistic studies and DFT calculations, it was suggested that benzaldehyde and HFIP formed an H-bond adduct that underwent a markedly slower H abstraction of the aldehydic C-H bond.



Scheme 6. Aerobic Auto-Oxidation of Methylarenes to Benzaldehydes

Recently, Moran and co-workers described the Brønsted acid-catalyzed method at the room temperature by a nucleophilic ring opening of donor-acceptor cyclopropanes in HFIP.[15] The combination of TfOH and HFIP provided a simple highly active Brønsted acid system to engage in nucleophilic ring-opening reactions for the first time. Initial observations suggested that ring

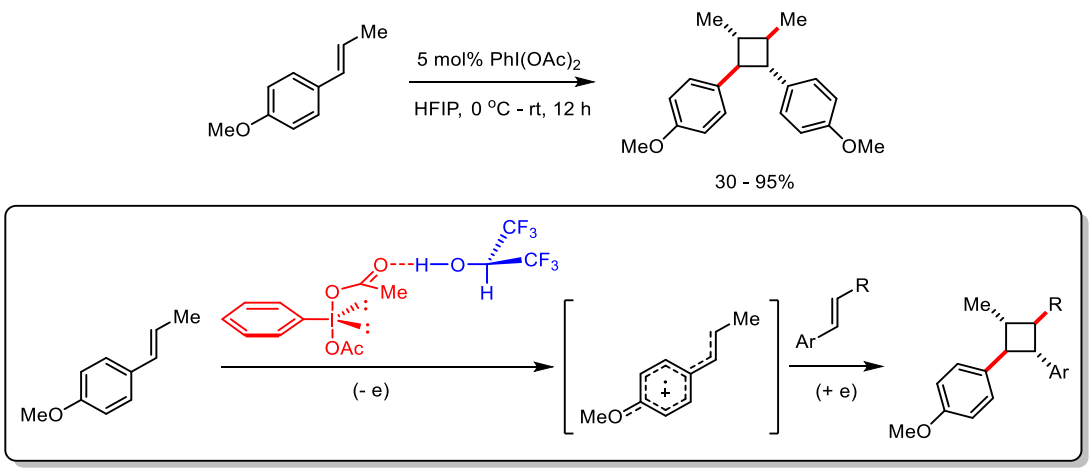
opening occurred via an S_N2-like mechanistic pathway.



Scheme 7. Brønsted Acid-Catalyzed Nucleophilic Ring Opening of Cyclopropanes

III. 2. Activation of Hypervalent Iodine Reagent

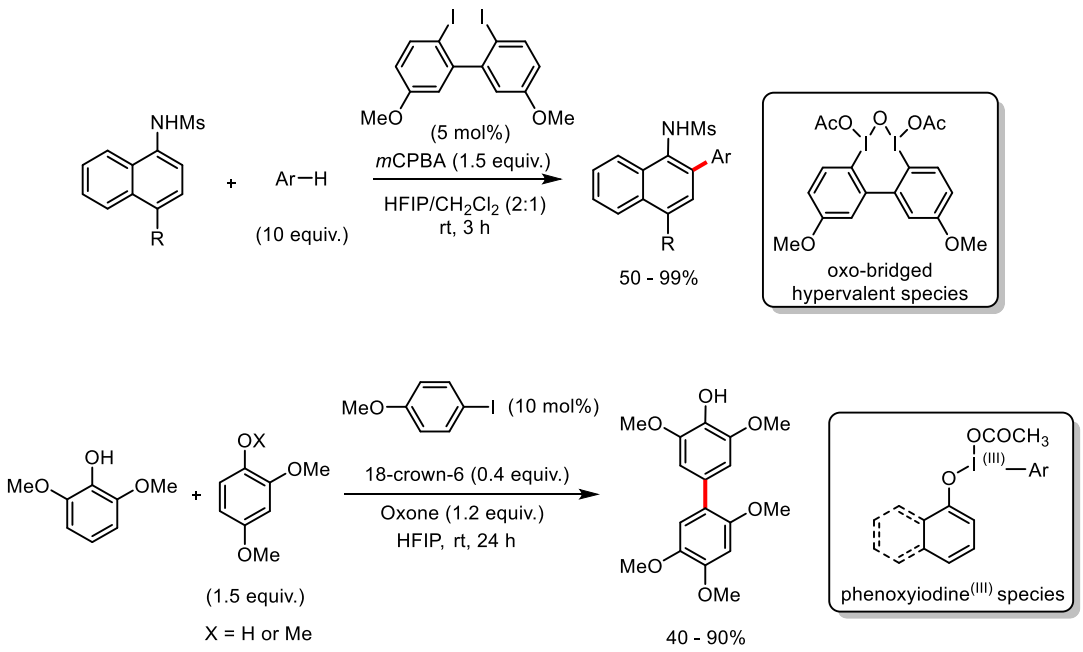
Due to the existence of carbonyl groups in hypervalent iodine reagents, fluorinated alcohols also can activate the hypervalent iodine reagents. In 2016, Donohoe and co-workers reported a highly diastereoselective synthesis of *tetra*-substituted cyclobutanes through dimerization of styrenes using catalytic quantities of hypervalent iodine reagents.[16] Soon after, they have demonstrated that the formation of a strongly hydrogen-bonded adduct between the fluorinated solvent and hypervalent iodine reagents which enhanced its reactivity.[17]



Scheme 8. Hypervalent Iodine-Initiated [2+2] Cycloaddition of Styrenes

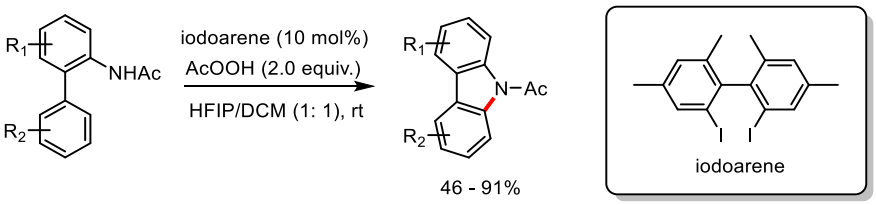
This idea has been extended to oxidative C–H/C–H cross-coupling of *N*-methanesulfonyl anilides[18] and phenols[19] in combination with electron-rich arenes to generate functionalized

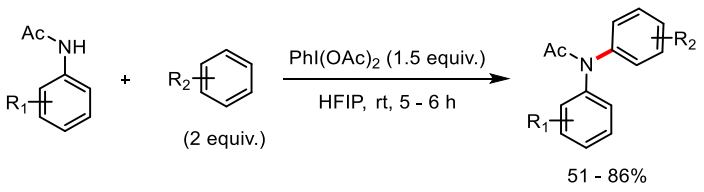
biaryl compounds by Yasuyuki Kita and co-workers. Although no mechanistic study was provided, the authors speculated that the coupling proceeded via an oxo-bridged hypervalent species for anilides and via a phenoxyiodine(III) species in the case of phenols.



Scheme 9. Oxidative Cross-Coupling of *N*-methanesulfonyl Anilides and Phenols

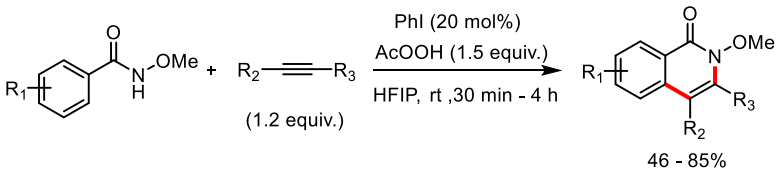
Meanwhile, Andrey P. Antonchick and co-workers in Germany also contributed to the reaction catalyzed by hypervalent iodine reagent in fluorinated alcohol. For example, they developed an organocatalytic synthesis of carbazoles throught intermolecular C-H bond amination of unactivated arenes.[20] They found that the application of iodoarene as organo-catalyst in combination with 2.0 equiv. of AcOOH as terminal oxidant could provide the products in moderate to good yields. In addition, the methodology has been extended to the unprecedented metal-free cross-amination of nonactivated arenes with various aniline derivatives.





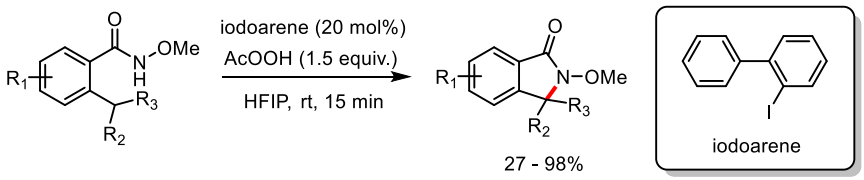
Scheme 10. Intramolecular C-H Bond Amination and Cross-Amination of Unactivated Arenes

Moreover, the annulation reaction benzamide derivatives with alkynes for the synthesis of isoquinolines under the similar conditions have been also reported by P. Antonchick and co-workers in 2014.[21]



Scheme 11. Intramolecular C-H Bond Amination and Cross-Amination of Unactivated Arenes

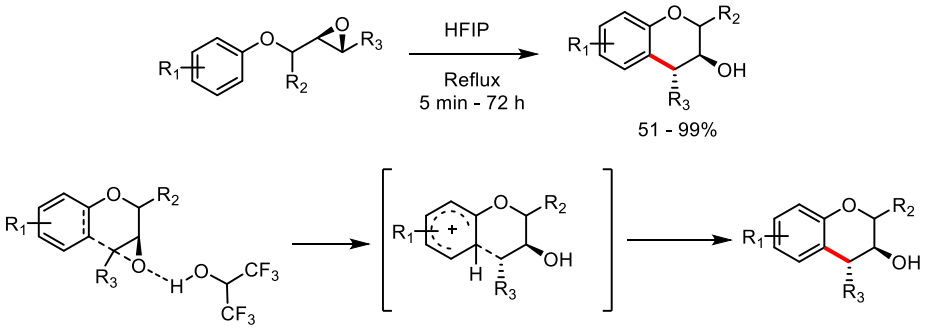
Meanwhile, Shi and co-workers developed a new synthesis of *γ*-lactams via an iodoarene-catalyzed intramolecular tertiary C-H amination in HFIP.[22] The products formed efficiently using a simple iodoarene as catalyst and *m*-CPBA as oxidant *in-situ* generating iodine(III) reagents under mild conditions in short times.



Scheme 12. Iodoarene-Catalyzed Intramolecular Tertiary C-H Amination

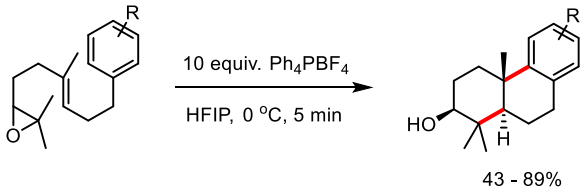
III. 3. Activation of Epoxide

In 2010, Qu and co-workers investigated the intramolecular and intermolecular Friedel-Crafts alkylation of electron-rich arenes with epoxides being activated by HFIP without any additional catalyst or reagent.[23] This Friedel-Crafts alkylation didn't need strict anhydrous conditions which were usually required for Lewis acid catalyzed reactions. The authors proposed an acid-catalyzed pathway involving concerted C-O bond cleavage and C-C bond formation, which was supported by an inversion of stereochemistry.



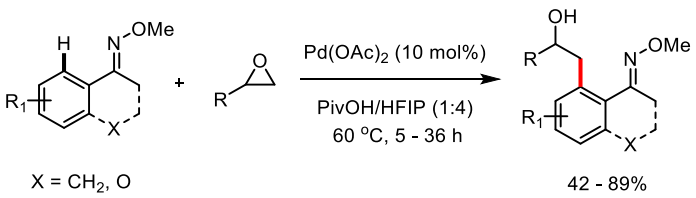
Scheme 13. HFIP Promoted Friedel-Crafts alkylation of Arenes with Epoxides

Later on, in 2016, the same group applied their methodology to epoxide-initiated cation-olefin polycyclization reactions.[24] Although HFIP promoted the reaction, the use of an excess of Ph_4PBF_4 resulted in an increased yield to 60%, and an increased rate of reaction to 5 min. The authors proposed that in HFIP, the epoxide substrate was activated by traces of HF generated by BF_4 solvolysis in HFIP, and the intermediate cation was stabilized by HFIP or by BF_4 anions.



Scheme 14. HFIP Promoted Epoxide-Initiated Cation-Olefin Polycyclizations

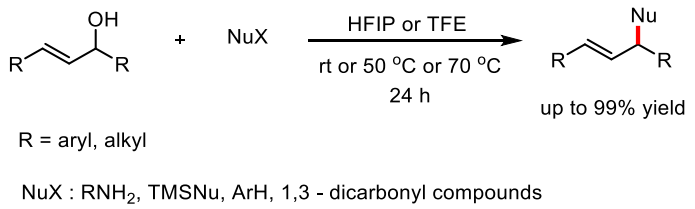
In the same year, Wu and co-workers demonstrated a palladium-catalyzed *ortho*-selective alkylation of *o*-methyl ketoximes with epoxides using a mixture of PivOH and HFIP as the solvent.[25] Various *o*-methyl ketoximes that contain either electron-donating or electron-withdrawing groups reacted with different type of epoxides, proceeded smoothly to give the corresponding products in moderate to good yields.



Scheme 15. Palladium-Catalyzed *ortho*-Selective Alkylation of *o*-Methyl Ketoximes with Epoxides

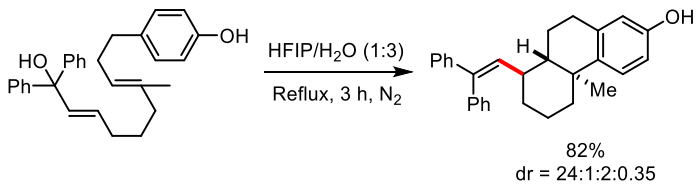
III. 4. Activation of Alcohol

In 2012, Baeza and Nájera reported the metal-free substitution of allylic alcohols, represents one of the first examples of alcohol activation in HFIP.[26] Nucleophiles including amines, sulfonamides, and carbamates were used, affording allylic amines with modest to good yields. Additionally, the C-C bond formation was achieved using allyl silanes, 1,3-dicarbonyl compounds or electron-rich aromatic compounds in a Friedel-Crafts type reaction.



Scheme 16. Fluorinated Alcohols Promote the Substitution of Allylic Alcohols

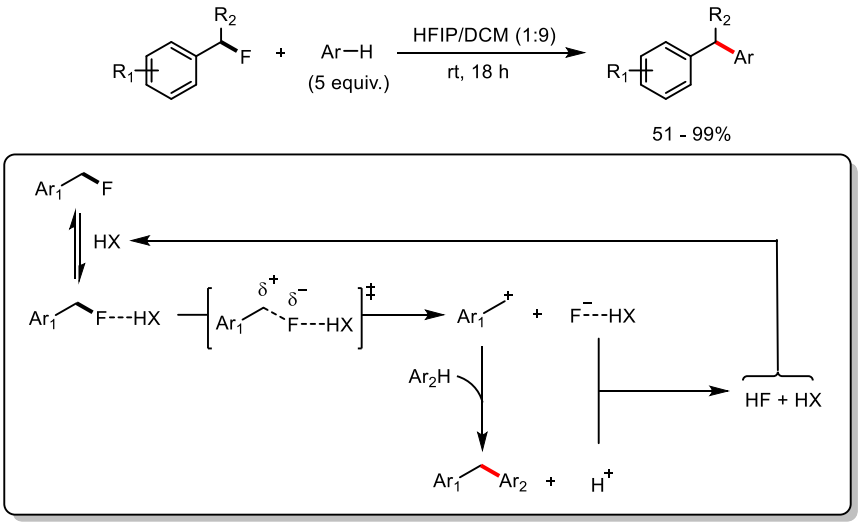
In 2015, Qu and co-workers reported intramolecular polyene cyclization of allylic alcohols promoted by a mixture of HFIP and H_2O.[27] It was noteworthy that the use of neat HFIP afforded tricyclization products in a high yield and didn't require the protection of the phenoxy group.



Scheme 17. HFIP Promoted Intramolecular Polyene Cyclization of Allylic Alcohols

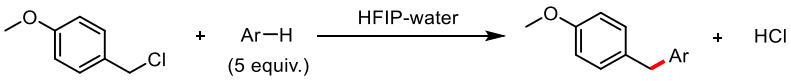
III. 5. Activation of Halide

In 2014, Paquin and co-workers reported the Friedel-Crafts benzylation of various arenes with benzylic fluorides using HFIP as the solvent and hydrogen-bond donor.[28] A mechanism involving selective activation of the C-F bond by HFIP and HF through hydrogen bonding was proposed.



Scheme 18. Friedel-Crafts Benzylation of Arenes with Benzylic Fluorides

In 2016, Khaledi and co-workers have developed the Friedel-Crafts benzylation of arenes and heteroarenes with benzyl chloride in the aqueous HFIP two-phase system.[29] Surprisingly, the reactions performed in the two-phase systems outperformed those in pure HFIP.

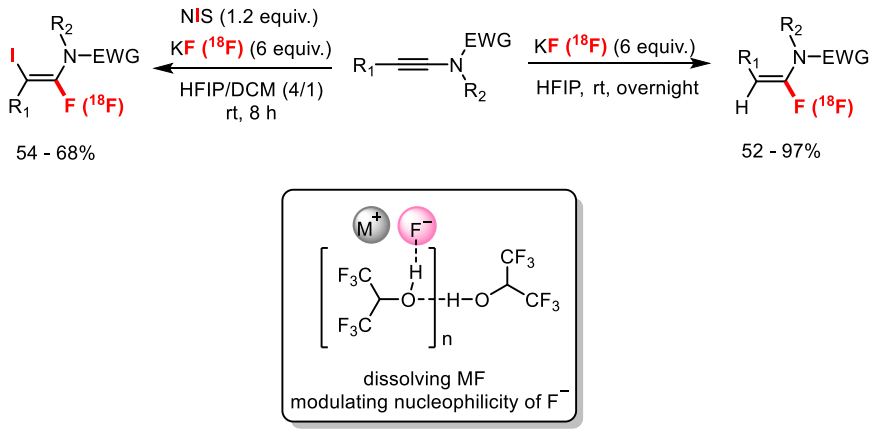


Entry	Nucleophile	HFIP (%)	Yield (%)
1	Mesitylene	0	0
2	Mesitylene	10	61.2
3	Mesitylene	20	81
4	Mesitylene	50	77.5
5	Mesitylene	100	14.5

Entry	Nucleophile	HFIP (%)	Yield (%)
6	2-Methylfuran	0	< 5
7	2-Methylfuran	10	80
8	2-Methylfuran	20	85
9	2-Methylfuran	50	69
10	2-Methylfuran	100	< 5

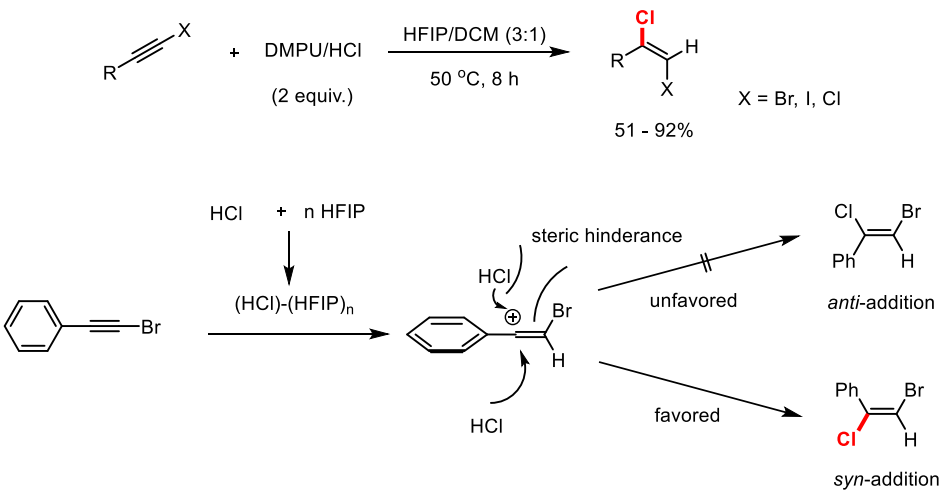
Scheme 19. Friedel-Crafts Benzylation of Arenes with Benzylic Chlorides

In 2017, Xu and co-workers reported a widely applicable nucleophilic (radio)fluoro-click reaction of ynamides with readily available and easy handling KF(^{18}F) in HFIP.[30] Because HFIP is a stronger hydrogen-bond donor and fluoride itself is a good hydrogen bonding acceptor, an hydrogen-bond network with HFIP could complex with KF(^{18}F) and make it highly soluble. Moreover, it has a stronger effect on the modulation of the nucleophilicity of fluoride. Most importantly, this is the first ^{18}F addition protocol to C-C unsaturated bonds with extraordinarily high radiochemical yields.



Scheme 20. Nucleophilic (Radio)Fluoro-Click Reaction of Ynamides

This year, the same group developed an efficient synthesis of (*E*)-chlorohaloalkenes via hydrochlorination of haloalkynes with DMPU/HCl reagent in a mixture of HFIP and DCM.[31] The hydrogen-bonding cluster generated from HFIP forms a hydrogen-bonding complex with HCl and granted the HCl increased acidity. This gave rise to the intermediate vinyl cation, which should have a linear geometry. Attacked at the upper face is hindered by the bulky bromine atom, thus favoring chloride attack syn to the H atom.

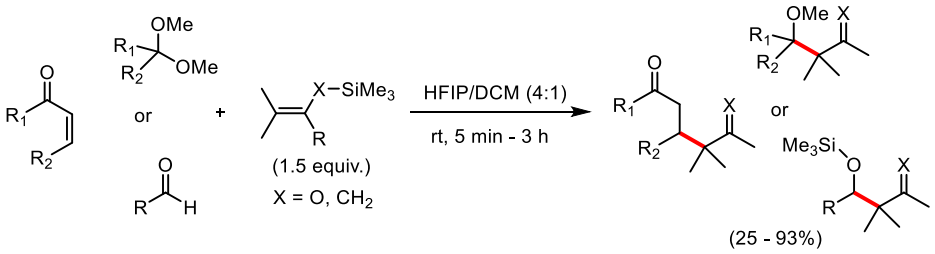


Scheme 21. Synthesis of (*E*)-Chlorohaloalkenes via Hydrochlorination of Haloalkynes

III. 6. Activation of Other Groups

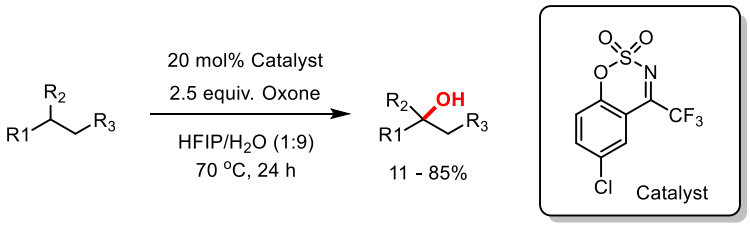
In 2008, Smit and co-workers reported the applicability of HFIP as both medium and activator for a number of classical reactions such as Hosomi-Sakurai acetal allylation, the Mukaiyama aldol reaction, and Sakurai-Mukaiyama conjugate additions, which were usually

carried out using Lewis acid catalysts.[32] All of these reactions proceeded in a mixture of HFIP/DCM under mild conditions without any catalysts or reagents, to give the respective adducts in good to excellent yields.



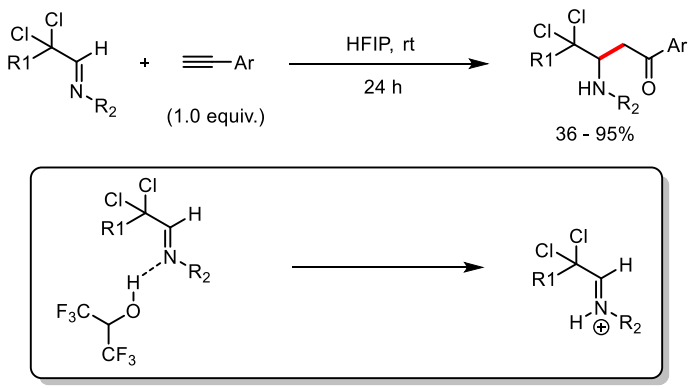
Scheme 22. Electrophilic Alkylation of Silicon-Capped π Donors in HFIP

In 2014, Du Bois and co-workers reported a new example of a catalytic C(sp^3)-H hydroxylation reaction using an oxaziridine as the active catalyst, oxone as the terminal oxidant. The choice of solvent was uniquely effective for this process in which the optimum solvent was shown to be 1:9 HFIP-H_2O.[33] The process was shown to be highly selective for tertiary and benzylic C-H bonds and afforded the corresponding alcohols in modest to excellent yields.



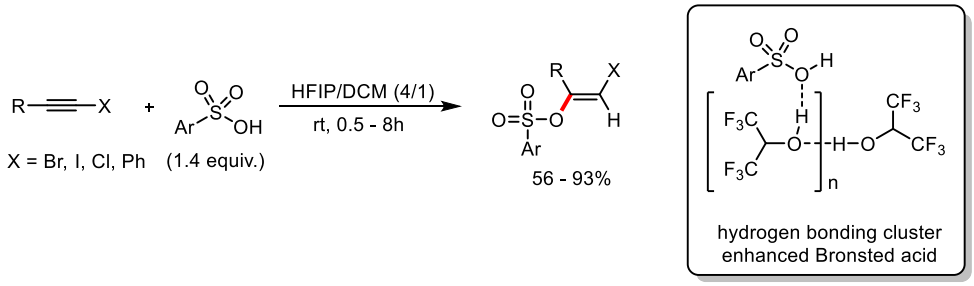
Scheme 23. Oxaziridine-Catalyzed C(sp^3)-H hydroxylation

In 2016, Tehrani and co-workers reported a metal-free reaction of terminal arylacetylenes with α, α-dichloroaldimines using HFIP as the solvent results in the rapid and selective formation of γ, γ-dichloro-β-amino ketones.[34] Mechanistic experiments suggested that HFIP activated the imine by protonation, resulting in a reactive imino carbon that can be attacked by electron-rich arylacetylenes.



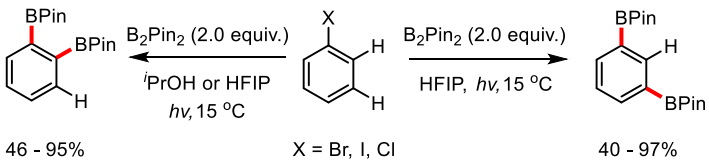
Scheme 24. Synthesis of β-Amino Ketones via Reaction of Imines with Arylacetylenes

In the same year, Xu and co-workers developed a metal-free hydrogen bonding cluster-enabled addition of sulfonic acids to alkynes using a mixture of HFIP and DCM as the solvent at room temperature.[35] The reactivity of sulfonic acids could be significantly enhanced in the presence of strong hydrogen bonding donors.



Scheme 25. Hydrogen Bonding Cluster-Enabled Addition of Sulfonic Acids to Alkynes

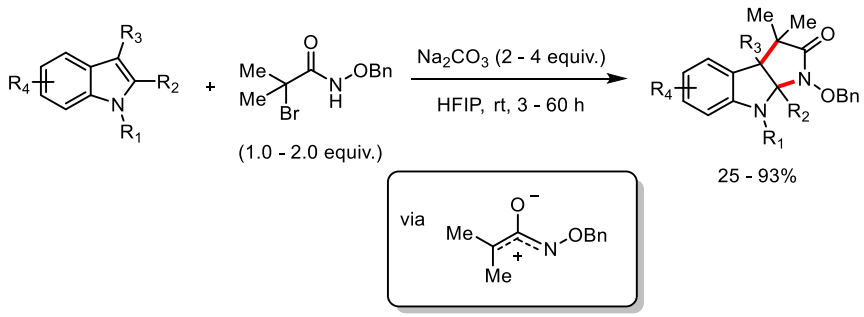
In the same year, Larionov and co-workers reported a metal-free, regioselective, photoinduced dual C-H/C-X borylation approach to 1, 2-diborylarenes and 1, 3-diborylarenes under mild conditions.[36] The regioselectivity of the reaction was determined by the solvent (HFIP or ^{i}PrOH) and the substituents in the parent haloarenes.



Scheme 26. Metal-Free 1,2- and 1,3-Regioselective Borylation of Haloarenes

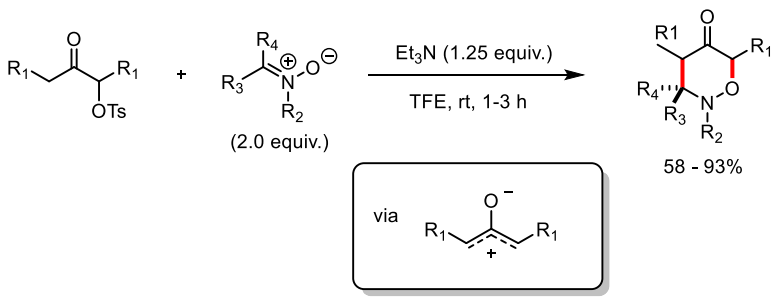
IV. Cation Stabilization

Due to the high dielectric constant and low nucleophilicity, fluorinated alcohols are ideal solvents to generate and stabilize cations. In 2015, Jeffrey group[37] and Wu[38] group reported almost at the same time the synthesis of pyrroloindolines by means of (3+2) dearomative annulation reactions between 3-substituted indoles and bromide. It was speculated that aza-oxyallyl cation formation occurs by a hydrogen-bond-mediated automerization followed by unimolecular ionization of bromide. DFT calculations indicated that the solvent, either TFE or HFIP, can stabilize the transition state through hydrogen-bonding interactions with the oxygen of azaoxyallyl cation, thereby increasing the rates of these reactions.



Scheme 27. Synthesis of Pyrroloindolines via Annulation of Indoles and Bromide

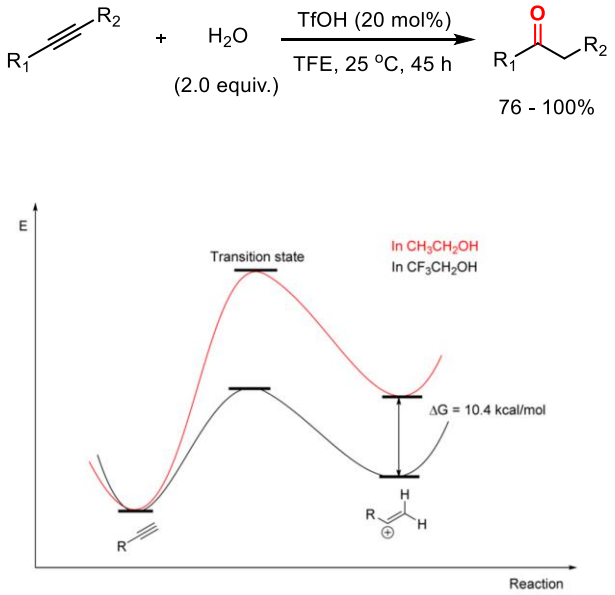
Recently, Archambeau and co-worker developed a (3+3) cycloaddition involving an oxyallyl cation intermediates which were prepared *in situ* from readily available α-tosyloxy ketones and nitrones as the nucleophilic partner.[39] This strategy provides straightforward access to valuable N-O heterocycles bearing a vast array of functional groups as well as spiro and polycyclic compounds.



Scheme 28. Cycloaddition of α-Tosyloxy Ketones with Nitrones

In 2016, Li and co-workers presented a Markovnikov-type hydration of alkyne using 20% TfOH as the catalyst in fluorinated solvents.[40] Throught DFT calculation, they have demonstrated that the success of this reaction lied on the ability to stabilize a vinyl carbocation

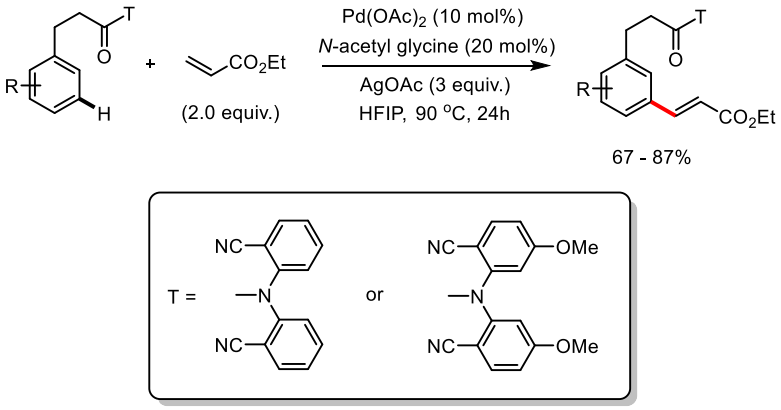
in TFE which can decrease the transition state energy to form the carbocation intermediate.



Scheme 29. Markovnikov-Type Hydration of Alkyne in TFE

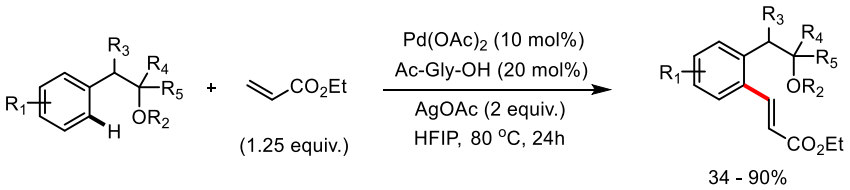
V. Metal-Catalyzed C–H Activation

In the past decade, fluorinated alcohols, particularly HFIP were found to be effective solvents for the direct C-H bond activation.[41] Although, the origin of this effect has not been fully investigated. Fluorinated alcohols were considered to be weakly coordinating with directing groups. For example, in 2012, Yu and co-workers reported a distal *meta*-C-H bonds (more than 10 bonds away) olefination of tethered arenes using removable nitrile-containing templates in HFIP.[42]



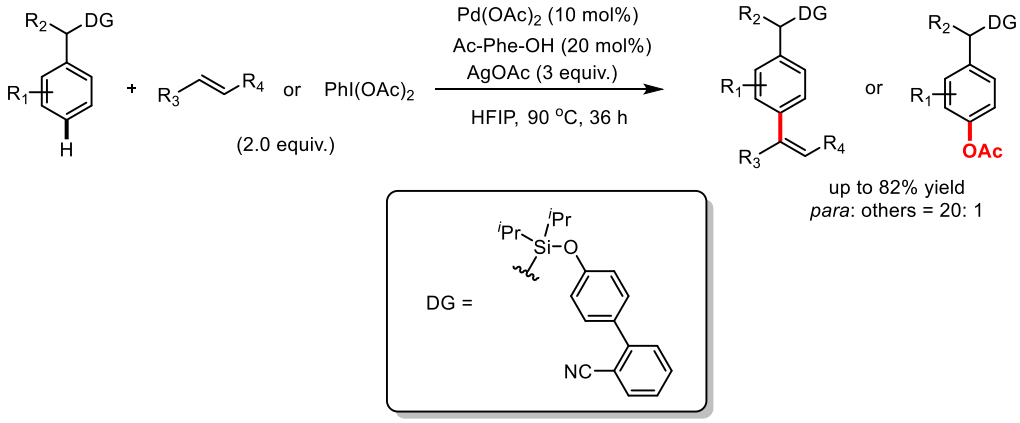
Scheme 30. Distal *meta*-C–H Bonds Olefination of Tethered Arenes

In the next year, the same group demonstrated for the first time that Pd(II) coordinating with monoprotected amino acid ligand promoted ether-directed *ortho*-C-H olefination of ethers in HFIP, which provided a method to functionalize readily available arylethyl ethers to afford novel cinnamate derivatives.[43]



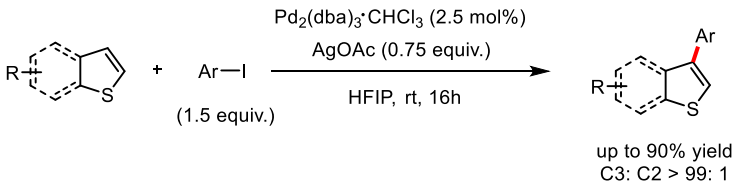
Scheme 31. Directed *ortho*-C-H Olefination of Ethers

In 2015, Maiti and co-workers reported an easily recyclable, novel Si-containing biphenyl-based template that directed efficient olefination and acetoxylation of the distal *para*-C-H bond of toluenes by forming a D-shaped assembly in HFIP.[44]



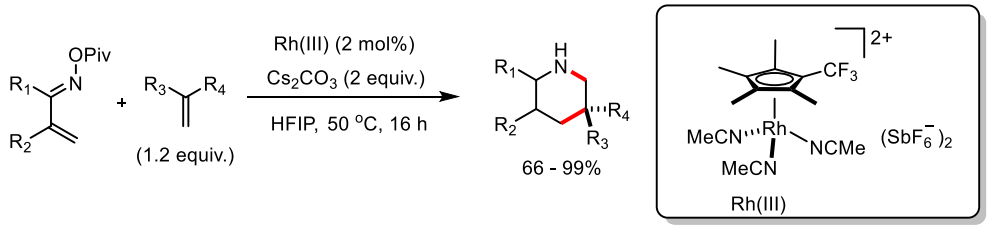
Scheme 32. Distal *para*-C-H Bonds Olefination and Acetoxylation of Tethered Toluene

A further example of the importance of HFIP as a solvent was the *β*-arylation of thiophenes and benzothiophenes with aryl iodides at room temperature reported by Larrosa and co-workers in 2016.[45] This system delivered very high regioselectivities, presented broad functional group tolerance, and could be carried out in an open flask and in the absence of phosphine ligands.



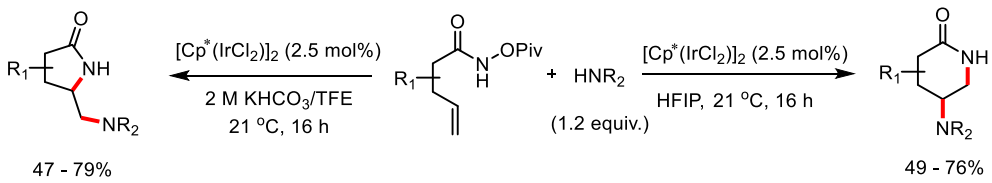
Scheme 33. *β*-Arylation of Thiophenes and Benzo[b]thiophenes

Except commonly used as a solvent for Pd(II)-catalyzed C-H activation reactions, HFIP has also found applications in reactions catalyzed by other transition-metals. For example, in 2015, Rovis and co-workers described an efficient Rh(III)-catalyzed synthesis of 2,3-dihydropyridines from α, β-unsaturated oxime using HFIP as solvent.[46]



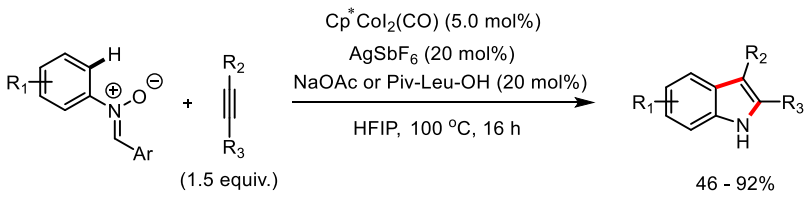
Scheme 34. Rh(III)-Catalyzed Synthesis of 2,3-Dihydropyridines from Unsaturated Oxime

Recently, the same group described a novel Ir(III)-catalyzed di-amination of alkene with simple secondary amines that delivered complementary γ- and δ-lactams under extraordinarily mild conditions.[47] The regioselectivity of the di-amination is controlled by the fluorinated solvent and the exogenous additive.



Scheme 35. Ir(III)-Catalyzed Diamination of Alkene with Amines

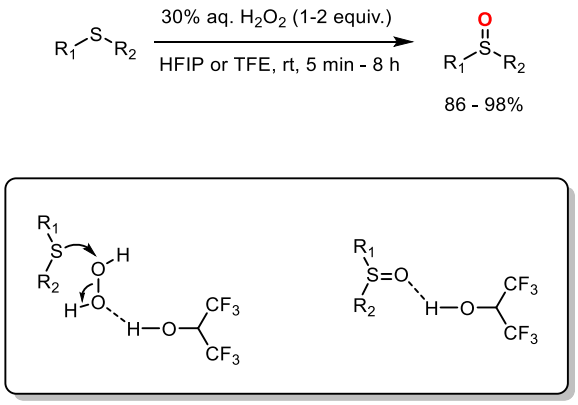
Meanwhile, In 2016, Ackermann and co-workers described the first indole synthesis via cobalt(III)-catalyzed C−H/N−O functionalization with nitrones in HFIP.[48] The robust cobalt-catalyzed indole synthesis was characterized by an excellent functional group tolerance and a unique *regio*-selectivity in the annulation of unsymmetrical alkynes.



Scheme 36. Cobalt(III)-Catalyzed C−H/N−O Functionalization with Nitrones

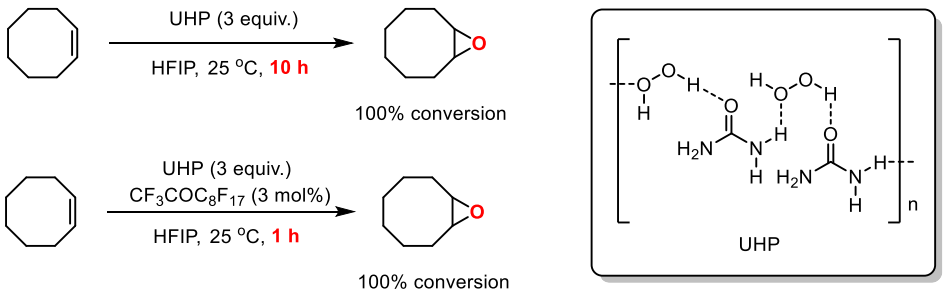
VI. Previous Works in The Laboratory

Earlier in our laboratory, the project with various oxidation reactions in the presence of H_2O_2 as oxidizing reagent has been initiated, for which fluorinated alcohols were expected to facilitate the O-O bond cleavage through hydrogen-bonding due to their high hydrogen bond donor ability. For example, when sulfides were treated with 1 or 2 equiv. of H_2O_2 (30%) at room temperature in HFIP, quantitative yields of sulfoxides were obtained in 5-15 mins without any trace of sulfones.[49] Similar processes were also effective in TFE, but reaction times were longer (4-8 h). it was suggested that the HFIP and the oxygen atom of the sulfoxide formed a hydrogen bond, which greatly decreased the nucleophilicity of the second available electron pair of the sulfur atom.



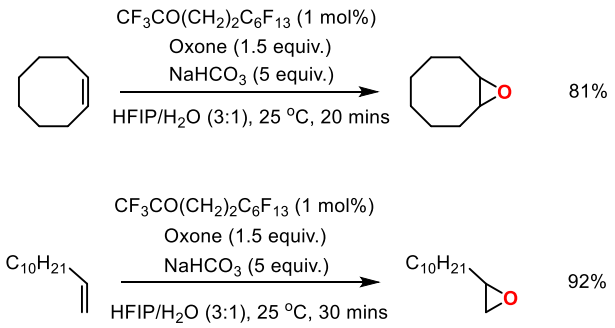
Scheme 37. Mild and Selective Oxidation of Sulfur Compounds in Fluorinated Alcohols

An efficient epoxidation of reactive alkenes using urea-H_2O_2 complex (UHP) as the oxidant in HFIP under mild reaction conditions has been developed.[50] UHP is an easy to handle and safe source of anhydrous H_2O_2 which formed by strong hydrogen bonds between urea and H_2O_2 in a ratio of 1:1. Although UHP is much less reactive than H_2O_2 due to its high stability. The ability of HFIP to cleave the UHP and to activate H_2O_2 allowed the epoxidation in high efficiency. Meanwhile, the use of perfluorodecan-2-one (3-5 mol%) as a catalyst reduced the time of the epoxidation to 1 h.



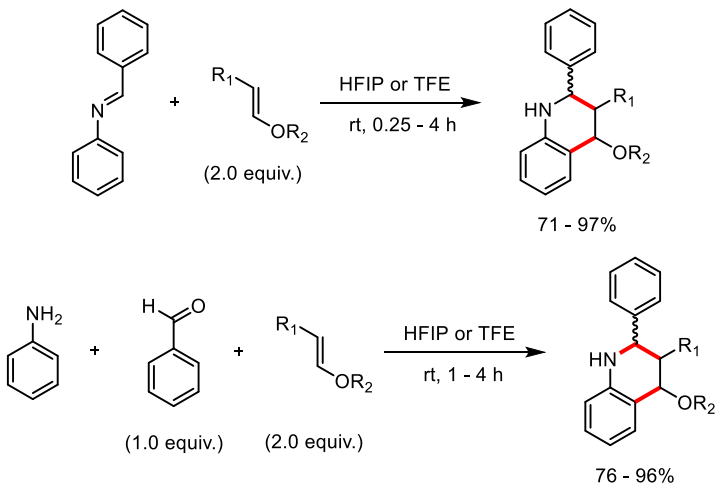
Scheme 38. Epoxidation of Alkenes Using UHP As the Oxidant

Besides, the application of oxone as oxidant in the presence of perfluoroketone as catalyst allowed the epoxidations to proceed under mild conditions in a mixture of HFIP and water.[51] Both terminal and internal olefins substrates provided the corresponding epoxides in yields of 68-95% with only 1% of $CF_3CO(CH_2)_2C_6F_{13}$ for reactive olefins and 5% for poorly reactive ones.



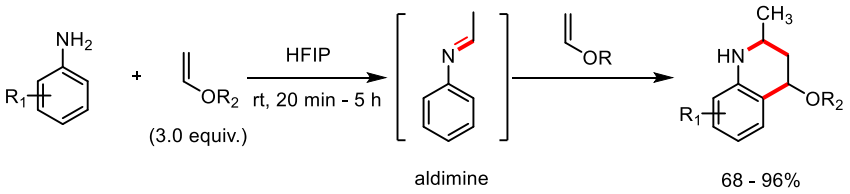
Scheme 39. Epoxidation of Alkenes Using Oxone As Oxidant

Fluorinated alcohols were also found able to promote imino-Diels-Alder reactions of the N-aryl aldimine with alkyl vinyl ethers without any Lewis acid under mild and neutral conditions.[52] In HFIP the reaction proceeded efficiently to afford cis/trans-tetrahydroquinolines in excellent yields. In TFE the reaction was efficient only with the most reactive enol ethers. The reaction was also efficient in a three-component process for the preparation of tetrahydroquinolines through a domino reaction from aldehyde, amine and vinyl ethers.



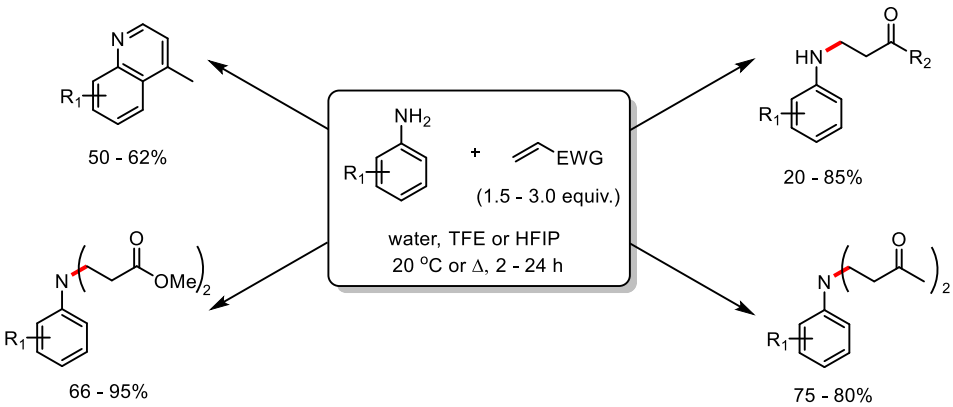
Scheme 40. Aza-Diels-Alder Reaction in Fluorinated Alcohols

HFIP was also found to promote the formation of tetrahydroquinolines in excellent yields starting from anilines and enol ethers in the absence of Lewis acid catalysis under mild conditions.[53] Besides to promote the aza-Diels-Alder cycloaddition, HFIP also showed the ability to activate enol ethers that can undergo nucleophilic addition of anilines for the formation of aldimines.



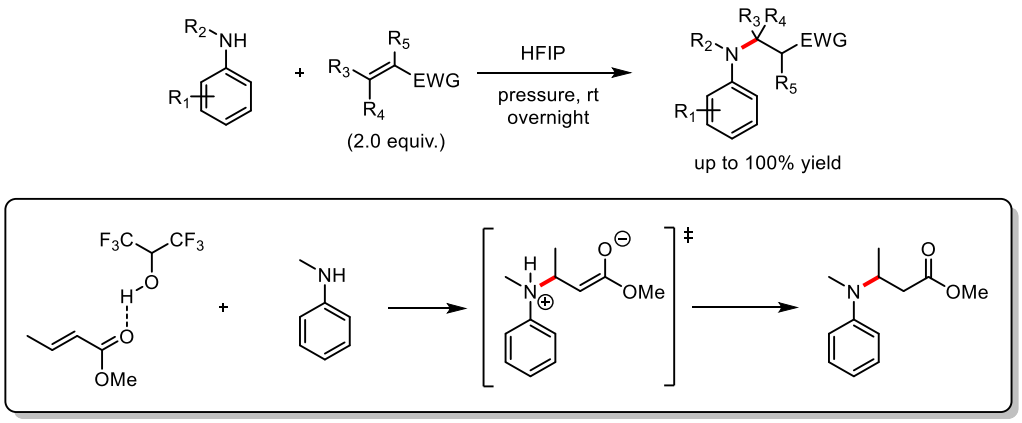
Scheme 41. Domino Aza-Diels–Alder Reaction in HFIP

Meanwhile, the Michael addition of primary anilines onto Michael acceptors in water, TFE, or HFIP as solvent without any external promoter has been developed.[54] Moreover, the selectivity of the reaction can be finely tuned according to the nature of the solvent and of the electrophile to afford mono- or di-addition products, or even quinolines, in a one-pot fashion.



Scheme 42. Michael Addition of Primary Anilines onto Michael Acceptors

Unfortunately, this 1,4-addition of anilines was strictly limited to simple, β-unsubstituted electrophilic partners, and failed with substituted Michael acceptors. Recently, the challenging 1,4- additions of poorly nucleophilic aromatic amines onto substituted Michael acceptors were realized by the combination of HFIP as solvent and hyperbaric conditions.[55] The effectiveness of the HFIP/pressure combination in the *aza*-Michael addition possibly rests on an increase of the acidity of HFIP under high pressure, affording an enhanced activation of the Michael acceptor as well as a favorable compact transition state in the transformation.



Scheme 43. Direct aza-Michael Addition of Anilines in HFIP under High Pressure

In our interest for the use of fluorinated alcohols in organic synthesis and in the pursuit of more efficient catalytic systems, we will present in the following chapters, the fluorinated alcohols as efficient reaction media in the C-H amination of anilines and inactive arenes with azodicarboxylates, the C-H alkylation of arenes and heterocycles with β-nitroalkenes and benzylic alcohols, and the C-H halogenation of arenes and heterocycles with N-halosuccinimides.

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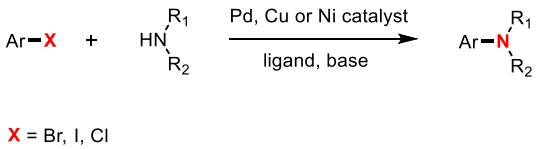
Chapter II

C-H Amination of Aromatics in Fluorinated Alcohols

I. Introduction

The development of efficient and novel aromatic C-N bond forming methods is always at the frontier of research in synthetic organic chemistry due to the ubiquity of arylamines in a variety of pharmaceuticals and natural products.[1-5] While many classical transformations have been established to form the aromatic C-N bond, the most representative examples are the Ullmann-Goldberg and Buchwald-Hartwig amination reaction.[6-12] Although the reactivity of this coupling can be readily improved by fine-tuning of the steric and/or electronic property of ligands, the functional groups, such as halide moieties, need to be introduced prior to the amination. Therefore, direct amination of aryl C-H bonds has been pursued as a more step-economical route.

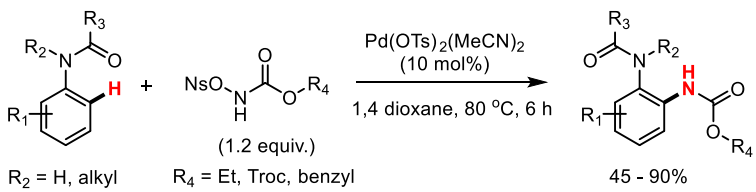


Scheme 1. Ullmann-Goldberg and Buchwald-Hartwig Amination

II. C-H Amination of Free Anilines with Azodicarboxylates

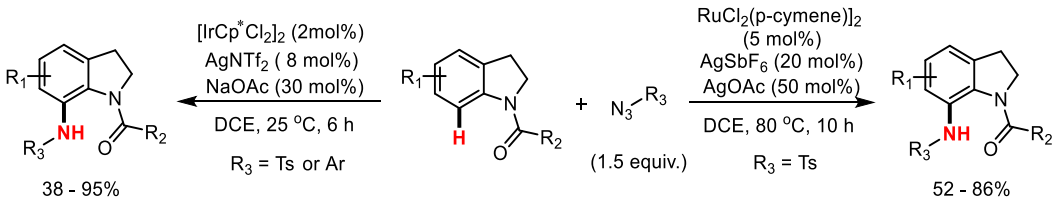
II. 1. Introduction

In the past decades, with the rapid development of transition metal-catalyzed C-H activation, significant advances have been made in the direct C-H amination of arenes, especially high regioselectivity can be achieved.[13-16] However, due to the high nucleophilicity of the free amino group which leads to the formation of salt in acidic medium and can chelate metal catalysts, the C-H amination of free anilines still remains great challenge. Thus, the *N*-protected anilines were usually employed to avoid the formation of by-products. In particular, the direct amination of the C-H bond at the *ortho*-position of *N*-protected anilines has been relatively well studied. For example, In 2010, Yu and co-workers developed a palladium(II)-catalyzed intermolecular *ortho*-C-H amidation of anilides using *N*-nosyloxycarbamate for the synthesis of 2-aminoanilines.[17]



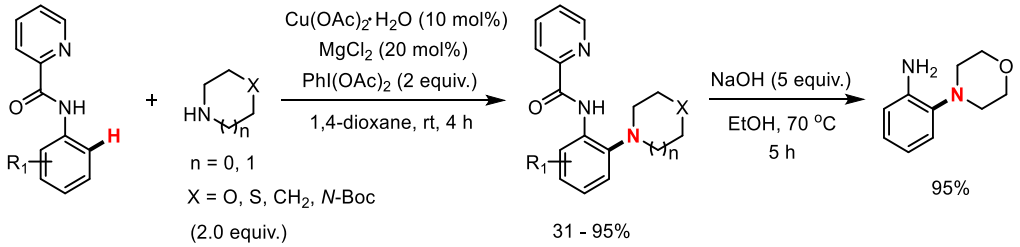
Scheme 2. Pd-Catalyzed *ortho*-C-H Amidation of Anilides

In 2014, the ruthenium- or iridium-catalyzed direct C-7 amidation of indoline C-H bonds with sulfonyl azides were developed by Zhu and Chang group.[18-19]



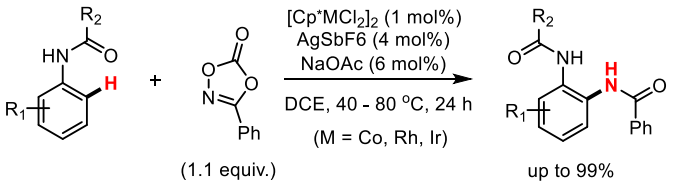
Scheme 3. C-7 Amidation of Indoline C-H Bonds with Sulfonyl Azides

Meanwhile, Chen and co-workers developed a highly efficient method to selectively install alkyl amino motifs onto the *ortho* position of *N*-protected anilines via Cu-catalyzed and carboxamide-directed amination at room temperature in 2014.[20] The directing group of the aminated products can be easily removed under simple basic conditions.



Scheme 4. Cu-Catalyzed Carboxamide-Directed Amination of Anilines

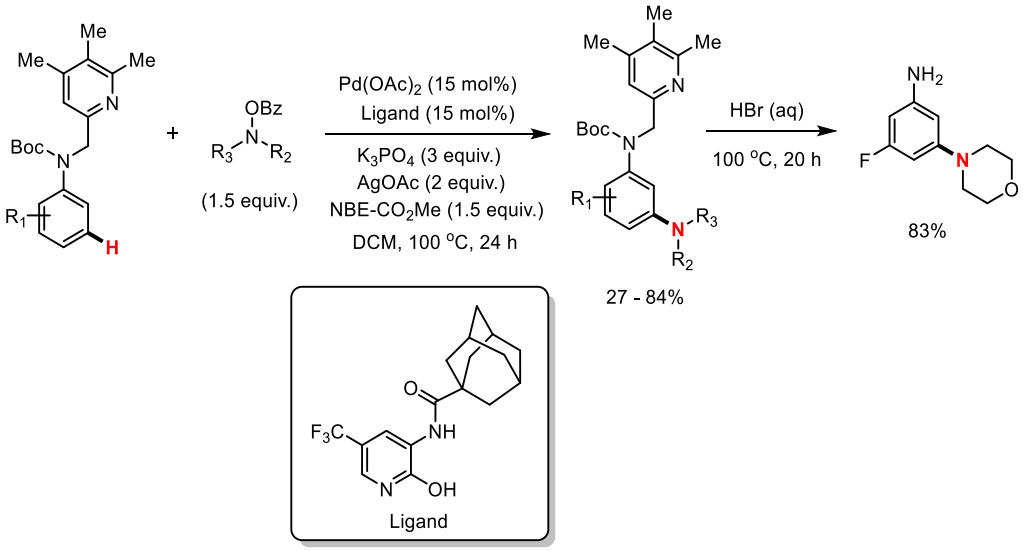
In 2015, Chang and co-worker developed a [Cp*Co^{III}]-catalyzed C-H amidation of *N*-protected anilines with 1, 4, 2-dioxazol-5-ones as amidating reagents.[21] This cobalt catalyst system would suitable for practical applications, as a low catalyst loading was sufficient for the formation of amidated products in high yield under mild conditions.



Scheme 5. Co-Catalyzed C-H Amidation of Anilines with 1,4,2-Dioxazol-5-ones

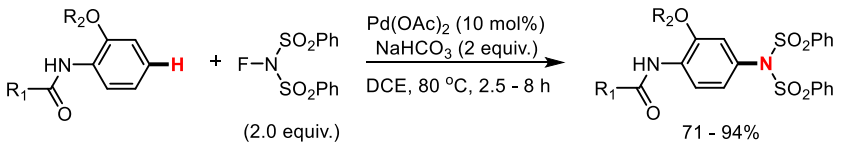
In contrast, the *meta*-selective C-H amination of *N*-protected anilines methodology is

considerably less developed. Recently, Yu and co-workers have developed *meta*-C-H amination of aniline substrates for the first time using a modified norbornene (methyl bicyclo[2.2.1]hept-2-ene-2-carboxylate) as a transient mediator.[22] Both high yields and a broad substrate scope have been achieved for these *meta*-C-H amination reactions using N-benzoyloxyamines as electrophilic reagents.



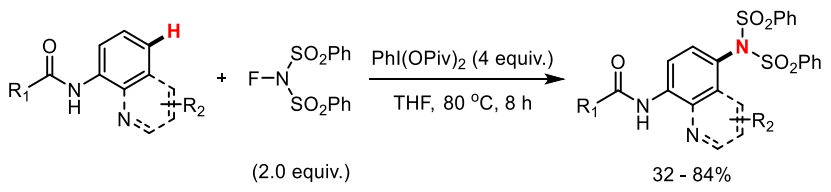
Scheme 6. Pd-Catalyzed *meta*-C−H Amination of Aniline with N-benzoyloxyamines

Similarly, only a handful of examples of *para*-selective C-H amination of *N*-protected anilines were reported in last years. In 2011, Zhang and co-workers described the first Pd-catalyzed, highly *para*-selective C-H amination of anilides using N-fluorobenzenesulfonimide (NFSI) as a source of nitrogen.[23] The protocol showed good functional groups compatibility and gave the highly *para*-selective amination products in moderate to good yields.



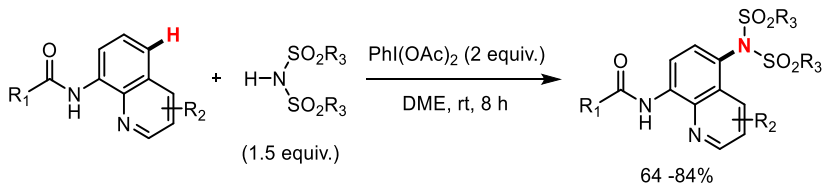
Scheme 7. Pd-Catalyzed *para*-C-H Amination of Anilides with NFSI

In 2016, Li and co-workers reported a metal-free, hypervalent iodine reagent mediated oxidative *para*-selective C-H amination of 8-acylaminoquinolines and anilides with NFSI under mild reaction conditions without any metallic catalyst or oxidant, which gave the highly selective C5-aminated quinolines and *para*-aminated anilides in moderate to good yields.[24]



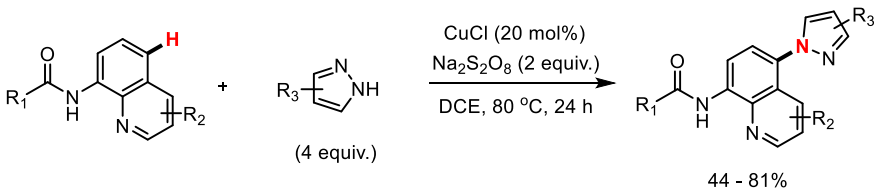
Scheme 8. PhI(OPiv)$_2$ Mediated C-H Amination of 8-Acylaminoquinolines and Anilides

Almost at the same time, Xu and co-workers also developed a hypervalent iodine reagent mediated C-H bond amidation of 8-amidoquinolines on the C-5 position using dibenzenesulfonimide as the nitrogen sources.[25]



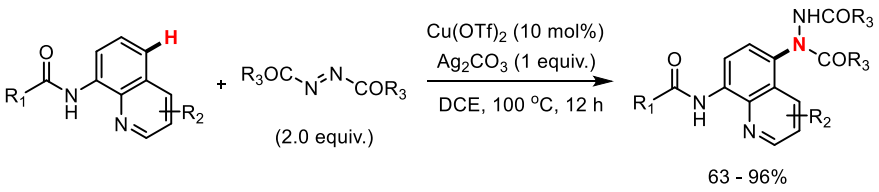
Scheme 9. PhI(OAc)$_2$ Mediated C-H Bond Amidation of 8-Amidoquinolines

Last year, another copper-catalyzed amination of 8-aminoquinolines on the C5 position was developed by Lei and co-workers, which they employed azoles as the source of amine.[26] Various kinds of 8-aminoquinolines and differently substituted azoles were compatible to afford the corresponding C-N coupling products.



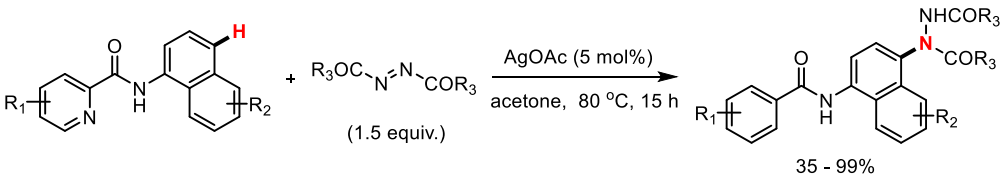
Scheme 10. Cu-Catalyzed C-H Amination of 8-Aminoquinolines with Azoles

Moreover, the use of readily available azodicarboxylates proceeded as the nitrogen sources have also been reported. In 2016, Baidya and co-workers reported a copper-catalyzed 8-amidechelation-induced remote C-H amination of quinolines with perfect C5-regioselectivity offering amino-substituted 8-aminoquinolines in very high yield.[27]



Scheme 11. Cu-Catalyzed C-H Amination of 8-Aminoquinolines with Azodicarboxylates

Recently, Wu and co-workers developed a simple and efficient protocol for silver(I)-catalyzed picolinamide directed C4-H amination of 1-naphthylamine derivatives, demonstrating a new approach to 1, 4-naphthalenediamine derivatives in high yields.[28] It was noteworthy that this reaction system could proceed under external oxidant- and additive-free conditions.



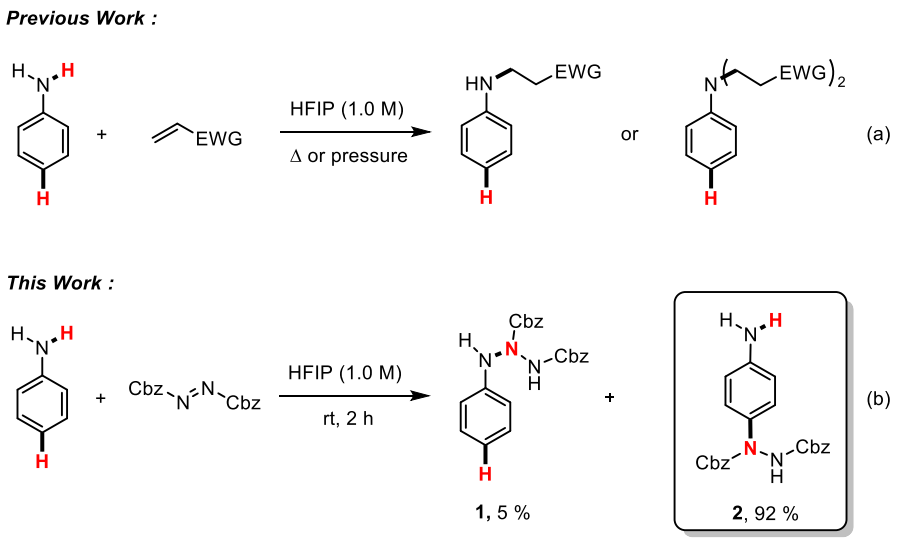
Scheme 12. Ag-Catalyzed C4−H Amination of 1-Naphthylamine with Azodicarboxylates

However, The introduction and subsequent removal of protecting groups not only required additional operations but also significantly decreased the functional group compatibility. Undoubtedly, the most attractive and ideal route is the direct C-H amination of free anilines.

II. 2. Result and Discussion

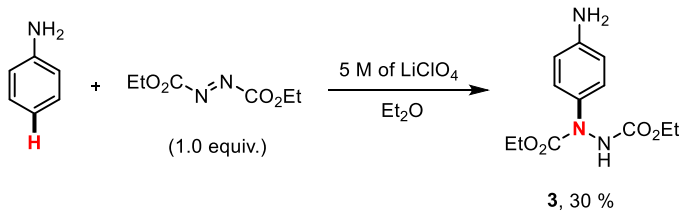
II. 2. 1. Project Proposed

In recent reports from our laboratory, it was described that HFIP can promote the Michael addition of primary anilines onto Michael acceptors without any external promoter (**Scheme 13, a)**. The results encouraged us to check the reaction between primary aniline and azodicarboxylate which we thought triazane should be the major product. To our surprise, the *para*-substituted product was obtained with high yield and selectivity instead of triazane (**Scheme 13, b)**.



Scheme 13. C-H Amination of Free Anilines with Azodicarboxylate in HFIP

This unexpected result led us to consult the related literature. To our delight, to the best of our knowledge, there was only one report on the C-H amination of free anilines with azodicarboxylate.[29] However, this method suffered from the utilization of a large amount of catalyst ($LiClO_4$) and of low yield (30%).



Scheme 14. C-H Amination of Free Anilines with Azodicarboxylate in Et_2O

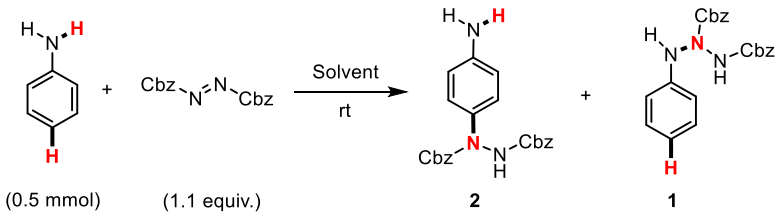
Thus, In this chapter, we studied the C-H amination of free anilines with azodicarboxylates using fluorinated solvents as solvent without the use of any catalysts and reagents.

II. 2. 2. Optimization of the Reaction Condition

In our initial study, the C-H amination of aniline (0.5 mmol) with dibenzyl azodicarboxylate (1.1 equiv.) was chosen as the model system to optimize the reaction conditions. We first examined the reaction in different fluorinate alcohols at room temperature (**Table 1**). It was observed that the yield and selectivity of product highly dependent on the fluorinated alcohol used and the molar concentration of the substrate. When the reaction was performed in 0.25 M of HFIP, the product **2** was isolated in 94% yield and only trace of triazane **1** was detected

(entry 2). When performed the reaction in TFE (p*K*a = 12.8) which the acidity and hydrogen-bond donating (HBD) ability is less than HFIP (p*K*a = 9.3), low yield and more by-product was obtained (entry 3). However, the reaction was also not so effective in more acid and higher hydrogen-bond donating perfluoro-2-methylpropan-2-ol (PFTB, p*K*a = 5.4) (entries 4). Those results implied that the acidity and hydrogen-bond donating (HBD) ability of fluorinated solvent were not all helpful for the reaction.

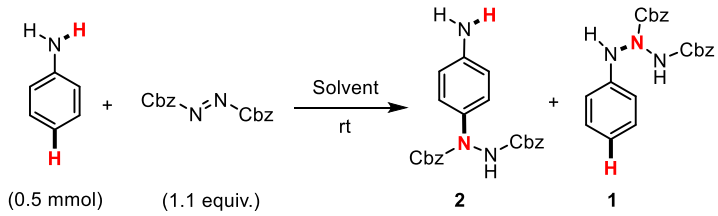
Table 1. Optimization of the Fluorinated Solvents



Entry	Solvent	Concentration (M)	Time (h)	Yield (%)	
				2	**1**
1	HFIP	1.0	2	92	5
2	**HFIP**	**0.25**	**2**	**94**	**trace**
3	PFTB	0.25	0.75	54	43
4	TFE	0.25	2	59	28

Next, in contrast to HFIP, when used ^{i}PrOH as solvent, the reaction was slow and both low yield and selectivity were observed (entry 2). Other common non-fluorinated solvents such as EtOH, CH_3CN, THF, DCM, Toluene and H_2O were checked (entries 3-7). All resulted in low yields and selectivity. At last, the reaction was checked in HOAc (p*K*a = 4.7) (entry 8), triazane **1** was obtained as the major product. These different results showed very well that the hydrogen-bond donating ability of HFIP is essential for the good running of the C-H amination.

Table 2. Optimization of the Common Solvent

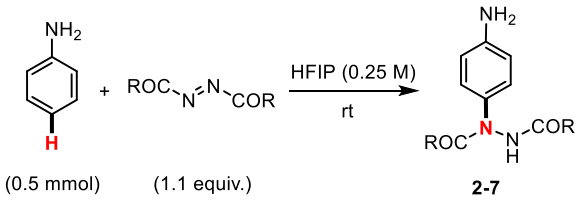


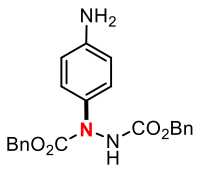
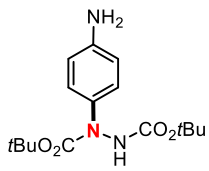
Entry	Solvent (0.25 M)	Time (h)	Yield (%)	
			2	**1**
1	**HFIP**	**2**	**94**	**trace**
2	^{i}PrOH	24	22	46
3	CH_3CN	24	13	57
4	THF	24	52	25
5	DCM	24	46	19
6	Toluene	24	27	55
7	H_2O	24	28	30
8	HOAc	24	19	45

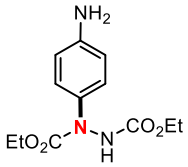
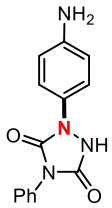
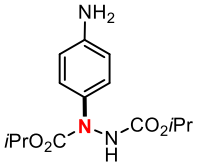
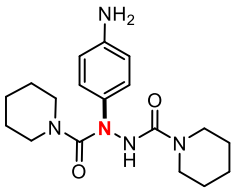
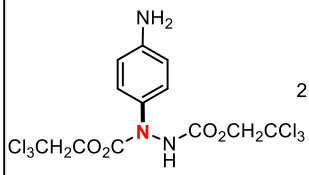
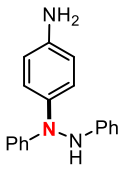
II. 2. 3. Expanding the Substrate Scope

With the optimized reaction conditions in hand (**Table 1**, entry 2), we next investigated other azodicarboxylates with the free aniline (**Table 3**). The diethyl-, diisopropyl- and bis(2,2,2-trichloroethyl) azodicarboxylates reacted smoothly with aniline to afford the corresponding hydrazides **3-5** in excellent yields. However, when using di-*tert*-butyl azodicarboxylate, the reaction proceeded badly to lead to the corresponding product **6** only in 34% yield. This low yield could be explained by its decomposition in HFIP which is slightly acid.[30] Moreover, the hydrazide **7** was obtained from the cyclic azodicarboxylate in moderate yield. Unfortunately, the diazene-1,2-diylbis(piperidin-1-ylmethanone) and diphenyldiazene were not suitable for this reaction.

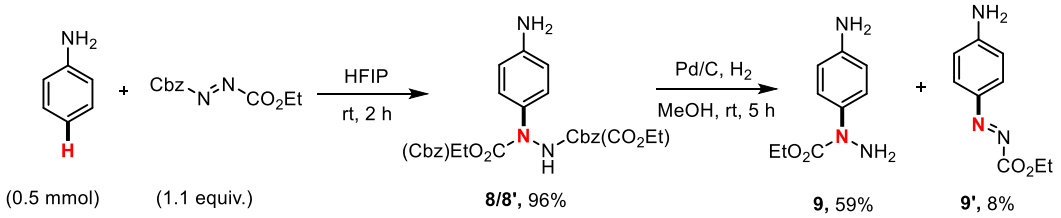
Table 3. The Amination of Aniline with Different Azodicarboxylates



Entry	Product	Time (h)	Yield (%)	Entry	Product	Time (h)	Yield (%)
1	 **2**	2	94	5	 **6**	2	34

2	 **3**	2	88	6	 **7**	2	57
3	 **4**	2	90	7		16	n.d.
4	 **5**	2	94	8		16	n.d.

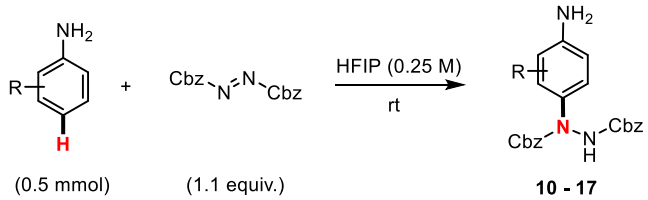
Meanwhile, when aniline was treated with the dissymmetric azodicarboxylate, a mixture of hydrazides **8/8'** were obtained. The ratio was analyzed after hydrogenolysis of the benzyloxycarbonyl group. Both products **9/9'** are obtained in a proportion 7.6/1.0 respectively. The regioselective attack could be explained by the less steric demand of nitrogen bearing CO_2Et group than that bearing a Cbz group (**Scheme 15**).

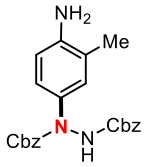
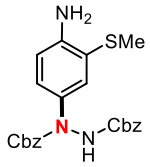
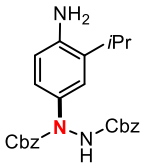
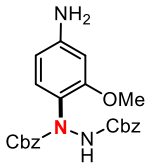
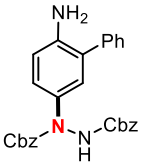
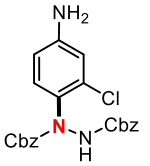
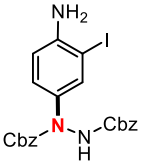
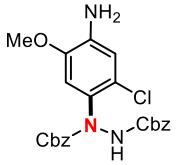


Scheme 15. The Amination of Aniline with Dissymmetric Azodicarboxylate.

We then turned our attention to the scope of aniline derivatives (**Table 4**). A variety of primary anilines substituted in *ortho*- and *meta*- position or both reacted with dibenzyl azodicarboxylate smoothly, generating the desired products **10-17** in excellent yields.

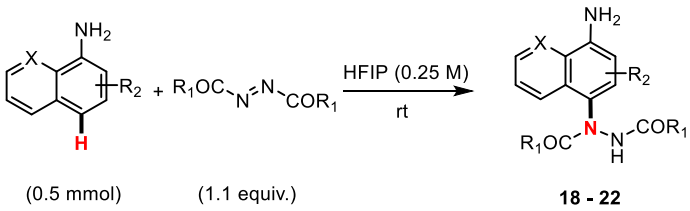
Table 4. The Amination of Primary Anilines with Azodicarboxylate

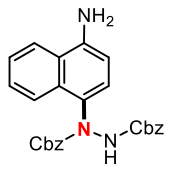
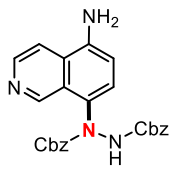
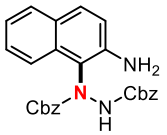
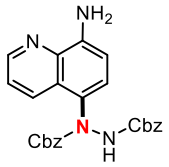
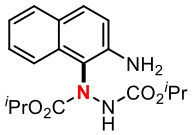


Entry	Product	Time (h)	Yield (%)	Entry	Product	Time (h)	Yield (%)
1	 **10**	2	97	5	 **14**	2	91
2	 **11**	2	94	6	 **15**	2	92
3	 **12**	2	94	7	 **16**	2	87
4	 **13**	2	84	8	 **17**	2	95

Naphthyl amines were also applicable in this reaction providing the products **18-20** in very good yields. It was noteworthy that the quinoline amines also showed good reactivity, giving **21** and **22** in 92% and 90% yield, respectively.

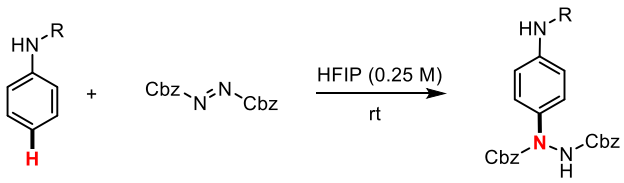
Table 5. The Amination of Naphthyl and Quinoline Anilines with Azodicarboxylate



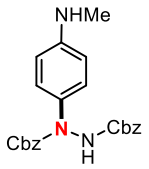
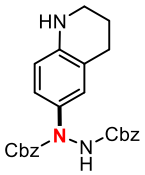
Entry	Product	Time (h)	Yield (%)	Entry	Product	Time (h)	Yield (%)
1	 **18**	2	95	4	 **21**	2	92
2	 **19**	2	97	5	 **22**	2	90
3	 **20**	2	92				

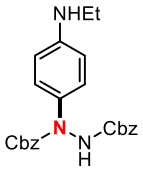
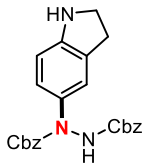
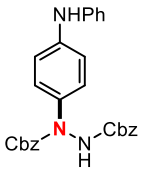
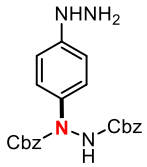
Then, a variety of secondary anilines including tetrahydroquinoline and indoline were reacted with dibenzyl azodicarboxylate under the optimized conditions, affording the corresponding products **23-27** in a good to moderate yields. However, when phenylhydrazine was used, the reaction was a mixture of compounds.

Table 6. The Amination of Secondary Anilines with Azodicarboxylate



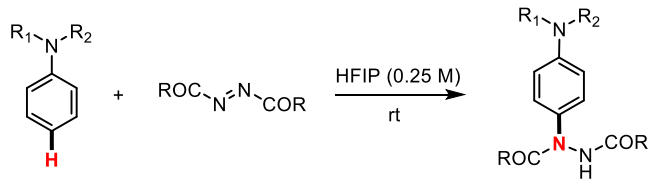
(0.5 mmol) (1.1 equiv.) **23 - 27**

Entry	Product	Time (h)	Yield (%)	Entry	Product	Time (h)	Yield (%)
1	 **23**	2	93	4	 **26**	2	78

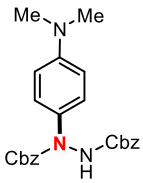
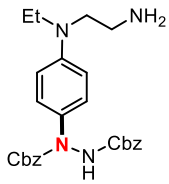
2	 **24**	2	96	5	 **27**	2	74
3	 **25**	2	89 (mono/bis: 82/18)	6		2	mixture of compounds

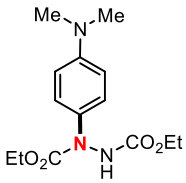
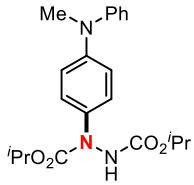
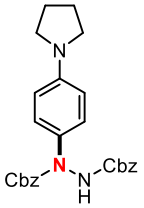
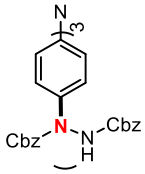
From tertiary anilines, the amination reactions were faster. The dimethyl aniline reacted with dibenzyl and diethyl azodicarboxylates, providing the hydrazides **28, 29** in excellent yields. The *N*-phenylpyrrolidine, the *N*-(2-aminoethyl)-*N*-ethylaniline and the *N*-methyl-*N*-phenylaniline all reacted efficiently to afford only the *para*-hydrazide derivatives **30-32** in 87, 95 and 90% yields, respectively. It is noteworthy that the free alkyl amine did not interfere in the reaction due to its deactivation through the hydrogen bond formed with HFIP (product **31**). When triphenylamine reacted with 3.3 equiv. of dibenzyl azodicarboxylate, a mixture of *tri*- and *bis*-substituted products **33/33'** (ratio 63/37) were isolated in 92% yield.

Table 7. The Amination of Tertiary Anilines with Azodicarboxylate



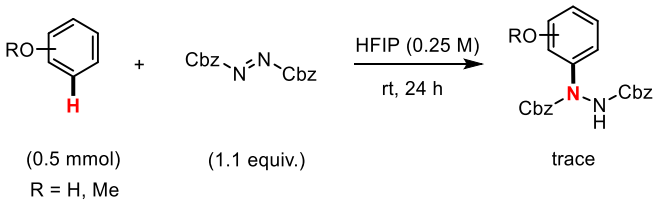
(0.5 mmol) (1.1 equiv.) **28 - 33**

Entry	Product	Time (min)	Yield (%)	Entry	Product	Time (min)	Yield (%)
1	 **28**	15	93	4	 **31**	15	90

2	 **29**	15	91	5	 **32/32'**	15	95% (mono/bis: 90/10)
3	 **30**	15	87	6[a]	 **33/33'**	2 h	92 (tri/bis: 63/37)

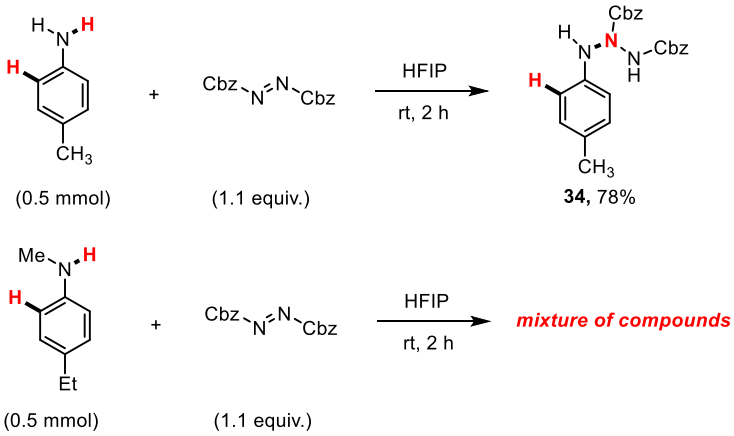
[a] 3.3 equiv. of dibenzyl azodicarboxylate was used

After we have developed the amination of free anilines, we next focus on the amination of arenes with less electron-donating groups such as methoxyl and hydroxyl groups. Unfortunately, when phenol or anisole was treated with dibenzyl azodicarboxylate at rt for 24 h, only trace of products was obtained.



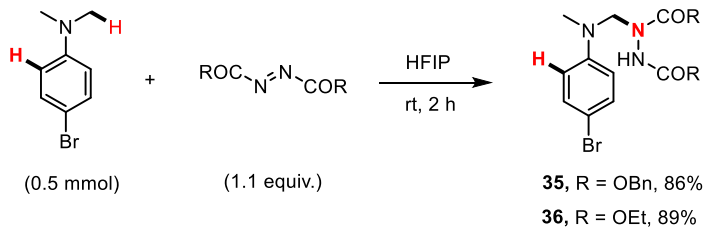
Scheme 16. The Amination of Phenol and Anisole with Azodicarboxylate

Furthermore, we were interested in C-H reactivity in different positions. For primary aniline, being substituted in the *para*-position, quite expectedly, only the triazane **34** was isolated in 78% yield. However, the amination of *para*-substituted secondary aniline **1y** was a mixture of compounds.



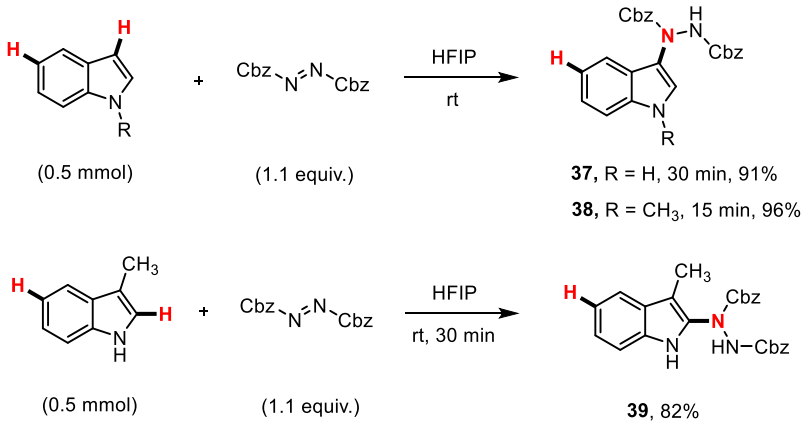
Scheme 17. Selective Amination of Different C-H Bonds of Primary and Secondary Aniline

When the *para*-position of dimethyl aniline was substituted, the oxidized products **35** and **36** were selectively obtained in good yields. In all cases, no *ortho*-substituted products were detected.



Scheme 18. Selective Amination of Different C-H Bonds of Tertiary Aniline

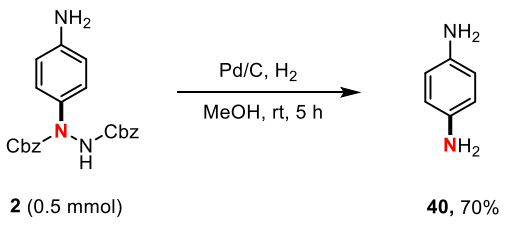
Representatively, in the case of the indole and the *N*-methylindole, the usual C3-amination products **37** and **38** were isolated as the sole product in excellent yield. Meanwhile, when the C3-position of indole was substituted, the C2-amination product **39** was selectively obtained in good yield.



Scheme 19. Selective Amination of Different C-H Bonds of Indole

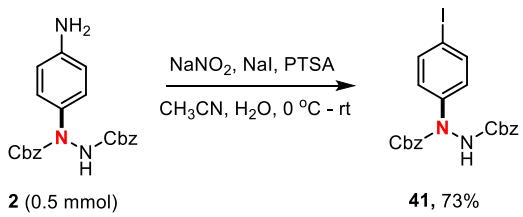
II. 2. 4. Practical Experiments

To illustrate the high synthetic potential of the new hydrazide primary anilines, different reactions have been performed. For example, the hydrazide product **2** could be straightforwardly transformed into *p*-phenylenediamine **40** with 70% yield by removal of the carboxybenzyl (Cbz) group and cleavage of the N-N bond in a single step.[27]



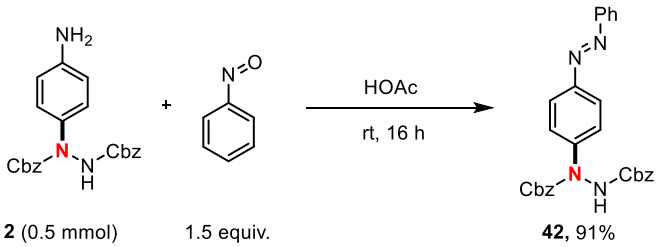
Scheme 20. The Cbz-Deprotection

One of the advantages to keep a primary amino in reactions is the possibility that it can be removed or used in other transformations. By means of the well-known Sandmeyer reaction, diazotization of **2** with $NaNO_2$ followed by treatment with NaI produced 4-iodophenylhydrazine **41** in 73% yield.[31]



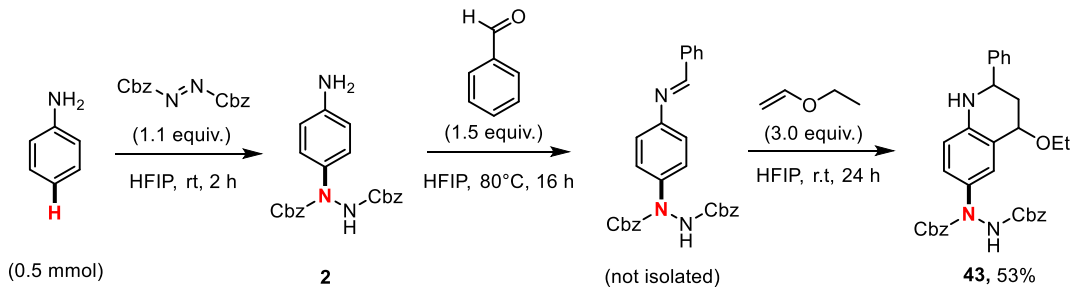
Scheme 21. The Sandmeyer Reaction

Moreover, the azo aromatic compound **42** could be obtained from the compound **2** with the nitrobenzene in acetic acid at room temperature in 91% yield.[32]



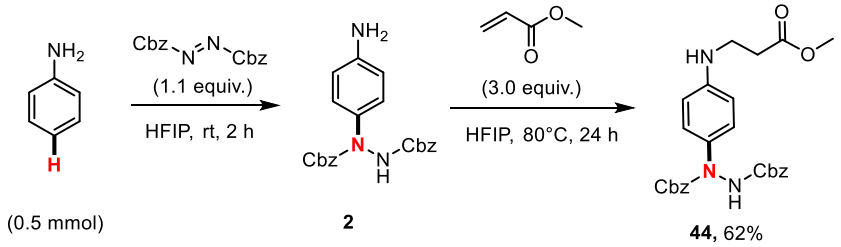
Scheme 22. Synthesis of Azo Aromatic Compound

Besides, from the starting material aniline, after aminated by dibenzyl azodicarboxylate, the [4+2] aza-Diels-Alder cycloaddition could be realized in one-pot in HFIP after addition of an aldehyde followed by the vinyl enol ether.[33] The corresponding tetrahydroquinoline **43** was obtained in reasonable yield of 57% over three steps.



Scheme 23. The [4+2] Aza Diels-Alder Cycloaddition of One-Pot Synthesis of Tetrahydroquinoline

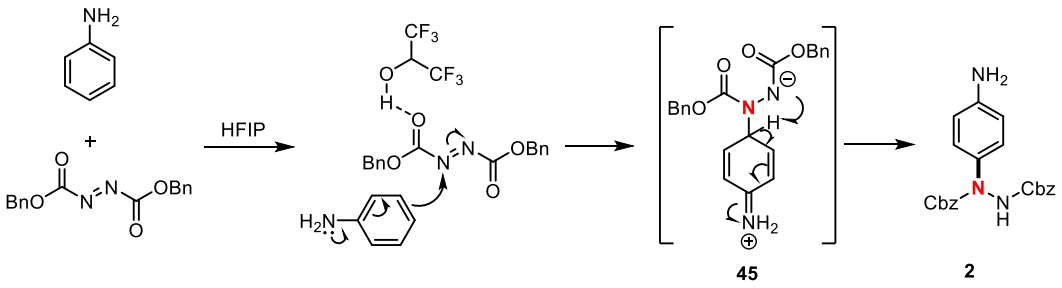
Also, in one-pot, the Michael addition was carried out with methyl acrylate to afford the mono alkylated product **44** in moderate yield.[34]



Scheme 24. The Michael Addition with Methyl Acrylate

II. 2. 5. Proposed Mechanism

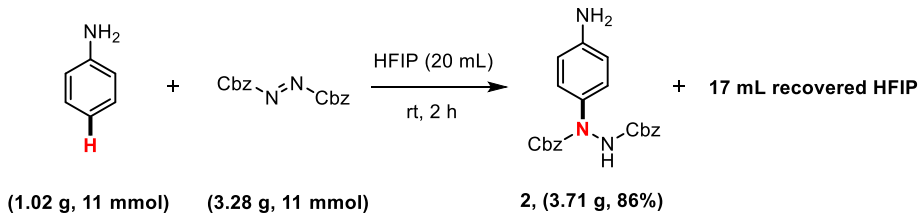
A plausible H-bond activation mechanism for this HFIP-promoted direct amination of free anilines with azodicarboxylates is proposed in **Scheme 25**, with the reaction of aniline and dibenzyl azodicarboxylate shown as an example. First, because of the strong negative inductive effect of -CF_3, HFIP performs as a good hydrogen bond donator and a poor nucleophile to activate the carbonyl group of the dibenzyl azodicarboxylate, followed by nucleophilic attack of the aniline to generate intermediate **45**, which undergoes the subsequent hydrogen transfer to afford the expected product **2**.



Scheme 25. Proposed Mechanism

II. 2. 6. Gram-Scale Reaction

A gram-scale reaction was also evaluated. The *para*-selective amination of aniline with dibenzyl azodicarboxylates was performed on 11.0 mmol in 20 mL HFIP for 2h. Not only the desired product **2** could be obtained smoothly in 86% yield, but also a 17 mL of HFIP was recovered after distillation directly from the reaction.

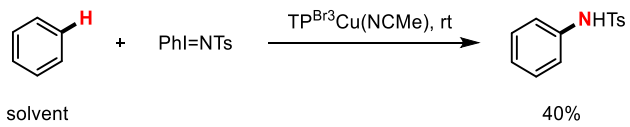


Scheme 26. Gram-Scale Reaction

III. C-H Amination of Inactive Arenes with Azodicarboxylates

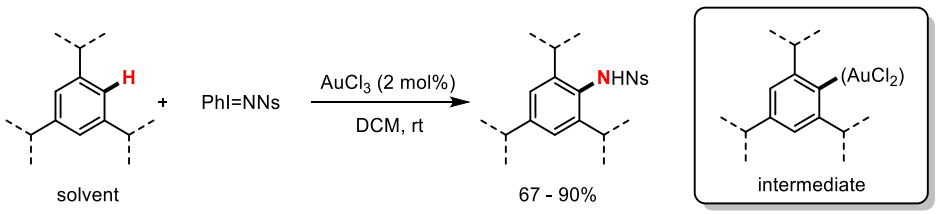
III. 1. Introduction

As we mentioned previously, significant advances have been made in the direct C-H amination of arenes in the past decades due to the rapid development of transition metal-catalyzed C-H activation. But the requirement for a coordinating directing group limits the potential substrate scope. Therefore, the C-H amination of simple arenes without the aid of directing groups has become a focus of an increasing amount of research in recent years. The first example of nitrene insertion into C-H bond of unsubstituted benzene was reported by Pérez and co-workers using $Tp^{Br3}Cu(NCMe)$ as a catalyst in 2003.[35] Although the reaction required benzene as the solvent, they proved that the C-H bond of simple arenes could be amidated.



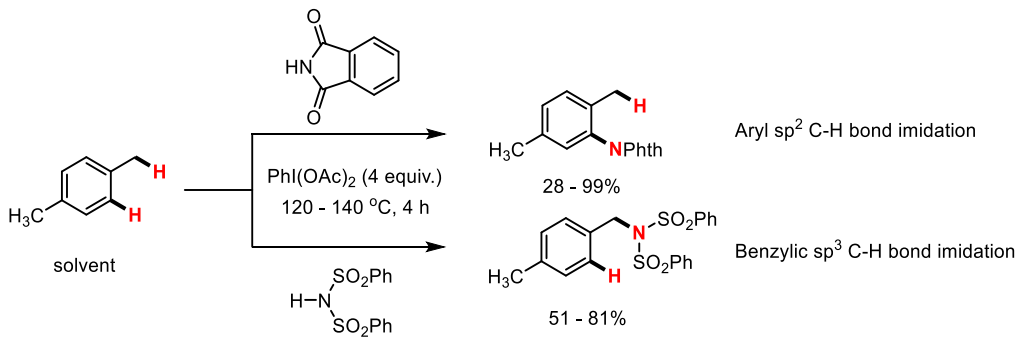
Scheme 27. Cu-Catalyzed Nitrene Insertion into C-H Bond of Benzene

In 2007, He and co-workers reported an Au-catalyzed direct C-H amidation of arenes in the presence of iminoiodinane.[36] They proposed that the reaction of arenes with electrophilic gold(III) chloride affords the corresponding aryl-gold intermediates, which reacted with PhI=NNs to give the amidated product.



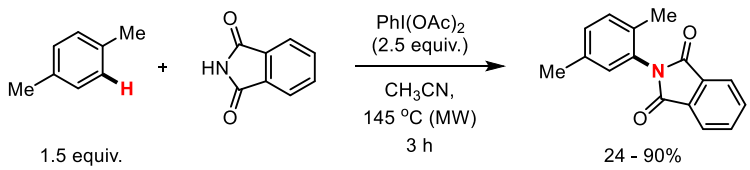
Scheme 28. Au-Catalyzed C−H Amidation of Arenes with Iminoiodinane

In 2011, Chang and co-workers reported a metal-free protocol for intermolecular C-N imidation of arenes using $PhI(OAc)_2$ as an oxidant.[37] This protocol could control chemo-selectivity in the amination between aryl sp^2 and benzylic sp^3 C-H bonds by the choice of nitrogen sources: phthalimide reacted at aromatic sp^2 C-H bonds and dibenzenesulfonimide reacted at benzylic sp^3 C-H bonds.



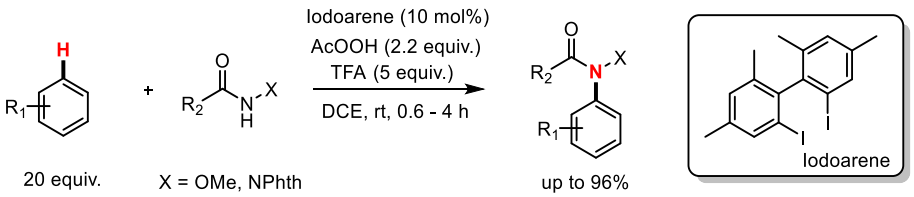
Scheme 29. Selective Aryl sp^2 or Benzylic sp^3 C–H Bonds Imidation of Arenes with Phthalimide

Almost at the same time, DeBoef and co-workers described another amination of simple arenes with phthalimide using $PhI(OAc)_2$ as an oxidant.[38] The reaction proceeded chemo-selectively at Csp^2-H bonds.



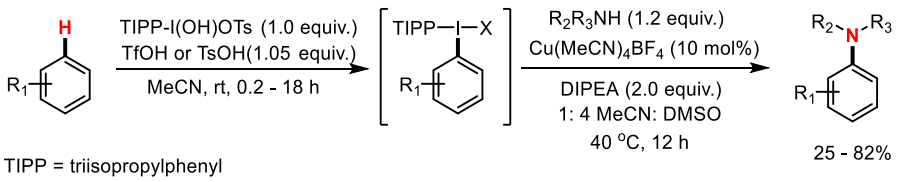
Scheme 30. $PhI(OAc)_2$ Oxidative Amination of Simple Arenes with Phthalimide

In 2012, Antonchick and co-workers reported an organo-catalyzed oxidative intermolecular aromatic C-H amidation reaction under room temperature.[39] A catalytic amount of aryl iodide was used in the presence of stoichiometric amount of peracetic acid.



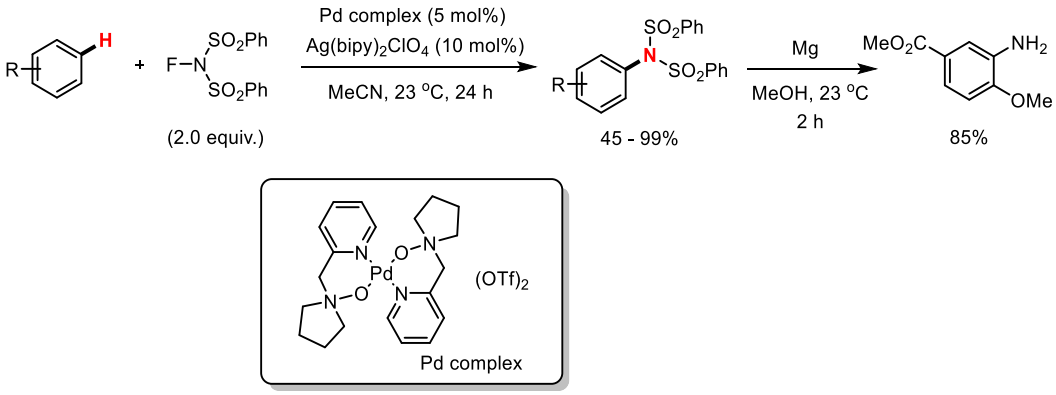
Scheme 31. Organo-Catalyzed Oxidative Aromatic C-H Amidation

In 2015, Suna and co-workers reported a one-pot two-step method for *para*-selective C-H amination of relatively electron-rich arenes.[40] The reaction comprised the *in situ* formation of unsymmetrical diaryl-λ^3-iodanes followed by their Cu(I)-catalyzed reaction with a range of N-unprotected amines.



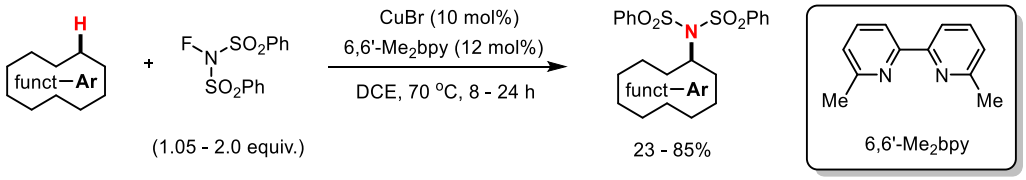
Scheme 32. Cu-Catalyzed *Para*-Selective C−H Amination of Arenes

Due to their low reactivity, aromatic C-H amination of simple arenes as the limiting reagents is very difficult. Recently, transition-metal-catalyzed radical approaches have enabled the functionalization of 1.0 equiv. of arenes with various imides. In 2013, Ritter and co-workers devised a novel catalytic system enabling a catalytic C-H amidation of arenes with NFSI as the amino group source.[41] Pd(II) complex bearing 1-(pyridin-2-ylmethyl)pyrrolidine 1-oxide was especially active in the presence of silver co-catalyst, and enablesd imidation of a variety of arenes at or below room temperature.



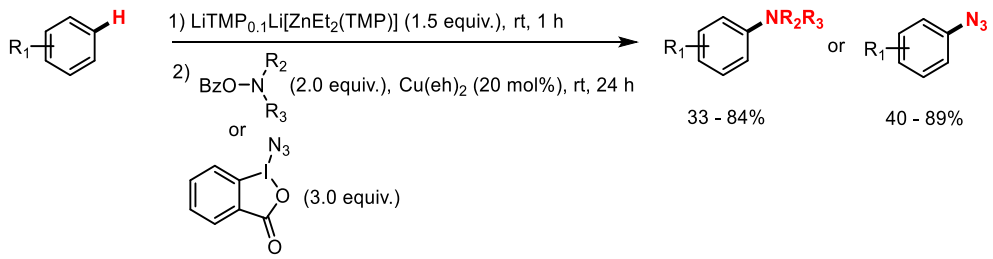
Scheme 33. Pd-Catalyzed C−H amidation of arenes with NFSI

In 2015, Itami and co-workers developed a Cu(I)-based catalyst system for the C−H amidation of arenes with NFSI as the amino group source.[42] 6,6′-Dimethylbipyridine (6,6′-Me_2bpy) was an especially effective ligand, and the substrate scope was broad, including heteroarenes and simple benzenes.



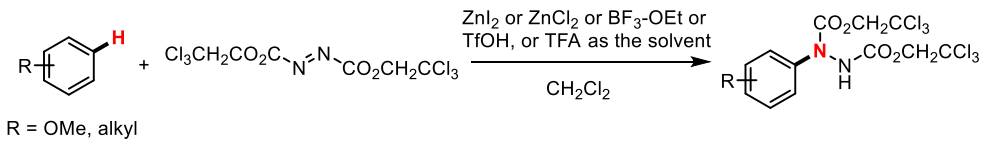
Scheme 34. Cu-Catalyzed C-H Amidation of Arenes with NFSI

In 2017, Wang and co-workers reported a highly general copper-catalyzed C-H amination strategy that provides effective and rapid access to diverse amino-heteroarenes and aminoarenes.[43] Readily available O-benzoylhydroxylamines and azidoiodinane serve as convenient electrophilic nitrogen sources for amination and azidation reactions, respectively.



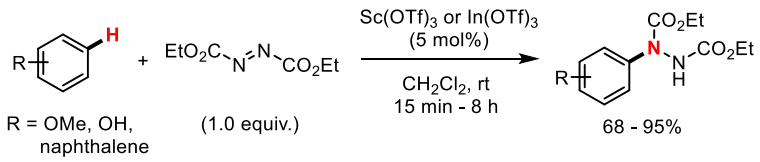
Scheme 35. Cu-Catalyzed C-H Amination and Azidation of Arenes

Meanwhile, electrophilic amination of simple arenes also ranks as one of the most useful protocols for the C-H amination of simple arenes. Various amination systems using azodicarboxylates in the presence of Lewis acids or Brønsted acids have been developed in the past decades. The representative examples include the catalytic amination of electron-rich arenes by electron-deficient *bis*-(2,2,2-trichloroethyl) azodicarboxylate developed by Leblancetal and co-worker.[44-45]



Scheme 36. Catalytic Amination of Arenes by Bis(2,2,2-trichloroethyl) Azodicarboxylate

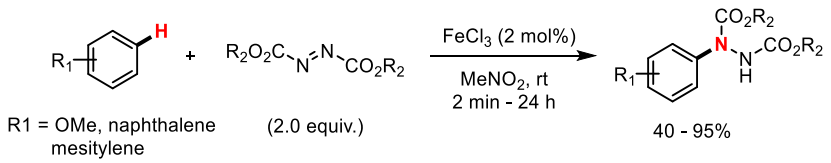
Later, diethyl azodicarboxylate (DEAD) was also proven to be a suitable reagent for catalytic amination of electron-rich arenes with strong Lewis acid $Sc(OTf)_3$ or $In(OTf)_3$.[46]



Scheme 37. Sc-Catalyzed Amination of Electron-rich Arenes with DEAD

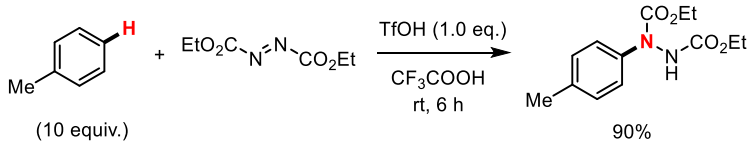
Recently, Fang and co-workers reported an iron(III) chloride-catalyzed direct amination of

electron-rich arenes with azodicarboxylates giving the corresponding aryl hydrazides in moderate to good yields within two minutes under mild conditions.[47]



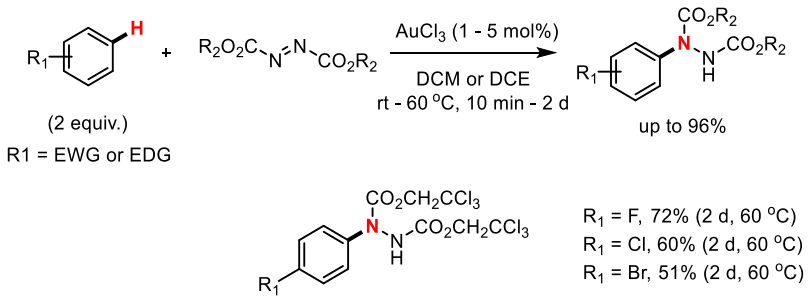
Scheme 38. Fe-Catalyzed Amination of Electron-rich Arenes with Azodicarboxylates

However, only electron-rich arenes are active in these reaction systems. In 2001, J. N. Kim and co-workers modified Leblanc's method, and the resulting method could be applied to the amination of a broader range of arene substrates including arenes with certain electron-withdrawing groups.[48] However the modified method used a large amount of super acid (TfOH) as catalyst and trifluoroacetic acid as solvent that limited its application.



Scheme 39. TfOH-Catalyzed Amination of Unactive Arenes with DEAD in TFA

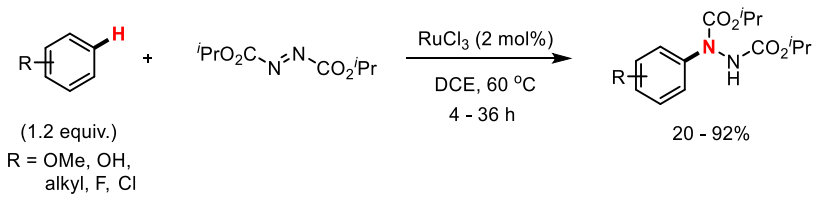
In 2011, Zhang and co-workers reported gold catalyzed amination of electron rich as well as electron poor arenes with azodicarboxylates.[49] Although these reactions were efficient, they suffered from one or more disadvantages such as the use of sensitive and expensive metal catalysts ($AuCl_3$), and poor reactivity for electron poor arenes which need to use expensive electron-deficient bis(2,2,2-trichloroethyl) azodicarboxylate as the nitrogen sources.



Scheme 40. Au-Catalyzed Amination of Arenes with Azodicarboxylate

In 2013, Mandal and co-workers described a ruthenium chloride-catalyzed direct amination

of arenes with azodicarboxylates.[50] This method can be applied to amination of a broad spectrum of arenes, including those with certain electron-withdrawing groups, which give modest to low yields.



Scheme 41. Ru-Catalyzed Amination of Arenes with Azodicarboxylate

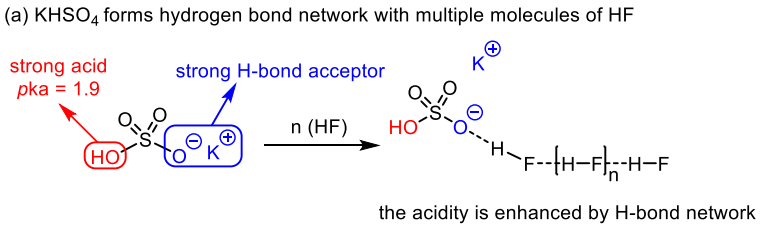
In view of these facts, we still consider it highly desirable to develop an efficient system for the direct amination of electron rich as well as electron poor arenes that do not involve expensive metal catalysts and reagents or harsh conditions.

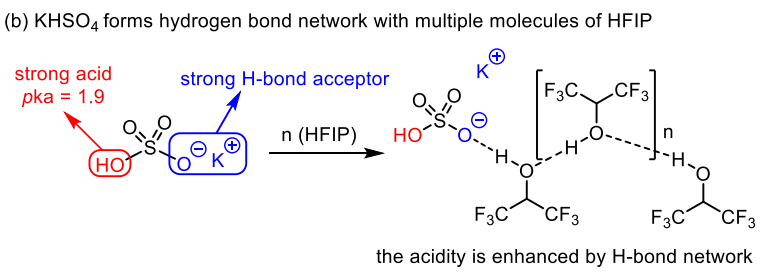
III. 2. Result and Discussion

III. 2. 1. Project Proposed

We studied previously that the amination of anisole or phenol with dibenzyl azodicarboxylate only in HFIP was not efficient. In order to improve the reactivity, a catalyst has to be used. However, we were interested in the use of green and cheap catalysts to replace the use of very strong Bronsted acid such as TfOH or expensive metal catalysts.

Potassium bisulfate, ($KHSO_4$) is a green, inexpensive and readily available inorganic salt which have strong hydrogen-bond accepting ability due to its ionic $-O^-K^+$ terminus which is a strong hydrogen bond acceptor. Meanwhile, $KHSO_4$ itself is a strong acid, the p*K*a of −OH terminus is 1.9. Encouraged by Hammond and Xu' work that $KHSO_4$ can form a hydrogen bond network with multiple molecules of HF which is another strong hydrogen-bond donor (**Scheme 42**, a).[51] We thought that $KHSO_4$ can also form a hydrogen bond network with fluorinated solvents such as hexafluoro-2-propanol (HFIP) and trifluoroethanol (TFE) due to their strong hydrogen-bond donating (HBD) ability and aggregation. Moreover, the acidity of $KHSO_4$ can be further enhanced by $(HFIP)_n$ hydrogen network (**Scheme 42**, b).



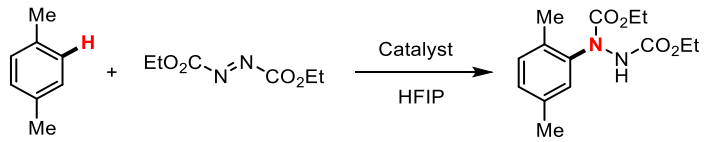


Scheme 42. Hydrogen-Bonding Network Assisted $KHSO_4$

III. 2. 2. Optimization of the Reaction Condition

In our initial study, the direct amination of *p*-xylene with diethyl azodicarboxylate (DEAD) was chosen as the model system to optimize the reaction conditions (**Table 8**). We first examined the reaction in HFIP as the solvent and the reaction mixture was stirred at room temperature and reflux. After 16 h, the product **46** was isolated in 26% and 29% yield, respectively (entry 1-2). To our great satisfaction, the use of 10 mol% of $KHSO_4$ as the catalyst can improve the yield to 91% in 2 h (entry 3). Unexpectedly, when another widely used fluorinated solvent TFE was used, only a trace amount of product was observed (entry 4). In addition, when 1.0 equiv. of *o*-xylene was used, resulting in a reduced yield of product **46** in 81% yield with 12% of *bis*-aminated product (based on DEAD) was isolated (entry 5).

Table 8. Optimization of the Catalysts



(3 equiv.) (0.5 mmol) **46**

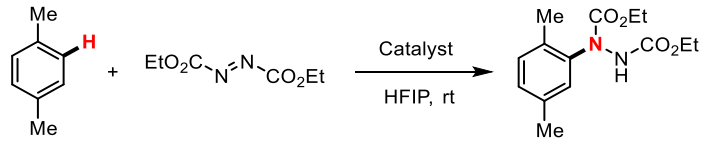
Entry	Catal. (10 mol%)	Sol.	Temp.	t (h)	Yield (%)
1	-	HFIP	rt	16	26
2	-	HFIP	reflux	16	29
3	**$KHSO_4$**	**HFIP**	**rt**	**2**	**91**
4	$KHSO_4$	TFE	rt	2	trace
5 [a]	$KHSO_4$	HFIP	rt	2	81 (12) [b]

[a] 1.0 equiv. of *o*-xylene was used. [b] Isolated yield of *bis*-aminated product.

After, different catalysts were checked (**Table 9**). A similar result was obtained using $NaHSO_4$ as catalyst (entry 2). Replacement of $KHSO_4$ by Na_2SO_4 led to dramatically drop in yield to 38% (entry 3), here we can see that the presence of the OH group of the salt is essential.

Other acid salts such as NaH_2PO_4 and $NaHCO_3$ gave trace of product (entry 4-5). It was noteworthy that strong protic acid TFA (p*K*a = 0.3) nearly had no improvement for the reaction (entry 6). The use of the super acid TfOH (p*K*a = −14.7) provided the product **46** with excellent yield in 5 min (entry 7).

Table 9. Optimization of the Catalysts

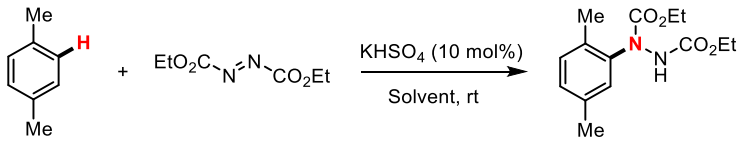


(3 equiv.) (0.5 mmol) **46**

Entry	Catalyst (10 mol%)	t (h)	Yield (%)
1	**$KHSO_4$**	**2**	**91**
2	$NaHSO_4$	2	90
3	Na_2SO_4	16	38
4	NaH_2PO_4	16	trace
5	$NaHCO_3$	16	trace
6	TFA	16	32
7	TfOH	5 min	94

We next investigated the effect of different solvents in this amination (**Table 10**). Other several non-fluorinated common solvents such as ^{i}PrOH, DCM, THF, H_2O, CH_3CN, CH_3NO_2 or neat did not produce a detectable amount of product (entry 3-9).

Table 10. Optimization of the Solvents



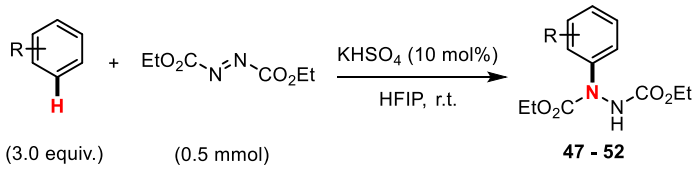
(3 equiv.) (0.5 mmol) **46**

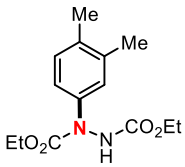
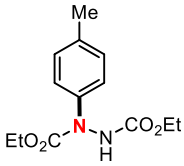
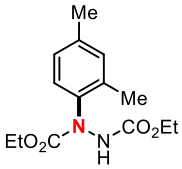
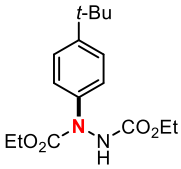
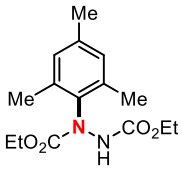
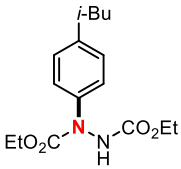
Entry	Solvent	t (h)	Yield (%)
1	**HFIP**	**2**	**91**
2	^{i}PrOH	16	0
3	DCM	16	0
4	THF	16	0
5	H_2O	16	0
6	CH_3CN	16	0
7	$MeNO_2$	16	0
8	Neat	16	0

III. 2. 3. Expanding the Substrate Scope

With the optimized reaction conditions in hand (**Table 8**, entry 3), we further examined the substrate scope of arenes in order to survey the generality of this reaction (**Table 11**). Under the standard conditions, *o*-xylene, *m*-xylene, and mesitylene were aminated rapidly to afford the corresponding aryl hydrazides **47-49** in excellent yields with single *regio*-isomer. In addition, corresponding aminated derivatives **50-52** of the toluene, *tert*-butylbenzene and *iso*-butylbenzene were obtained in good yields and *para*-selectivity.

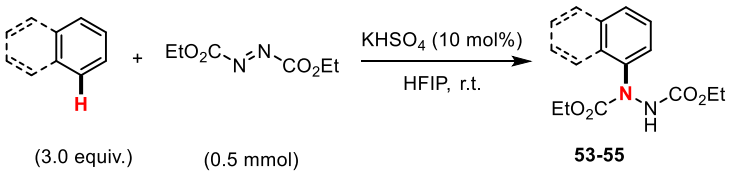
Table 11. The Amination of Unactive Arenes with DEAD

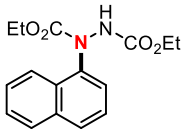
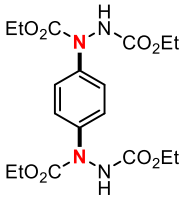
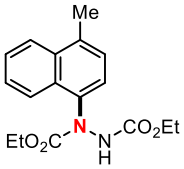


Entry	Product	Time (h)	Yield (%)	Entry	Product	Time (h)	Yield (%)
1	 **47**	16	94	4	 **50**	2	86 (mono/di: 8.6/1)
2	 **48**	2	92	5	 **51**	2	84 (p/o: 7.2/1)
3	 **49**	2	95	6	 **52**	2	75 (p/o: 5.8/1)

Meanwhile, naphthalene and 1-methylnaphthalene were aminated rapidly to afford the corresponding aryl hydrazides **53** and **54** in 93% and 95% yields, respectively. The regioselectivity of **54** was determined by X-ray. For benzene, a 1,4-bisaminated product **55** was obtained as a single product.

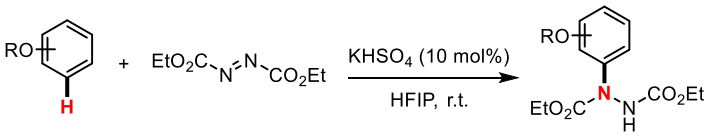
Table 12. The Amination of Naphthalene and Benzene with DEAD

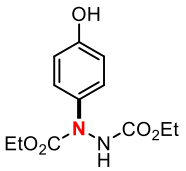
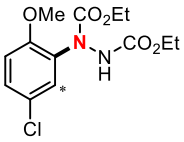


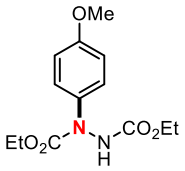
Entry	Product	Time (h)	Yield (%)	Entry	Product	Time (h)	Yield (%)
1	 **53**	2	93	3	 **55**	16	89
2	 **54**	2	95				

The amination of phenol resulted in corresponding aminated products in favour of the *para* position (p/o ratio of 7.5/1) with **56** was isolated in 82% yield. This system also proved efficient toward amination of anisole resulting in 96% yield to corresponding aminated products **57** (p/o ratio 4.9/1). For the para-substituted anisole, the amination took place at the ortho/meta position (o/m ratio 9.6/1) (**58**).

Table 13. The Amination of Electro-rich Arenes with DEAD



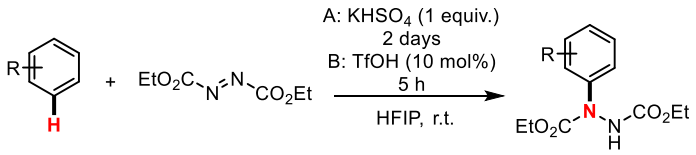
Entry	Product	Time (h)	Yield (%)	Entry	Product	Time (h)	Yield (%)
1	 **56**	0.5	82% (p/o: 7.5/1)	3	 **58**	10 min	85% (9.6/1)

2 [a]	 **57**	10 min	96% (p/o: 4.9/1)		

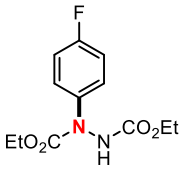
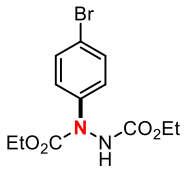
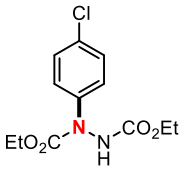
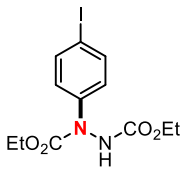
[a] combined yields of isomers.

To our disappointment, the reactions were not efficient with electron deficient arenes such as halo benzenes as substrates which needed 1 equiv. of catalyst and gave low yields after 2 days. Gratifyingly, with only 10 mol% of TfOH, the inactive arenes halo benzenes could be converted to the corresponding aryl hydrazides **59-62** in good to moderate yields after 5 h. The more electron-poor arenes such as benzotrifluoride, nitrobenzene or benzonitrile did not work in the present $KHSO_4$ or TfOH/HFIP system.

Table 14. The Amination of Electro-deficient Arenes with DEAD



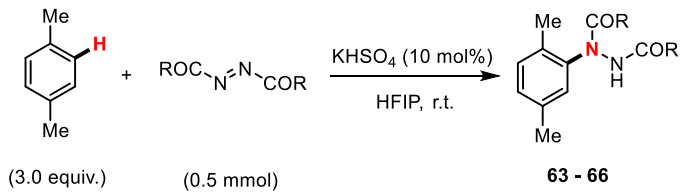
(3.0 equiv.) (0.5 mmol) **59 - 62**

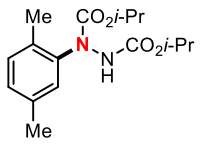
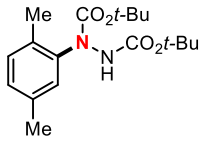
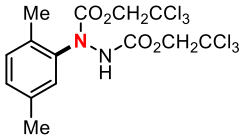
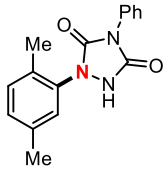
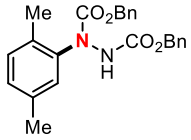
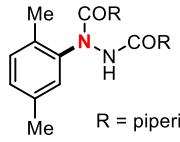
Entry	Product	Method	Yield (%)	Entry	Product	Method	Yield (%)
1	 **59**	A B	49 83	3	 **61**	A B	39 75
2	 **60**	A B	46 81	4	 **62**	A B	25 67

We next investigated the substituent effect of azodicarboxylates on this amination of simple arenes (**Table 15**). In addition to the DEAD, the tested *di*-isopropyl and *bis*-(2,2,2-trichloroethyl) azodicarboxylates were also reacted smoothly with *p*-xylene to afford the corresponding aryl hydrazides **63, 64** in excellent yields. However, the reaction of *p*-xylene with dibenzyl azodicarboxylate was not so efficient, the aminated product **65** was obtained in 57% yield after

16 h. Unfortunately, for *di-t*-butyl azodicarboxylate, only trace of the corresponding aryl hydrazide was observed. This result could be explained by its decomposition in $KHSO_4$/HFIP system. It was noteworthy that the reaction also worked with 4-phenyl-1,2,4-triazoline-3,5-dione, affording the corresponding aryl hydrazide **66** in 65% yield. Unfortunately, diazene-1,2-diylbis(piperidin-1-ylmethanone) was not suitable for this reaction.

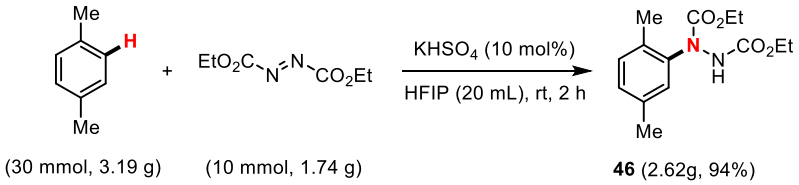
Table 15. The Amination of *p*-Xylene with Different Azodicarboxylate



Entry	Product	Time (h)	Yield (%)	Entry	Product	Time (h)	Yield (%)
1	 **63**	2	91	4		2	trace
2	 **64**	2	90	5	 **66**	16	65
3	 **65**	16	57	6	 R = piperidine	16	n.d.

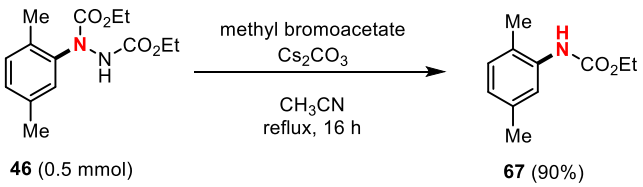
III. 2. 4. Gram Scale and Deprotection Reaction

To highlight the synthetic utility of this protocol, we conducted the reaction on a gram scale (**Scheme 43**). Under the optimized conditions, the gram-scale amination of *p*-xylene with DEAD proceeded smoothly in 2 h and the corresponding aryl hydrazide **46** was isolated in 94% yield.



Scheme 43. The Gram Scale Reaction

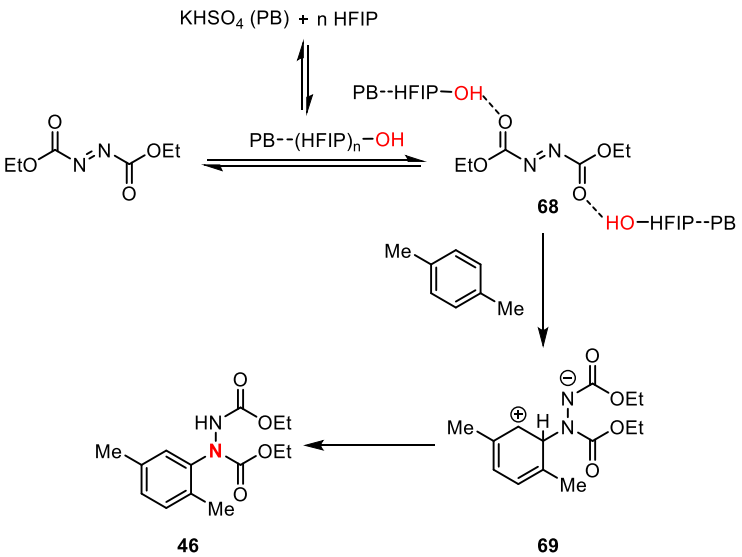
Furthermore, the diethoxycarbonyl hydrazine could be cleaved easily under mild conditions using reported protocol.[52] For example, the hydrazine group of **46** can be cleaved using the methyl bromoacetate/Cs_2CO_3 system and converted to amine **67** in 90% yield.



Scheme 44. The Cleavage of Hydrazine Group

III. 2. 5. Plausible Mechanism

The proposed mechanism is shown in **Scheme 58**, with the reaction of *p*-xylene and diethyl azodicarboxylate shown as an example.



Scheme 58. Plausible Mechanism

First, the hydrogen-bonding cluster generated from HFIP forms a hydrogen-bonding

complex with $KHSO_4$ (PB) and grants the $KHSO_4$ increased acidity. This catalytic acid complex performs as a good hydrogen bond donator to activate the carbonyl group on the DEAD, affording complex **68**. After, an electrophilic substitution reaction occurred quickly in complex **68** with *p*-xylene resulting in the formation of intermediate **69**, which undergoes the hydrogen transfer to afford the expected product **46**.

IV. Conclusion

HFIP was used as an efficient solvent for mild and clean C-H amination with azodicarboxylate derivatives. A wide range of arenes from anilines to halo-arenes were aminated smoothly in short times at room temperature, providing a series of phenylhydrazine derivatives in excellent yields.

Interestingly the particular physicochemical properties of these alcohols allowed performing reaction with free anilines. The reaction is highly regioselective to proceed at the *para*-position without the use of any additional catalyst or reagent. Meanwhile, the compatibility of the free amino group in this procedure is of high synthetic value. After the completion of the reaction, HFIP can be easily recovered and reused.

In the case of less active arenes, a very efficient and mild amination system using catalytic amount of $KHSO_4$ in HFIP have been developed. This protocol offers practical amination for a wide variety of a broad range of arenes, including arenes with certain electron-withdrawing groups. The higher activated acid complex which generated by the interactions between $KHSO_4$ and HFIP has strong hydrogen-bond donating ability that plays an important role. An additional advantage of $KHSO_4$ is its low cost, ready availability and easy removal in the aqueous workup.

V. Experimental Section

General Information and Reagents

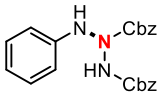
High-resolution mass spectra (HRMS) were obtained from waters LCT Premier (ESI/TOF). Melting points were determined on a Kofler melting point apparatus. NMR spectra were measured on an Ultrafield AVANCE300 (^{1}H, 300 MHz; ^{13}C, 75 MHz) spectrometer. Unless otherwise stated, NMR data were obtained under ambient temperature conditions in DMSO-d_6. Chemical shifts for ^{1}H NMR and ^{13}C NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the solvent resonance as the internal standard.

Unless otherwise noted, all commercial materials were purchased from various commercial sources (Sigma-Aldrich, Alfa Aesar, FluoroChem) and used as received, without further purification. HFIP was provided by. Central Glass Co. Ltd.

General Procedure for The Synthesis of 4-Aminophenylhydrazine

Azodicarboxylates (0.55 mmol) was added to a stirred solution of anilines (0.5 mmol) in HFIP (2 mL) at room temperature. The reaction mixture was stirred at this temperature for 2 h. When the reaction was complete (TLC monitored), the reaction mixture was evaporated under reduce pressure to get crude product. Then the crude product was purified by column chromatography on silica gel using cyclohexane - ether as the eluent afforded the aminated products.

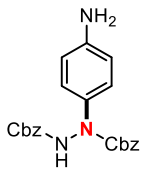
dibenzyl 3-phenyltriazane-1,2-dicarboxylate (1)



The title compound was prepared according to the general procedure described above by the reaction between aniline and dibenzyl azodicarboxylate and purified by 30% Et_2O in cyclohexane as a yellow solid.

M.p. 90 - 92 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.42 (s, NH), 8.48 (s, NH), 7.33 (m, 10H), 7.15 (t, J = 7.5 Hz, 2H), 6.86 (d, J = 7.8 Hz, 2H), 6.76 (t, J = 7.2 Hz, 1H), 5.14 (s, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.7, 155.6, 147.0, 136.2, 136.1, 128.7, 128.4, 128.3, 128.1, 127.9, 127.2, 119.3, 112.4, 67.6, 66.4; HRMS calcd. for $C_{22}H_{22}N_3O_4$ $[M+H]^+$ m/z 392.1610, found 392.1608.

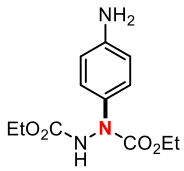
dibenzyl 1-(4-aminophenyl)hydrazine-1,2-dicarboxylate (2)



The title compound was prepared according to the general procedure described above by the reaction between aniline and dibenzyl azodicarboxylate and purified by 50% Et_2O in cyclohexane as a light-yellow solid (184 mg, 94%).

M.p. 118 - 120 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.97 (s, NH), 7.33 (m, 10H), 7.03 (br, 2H), 6.54 (d, J = 8.4 Hz, 2H), 5.13 (s, 2H), 5.12 (s, 2H), 5.01 (s, NH_2); ^{13}C NMR (101 MHz, DMSO-d_6) δ 155.6, 154.5, 147.2, 136.2, 132.7, 128.1, 128.0, 127.6, 127.5, 127.4, 127.0, 125.9, 113.2, 66.7, 66.0; HRMS calcd. for $C_{22}H_{22}N_3O_4$ $[M+H]^+$ m/z 392.1610, found 392.1618.

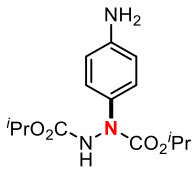
diethyl 1-(4-aminophenyl)hydrazine-1,2-dicarboxylate (3)



The title compound was prepared according to the general procedure described above by the reaction between aniline and diethyl azodicarboxylate and purified by 50% Et_2O in cyclohexane as a light-yellow solid (118 mg, 88%).

M.p. 121 - 123 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.81 (s, NH), 6.97 (d, J = 8.2 Hz, 2H), 6.50 (d, J = 8.4 Hz, 2H), 5.10 (s, NH_2), 4.10-4.03 (m, 4H), 1.18 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.9, 154.9, 147.4, 131.0, 126.3, 113.3, 61.6, 60.7, 14.5, 14.4; HRMS calcd. for $C_{12}H_{17}N_3O_4Na$ $[M+Na]^+$ m/z 290.1117, found 290.1119.

diisopropyl 1-(4-aminophenyl)hydrazine-1,2-dicarboxylate (4)

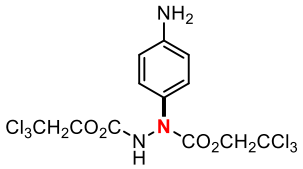


The title compound was prepared according to the general procedure described above by the reaction between aniline and diisopropyl azodicarboxylate and purified by 50% Et_2O in cyclohexane as a light-yellow solid (133 mg, 90%).

M.p. 136 - 138 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.70 (s, NH), 6.94 (br, 2H), 6.48 (d, J =

8.5 Hz, 2H), 5.11 (s, NH_2), 4.82-4.76 (m, 2H), 1.20 (br, 6H), 1.18 (br, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.6, 154.4, 147.3, 131.1, 125.9, 113.3, 69.1, 68.2, 21.9, 21.8; HRMS calcd. for $C_{14}H_{22}N_3O_4$ $[M+H]^+$ m/z 296.1610, found 296.1612.

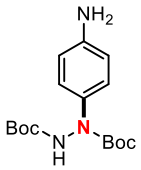
bis(2,2,2-trichloroethyl) 1-(4-aminophenyl)hydrazine-1,2-dicarboxylate (5)



The title compound was prepared according to the general procedure described above by the reaction between aniline and bis(2,2,2-trichloroethyl) azodicarboxylate and purified by 50% Et_2O in cyclohexane as a yellow solid (221 mg, 94%).

M.p. 94 - 96 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 10.75 (d, J = 20.9 Hz, NH), 7.10-7.02 (m, 2H), 6.52 (d, J = 8.1 Hz, 2H), 5.23 (s, NH_2), 4.89 (s, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.2, 153.3, 148.2, 148.0, 129.4, 127.0, 125.9, 113.4, 95.6, 95.4, 74.7, 73.9; HRMS calcd. for $C_{12}H_{12}N_3O_4Cl_6$ $[M+H]^+$ m/z 473.8929, found 473.8938.

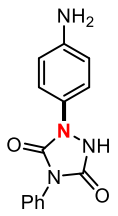
di-tert-butyl 1-(4-aminophenyl)hydrazine-1,2-dicarboxylate (6)



The title compound was prepared according to the general procedure described above by the reaction between aniline and ditertbutyl azodicarboxylate and purified by 50% Et_2O in cyclohexane as a yellow solid (55 mg, 34%).

M.p. 84 - 86 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 9.40 (s, NH), 6.92 (br, 2H), 6.47 (d, J = 8.4 Hz, 2H), 5.02 (s, NH_2), 1.40 (s, 9H), 1.39 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.0, 153.7, 146.7, 131.5, 125.6, 113.2, 79.9, 79.3, 28.1, 27.9; HRMS calcd. for $C_{16}H_{26}N_3O_4$ $[M+H]^+$ m/z 324.1923, found 324.1934.

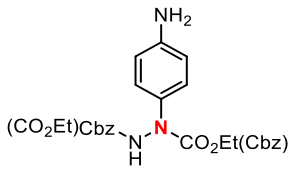
1-(4-aminophenyl)-4-phenyl-1,2,4-triazolidine-3,5-dione (7)



The title compound was prepared according to the general procedure described above by the reaction between aniline and 4-phenyl-1,2,4-triazoline-3,5-dione and purified by 5% MeOH in DCM as a gray solid (76 mg, 57%).

M.p. 222 - 224 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.51 (m, 4H), 7.44 - 7.40 (m, 1H), 7.21 (d, J = 8.6 Hz, 2H), 6.63 (d, J = 8.6 Hz, 2H), 3.33 (s, NH_2); ^{13}C NMR (75 MHz, DMSO-d_6) δ 151.9, 149.7, 147.5, 131.8, 128.8, 127.9, 126.4, 124.8, 123.1, 113.7; HRMS calcd. for $C_{14}H_{13}N_4O_2$ $[M+H]^+$ m/z 269.1039, found 269.1030.

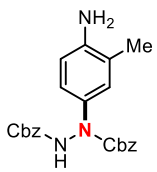
mixture of 2-benzyl 1-ethyl 1-(4-aminophenyl)hydrazine-1,2-dicarboxylate and 1-benzyl 2-ethyl 1-(4-aminophenyl)hydrazine-1,2-dicarboxylate (8/8')



The title compound was prepared according to the general procedure described above by the reaction between aniline and 1-benzyl 2-ethyl (E)-diazene-1,2-dicarboxylate and purified by 50% Et_2O in cyclohexane as a light-yellow solid (158 mg, 96%)

M.p. 132 - 134 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.04 (NH, 1H), 7.35 (m, 5H), 7.00 (d, J = 8.1 Hz, 2H), 6.52 (d, J = 8.3 Hz, 2H), 5.16 (s, 2H), 5.12 (s, 2H), 4.11-4.04 (m, 2H), 1.19-1.08 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.9, 154.9, 147.5, 136.5, 130.9, 128.4, 128.4, 128.1, 127.8, 127.4, 127.3, 126.2, 113.4, 66.9, 66.2, 61.8, 60.9, 14.5, 14.4; HRMS calcd. for $C_{17}H_{20}N_3O_4$ $[M+H]^+$ m/z 330.1454, found 330.1448.

dibenzyl 1-(4-amino-3-methylphenyl)hydrazine-1,2-dicarboxylate (10)

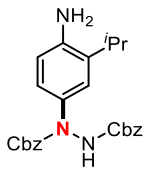


The title compound was prepared according to the general procedure described above by the

reaction between o-toluidine and dibenzyl azodicarboxylate and purified by 50% Et_2O in cyclohexane as a white solid (197 mg, 97%).

M.p. 103 - 105 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.10 (s, NH), 7.34 (m, 10H), 6.92 (br, 2H), 6.56 (d, J = 8.2 Hz, 1H), 5.13 (s, 2H), 5.11 (s, 2H), 4.93 (s, NH_2), 2.03 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.8, 154.7, 145.5, 136.4, 136.4, 130.8, 128.4, 128.3, 128.0, 127.8, 127.5, 127.3, 123.5, 120.7, 113.3, 66.9, 66.2, 17.4; HRMS calcd. for $C_{23}H_{23}N_3O_4Na$ $[M+Na]^+$ m/z 428.1586, found 428.1584.

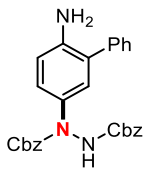
dibenzyl 1-(4-amino-3-isopropylphenyl)hydrazine-1,2-dicarboxylate (11)



The title compound was prepared according to the general procedure described above by the reaction between 2-isopropylaniline and dibenzyl azodicarboxylate and purified by 50% Et_2O in cyclohexane as a light-yellow oil (204 mg, 94%).

^{1}H NMR (300 MHz, DMSO) δ 10.09 (s, NH), 7.34 (m, 10H), 7.00 (s, 1H), 6.88 (d, J = 7.9 Hz, 1H), 6.56 (d, J = 8.3 Hz, 1H), 5.13 (s, 4H), 5.12 (s, 4H), 4.96 (s, NH_2), 2.97 – 2.89 (m, 1H), 1.10 – 1.00 (m, 6H); ^{13}C NMR (75 MHz, DMSO) δ 155.9, 144.2, 136.4, 131.3, 130.8, 128.4, 128.3, 128.0, 127.9, 127.8, 127.4, 123.1, 114.2, 66.9, 66.1, 26.4, 22.2; HRMS calcd. for $C_{25}H_{31}N_4O_4$ $[M+NH_4]^+$ m/z 452.2345, found 451.2348.

dibenzyl 1-(6-amino-[1,1'-biphenyl]-3-yl)hydrazine-1,2-dicarboxylate (12)

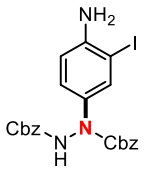


The title compound was prepared according to the general procedure described above by the reaction between biphenylamine and dibenzyl azodicarboxylate and purified by 50% Et_2O in cyclohexane as a white solid (219 mg, 94%).

M.p. 100 - 102 °C; ^{1}H NMR (300 MHz, DMSO) δ 10.28 (s, NH), 7.40 (m, 15H), 7.16 (m, 2H), 6.83 (d, J = 8.3 Hz, 1H), 5.21 (s, 2H), 5.17 (s, 2H), 5.00 (s, NH_2); ^{13}C NMR (75 MHz, DMSO) δ 156.1, 154.8, 143.9, 139.0, 136.4, 131.8, 128.9, 128.5, 128.4, 128.1, 128.0, 127.9, 127.5, 127.1, 125.4, 115.0, 67.2, 66.4; HRMS calcd. for $C_{28}H_{29}N_4O_4$ $[M+NH_4]^+$ m/z 485.2189, found

485.2183.

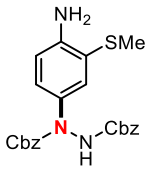
dibenzyl 1-(4-amino-3-iodophenyl)hydrazine-1,2-dicarboxylate (13)



The title compound was prepared according to the general procedure described above by the reaction between 2-iodoaniline and dibenzyl azodicarboxylate and purified by 50% Et_2O in cyclohexane as a yellow solid (218 mg, 84%).

M.p. 58 - 60 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.17 (s, NH), 7.56 (s, 1H), 7.35 (m, 10H), 7.10 (br, 1H), 6.73 (d, J = 8.5 Hz, 1H), 5.33 (s, NH_2), 5.15 (s, 2H), 5.12 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.9, 154.5, 147.5, 136.2, 136.2, 134.9, 131.8, 128.4, 128.4, 128.1, 127.9, 127.9, 127.5, 127.4, 125.9, 113.3, 81.3, 67.2, 66.4; HRMS calcd. for $C_{22}H_{21}N_3O_4I$ $[M+H]^+$ m/z 518.0577, found 518.0574.

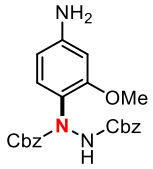
dibenzyl 1-(4-amino-3-(methylthio)phenyl)hydrazine-1,2-dicarboxylate (14)



The title compound was prepared according to the general procedure described above by the reaction between 2-(methylthio)aniline and dibenzyl azodicarboxylate and purified by 50% Et_2O in cyclohexane as a white solid (198 mg, 91%).

M.p. 112 - 114 °C; ^{1}H NMR (300 MHz, DMSO) δ 10.13 (s, NH), 7.34 (s, 10H), 7.21 (s, 1H), 6.99 (d, J = 8.0 Hz, 1H), 6.67 (d, J = 8.2 Hz, 1H), 5.28 (s, NH_2), 5.13 (s, 2H), 5.12 (s, 2H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 155.9, 154.6, 146.7, 136.3, 131.3, 128.3, 128.0, 127.9, 127.8, 127.3, 125.2, 118.1, 113.6, 67.1, 66.1, 66.3, 16.2; HRMS calcd. for $C_{23}H_{24}N_3O_4S$ $[M+H]^+$ m/z 438.1488, found 438.1484.

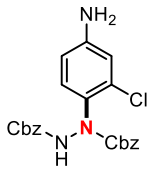
dibenzyl 1-(4-amino-2-methoxyphenyl)hydrazine-1,2-dicarboxylate (15)



The title compound was prepared according to the general procedure described above by the reaction between 3-methoxyaniline and dibenzyl azodicarboxylate and purified by 50% Et_2O in cyclohexane as a white solid (194 mg, 92%).

M.p. 126 - 128 ºC; ^{1}H NMR (300 MHz, DMSO) δ 9.96 (d, *J* = 25.0 Hz, NH), 7.30 (m, 10H), 7.07 – 7.05 (m, 1H), 6.22 (s, 1H), 6.09 (br, 1H), 5.25 (s, NH_2), 5.10 (m, 4H), 3.64 (d, *J* = 13.5 Hz, 3H); ^{13}C NMR (75 MHz, DMSO) δ 156.2 – 154.9 (2C), 154.9, 150.0, 136.6 (d, *J* = 11.0 Hz), 129.3, 128.9, 128.3, 128.2, 127.9, 127.8, 127.7, 127.1, 119.2 (d, *J* = 4.6 Hz), 105.0, 97.3 (d, *J* = 10.2 Hz), 66.7, 66.0, 54.9; HRMS calcd. for $C_{23}H_{23}N_3O_5Na$ $[M+Na]^+$ m/z 444.1535, found 444.1534.

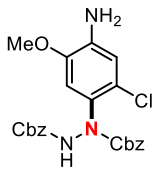
dibenzyl 1-(4-amino-2-chlorophenyl)hydrazine-1,2-dicarboxylate (16)



The title compound was prepared according to the general procedure described above by the reaction between 3-chloroaniline and dibenzyl azodicarboxylate and purified by 50% Et_2O in cyclohexane as a yellow solid (185 mg, 87%).

M.p. 46 - 48 ºC; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.26 (d, *J* = 30.0 Hz, NH), 7.37-7.25 (m, 11H), 6.64 (s, 1H), 6.50 (t, *J* = 7.1 Hz, 1H), 5.58 (s, NH_2), 5.13 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.3, 154.8, 145.0, 136.3, 131.9, 130.1, 128.5, 128.4, 127.9, 127.3, 126.8, 113.1, 112.6, 67.2, 66.3; HRMS calcd. for $C_{22}H_{20}N_3O_4NaCl$ $[M+Na]^+$ m/z 448.1040, found 448.1042.

dibenzyl 1-(4-amino-2-chloro-5-methoxyphenyl)hydrazine-1,2-dicarboxylate (17)

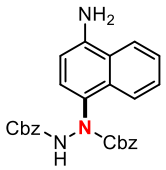


The title compound was prepared according to the general procedure described above by the reaction between 5-chloro-2-methoxyaniline and dibenzyl azodicarboxylate and purified by 50%

Et_2O in cyclohexane as a white solid (216 mg, 95%).

M.p. 122 - 124 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.28 (d, J = 30.2 Hz, NH), 7.37 (m, 10H), 7.00 (s, 1H), 6.67 (s, 1H), 5.31 - 5.05 (m, 6H), 3.69 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.4, 154.8, 144.7, 139.3, 136.4, 136.2, 128.4, 128.3, 128.1, 127.9, 127.5, 127.3, 126.5, 123.2, 112.0, 111.0, 67.4, 66.3, 55.5; HRMS calcd. for $C_{23}H_{23}N_3O_5Cl$ $[M+H]^+$ m/z 456.1326, found 456.1333.

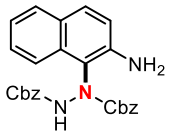
dibenzyl 1-(4-aminonaphthalen-1-yl)hydrazine-1,2-dicarboxylate (18)



The title compound was prepared according to the general procedure described above by the reaction between naphthalen-1-amine and dibenzyl azodicarboxylate and purified by 50% Et_2O in cyclohexane as a white solid (210 mg, 95%).

M.p. 150 - 152 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.34 (d, J = 35.0 Hz, NH), 8.13-7.87 (m, 2H), 7.49-7.24 (m, 12H), 7.09 (br, 1H), 6.64 (d, J = 7.7 Hz, 1H), 5.98 (s, NH_2), 5.13 (m, 4H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.2, 155.8, 145.4, 136.5, 136.4, 130.7, 128.4, 128.1, 128.0, 127.9, 127.8, 127.0, 126.8, 126.1, 123.9, 123.1, 122.7, 122.5, 106.1, 66.9, 66.2; HRMS calcd. for $C_{26}H_{24}N_3O_4$ $[M+H]^+$ m/z 442.1767, found 442.1763.

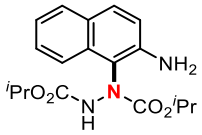
dibenzyl 1-(2-aminonaphthalen-1-yl)hydrazine-1,2-dicarboxylate (19)



The title compound was prepared according to the general procedure described above by the reaction between naphthalen-2-amine and dibenzyl azodicarboxylate and purified by 50% Et_2O in cyclohexane as a white solid (214 mg, 97%).

M.p. 164 - 166 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (br, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.8 Hz, 1H), 7.25-7.07 (m, 12H), 6.93-6.84 (m, 3H), 5.05 (s, 2H), 5.00 (s, 2H), 4.53 (s, NH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 156.8, 142.9, 135.9, 135.3, 131.8, 130.4, 129.6, 128.5, 128.5, 128.2, 128.0, 127.8, 127.7, 127.3, 122.4, 119.5, 119.0, 117.4, 68.4, 68.2; HRMS calcd. for $C_{26}H_{24}N_3O_4$ $[M+H]^+$ m/z 442.1767, found 442.1768.

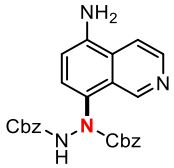
diisopropyl 1-(2-aminonaphthalen-1-yl)hydrazine-1,2-dicarboxylate (20)



The title compound was prepared according to the general procedure described above by the reaction between naphthalen-2-amine and diisopropyl azodicarboxylate and purified by 50% Et_2O in cyclohexane as a white solid (159 mg, 92%).

M.p. 159 - 161 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.03 (d, J = 21.4 Hz, NH), 7.68 - 7.59 (m, 3H), 7.35 (t, J = 7.5 Hz, 1H), 7.14 (t, J = 7.4 Hz, 1H), 7.03 (d, J = 8.8 Hz, 1H), 5.89 (s, NH_2), 4.92 - 4.77 (m, 2H), 1.30 - 1.18 (m, 8H), 1.02 (d, J = 6.2 Hz, 2H), 0.90 (d, J = 6.2 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.8, 155.2, 154.0, 144.0, 143.6, 132.2, 131.9, 129.2, 127.7, 126.6, 126.4, 121.1, 120.7, 118.9, 116.4, 69.5, 68.8, 21.9, 21.8, 21.7, 21.6; HRMS calcd. for $C_{18}H_{24}N_3O_4$ $[M+H]^+$ m/z 346.1767, found 346.1762.

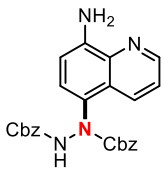
dibenzyl 1-(5-aminoisoquinolin-8-yl)hydrazine-1,2-dicarboxylate (21)



The title compound was prepared according to the general procedure described above by the reaction between isoquinolin-5-amine and dibenzyl azodicarboxylate and purified by 50% Et_2O in cyclohexane as a light-yellow solid (203 mg, 92%).

M.p. 154 - 156 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.07 (d, J = 22.0 Hz, NH), 8.83 (br, 1H), 8.58 (br, 1H), 7.64 (br, 1H), 7.43 - 7.03 (m, 11H), 6.68 (br, 1H), 6.24 (s, NH_2), 5.11 (m, 4H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.4, 156.1, 150.0, 145.9, 144.2, 136.6, 131.4, 129.6, 128.4, 128.1, 127.9, 127.7, 127.0, 119.2, 117.6, 106.1, 66.7, 66.0; HRMS calcd. for $C_{25}H_{23}N_4O_4$ $[M+H]^+$ m/z 443.1719, found 443.1727.

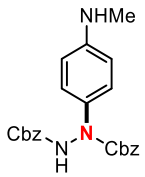
dibenzyl 1-(8-aminoquinolin-5-yl)hydrazine-1,2-dicarboxylate (22)



The title compound was prepared according to the general procedure described above by the reaction between quinolin-8-amine and dibenzyl azodicarboxylate and purified by 50% Et_2O in cyclohexane as a light-yellow solid (199 mg, 90%).

M.p. 146 - 148 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.38 (d, J = 36.1 Hz, NH), 8.75 (d, J = 2.2 Hz, 1H), 8.39 (br, 1H), 7.49 - 7.25 (m, 11H), 7.09 (br, 1H), 6.84 (d, J = 7.4 Hz, 1H), 6.20 (s, NH_2), 5.14 (m, 4H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.2, 155.6, 147.1, 145.9, 136.8, 136.3, 131.6, 128.4, 128.3, 128.1, 127.9, 127.4, 127.2, 125.7, 121.9, 107.1, 67.2, 66.3; HRMS calcd. for $C_{25}H_{23}N_4O_4$ $[M+H]^+$ m/z 443.1719, found 443.1722.

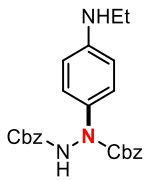
dibenzyl 1-(4-(methylamino)phenyl)hydrazine-1,2-dicarboxylate (23)



The title compound was prepared according to the general procedure described above by the reaction between N-methylaniline and dibenzyl azodicarboxylate and purified by 50% Et_2O in cyclohexane as a light-yellow solid (188 mg, 93%).

M.p. 132 - 134 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.14 (s, NH), 7.34 (m, 10H), 7.11 (d, J = 8.2 Hz, 2H), 6.50 (d, J = 8.4 Hz, 2H), 5.75 (s, NH), 5.14 (s, 2H), 5.12 (s, 2H), 2.66 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.9, 154.8, 148.7, 136.4, 136.3, 130.6, 128.4, 128.3, 128.0, 127.8, 127.3, 125.9, 111.1, 67.0, 66.2, 29.8; HRMS calcd. for $C_{23}H_{24}N_3O_4$ $[M+H]^+$ m/z 406.1767, found 406.1756.

dibenzyl 1-(4-(ethylamino)phenyl)hydrazine-1,2-dicarboxylate (24)

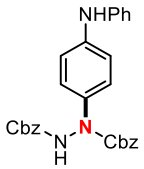


The title compound was prepared according to the general procedure described above by the reaction between N-ethyl aniline and dibenzyl azodicarboxylate and purified by 50% Et_2O in cyclohexane as a light-yellow solid (202 mg, 96%).

M.p. 147 - 149 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.11 (s, NH), 7.34 (m, 10H), 7.07 (d, J = 8.3 Hz, 2H), 6.50 (d, J = 8.5 Hz, 2H), 5.63 (s, NH), 5.13 (s, 2H), 5.11 (s, 2H), 3.01 (d, J = 6.7 Hz, 2H), 1.14 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.9, 154.7, 147.8, 136.4,

136.3, 130.4, 128.4, 128.2, 128.0, 127.8, 127.2, 125.9, 111.3, 66.9, 66.2, 37.4, 14.3; HRMS calcd. for $C_{24}H_{26}N_3O_4$ $[M+H]^+$ m/z 420.1923, found 420.1914.

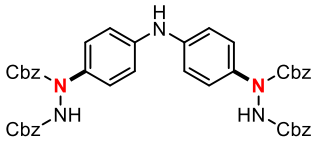
dibenzyl 1-(4-(phenylamino)phenyl)hydrazine-1,2-dicarboxylate (25)



The title compound was prepared according to the general procedure described above by the reaction between diphenylamine and dibenzyl azodicarboxylate and purified by 50% Et_2O in cyclohexane as a white solid (169 mg, 72%).

M.p. 124 - 126 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.23 (s, NH), 8.24 (s, NH), 7.35 (m, 10H), 7.24 (t, J = 7.6 Hz, 4H), 7.07 (t, J = 7.9 Hz, 4H), 6.84 (t, J = 7.1 Hz, 1H), 5.14 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.0, 154.5, 143.2, 141.9, 136.3, 133.9, 129.2, 128.4, 128.0, 127.9, 127.3, 125.6, 119.9, 116.9, 116.3, 67.2, 66.3; HRMS calcd. for $C_{28}H_{26}N_3O_4$ $[M+H]^+$ m/z 468.1923, found 468.1914.

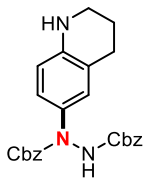
tetrabenzyl 1,1'-(azanediylbis(4,1-phenylene))bis(hydrazine-1,2-dicarboxylate) (25')



The title compound was prepared according to the general procedure described above by the reaction between diphenylamine and dibenzyl azodicarboxylate and purified by 50% Et_2O in cyclohexane as a white solid (40 mg, 17%).

M.p. 136 - 138 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.25 (s, 2NH), 8.34 (s, NH), 7.36 - 7.21 (m, 24H), 7.06 (d, J = 8.4 Hz, 4H), 5.18 (s, 4H), 5.14 (s, 4H); ^{3}C NMR (75 MHz, DMSO-d_6) δ 156.0, 154.5, 141.6, 136.3, 136.2, 134.1, 128.4, 128.1, 127.9, 127.4, 125.5, 116.5, 67.2, 66.4; HRMS calcd. for $C_{44}H_{39}N_5O_8Na$ $[M+Na]^+$ m/z 788.2696, found 788.2685.

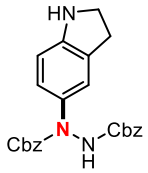
dibenzyl 1-(1,2,3,4-tetrahydroquinolin-6-yl)hydrazine-1,2-dicarboxylate (26)



The title compound was prepared according to the general procedure described above by the reaction between 1,2,3,4-tetrahydroquinoline and dibenzyl azodicarboxylate and purified by 50% Et_2O in cyclohexane as a light-yellow solid (168 mg, 78%).

M.p. 118 - 120 ºC; ^{1}H NMR (300 MHz, DMSO) δ 10.08 (s, NH), 7.34 (m, 10H), 6.86 - 6.77 (m, 2H), 6.36 (t, *J* = 7.9 Hz, 1H), 5.78 (s, NH), 5.13 (s, 2H), 5.11 (s, 2H), 3.16 (t, *J* = 5.1 Hz, 2H), 2.62 (t, *J* = 6.0 Hz, 2H), 1.78 – 1.75 (m, 2H); ^{13}C NMR (75 MHz, DMSO) δ 155.9, 154.8, 144.2, 136.5, 136.4, 130.0, 128.4, 128.4, 128.0, 127.9, 127.5, 127.3, 125.9, 124.4, 123.6, 119.4, 112.8, 66.9, 66.2, 40.7, 26.7, 21.3; HRMS calcd. for $C_{25}H_{26}N_3O_4$ $[M+H]^+$ m/z 432.1923, found 432.1924.

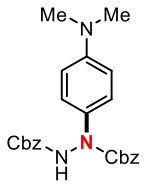
dibenzyl 1-(indolin-5-yl)hydrazine-1,2-dicarboxylate (27)



The title compound was prepared according to the general procedure described above by the reaction between indoline and dibenzyl azodicarboxylate and purified by 50% Et_2O in cyclohexane as a light-yellow solid (155 mg, 74%).

M.p. 128 - 130 ºC; ^{1}H NMR (300 MHz, DMSO) δ 10.11 (s, NH), 7.34 (m, 10H), 7.01 (s, 1H), 6.90 (d, *J* = 8.6 Hz, 1H), 6.43 (d, *J* = 8.2 Hz, 1H), 5.60 (s, NH), 5.13 (s, 2H), 5.11 (s, 2H), 3.42 (t, *J* = 8.4 Hz, 2H), 2.88 (t, *J* = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, DMSO) δ 155.9, 154.8, 151.4, 136.4, 136.4, 131.8, 129.0, 128.4, 128.4, 128.1, 127.9, 127.5, 127.3, 124.3, 121.8, 107.4, 67.0, 66.2, 46.8, 29.1; HRMS calcd. for $C_{24}H_{24}N_3O_4$ $[M+H]^+$ m/z 418.1767, found 418.1761.

dibenzyl 1-(4-(dimethylamino)phenyl)hydrazine-1,2-dicarboxylate (28)

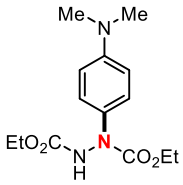


The title compound was prepared according to the general procedure described above by the

reaction between N, N-dimethylaniline and dibenzyl azodicarboxylate and purified by 30% Et_2O in cyclohexane as a white solid (194 mg, 93%).

M.p. 145 - 147 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.17 (s, NH), 7.35 (m, 10H), 7.19 (d, J = 8.3 Hz, 2H), 6.68 (d, J = 8.7 Hz, 2H), 5.15 (s, 2H), 5.12 (s, 2H), 2.88 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.9, 154.7, 149.0, 136.3, 131.1, 128.3, 128.0, 127.8, 127.3, 125.4, 111.9, 67.0, 66.2, 40.2; HRMS calcd. for $C_{24}H_{26}N_3O_4$ $[M+H]^+$ m/z 420.1923, found 420.1919.

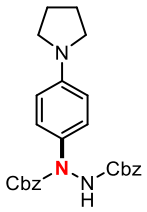
diethyl 1-(4-(dimethylamino)phenyl)hydrazine-1,2-dicarboxylate (29)



The title compound was prepared according to the general procedure described above by the reaction between N, N-dimethylaniline and diethyl azodicarboxylate and purified by 30% Et_2O in cyclohexane as a white solid (134 mg, 91%).

M.p. 101 - 103 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.88 (s, NH), 7.14 (d, J = 8.4 Hz, 2H), 6.67 (d, J = 8.8 Hz, 2H), 4.11 - 4.03 (m, 4H), 2.87 (s, 6H), 1.18 (t, J = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.9, 154.8, 148.9, 131.5, 125.7, 112.0, 61.7, 60.8, 40.3, 14.5, 14.5; HRMS calcd. for $C_{14}H_{22}N_3O_4$ $[M+H]^+$ m/z 296.1610, found 296.1602.

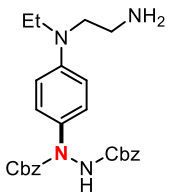
dibenzyl 1-(4-(pyrrolidin-1-yl)phenyl)hydrazine-1,2-dicarboxylate (30)



The title compound was prepared according to the general procedure described above by the reaction between 1-phenylpyrrolidine and dibenzyl azodicarboxylate and purified by 30 % Et_2O in cyclohexane as a white solid (194 mg, 87%).

M.p. 180 - 182 °C; ^{1}H NMR (300 MHz, DMSO) δ 10.14 (s, NH), 7.34 (m, 10H), 7.17 (d, J = 7.9 Hz, 2H), 6.48 (d, J = 8.3 Hz, 2H), 5.14 (s, 2H), 5.11 (s, 2H), 3.19 (br, 4H), 1.93 (br, 4H); ^{13}C NMR (75 MHz, DMSO) δ 155.9, 154.8, 146.5, 136.4, 136.3, 130.2, 128.3, 128.0, 127.8, 127.3, 125.8, 111.1, 67.0, 66.2, 47.4, 25.0; HRMS calcd. for $C_{26}H_{28}N_3O_4$ $[M+H]^+$ m/z 446.2080, found 446.2074.

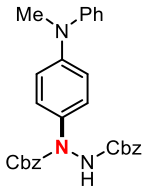
dibenzyl 1-(4-((2-aminoethyl)(methyl)amino)phenyl)hydrazine-1,2-dicarboxylate (31)



The title compound was prepared according to the general procedure described above by the reaction between N-ethyl-N-phenyl-1,2-ethanediamine and dibenzyl azodicarboxylate and purified by 50 % Et_2O in cyclohexane as a yellow oil (219 mg, 95%).

^{1}H NMR (300 MHz, DMSO) δ 10.16 (s, NH), 7.34 (m, 10H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.64 (d, *J* = 8.6 Hz, 2H), 5.14 (s, 2H), 5.11 (s, 2H), 3.34 (t, *J* = 6.8 Hz, 2H), 3.24 (t, *J* = 6.9 Hz, 2H), 2.68 (m, 4H), 1.06 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, DMSO) δ 155.8, 154.7, 146.4, 136.4, 136.3, 130.0, 128.4, 128.3, 128.0, 127.8, 127.3, 125.8, 110.9, 67.0, 66.2, 52.9, 44.5, 39.2, 12.0; HRMS calcd. for $C_{26}H_{31}N_4O_4$ $[M+H]^+$ m/z 463.2345, found 463.2333.

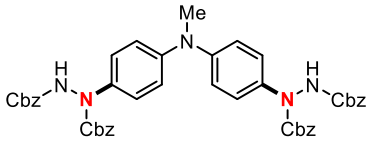
dibenzyl 1-(4-(methyl(phenyl)amino)phenyl)hydrazine-1,2-dicarboxylate (32)



The title compound was prepared according to the general procedure described above by the reaction between N-methyl-N-phenylaniline and dibenzyl azodicarboxylate and purified by 30 % Et_2O in cyclohexane as a white solid (196 mg, 82%).

M.p. 116 - 118 ^{o}C; ^{1}H NMR (300 MHz, DMSO) δ 10.28 (s, NH), 7.35 – 7.27 (m, 14H), 7.04 – 6.95 (m, 5H), 5.18 (s, 2H), 5.14 (s, 2H), 3.25 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 156.0, 154.4, 148.4, 146.7, 136.3, 136.2, 134.9, 129.3, 128.4, 128.1, 127.9, 127.9, 127.5, 127.4, 124.9, 121.6, 120.6, 119.4, 67.3, 66.4, 40.0; HRMS calcd. for $C_{29}H_{28}N_3O_4$ $[M+H]^+$ m/z 482.2080, found 482.2086.

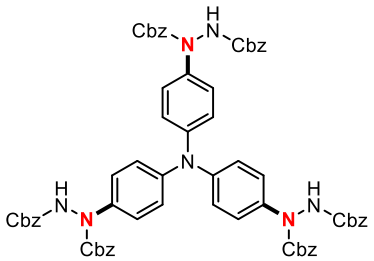
tetrabenzyl 1,1'-((methylazanediyl)bis(4,1-phenylene))bis(hydrazine-1,2-dicarboxylate) (32')



The title compound was prepared according to the general procedure described above by the reaction between N-methyl-N-phenylaniline and dibenzyl azodicarboxylate and purified by 30 % Et_2O in cyclohexane as a white solid (32 mg, 8%).

M.p. 142 - 144 °C; ^{1}H NMR (300 MHz, DMSO) δ 10.29 (s, 2H), 7.35 – 7.30 (m, 24H), 7.00 (d, *J* = 8.0 Hz, 4H), 5.18 (s, 4H), 5.14 (s, 4H), 3.25 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 156.0, 154.3, 146.4, 136.2, 136.2, 136.2, 128.4, 128.1, 127.9, 127.9, 127.5, 127.4, 125.0, 119.9, 67.3, 66.4; HRMS calcd. for $C_{45}H_{42}N_5O_8$ $[M+H]^+$ m/z 780.3033, found 780.3041.

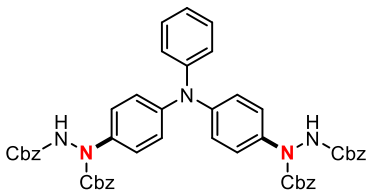
hexabenzyl 1,1',1''-(nitrilotris(benzene-4,1-diyl))tris(hydrazine-1,2-dicarboxylate) (33)



The title compound was prepared according to the general procedure described above by the reaction between triphenylamine and dibenzyl azodicarboxylate and purified by 30 % Et_2O in cyclohexane as a white solid (330 mg, 58%).

M.p. 198 - 200 °C; ^{1}H NMR (300 MHz, DMSO) δ 10.32 (s, 3H), 7.36 (m, 36H), 7.01 (d, *J* = 8.3 Hz, 6H), 5.21 (s, 6H), 5.16 (s, 6H); ^{13}C NMR (75 MHz, DMSO) δ 156.5, 154.6, 145.1, 137.4, 136.7, 136.6, 128.9, 128.6, 128.4, 128.4, 128.0, 127.9, 125.2, 124.1, 67.9, 67.0; HRMS calcd. for $C_{66}H_{61}N_8O_{12}$ $[M+H]^+$ m/z 1157.4409, found 1157.4417.

tetrabenzyl 1,1'-((phenylazanediyl)bis(4,1-phenylene))bis(hydrazine-1,2-dicarboxylate) (33')

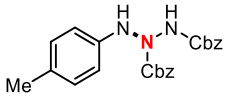


The title compound was prepared according to the general procedure described above by the reaction between triphenylamine and dibenzyl azodicarboxylate and purified by 30 % Et_2O in cyclohexane as a white solid (143 mg, 34%).

M.p. 110 - 112 °C; ^{1}H NMR (300 MHz, DMSO) δ 10.30 (s, 2H), 7.35 - 7.29 (m, 26H), 7.08 – 6.98 (m, 7H), 5.19 (s, 4H), 5.15 (s, 4H); ^{13}C NMR (75 MHz, DMSO) δ 156.0, 154.1, 146.9,

144.8, 136.7, 136.2, 136.1, 129.6, 128.4, 128.4, 128.1, 127.9, 127.9, 127.5, 127.4, 124.8, 123.9, 123.5, 123.2, 67.4, 66.5; HRMS calcd. for $C_{50}H_{47}N_6O_8$ $[M+NH_4]^+$ m/z 859.3455, found 859.3400.

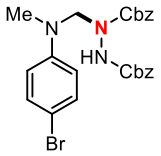
dibenzyl 3-(p-tolyl)triazane-1,2-dicarboxylate (34)



The title compound was prepared according to the general procedure described above by the reaction between *p*-toluidine and dibenzyl azodicarboxylate and purified by 30 % Et_2O in cyclohexane as a yellow solid (159 mg, 78%).

M.p. 124 - 126 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.39 (s, NH), 8.29 (s, NH), 7.36 - 7.28 (m, 10H), 6.96 (d, J = 8.2 Hz, 2H), 6.77 (d, J = 8.1 Hz, 2H), 5.14 (s, 2H), 5.13 (s, 2H), 2.19 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.6, 144.7, 136.2, 136.1, 129.1, 128.4, 128.3, 128.1, 127.9, 127.9, 127.2, 112.7, 67.5, 66.3, 20.1; HRMS calcd. for $C_{23}H_{24}N_3O_4$ $[M+H]^+$ m/z 406.1767, found 406.1757.

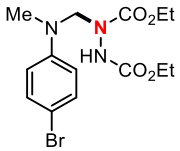
dibenzyl 1-(((4-bromophenyl)(methyl)amino)methyl)hydrazine-1,2-dicarboxylate (35)



The title compound was prepared according to the general procedure described above by the reaction between 4-bromo-N, N-dimethylaniline and dibenzyl azodicarboxylate and purified by 20 % Et_2O in cyclohexane as a white solid (215 mg, 86%).

M.p. 118 - 120 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.72 (s, NH), 7.32 (m, 10H), 7.26 (br, 2H), 6.74 (br, 2H), 5.23 - 4.90 (m, 6H), 2.90 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.5, 147.2, 136.3, 136.1, 131.2, 128.3, 127.9, 127.7, 127.4, 127.2, 114.8, 108.4, 67.0, 66.1, 65.3, 37.7; HRMS calcd. for $C_{24}H_{25}N_3O_4Br$ $[M+H]^+$ m/z 500.1008, found 500.1000.

diethyl 1-(((4-bromophenyl)(methyl)amino)methyl)hydrazine-1,2-dicarboxylate (36)

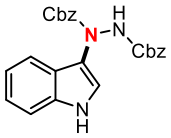


The title compound was prepared according to the general procedure described above by the

reaction between 4-bromo-N, N-dimethylaniline and diethyl azodicarboxylate and purified by 20 % Et_2O in cyclohexane as a white solid (166 mg, 89%).

M.p. 100 - 102 °C; ^{1}H NMR (300 MHz, DMSO) δ 9.41 (s, NH), 7.30 (d, *J* = 8.8 Hz, 2H), 6.76 (d, *J* = 8.7 Hz, 2H), 5.20 - 4.81 (m, 2H), 4.10 - 3.97 (m, 4H), 2.91 (s, 3H), 1.17 - 0.99 (m, 6H); ^{13}C NMR (75 MHz, DMSO) δ 155.5, 147.2, 131.2, 114.8, 108.4, 65.3, 61.7, 60.7, 37.7, 14.4, 14.4; HRMS calcd. for $C_{14}H_{21}N_3O_4Br$ $[M+H]^+$ m/z 374.0706, found 374.0715.

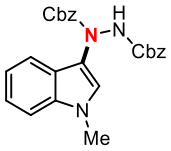
dibenzyl 1-(1H-indol-3-yl)hydrazine-1,2-dicarboxylate (37)



The title compound was prepared according to the general procedure described above by the reaction between indole and dibenzyl azodicarboxylate and purified by 50 % Et_2O in cyclohexane as a light-yellow solid (189 mg, 91%).

M.p. 136 - 138 °C; ^{1}H NMR (300 MHz, DMSO) δ 11.14 (s, NH), 10.30 (d, *J* = 31.7 Hz, NH), 7.59 (d, *J* = 7.9 Hz, 1H), 7.37 (m, 12H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.02 (t, *J* = 7.4 Hz, 1H), 5.12 (m, 4H); ^{13}C NMR (75 MHz, DMSO) δ 155.9, 155.6, 136.4, 134.2, 128.4, 128.3, 128.0, 127.9, 127.6, 127.3, 123.1, 121.9, 121.5, 119.1, 118.3, 111.8, 67.1, 66.2; HRMS calcd. for $C_{24}H_{21}N_3O_4$ $[M+Na]^+$ m/z 438.1430, found 438.1428.

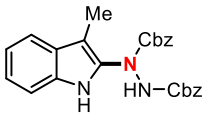
dibenzyl 1-(1-methyl-1H-indol-3-yl)hydrazine-1,2-dicarboxylate (38)



The title compound was prepared according to the general procedure described above by the reaction between 1-methyl-1H-indole and dibenzyl azodicarboxylate and purified by 30 % Et_2O in cyclohexane as a white solid (205 mg, 96%).

M.p. 122 - 124 °C; ^{1}H NMR (300 MHz, DMSO) δ 10.34 (d, *J* = 34.9 Hz, NH), 7.60 (s, 1H), 7.43 – 7.16 (m, 13H), 7.06 (t, *J* = 5.7 Hz, 1H), 5.13 (m, 4H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 155.9, 155.5, 136.4, 134.7, 128.4, 128.3, 128.0, 127.8, 127.7, 127.3, 126.1, 125.6, 121.6, 119.3, 118.5, 117.3, 109.9, 67.2, 66.2, 32.5; HRMS calcd. for $C_{25}H_{24}N_3O_4$ $[M+H]^+$ m/z 430.1767, found 430.1772.

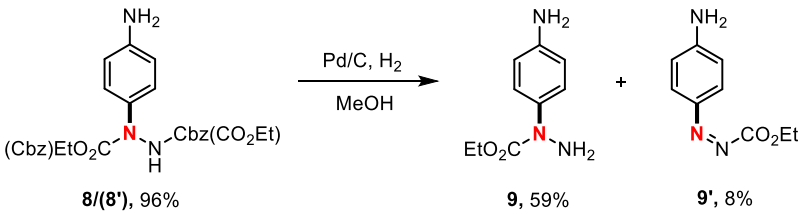
dibenzyl 1-(3-methyl-1H-indol-2-yl)hydrazine-1,2-dicarboxylate (39)



The title compound was prepared according to the general procedure described above by the reaction between 3-methyl-1H-indole and dibenzyl azodicarboxylate and purified by 50 % Et_2O in cyclohexane as a yellow oil (176 mg, 82%).

^{1}H NMR (300 MHz, DMSO) δ 10.74 (s, NH), 10.36 (d, *J* = 31.1 Hz, NH), 7.46 – 7.33 (m, 12H), 7.11 (t, *J* = 7.5 Hz, 1H), 6.99 (t, *J* = 7.4 Hz, 1H), 5.16 (m, 4H), 2.13 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 156.1, 154.6, 136.2, 124.0, 133.4, 131.2, 128.4, 128.1, 128.1, 126.0, 127.7, 127.4, 126.8, 121.9, 118.6, 111.6, 104.4, 67.6, 66.5, 7.9; HRMS calcd. for $C_{25}H_{24}N_3O_4$ $[M+H]^+$ m/z 430.1767, found 430.1775.

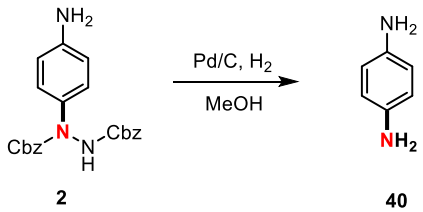
The Cbz-Deprotection



The mixture of compounds **8** and **8'** (158 mg, 0.48 mmol) and Pd/C (5 mg) were taken in a dried tube with a magnetic stir bar under hydrogen. Then MeOH (4 mL) was added with a syringe and the resulting mixture was vigorously stirred for 5 h at room temperature. After completion of the reaction (TLC monitored), it was diluted with CH_2Cl_2 and filtered through celite. The filtrate was evaporated to dryness and the crude reaction mixture was loaded directly on to silica gel column and purified rapidly by column chromatography on silica gel using cyclohexane - ether (2:1 to pure ether) as the eluent to provide **9** as a yellow oil (55 mg, 59%) and **9'** as a yellow solid (8 mg, 8%).

9: ^{1}H NMR (300 MHz, DMSO) δ 6.99 (d, *J* = 8.4 Hz, 2H), 6.49 (d, *J* = 8.6 Hz, 2H), 4.94 (s, 4H), 4.05 (q, *J* = 7.1 Hz, 2H), 1.16 (t, *J* = 7.1 Hz, 4H); ^{13}C NMR (75 MHz, DMSO) δ 156.0, 146.2, 125.5, 114.9, 113.3, 61.1, 14.6; HRMS calcd. for $C_9H_{13}N_3O_2Na$ $[M+Na]^+$ m/z 218.0905, found 218.0902.

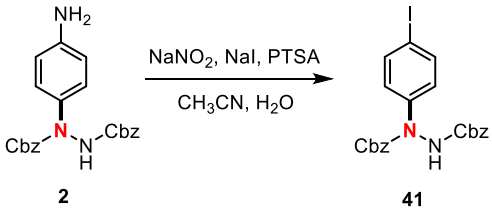
9': ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.7 Hz, 2H), 6.69 (d, *J* = 8.8 Hz, 2H), 4.52 – 4.41 (m, 4H), 1.45 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3, 153.1, 144.7, 127.6, 114.4, 64.0, 14.4; HRMS calcd. for $C_9H_{12}N_3O_2$ $[M+H]^+$ m/z 194.0930, found 194.0925.



The compound **3aa** (195.5 mg, 0.5 mmol) and Pd/C (5 mg) were taken in a dried tube with a magnetic stir bar under hydrogen. Then MeOH (4 mL) was added with a syringe and the resulting mixture was vigorously stirred for 5 h at room temperature. After completion of the reaction (TLC monitored), it was diluted with CH_2Cl_2 and filtered through celite. The filtrate was evaporated to dryness and the crude reaction mixture was loaded directly on to silica gel column and purified rapidly by column chromatography on silica gel using pure ether as the eluent to provide **40** as a black solid (38 mg, 70%).

M.p. 138 - 140 °C; ^{1}H NMR (300 MHz, DMSO) δ 6.36 (s, 4H), 4.18 (s, 4H); ^{13}C NMR (75 MHz, DMSO) δ 138.9, 115.4.

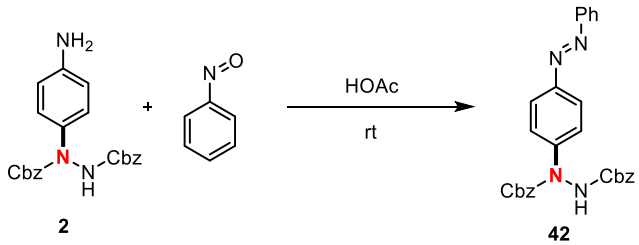
The Sandmeyer Reaction



To a solution of *p*-TsOH·H_2O (286.5 mg, 1.5 mmol) in MeCN (6 mL) was added **2** (195.5 mg, 0.5 mmol). The resulting suspension of amine salt was cooled to 5-10 °C and to this was added, gradually, a solution of $NaNO_2$ (69 mg, 1 mmol) and NaI (187.5 mg, 1.25 mmol) in H_2O (0.3 mL). The reaction mixture was stirred for 10 min then allowed to come to 20 °C and stirred for 30 min. To the reaction mixture was then added H_2O (10 mL), $NaHCO_3$ (1 M; until pH = 9-10) and $Na_2S_2O_3$ (2 M, 1 mL). The crude product was extracted EtOAc and purified by column chromatography on silica gel using cyclohexane - ethyl acetate (10:1) as the eluent to provide **41** as a white solid (184 mg, 73%).

M.p. 152 - 154 °C; ^{1}H NMR (300 MHz, DMSO) δ 10.36 (s, NH), 7.72 (d, J = 8.5 Hz, 2H), 7.35 (m, 10H), 7.23 (d, J = 8.3 Hz, 2H), 5.19 (s, 2H), 5.14 (s, 2H); ^{13}C NMR (75 MHz, DMSO) δ 155.9, 153.8, 141.7, 137.4, 136.1, 135.8, 128.6, 128.4, 128.1, 128.1, 127.9, 127.7, 127.6, 127.3, 124.9, 67.7, 66.6; HRMS calcd. for $C_{22}H_{19}N_2O_4Na$ $[M+Na]^+$ m/z 525.0287, found 525.0292.

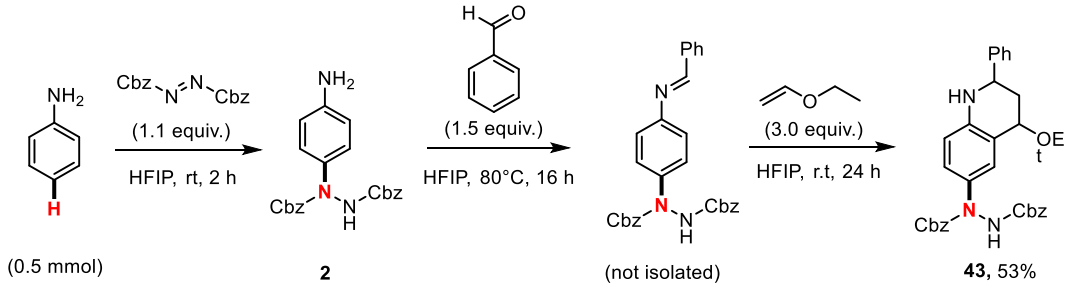
Synthesis of Azo Aromatic Compound



To a solution of nitrosobenzene (80.25, 0.75mmol) in HOAc (2 mL) was added **2** (195.5 mg, 0.5 mmol). the reaction mixture was stirred at room temperature for one day. After completion of the reaction (TLC monitored), the reaction mixture was evaporated under reduce pressure to get crude product. Then the crude product was purified by column chromatography on silica gel using cyclohexane - ethyl acetate (5:1) as the eluent afforded **42** as a yellow solid (218 mg, 91%).

M.p. 142 - 144 ºC; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.48 (s, NH), 7.91 (m, 4H), 7.67 - 7.54 (m, 4H), 7.38 - 7.28 (m, 10H), 6.87 (t, J = 7.1 Hz, 1H), 5.25 (s, 2H), 5.17 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.0, 153.7, 151.9, 148.9, 144.3, 136.1, 135.8, 131.5, 129.5, 129.0, 128.5, 128.1, 127.9, 127.6, 123.1, 122.5, 120.8, 119.7, 67.9, 66.7; HRMS calcd. for $C_{28}H_{25}N_4O_4$ $[M+H]^+$ m/z 481.1876, found 481.1867.

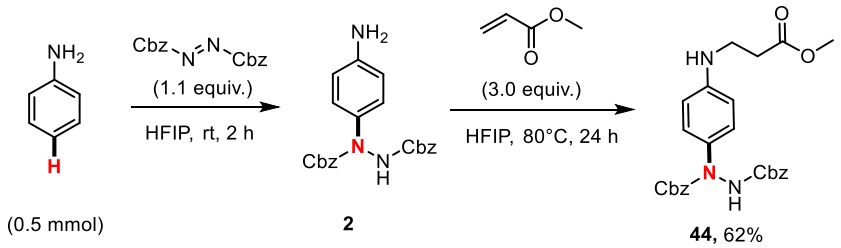
The [4+2] Aza Diels-Alder Cycloaddition of One-Pot Synthesis of Tetrahydroquinoline



To a stirred solution of anline (46.5 mg, 0.5 mmol) in HFIP (2 mL) was added dibenzyl azodicarboxylate (164.5 mg, 0.55 mmol). The reaction mixture was stirred at room temperature for 2 h. Then added benzaldehyde (79.5 mg, 0.75mmol) and the mixture was stirred at 80 ºC for 16 h, after removed the heating, cooled down to room temperature, added ethyl vinyl ether (108 mg, 1.5 mmol) and the mixture was stirred for one day. After, the reaction mixture was evaporated under reduce pressure to get crude product. Then the crude product was purified by column chromatography on silica gel using cyclohexane - ethyl acetate (5:1) as the eluent afforded **43** as a light-yellow solid (145 mg, 53%).

M.p. 140 - 142 ºC; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.13 (s, NH), 7.45 - 7.23 (m, 17H), 6.96 (br, 1H), 6.56 (d, J = 8.5 Hz, 1H), 5.14 (s, 2H), 5.12 (s, 2H), 4.72 - 4. 67 (m, 1H), 4.52 (d, J = 9.1 Hz, 1H), 3.64 - 3.44 (m, 2H), 2.32 (d, J = 10.7 Hz, 1H), 1.77 (q, J = 11.2 Hz, 1H), 1.14 - 1.04 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.8, 154.7, 143.9, 136.4, 130.8, 128.4, 128.3, 128.0, 127.8, 127.3, 126.6, 121.5, 113.3, 73.0, 67.0, 66.2, 62.9, 54.3, 36.4, 15.5; HRMS calcd. for $C_{33}H_{34}N_3O_5$ $[M+H]^+$ m/z 552.2498, found 552.2507.

Michael Addition with Methyl Acrylate



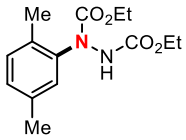
To a stirred solution of anline (46.5 mg, 0.5 mmol) in HFIP (2 mL) was added dibenzyl azodicarboxylate (164.5 mg, 0.55 mmol). The reaction mixture was stirred at room temperature for 2 h. Then added methyl acrylate (1.5 mmol) and the mixture was stirred at 80 ºC for 24 h, after removed the heating, cooled down to room temperature, the reaction mixture was evaporated under reduce pressure to get crude product. Then the crude product was purified by column chromatography on silica gel using cyclohexane - ethyl acetate (5:1) as the eluent afforded **44** as a light-yellow solid (147 mg, 62%).

M.p. 108 - 110 ºC; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.14 (s, NH), 7.34 (m, 10H), 7.08 (d, J = 8.0 Hz, 2H), 6.53 (d, J = 8.4 Hz, 2H), 5.79 (s, NH), 5.13 (s, 2H), 5.10 (s, 2H), 3.60 (s, 3H), 3.30 - 3.24 (m, 2H), 2.57 (t, J = 6.7 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.1, 155.9, 154.7, 136.3, 128.4, 128.4, 128.1, 127.9, 127.3, 125.8, 113.3, 111.6, 67.0, 66.2, 51.4, 33.4, 31.6; HRMS calcd. for $C_{26}H_{28}N_3O_6$ $[M+H]^+$ m/z 478.1978, found 478.1988.

General Procedure for Direct Amination of Simple Arenes with Azodicarboxylates

To a stirred solution of arenes (1.5 mmol, 3 equiv.) and diethyl azodicarboxylates (0.5 mmol, 1 equiv.) in HFIP (2 mL) was added $KHSO_4$ (6.8 mg, 0.05 mmol, 0.1 equiv.) or TfOH (4 μL, 0.05 mmol, 0.1 equiv.) under air. The reaction mixture was stirred at rt for 0.5 ~ 16 h. After that, the reaction mixture was evaporated under reduce pressure and the crude product was purified by column chromatography on silica gel using cyclohexane: ethyl acetate as the eluent to afford aryl hydrazides.

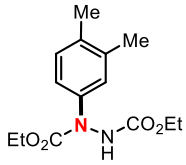
diethyl 1-(2,5-dimethylphenyl)hydrazine-1,2-dicarboxylate (46)



The title compound was prepared between *p*-xylene (159.0 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol) and $KHSO_4$ (6.8 mg, 0.05 mmol, 0.1 equiv) in HFIP (2 ml) at rt for 2 h and purified by 25 % EtOAc in cyclohexane as a white solid (128 mg, 91%).

M.p. 114 - 116 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.98 (d, J = 11.3 Hz, 1H), 7.17 (s, 1H), 7.11 (d, J = 7.7 Hz, 1H), 7.02 (d, J = 7.7 Hz, 1H), 4.11 – 4.04 (m, 4H), 2.25 (s, 3H), 2.20 (s, 3H), 1.21 – 1.10 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.1, 154.5, 140.7, 135.6, 132.1, 130.2, 128.4, 127.4, 61.8, 60.8, 20.4, 16.9, 14.4; HRMS calcd. for $C_{14}H_{21}N_2O_4$ $[M+H]^+$ m/z 281.1501, found 281.1497.

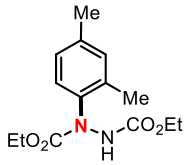
diethyl 1-(3,4-dimethylphenyl)hydrazine-1,2-dicarboxylate (47)



The title compound was prepared between *o*-xylene (159.0 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol) and $KHSO_4$ (6.8 mg, 0.05 mmol, 0.1 equiv) in HFIP (2 ml) at rt for 16 h and purified by 25 % EtOAc in cyclohexane as a white solid (132 mg, 94%).

M.p. 68 - 70 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.95 (s, 1H), 7.12 – 7.04 (m, 3H), 4.15 – 4.05 (m, 4H), 2.19 (s, 3H), 2.19 (s, 3H), 1.22 – 1.15 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.9, 154.3, 139.8, 136.2, 133.8, 129.4, 124.7, 121.2, 61.9, 60.9, 19.5, 18.8, 14.5, 14.4; HRMS calcd. for $C_{14}H_{20}N_2O_4Na$ $[M+Na]^+$ m/z 303.1321, found 303.1314.

diethyl 1-(2,4-dimethylphenyl)hydrazine-1,2-dicarboxylate (48)

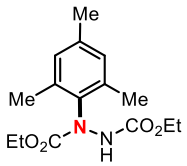


The title compound was prepared between *m*-xylene (159.0 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol) and $KHSO_4$ (6.8 mg, 0.05 mmol, 0.1 equiv.) in HFIP (2 ml) at rt for 2 h and purified

by 25 % EtOAc in cyclohexane as a white solid (130 mg, 93%).

M.p. 96 - 98 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.97 (d, J = 14.7 Hz, 1H), 7.23 (d, J = 7.9 Hz, 1H), 7.03 – 6.98 (m, 2H), 4.10 - 4.03 (m, 4H), 2.25 (s, 3H), 2.20 (2, 3H), 1.20 – 1.08 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.1, 154.6, 138.4, 137.1, 135.0, 130.9, 128.3, 127.0, 61.8, 60.8, 20.5, 17.2, 14.4; HRMS calcd. for $C_{14}H_{20}N_2O_4Na$ $[M+Na]^+$ m/z 303.1321, found 303.1320.

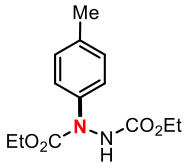
diethyl 1-mesitylhydrazine-1,2-dicarboxylate (49)



The title compound was prepared between mesitylene (180.0 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol) and $KHSO_4$ (6.8 mg, 0.05 mmol, 0.1 equiv.) in HFIP (2 ml) at rt for 2 h and purified by 25 % EtOAc in cyclohexane as a white solid (140 mg, 95%).

M.p. 162 - 164 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.79 (d, J = 18.3 Hz, 1H), 6.85 (s, 2H), 4.15 – 4.02 (m, 4H), 2.23 (s, 6H), 2.21 (s, 3H), 1.24 – 1.05 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.2, 155.9, 154.8, 154.2, 136.9, 136.9, 136.5, 136.1, 135.7, 128.9, 61.9, 60.7, 20.4, 18.0, 14.5; HRMS calcd. for $C_{15}H_{22}N_2O_4Na$ $[M+Na]^+$ m/z 317.1477, found 317.1501.

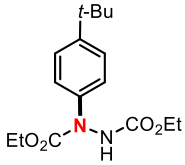
diethyl 1-(p-tolyl)hydrazine-1,2-dicarboxylate (50)



The title compound was prepared between toluene (138.0 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol) and $KHSO_4$ (6.8 mg, 0.05 mmol, 0.1 equiv.) in HFIP (2 ml) at rt for 2 h and purified by 25 % EtOAc in cyclohexane as a colorless oil (115 mg, 86%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.97 (s, 1H), 7.24 (d, J = 8.3 Hz, 2H), 7.15 (d, J = 8.1 Hz, 2H), 4.16 – 4.05 (m, 4H), 2.28 (s, 3H), 1.22 – 1.16 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.9, 154.3, 139.6, 135.0, 128.9, 123.6, 62.0, 60.9, 20.4, 14.4, 14.3; HRMS calcd. for $C_{13}H_{19}N_2O_4$ $[M+H]^+$ m/z 267.1345, found 267.1340.

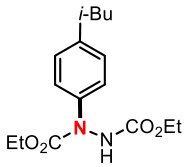
diethyl 1-(4-(tert-butyl)phenyl)hydrazine-1,2-dicarboxylate (51)



The title compound was prepared between *tert*-butylbenzene (201.0 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol) and $KHSO_4$ (6.8 mg, 0.05 mmol, 0.1 equiv.) in HFIP (2 ml) at rt for 2 h and purified by 25 % EtOAc in cyclohexane as a colorless oil (130 mg, 84%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.99 (s, 1H), 7.37 (d, J = 8.5 Hz, 2H), 7.27 (d, J = 8.5 Hz, 2H), 4.17 – 4.05 (m, 4H), 1.27 (s, 9H), 1.22 – 1.16 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.9, 154.3, 148.0, 139.5, 125.2, 123.1, 62.0, 60.9, 34.1, 31.1, 14.5, 14.3; HRMS calcd. for $C_{16}H_{24}N_2O_4Na$ $[M+Na]^+$ m/z 331.1634, found 331.1626.

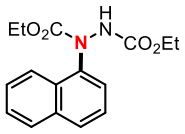
diethyl 1-(4-isobutylphenyl)hydrazine-1,2-dicarboxylate (52)



The title compound was prepared between *iso*-butylbenzene (201.0 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol) and $KHSO_4$ (6.8 mg, 0.05 mmol, 0.1 equiv.) in HFIP (2 ml) at rt for 2 h and purified by 25 % EtOAc in cyclohexane as a colorless oil (115 mg, 75%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.98 (s, 1H), 7.25 (d, J = 8.2 Hz, 2H), 7.13 (d, J = 8.1 Hz, 2H), 4.16 – 4.06 (m, 4H), 2.42 (d, J = 7.1 Hz, 2H), 1.86 – 1.77 (m, 1H), 1.22 – 1.13 (m, 6H), 0.87 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.0, 154.3, 139.8, 138.6, 128.9, 123.2, 62.0, 60.9, 44.0, 29.6, 22.1, 14.5, 14.3; HRMS calcd. for $C_{16}H_{24}N_2O_4Na$ $[M+Na]^+$ m/z 331.1634, found 331.1630.

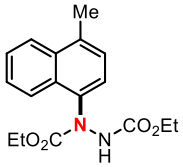
diethyl 1-(naphthalen-1-yl)hydrazine-1,2-dicarboxylate (53)



The title compound was prepared between naphthalene (192.0 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol) and $KHSO_4$ (6.8 mg, 0.05 mmol, 0.1 equiv.) in HFIP (2 ml) at rt for 2 h and purified by 25 % EtOAc in cyclohexane as a white solid (140 mg, 93%).

M.p. 148 - 150 ºC; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.22 (s, 1H), 8.10 (bs, 1H), 7.98 – 7.91 (m, 2H), 7.63 – 7.52 (m, 4H), 4.12 – 4.05 (m, 4H), 1.20 – 0.98 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.3, 155.2, 138.3, 133.9, 129.7, 128.3, 128.0, 126.5, 126.3, 125.7, 125.4, 123.2, 62.1, 61.0, 14.5, 14.4; HRMS calcd. for $C_{16}H_{19}N_2O_4$ $[M+H]^+$ m/z 303.1345, found 303.1351.

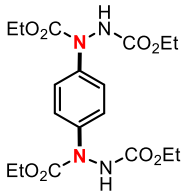
diethyl 1-(1-methylnaphthalen-2-yl)hydrazine-1,2-dicarboxylate (54)



The title compound was prepared between 1-methylnaphthalene (213.0 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol) and $KHSO_4$ (6.8 mg, 0.05 mmol, 0.1 equiv.) in HFIP (2 ml) at rt for 2 h and purified by 25 % EtOAc in cyclohexane as a white solid (150 mg, 95%).

M.p. 156 - 158 ºC; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.17 (s, 1H), 8.13 (bs, 1H), 8.05 – 8.05 (m, 1H), 7.60 – 7.52 (m, 3H), 7.38 (d, J = 7.5 Hz, 1H), 4.12 – 4.05 (m, 4H), 2.65 (s, 3H), 1.20 – 0.98 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.2, 155.3, 136.7, 134.7, 132.6, 129.7, 126.1, 125.0, 124.4, 123.7, 61.9, 60.9, 19.0, 14.4, 14.4; HRMS calcd. for $C_{17}H_{21}N_2O_4$ $[M+H]^+$ m/z 317.1501, found 317.1496.

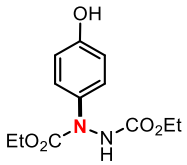
tetraethyl 1,1'-(1,4-phenylene)bis(hydrazine-1,2-dicarboxylate) (55)



The title compound was prepared between benzene (117.0 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol) and $KHSO_4$ (6.8 mg, 0.05 mmol, 0.1 equiv.) in HFIP (2 mL) at rt for 16 h and purified by 25 % EtOAc in cyclohexane as a white solid (95 mg, 89%).

M.p. 182 - 184 ºC; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.03 (s, 1H), 7.33 (s, 2H), 4.18 – 4.06 (m, 4H), 1.23 – 1.14 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.9, 154.2, 139.4, 123.5, 62.2, 61.1, 14.4, 14.3; HRMS calcd. for $C_{18}H_{30}N_5O_8$ $[M+NH_4]^+$ m/z 444.2094, found 444.2086.

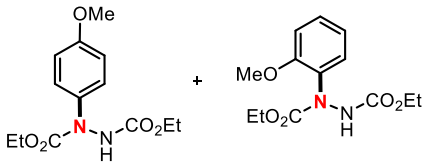
diethyl 1-(4-hydroxyphenyl)hydrazine-1,2-dicarboxylate (56)



The title compound was prepared between phenol (141.0 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol) and $KHSO_4$ (6.8 mg, 0.05 mmol, 0.1 equiv.) in HFIP (2 ml) at rt for 0.5 and purified by 50 % EtOAc in cyclohexane as a white solid (110 mg, 82%).

M.p. 148 - 150 ºC; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.91 (s, 1H), 9.50 (s, 1H), 7.13 (d, J = 8.4 Hz, 2H), 6.72 (d, J = 8.7 Hz, 2H), 4.12 – 4.03 (m, 4H), 1.20 – 1.13 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.0, 155.8, 154.7, 133.7, 126.0, 115.0, 61.9, 60.9, 14.5, 14.4; HRMS calcd. for $C_{12}H_{16}N_2O_5Na$ $[M+Na]^+$ m/z 291.0957, found 291.0954.

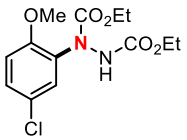
diethyl 1-(4-methoxyphenyl)hydrazine-1,2-dicarboxylate and diethyl 1-(2-methoxyphenyl)hydrazine-1,2-dicarboxylate (4.9: 1) (57)



The title compound was prepared between anisol (162.0 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol) and $KHSO_4$ (6.8 mg, 0.05 mmol, 0.1 equiv.) in HFIP (2 ml) at rt for 10 min and purified by 30 % EtOAc in cyclohexane as a colorless oil (135 mg, 96%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.94 (s, 0.84 × 1H), 9.57 (s, 0.16 × 1H), 7.25 (d, J = 8.7 Hz, 2H), 7.05 (d, J = 8.2 Hz, 0.16 × 2H), 6.91 (d, J = 8.8 Hz, 0.84 × 1H), 4.14 – 4.04 (m, 4H), 3.77 (s, 0.16 × 3H), 3.74 (s, 0.84 × 3H), 1.21 – 1.14 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.3, 155.9, 154.5, 135.1, 128.9, 128.0, 125.7, 120.2, 113.7, 112.2, 61.9, 61.7, 60.9, 60.8, 55.5, 55.3, 14.4, 14.4; HRMS calcd. for $C_{13}H_{19}N_2O_5$ $[M+H]^+$ m/z 283.1294, found 283.1289.

diethyl 1-(5-chloro-2-methoxyphenyl)hydrazine-1,2-dicarboxylate (58)

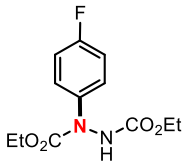


The title compound was prepared between 4-chloroanisole (214.5 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol) and $KHSO_4$ (6.8 mg, 0.05 mmol, 0.1 equiv.) in HFIP (2 ml) at rt for 10 min and purified by using 30 % EtOAc in cyclohexane as a white solid (134 mg, 85%).

M.p. 110 - 112 ºC; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.98 (s, 1H), 7.34 (bs, 2H), 7.11 (d, J =

8.1 Hz, 1H), 4.09 – 4.07 (m, 4H), 3.79 (s, 3H), 1.20 – 1.13 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.3, 154.4, 153.4, 131.6, 128.6, 127.5, 123.2, 113.9, 62.0, 61.0, 56.0, 14.4, 14.3; HRMS calcd. for $C_{13}H_{17}N_2O_5NaCl$ $[M+Na]^+$ m/z 339.0724, found 339.0712.

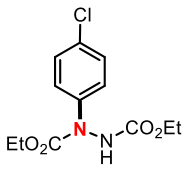
diethyl 1-(4-fluorophenyl)hydrazine-1,2-dicarboxylate (59)



The title compound was prepared between fluorobenzene (144.0 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol) and TfOH (4 µL, 0.05 mmol, 0.1 equiv.) in HFIP (2 ml) at rt for 5 h and purified by 25 % EtOAc in cyclohexane as a colorless oil (112 mg, 83%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.03 (s, 1H), 7.40 – 7.35 (m, 2H), 7.23 – 7.16 (m, 2H), 4.17 – 4.06 (m, 4H), 1.22 – 1.16 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.2 (J = 241.5 Hz), 156.0, 154.2, 138.4, 125.8, 115.3 (J = 23.25 Hz), 62.2, 61.1, 14.4, 14.3; HRMS calcd. for $C_{12}H_{16}N_2O_4F$ $[M+H]^+$ m/z 271.1094, found 271.1098.

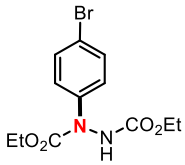
diethyl 1-(4-chlorophenyl)hydrazine-1,2-dicarboxylate (60)



The title compound was prepared between chlorobenzene (168.8 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol) and TfOH (4 µL, 0.05 mmol, 0.1 equiv.) in HFIP (2 ml) at rt for 5 h and purified by 25 % EtOAc in cyclohexane as a white solid (116 mg, 83%).

M.p. 72 - 74 ºC; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.07 (s, 1H), 7.44 – 7.36 (m, 4H), 4.19 – 4.07 (m, 4H), 1.23 – 1.17 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.0, 154.0, 141.0, 129.6, 128.5, 124.6, 62.3, 61.1, 14.4, 14.2; HRMS calcd. for $C_{12}H_{16}N_2O_4Cl$ $[M+H]^+$ m/z 287.0799, found 287.0796.

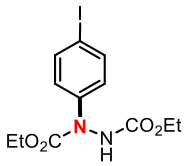
diethyl 1-(4-bromophenyl)hydrazine-1,2-dicarboxylate (61)



The title compound was prepared between bromobenzene (235.5 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol) and TfOH (4 µL, 0.05 mmol, 0.1 equiv.) in HFIP (2 ml) at rt for 5 h and purified by 25 % EtOAc in cyclohexane as a white solid (124 mg, 75%).

M.p. 70 - 72 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.07 (s, 1H), 7.55 (d, J = 8.6 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 4.19 – 4.07 (m, 4H), 1.23 – 1.17 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.9, 153.9, 141.4, 131.4, 124.9, 117.7, 62.4, 61.2, 14.4, 14.3; HRMS calcd. for $C_{12}H_{16}N_2O_4Br$ $[M+H]^+$ m/z 331.0293, found 331.0298.

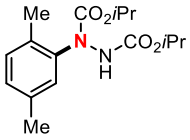
diethyl 1-(4-iodophenyl)hydrazine-1,2-dicarboxylate (62)



The title compound was prepared between iodobenzene (306.0 mg, 1.5 mmol), DEAD (87.0 mg, 0.5 mmol) and TfOH (4 µL, 0.05 mmol, 0.1 equiv.) in HFIP (2 ml) at rt for 5 h and purified by 25 % EtOAc in cyclohexane as a white solid (127 mg, 67%).

M.p. 76 - 78 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.05 (s, 1H), 7.71 (d, J = 8.5 Hz, 2H), 7.19 (d, J = 8.5 Hz, 2H), 4.19 – 4.07 (m, 4H), 1.23 – 1.09 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.9, 153.9, 141.9, 137.3, 125.0, 90.1, 62.3, 61.1, 14.4, 14.2; HRMS calcd. for $C_{12}H_{15}N_2O_4NaI$ $[M+Na]^+$ m/z 400.9974, found 400.9970.

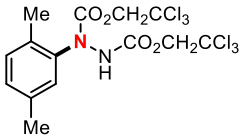
diisopropyl 1-(2,5-dimethylphenyl)hydrazine-1,2-dicarboxylate (63)



The title compound was prepared between *p*-xylene (159.0 mg, 1.5 mmol), diisopropyl azodicarboxylate (101.0 mg, 0.5 mmol) and $KHSO_4$ (6.8 mg, 0.05 mmol, 0.1 equiv.) in HFIP (2 ml) at rt for 2 h and purified by 25 % EtOAc in cyclohexane as a white solid (145 mg, 94%).

M.p. 106 - 108 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.86 (s, 1H), 7.16 (s, 1H), 7.09 (d, J = 7.7 Hz, 1H), 7.01 (d, J = 7.6 Hz, 1H), 4.86 – 4.80 (m, 2H), 2.24 (s, 3H), 2.19 (s, 3H), 1.21 – 1.10 (m, 12H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.8, 154.0 (d, J = 25.5 Hz), 140.8, 135.4, 132.0, 130.1, 128.2, 127.4, 69.4 (d, J = 22.5 Hz), 68.3, 21.8, 20.4, 16.9; HRMS calcd. for $C_{16}H_{24}N_2O_4Na$ $[M+Na]^+$ m/z 331.1634, found 331.1629.

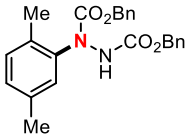
bis(2,2,2-trichloroethyl) 1-(2,5-dimethylphenyl)hydrazine-1,2-dicarboxylate (64)



The title compound was prepared between *p*-xylene (159.0 mg, 1.5 mmol), bis(2,2,2-trichloroethyl) azodicarboxylates (190.0 mg, 0.5 mmol) and $KHSO_4$ (6.8 mg, 0.05 mmol, 0.1 equiv.) in HFIP (2 ml) at rt for 2 h and purified by 25 % EtOAc in cyclohexane as a colorless oil (218 mg, 90%).

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.90 (d, J = 30.6 Hz, 1H), 7.41 – 7.03 (m, 3H), 4.95 (s, 2H), 4.93 (s, 2H), 2.31 – 2.26 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.4, 154.2, 153.3, 153.2, 139.4, 137.9, 137.8, 135.3, 132.4, 131.1, 130.4, 129.2, 129.0, 128.0, 127.4, 127.1, 126.6, 95.5, 95.3, 74.7, 74.0, 74.0, 20.6, 20.4, 17.2, 16.9; HRMS calcd. for $C_{14}H_{14}N_2O_4Na35Cl_537Cl$ $[M+Na]^+$ m/z 508.8953, found 508.8943.

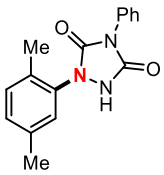
dibenzyl 1-(2,5-dimethylphenyl)hydrazine-1,2-dicarboxylate (65)



The title compound was prepared between *p*-xylene (159.0 mg, 1.5 mmol), dibenzyl azodicarboxylate (149.0 mg, 0.5 mmol) and $KHSO_4$ (6.8 mg, 0.05 mmol, 0.1 equiv.) in HFIP (2 ml) at rt for 0.5 h and purified by 25 % EtOAc in cyclohexane as a white solid (115 mg, 57%).

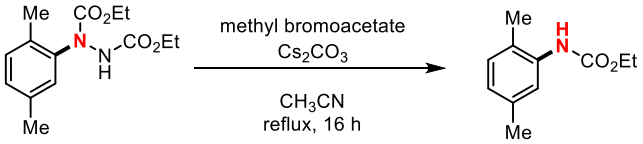
M.p. 110 - 112 ºC; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.26 (d, J = 35.1 Hz, 1H), 7.33 – 7.04 (m, 13H), 5.12 (m, 4H), 2.24 – 2.08 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.0, 154.6, 154.1, 140.5, 136.2, 135.7, 132.1, 130.3, 128.6, 128.5, 128.4, 128.3, 128.1, 127.9, 127.7, 127.4, 127.2, 67.2, 66.3, 20.4, 16.9; HRMS calcd. for $C_{24}H_{24}N_2O_4Na$ $[M+Na]^+$ m/z 427.1634, found 427.1638.

1-(2,5-dimethylphenyl)-4-phenyl-1,2,4-triazolidine-3,5-dione (66)



The title compound was prepared between *p*-xylene (159.0 mg, 1.5 mmol), 4-phenyl-1,2,4-triazoline-3,5-dione (83.0 mg, 0.5 mmol) and $KHSO_4$ (6.8 mg, 0.05 mmol, 0.1 equiv.) in HFIP (2 ml) at rt for 16 h and purified by 25 % EtOAc in cyclohexane as a white solid (88 mg, 81%). M.p. 218 - 220 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.30 (s, 1H), 7.54 – 7.43 (m, 5H), 7.33 (s, 1H), 7.26 (d, J = 7.8 Hz, 1H), 7.17 (d, J = 8.1 Hz, 1H), 2.32 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.2, 150.3, 136.2, 134.9, 132.5, 131.7, 130.8, 129.4, 128.9, 127.9, 126.8, 126.3, 20.3, 17.2; HRMS calcd. for $C_{16}H_{16}N_3O_2$ $[M+H]^+$ m/z 282.1243, found 282.1249.

Deprotection Reaction

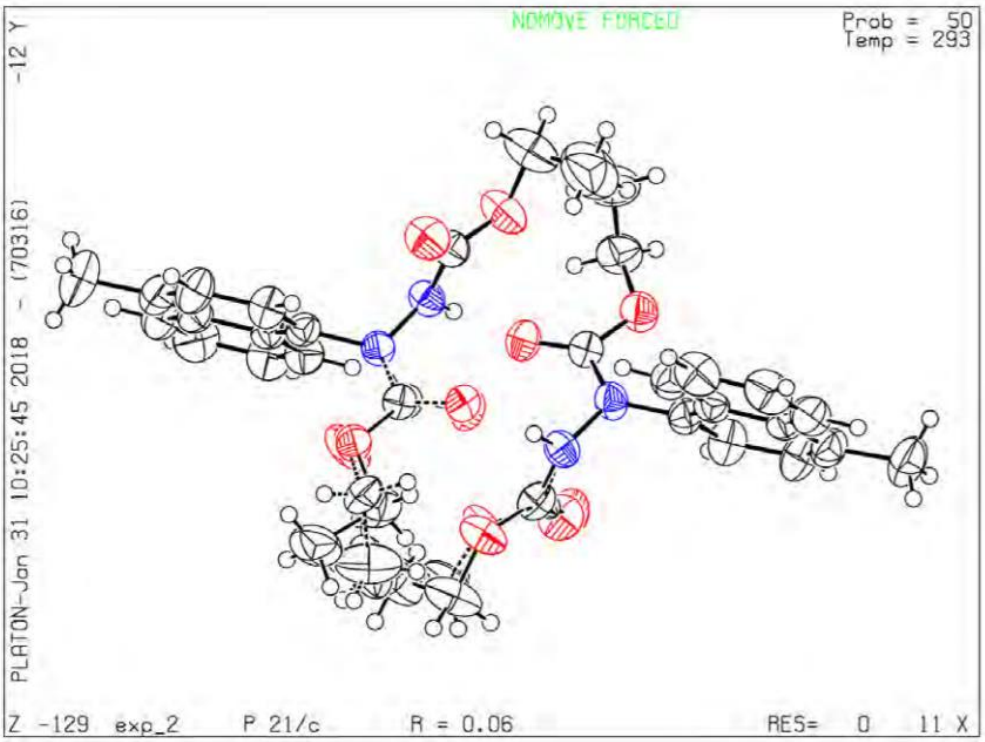


46 (0.5 mmol) **67** (90%)

To a stirred solution of **46** (0.5 mmol, 140 mg) and Cs_2CO_3 (2.0 mmol, 652 mg) in CH_3CN (2 mL) was added methyl bromoacetate (1.0 mmol, 167 mg), and the mixture was refluxed for 16 h. After that, the mixture was quenched with saturated NH_4Cl, and extracted with DCM. The organic layer was washed with brine, dried over Na_2SO_4 and filtration. The mixture was evaporated under reduce pressure and the crude product was purified by column chromatography on silica gel using cyclohexane/ethyl acetate (10: 1) as the eluent to give **67** as white solid (87 mg, 90%).

M.p. 98 - 100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.03 (d, J = 7.6 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), 6.34 (s, 1H), 4.23 (q, J = 7.1 Hz, 2H), 2.32 (s, 3H), 2.21 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.07, 136.74, 135.82, 131.18, 130.28, 124.92, 121.85, 61.33, 21.32, 17.33, 14.71; HRMS calcd. for $C_{11}H_{15}NO_2Na$ $[M+Na]^+$ m/z 216.1000, found 216.1000.

Crystallographic data for 54

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Bond precision:  C-C = 0.0028 A          Wavelength=0.71073

Cell:            a=20.5213(11)    b=10.0563(5)       c=16.5578(9)
                 alpha=90         beta=102.033(5)    gamma=90
Temperature:     293 K

                 Calculated                  Reported
Volume           3341.9(3)                   3341.9(3)
Space group      P 21/c                      P 21/c
Hall group       -P 2ybc                     -P 2ybc
Moiety formula   C17 H20 N2 O4               C17 H20 N2 O4
Sum formula      C17 H20 N2 O4               C17 H20 N2 O4
Mr               316.35                      316.35
Dx,g cm-3        1.258                       1.257
Z                8                           8
Mu (mm-1)        0.090                       0.090
F000             1344.0                      1344.0
F000'            1344.66
h,k,lmax         28,14,23                    28,13,22
Nref             9426                        8604
Tmin,Tmax        0.964,0.987                 0.197,1.000
Tmin'            0.958

Correction method= # Reported T Limits: Tmin=0.197 Tmax=1.000
AbsCorr = MULTI-SCAN

Data completeness= 0.913          Theta(max)= 29.654

R(reflections)= 0.0602( 5729)     wR2(reflections)= 0.1593( 8603)

S = 1.022                  Npar= 514
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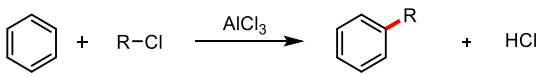
Chapter III

The Friedel–Crafts Alkylation in Fluorinated Alcohols

I. Introduction

The Friedel-Crafts (FC) alkylation reaction is one of the most powerful tools for the carbon-carbon bond formation and has been widely used to generate important classes of building blocks.[1-5] Although the original procedure reported by Charles Friedel and James M. Crafts in 1877 which suffered from drastic reaction conditions and more than stoichiometric amounts of catalysts[6] has subsequently been replaced by milder and more environmentally friendly conditions. The development of greener and/or sustainable methods for this fundamental transformation still has been recognized as one of the central issues in synthetic chemistry community for a long time.

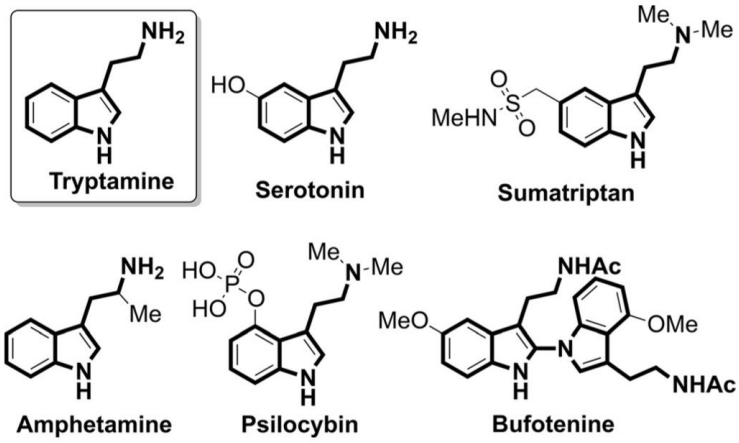


Scheme 1. Classical FC Alkylation

II. FC Alkylation of Indoles and Arenes with *β*-Nitroalkenes

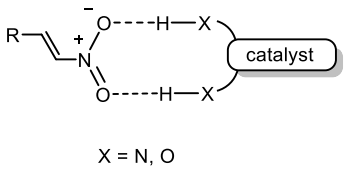
II. 1. Introduction

The FC alkylation reaction between indoles and *β*-nitroalkenes is of particular interest, as this reaction is currently the most widely used approach for the synthesis of tryptamine structure, which as a potent template has been found in many psychoactive compounds, such as serotonin, sumatriptan, amphetamine, psilocybin, bufotenine and so on.



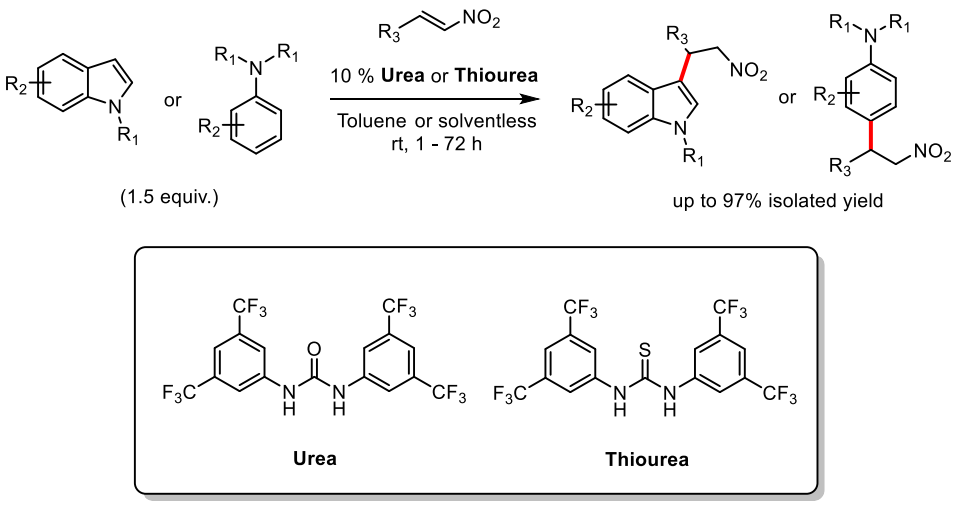
Scheme 2. Tryptamine and Its Valuable Derivatives

Numerous FC alkylation reactions of indoles with *β*-nitroalkenes in the presence of protic acids[7-8] and Lewis acids[9-10] have been developed in the past decades.[11] Among them, the hydrogen-bond-donating (HBD) organo-catalysts which are able to activate *β*-nitroalkenes toward indoles addition via co-operative H-bonding have become a focus of an increasing amount of research in recent years. Many examples of HBD organo-catalytic FC alkylation processes have been successfully reported in the literature.



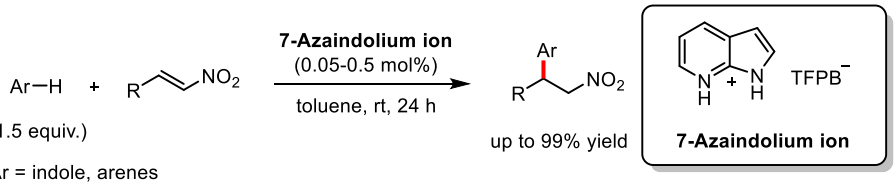
Scheme 3. Model for the H-Bonding Interactions Between Nitroalkene and HBD Organo-catalyst

In 2004, Ricci and co-workers reported that catalytic amounts (10 mol%) of *bis*-arylureas and -thioureas could promote the FC alkylation with nitroolefins of aromatics and heteroaromatic. Michael adducts were obtained in good to excellent yields with high selectivity.[12]



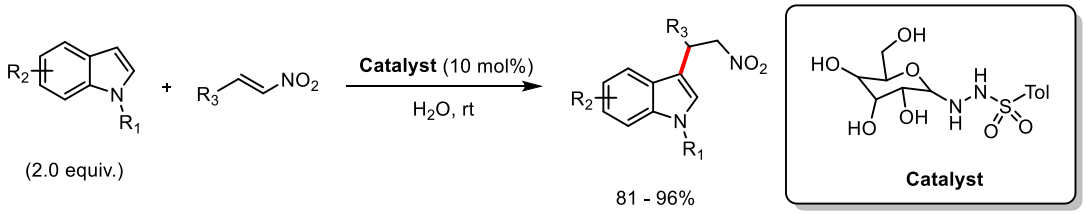
Scheme 4. Urea and Thiourea Catalyzed FC Alkylation of Aromatics and Heteroaromatics

In 2007, Seerla and co-workers reported the 7-azaindolium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (TFPB) catalyzed FC alkylation of indoles and aromatics to nitroalkenes with low catalyst loadings.[13]



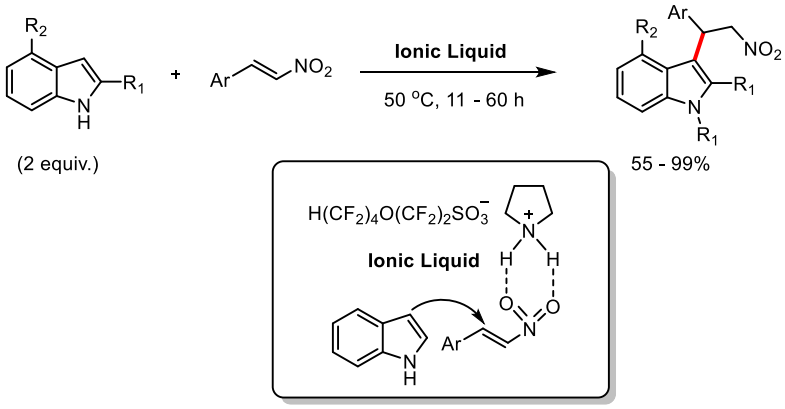
Scheme 5. 2-Aminopyridinium Ions Catalyzed FC Alkylation and Diels-Alder Reaction

In 2008, Cai and co-workers reported tosylhydrazines bearing carbohydrate scaffolds were also effective organo-catalysts for the FC alkylation of indoles with nitroalkenes.[14] These reactions were carried out in water as solvent and the catalyst charge was limited to 10 mol%.



Scheme 6. Tosylhydrazines-Catalyzed FC Alkylation of Indoles with Nitroalkenes

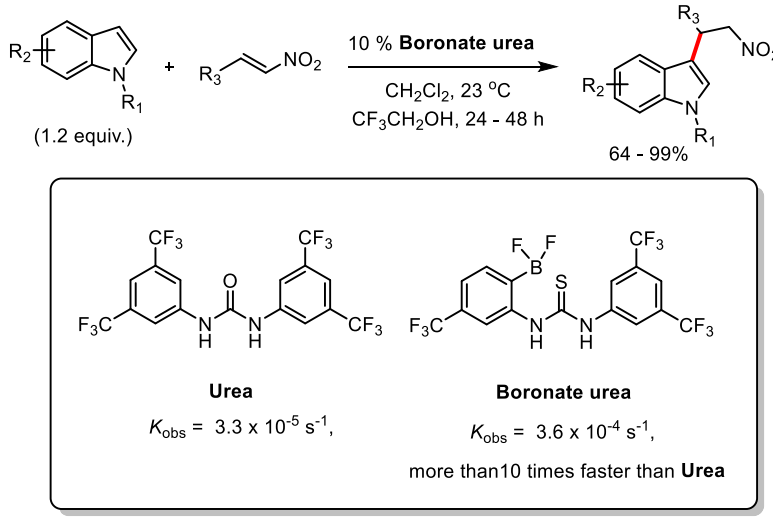
In 2009, Xiao and co-workers reported pyrrolidinium sulfonate ionic liquid can be used as solvent and efficient catalyst for FC alkylation of indoles with nitroalkenes.[15] The reaction proceeded via an ionic liquid-nitroalkene complex involving an intermolecular double hydrogen bond between the protons on the nitrogen of the cation and the oxygens of the nitro group. Meanwhile, the residual ionic liquid can be reused several times with similar performances.



Scheme 7. Ionic Liquid as the Solvent and Catalyst for FC Alkylation

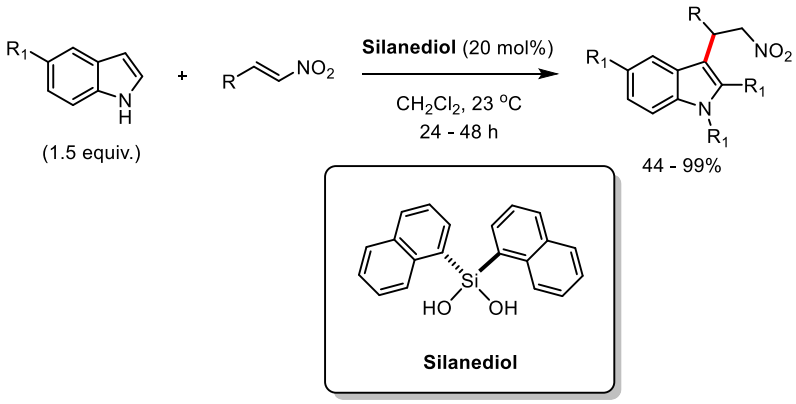
In 2011, Mattson and co-workers reported boronate ureas were introduced as a new class of

noncovalent catalysts for FC alkylation of indoles to β-nitrostyrenes with enhanced activity.[16] Through the intramolecular coordination of the urea functionality to a strategically placed Lewis acid, rate enhancements up to 10 times that of more conventional urea catalysts were observed.



Scheme 8. Boronate Urea Catalyzed FC Alkylation of Indoles with Nitroalkenes

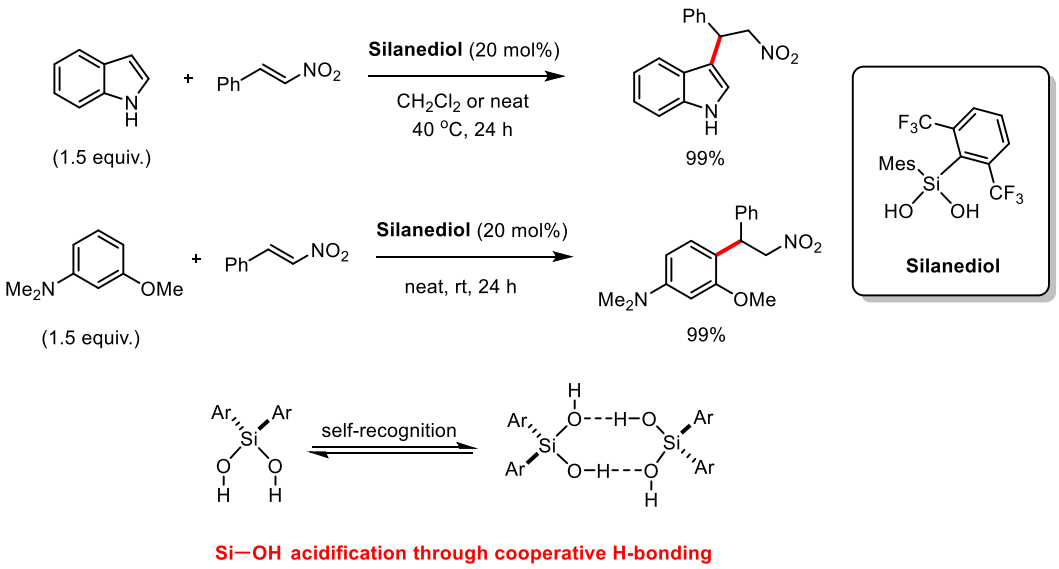
In the same year, silanediols as another new class of HBD catalysts for the activation of nitroalkenes toward nucleophilic attack was introduced by the same group.[17] Excellent yields of products were obtained catalyzed by a stable, storable dinaphthyl-derived silanediol.



Scheme 9. Silanediol Catalyzed FC Alkylation of Indoles with Nitroalkenes

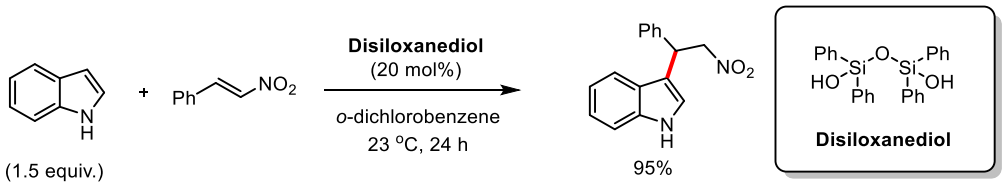
In 2012, Franz and co-workers demonstrated the importance of cooperative H-bonding effects and Si-OH acidification for silanediol catalysis.[18] The self-recognition of the silanediol created a unique dimeric structure with enhanced H-bonding capabilities. They proposed that

the cyclic dimer was the predominant catalytic species capable of activating *β*-nitrostyrene. This assumption was further strengthened by computational and NMR binding studies and by the observation that solvent-free conditions greatly improve the efficiency of the reaction affecting the aggregation state of the catalyst.



Scheme 10. Cooperative Hydrogen-Bonding Effects in Silanediol Catalysis

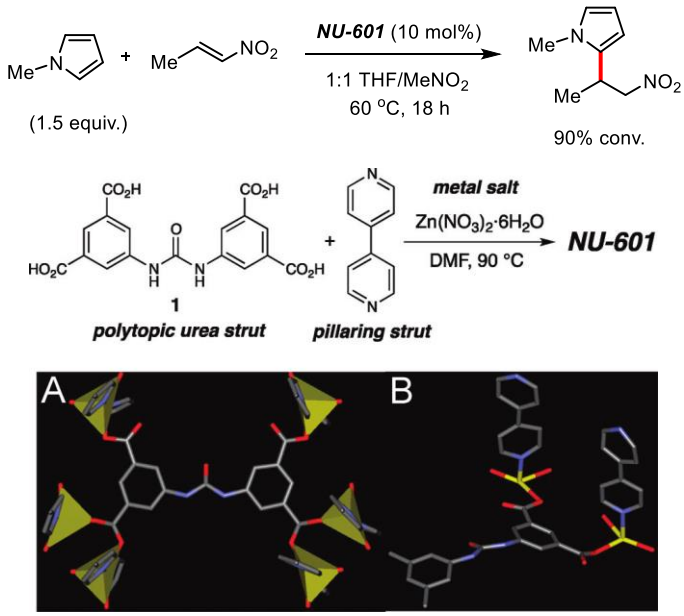
In 2017, the same group reported a detailed kinetic study of 1,3-disiloxanediols as effective hydrogen-bonding catalysts that exhibited enhanced activity relative to silanediols for the FC alkylation of indoles with nitroalkenes.[19] Reaction progress kinetic analysis (RPKA) proposed that a monomer was the active catalyst species for hydrogen-bonding catalysis over all reaction and catalyst self-association did not play a main role in this mode of activation.



Scheme 11. Disiloxanediol Catalyzed FC Alkylation of Indoles with Nitroalkenes

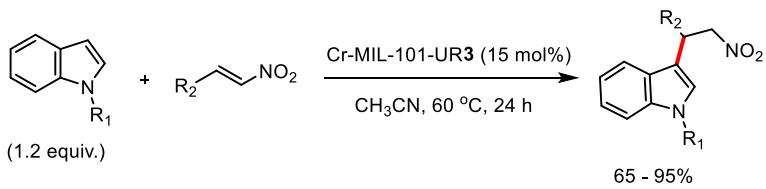
Recently, urea metal-organic frameworks (MOFs) have been introduced as effective heterogeneous catalysts for the FC alkylation of indoles with nitroalkenes. That because the strong hydrogen-bonding nature of the HBD urea-based catalysts can lead to self-association and aggregation, resulting in loss of catalytic competency. Therefore, immobilizing the acidic

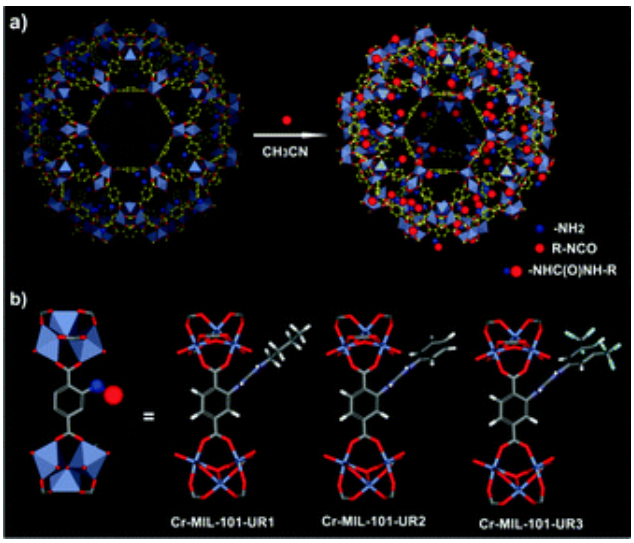
HBD fragments onto the structure of a MOF would prevent this self-association, promote hydrogen-bond-accepting substrate recognition, and improve catalytic activity. In 2012, Scheidt and co-workers reported the first example of specific engineering of successful hydrogen-bonding catalysis into a MOF material.[20] A new urea-containing MOF was synthesized to act as an effective HBD catalyst for FC alkylation between pyrroles and nitroalkenes, whereas a homogeneous urea was much less efficient.



Scheme 12. Urea MOF as Effective HBD Catalysts for FC Alkylation

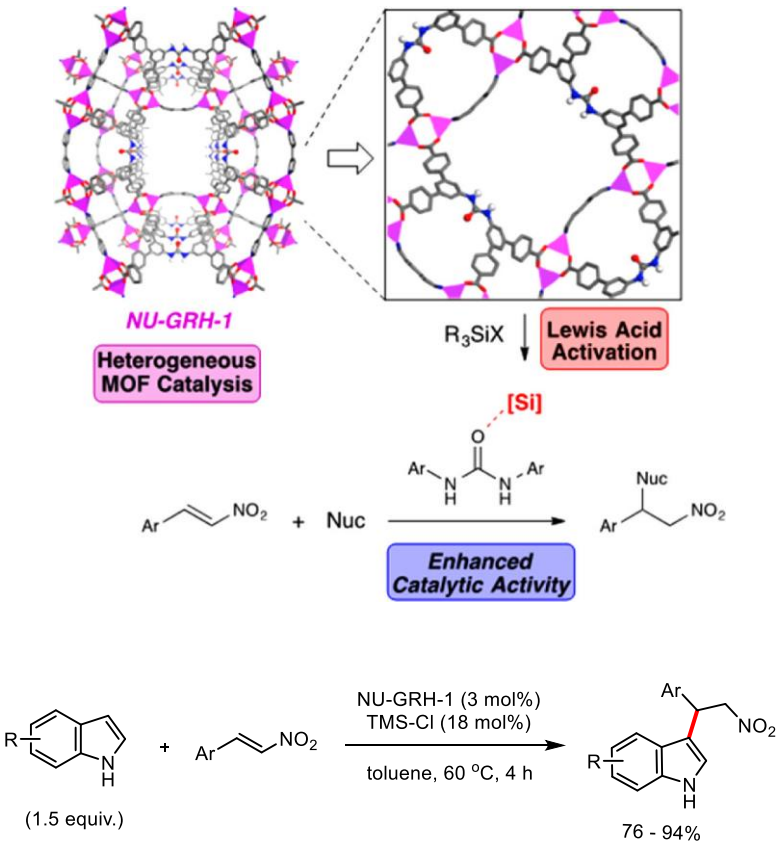
In 2013, Che and co-workers reported new functionally diverse urea-derived MOF catalysts synthesized via postsynthetic modification.[21] The resulting robust MOFs have shown remarkable catalytic activities in the FC reactions.





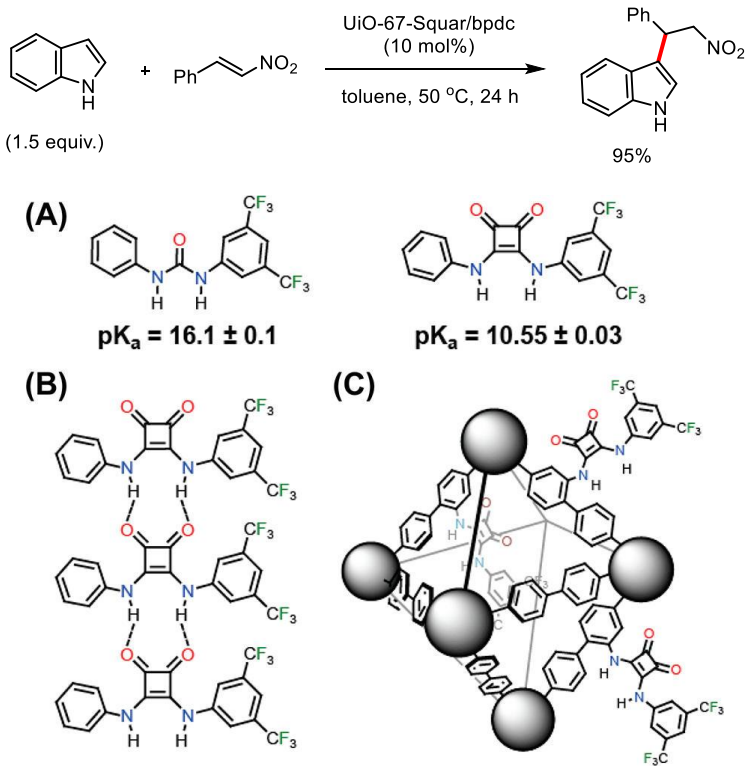
Scheme 13. Urea Postmodified in MOF as A Catalytically Active HBD Catalyst

In 2016, Scheidt and co-workers reported a Lewis acid activation of ureas which were feasible through specific design and judicious incorporation of HBD organo-catalysts into a heterogeneous metal-organic structure.[22] These activated MOF catalysts were recyclable and displayed superior reactivity compared to their homogeneous urea counterparts.



Scheme 14. Lewis Acid Activation of a Ureas MOF for Catalysis

In 2015, Mirkin and co-workers demonstrated the incorporation of a HBD squaramide moiety into a porous UiO-67 MOF derivative which led to a dramatic acceleration of the FC alkylation between indole and β-nitrostyrene.[23] Squaramide-based HBD catalysts are more acidic than their urea counterparts. However, the strong hydrogen-bonding nature of the squaramide-based catalysts also derived catalytically detrimental self-association, resulting in no catalytic activity.[24-25] This was the first demonstration of the functionalization of a heterogeneous framework with an acidic squaramide derivative.

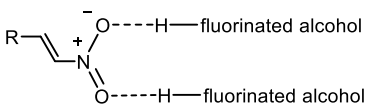


Scheme 15. Squaramide-Base MOF as Effective HBD Catalysts for FC Alkylation

II. 2. Result and Discussion

II. 2. 1. Project Proposed

As we all know, fluorinated alcohols are stronger hydrogen-bond donor. We expect they will have an effect toward the activation of nitroalkenes through hydrogen-bonding interactions.

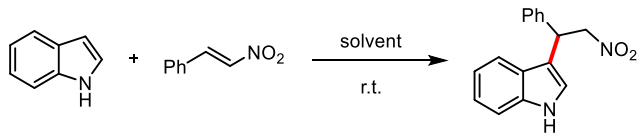


Scheme 16. Activation of Nitroalkenes by Fluorinated Alcohols

II. 2. 2. Optimization of the Reaction Condition

The FC alkylation between indole and β-nitroalkene was used as model system to optimize the reaction conditions (**Table 1**). We first examined the reaction in pure HFIP solvent and the reaction mixture was stirred at r.t. for 2 h. To our delight, 99% NMR yield of product **70** using mesitylene as internal standard was obtained (entry 1). Changing the molar concentration of the substrates had virtually no effect on the yield (entry 2-3). Then we tested other fluorinated alcohols, perfuoro-2-methylpropan-2-ol (PFTB) was very efficient and the reaction finished in 45 mins (entry 4), however the high price limited its broad application. Trifluoroethanol (TFE) was less sufficient and required longer time to finish the reaction (entry 5). When performed the reaction in the dark had no effect on the yield (entry 6), which suggested HFIP promoted FC alkylation was not a photochemical pathway.[26]

Table 1. Optimization of The Fluorinated Alcohols



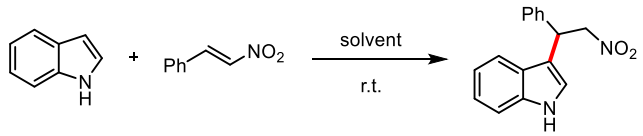
(1.2 equiv.) (0.5 mmol) **70**

Entry	Solvent (0.25 M)	Time (h)	Yield (%) [a]
1	HFIP	2	99 (96) [b]
2	HFIP (0.5 M)	2	99
3	HFIP (0.1 M)	2	99
4	PFTB	0.75	99
5	TFE	8	90
6 [c]	HFIP	2	99

[a] NMR yields using mesitylene as internal standard. [b] Isolated yield in parentheses. [c] in the dark.

When HFIP was used as additive with other solvents, good to moderate yields of **70** were obtained (**Table 2**). In DCM, the addition of HFIP from 2.0 to 9.5 equiv. (entries 1-3) decreased product yield and reaction rate. Good results were obtained when added 9.5 equiv. HFIP in water and toluene (entries 4 and 5). With THF the reaction was completely unfavourable (entry 6), probably because of the hydrogen bond between HFIP and THF which inhibited the reaction.

Table 2. Optimization of The Mixed Solvents



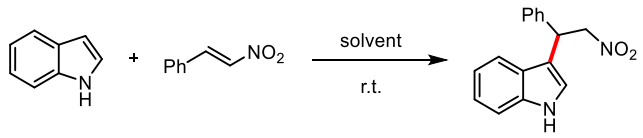
(1.2 equiv.) (0.5 mmol) **70**

Entry	Solvent (0.25 M)	Time (h)	Yield (%) [a]
1	DCM/HFIP (3:1)	4	97
2	DCM/HFIP (6.7:1)	16	89
3	DCM/HFIP (17.2:1)	24	45
4	H_2O/HFIP (3:1)	6	93
5	Toluene/HFIP (3:1)	6	85
6	THF/HFIP (3:1)	6	24

[a] NMR yields using mesitylene as internal standard.

After, commonly used solvents were tested (**Table 3**). In contrast to TFE, only trace of product **70** was observed when used EtOH as solvent (entry 1). Other commonly used solvents such as DCM, toluene, CH_3CN, THF and DMF also gave bad results (entries 2-6). At last, the reaction was checked in HOAc (p*K*a = 4.7) (entry 7), only 25% of product **70** was detected, which means the acidity of fluorinated alcohols was not the key factor to promote the reaction.

Table 3. Optimization of The Common Solvents



(1.2 equiv.) (0.5 mmol) **70**

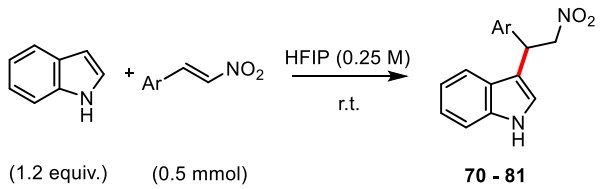
Entry	Solvent (0.25 M)	Time (h)	Yield (%) [a]
1	EtOH	16	trace
2	DCM	16	28
3	Toluene	16	9
4	CH_3CN	16	23
5	THF	16	18
6	DMF	16	0
7	HOAc	16	25

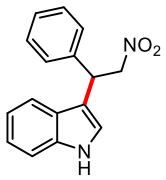
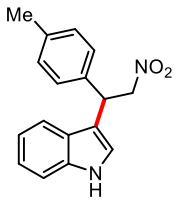
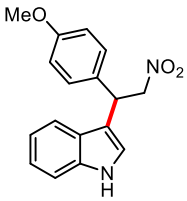
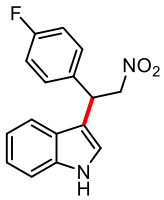
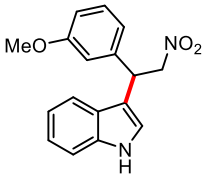
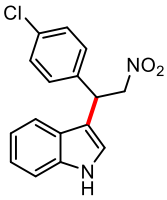
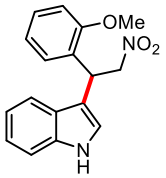
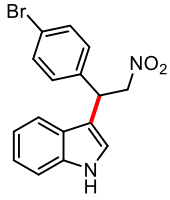
[a] NMR yields using mesitylene as internal standard.

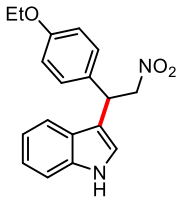
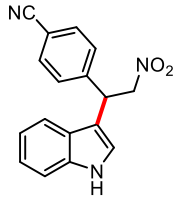
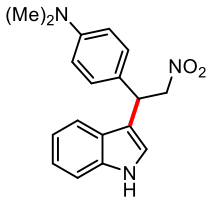
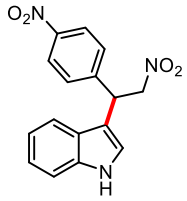
II. 2. 3. Expanding the Substrate Scope

Under the optimized conditions (**Table 1**, entry 1), the substrate scope and limitation for this FC alkylation between various indoles and *β*-nitroalkenes were explored. As shown by the results in **Table 4**, all the aryl-*β*-nitroalkene analogs tested reacted with indole to produce the corresponding products **70-81** in excellent yields in HFIP, no matter the presence of substituents with electron withdrawing or electron donating groups in various positions. A variety of functional groups such as methoxy (**71-73**), ethoxy (**74**), *N*, *N*-dimethylamino (**75**), halides (**77-79**), nitrile (**80**) and nitro (**81**) were tolerated.

Table 4. FC Alkylation of Indole with Different Aryl-*β*-Nitroalkenes

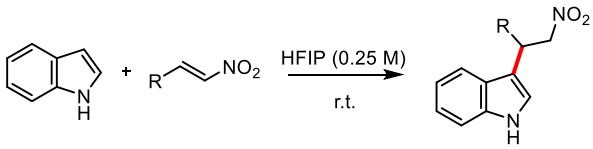


Entry	Product	Time (h)	Yield (%)	Entry	Product	Time (h)	Yield (%)
1	 **70**	2	96	7	 **76**	2	95
2	 **71**	2	95	8	 **77**	2	92
3	 **72**	2	95	9	 **78**	2	96
4	 **73**	2	93	10	 **79**	2	94

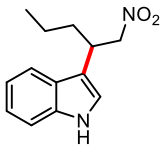
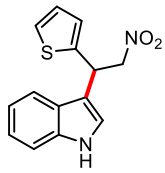
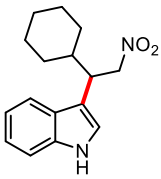
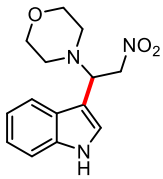
5	 **74**	2	96	11	 **80**	2	94
6	 **75**	2	97	12	 **81**	2	95

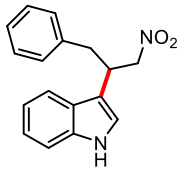
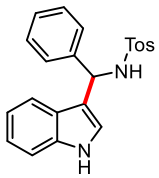
Meanwhile, the reaction with the aliphatic nitroalkenes which showed less stable under acid conditions and gave low yields were successfully transformed into the desired products (**82-84**) in good yields after 8 h under this mild conditions. *Trans*-2-(2-nitrovinyl)-thiophene was also applicable in this reaction providing the product **85** in 92% yield. Unfortunately, 4-(2-nitrovinyl)morpholine was not suitable for this reaction. It was noteworthy that less reactive substrate *N*-tosyl imine also showed good reactivity, giving **86** in 86% yield after 16 h. This study expands upon our scope of imines with similarly satisfying results.

Table 5. FC Alkylation of Indole with Different *β*-Nitroalkenes



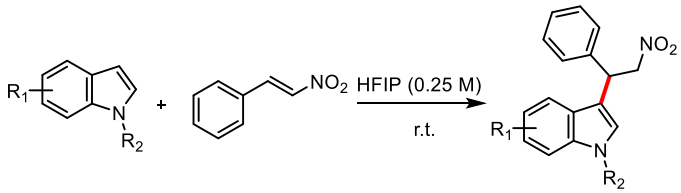
(1.2 equiv.) (0.5 mmol) **82-86**

Entry	Product	Time (h)	Yield (%)	Entry	Product	Time (h)	Yield (%)
1	 **82**	8	90	4	 **85**	2	92
2	 **83**	8	88	5		16	n.d.

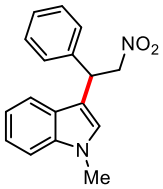
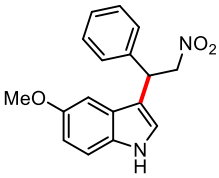
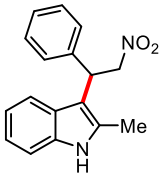
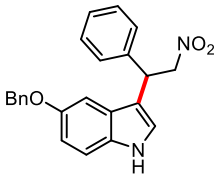
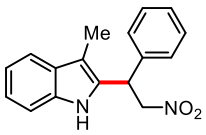
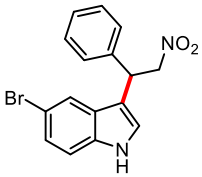
3	 **84**	8	84	6	 **86**	16	86

Then various indoles with *β*-nitroalkene were tested (**Table 6**). N-methyl- and 2-methylindole were reacted with *β*-nitroalkene to produce the corresponding products **87**, **88** in 97% and 95% respectively. When the C3 position of indole was substituted, the reaction happened at C2 position in good yield (**89**). Reactions of indoles with electron withdrawing or electron donating groups at C5 positions with *β*-nitroalkene led to the corresponding products smoothly in excellent yields (**90-92**).

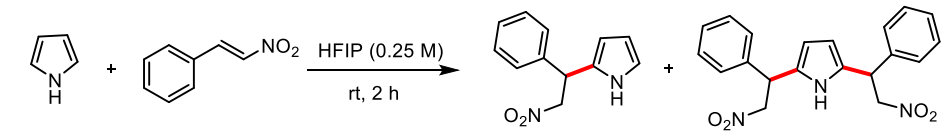
Table 6. FC Alkylation of Different Indoles with *β*-Nitroalkene



(1.2 equiv.) (0.5 mmol) **87-92**

Entry	Product	Time (h)	Yield (%)	Entry	Product	Time (h)	Yield (%)
1	 **87**	2	97	4	 **90**	2	96
2	 **88**	2	95	5	 **91**	2	96
3	 **89**	2	82	6	 **92**	2	92

Meanwhile, treatment of the pyrrole with *β*-nitroalkene afforded a mixture of *mono*- and *bis*-substituted products **93** in 85% yield.



(1.2 equiv.) (0.5 mmol) **93**, 85% (mono/bis: 77/23)

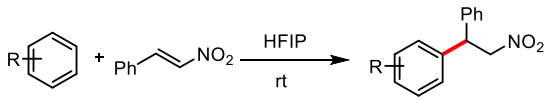
Scheme 17. FC Alkylation of Pyrrole with *β*-Nitroalkene

II. 2. 4. FC Alkylation of Electron-Rich Arenes with β-Nitroalkene

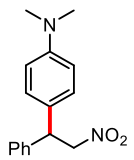
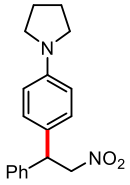
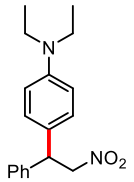
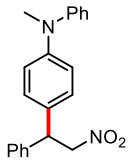
After development of FC alkylation of indoles and pyrrole, we then focused on the FC alkylation of arene derivatives. To the best of our knowledge, there are only a few reports on the FC alkylation of arenes with *β*-nitroalkene in the literature.[12, 18, 21, 27] So, there is a need to develop a novel FC alkylation of electron-rich arenes.

In preliminary experiments, we tested *N*, *N*-dimethyl aniline with *β*-nitroalkene in HFIP at room temperature. To our delight, the corresponding product **94** was obtained after 16 h in 94% yield. Other tertiary anilines such as *N*, *N*-diethyl aniline *N*-phenylpyrrolidine and *N*-methyl-*N*-phenylaniline were also efficient in these conditions to afford regioselectively only the *para*-alkylated products **95-97** in excellent yields. Triphenylamine showed no reactivity under the same conditions, probably because of the lower electron density at the phenyl ring.

Table 7. FC Alkylation of Tertiary Anilines with *β*-Nitroalkene

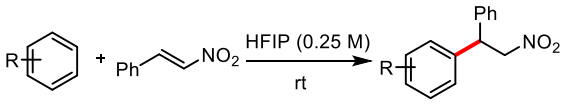


(1.2 equiv.) (0.5 mmol) **94-97**

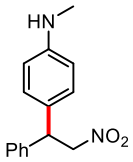
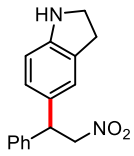
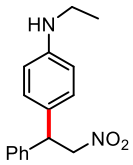
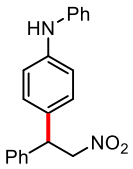
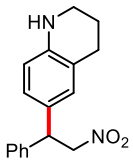
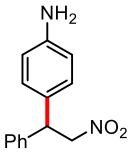
Entry	Product	Time (h)	Yield (%)	Entry	Product	Time (h)	Yield (%)
1	 **94**	16	94	3		16	94
2	 **95**	16	90	4	 **97**	16	78 (mono/bis: 84/16)

Interestingly, the reaction also worked with secondary anilines including tetrahydroquinoline and indoline, affording the corresponding products **98-101** in a moderate yield with trace of the Aza Michael product after 24 h. For diphenylamine, only 45% of mono-alkylated product **102** was obtained. In contrast to the primary aniline, only trace of alkylated product was detected, the major product was the Aza-Michael adduct.

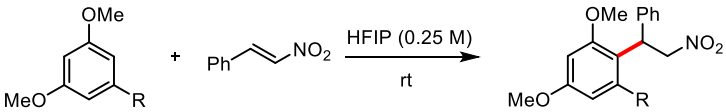
Table 8. FC Alkylation of Secondary and Primary Anilines with *β*-Nitroalkene



(1.2 equiv.) (0.5 mmol) **98 - 102**

Entry	Product	Time (h)	Yield (%)	Entry	Product	Time (h)	Yield (%)
1	 **98**	24	67	4	 **101**	24	61
2	 **99**	24	64	5	 **102**	24	45
3	 **100**	24	65	6		24	trace

Besides, the electron-rich arenes, 1,3,5-trimethoxybenzene reacted with *β*-nitroalkene to afford the corresponding alkylated product **103** in good yield after 16 h. However, the less electron-rich arenes, 1,3-dimethoxybenzene was failed under the same condition.

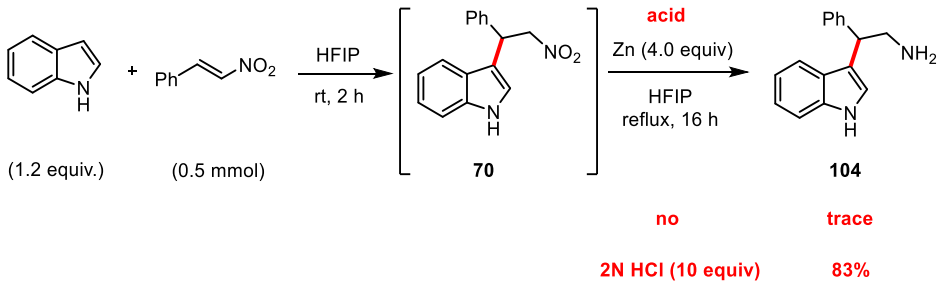


(1.2 equiv.) (0.5 mmol) **103**, R = OMe, 16 h, 87%
R = H, 16 h, trace

Scheme 18. FC Alkylation of Electron-Rich Arenes with *β*-Nitroalkene

II. 2. 5. One-Pot Combination FC Alkylation/NO_2 Reduction

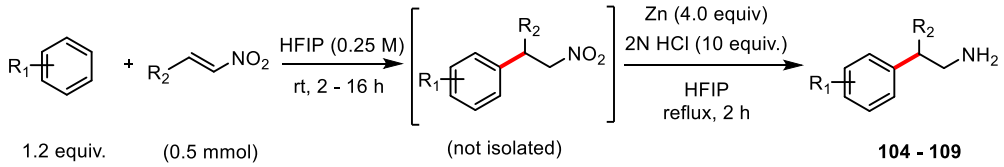
Then following to these effective and mild conditions, we investigated the one-pot combination FC alkylation/NO_2 reduction. Interestingly, the one-pot synthesis of tryptamines has not been reported previously. In preliminary experiments after completion of the first step, 4.0 equiv. of zinc powder was added. Unfortunately, despite the slight acidity of HFIP, the reduction of the nitro group was not observed at room temperature or at reflux. On the other hand, when 10 equiv. of HCl (2N) was added, the corresponding tryptamine **104** was obtained successfully in 83% after 2 h at reflux.

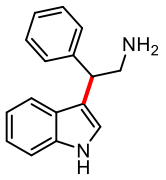
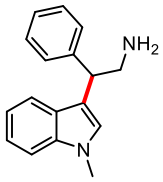


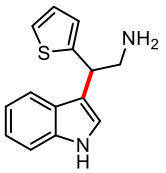
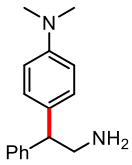
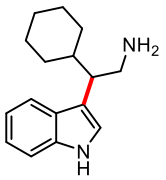
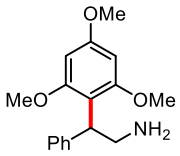
Scheme 19. One-Pot FC Alkylation and Reduction of Nitro Group in HFIP

Thus, different reactions have been performed and reported in **Table 9**. Numerous indoles and *β*-nitroalkenes with aromatic, heterocycle and aliphatic rings were tolerated **(104-107)**. Additionally, reaction with electron-rich arenes such as *N*, *N*-dimethylaniline and 1,3,5-trimethoxybenzene succeed to lead to the corresponding products **108-109** in good yields.

Table 9. One-pot FC Alkylation and Reduction of Nitro Group

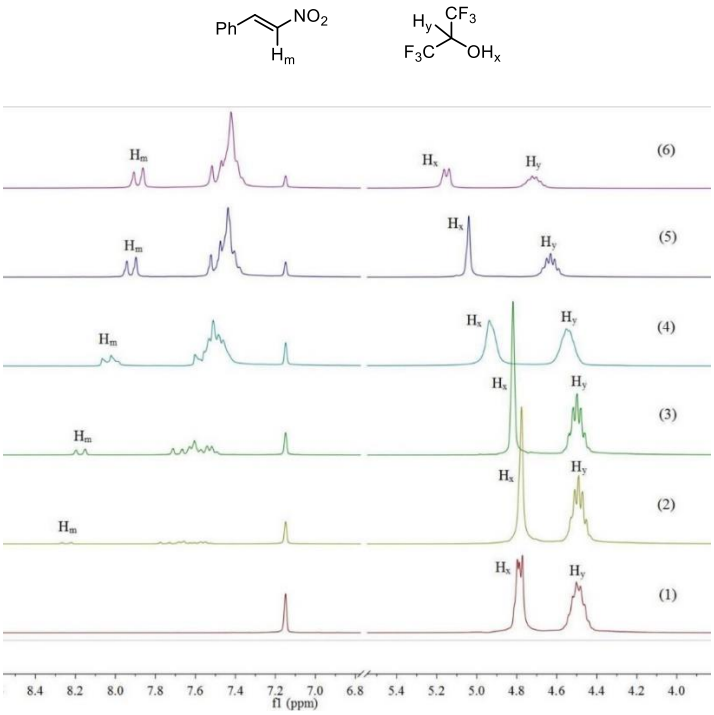


Entry	Product	Yield (%)	Entry	Product	Yield (%)
1	 **104**	83	4	 **107**	84

2	 **105**	77	5	 **108**	81
3	 **106**	62	6	 **109**	75

II. 2. 6. Mechanism Studies

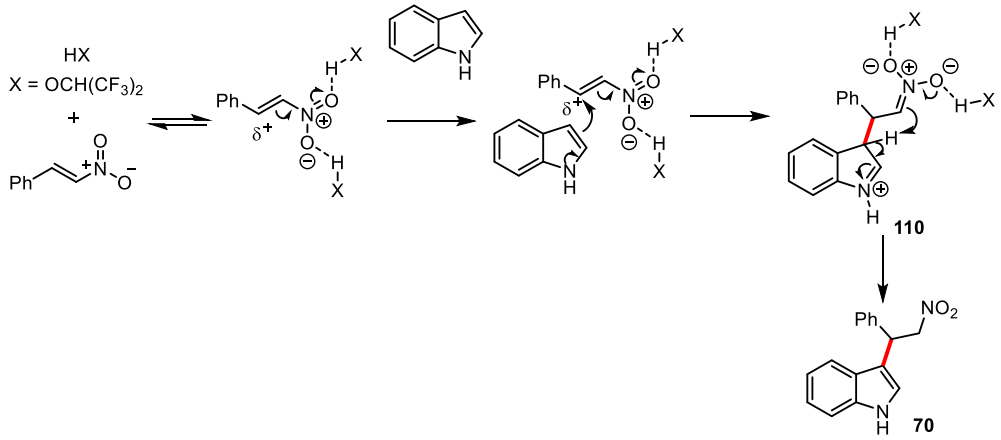
To prove the hydrogen-bonding interactions between *β*-nitroalkene and HFIP, a solution of HFIP was titrated with *β*-nitroalkene and monitored by ^{1}H NMR (**Scheme 20**). In NMR tube, different quantities of *β*-nitroalkene were dissolved in 1.0 mmol of HFIP. After, a capillary with C_6D_6 was placed into the NMR tube (external standard), and NMR spectrum (1) - (5) were subsequently taken. An increasingly downfield shift of the OH proton (H_x) of HFIP was observed with increasing concentrations of *β*-nitroalkene, indicating that HFIP able to activate *β*-nitroalkene through hydrogen-bonding interactions.



[a] Spectra were acquired in the presence of the following quantities of *β*-nitroalkenes: (1) 0 mol%; (2) 1 mol%; (3) 5 mol%; (4) 20 mol%; (5) 50 mol%; (6) 100 mol%.

Scheme 20. ^{1}H NMR Titration of a Mixture of HFIP and β-Nitroalkenes

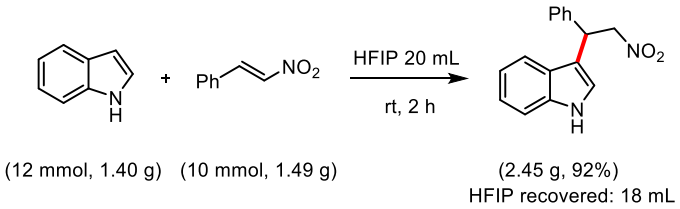
A plausible hydrogen-bond activation mechanism was proposed in **Scheme 21**. First HFIP activated the nitro group through hydrogen-bond and following by the nucleophilic attack of the indole. The generated intermediate **110** underwent to the subsequent hydrogen transfer to afford the expected product **70**.



Scheme 21. Proposed Mechanism

II. 2. 7. Gram Scale Reaction

Meanwhile, to further explore the synthetic utility of this system, a gram-scale reaction was also evaluated (**Scheme 22**). The FC alkylation of **1a** (12 mmol, 1.40 g) with **2a** (10.0 mmol, 1.49 g) was performed in 20 mL HFIP for 2 h. The desired product **3aa** was obtained in 92% yield (2.45 g) and 18 mL of HFIP was recovered after distillation directly from the reaction.

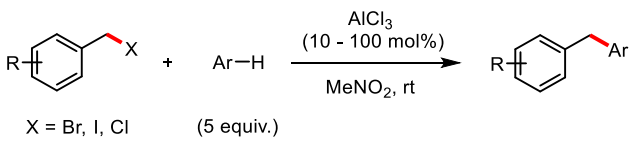


Scheme 22. Gram scale reaction

III. FC Benzylation of Arenes with Benzylic Alcohols

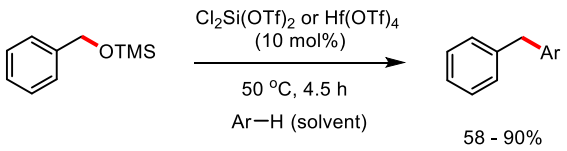
III. 1. Introduction

The FC benzylation of arenes is one of the fundamental synthetic protocols for diarylmethane moiety, a privileged structural unit that has diverse applications in the fields of pharmacologically active compounds and functional materials.[28-33] In its traditional form, the reaction is promoted by strong Lewis acids (e.g., $AlCl_3$, $FeCl_3$), generally requiring a full equivalent of catalyst or more due to product inhibition.[34-35] And moreover, the reaction uses toxic alkyl halide as starting material, which hydrolyzes readily to generate irritating halo-acid gas (HX) as the byproduct. Therefore, these old reaction conditions are far from ideal from the standpoint of atom economy and green chemistry.



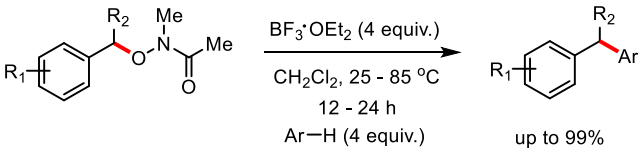
Scheme 23. Classical FC Benzylation with Benzylic Chlorides.

In an effect to looking for better conditions, a number of attractive methods employing various alcohol derivatives as nonhalogenated substrates, such as ether and ester derivatives have been reported. For example, in 2002, Suzuki and co-worker reported Lewis acid promoted FC benzylation of various aromatic compounds with benzyl silyl ethers under mild reaction conditions.[36]



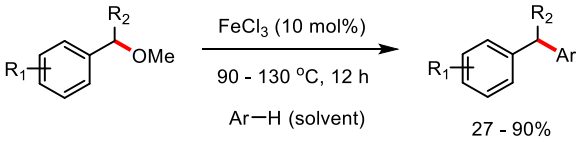
Scheme 24. Lewis acid Promoted FC Benzylation with Benzyl Silyl Ethers

In 2011, Bode and co-workers described the use of benzylic hydroxamates and a stoichiometric amount of boron trifluoroborate as a remarkably effective method for the FC benzylation of neutral and deactivated arenes with a wide range of compatible functional groups on both substrates.[37]



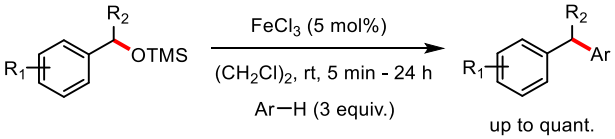
Scheme 25. $BF_3 \cdot OEt_2$-Catalyzed FC Benzylation with Benzyl Hydroxamates

In 2008, Shi and co-workers developed a $FeCl_3$-catalyzed FC benzylation of electron rich arenes and substituted thiophenes through benzylic sp^3 C-O activation of benzyl methyl ether.[38] Various benzyl ethers were converted to benzyl arenes under mild condition in good yields.



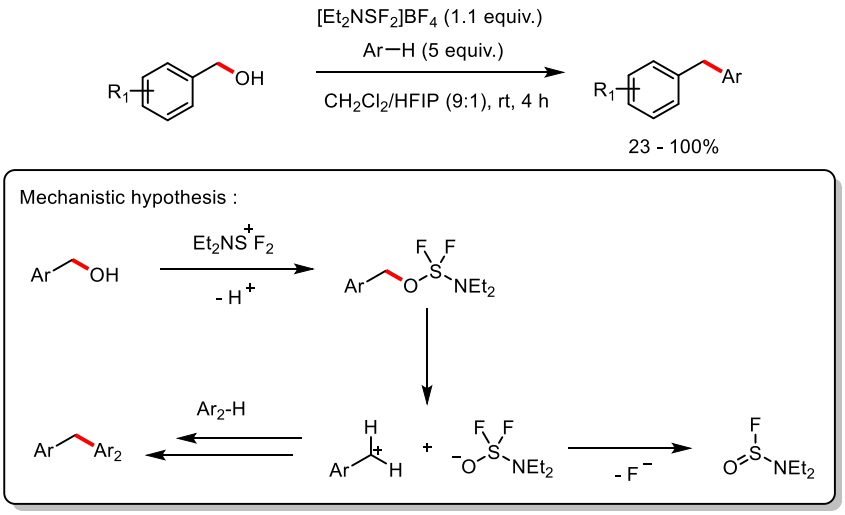
Scheme 26. $FeCl_3$-Catalyzed FC Benzylation with Benzyl Methyl Ethers

In 2014, Sajiki and co-workers established an efficient FC benzylation of unactivated arenes that used benzyl TMS ethers as substrates, which were poorly reactive under common nucleophilic substitution conditions.[39] The present reactions were catalyzed by the safe and cheap iron catalyst $FeCl_3$ and proceed at room temperature to give versatile polyaryl products with di- and tri-arylmethane skeletons.



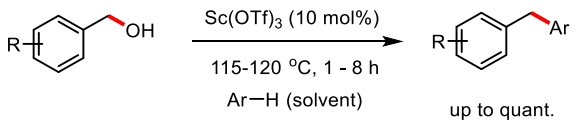
Scheme 27. $FeCl_3$-Catalyzed FC Benzylation with Benzyl TMS Ethers

Recently, a FC benzylation of arenes using benzyl alcohols activated *in-situ* with a stoichiometric amount of a fluorination reagent $[Et_2NSF_2]BF_4$ was reported by Paquin and co-workers.[40] A wide range of 1,1-diarylmethanes and 1,1,1-triarylmethanes were prepared under experimentally simple and mild conditions, without the need for a transition metal or a strong Lewis acid.



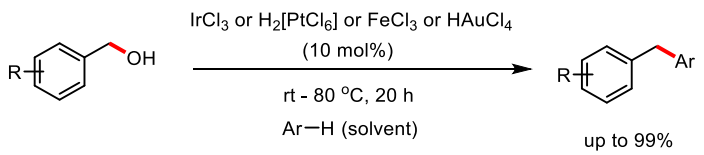
Scheme 28. FC Benzylation with Benzyl Alcohols Activated in Situ with XtalFluor-E

Although most of these methods do bypass the use of toxic benzylic halides they often generated byproducts resulting from the release of the activating group. These procedures are thus less atom economical compared to the use of free alcohols, where water would be generated as the only byproduct. In the past decade, however, that successful efforts to use benzylic alcohols replace benzylic halides have appeared. In 1997, Fukuzawa and co-workers reported the first example of benzylation of activated arenes with benzylic alcohols as the alkylating agent catalyzed by scandium triflate, affording diarylmethanes or allylbenzene derivatives with highly selectively.[41]



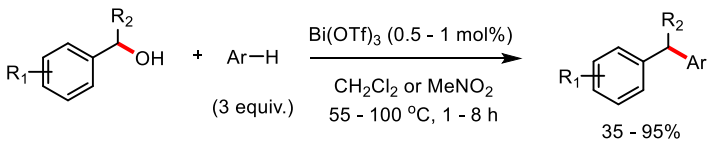
Scheme 29. $Sc(OTf)_3$-Catalyzed FC Benzylation with Benzyl Alcohols

Subsequently, a number of other metal-catalyzed procedures were developed for direct FC benzylations with benzylic alcohols. Beller and co-workers developed another new general benzylation reaction of arenes and heteroarenes in the presence of several transition-metal compounds, of which $IrCl_3$, $H_2[PtCl_6]$, $FeCl_3$ and $HAuCl_4$ were the most active catalysts.[42-44] Often the reactions proceed under mild conditions (RT-80 °C, without strong acid or base) with high selectivity.



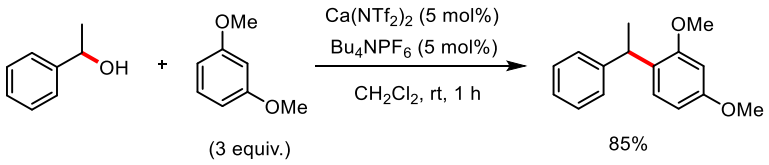
Scheme 30. $IrCl_3$, $H_2[PtCl_6]$, $FeCl_3$ and $HAuCl_4$-Catalyzed FC Benzylation with Benzyl Alcohols

In 2006, Rueping and co-workers reported a highly efficient $Bi(OTf)_3$-catalyzed FC benzylation of arenes and heteroarenes.[45] Compared to the previous benzylation with benzyl alcohol and derivatives which needed high catalyst loading (10 mol%), this method required remarkably small amounts (0.5 - 1 mol%) of highly reactive, inexpensive and non-toxic catalyst.



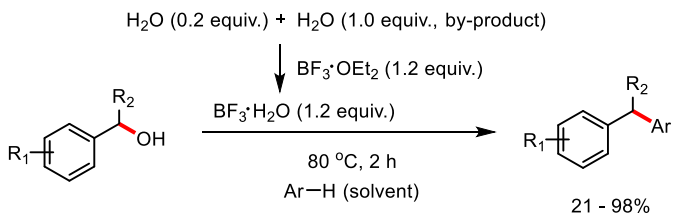
Scheme 31. $Bi(OTf)_3$-Catalyzed FC Benzylation with Benzyl Alcohols

In 2010, Niggemann and co-worker developed a general calcium-catalyzed FC benzylation that allowed the selective alkylation of arenes using secondary and tertiary benzylic alcohols.[46] Typical reactions proceed at room temperature, with no added strong acids or bases, and special precautions for exclusion of moisture or air were unnecessary.



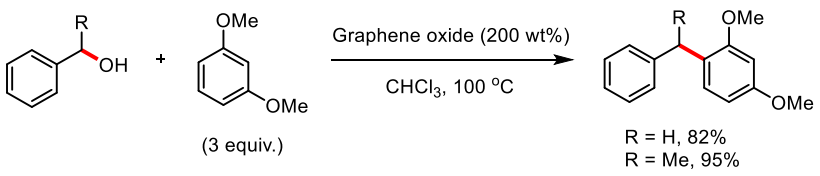
Scheme 32. Calcium-Catalyzed FC Benzylation with Benzyl Alcohols

In 2014, Xiong and co-workers developed a simple and straightforward method for synthesis of diarylalkanes using commercially available BF_3-OEt_2 starting from benzylic alcohols.[47] With a combination of control experiments and ^{11}B NMR analysis, super-acid BF_3-H_2O in situ generated by BF_3-OEt_2 with the trace of water and self-released by-product water as the true promoter has been illuminated. This method was compatible with a number of functional groups and generally gave good to excellent isolated yields.



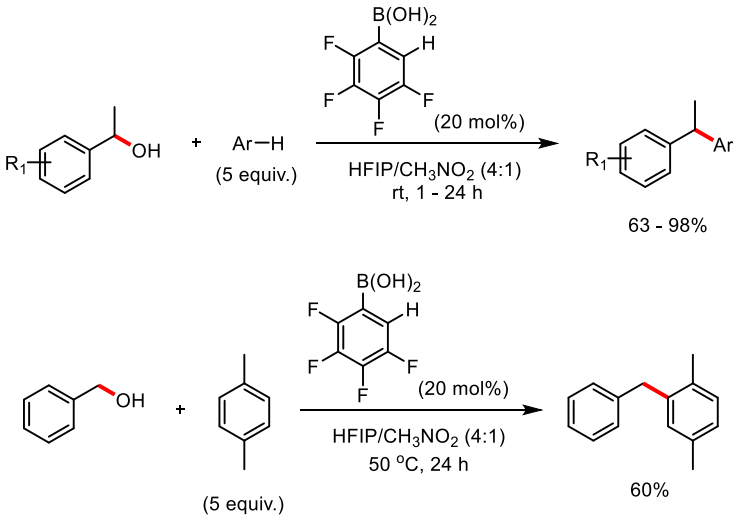
Scheme 33. Super-acid BF_3-H_2O Promoted FC Benzylation with Benzyl Alcohols

In 2015, Szostak and co-workers reported the first general strategy for alkylation of arenes with alcohols catalyzed by carbon-based materials, exploiting the unique property of graphenes oxide to produce valuable diarylalkane products in high yields and excellent regioselectivity.[48]



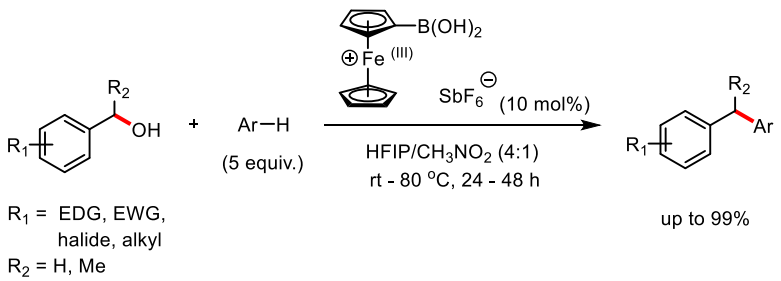
Scheme 34. Graphene-Catalyzed FC Benzylation with Benzyl Alcohols and Styrenes

In 2015, Hall and co-workers reported the first catalytic activation of alcohols with boronic acids by using a potent air- and moisture-tolerant metal-free and highly Lewis acidic 2,3,4,5-tetrafluorophenylboronic acid in regioselective FC reactions of activated benzylic alcohols with activated electron-rich arenes or heteroarenes.[49]



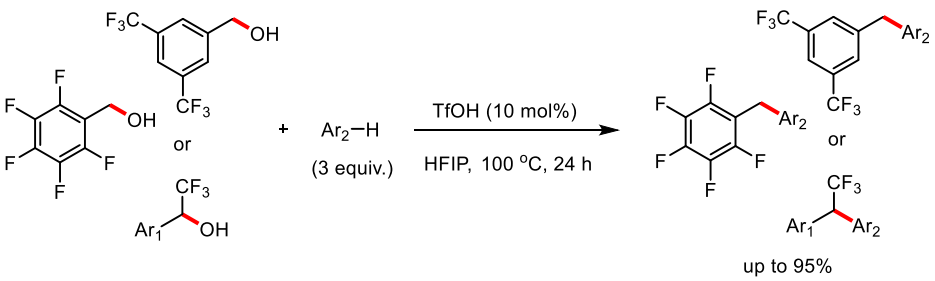
Scheme 35. Boronic Acid-Catalyzed FC Benzylation with Benzyl Alcohols

However, although secondary benzylic alcohols reacted smoothly at room temperature, the reaction of benzyl alcohol as a prototypic primary alcohol with both *meta*- and *ortho*-xylene afforded moderate yields of products. After, the same group demonstrated that the ionized form of ferroceneboronic acid, the ferroceniumboronic acid hexafluoroantimonate salt, was a significantly more powerful activator of electronically deactivated primary benzylic alcohols and could catalyze FC alkylations of a wide range of neutral arenes functionalized with various substituents.[50]



Scheme 36. Ferroceniumboronic Acid-Catalyzed FC Benzylation with Benzyl Alcohols

Although, the past years have witnessed numerous reports of Lewis or Brønsted acid catalyzed FC benzylations of electronically activated or modest deactivated benzylic alcohols, but the inability of the reaction to highly electronically deactivated alcohols remained a striking limitation. Recently, Moran and co-workers reported a FC benzylations of arenes with highly electronically deactivated benzylic alcohols, including those with a CF_3 group adjacent to the OH-bearing carbon using super Brønsted acid TfOH as catalyst.[51]



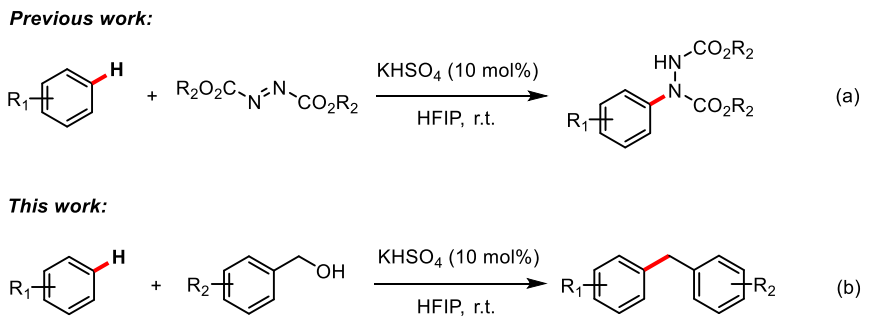
Scheme 37. TfOH-Catalyzed FC Benzylation with Highly Electronically Deactivated Benzyl Alcohols

In view of the previous literature, only one example reported a general produce of FC benzylation with different benzylic alcohols. It is highly desirable to develop new general and efficient ways without metals and with gentle, cheap and green catalysts.

III. 2. Result and Discussion

III. 2. 1. Project Proposed

In the chapter II, we developed a bisulfate salt-catalyzed amination of arenes with azodicarboxylates in HFIP (**Scheme 38,** a). Given the importance of the mildness and green of this system, we sought to extend this system to the FC benzylation with benzylic alcohols (**Scheme 38**, b).

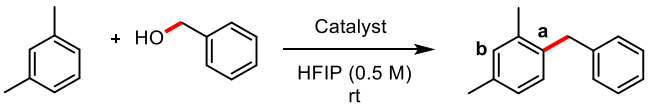


Scheme 38. Optimization of The Reaction Conditions

III. 2. 2. Optimization of the Reaction Condition

The FC benzylation of *m*-xylene with benzyl alcohol was chosen as the model system to optimize the reaction conditions (**Table 10**). We first tested the benzylation of *m*-xylene with benzyl alcohol using 10 mol% of $KHSO_4$ as the catalyst and HFIP as the solvent at room temperature. To our delight, the desired diarylmethane isomers **111** were isolated in 84% after 16 h (entry 1). A similar result was obtained using $NaHSO_4$ as catalyst (entry 2). The use of Na_2SO_4, NaH_2PO_4, $NaHCO_3$ or no catalyst completely shut down the reaction (entry 3-6). It was noteworthy that the protic acid H_3PO_4 (p*K*a = 2.1) with a p*K*a close to the $KHSO_4$ (p*K*a = 1.9) and the strong protic acid TFA (p*K*a = 0.3) gave trace of products **3** (entry 7-8).

Table 10. Optimization of The Catalysts



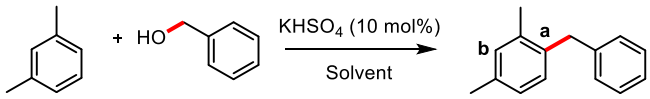
(5 equiv.) (0.5 mmol) **111**

Entry	Catalyst (10 mol%)	Time (h)	Yield (%)	**111a: 111b**
1	$KHSO_4$	16	84	77: 23
2	$NaHSO_4$	16	75	75: 25
3	Na_2SO_4	16	n.r.	-
4	NaH_2PO_4	16	n.r.	-
5	$NaHCO_3$	16	n.r.	-

6	-	16	n.r.	-
7	H_3PO_4	16	trace	-
8	TFA	16	trace	-

We next investigated the effect of different solvents in this benzylation (**Table 11**). Unexpectedly, the application of another widely used fluorinated solvent TFE resulted in trace of the products **3** (entry 1). Other several non-fluorinated common solvents such as EtOH, DCM, THF, CH_3NO_2 or *m*-xylene did not produce detectable amounts of products (entry 2-6). In addition, changing the reaction temperature to 50 °C was found to provide the products **111** in 86% yield within 2 h (entry 7). The products **3** were not observed in the presence of molecular sieves that would promote the formation of potassium disulfate (entry 8). Moreover, the amount of $KHSO_4$ can be reduced to 2 mol% (entry 9).

Table 11. Optimization of The Solvents



(5 equiv.) (0.5 mmol) **111**

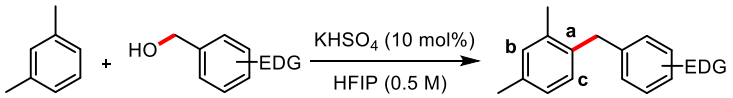
Entry	Solvent (0.5 M)	Time (h)	Temperature	Yield (%)	**111a: 111b**
1	TFE	16	rt	trace	-
2	EtOH	16	rt	n.r.	-
3	DCM	16	rt	n.r.	-
4	THF	16	rt	n.r.	-
5	CH_3NO_2	16	rt	n.r.	-
6	*m*-xylene	16	rt	n.r.	-
7	**HFIP**	**2**	**50 °C**	**86**	**76: 24**
8 [a]	HFIP	2	50 °C	n.r.	-
9 [b]	HFIP	5	50 °C	80	76: 24

[a] 200 mg of M.S. was added. [b] 2% of $KHSO_4$ was used.

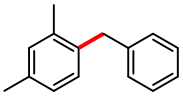
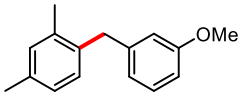
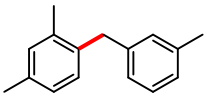
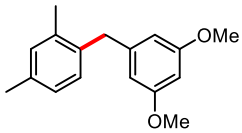
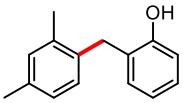
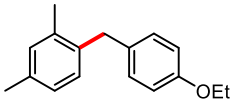
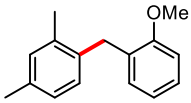
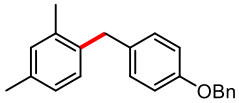
III. 2. 3. Expanding the Substrate Scope

Under the optimized conditions (**Table 11**, entry 7), the substrate scope and limitation of this FC benzylation were explored. The effect of substituents on the benzylic alcohol moiety is listed in **Table 12**. Benzylic alcohols bearing electron-donating substituents such as methyl, hydroxy, methoxy, ethoxy, and benzyloxy at various positions were successfully transformed into the desired diarylmethane products **111-118** in moderate to good yields at or below 50 °C.

Table 12. The FC Benzylation of Benzyl Alcohols with Electron-Donating Groups

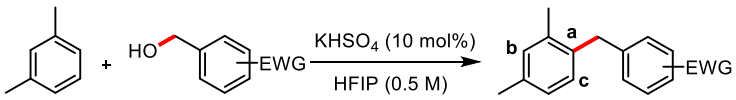


(5 equiv.) (1.0 mmol) **111 - 118**

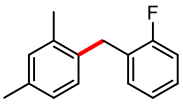
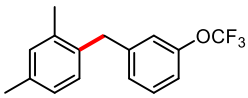
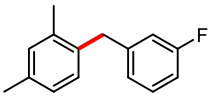
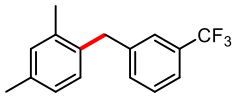
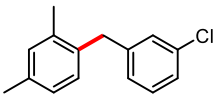
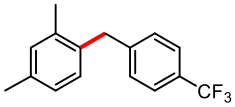
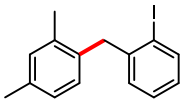
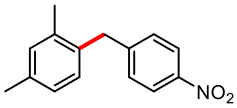
Entry	Product	Temp./Time	Yield (%)	Entry	Product	Temp./Time	Yield (%)
1	 **111**	50 °C 2 h	86 (**a** : **b** = 76 : 24)	5	 **115**	50 °C 2 h	77 (**a** : **b** = 76 : 24)
2	 **112**	50 °C 2 h	86 (**a** : **b** = 77 : 23)	6	 **116**	rt 2 h	74 (**a** : **b** = 75 : 25)
3	 **113**	rt 1 h	87 (**a** : **b** > 95 : 5)	7	 **117**	rt 2 h	56 (**a** : **b** > 95 : 5)
4	 **114**	50 °C 2 h	85 (**a** : **b** > 95 : 5)	8	 **118**	rt 2 h	72 (**a** : **b** > 95 : 5)

Furthermore, benzylic alcohols with slightly deactivating substituents such as fluoride, chloride, iodide or trifluoromethoxy also led to high yields of products **119-123.** It is remarkable that benzylic alcohols with strongly electron-withdrawing substituents such as trifluoromethyl were also applicable in this reaction providing the products **124** and **125** in 75% and 51% yields after 48 h at 100 °C, respectively. Unfortunately, the reactions gave very low yield with benzylic alcohols bearing other strongly electron-withdrawing substituents such as nitro group (product **126**).

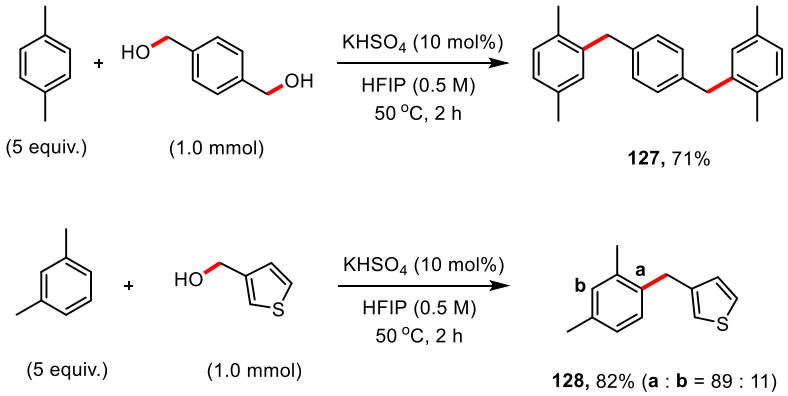
Table 13. The FC Benzylation of Benzyl Alcohols with Electron-Withdrawing Groups



(5 equiv.) (1.0 mmol) **119 - 126**

Entry	Product	Temp./Time	Yield (%)	Entry	Product	Temp./Time	Yield (%)
1	 **119**	80 °C 2 h	80 (**a** : **b** = 76 : 24)	5	 **123**	80 °C 16 h	61 (**a** : **b** = 76 : 24)
2	 **120**	80 °C 16 h	77 (a : b = 77 : 23)	6	 **124**	100 °C 48 h	75 (**a** : **b** = 77 : 23)
3	 **121**	80 °C 16 h	84 (**a** : **b** = 78 : 22)	7	 **125**	100 °C 48 h	51 (**a** : **b** = 80 : 20)
4	 **122**	50 °C 16 h	73 (**a** : **b** = 91 : 9)	8	 **126**	100 °C 48 h	15 (**a** : **b** = 80 : 20)

Treatment of the 1,4-benzenedimethanol with *p*-xylene provided the disubstituted products **127** in 71% yield. In addition, the reaction with 3-thiophenemethanol processed successfully to give the corresponding products **128** in high yields.

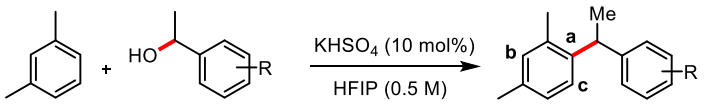


Scheme 39. The FC Benzylation of 1,4-Benzenedimethanol and 3-Thiophenemethanol

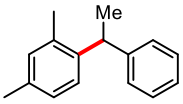
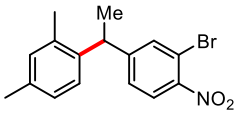
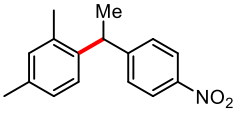
Moreover, secondary benzylic alcohol 1-phenylethanol was able to alkylate *m*-xylene in high yield at room temperature (product **129**). It was noteworthy that the secondary benzylic alcohol bearing strongly electron-withdrawing substituent such as nitro group worked well and afforded

products **130** in high yield. However, the reaction was failed with more strongly deactivated arene unit such as 3-bromo-4-nitrophenyl employed as part of a secondary benzylic alcohol

Table 14. The FC Benzylation of Secondary Benzylic Alcohols with *m*-Xylene

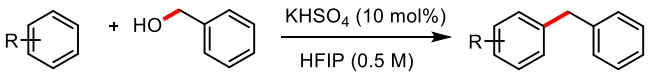


(5 equiv.) (1.0 mmol) **129 - 130**

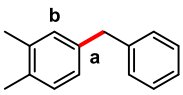
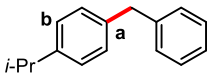
Entry	Product	Temp./Time	Yield (%)	Entry	Product	Temp./Time	Yield (%)
1	 **129**	rt 2 h	90 (**a** : **b** > 95 : 5)	3		100 °C 48 h	trace
2	 **130**	100 °C 16 h	87 (**a** : **b** = 86 : 14)				

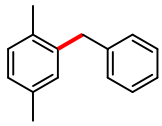
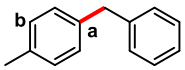
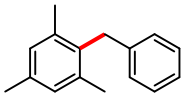
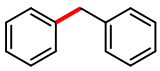
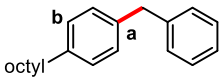
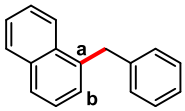
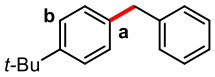
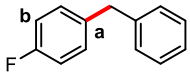
On the other hand, a series of arenes were subjected to this benzylation conditions. The reaction was found to be very facile with alkyl-substituted benzene derivatives like *o*-xylene, *m*-xylene, mesitylene, 1-phenyloctane, *tert*-butylbenzene, *iso*-butylbenzene and toluene (product **131-137**). Meanwhile, the benzylation of benzene and naphthalene were successfully to afford the corresponding products **138** and **139** in 88% and 87% yields, respectively. To our disappointment, the reactions gave low yields with electron deficient arenes such as fluorobenzene as substrate (product **140**).

Table 15. The FC Benzylation of Different Arenes with Benzyl Alcohols



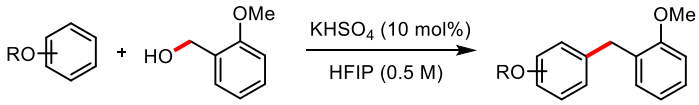
(5 equiv.) (1.0 mmol) **131 - 140**

Entry	Product	Temp./Time	Yield (%)	Entry	Product	Temp./Time	Yield (%)
1	 **131**	50 °C 2 h	87 (**a** : **b** = 62 : 38)	5	 **136**	50 °C 2 h	85 (**a** : **b** = 66 : 34)

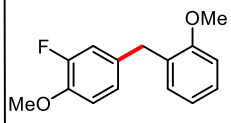
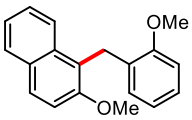
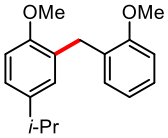
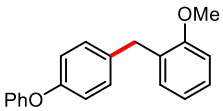
2	 **132**	50 °C 2 h	85	6	 **137**	50 °C 16 h	85 (**a** : **b** = 54 : 46)
3	 **133**	50 °C 2 h	87	7	 **138**	80 °C 16 h	88
4	 **134**	50 °C 2 h	72 (**a** : **b** = 62 : 38)	8	 **139**	50 °C 2 h	87 (**a** : **b** = 70 : 30)
5	 **135**	50 °C 2 h	89 (**a** : **b** = 65 : 35)	9	 **140**	80 °C 48 h	55 (**a** : **b** = 80 : 20)

Gratifyingly, electron-rich methoxybenzene derivatives and diphenyl ether, provided the corresponding products **141-144** in good yields at room temperature (The use of 2-methoxybenzyl alcohol as a prototypical benzylating agent is for better products separation).

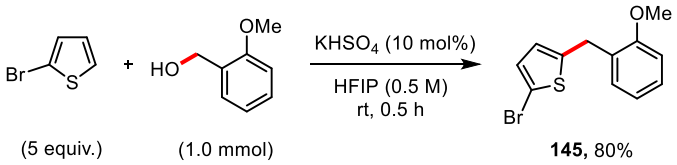
Table 16. The FC Benzylation of Electron-Rich Arenes with Benzyl Alcohols



(5 equiv.) (1.0 mmol) **141 - 144**

Entry	Product	Temp./Time	Yield (%)	Entry	Product	Temp./Time	Yield (%)
1	 **141**	rt 2 h	81	3	 **143**	rt 0.5 h	75
2	 **142**	rt 0.5 h	78	4	 **144**	rt 2 h	88 (**a** : **b** = 87 : 13)

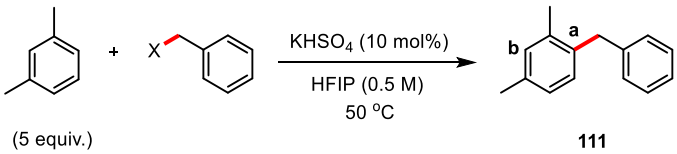
Meanwhile, heteroaromatic nucleophiles were also compatible with the reaction conditions. For example, when 2-bromothiphene was treated with 2-methoxybenzyl alcohol under the optimized condition, giving the corresponding benzylated product **145** in 80% yield. It is noteworthy that the selectivity in these conditions is very similar to that obtained in Hall[50] and McCubbin method and classical FC benzylations with benzylic halides.[34-35]



Scheme 40. The FC Benzylation of 2-Bromothiphene with 2-Methoxybenzyl Alcohol

Moreover, other potential hydrogen-bond-accepting leaving groups were also evaluated (**Table 17**). Benzyl acetate, benzyl methyl ether and (benzyloxy)benzene were successfully afforded the desired diarylmethanes **111** under the standard reaction conditions entries (2-4). Besides, we also compared the reactivity of various benzylic halides which are very weak hydrogen-bond acceptors (entries 5-6).[52] Remarkably, both benzylic chloride and benzylic bromide were reacted completely.

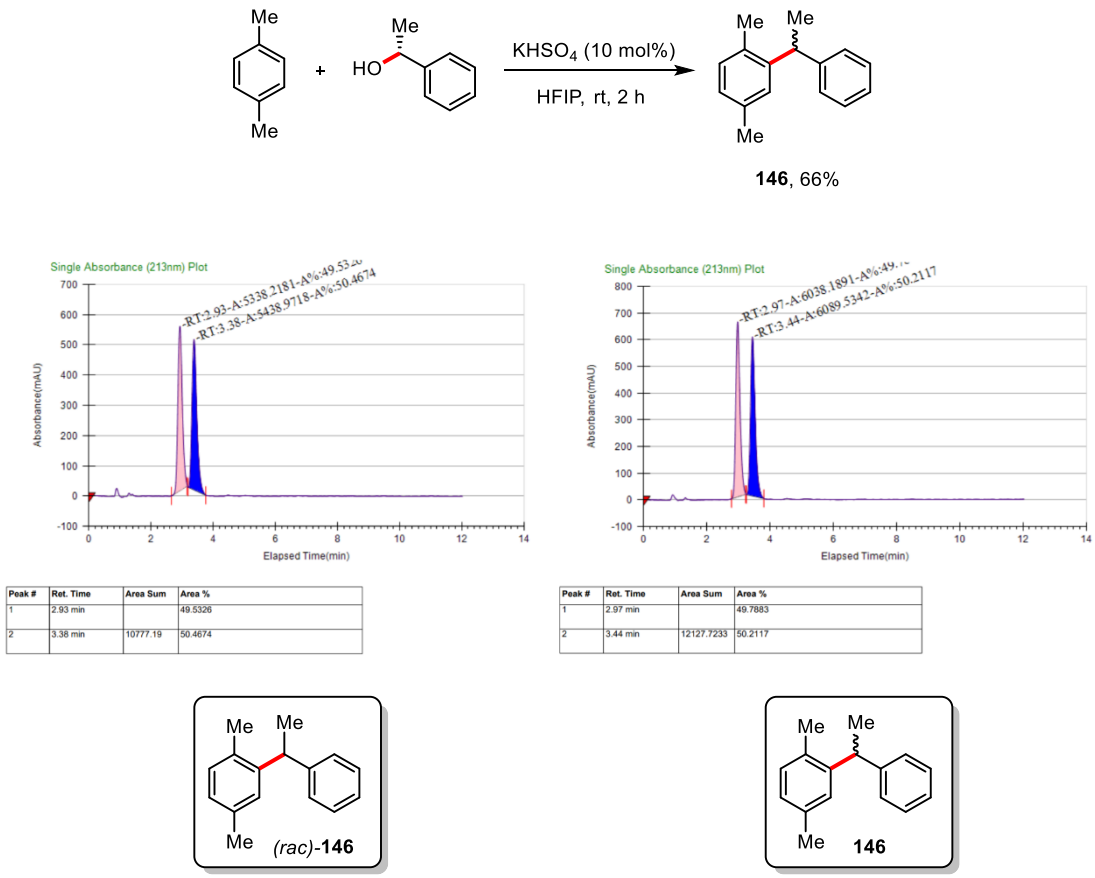
Table 17. Comparison of Different Leaving Groups



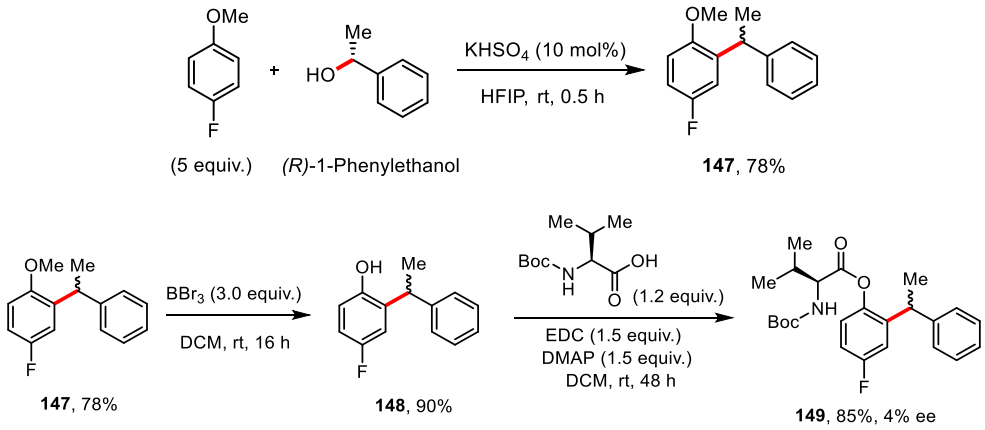
Entry	X	Time (h)	Yield (%)	**111a : 111b**
1	OH	2	86	76 : 24
2	OAc	2	77	74 : 26
3	OMe	16	64	79 : 21
4	OPh	2	72	78 : 22
5	Cl	2	85	78 : 22
6	Br	2	82	78 : 22

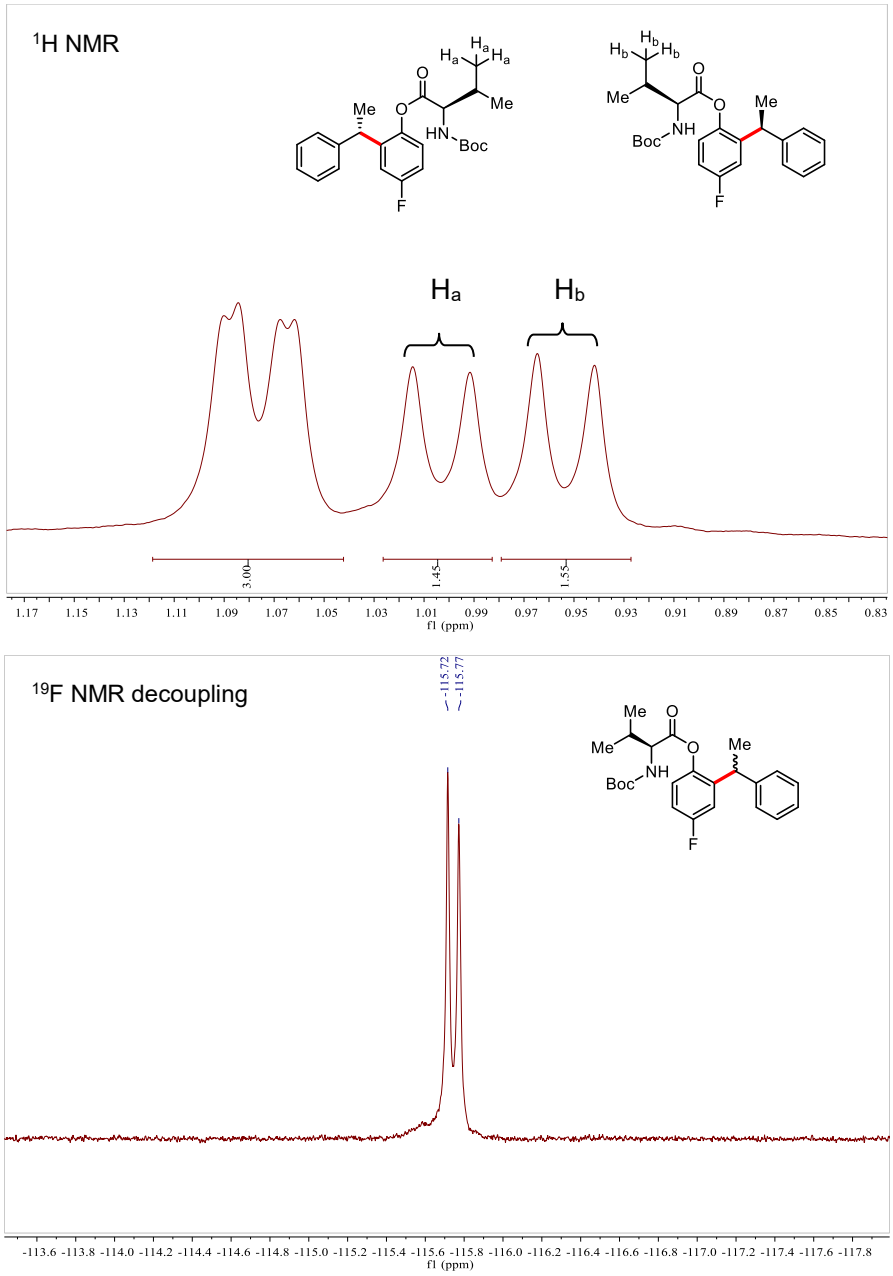
III. 2. 4. Stereochemical Studies

In order to know if the mechanism involved a carbocation in intermedium, the reaction of *(R)*-1-phenylethanol with *p*-xylene and 4-fluoroanisole under standard conditions was performed.



Scheme 41. Stereochemical Studies-1



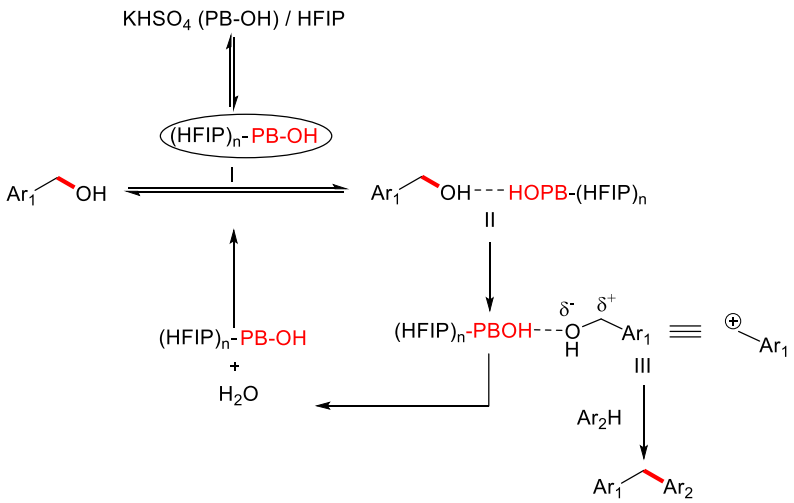


Scheme 42. Stereochemical Studies-2

The stereoselectivities were determinate by Chiral SFC chromatogram (8-OJ 4.6x250mm co-solvent: 1-Isopropanol) for product **146** and ^{1}H NMR and ^{19}F NMR analysis of the resulting phenyl valinate for product **147**, which were found almost complete loss of stereochemical information. This result indicates that a carbocation is formed in the media of potassium bisulfate and HFIP.

III. 2. 5. Plausible Mechanism

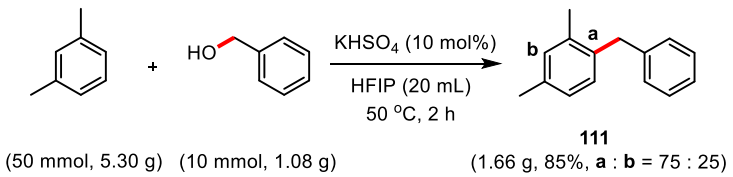
A plausible mechanism was proposed in **Scheme 43**. The substrate scope of the reaction supports an S_N1-type mechanism. First, the hydrogen-bonding cluster generated from HFIP forms a hydrogen-bonding complex with $KHSO_4$ (PB) to grant the $KHSO_4$ increased acidity and generate a superior catalytic specie **I.** Several other Brønsted acids in HFIP catalyzed reactions have been reported recently.[53-58] The hydrogen bonding between the benzylic alcohols and **I**, would generate complex **II**. The ionization of complex **II** to Intermediate **III** which then react by electrophilic aromatic substitution with Ar_2-H to yield the desired diarylmethanes, along with a proton, which would eventually combine with hydroxide ions to generate water.



Scheme 43. A Plausible Mechanism for The FC Benzylation

III. 2. 6. Gram Scale Reaction

To highlight the synthetic utility of this protocol, we conducted the reaction on a gram scale (**Scheme 44**). Under the optimized conditions, the gram-scale benzylation of *m*-xylene with benzyl alcohol proceeded smoothly to give the corresponding diarylmethanes **111** in 85% yield.



Scheme 44. Gram Scale Reaction

IV Conclusion

We have developed an effective and clean FC alkylation of indoles and electron-rich arenes with β-nitroalkenes in HFIP. The desired products formed smoothly in short times at ambient temperature without any additional catalysts or reagents. Further, this methodology can be applied to one-pot synthesis of biologically active tryptamine derivatives.

Meanwhile, mild and efficient catalytic processes for FC benzylation of a variety of slightly activated and neutral arenes with a variety of benzyl alcohols including modestly electronically deactivated benzylic alcohols and secondary benzylic alcohols have been developed. The optimal reaction conditions, using the cheap and green $KHSO_4$ in HFIP as solvent, providing a wide variety of unsymmetrical diarylmethanes and other 1,1-diarylalkane products in high yield with good to high regioselectivity compared to previously reported catalysts for similar Friedel-Crafts procedures with benzylic alcohols, including $FeCl_3$, $Bi(OTf)_3$, and ferroceniumboronic acid salt. An S_N1 mechanism was proposed according to the substrates scope and stereochemical studies.

V. Experimental Section

General Information and Reagents

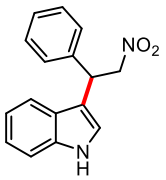
High-resolution mass spectra (HRMS) were obtained from waters LCT Premier (ESI/TOF). Melting points were determined on a Kofler melting point apparatus. NMR spectra were measured on an Ultrafield AVANCE300 (^{1}H, 300 MHz; ^{13}C, 75 MHz) spectrometer. Unless otherwise stated, NMR data were obtained under ambient temperature conditions in $CDCl_3$. Chemical shifts for ^{1}H NMR and ^{13}C NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the solvent resonance as the internal standard.

Unless otherwise noted, all commercial materials were purchased from various commercial sources (Sigma-Aldrich, Alfa Aesar, FluoroChem) and used as received, without further purification. HFIP was provided by. Central Glass Co. Ltd.

General Procedure for The FC Alkylation of Indoles with *β*-Nitroalkenes

To a stirred solution of indoles (0.6 mmol) in HFIP (2 mL) was added *β*-nitroalkene (0.5 mmol) under air. The reaction mixture was stirred at room temperature for 2 ~ 16 h. After, the reaction mixture was evaporated under reduce pressure and the crude product was purified by column chromatography on silica gel using cyclohexane/ethyl acetate as the eluent to give the corresponding products.

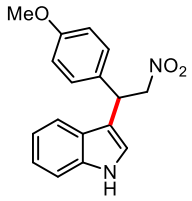
3-(2-nitro-1-phenylethyl)-1H-indole (70) [59]



The title compound was prepared between indole (70.2 mg, 0.6 mmol, 1.2 equiv.) and (2-nitrovinyl)benzene (74.5 mg, 0.5 mmol) in HFIP (2 ml) at rt for 2 h and purified by 10% of ethyl acetate in cyclohexane as a white solid (128 mg, 96%).

M.p. 102 - 104 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.50 (d, J = 7.9 Hz, 1H), 7.38 – 7.22 (m, 7H), 7.13 (t, J = 7.5 Hz, 1H), 7.00 (d, J = 2.3 Hz, 1H), 5.24 (t, J = 8.0 Hz, 1H), 5.13 – 5.06 (m, 1H), 5.01 – 4.94 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.3, 136.6, 129.0, 127.9, 127.6, 126.2, 122.7, 121.7, 120.0, 119.0, 114.4, 111.5, 79.6, 41.6.

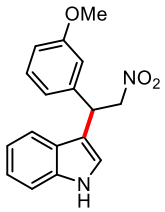
3-(1-(4-methoxyphenyl)-2-nitroethyl)-1H-indole (71) [59]



The title compound was prepared between indole (70.2 mg, 0.6 mmol, 1.2 equiv.) and 1-methoxy-4-(2-nitrovinyl)benzene (89.5 mg, 0.5 mmol) in HFIP (2 ml) at rt for 2 h and purified by 10% of ethyl acetate in cyclohexane as a white solid (141 mg, 95%).

M.p. 154 - 156 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.25 – 7.17 (m, 3H), 7.07 (t, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 1.8 Hz, 1H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.14 (t, *J* = 7.9 Hz, 1H), 5.08 – 5.01 (m, 1H), 4.93 – 4.86 (m, 1H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 136.7, 131.3, 128.9, 126.3, 122.8, 121.6, 120.1, 119.2, 115.0, 114.4, 111.5, 79.9, 55.4, 41.0.

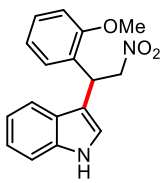
3-(1-(3-methoxyphenyl)-2-nitroethyl)-1H-indole (72) [59]



The title compound was prepared between indole (70.2 mg, 0.6 mmol, 1.2 equiv.) and 1-methoxy-3-(2-nitrovinyl)benzene (89.5 mg, 0.5 mmol) in HFIP (2 ml) at rt for 2 h and purified by 10% of ethyl acetate in cyclohexane as a light yellow liquid (141 mg, 95%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.28 – 7.18 (m, 2H), 7.09 (t, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 2.3 Hz, 1H), 6.94 (d, *J* = 7.9 Hz, 1H), 6.88 (s, 1H), 6.82 – 6.79 (m, 1H), 5.17 (t, *J* = 7.9 Hz, 1H), 5.08 – 5.02 (m, 1H), 4.97 – 4.90 (m, 1H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 140.9, 136.6, 130.0, 126.2, 122.8, 121.7, 120.1, 120.1, 119.0, 114.4, 114.1, 112.6, 111.5, 79.6, 55.3, 41.6.

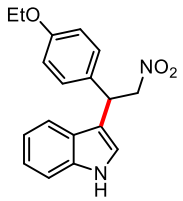
3-(1-(2-methoxyphenyl)-2-nitroethyl)-1H-indole (73) [60]



The title compound was prepared between indole (70.2 mg, 0.6 mmol, 1.2 equiv.) and 1-methoxy-3-(2-nitrovinyl)benzene (89.5 mg, 0.5 mmol) in HFIP (2 ml) at rt for 2 h and purified by 10% of ethyl acetate in cyclohexane as a white solid (137 mg, 93%).

M.p. 92 - 94 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.49 (d, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.26 – 7.06 (m, 5H), 6.93 (d, *J* = 8.2 Hz, 1H), 6.85 (t, *J* = 7.5 Hz, 1H), 5.62 (t, *J* = 7.5 Hz, 1H), 5.09 – 4.95 (m, 2H), 3.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 136.5, 129.1, 128.8, 127.4, 126.7, 122.6, 122.1, 120.9, 119.9, 119.2, 114.1, 111.4, 111.0, 78.3, 55.7, 35.7.

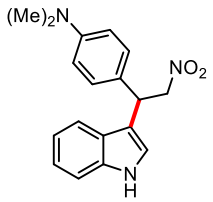
3-(1-(4-ethoxyphenyl)-2-nitroethyl)-1H-indole (74)



The title compound was prepared between indole (70.2 mg, 0.6 mmol, 1.2 equiv.) and 1-ethoxy-4-(2-nitrovinyl)benzene (96.5 mg, 0.5 mmol) in HFIP (2 ml) at rt for 2 h and purified by 10% of ethyl acetate in cyclohexane as a yellow solid (149 mg, 96%).

M.p. 114 - 116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.45 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.26 – 7.18 (m, 3H), 7.08 (t, *J* = 7.5 Hz, 1H), 7.00 (s, 1H), 6.84 (d, *J* = 8.5 Hz, 2H), 5.14 (t, *J* = 7.9 Hz, 1H), 5.08 – 5.01 (m, 1H), 4.93 – 4.86 (m, 1H), 4.00 (q, *J* = 7.0 Hz, 2H), 1.40 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 136.6, 131.1, 128.9, 126.2, 122.7, 121.6, 120.0, 119.1, 114.9, 111.5, 110.1, 79.9, 63.6, 41.0, 14.9; HRMS calcd. for $C_{18}H_{19}N_2O_3$ $[M+H]^+$ m/z 311.1396, found 311.1389.

4-(1-(1H-indol-3-yl)-2-nitroethyl)-N, N-dimethylaniline (75) [61]

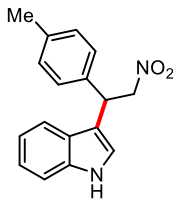


The title compound was prepared between indole (70.2 mg, 0.6 mmol, 1.2 equiv.) and N, N-dimethyl-4-(2-nitrovinyl)aniline (96.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 2 h and purified by 10% of ethyl acetate in cyclohexane as a white solid (150 mg, 97%).

M.p. 132 - 134 °C; ^{1}H NMR (300 MHz, DMSO) δ 10.99 (s, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.94 (t, *J* = 7.4 Hz, 1H),

6.64 (d, J = 8.5 Hz, 2H), 5.30 – 5.14 (m, 2H), 4.93 (t, J = 8.1 Hz, 1H), 2.82 (s, 6H); ^{13}C NMR (75 MHz, DMSO) δ 149.3, 136.3, 128.3, 128.0, 126.1, 121.9, 121.3, 118.5, 118.5, 114.1, 112.4, 111.5, 79.6, 40.2, 40.1.

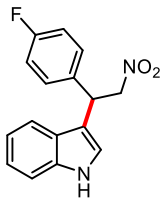
3-(2-nitro-1-(p-tolyl)ethyl)-1H-indole (76) [59]



The title compound was prepared between indole (70.2 mg, 0.6 mmol, 1.2 equiv.) and 1-methyl-4-(2-nitrovinyl)benzene (81.5 mg, 0.5 mmol) in HFIP (2 ml) at rt for 2 h and purified by 10% of ethyl acetate in cyclohexane as a light yellow liquid (133 mg, 95%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.48 (d, J = 7.9 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.26 – 7.19 (m, 3H), 7.16 – 7.08 (m, 3H), 7.00 (d, J = 2.2 Hz, 1H), 5.17 (t, J = 7.9 Hz, 1H), 5.09 – 5.02 (m, 1H), 4.96 – 4.89 (m, 1H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3, 136.6, 136.3, 129.7, 127.7, 126.2, 122.7, 121.7, 120.0, 119.0, 114.7, 111.5, 79.7, 41.3, 21.2.

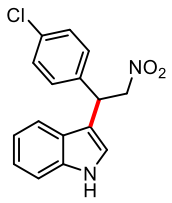
3-(1-(4-fluorophenyl)-2-nitroethyl)-1H-indole (77) [59]



The title compound was prepared between indole (70.2 mg, 0.6 mmol, 1.2 equiv.) and 1-fluoro-4-(2-nitrovinyl)benzene (83.5 mg, 0.5 mmol) in HFIP (2 ml) at rt for 2 h and purified by 10% of ethyl acetate in cyclohexane as a light yellow liquid (131 mg, 92%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.44 – 7.20 (m, 5H), 7.11 (t, J = 7.5 Hz, 1H), 7.04 – 6.99 (m, 3H), 5.19 (t, J = 8.0 Hz, 1H), 5.09 – 5.03 (m, 1H), 4.94 – 4.87 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.2 (d, J = 244.5 Hz), 136.6, 135.1 (d, J = 3.0 Hz), 129.5 (d, J = 8.1 Hz), 126.0, 122.9, 121.6, 120.1, 118.9, 115.9 (d, J = 21.4 Hz), 114.3, 111.6, 79.6, 41.0.

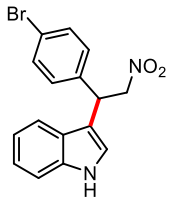
3-(1-(4-chlorophenyl)-2-nitroethyl)-1H-indole (78) [59]



The title compound was prepared between indole (70.2 mg, 0.6 mmol, 1.2 equiv.) and 1-chloro-4-(2-nitrovinyl)benzene (92.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 2 h and purified by 10% of ethyl acetate in cyclohexane as a white solid (143 mg, 96%).

M.p. 108 - 110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.42 – 7.19 (m, 7H), 7.09 (t, *J* = 7.5 Hz, 1H), 7.01 (s, 1H), 5.17 (t, *J* = 7.9 Hz, 1H), 5.09 – 5.02 (m, 1H), 4.94 – 4.87 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 136.6, 133.5, 129.3, 129.2, 126.0, 123.0, 121.7, 120.2, 118.9, 114.1, 111.6, 79.4, 41.1.

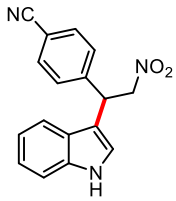
3-(1-(4-bromophenyl)-2-nitroethyl)-1H-indole (79) [59]



The title compound was prepared between indole (70.2 mg, 0.6 mmol, 1.2 equiv.) and 1-bromo-4-(2-nitrovinyl)benzene (113.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 2 h and purified by 10% of ethyl acetate in cyclohexane as a white solid (161 mg, 94%).

M.p. 128 - 130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.46 – 7.35 (m, 4H), 7.26 – 7.20 (m, 3H), 7.10 (t, *J* = 7.3 Hz, 1H), 7.00 (d, *J* = 1.8 Hz, 1H), 5.16 (t, *J* = 7.9 Hz, 1H), 5.08 – 5.02 (m, 1H), 4.94 – 4.87 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 136.6, 132.2, 129.6, 126.0, 123.0, 121.6, 120.2, 118.9, 114.0, 111.6, 110.1, 79.3, 41.1.

4-(1-(1H-indol-3-yl)-2-nitroethyl)benzonitrile (80)

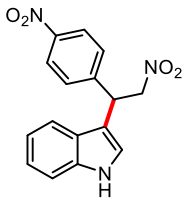


The title compound was prepared between indole (70.2 mg, 0.6 mmol, 1.2 equiv.) and 4-(2-nitrovinyl)benzonitrile (87.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 2 h and purified by 10% of ethyl acetate in cyclohexane as a white solid (137 mg, 94%).

M.p. 160 - 162 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.46

(d, J = 8.1 Hz, 2H), 7.38 (t, J = 7.6 Hz, 2H), 7.22 (d, J = 7.8 Hz, 1H), 7.10 (t, J = 7.6 Hz, 1H), 7.04 (s, 1H), 5.30 – 5.22 (m, 1H), 5.12 – 5.05 (m, 1H), 4.99 – 4.92 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.9, 136.6, 132.9, 128.8, 125.8, 123.2, 121.7, 120.4, 118.7, 118.6, 113.2, 111.8, 78.9, 41.6; HRMS calcd. for $C_{17}H_{14}N_3O_2$ $[M+H]^+$ m/z 292.1086, found 292.1093.

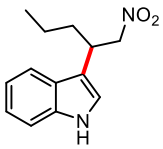
3-(2-nitro-1-(4-nitrophenyl)ethyl)-1H-indole (81) [62]



The title compound was prepared between indole (70.2 mg, 0.6 mmol, 1.2 equiv.) and 1-nitro-4-(2-nitrovinyl)benzene (97.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 2 h and purified by 10% of ethyl acetate in cyclohexane as a yellow solid (147 mg, 95%).

M.p. 154 - 156 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 – 8.16 (m, 3H), 7.52 (d, J = 8.6 Hz, 2H), 7.38 (t, J = 7.5 Hz, 2H), 7.23 (t, J = 7.5 Hz, 1H), 7.12 – 7.05 (m, 2H), 5.30 (t, J = 7.8 Hz, 1H), 5.15 – 5.08 (m, 1H), 5.03 – 4.95 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.8, 136.6, 128.9, 125.7, 124.3, 123.3, 121.7, 120.5, 118.6, 113.1, 111.8, 110.1, 78.9, 41.4.

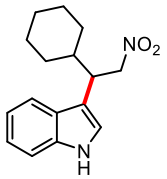
3-(1-nitropentan-2-yl)-1H-indole (82) [63]



The title compound was prepared between indole (70.2 mg, 0.6 mmol, 1.2 equiv.) and 1-nitropent-1-ene (57.5 mg, 0.5 mmol) in HFIP (2 ml) at rt for 8 h and purified by 10% of ethyl acetate in cyclohexane as a light-yellow liquid (104 mg, 90%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.26 – 7.12 (m, 2H), 7.04 (d, J = 2.2 Hz, 1H), 4.72 – 4.60 (m, 2H), 3.87 – 3.77 (m, 1H), 1.95 – 1.70 (m, 2H), 1.40 – 1.26 (m, 2H), 0.90 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.6, 126.3, 122.6, 122.0, 119.9, 118.9, 114.3, 111.6, 80.7, 36.2, 34.7, 20.5, 14.0.

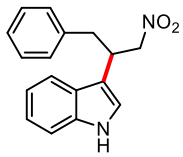
3-(1-cyclohexyl-2-nitroethyl)-1H-indole (83) [16]



The title compound was prepared between indole (70.2 mg, 0.6 mmol, 1.2 equiv.) and (2-nitrovinyl)cyclohexane (77.5 mg, 0.5 mmol) in HFIP (2 ml) at rt for 8 h and purified by 10% of ethyl acetate in cyclohexane as a light-yellow liquid (119 mg, 88%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.26 – 7.12 (m, 2H), 6.97 (d, J = 2.0 Hz, 1H), 4.86 – 4.69 (m, 2H), 3.73 – 3.65 (m, 1H), 1.87 – 1.65 (m, 6H), 1.33 – 0.89 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.4, 127.0, 122.4, 119.8, 119.2, 113.4, 111.5, 78.6, 42.0, 40.6, 31.3, 30.6, 26.4, 26.3.

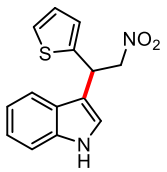
3-(1-nitro-3-phenylpropan-2-yl)-1H-indole (84)



The title compound was prepared between indole (70.2 mg, 0.6 mmol, 1.2 equiv.) and (3-nitroallyl)benzene (81.5 mg, 0.5 mmol) in HFIP (2 ml) at rt for 8 h and purified by 10% of ethyl acetate in cyclohexane as a yellow liquid (117 mg, 84%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.36 – 7.14 (m, 8H), 6.88 (d, J = 1.9 Hz, 1H), 4.77 – 4.64 (m, 2H), 4.20 – 4.10 (m, 1H), 3.29 – 3.22 (m, 1H), 3.15 – 3.08 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 136.5, 129.2, 128.6, 126.7, 126.0, 122.5, 122.1, 119.9, 118.7, 113.7, 111.7, 79.2, 38.9, 38.1; HRMS calcd. for $C_{17}H_{17}N_2O_2$ $[M+H]^+$ m/z 281.1290, found 281.1292.

3-(2-nitro-1-(thiophen-2-yl)ethyl)-1H-indole (85) [62]

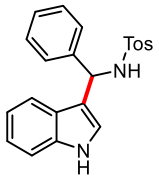


The title compound was prepared between indole (70.2 mg, 0.6 mmol, 1.2 equiv.) and 2-(2-nitrovinyl)thiophene (69.5 mg, 0.5 mmol) in HFIP (2 ml) at rt for 2 h and purified by 10% of ethyl acetate in cyclohexane as a yellow liquid (118 mg, 92%).

Yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.40 – 7.35

(m, 2H), 7.26 – 7.09 (m, 3H), 6.33 – 6.32 (m, 1H), 6.18 (d, J = 3.1 Hz, 1H), 5.27 (t, J = 7.8 Hz, 1H), 5.10 – 5.04 (m, 1H), 4.96 – 4.89 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.3, 142.4, 136.4, 125.8, 122.8, 122.8, 120.2, 118.8, 111.7, 110.6, 110.1, 107.5, 78.0, 35.8.

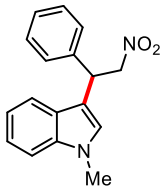
N-((1H-indol-3-yl)(phenyl)methyl)-4-methylbenzenesulfonamide (86) [22]



The title compound was prepared between indole (70.2 mg, 0.6 mmol, 1.2 equiv.) and N-benzylidene-*p*-toluenesulfonamide (129.5 mg, 0.5 mmol) in HFIP (2 ml) at rt for 16 h and purified by 15% of ethyl acetate in cyclohexane as a white solid (161 mg, 86%).

M.p. 160 - 162 °C; ^{1}H NMR (300 MHz, DMSO) δ 10.87 (s, 1H), 8.50 (d, J = 8.8 Hz, 1H), 7.50 (d, J = 8.0 Hz, 2H), 7.33 – 7.26 (m, 4H), 7.17 – 7.01 (m, 6H), 6.88 (t, J = 7.4 Hz, 1H), 6.79 (s, 1H), 5.75 (d, J = 8.7 Hz, 1H), 2.26 (d, J = 10.8 Hz, 3H); ^{13}C NMR (75 MHz, DMSO) δ 141.8, 141.7, 138.8, 136.4, 128.9, 127.9, 127.1, 126.6, 126.4, 125.5, 123.7, 121.2, 118.9, 118.5, 115.72, 111.4, 54.5, 20.9.

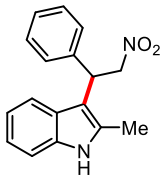
1-methyl-3-(2-nitro-1-phenylethyl)-1H-indole (87) [64]



The title compound was prepared between 1-methyl-1H-indole (78.6 mg, 0.6 mmol, 1.2 equiv.) and (2-nitrovinyl)benzene (74.5 mg, 0.5 mmol) in HFIP (2 ml) at rt for 2 h and purified by 10% of ethyl acetate in cyclohexane as a white solid (136 mg, 97%).

M.p. 96 - 98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, J = 8.0 Hz, 1H), 7.36 – 7.22 (m, 7H), 7.10 (t, J = 7.3 Hz, 1H), 6.88 (s, 1H), 5.21 (t, J = 8.0 Hz, 1H), 5.10 – 5.03 (m, 1H), 4.98 – 4.91 (m, 1H), 3.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.5, 137.4, 129.0, 127.8, 127. 6, 126.6, 126.5, 122.3, 119.6, 119.1, 112.9, 109.6, 79.7, 41.6, 32.9.

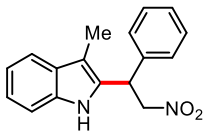
2-methyl-3-(2-nitro-1-phenylethyl)-1H-indole (88) [64]



The title compound was prepared between 2-methyl-1H-indole (78.6 mg, 0.6 mmol, 1.2 equiv.) and (2-nitrovinyl)benzene (74.5 mg, 0.5 mmol) in HFIP (2 ml) at rt for 2 h and purified by 10% of ethyl acetate in cyclohexane as a white solid (133 mg, 95%).

M.p. 110 - 112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.41 – 7.25 (m, 7H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.08 – 7.03 (m, 1H), 5.28 – 5.11 (m, 3H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.6, 135.5, 133.0, 128.9, 127.4, 127.2, 127.0, 121.4, 119.9, 118.7, 110.8, 109.0, 78.7, 40.6, 12.1.

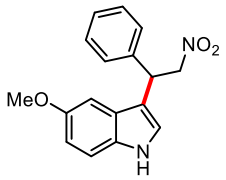
3-methyl-2-(2-nitro-1-phenylethyl)-1H-indole (89) [65]



The title compound was prepared between 3-methyl-1H-indole (115.8 mg, 0.6 mmol, 1.2 equiv.) and (2-nitrovinyl)benzene (74.5 mg, 0.5 mmol) in HFIP (2 mL) at rt for 4 h and purified by 10% of ethyl acetate in cyclohexane as a white solid (115 mg, 82%).

M.p. 130 - 132 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.55 (d, *J* = 7.1 Hz, 1H), 7.42 – 7.23 (m, 6H), 7.19 – 7.10 (m, 2H), 5.26 (t, *J* = 7.9 Hz, 1H), 5.12 – 5.05 (m, 1H), 4.98 – 4.92 (m, 1H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.1, 135.9, 130.7, 129.5, 129.2, 128.2, 127.4, 122.4, 119.8, 118.9, 110.9, 109.6, 77.7, 41.2, 8.8.

5-methoxy-3-(2-nitro-1-phenylethyl)-1H-indole (90) [62]

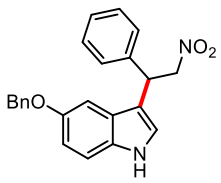


The title compound was prepared between 5-methoxy-1H-indole (88.2 mg, 0.6 mmol, 1.2 equiv.) and (2-nitrovinyl)benzene (74.5 mg, 0.5 mmol) in HFIP (2 mL) at rt for 2 h and purified by 10% of ethyl acetate in cyclohexane as a yellow solid (142 mg, 96%).

M.p. 104 - 106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.34 – 7.21 (m, 6H), 6.98 (d, *J*

= 2.3 Hz, 1H), 6.88 – 6.85 (m, 2H), 5.14 (t, *J* = 7.9 Hz, 1H), 5.08 – 5,01 (m, 1H), 4.97 – 4.90 (m, 1H), 3.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 139.3, 131.7, 129.0, 127.9, 127.7, 126.7, 122.4, 114.2, 112.9, 112.2, 101.0, 79.6, 56.0, 41.7.

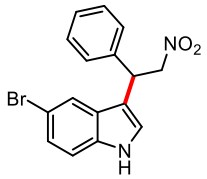
5-(benzyloxy)-3-(2-nitro-1-phenylethyl)-1H-indole (91) [22]



The title compound was prepared between 5-(benzyloxy)-1H-indole (133.8 mg, 0.6 mmol, 1.2 equiv.) and (2-nitrovinyl)benzene (74.5 mg, 0.5 mmol) in HFIP (2 mL) at rt for 2 h and purified by 10% of ethyl acetate in cyclohexane as a white solid (179 mg, 96%).

M.p. 102 - 104 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.46 – 7.21 (m, 11H), 6.95 – 6.93 (m, 3H), 5.12 (t, *J* = 8.1 Hz, 1H), 5.03 – 4.88 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.4, 139.2, 137.5, 131.9, 129.1, 128.7, 128.0, 127.9, 127.8, 127.7, 126.6, 122.4, 114.2, 113.6, 112.2, 102.7, 79.5, 71.0, 41.7.

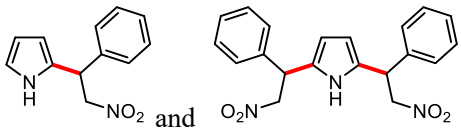
5-bromo-3-(2-nitro-1-phenylethyl)-1H-indole (92) [64]



The title compound was prepared between 5-bromo-1H-indole (117.6 mg, 0.6 mmol, 1.2 equiv.) and (2-nitrovinyl)benzene (74.5 mg, 0.5 mmol) in HFIP (2 mL) at rt for 2 h and purified by 10% of ethyl acetate in cyclohexane as a white solid (158 mg, 92%).

M.p. 130 - 132 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.56 (s, 1H), 7.36 – 7.18 (m, 7H), 7.04 (d, *J* = 2.0 Hz, 1H), 5.13 (t, *J* = 7.9 Hz, 1H), 5.05 – 4.99 (m, 1H), 4.95 – 4.88 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 135.2, 129.2, 128.0, 127.9, 127.8, 125.8, 122.9, 121.6, 114.2, 113.4, 113.0, 79.5, 41.4.

3-(2-nitro-1-phenylethyl)-1H-pyrrole and 2,5-bis(2-nitro-1-phenylethyl)-1H-pyrrole (93) [62]



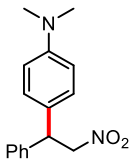
The title compound was prepared between 1H-pyrrole (40.2 mg, 0.6 mmol, 1.2 equiv.) and (2-nitrovinyl)benzene (74.5 mg, 0.5 mmol) in HFIP (2 mL) at rt for 2 h and purified by 10% of ethyl acetate in cyclohexane as a yellow liquid (122 mg, 85%).

Yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 0.77 × 1H), 7.58 (s, 0.23 × 1H), 7.39 – 7.15 (m, 0.77 × 5H + 0.23 × 10H), 6.69 (s, 0.77 × 1H), 6.18 – 6.16 (m, 0.77 × 1H), 6.10 (br, 0.77 × 1H), 6.02 – 5.99 (m, 0.23 × 2H), 5.02 – 4.70 (m, m, 0.77 × 3H + 0.23 × 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 137.9, 129.7, 129.3, 129.2, 128.2, 128.0, 127.9, 127.9, 118.3, 108.8, 106.6, 106.3, 105.9, 79.3, 79.3, 43.1, 42.9.

General Procedure for The FC Alkylation of Electron-Rich Arenes with *β*-Nitroalkenes

To a stirred solution of electron-rich arenes (0.6 mmol) in HFIP (2 mL) was added *β*-nitroalkene (0.5 mmol) under air. The reaction mixture was stirred at room temperature for 16 ~ 24 h. After, the reaction mixture was evaporated under reduce pressure and the crude product was purified by column chromatography on silica gel using cyclohexane: ethyl acetate as the eluent to give title products.

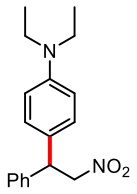
N, N-dimethyl-4-(2-nitro-1-phenylethyl)aniline (94) [12]



The title compound was prepared between N, N-dimethylaniline (72.6 mg, 0.6 mmol, 1.2 equiv.) and (2-nitrovinyl)benzene (74.5 mg, 0.5 mmol) in HFIP (2 mL) at rt for 16 h and purified by 5% of ethyl acetate in cyclohexane as a light-yellow liquid (127 mg, 94%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 - 7.26 (m, 5H), 7.12 (d, J = 8.7 Hz, 2H), 6.70 (d, J = 8.7 Hz, 2H), 4.99 - 4.95 (m, 2H), 4.91 – 4.81 (m, 1H), 2.95 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9, 140.1, 129.0, 128.5, 127.7, 127.4, 126.8, 112.9, 79.7, 48.3, 40.6.

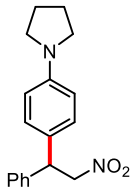
N, N-diethyl-4-(2-nitro-1-phenylethyl)aniline (95) [12]



The title compound was prepared between N, N-diethylaniline (89.4 mg, 0.6 mmol, 1.2 equiv.) and (2-nitrovinyl)benzene (74.5 mg, 0.5 mmol) in HFIP (2 mL) at rt for 16 h and purified by 5% of ethyl acetate in cyclohexane as a light-yellow liquid (134 mg, 90%).

Light yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.22 (m, 5H), 7.07 (d, J = 8.4 Hz, 2H), 6.62 (d, J = 7.8 Hz, 2H), 5.01 – 4.88 (m, 2H), 4.81 (t, J = 7.8 Hz, 1H), 3.33 (q, J = 7.0 Hz, 4H), 1.15 (t, J = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.2, 140.2, 129.0, 128.7, 127.7, 127.4, 125.6, 112.0, 79.8, 48.4, 44.4, 12.7.

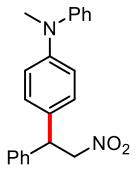
1-(4-(2-nitro-1-phenylethyl)phenyl)pyrrolidine (96) [12]



The title compound was prepared between 1-phenylpyrrolidine (88.2 mg, 0.6 mmol, 1.2 equiv.) and (2-nitrovinyl)benzene (74.5 mg, 0.5 mmol) in HFIP (2 mL) at rt for 16 h and purified by 5% of ethyl acetate in cyclohexane as a light-green solid (139 mg, 94%).

M.p. 90 - 92 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.21 (m, 5H), 7.09 (d, J = 8.6 Hz, 2H), 6.55 (d, J = 8.1 Hz, 2H), 5.01 – 4.89 (m, 2H), 4.82 (t, J = 8.1 Hz, 1H), 3.27 (t, J = 6.3 Hz, 4H), 2.02 – 1.98 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 140.3, 129.0, 128.6, 127.7, 127.4, 126.0, 112.3, 79.8, 48.5, 48.0, 25.6.

N-methyl-4-(2-nitro-1-phenylethyl)-N-phenylaniline (97)

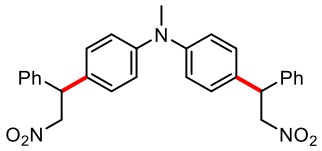


The title compound was prepared between N-methyl-N-phenylaniline (109.8 mg, 0.6 mmol, 1.2 equiv.) and (2-nitrovinyl)benzene (74.5 mg, 0.5 mmol) in HFIP (2 mL) at rt for 16 h and purified by 5% of ethyl acetate in cyclohexane as a light-yellow liquid (108 mg, 65%).

Light yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.25 (m, 7H), 7.13 – 7.00 (m, 5H),

6.93 (d, J = 8.6 Hz, 2H), 4.98 – 4.95 (m, 2H), 4.85 (t, J = 7.2 Hz, 1H), 3.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7, 148.4, 139.7, 131.0, 129.5, 129.1, 128.5, 127.7, 127.6, 122.6, 122.06, 119.4, 79.6, 48.5, 40.4; HRMS calcd. for $C_{21}H_{21}N_2O_2$ $[M+H]^+$ m/z 333.1603, found 333.1605.

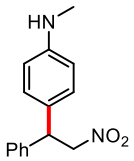
N-methyl-4-(2-nitro-1-phenylethyl)-N-(4-(2-nitro-1-phenylethyl)phenyl)aniline (97')



The title compound was prepared between N-methyl-N-phenylaniline (109.8 mg, 0.6 mmol, 1.2 equiv.) and (2-nitrovinyl)benzene (74.5 mg, 0.5 mmol) in HFIP (2 mL) at rt for 16 h and purified by 10% of ethyl acetate in cyclohexane as a light-yellow solid (21 mg, 13%).

M.p. 130 - 132 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.26 (m, 10H), 7.17 (d, J = 8.6 Hz, 4H), 6.98 (d, J = 8.5 Hz, 4H), 5.00 – 4.87 (m, 6H), 3.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.0, 139.6, 132.1, 129.1, 128.6, 127.7, 127.6, 120.9, 79.5, 48.5, 40.24; HRMS calcd. for $C_{29}H_{28}N_3O_4$ $[M+H]^+$ m/z 482.2080, found 482.2080.

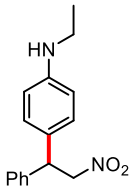
N-methyl-4-(2-nitro-1-phenylethyl)aniline (98)



The title compound was prepared between N-methylaniline (64.2 mg, 0.6 mmol, 1.2 equiv.) and (2-nitrovinyl)benzene (74.5 mg, 0.5 mmol) in HFIP (2 mL) at rt for 24 h and purified by 10% of ethyl acetate in cyclohexane as a light-green solid (86 mg, 67%).

M.p. 94 - 96 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.23 (m, 5H), 7.06 (d, J = 8.4 Hz, 2H), 6.58 (d, J = 8.4 Hz, 2H), 4.96 – 4.88 (m, 2H), 4.81 (t, J = 8.1 Hz, 1H), 3.75 (s, 1H), 2.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5, 140.0, 129.0, 128.6, 127.8, 127.7, 127.4, 113.0, 79.7, 48.4, 30.9; HRMS calcd. for $C_{15}H_{17}N_2O_2$ $[M+H]^+$ m/z 257.1290, found 257.1282.

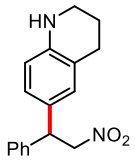
N-ethyl-4-(2-nitro-1-phenylethyl)aniline (99)



The title compound was prepared between N-ethylaniline (72.6 mg, 0.6 mmol, 1.2 equiv.) and (2-nitrovinyl)benzene (74.5 mg, 0.5 mmol) in HFIP (2 mL) at rt for 24 h and purified by 10% of ethyl acetate in cyclohexane as a light-yellow liquid (87 mg, 64%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.22 (m, 5H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.56 (d, *J* = 8.5 Hz, 2H), 4.99 – 4.87 (m, 2H), 4.80 (d, *J* = 7.8 Hz, 1H), 3.16 – 3.09 (m, 3H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.7, 140.0, 129.0, 128.6, 127.7, 127.4, 113.2, 79.8, 48.4, 38.6, 14.9; HRMS calcd. for $C_{16}H_{19}N_2O_2$ $[M+H]^+$ m/z 271.1447, found 271.1439.

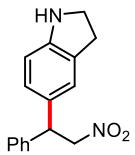
6-(2-nitro-1-phenylethyl)-1,2,3,4-tetrahydroquinoline (100)



The title compound was prepared between 1,2,3,4-tetrahydroquinoline (79.8 mg, 0.6 mmol, 1.2 equiv.) and (2-nitrovinyl)benzene (74.5 mg, 0.5 mmol) in HFIP (2 mL) at rt for 24 h and purified by 10% of ethyl acetate in cyclohexane as a yellow liquid (92 mg, 65%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.23 (m, 5H), 6.83 (m, 2H), 6.42 (d, *J* = 7.8 Hz, 1H), 4.99 – 4.87 (m, 2H), 4.77 (t, *J* = 7.8 Hz, 1H), 3.88 (s, 1H), 3.27 (t, *J* = 5.4 Hz, 2H), 2.72 (t, *J* = 6.4 Hz, 2H), 1.96 – 1.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 140.2, 128.9, 128.9, 127.6, 127.4, 127.3, 125.9, 121.9, 114.5, 79.7, 48.5, 41.9, 27.0, 22.0; HRMS calcd. for $C_{17}H_{19}N_2O_2$ $[M+H]^+$ m/z 283.1447, found 283.1439.

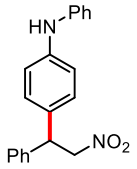
5-(2-nitro-1-phenylethyl)indoline (101)



The title compound was prepared between indoline (71.4 mg, 0.6 mmol, 1.2 equiv.) and (2-nitrovinyl)benzene (74.5 mg, 0.5 mmol) in HFIP (2 mL) at rt for 24 h and purified by 10% of ethyl acetate in cyclohexane as a gray liquid (82 mg, 61%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.32 (m, 2H), 7.28 – 7.25 (m, 3H), 6.98 (s, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.60 (d, *J* = 8.0 Hz, 1H), 5.01 – 4.89 (m, 2H), 4.84 – 4.82 (m, 1H), 3.56 (t, *J* = 8.4 Hz, 3H), 3.00 (t, *J* = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.8, 140.1, 130.5, 129.6, 129.0, 127.6, 127.4, 126.7, 124.2, 109.7, 79.8, 48.7, 47.5, 29.8; HRMS calcd. for $C_{16}H_{17}N_2O_2$ $[M+H]^+$ m/z 269.1290, found 269.1289.

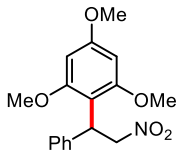
4-(2-nitro-1-phenylethyl)-N-phenylaniline (102)



The title compound was prepared between N-phenylaniline (101.4 mg, 0.6 mmol, 1.2 equiv.) and (2-nitrovinyl)benzene (74.5 mg, 0.5 mmol) in HFIP (2 mL) at rt for 24 h and purified by 10% of ethyl acetate in cyclohexane as a light-yellow liquid (72 mg, 45%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.25 (m, 7H), 7.14 – 6.94 (m, 7H), 5.88 (s, 1H), 4.98 – 4.95 (m, 2H), 4.86 (t, J = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7, 142.6, 139.7, 131.5, 129.5, 129.1, 128.7, 127.7, 127.6, 121.7, 118.5, 117.9, 79.6, 48.5, 27.1; HRMS calcd. for $C_{20}H_{19}N_2O_2$ $[M+H]^+$ m/z 319.1447, found 319.1451.

1,3,5-trimethoxy-2-(2-nitro-1-phenylethyl)benzene (103) [66]



The title compound was prepared between 1,3,5-trimethoxylbenzene (100.8 mg, 0.6 mmol, 1.2 equiv.) and (2-nitrovinyl)benzene (74.5 mg, 0.5 mmol) in HFIP (2 mL) at rt for 16 h and purified by 10% of ethyl acetate in cyclohexane as a white solid (138 mg, 87%).

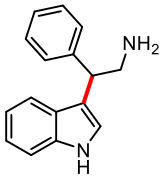
M.p. 122 - 124 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.15 (m, 5H), 6.12 (s, 2H), 5.49 (t, J = 7.8 Hz, 1H), 5.27 – 5.20 (m, 1H), 5.16 – 5.09 (m, 1H), 3.79 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7, 159.1, 140.7, 128.4, 127.7, 126.7, 108.8, 91.3, 78.5, 55.9, 55.4, 38.7.

General Procedure for One-Pot Synthesis of Substituted Tryptamines

To a stirred solution of indoles or electron-rich arenes (0.6 mmol) in HFIP (2 mL) was added *β*-nitroalkene (0.5 mmol) under air. The reaction mixture was stirred at room temperature for 2 ~ 16 h. Then zink power (2.0 mmol) and 2 N HCl (2.5 ml) were added and the mixture was refluxed for 2 h, cooled down to room temperature, NaOH (10%) was added to the above mixture until pH 10, then extracted with DCM (15 mL x 3). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduce pressure to get crude product. Then the crude product was purified by column chromatography on silica gel using

DCM/methanol as the eluent to give title products.

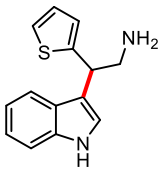
2-(1H-indol-3-yl)-2-phenylethan-1-amine (104) [67]



The title compound was prepared between indole (70.2 mg, 0.6 mmol, 1.2 equiv.) and (2-nitrovinyl)benzene (74.5 mg, 0.5 mmol) and purified by 5% of methanol in DCM as a white solid (98 mg, 83%).

M.p. 134 - 136 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.47 (d, J = 7.9 Hz, 1H), 7.35 – 7.26 (m, 5H), 7.24 – 7.15 (m, 2H), 7.07 – 7.03 (m, 2H), 4.26 (t, J = 7.4 Hz, 1H), 3.48 – 3.41 (m, 1H), 3.33 – 3.26 (m, 1H), 1.61 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1, 136.6, 128.6, 128.3, 127.2, 126.6, 122.2, 121.4, 119.5, 119.5, 117.6, 111.3, 47.4, 47.3, 47.0.

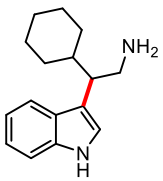
2-(1H-indol-3-yl)-2-(thiophen-2-yl)ethan-1-amine (105) [67]



The title compound was prepared between indole (70.2 mg, 0.6 mmol, 1.2 equiv.) and 2-(2-nitrovinyl)thiophene (77.5 mg, 0.5 mmol) and purified by 5% of methanol in DCM as a gray solid (93 mg, 77%).

M.p. 126 - 128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.36 – 7.34 (m, 2H), 7.19 (t, J = 7.5 Hz, 1H), 7.11 – 7.09 (m, 2H), 6.31 (br, 1H), 6.12 (d, J = 2.8 Hz, 1H), 4.34 (t, J = 7.0 Hz, 1H), 3.40 – 3.28 (m, 2H), 1.56 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5, 141.5, 136.6, 126.7, 122.4, 122.3, 119.6, 119.4, 115.0, 111.4, 110.2, 106.2, 45.9, 40.9.

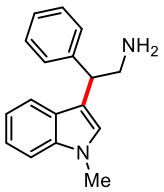
2-cyclohexyl-2-(1H-indol-3-yl)ethan-1-amine (106)



The title compound was prepared between indole (70.2 mg, 0.6 mmol, 1.2 equiv.) and (2-nitrovinyl)cyclohexane (77.5 mg, 0.5 mmol) and purified by 5% of methanol in DCM as a light-yellow liquid (75 mg, 62%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.97 (s, 1H), 3.04 – 2.99 (m, 2H), 2.79 – 2.72 (m, 1H), 1.93 – 1.43 (m, 8H), 1.31 – 0.89 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.7, 128.0, 122.3, 122.0, 119.7, 119.2, 116.6, 111.3, 44.2, 40.9, 31.8, 31.3, 26.7, 26.7; HRMS calcd. for $C_{16}H_{23}N_2$ $[M+H]^+$ m/z 243.1861, found 243.1856.

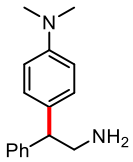
2-(1-methyl-1H-indol-3-yl)-2-phenylethan-1-amine (107) [68]



The title compound was prepared between 1-methyl-1H-indole (78.6 mg, 0.6 mmol, 1.2 equiv.) and (2-nitrovinyl)benzene (74.5 mg, 0.5 mmol) and purified by 5% of methanol in DCM as a light-yellow liquid (105 mg, 84%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.9 Hz, 1H), 7.37 – 7.29 (m, 5H), 7.26 – 7.20 (m), 7.06 (t, *J* = 7.4 Hz, 1H), 6.93 (s, 1H), 4.30 (t, *J* = 7.4 Hz, 1H), 3.75 (s, 3H), 3.48 – 3.41 (m, 1H), 3.33 – 3.26 (m, 1H), 2.13 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1, 137.3, 128.6, 128.2, 127.5, 126.5, 126.2, 121.8, 119.5, 118.9, 116.0, 109.3, 47.2, 46.6, 32.8.

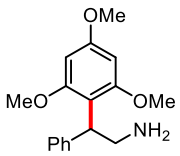
4-(2-amino-1-phenylethyl)-N, N-dimethylaniline (108)



The title compound was prepared between N, N-dimethylaniline (72.6 mg, 0.6 mmol, 1.2 equiv.) and (2-nitrovinyl)benzene (74.5 mg, 0.5 mmol) and purified by 5% of methanol in DCM as a light-yellow liquid (97 mg, 81%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.16 (m, 5H), 7.12 (d, *J* = 8.7 Hz, 2H), 6.69 (d, *J* = 8.6 Hz, 2H), 3.93 (t, *J* = 7.7 Hz, 1H), 3.28 (d, *J* = 7.7 Hz, 2H), 2.93 (d, *J* = 11.1 Hz, 6H), 2.13 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5, 143.5, 130.4, 128.8, 128.7, 128.1, 126.5, 113.0, 53.7, 47.0, 40.8; HRMS calcd. for $C_{16}H_{21}N_2$ $[M+H]^+$ m/z 241.1705, found 241.1708.

2-phenyl-2-(2,4,6-trimethoxyphenyl)ethan-1-amine (109)



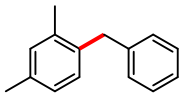
The title compound was prepared between 1,3,5-trimethoxylbenzene (100.8 mg, 0.6 mmol, 1.2 equiv.) and (2-nitrovinyl)benzene (74.5 mg, 0.5 mmol) and purified by 5% of methanol in DCM as a light-yellow liquid (107 mg, 75%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, *J* = 7.3 Hz, 2H), 7.25 (t, *J* = 7.5 Hz, 2H), 7.14 (t, *J* = 7.1 Hz, 1H), 6.15 (s, 2H), 4.64 (t, *J* = 7.9 Hz, 1H), 3.79 (s, 3H), 3.74 (s, 6H), 3.46 (d, *J* = 7.9 Hz, 2H), 2.19 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 159.4, 143.4, 128.0, 127.8, 125.5, 111.1, 91.1, 55.6, 55.2, 44.1, 44.0; HRMS calcd. for $C_{17}H_{22}NO_3$ $[M+H]^+$ m/z 288.1600, found 288.1592.

General Procedure for FC Benzylation of Arenes with Benzylic Alcohols

To a stirred solution of arenes (5.0 mmol, 5 equiv.) and benzyl alcohols (1.0 mmol, 1 equiv.) in HFIP (2 mL) was added $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) under air. The reaction mixture was stirred at rt ~ 100 °C for 2 ~ 48 h. After that, the reaction mixture was evaporated under reduce pressure and the crude product was purified by column chromatography on silica gel using petroleum ether or cyclohexane: dichloromethane as the eluent to afford diarylmethanes**.**

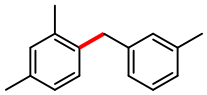
1-benzyl-2,4-dimethylbenzene (111) [50]



The title compound was prepared between *m*-xylene (530.0 mg, 5.0 mmol), benzyl alcohol (108.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP (2 ml) at 50 °C for 2 h and purified by petroleum ether as a colorless oil (168 mg, 86%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.00 (m, 8H), 4.12 (s, 0.48H, minor), 4.01 (s, 1.52H, major), 2.36 (s, 2.09H, major), 2.30 (s, 1.43H, minor), 2.26 (s, 2.16H, major); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.8, 139.9, 137.3, 137.0, 136.5, 136.0, 131.25, 130.0, 128.8, 128.5, 128.3, 128.0, 126.7, 126.5, 126.0, 125.9, 39.2 (major), 35.2 (minor), 21.1 (major), 20.4 (minor), 19.7 (major).

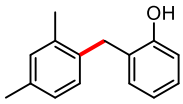
2,4-dimethyl-1-(3-methylbenzyl)benzene (112)



The title compound was prepared between *m*-xylene (530.0 mg, 5.0 mmol), 3-methylbenzyl alcohol (122.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP (2 ml) at 50 ºC for 2 h and purified by petroleum ether as a colorless oil (180 mg, 86%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 – 6.85 (m, 7H), 4.10 (s, 0.47H, minor), 3.98 (s, 1.53H, major), 2.38 (s, 2.56, major), 2.37 (s, 1.67, major), 2.35 (s, 0.73, minor), 2.32 (s, 1.52, minor), 2.29 (s, 2.51, major); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.8, 139.9, 138.0, 137.3, 137.1, 136.5, 136.1, 135.9, 131.2, 130.0, 129.6, 128.8, 128.4 , 128.2, 126.7, 126.7, 126.4, 125.9, 125.0, 39.1 (major), 35.1 (minor), 21.6 (major), 21.1 (major), 20.4 (minor), 19.8; HRMS (APCI$^+$) calcd. for $C_{16}H_{18}$ $[M]^+$ m/z 210.1403, found 210.1403.

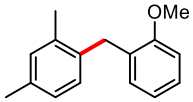
2-(2,4-dimethylbenzyl)phenol (113) [69]



The title compound was prepared between *m*-xylene (530.0 mg, 5.0 mmol), 2-(hydroxymethyl)phenol (124.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP (2 ml) at rt for 1 h and purified by 20% of DCM in cyclohexane as a colorless oil (185 mg, 87%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (t, J = 7.5 Hz, 1H), 7.09 (s, 1H), 7.02 (br, 3H), 6.92 (t, J = 7.4 Hz, 1H), 6.84 (d, J = 7.9 Hz, 1H), 4.85 (s, 1H), 3.99 (s, 2H), 2.37 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 136.8, 136.3, 134.5, 131.4, 130.7, 129.2, 127.7, 127.0, 126.5, 121.0, 115.7, 33.6, 21.1, 19.7.

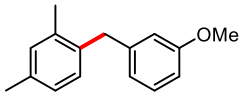
1-(2-methoxybenzyl)-2,4-dimethylbenzene (114)



The title compound was prepared between *m*-xylene (530.0 mg, 5.0 mmol), 2-methoxybenzyl alcohol (138.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP (2 ml) at 50 ºC for 2 h and purified by 10% of DCM in cyclohexane as a colorless oil (191 mg, 85%).

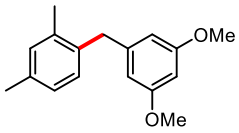
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 – 7.22 (m, 1H), 7.07 (s, 1H), 7.01 (br, 2H), 6.95 – 6.87 (m, 3H), 3.99 (s, 2H), 3.89 (s, 3H), 2.37 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 136.7, 135.7, 135.7, 131.0, 129.9, 129.8, 129.2, 127.2, 126.7, 120.6, 110.2, 55.4, 32.8, 21.1, 19.6; HRMS (ESI$^+$) calcd. for $C_{16}H_{18}ONa$ $[M+Na]^+$ m/z 249.1255, found 249.1251.

1-(3-methoxybenzyl)-2,4-dimethylbenzene (115)



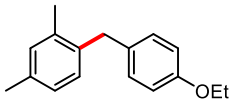
The title compound was prepared between *m*-xylene (530.0 mg, 5.0 mmol), 3-methoxybenzyl alcohol (138.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP (2 ml) at 50 ºC for 2 h and purified by 10% of DCM in cyclohexane as a colorless oil (175 mg, 77%).
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 – 7.03 (m, 1.19H), 6.96 (s, 0.72H), 6.91 – 6.84 (m, 2.22H), 6.63 – 6.58 (m, 2.33H), 6.53 – 6.48 (m, 0.60H), 3.94 (s, 0.46H, minor), 3.82 (s, 1.48H, major), 3.65 (s, 1.93H, major), 3.64 (s, 0.85H, minor), 2.20 (s, 2.01H, major), 2.15 (s, 1.28H, minor), 2.11 (s, 2.34H, major); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 159.8, 142.5, 141.7, 137.3, 136.8, 136.5, 136.0, 135.8, 131.2, 130.0, 129.4, 128.2, 126.7, 126.5, 121.3, 120.5, 114.8, 114.1, 111.1, 110.8, 110.0, 55.2, 55.2, 39.2 (major), 35.2 (minor), 21.1 (major), 20.3 (minor), 19.7 (major) ; HRMS (ESI$^+$) calcd. for $C_{16}H_{19}O$ $[M+H]^+$ m/z 227.1436, found 227.1431

1-(3,5-dimethoxybenzyl)-2,4-dimethylbenzene (116)



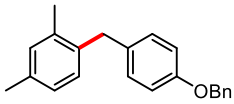
The title compound was prepared between *m*-xylene (530.0 mg, 5.0 mmol), 3,5-dimethoxybenzyl alcohol (168.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP (2 ml) at rt for 2 h and purified by 20% of DCM in cyclohexane as a colorless oil (190 mg, 74%).
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 – 6.96 (m, 3H), 6.32 (s, 2.44H), 6.21 (s, 0.48H), 4.03 (s, 0.5H, minor), 3.91 (s, 2H, major), 3.76 (s, 4.41H, major), 3.75 (s, 1.69H, minor), 2.33 (s, 2.33H, major), 2.28 (s, 1.39H, minor), 2.25 (s, 2.24H, major); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 143.3, 142.6, 137.3, 136.6, 136.5, 136.0, 135.6, 131.2, 129.9, 128.2, 126.7, 126.5, 107.1, 106.3, 97.8, 97.5, 55.3, 55.3, 39.4, 35.3, 21.1, 20.3, 19.7; HRMS (ESI$^+$) calcd. for $C_{17}H_{21}O_2$ $[M+H]^+$ m/z 257.1542, found 257.1535.

1-(4-ethoxybenzyl)-2,4-dimethylbenzene (117)



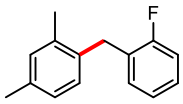
The title compound was prepared between *m*-xylene (530.0 mg, 5.0 mmol), 4-ethoxybenzyl alcohol (152.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP (2 ml) at rt for 2 h and purified by 20% of DCM in cyclohexane as a colorless oil (135 mg, 56%).
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 – 6.97 (m, 5H), 6.84 (d, *J* = 8.5 Hz, 2H), 4.03 (q, *J* = 7.0 Hz, 2H), 3.92 (s, 2H), 2.34 (s, 3H), 2.24 (s, 3H), 1.43 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 136.5, 135.9 132.7, 131.2, 129.9, 129.7, 126.7, 114.5, 63.5, 38.3, 21.1, 19.7, 15.0; HRMS (APCI$^+$) calcd. for $C_{17}H_{20}O$ $[M]^+$ m/z 240.1509, found 240.1497.

1-(4-(benzyloxy)benzyl)-2,4-dimethylbenzene (118)



The title compound was prepared between *m*-xylene (530.0 mg, 5.0 mmol), 4-benzyloxybenzyl alcohol (214.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP (2 ml) at rt for 2 h and purified by 20% of DCM in cyclohexane as a colorless oil (218 mg, 72%).
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 – 7.36 (m, 5H), 7.10 – 6.99 (m, 5H), 6.94 (d, *J* = 8.6 Hz, 2H), 5.07 (s, 2H), 3.94 (s, 2H), 2.36 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 137.4, 136.5, 136.4, 135.9, 133.2, 131.2, 129.9, 129.7, 128.7, 128.0, 127.6, 126.7, 114.9, 70.2, 38.3, 21.1, 19.7; HRMS (ESI$^+$) calcd. for $C_{22}H_{22}ONa$ $[M+Na]^+$ m/z 325.1568, found 325.1562.

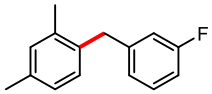
1-(2-fluorobenzyl)-2,4-dimethylbenzene (119)



The title compound was prepared between *m*-xylene (530.0 mg, 5.0 mmol), 2-fluorobenzyl alcohol (126.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP (2 ml) at 80 ºC for 2 h and purified by petroleum ether as a colorless oil (172 mg, 80%).
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 – 6.95 (m, 6.78H), 6.89 (s, 0.23H, minor), 6.65 (t, *J* = 7.0 Hz, 0.25H, minor), 4.09 (s, 0.48H, minor), 4.00 (s, 1.52H, major), 2.35 (s, 2.16H, minor), 2.28 (s, 3.82H, major); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3 (d, *J* = 243.0 Hz), 161.1 (d, *J* = 243.8

Hz), 138.1, 137.5, 136.5, 136.2, 135.6, 134.6, 131.3 , 130.7 (d, J = 4.5 Hz), 129.8, 128.8 (d, J = 4.5 Hz), 128.3, 127.8, 127.7, 127.6, 127.5, 127.4, 126.8, 126.7, 124.2, 124.1, 124.1, 115.4, 115.1, 114.8, 31.7, 27.6, 21.1, 20.1, 19.5; ^{19}F NMR ($CDCl_3$, 188 MHz): δ -117.6 (m, 1F); HRMS (APCI$^+$) calcd. for $C_{15}H_{16}F$ $[M+H]^+$ m/z 215.1231, found 215.1226.

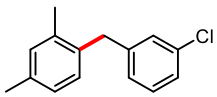
1-(3-fluorobenzyl)-2,4-dimethylbenzene (120) [50]



The title compound was prepared between *m*-xylene (530.0 mg, 5.0 mmol), 3-fluorobenzyl alcohol (126.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP (2 ml) at 80 ºC for 16 h and purified by petroleum ether as a colorless oil (165 mg, 77%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 – 7.21 (m, 1.21H), 7.16 – 7.09 (m, 0.91H), 7.04 – 7.00 (m, 2.42H), 6.96 – 6.82 (m, 3.02H), 6.73 (d, J = 10.2 Hz, 0.26H), 4.09 (s, 0.44H, minor), 3.98 (s, 1.51H, major), 2.35 (s, 2.21H, major), 2.28 (s, 1.36H, minor), 2.23 (s, 2.51H, major); NMR (75 MHz, $CDCl_3$) δ 163.3 (d, J = 243.8 Hz), 163.2 (d, J = 243.8 Hz), 143.6 (d, J = 6.8 Hz), 142.8 (d, J = 7.5 Hz) , 138.2, 137.2, 136.5, 136.4, 136.2, 135.2, 131.4, 130.1, 129.9, 129.8, 128.4, 128.1, 126.9, 126.7, 124.4 (d, J = 2.3 Hz), 123.7 (d, J = 2.1 Hz), 115.6 (d, J = 21.2 Hz), 114.8 (d, J = 21.5 Hz), 112.9 (d, J = 21.2 Hz), 112.8 (d, J = 21.1 Hz), 38.9, 34.9, 21.1, 20.3, 19.7; ^{19}F NMR ($CDCl_3$, 188 MHz): δ -113.6 (m, 1F).

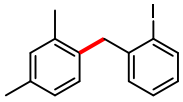
1-(3-chlorobenzyl)-2,4-dimethylbenzene (121)



The title compound was prepared between *m*-xylene (530.0 mg, 5.0 mmol), 3-chlorobenzyl alcohol (126.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP (2 ml) at 80 ºC for 16 h and purified by petroleum ether as a colorless oil (193 mg, 84%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 – 7.16 (m, 1.98H), 7.12 – 7.10 (m, 1.41H), 7.02 – 7.00 (m, 3.14H), 6.91 – 6.89 (m, 0.43H), 4.05 (s, 0.42H, minor), 3.94 (s, 1.52H, major), 2.33 (s, 2.30H, major), 2.25 (s, 1.34H, minor), 2.21 (s, 2.51H, major); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.0, 142.2, 137.2, 136.5, 136.4, 136.1, 135.1, 134.4, 134.3, 131.4, 130.1, 129.7, 128.9, 128.4, 128.1, 127.0, 126.9, 126.8, 126.2, 126.2, 38.9, 34.9, 21.1, 20.3, 19.7; HRMS (APCI$^+$) calcd. for $C_{15}H_{15}Cl$ $[M]^+$ m/z 230.0857, found 230.0857.

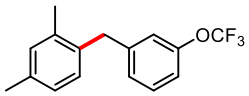
1-(2-iodobenzyl)-2,4-dimethylbenzene (122)



The title compound was prepared between *m*-xylene (530.0 mg, 5.0 mmol), 2-iodobenzyl alcohol (234.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP (2 ml) at 50 ºC for 16 h and purified by petroleum ether as a colorless oil (236 mg, 73%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.7 Hz, 1H), 7.24 (t, *J* = 7.3 Hz, 0.92H), 7.20 – 7.10 (m, 0.83H), 7.07 (s, 0.81H), 6.99 (t, *J* = 7.9 Hz, 1H), 6.95 – 6.86 (m, 2.37H), 6.56 (d, *J* = 7.6 Hz, 0.18H, minor), 4.07 (s, 0.17H, minor), 4.02 (s, 1.80H, major), 2.36 (s, 2.21H, major), 2.33 (s, 0.45H, minor), 2.23 (d, *J* = 3.5 Hz, 3.23H, major); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 142.0, 139.5, 139.3, 138.1, 137.4, 136.7, 136.6, 136.2, 134.8, 131.3, 130.4, 129.7, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.1, 126.9, 126.8, 102.0, 101.7, 44.5, 41.5, 21.1, 20.2, 19.7; HRMS (APCI$^+$) calcd. for $C_{15}H_{16}I$ $[M+H]^+$ m/z 323.0290, found 323.0276.

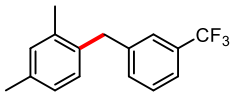
2,4-dimethyl-1-(3-(trifluoromethoxy)benzyl)benzene (123)



The title compound was prepared between *m*-xylene (530.0 mg, 5.0 mmol), 3-trifluoromethoxybenzyl alcohol (192.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP (2 ml) at 80 ºC for 16 h and purified by petroleum ether as a colorless oil (170 mg, 61%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 1.09H), 7.16 – 6.92 (m, 5.90H), 4.11 (s, 0.47H, minor), 4.00 (s, 1.51H, major), 2.36 (s, 2.17H, major), 2.28 (s, 1.41H, minor), 2.23 (s, 2.27H, major); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.6, 143.3, 142.5, 136.5, 136.0, 135.0, 131.4, 130.0, 130.0, 129.7, 128.4, 127.1, 126.9, 126.8, 126.3, 121.34 , 120.6, 120.6 (q, *J* = 255.0 Hz), 118.4 118.3, 38.9, 34.9, 21.1, 20.3, 19.6; ^{19}F NMR ($CDCl_3$, 188 MHz): δ -57.7 (s, 2.3F, major), δ -57.8 (s, 0.7F, minor); HRMS (APCI$^+$) calcd. for $C_{16}H_{15}F_3O$ $[M]^+$ m/z 280.1070, found 280.1071.

2,4-dimethyl-1-(3-(trifluoromethyl)benzyl)benzene (124) [50]

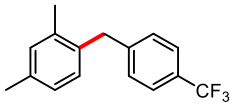


The title compound was prepared between *m*-xylene (530.0 mg, 5.0 mmol), 3-

trifluoromethylbenzyl alcohol (176.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP (2 ml) at 100 °C for 48 h and purified by petroleum ether as a colorless oil (198 mg, 75%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.42 (m, 1.72H), 7.40 – 7.33 (m, 1.26H), 7.33 – 7.30 (m, 0.86H), 7.18 – 7.11 (m, 1.03H), 7.05 – 7.03 (m, 2.07H), 4.15 (s, 0.43H, minor), 4.04 (s, 1.40H, major), 2.36 (s, 2.51H, major), 2.28 (s, 1.28H, minor), 2.24 (s, 2.18H, major); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.9, 141.1, 137.2, 136.5, 136.5, 135.9, 134.9, 132.1, 131.5, 131.1, 130.0, 129.0, 128.9, 128.5, 127.2 (q, J = 154.5 Hz) , 127.0, 126.9, 125.5 (q, J = 3.8 Hz), 124.9 (q, J = 4.5 Hz), 123.0, 122.9 (q, J = 3.8 Hz), 39.0 (major), 35.0 (minor), 21.1 (major), 20.3 (minor), 19.7 (major); ^{19}F NMR ($CDCl_3$, 188 MHz): δ -62.5 (s, 3F).

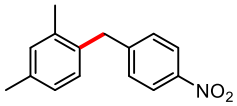
2,4-dimethyl-1-(4-(trifluoromethyl)benzyl)benzene (125) [50]



The title compound was prepared between *m*-xylene (530.0 mg, 5.0 mmol), 4-trifluoromethylbenzyl alcohol (176.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP (2 ml) at 100 °C for 48 h and purified by petroleum ether as a colorless oil (135 mg, 51%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 – 7.53 (m, 2.04H), 7.36 – 7.26 (m, 1.84H), 7.18 – 7.11 (m, 1.15H), 7.06 – 7.04 (m, 2.23H), 4.16 (s, 0.40H, minor), 4.05 (s, 1.61H, major), 2.37 (s, 2.51H, major), 2.28 (s, 1.19H, minor), 2.24 (s, 2.36H, major); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 144.3, 138.3, 137.2, 136.5 (d, J = 3.0Hz), 136.0, 134.9, 131.5, 130.1, 129.3, 129.0, 128.6, 128.5, 128.3, 127.0, 126.9, 125.5 (q, J = 3.8Hz), 124.5 (q, J = 270.0Hz), 39.1, 35.1, 21.1, 20.3, 19.7; ^{19}F NMR ($CDCl_3$, 188 MHz): δ -62.3 (s, 3F).

2,4-dimethyl-1-(4-nitrobenzyl)benzene (126) [50]

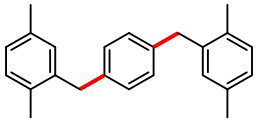


The title compound was prepared between *m*-xylene (530.0 mg, 5.0 mmol), 4-nitrobenzyl alcohol (153.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP (2 ml) at 100 °C for 48 h and purified by 10% of DCM in cyclohexane as a light-yellow solid (36 mg, 15%).

M.p.: 90 - 92 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.3 Hz,

0.18H), 7.29 (d, J = 8.2 Hz, 1.61H), 7.22 – 7.11 (m, 1H), 7.05 – 7.02 (m, 2H), 4.18 (s, 0.40H, minor), 4.07 (s, 1.57H, major), 2.35 (s, 2.42H, major), 2.25 (s, 1.13H, minor), 2.20 (s, 2.31H, major); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.8, 148.1, 137.1, 136.9, 136.5, 135.3, 134.2, 131.6, 130.1, 129.8, 129.5, 128.7, 128.6, 128.5, 127.1, 127.1, 126.9, 123.8, 123.8, 39.1, 35.2, 21.1, 20.3, 19.7.

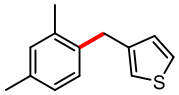
1,4-bis(2,5-dimethylbenzyl)benzene (127)



The title compound was prepared between *m*-xylene (530.0 mg, 5.0 mmol), 1,4-phenylenedimethanol (138.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP (2 ml) at 50 ºC for 2 h and purified by 10% of DCM in cyclohexane as a white solid (223 mg, 71%).

M.p.: 88 - 90 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 – 7.09 (m, 6H), 7.03 (s, 1H), 7.00 (s, 3H), 3.98 (s, 4H), 2.35 (s, 6H), 2.26 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0, 138.1, 135.4, 133.5, 130.9, 130.3, 128.8, 127.2, 39.1, 21.1, 19.3; HRMS (APCI$^+$) calcd. for $C_{24}H_{26}$ $[M]^+$ m/z 314.2029, found 314.2028.

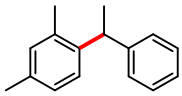
3-(2,4-dimethylbenzyl)thiophene (128)



The title compound was prepared between *m*-xylene (530.0 mg, 5.0 mmol), 3-thiophenemethanol (114.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP (2 ml) at 50 ºC for 2 h and purified by petroleum ether as a colorless oil (166 mg, 82%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 – 7.26 (m, 1H), 7.11 – 6.99 (m, 3H), 6.93 (d, J = 4.4 Hz, 1H), 6.85 (s, 0.90H, major), 6.67 (s, 0.11H, minor), 4.04 (s, 0.22H, minor), 3.97 (s, 1.74H, major), 2.35 (s, 2.51H, major), 2.32 (s, 0.72H, minor), 2.28 (s, 2.80H, major); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3, 140.4, 137.2, 136.8, 136.3, 136.0, 135.8, 131.2, 129.6, 128.5, 128.3, 128.2, 126.8, 126.4, 125.5, 121.1, 120.4, 34.0, 30.5, 21.1, 20.2, 19.5; HRMS (APCI$^+$) calcd. for $C_{13}H_{14}S$ $[M]^+$ m/z 202.0811, found 202.0806.

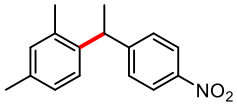
(S)-2,4-dimethyl-1-(1-phenylethyl)benzene (129) [49]



The title compound was prepared between *m*-xylene (530.0 mg, 5.0 mmol), 1-phenylethanol (167.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv) in HFIP (2 ml) at rt for 2 h and purified by petroleum ether as a colorless oil (189 mg, 90%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 2H), 7.23 – 7.21 (m, 4H), 7.08 (d, J = 8.0 Hz, 1H), 7.02 (s, 1H), 4.35 (q, J = 7.1 Hz, 1H), 2.36 (s, 3H), 2.26 (s, 3H), 1.66 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 146.6, 141.1, 136.0, 135.6, 131.4, 128.4, 127.8, 126.8, 125.9, 40.8, 22.3, 21.0, 19.8.

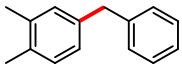
(S)-2,4-dimethyl-1-(1-(4-nitrophenyl)ethyl)benzene (130) [69]



The title compound was prepared between *m*-xylene (530.0 mg, 5.0 mmol), 1-(4-nitrophenyl)ethanol (167.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP (2 ml) at 100 °C for 16 h and purified by 10% of DCM in cyclohexane as a light yellow solid (221 mg, 87%).

M.p.: 92 - 94 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, J = 8.5 Hz, 2H), 7.31 (d, J = 8.8 Hz, 2H), 7.14 (d, J = 7.8 Hz, 1H), 7.05 (d, J = 8.1 Hz, 1H), 6.99 (s, 1H), 4.38 (q, J = 7.1 Hz, 1H), 2.32 (s, 3H), 2.17 (s, 3H), 1.63 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5, 139.4, 136.4, 135.9, 131.7, 128.5, 127.1, 126.7, 123.8, 40.9, 22.0, 21.0, 19.8;

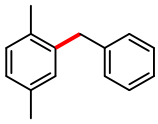
4-benzyl-1,2-dimethylbenzene (131) [70]



The title compound was prepared between *o*-xylene (530.0 mg, 5.0 mmol), benzyl alcohol (108.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP (2 ml) at 50 °C for 2 h and purified by petroleum ether as a colorless oil (170 mg, 87%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.02 (m, 8H), 4.13 (s, 0.76H, minor), 4.03 (s, 1.22H, major), 2.40 (s, 1.19H, minor), 2.33 (s, 3.45H, major), 2.25 (s, 1.32H, minor); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.7 140.9, 138.8, 138.7, 137.1, 136.7, 135.3, 134.3, 130.4, 129.8, 129.0, 128.8, 128.5, 128.5, 128.4, 128.2, 126.4, 126.1, 125.9, 125.5, 41.7, 40.2, 20.8, 19.9, 19.4, 15.5.

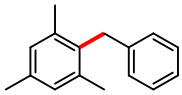
2-benzyl-1,4-dimethylbenzene (132) [70]



The title compound was prepared between *p*-xylene (530.0 mg, 5.0 mmol), benzyl alcohol (108.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP (2 ml) at 50 °C for 2 h and purified by petroleum ether as a colorless oil (166 mg, 85%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (t, *J* = 7.2 Hz, 2H), 7.25 (d, *J* = 7.1 Hz, 1H), 7.19 (d, *J* = 7.8 Hz, 2H), 7.12 (d, *J* = 7.6 Hz, 1H), 7.08 – 6.97 (m, 2H), 4.02 (s, 2H), 2.36 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.7, 138.8, 135.5, 133.6, 130.9, 130.3, 128.8, 128.5, 127.2, 126.0, 39.6, 21.1, 19.3.

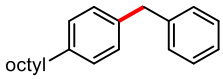
2-benzyl-1,3,5-trimethylbenzene (133) [70]



The title compound was prepared between mesitylene (600.0 mg, 5.0 mmol), benzyl alcohol (108.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP (2 ml) at 50 °C for 2 h and purified by petroleum ether as a colorless oil (183 mg, 87%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.2 Hz, 2H), 7.22 (t, *J* = 7.1 Hz, 1H), 7.09 (d, *J* = 7.2 Hz, 2H), 6.97 (s, 2H), 4.10 (s, 2H), 2.37 (s, 3H), 2.28 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.3, 137.2, 135.8, 133.9, 129.0, 128.5, 128.0, 125.8, 34.9, 21.1, 20.3.

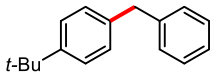
1-benzyl-4-octylbenzene (134)



The title compound was prepared between 1-phenyloctane (950.0 mg, 5.0 mmol), benzyl alcohol (108.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP/DCM (9/1, 2 ml) at 50 °C for 2 h and purified by petroleum ether as a colorless oil (202 mg, 72%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.10 (m, 9H), 4.06 (s, 0.76H, minor), 3.99 (s, 1.24H, major), 2.64 – 2.57 (m, 2H), 1.65 – 1.50 (m, 2H), 1.31 (m, 10H), 0.92 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, Chloroform-*d*) δ 141.5, 141.5, 141.2, 140.8, 138.4, 138.4, 130.5, 129.5, 129.1, 128.9, 128.6, 128.6, 128.5, 128.3, 126.6, 126.1, 126.0, 126.0, 42.1, 41.7, 39.0, 36.2, 35.7, 33.1, 32.1, 31.7, 31.1, 29.9, 29.6, 29.5, 29.4, 22.8, 14.3; HRMS (APCI$^+$) calcd. for $C_{21}H_{28}$ $[M]^+$ m/z 280.2186, found 280.2175.

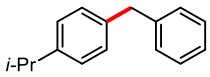
1-benzyl-4-(tert-butyl)benzene (135) [71]



The title compound was prepared between *tert*-butylbenzene (670.0 mg, 5.0 mmol), benzyl alcohol (108.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP (2 ml) at 50 °C for 2 h and purified by petroleum ether as a colorless oil (200 mg, 89%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.26 (m, 7H), 7.20 (d, J = 8.3 Hz, 1.57H), 7.06 (d, J = 6.0 Hz, 0.43H), 4.07 (s, 0.69H, minor), 4.03 (s, 1.29H, major), 1.38 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.4, 149.0, 141.4, 140.8, 138.2, 129.1, 129.1, 128.7, 128.6, 128.3, 126.2, 126.1, 125.5, 123.2, 42.3, 41.6, 34.8, 34.5, 31.5.

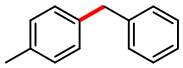
1-benzyl-4-isopropylbenzene (136) [72]



The title compound was prepared between *iso*-propylbenzene (600.0 mg, 5.0 mmol), benzyl alcohol (108.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP (2 ml) at 50 °C for 2 h and purified by petroleum ether as a colorless oil (178 mg, 85%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.16 (m, 9H), 4.15 (s, 0.69H, minor), 4.04 (s, 1.30H, major), 3.27 – 3.18 (m, 0.34H, minor), 3.00 – 2.91 (m, 0.65H, major), 1.32 (d, J = 6.9 Hz, 3.88H, major), 1.22 (d, J = 6.8 Hz, 2.24H, minor); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.3, 146.7, 141.5, 138.6, 137.4, 130.7, 129.1, 128.9, 128.8, 128.6, 128.5, 127.4, 127.0, 126.6, 126.1, 126.0, 125.8, 125.7, 124.2, 41.7, 39.0, 33.8, 29.1, 24.2, 23.9;

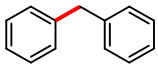
1-benzyl-4-methylbenzene (137) [70]



The title compound was prepared between toluene (460.0 mg, 5.0 mmol), benzyl alcohol (108.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP (2 ml) at 50 °C for 16 h and purified by petroleum ether as a colorless oil (155 mg, 85%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 2H), 7.26 – 7.14 (m, 7H), 4.05 (s, 0.91H, minor), 4.00 (s, 1.08H, major), 2.37 (s, 1.60H, major), 2.30 (s, 1.37H, minor); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.5, 140.5, 139.1, 138.2, 136.8, 135.7, 130.4, 130.1, 129.3, 129.0, 128.9, 128.9, 128.6, 128.5, 127.0, 126.6, 126.1, 126.0, 41.7, 39.6, 21.1, 19.8.

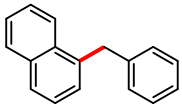
diphenylmethane (138) [70]



The title compound was prepared between benzene (390.0 mg, 5.0 mmol), benzyl alcohol (108.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP (2 ml) at 80 ºC for 16 h and purified by petroleum ether as a colorless oil (148 mg, 88%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.33 (m, 4H), 7.32 – 7.24 (m, 6H), 4.07 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 129.1, 128.6, 126.2, 42.1.

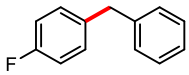
1-benzylnaphthalene (139) [70]



The title compound was prepared between naphthalene (640.0 mg, 5.0 mmol), benzyl alcohol (108.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP (2 ml) at 50 ºC for 2 h and purified by petroleum ether as a colorless oil (189 mg, 87%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 – 7.85 (m, 0.73H), 7.79 – 7.69 (m, 0.73H), 7.63 (d, J = 7.8 Hz, 1.46H), 7.50 (s, 0.34H), 7.33 – 7.26 (m, 2.68H), 7.17 – 7.06 (m, 5.73H), 4.32 (s, 1.41H, major), 4.01 (s, 0.59H, minor); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1, 140.8, 138.7, 136.8, 134.1, 133.8, 132.3, 132.2, 129.2, 128.9, 128.8, 128.6, 128.6, 128.2, 127.8, 127.7, 127.5, 127.3, 127.2, 126.3, 126.2, 126.1, 126.0, 125.7, 125.5, 124.4, 42.2, 39.2.

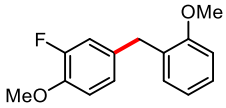
1-benzyl-4-fluorobenzene (140)



The title compound was prepared between fluorobenzene (480.0 mg, 5.0 mmol), benzyl alcohol (108.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP (2 ml) at 80 ºC for 16 h and purified by petroleum ether as a colorless oil (102 mg, 55%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.07 (m, 7H), 7.01 (t, J = 8.6 Hz, 2H), 4.05 (s, 0.41H, minor), 3.99 (s, 1.61H, major); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6 (d, J = 242.3Hz), 141.1, 140.0, 136.9 (d, J = 3.8Hz), 131.2 (d, J = 4.5Hz), 130.4 (d, J = 8.3Hz), 129.0, 128.7, 128.1, 128.0 126.3, 124.2 (d, J = 3.0Hz), 115.4 (d, J = 22.5Hz), 115.3 (d, J = 21.0Hz), 41.2, 35.0; ^{19}F NMR ($CDCl_3$, 188 MHz): δ -117.4 (m, 0.8F), -117.9 (m, 0.2F); HRMS (APCI$^+$) calcd. for $C_{13}H_{11}F$ $[M]^+$ m/z 186.0839, found 186.0838.

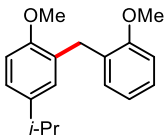
2-fluoro-1-methoxy-4-(2-methoxybenzyl)benzene (141)



The title compound was prepared between 2-fluoroanisol (630.0 mg, 5.0 mmol), benzyl alcohol (108.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP (2 ml) at rt for 2 h and purified by 20% of DCM in cyclohexane as a colorless oil (200 mg, 81%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (t, *J* = 6.6, 1H), 7.10 (d, *J* = 7.1 Hz, 1H), 6.99 – 6.84 (m, 5H), 3.92 (s, 2H), 3.87 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 154.0, 150.8, 145.8 (d, *J* = 10.5 Hz), 134.4 (d, *J* = 6.0 Hz), 130.3, 129.4, 127.7, 124.4 (d, *J* = 3.0 Hz), 120.6, 116.7 (d, *J* = 18.0 Hz), 113.5, 110.6, 56.5, 55.4, 35.1; ^{19}F NMR ($CDCl_3$, 188 MHz): δ -135.8 (dd, *J* = 13.2 Hz, 1F); HRMS (APCI$^+$) calcd. for $C_{15}H_{15}O_2F$ $[M]^+$ m/z 246.1039, found 246.1044.

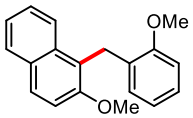
4-isopropyl-1-methoxy-2-(2-methoxybenzyl)benzene (142)



The title compound was prepared between 4-isopropylanisol (750.0 mg, 5.0 mmol), benzyl alcohol (108.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP/DCM (9/1, 2 ml) at rt for 0.5 h and purified by 20% of DCM in cyclohexane as a white solid (210 mg, 78%).

M.p.: 64 - 66 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (t, *J* = 7.0 Hz, 1H), 7.07 (t, *J* = 6.6 Hz, 2H), 7.01 (s, 1H), 6.90 (d, *J* = 7.8 Hz, 2H), 6.84 (d, *J* = 8.3 Hz, 1H), 4.00 (s, 2H), 3.87 (s, 3H), 3.82 (s, 3H), 2.89 – 2.80 (m, 1H), 1.23 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 155.9, 140.8, 130.3, 129.5, 129.0, 128.8, 127.1, 124.7, 120.4, 110.3, 110.3, 55.6, 55.4, 33.4, 30.2, 24.4; HRMS (ESI$^+$) calcd. for $C_{18}H_{22}O_2Na$ $[M+Na]^+$ m/z 293.1517, found 293.1520.

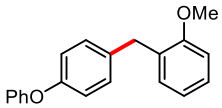
2-methoxy-1-(2-methoxybenzyl)naphthalene (143)



The title compound was prepared between 2-methoxylnaphthalene (790.0 mg, 5.0 mmol), benzyl alcohol (108.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP (2

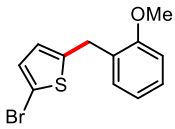
ml) at rt for 0.5 h and purified by 20% of DCM in cyclohexane as a white solid (208 mg, 75%). M.p.: 128 - 130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 – 7.82 (m, 3H), 7.42 – 7.32 (m, 3H), 7.16 (t, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 8.1 Hz, 1H), 6.71 (t, *J* = 7.4 Hz, 1H), 6.62 (d, *J* = 7.3 Hz, 1H), 4.49 (s, 2H), 4.00 (s, 3H), 3.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 155.4, 133.8, 129.4, 129.4, 128.7, 128.4, 128.3, 126.7, 126.5, 124.2, 123.4, 121.5, 120.5, 113.8, 109.9, 56.9, 55.6, 24.4; HRMS (ESI$^+$) calcd. for $C_{19}H_{19}O_2$ [M+H]$^+$ m/z 279.1385, found 249.1394.

1-methoxy-2-(4-phenoxybenzyl)benzene (144)



The title compound was prepared between diphenyl ether (850.0 mg, 5.0 mmol), benzyl alcohol (108.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP (2 ml) at rt for 0.5 h and purified by 20% of DCM in cyclohexane as a white solid (255 mg, 88%).
M.p.: 70 - 72 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (t, *J* = 7.7 Hz, 2H), 7.27 – 7.21 (m, 3.09H), 7.18 – 7.01 (m, 4.20H), 7.01 – 6.84 (m, 4.31H), 4.06 (s, 0.25H, minor), 4.00 (s, 1.74H, major), 3.86 (s, 2.63H, major), 3.80 (s, 0.33H, minor); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 157.6, 136.2, 132.8, 131.1, 130.7, 130.4, 130.3, 129.9, 129.8, 129.7, 127.6, 127.4, 123.9, 123.0, 122.6, 120.6, 120.5, 119.5, 119.0, 118.7, 118.0, 110.6, 110.4, 110.1, 55.5, 35.3 30.0; HRMS (ESI$^+$) calcd. for $C_{20}H_{18}O_2Na$ [M+Na]$^+$ m/z 313.1204, found 313.1212.

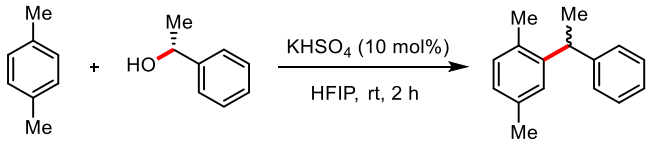
2-bromo-5-(2-methoxybenzyl)thiophene (145)



The title compound was prepared between 2-bromothiophene (810.0 mg, 5.0 mmol), benzyl alcohol (108.0 mg, 1.0 mmol) and $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) in HFIP/DCM (9/1, 2 ml) at rt for 0.5 h and purified by 20% of DCM in cyclohexane as a colorless oil (226 mg, 80%).
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (t, *J* = 7.7 Hz, 1H), 7.18 (d, *J* = 7.1 Hz, 1H), 6.98 – 6.88 (m, 2H), 6.86 (d, *J* = 3.6 Hz, 1H), 6.59 (d, *J* = 3.5 Hz, 1H), 4.09 (s, 2H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 145.9, 130.1, 129.4, 128.3, 128.3, 125.3, 120.7, 110.6, 109.6, 55.4, 31.0; HRMS (APCI$^+$) calcd. for $C_{12}H_{12}BrOS$ [M+H]$^+$ m/z 282.9787, found 282.9776.

FC Benzylation with (R)-(+)-1-Phenylethanol

(1)

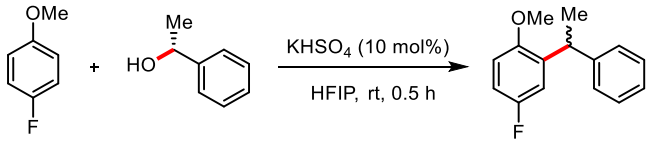


146, 66%

To a stirred solution of *p*-xylene (530 mg, 5.0 mmol, 5 equiv.) and (R)-(+)-1-phenylethanol (122, 1.0 mmol) in HFIP (2 mL) was added $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) under air. The reaction mixture was stirred at rt for 2 h. After that, the reaction mixture was evaporated under reduce pressure and the crude product was purified by column chromatography on silica gel using petroleum ether as the eluent to afford the diarylmethane **146** as a colorless oil. (139 mg, 66%).[73]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 2H), 7.24 – 7.21 (m, 3H), 7.14 (s, 1H), 7.08 (d, J = 7.6 Hz, 1H), 7.00 (d, J = 7.6 Hz, 1H), 4.35 (q, J = 7.2 Hz, 1H), 2.38 (s, 3H), 2.25 (s, 3H), 1.66 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.5, 143.8, 135.4, 133.0, 130.4, 128.4, 127.8, 127.6, 126.9, 125.9, 41.1, 22.2, 21.4, 19.4.

(2)

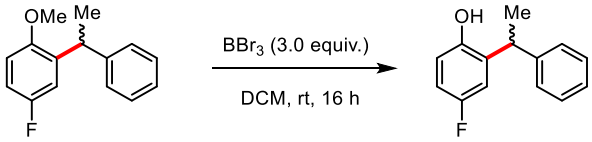


147, 78%

To a stirred solution of 4-fluoroanisol (5.0 mmol, 5 equiv.) and (R)-(+)-1-phenylethanol (1.0 mmol, 1.0 equiv.) in HFIP (2 mL) was added $KHSO_4$ (13.6 mg, 0.1 mmol, 0.1 equiv.) under air. The reaction mixture was stirred at rt for 0.5 h. After that, the reaction mixture was evaporated under reduce pressure and the crude product was purified by column chromatography on silica gel using 10 % DCM in petroleum ether as the eluent to afford the diarylmethane **147** as a white solid. (179 mg, 78%). [74]

M.p.: 66 - 68 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.19 (m, 5H), 6.95 – 6.84 (m, 2H), 6.81 – 6.77 (m, 1H), 4.58 (q, J = 7.2 Hz, 1H), 3.78 (s, 3H), 1.60 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 155.8, 153.1, 145.7, 137.0 (d, J = 6.0 Hz), 128.1 (d, J = 44.3 Hz), 126.1, 114.8 (d, J = 23.3 Hz), 112.8 (d, J = 23.3 Hz), 111.66 (d, J = 7.5 Hz), 56.20, 37.65, 20.89; ^{19}F NMR ($CDCl_3$, 188 MHz): δ -123.6 (m).

Demethylation

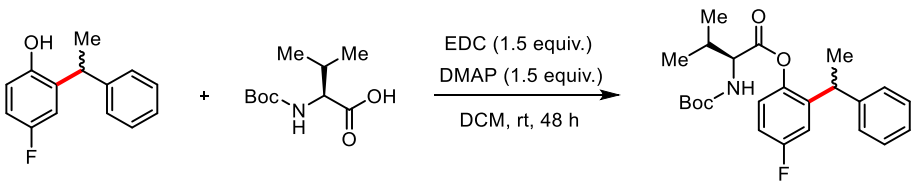


147 **148**, 90%

To a stirred solution of **147** (179 mg, 0.78 mmol, 1.0 equiv.) in anhydrous DCM (2 mL) at 0 °C was added BBr_3 (0.23 mL, 3.0 equiv.) via syringe over 5 min. The reaction mixture was stirred at rt for 16 h. After that, the reaction was carefully quenched with water and the mixture subsequently stirred until all precipitates dissolved. The mixture was transferred into a 100-mL separatory funnel. 20 mL DCM was added into the funnel and the mixture was washed by 10 mL X 3 brine. Then, the organic layer was dried by using anhydrous Na_2SO_4 and filtration. The mixture was evaporated under reduce pressure and the crude product was purified by column chromatography on silica gel using 30% of DCM in cyclohexane as the eluent to give **148** as a colorless oil (152 mg, 90%). [75]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.30 (m, 2H), 7.28 – 7.23 (m, 3H), 6.99 (dd, *J* = 9.7, 2.9 Hz, 1H), 6.87 – 6.80 (m, 1H), 6.73 – 6.69 (m, 1H), 4.54 (s, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 1.63 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 156.0, 149.3, 144.7 133.9 (d, *J* = 6.0 Hz), 128.3 (d, *J* = 100.5 Hz), 126.8, 116.9 (d, *J* = 8.3 Hz), 114.7 (d, *J* = 23.3 Hz), 113.7 (d, *J* = 23.3 Hz), 38.96, 21.07; ^{19}F NMR ($CDCl_3$, 188 MHz): δ -123.3.

Coupling with Boc-L-valine



148 **149**, 85%, 4% ee

To a stirred solution of **148** (0.5 mmol, 108 mg, 1.0 equiv.) and Boc-L-valine (0.75 mmol, 163 mg, 1.5 equiv.) in DCM (2 mL) was added EDC (0.75 mmol, 144 mg, 1.5 equiv.) and DMAP (0.75 mmol, 92 mg, 1.5 equiv.) under air. The reaction mixture was stirred at rt for 48 h. After that, the mixture was transferred into a 100-mL separatory funnel. 20 mL DCM was added into the funnel and the mixture was washed by 10 mL X 3 brine. Then, the organic layer was dried by using anhydrous Na_2SO_4 and filtration. The mixture was evaporated under reduce pressure and the crude product was purified by column chromatography on silica gel using 50% of DCM

in cyclohexane as the eluent to give **149** as a colorless oil (176 mg, 85%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 2H), 7.20 – 7.16 (m, 3H), 7.02 – 6.86 (m, 3H), 4.98 (t, *J* = 7.9 Hz, 1H), 4.45 – 4.39 (m, 1H), 4.30 – 4.27 (m, 1H), 2.31 – 2.18 (m, 1H), 1.56 (d, *J* = 7.2 Hz, 3H), 1.47 (d, *J* = 1.6 Hz, 9H), 1.05 (dd, *J* = 6.8, 1.9 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 1.48H), 0.93 (d, *J* = 6.9 Hz, 1.60H); ^{19}F NMR ($CDCl_3$, 188 MHz): δ -115.7, 115.8; HRMS (ESI^+) calcd. for $C_{24}H_{31}NO_4F$ $[M+H]^+$ m/z 416.2237, found 416.2241.

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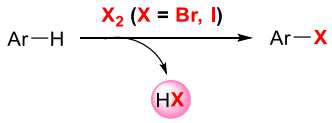
Chapter IV

Halogenation of Arenes and Heterocycles in Fluorinated Alcohols

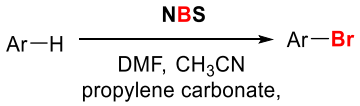
I. Introduction

The importance and value of aryl halides stem from their versatile applications as key precursors for metal-catalyzed cross-couplings[1-5] and widely employed in natural products, pharmaceuticals, and materials science.[6-8] The development of efficient and mild halogenation of aromatic compounds is an intensively investigated area of great significance. By far the most prevalent strategies for preparing aromatic bromides and iodides are relied on the use of hazardous and toxic X_2 (X = Br, I) which cause serious environmental issues.



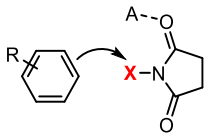
Scheme 1. Traditional Halogenation of Arenes with X_2

In order to replace the use of X_2, a large array of effective halogenating agents which are operationally safe have been successfully developed.[9-14] Among them, N-halosuccinimides (NBS, NIS and NCS) have turn out to be practically useful halogenating reagents due to their low-cost, easy of handling, as well as the convenient recycling of the by-product succinimide. At first, the bromination of activated aromatic compounds with NBS in few polar solvents such as DMF,[15] CH_3CN[16-17] and propylene carbonate[18] have been reported.



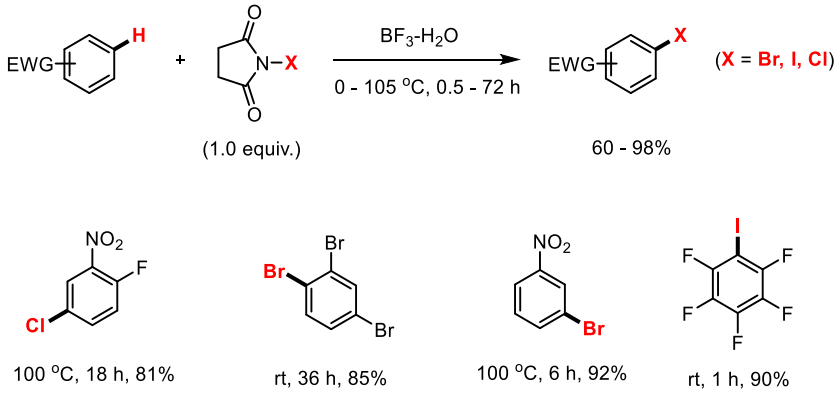
Scheme 2. Bromination of Arenes with NBS in Polar Solvents

However, these reactions are only applicable to electron-rich arenes and require long reaction times and sometimes heating. Besides, these conditions could not be extended to iodination and chlorination due to the lower reactivity of NIS and NCS. Therefore, in the last decades, numerous researchers have sought to activate NXS by using Lewis or Brønsted acids.



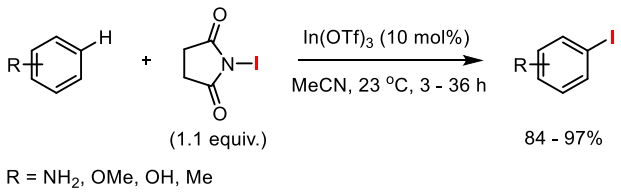
Scheme 3. Lewis or Bronsted Acid-Catalyzed Active NXS

In 2004, Olah and co-workers developed an efficient new electrophilic reagent combination of NXS/BF_3-H_2O which had an excellent ability for the halogenation of a wide variety of deactivated aromatic systems to mono-halogenated products in high selectivity and good yield at room temperature.[19] Halogenation of more deactivated systems was also achieved by varying the reaction conditions, such as raising the temperature and prolonged reaction time.



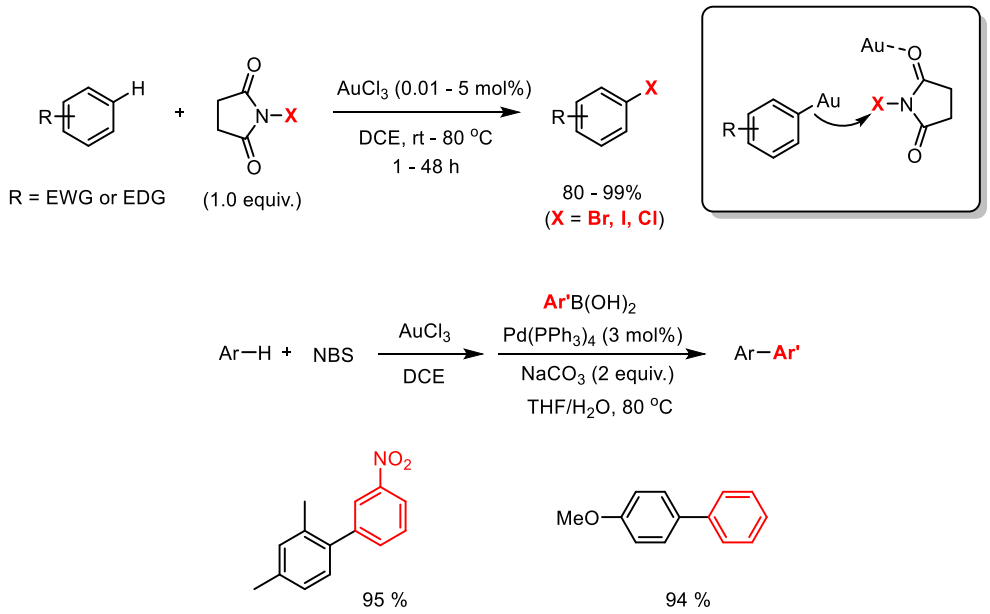
Scheme 4. BF_3-H_2O-Catalyzed Halogenation of Deactivated Aromatics with NXS

In 2010, Romo and co-workers developed an efficient and mild iodination method employing NIS in conjunction with catalytic $In(OTf)_3$ at ambient temperature.[20] Both electron-rich arenes and arenes with weaker activating groups participated in this process and the reaction was tolerant of several functional groups including free amino group.



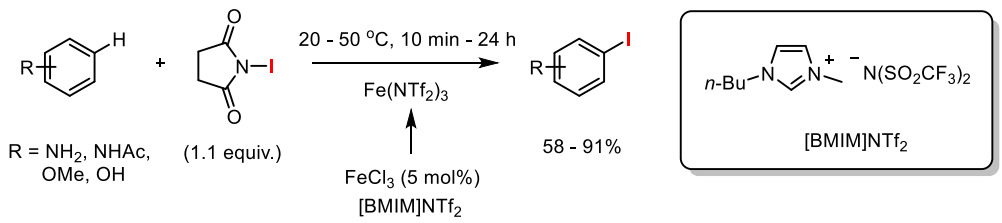
Scheme 5. $In(OTf)_3$-Catalyzed Iodination of Arenes with NIS

In the same year, Wang and co-workers developed a protocol for the halogenation of aromatic substrates, including some inactivated aromatic substrates with NXS using only 0.01 to 1 mol% of $AuCl_3$ as catalyst.[21]. The reaction involved a dual activation of both the aromatic ring and NXS which greatly enhanced the reactivity. Moreover, as demonstrated by several examples, the clean reactions allowed the combination of bromination with other transition metal-catalyzed reactions to realize functionalization of aromatic C-H bonds in one-pot manner.



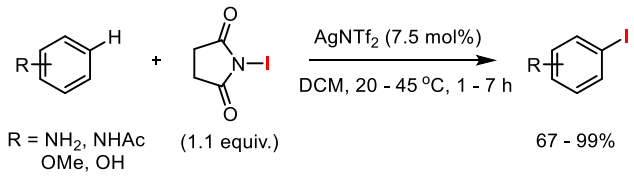
Scheme 6. $AuCl_3$-Catalyzed Halogenation of Arenes with NXS

In 2015, Sutherland and co-workers developed a highly regioselective, efficient Fe(III)-catalyzed iodination of activated arenes using a triflimide based ionic liquid as solvent.[22] The powerful Lewis acid, $Fe(NTf_2)_3$, generated from $FeCl_3$ and a readily available triflimide-based ionic liquid $[BMIM]NTf_2$ allowed the activation of NIS and the iodination of a wide range of substrates under mild conditions. Furthermore, the ionic liquid can be easily recycled after washing with water.



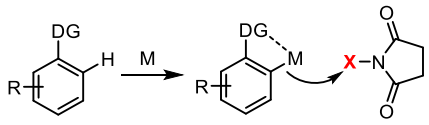
Scheme 7. $FeCl_3$-Catalyzed Iodination of Arenes with NIS in Ionic Liquid

In the next year, the same group reported another mild and rapid method for the iodination of arenes that utilizes silver triflimide as a catalyst for activation of NIS.[23]



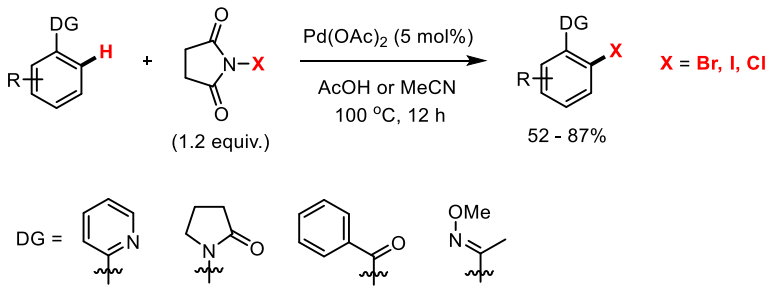
Scheme 8. $AgNTf_2$-Catalyzed Iodination of Arenes with NIS

Meanwhile, significant efforts have been devoted in functional-group directed halogenations of arenes with NXS catalyzed by transition-metal catalysts (Pd, Rh, etc.).



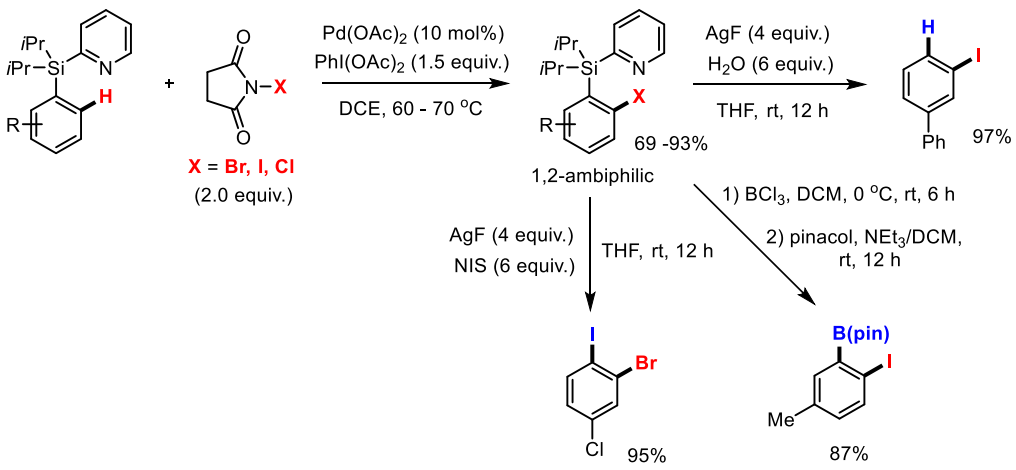
Scheme 9. Transition-Metals-Catalyzed Halogenation of Arenes with NXS

In 2006, Sanford and co-workers described a mild palladium-catalyzed method for the *ortho*-selective halogenation of arenes using NXS as terminal oxidants.[24] These transformations have been applied to a wide array of substrates and can provide products that are complementary to those obtained via conventional electrophilic aromatic substitution reactions.



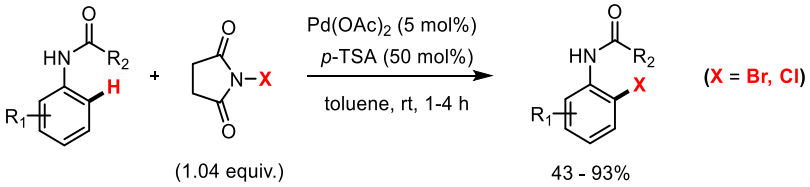
Scheme 10. $Pd(OAc)_2$-Catalyzed *ortho*-Selective Halogenation of Arenes with NXS

In 2010, Gevorgyan and co-workers developed a general and efficient strategy for the synthesis of 1,2-ambiphilic aromatic through palladium-catalyzed *ortho*-halogenation reaction of PyDipSi-arenes with NXS.[25] The directing group PyDipSi could be easily removed or modified to other functional groups.



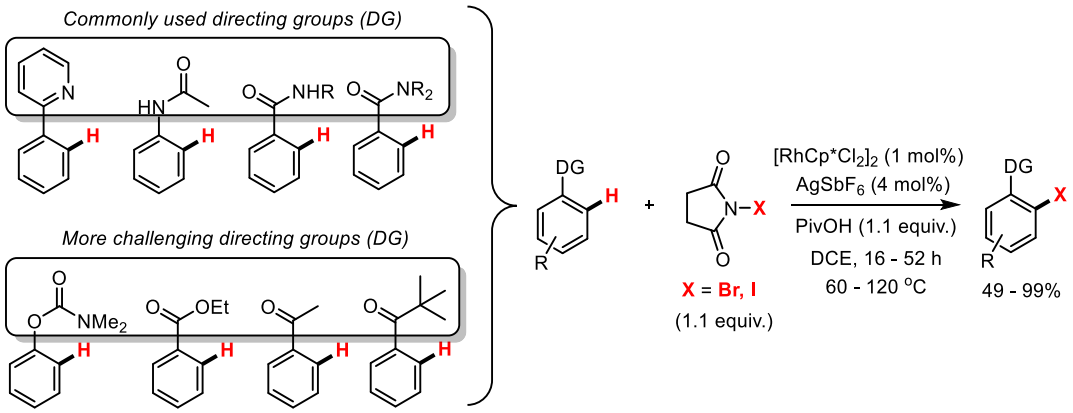
Scheme 11. Pd(OAc)$_2$-Catalyzed *ortho*-Selective Halogenation of PyDipSi-Arenes with NXS

In 2011, Webster and co-workers reported a palladium-catalyzed *ortho*-selective bromination of anilides with NBS under very mild reaction conditions (completed within 1-4 hours at room temperature under air).[26] This mild, operationally simple methodology could also be readily extended to *ortho*-selective chlorination.



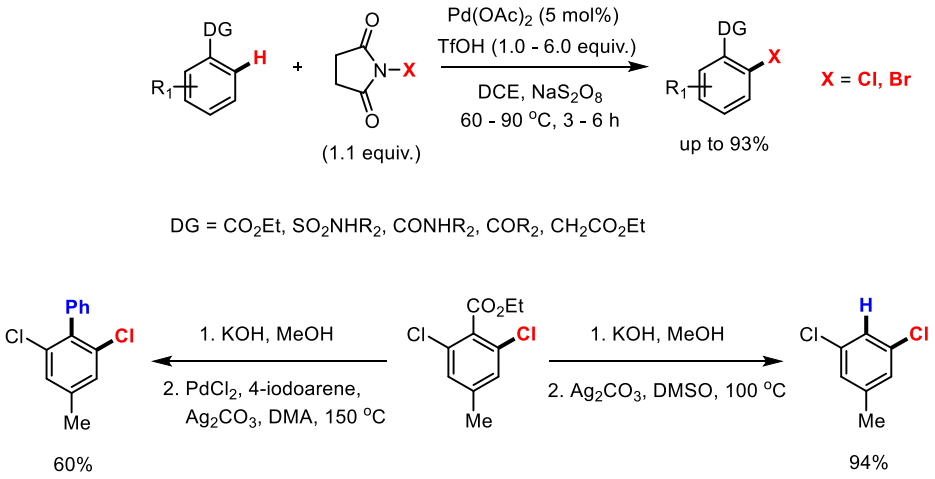
Scheme 12. Pd(OAc)$_2$-Catalyzed *ortho*-Selective Halogenation of PyDipSi-Arenes with NXS

In 2012, Glorius and co-workers reported a practical strategy for the *ortho*- bromination and iodination of arenes with NBS and NIS by a cationic Rh(III) catalyst.[27] This transformation was compatible not only with tertiary benzamide substrates but also with other different classes of aromatic compounds, such as secondary benzamides, acetamides, and phenylpyridines. Moreover, this reaction was the first example of the direct halogenations of simple ketones and benzoic esters occurring via C-H bond activation.



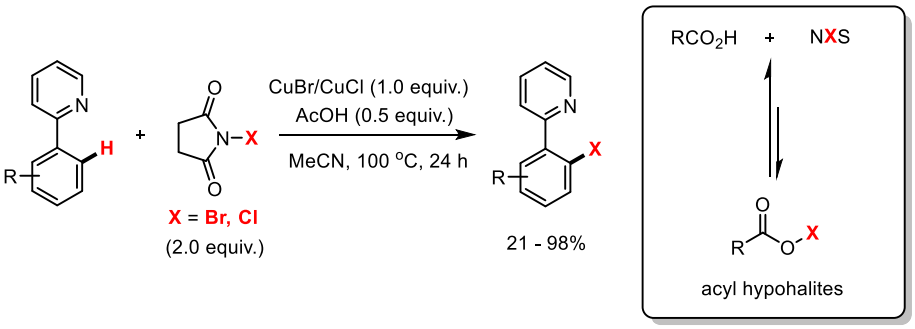
Scheme 13. Rh(III)-Catalyzed *ortho*-Selective Bromination/Iodination of Arenes with NBS/NIS

In 2013, Sun and co-workers developed a novel palladium-catalyzed ortho-chlorination/bromination reaction for the synthesis of a broad range of arene chlorides/bromides from easily accessible electron-deficient arenes and NCS/NBS.[28] It was found that both the co-oxidant and TfOH serve as critical factors for regio- and chemo-selective C-H activation. Furthermore, the directing group -CO_2Et could be efficiently removed or transformed into aryl group by decarboxylation and decarboxylative C-C coupling, respectively.



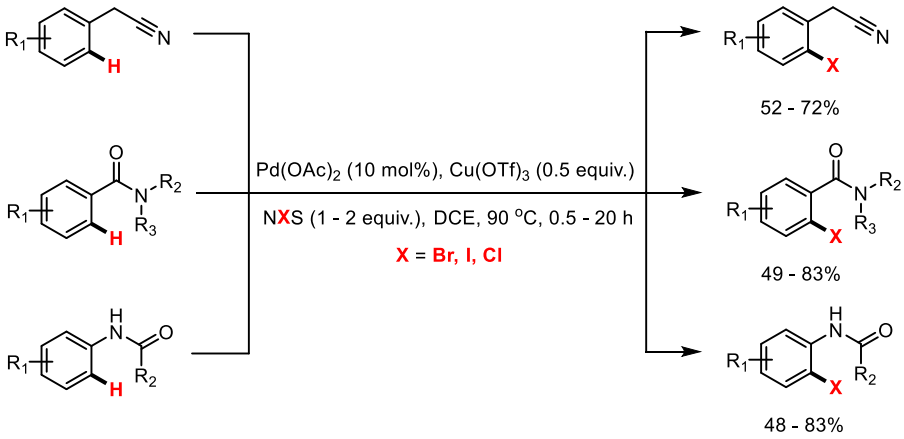
Scheme 14. Pd(II)-Catalyzed ortho-Selective Chlorination/Bromination of Arenes with NCS/NBS

In 2014, Han and co-workers presented a protocol for the copper-mediated direct aryl C-H halogenation.[29] Highly selective mono- and di-halogenations were achieved by using acyl hypohalites, generated in situ from the readily available carboxylic acid and NXS. The correct choice of carboxylic acid additives and solvents was essential for both high yield and selectivity.



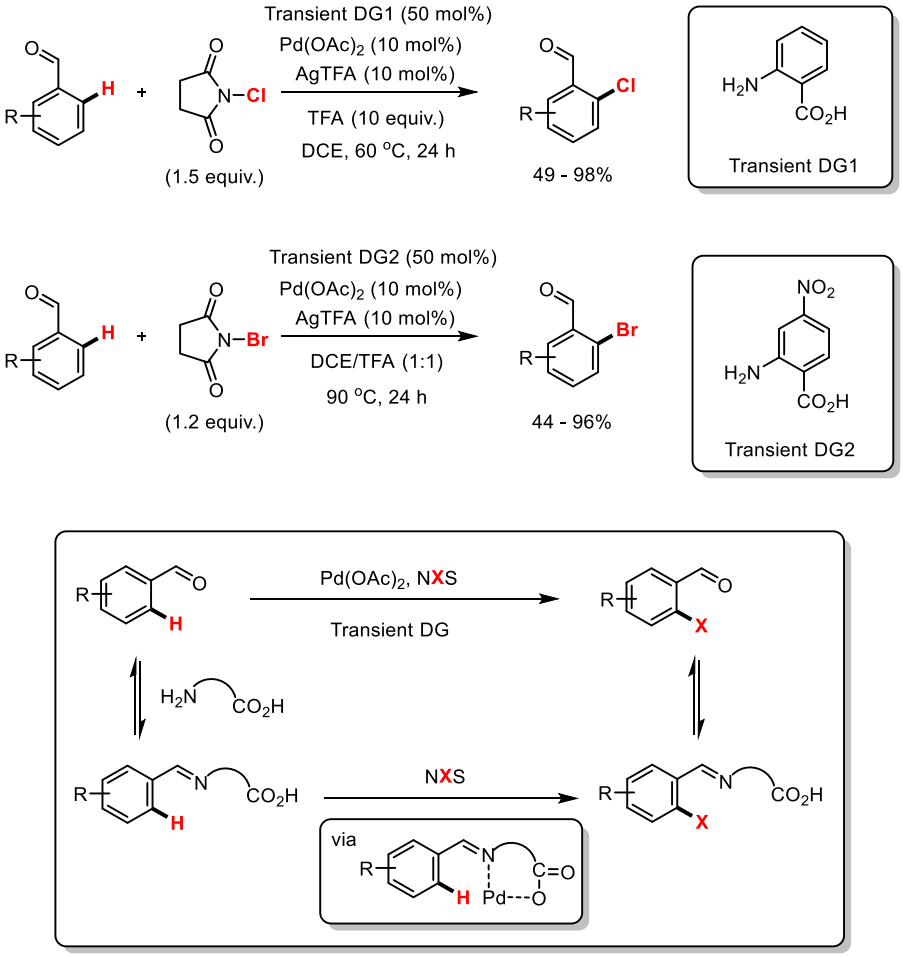
Scheme 15. Copper-Catalyzed ortho-Selective Halogenation of Arenes with NXS

Last year, Kapur and co-worker developed a new method for the palladium-catalyzed *ortho*-C−H halogenations of arenes bearing weak-coordinating groups such as benzyl nitriles, Weinreb amides, and anilides.[30] Of which the transition metal-catalyzed *ortho*-C−H halogenations of benzyl cyanides and Weinreb amides were reported for the first time, resulting in good yields of the halogenated products with excellent regioselectivity.



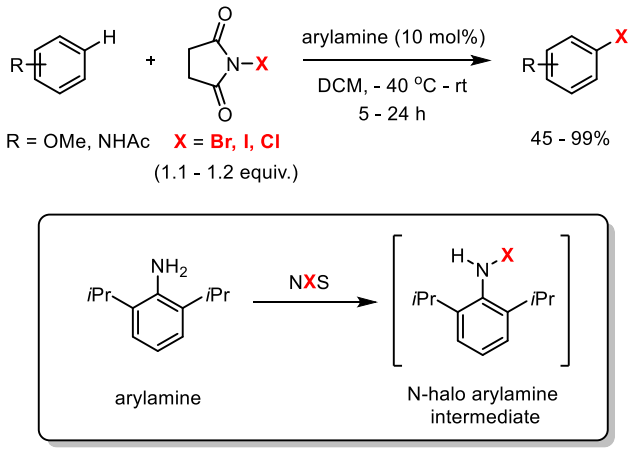
Scheme 16. $Pd(OAc)_2$-Catalyzed *ortho*-Selective Halogenation of Benzyl Nitriles, Weinreb Amides, and Anilides

Recently, Yu and co-workers reported a Pd(II)-catalyzed *ortho*-C-H halogenation of benzaldehyde substrates using bidentate amino acid-type as a transient directing group.[31] Benzaldehydes bearing different electron-donating groups and electron-withdrawing groups underwent smooth halogenation to provide the corresponding products in moderate to excellent yields. The transient directing groups formed *in situ* via imine linkage not only avoided the use of stoichiometric amount of reagents and additional steps for installation/removal of the directing group but also can override other coordinating functional groups capable of directing C-H activation or catalyst poisoning, significantly expanding the scope for metal-catalyzed C-H functionalization of benzaldehydes.



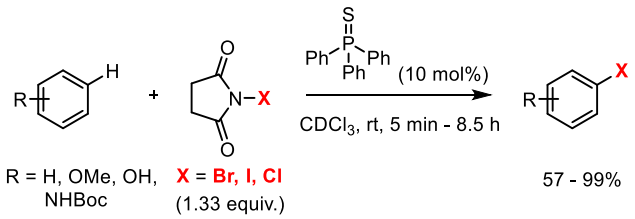
Scheme 17. Pd(OAc)2-Catalyzed ortho-Selective Halogenation of Benzaldehyde

More recently, a new class of Lewis base catalyzed systems has been developed for the electrophilic halogenation of aromatic compounds. For example, in 2015, Yamamoto and co-worker developed an efficient catalytic halogenation method using arylamine as catalyst and NXS as halogenating reagent.[32] The N-halo arylamine intermediate generated from arylamine and NXS acted as a highly reactive and selective catalytic electrophilic halogen source.



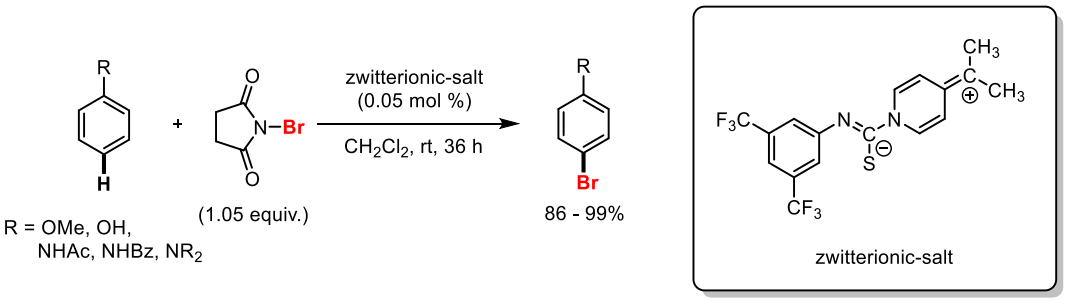
Scheme 18. Arylamine-Catalyzed Halogenation of Arenes with NXS

The same year, Gustafson and co-workers reported a mild electrophilic halogenation of arenes and heterocycles using phosphine sulfide as Lewis basic catalyst and NXS as halogenating source.[33] This methodology was shown to efficiently halogenated diverse aromatics, including simple arenes such as anthracene, and heterocycles such as indoles, pyrrolo, pyrimidines, and imidazoles.



Scheme 19. Phosphine Sulfide-Catalyzed Halogenation of Arenes with NXS

Recently, Yeung and co-workers developed a zwitterionic-salt-catalyzed highly *para*-selective monobromination of arenes with NBS.[34] The reaction could be operated using an extremely low catalyst loading (0.05 mol %) even with 0.01 mol % catalyst loading for the scale-up reaction, providing the selective brominated compound in quantitative yield.

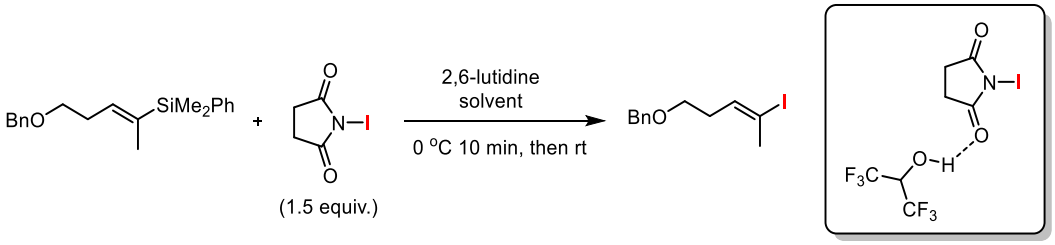


Scheme 20. Zwitterionic-Salt-Catalyzed Bromination of Arenes with NXS

II. Result and Discussion

II. 1. Project Proposed

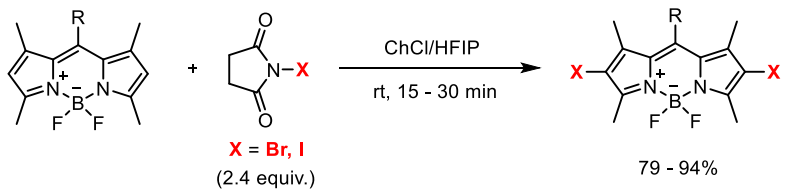
In 2008, Zakarian and co-workers reported the iododesilylation of vinylsilanes to iodoalkenes in high yield and with high stereoselectivity using HFIP as the solvent.[35] It is noteworthy that the iododesilylation reaction is the striking rate acceleration relative to other solvents. The author considered that this rate acceleration can be understood by the electrophilic activation of NIS through hydrogen bonding due to the strong hydrogen-bond donating ability of HFIP.

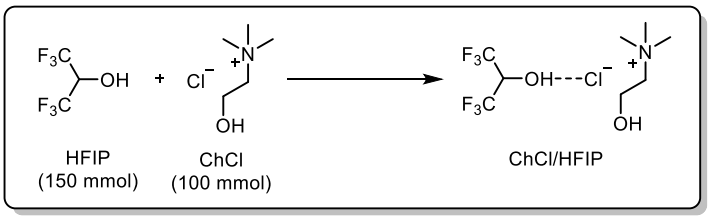


Entry	Solvent	Time (h)	*E*/*Z* ratio	Yield (%)
1	DCM	24	1: 1	Not completed
2	THF	24	1: 1.4	Not completed
3	MeCN	24	2.9: 1	Not completed
4	*i*-PrOH	24	1: 2.6	Not completed
5	HFIP	10 min	*E* only	90

Scheme 21. Iododesilylation of Vinylsilanes in HFIP

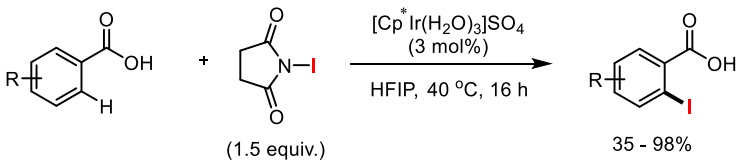
In 2015, He and co-workers prepared a deep eutectic solvent based on choline chloride and HFIP for the dihalogenation of boron dipyrromethenes (BODIPYs) in the presence of NXS. Also in the media, HFIP can activate the N-halosuccinimide via hydrogen bonding.





Scheme 22. Dihalogenation of Boron Dipyrromethenes in HFIP

Recently, Martín-Matute and co-workers developed a very efficient catalytic method for the iodination of benzoic acids which using a simple iridium complex under very mild reaction conditions and in the absence of any additive or base in HFIP, selectively gives *o*-iodinated carboxylic acids in excellent yields.[36]

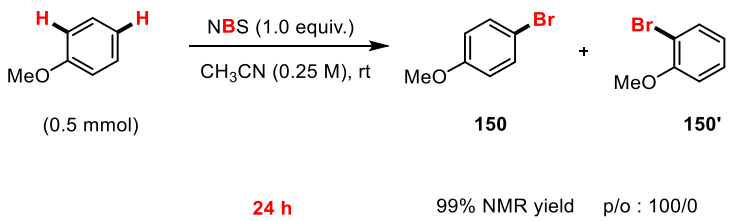


Scheme 23. Ir-Catalyzed *ortho*-Iodination of Benzoic Acids

Based on these results, we supposed that fluorinated alcohols could activate NXS through hydrogen bonding in order to perform the halogenation of simple arenes.

II. 2. Optimization of the Reaction Condition

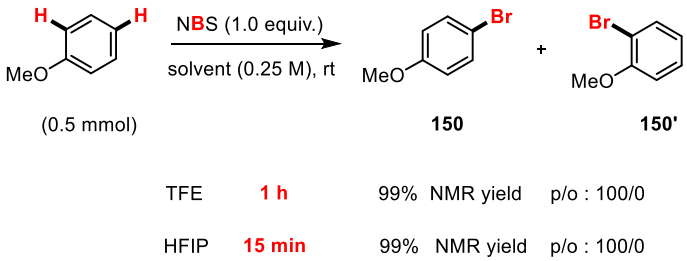
In our initial study, we first tested the bromination of anisole with 1.0 equiv. of NBS in CH_3CN at room temperature (**Scheme 24**). Although the reaction was very facile giving **150** in excellent yield, the reaction time was very long.



Scheme 24. Bromination of Anisole in CH_3CN

Then we tested bromination of anisole with 1.0 equiv. NBS in TFE at room temperature (**Scheme 25**). To our delight, clean conversion of anisole was observed, and the mono-

brominated product **150** was obtained exclusively after 1 h. The replacement of TFE with HFIP shortened the reaction time to 15 min.

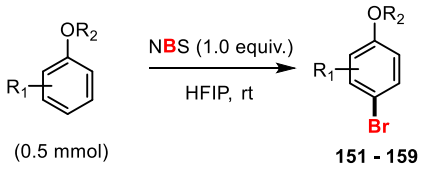


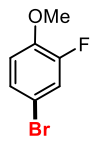
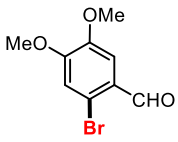
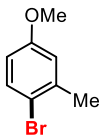
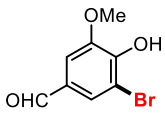
Scheme 25. Bromination of Anisole in Fluorinated Alcohols

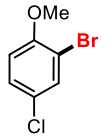
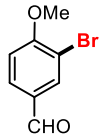
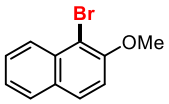
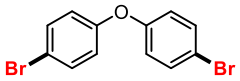
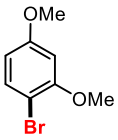
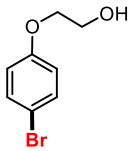
II. 3. Expanding the Substrate Scope

Having identified HFIP as a suitable media, then we examined the scope of the process with a wide range of anisol derivatives (**Table 1**). Substituted anisoles with electron donating groups or weak electron withdrawing groups were mono-brominated rapidly to afford the corresponding products **151-157** in excellent yields with single regioisomer. However, anisole with strong electron withdrawing group such as 4-methoxybenzaldehyde was failed under standard condition. The bromination of aryl ether with 2.0 equiv. of NBS afforded dibrominated product **158** in 95% yields. Phenoxyethanol was brominated smoothly in 92% yield (product **159**).

Table 1. Bromination of Anisole Derivatives in Fluorinated Alcohols



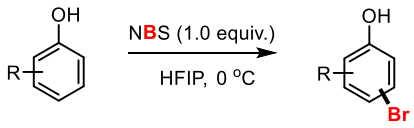
Entry	Product	Time	Yield (%)	Entry	Product	Time	Yield (%)
1	 **151**	0.5 h	96	6	 **156**	0.5 h	93
2	 **152**	15 min	94	7	 **157**	0.5 h	84

3	 **153**	2 h	94	8		16 h	trace
4	 **154**	2 h	96	9 [b]	 **158**	2 h	95
5 [a]	 **155**	0.5 h	94	10	 **159**	0.5 h	92

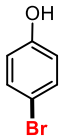
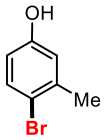
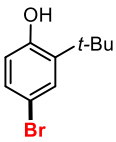
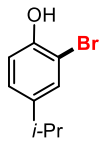
[a] HFIP/DCM (1: 1) was used as the solvent. [b] 2 equiv. of NBS was used.

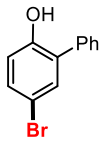
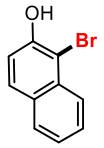
We also explored the bromination of phenol derivatives (**Table 2**). For the phenol, the regioselectivity was observed in favour of the para position (14/1 of p/o ratio) with **160** was isolated in 92% yield. The bromination of *ortho*- and *meta*-substituted phenols proceeded predominantly in *para*-position (products **161-163**). For the *para*-substituted phenols, the bromination took place exclusively at the *ortho*-position (products **164, 165**).

Table 2. Bromination of Phenol Derivatives in Fluorinated Alcohols



(0.5 mmol) **160 - 165**

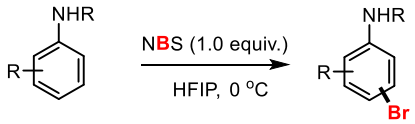
Entry	Product	Time	Yield (%)	Entry	Product	Time	Yield (%)
1	 **160**	2 h	90 (p/o:14/1.0)	6	 **163**	2 h	85 (p/o:6.0/1.0)
2	 **161**	2 h	89 (p/o:13/1.0)	7	 **164**	2 h	94

3	 **162**	2 h	91 (p/o:18/1.0)	8 [a]	 **165**	2 h	93

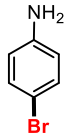
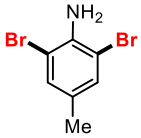
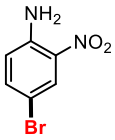
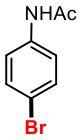
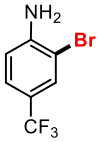
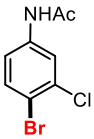
[a] at rt.

After, we were interested in the bromination of free aniline derivatives (**Table 3**). When free aniline was reacted with NBS in HFIP, the reaction was violent even reduced the temperature to 0 °C and a mixture of *mono*-, *di*- and *tri*-brominated products was detected. However, the condition worked with anilines with strong electron-withdrawing group, giving the corresponding brominated products **166-167** in excellent yields and with high selectivity. When treated *p*-methylaniline with 2.0 equiv. of NBS, the *di*-brominated product **168** was obtained as the only product in 75% yield. Meanwhile, the bromination of acetanilides succeeded to afford the *para*-brominated **169** and **170** products in 90% and 74% yields, respectively.

Table 3. Bromination of Anilines Derivatives in Fluorinated Alcohols



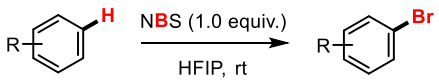
(R = H, Ac, 0.5 mmol) **166 - 171**

Entry	Product	Time	Yield (%)	Entry	Product	Time	Yield (%)
1		5 min	*mono-/di-/tri-*	6 [a]	 **168**	5 min	75
2	 **166**	15 min	90 (p/o: 20/1.0)	7	 **169**	2 h	90 (p/o: 12/1.0)
3	 **167**	15 min	91 (p/o:18/1.0)	8	 **170**	2 h	74 (p/o: 6.0/1.0)

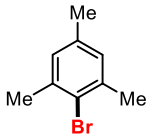
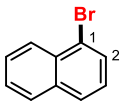
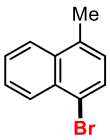
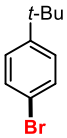
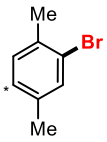
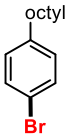
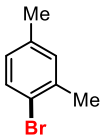
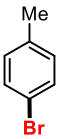
[a] 2 equiv. of NBS was used.

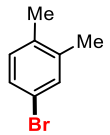
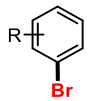
Then, we evaluated the bromination of alkyl-substituted benzene derivatives (**Table 4**). Under the standard conditions, mesitylene and 1-methylnaphthalene gave mono-brominated **171, 172** in 96% and 94% yields, respectively after 5h. It is noteworthy that the bromination of xylene derivatives performed successfully to afford brominated products **173-175** in high yields and with excellent regioselectivities, except to the *p*-xylene where 14% of dibromide product was present. In addition, corresponding brominated derivatives **176-178** of the naphthalene, *tert*-butylbenzene and 1-phenyloctane were obtained in good yields and selectivity. Toluene was brominated in a moderate yield (**179**). Less electron-rich than toluene such as benzene and the bromo, nitro benzenes did not react with NBS in HFIP. Additionally, it is important to note that the benzylic bromination did not occur on the alkyl-substituted benzene derivatives.

Table 4. Bromination of Alkyl-Substituted Benzene Derivatives in Fluorinated Alcohols



(0.5 mmol) **171 - 179**

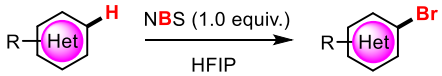
Entry	Product	Time	Yield (%)	Entry	Product	Time	Yield (%)
1	 **171**	8 h	96	6 [a]	 **176**	16 h	99 (1/2 : 24/1.0)
2	 **172**	8 h	94	7 [a]	 **177**	16 h	99
3 [a]	 **173**	16 h	85 (mono/di: 5.9/1.0)	8 [a]	 **178**	16 h	97 (p/o : 4.8/1.0)
4 [a]	 **174**	16 h	96	9 [a, b]	 **179**	16 h	81 (p/o : 3.0/1.0)

5 [a]	 **175**	16 h	98 (p/o : 4.8/1.0)	10	 R = H, Br. NO_2	24 h	trace

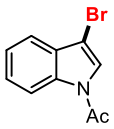
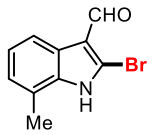
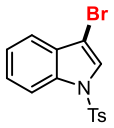
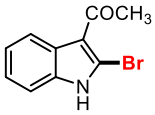
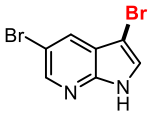
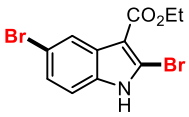
[a] Yields were determined by ^{1}H NMR using nitromethane as the internal standard, combined yield of regioisomers.
[b]Toluene (2.0 equiv) was used.

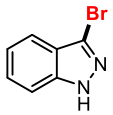
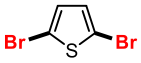
After explored the scope of arenes, we turned then our attention to the bromination of heteroaromatic derivatives. As illustrated in **Table 5**, electron-rich heteroarenes including indole, indazole, pyrazole, imidazole and thiophene were brominated to give corresponding products **180-186** in good to excellent yields. For indoles, pyrazole and indazole**,** the halogenation worked with complete C-3 selectivity (products **180-183**). When the C-3 position was substituted, the bromination took place at the C-2 position (products **184-186**). Besides, dibrominated indole and thiophene **186-187** were obtained in good yields when treated with 2.0 equiv. of NBS.

Table 5. Bromination of Heterocycles in Fluorinated Alcohols



(0.5 mmol) **180 - 187**

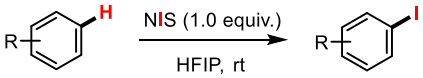
Entry	Product	Temp./Time	Yield (%)	Entry	Product	Temp./Time	Yield (%)
1 [a]	 **180**	rt 1 h	90	6	 **184**	0 °C 15 min	87
2 [a]	 **181**	rt 0.5 h	94	7	 **185**	0 °C 15 min	82
3	 **182**	0 °C 15 min	89	8 [b]	 **186**	rt 0.5 h	75

4	 **183**	0 °C 15 min	84	9 [b]	 **187**	rt 0.5 h	89

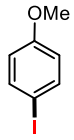
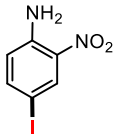
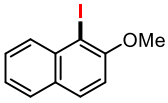
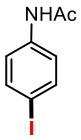
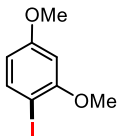
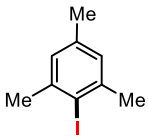
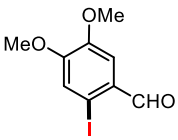
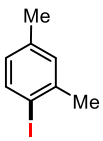
[a] HFIP/DCM (1: 4) was used as the solvent. [b] 2 equiv. of NBS was used.

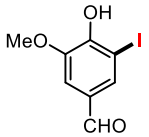
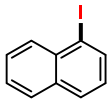
Thereafter we were also interested in the reactivity of NIS and NCS in HFIP with a series of arenes and heterocycles. The iodination of anisole and phenol derivatives performed well to afford iodinated products **188-192** in high yields. Aniline and acetanilide were iodinated in high yields (products **193-194**). Alkyl-substituted benzene derivatives performed successfully to afford *mono*-iodinated products **195-197** in high yields.

Table 6. Iodination of Arenes with NIS in Fluorinated Alcohols



(0.5 mmol) **188 - 197**

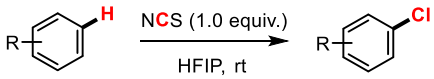
Entry	Product	Time	Yield (%)	Entry	Product	Time	Yield (%)
1	 **188**	0.5 h	95 (9.0/1.0)	6	 **193**	2 h	87 (14/1.0)
2	 **189**	0.5 h	93	7	 **194**	2 h	95
3	 **190**	0.5 h	96	8	 **195**	16 h	96
4	 **191**	0.5 h	94	9 [a]	 **196**	16 h	95

5	 **192**	5 h	92	10 [a]	 **197**	16 h	93 (10/1.0)

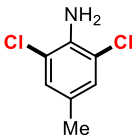
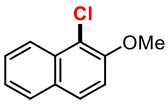
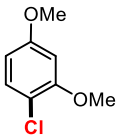
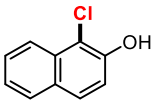
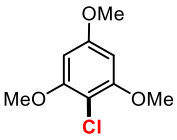
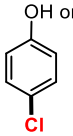
[a] Yield were determined by ^{1}H NMR using nitromethane as internal standard, combined yield of regioisomers.

On the other hand, the chlorination with NCS worked only with electron-rich arenes smoothly, affording *mono*-chlorinated products **198-201** in good to excellent yields. The chlorination of aniline afforded a mixture of compounds and the chlorination of phenol, anisole or aniline with strong electron-withdrawing group gave trace of desired products.

Table 7. Chlorination of Arenes with NCS in Fluorinated Alcohols



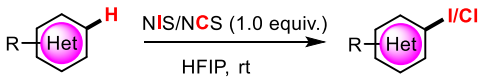
(0.5 mmol) **198 - 201**

Entry	Product	Time	Yield (%)	Entry	Product	Time	Yield (%)
1[a]		2 h	mixture of compounds	4	 **200**	16 h	92
2	 **198**	5 h	95	5	 **201**	16 h	88
3	 **199**	2 h	96	6	OH or OMe 	24 h	trace

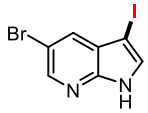
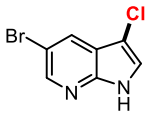
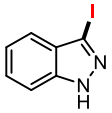
[a] 2 equiv. of NCS was used.

In addition to arenes, electron-rich heteroarenes including pyrazole and indazole were successfully iodinated in good yields (products **202-203**). Besides, pyrazole could also be chlorinated at the C-3 position in 94% yield after 2 h (product **204**).

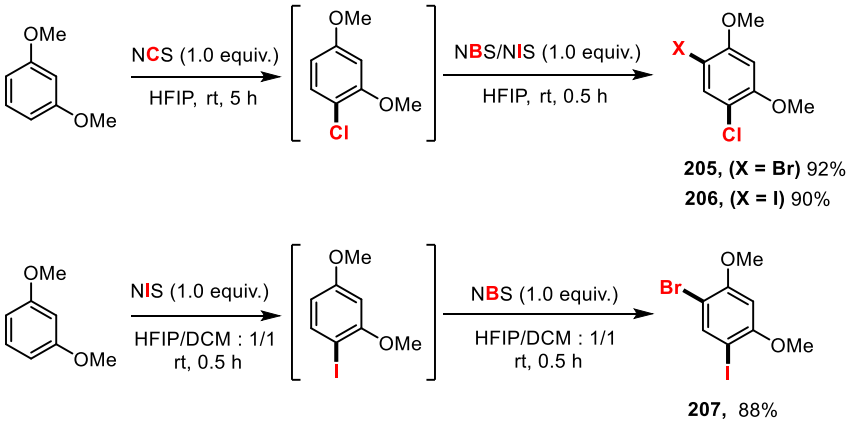
Table 8. Iodination/Chlorination of Heterocycles in Fluorinated Alcohols



(0.5 mmol) **202 - 204**

Entry	Product	Time	Yield (%)	Entry	Product	Time	Yield (%)
1	 **202**	0.5 h	96	3	 **204**	2 h	94
2	 **203**	0.5 h	85				

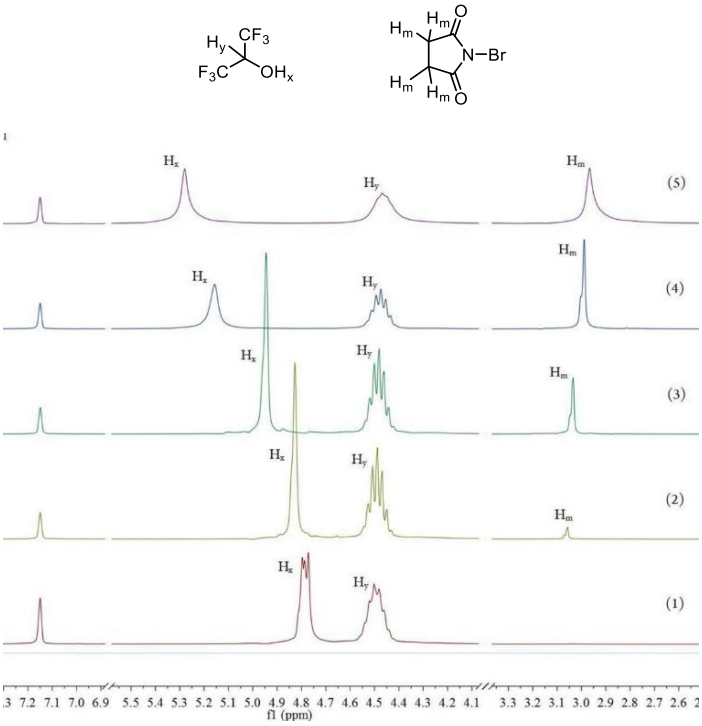
Face with that NXS showed different reactivities in HFIP, we then undertook the sequential halogenation in one-pot. The sequential halogenated products could be efficiently controlled by only adjusting the order of addition of NXS (**Scheme 25**). For example, when 1,3-dimethoxybenzene was treated successively by NCS then NBS or NIS, the chloro-bromo-substituted compound **205** and chloro-iodo-substituted compound **206** were obtained in 92% and 90% yields, respectively. Evenly the sequential treatment with NIS then NBS, the iodo-bromo-substituted compound **207** was isolated in 88% yield.



Scheme 25. One-Pot Sequential Halogenation

II. 4. Mechanism Studies

To prove the hydrogen-bonding interactions between NBS and HFIP, a solution of HFIP was titrated with NBS and monitored by ^{1}H NMR (**Scheme 26**). In NMR tube, different quantities of NBS were dissolved in 1.0 mmol of HFIP. The NMR spectrums (1-5, capillary of C_6D_6 as external standard) were subsequently taken. An increasingly downfield shift of the OH proton (H_x) of HFIP was observed with increasing concentrations of NBS, indicating that the strong hydrogen-bond donating ability of HFIP was responsible for the activation of NBS.

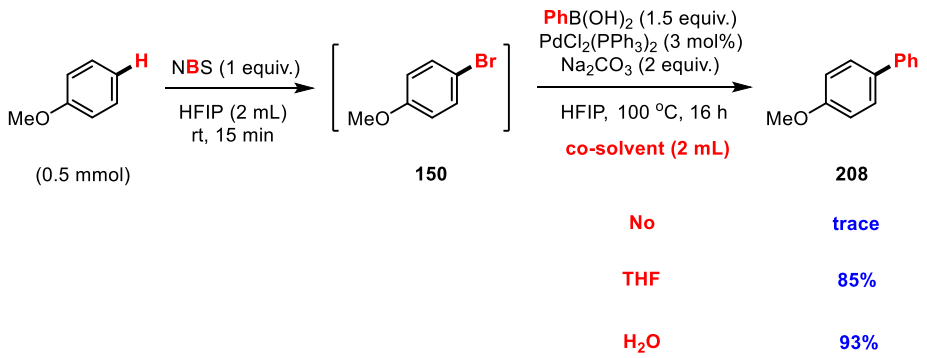


Spectra were acquired in the presence of the following quantities of NBS: (1) 0 mol%; (2) 1 mol%; (3) 5 mol%; (4) 20 mol%; (5) 20 - 50 mol% (because 50% of NBS can't be dissolved completely in HFIP).

Scheme 26. ^{1}H NMR Titration of a Mixture of HFIP and NBS

II. 5. One-Pot Halogenation/Suzuki Cross-Coupling Reaction

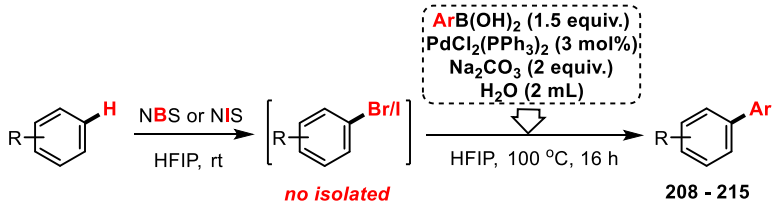
In order to take advantage of these effective and mild conditions, we examined the one-pot combination halogenation/Pd-catalyzed Suzuki cross-coupling reaction (**Scheme 27**). In preliminary experiments after completion of anisol into 4-bromoanisole with NBS, $PhB(OH)_2$ (1.5 equiv.), $PdCl_2(PPh_3)_2$ (3 mol%) and Na_2CO_3 (2 equiv.) were added into the reaction medium directly. After the reaction has proceeded at 100 °C for 16 h, unfortunately, only trace of **208** was observed. On the other hand, when THF and H_2O were used as the co-solvent. the product **208** was formed successfully in 85% and 93% yields, respectively.

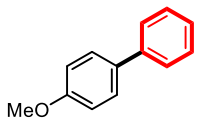
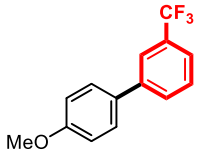
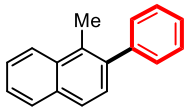
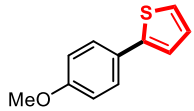
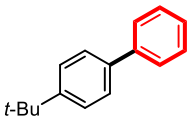
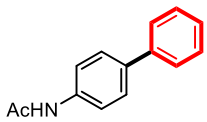


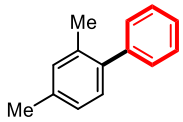
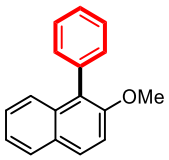
Scheme 27. One-Pot Halogenation/Suzuki Cross-Coupling Reaction

Thus, once again, different reactions have been performed and reported in **Table 9**. Different arenes with NBS or NIS and phenylboronic acids were tolerated. The corresponding coupling compounds **208-215** could be isolated in good to excellent yields (80-95%) in two steps.

Table 9. The Scope of One-Pot Halogenation/Suzuki Cross-Coupling Reaction

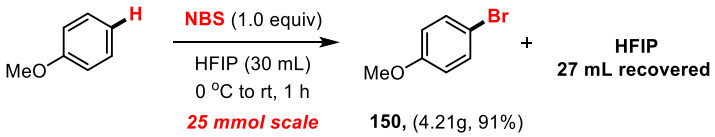


Entry	Product	NXS	Yield (%)	Entry	Product	NXS	Yield (%)
1	 **208**	NBS	93	5	 **212**	NBS	87%
2	 **209**	NBS	91	6	 **213**	NBS	80
3	 **210**	NBS	94	7	 **214**	NIS	93

4	 **211**	NBS	89	8	 **215**	NIS	95

II. 6. Gram Scale Reaction

Meanwhile, it is notable that this halogenation could be easily scaled up and the solvent could be recycled due to its low boiling point (b.p. = 59 °C) (**Scheme 28**). For example, when the bromination of anisole with NBS was performed on 25 mmol scale in 30 mL HFIP for 1 h. Not only the desired product **149** could be obtained smoothly in 91% yield, but also a 27 mL of HFIP was recovered after distillation directly from the reaction.



Scheme 28. Gram Scale Reaction

III. Conclusion

In conclusion, fluorinated alcohols have been proved to be very efficient solvents for the regioselective bromination of arenes and heterocycles with NBS. Due to the strong hydrogen-bond donation ability of the fluorinated alcohols, the aryl bromides formed smoothly in short times at room temperature without any additional catalyst or reagent. This fluorinated alcohols promoted reaction can also be extended to chlorination and iodination with NCS and NIS, respectively. Meanwhile, the clean conditions allow the combination of halogenation with Suzuki cross-coupling reaction without removal of the solvent or isolation of the intermediate bromide or iodide.

IV. Experimental Section

General Information and Reagents

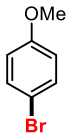
High-resolution mass spectra (HRMS) were obtained from waters LCT Premier (ESI/TOF). Melting points were determined on a Kofler melting point apparatus. NMR spectra were measured on an Ultrafield AVANCE300 (^{1}H, 300 MHz; ^{13}C, 75 MHz) spectrometer. Unless otherwise stated, NMR data were obtained under ambient temperature conditions in $CDCl_3$. Chemical shifts for ^{1}H NMR and ^{13}C NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the solvent resonance as the internal standard.

Unless otherwise noted, all commercial materials were purchased from various commercial sources (Sigma-Aldrich, Alfa Aesar, FluoroChem) and used as received, without further purification. HFIP was provided by. Central Glass Co. Ltd.

General Procedure for Bromination of Arenes with NBS

To a stirred solution of arenes 1 (0.5 mmol) in HFIP (2 mL) was added NBS (0.5 mmol) under air. The reaction mixture was stirred at rt for 0.25-16 h. After, the reaction mixture was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel using cyclohexane: ethyl acetate as the eluent to give the brominated products.

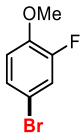
1-bromo-4-methoxybenzene (150) [34]



The title compound was prepared between anisole (54.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 15 min and purified by 5 % EtOAc in cyclohexane as a colorless oil (86 mg, 92%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, J = 8.9 Hz, 2H), 6.79 (d, J = 8.9 Hz, 2H), 3.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 132.4, 115.9, 112.9, 55.6.

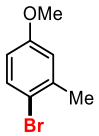
4-bromo-2-fluoro-1-methoxybenzene (151) [37]



The title compound was prepared between 2-fluoroanisole (63.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 30 min and purified by 5 % EtOAc in cyclohexane as a colorless oil (98 mg, 96%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 – 7.09 (m, 2H), 6.75 (t, J = 8.9 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4 (d, J = 249.0 Hz), 147.2 (d, J = 9.8 Hz), 127.3 (d, J = 4.5 Hz), 119.7 (d, J = 21.0 Hz), 114.7, 112.0 (d, J = 8.3 Hz), 56.5.

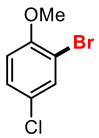
1-bromo-4-methoxy-2-methylbenzene (152) [34]



The title compound was prepared between 3-methylanisole (61.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at 0 °C for 15 min and purified by 5 % EtOAc in cyclohexane as a colorless oil (94 mg, 94%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, J = 8.7 Hz, 1H), 6.79 (d, J = 2.9 Hz, 1H), 6.62 (dd, J = 8.7, 3.0 Hz, 1H), 3.77 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 138.9, 132.9, 116.6, 115.5, 113.1, 55.5, 23.3.

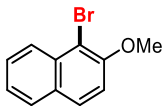
2-bromo-4-chloro-1-methoxybenzene (153) [38]



The title compound was prepared between 4-chloroanisole (72.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 2 h and purified by 5 % EtOAc in cyclohexane as a colorless oil (103 mg, 94%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, J = 2.5 Hz, 1H), 7.24 (dd, J = 9.3, 2.6 Hz, 1H), 6.82 (d, J = 8.8 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 133.1, 128.4, 126.1, 112.7, 112.3, 56.6.

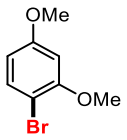
1-bromo-2-methoxynaphthalene (154) [34]



The title compound was prepared between 2-methoxynaphthalene (79.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 15 min and purified by 5 % EtOAc in cyclohexane as a white solid (113 mg, 96%).

M.p. 86 - 88 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.6 Hz, 1H), 7.80 (t, *J* = 9.2 Hz, 2H), 7.57 (d, *J* = 6.9 Hz, 1H), 7.40 (d, *J* = 6.9 Hz, 1H), 7.27 (d, *J* = 8.9 Hz, 1H), 4.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 133.3, 130.0, 129.1, 128.2, 127.9, 126.3, 124.5, 113.8, 108.8, 57.2.

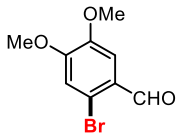
1-bromo-2,4-dimethoxybenzene (155) [34]



The title compound was prepared between 1,3-dimethoxybenzene (69.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP/DCM (1/1, 2 ml) at rt for 30 min and purified by 5 % EtOAc in cyclohexane as a colorless oil (102 mg, 94%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.7 Hz, 1H), 6.48 (d, *J* = 2.6 Hz, 1H), 6.39 (dd, *J* = 8.7, 2.7 Hz, 1H), 3.86 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3, 156.7, 133.3, 106.0, 102.6, 100.1, 56.3, 55.7.

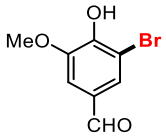
2-bromo-4,5-dimethoxybenzaldehyde (156) [39]



The title compound was prepared between 3,4-dimethoxybenzaldehyde (83.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 30 min and purified by 20 % EtOAc in cyclohexane as a white solid (114 mg, 93%).

M.p. 134 - 136 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.21 (s, 1H), 7.96 (s, 1H), 6.42 (s, 1H), 3.96 (s, 1H), 3.93 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.2, 163.1, 161.8, 133.0, 119.5, 103.6, 95.7, 56.6, 56.1.

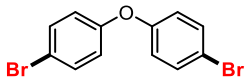
3-bromo-4-hydroxy-5-methoxybenzaldehyde (157) [10]



The title compound was prepared between 3-methoxy-4-hydroxybenzaldehyde (76.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 30 min and purified by 30 % EtOAc in cyclohexane as a white solid (97 mg, 84%).

M.p. 166 - 168 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.64 (s, 1H), 7.36 (s, 1H), 6.53 (s, 1H), 3.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.8, 149.0, 147.8, 130.2, 130.2, 108.3, 108.2, 56.8.

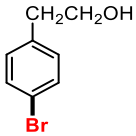
4,4'-oxybis(bromobenzene) (158) [40]



The title compound was prepared between diphenyl oxide (85.0 mg, 0.5 mmol) and NBS (178.0 mg, 1.0 mmol) in HFIP (2 ml) at rt for 2 h and purified by pure cyclohexane as a white solid (155 mg, 95%).

M.p. 60 - 62 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, J = 8.6 Hz, 4H), 6.88 (d, J = 8.6 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 133.0, 120.8, 116.3.

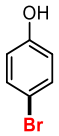
2-(4-bromophenyl)ethanol (159) [41]



The title compound was prepared between 2-phenylethanol (69.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 0.5 h and purified by 20 % EtOAc in cyclohexane as a white solid (99 mg, 92%).

M.p. 56 - 58 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, J = 8.6 Hz, 2H), 6.79 (d, J = 8.6 Hz, 2H), 4.03 (t, J = 4.2 Hz, 2H), 3.94 (t, J = 4.2 Hz, 2H), 2.22 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 132.4, 116.4, 113.4, 69.6, 61.4.

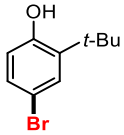
4-bromophenol (160) [42]



The title compound was prepared between phenol (47.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at 0 ºC for 2 h and purified by 10 % EtOAc in cyclohexane as a white solid (77 mg, 90%).

M.p. 66 - 68 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, J = 8.9 Hz, 2H), 6.72 (d, J = 8.9 Hz, 2H), 4.85 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 132.6, 117.3, 113.0.

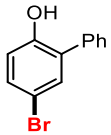
4-bromo-2-(tert-butyl)phenol (161) [43]



The title compound was prepared between 2-tert-butylphenol (75.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at 0 ºC for 2 h and purified by 10 % EtOAc in cyclohexane as a colorless oil (101 mg, 89%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, J = 2.2 Hz, 1H), 7.17 (dd, J = 8.4, 2.4 Hz, 1H), 6.55 (d, J = 8.4 Hz, 1H), 4.82 (s, 1H), 1.39 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.4, 138.7, 130.3, 129.7, 118.3, 113.1, 34.9, 29.5.

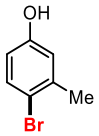
5-bromo-[1,1'-biphenyl]-2-ol (162) [42]



The title compound was prepared between 2-phenylphenol (85.5 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at 0 ºC for 2 h and purified by 15 % EtOAc in cyclohexane as a colorless oil (114 mg, 91%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.48 (m, 2H), 7.45 – 7.42 (m, 3H), 7.37 – 7.34 (m, 2H), 6.88 (d, J = 8.6 Hz, 1H), 5.21 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.7, 132.8, 132.0, 129.6, 129.1, 128.6, 117.8, 112.9.

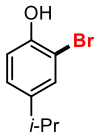
4-bromo-3-methylphenol (163) [10]



The title compound was prepared between 3-methylphenol (54.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at 0 °C for 2 h and purified by 10 % EtOAc in cyclohexane as a colorless oil (79 mg, 85%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.6 Hz, 1H), 6.73 (d, *J* = 2.7 Hz, 1H), 6.55 (dd, *J* = 8.6, 2.9 Hz, 1H), 5.00 (s, 1H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 139.3, 133.2, 117.9, 115.6, 114.6, 23.1.

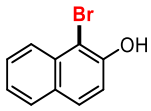
2-bromo-4-isopropylphenol (164) [44]



The title compound was prepared between 4-isopropylphenol (68.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at 0 °C for 2 h and purified by 10 % EtOAc in cyclohexane as a colorless oil (101 mg, 94%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 1.9 Hz, 1H), 7.08 (dd, *J* = 8.3, 1.7 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 5.37 (s, 1H), 2.90 – 2.76 (m, 1H), 1.22 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.3, 142.8, 129.8, 127.4, 116.0, 110.1, 33.3, 24.2.

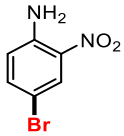
1-bromonaphthalen-2-ol (165) [34]



The title compound was prepared between β-naphthol (72.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 2 h and purified by 15 % EtOAc in cyclohexane as a white solid (103 mg, 93%).

M.p. 82 - 84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.5 Hz, 1H), 7.80 – 7.73 (m, 2H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 8.7 Hz, 1H), 5.93 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7, 132.4, 129.8, 129.5, 128.3, 128.0, 125.5, 124.3, 117.3, 106.3.

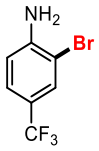
4-bromo-2-nitroaniline (166) [45]



The title compound was prepared between 2-nitroaniline (69.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at 0 ºC for 15 min and purified by 20 % EtOAc in cyclohexane as a yellow solid (97 mg, 90%).

M.p. 114 - 116 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, J = 2.0 Hz, 1H), 7.42 (dd, J = 8.9, 2.0 Hz, 1H), 6.73 (d, J = 8.9 Hz, 1H), 6.11 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 138.6, 128.4, 120.4, 108.0.

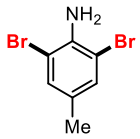
2-bromo-4-(trifluoromethyl)aniline (167) [46]



The title compound was prepared between 4-trifluoromethylaniline (80.5 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at 0 ºC for 15 min and purified by 10 % EtOAc in cyclohexane as a colorless oil (94 mg, 79%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.34 (d, J = 8.4 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H), 4.37 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 130.1 (d, J = 3.0 Hz), 125.7 (d, J = 3.8 Hz), 122.2, 121.1 (d, J = 33.0 Hz), 114.9, 108.2.

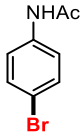
2,6-dibromo-4-methylaniline (168) [45]



The title compound was prepared between 4-methylaniline (53.5 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at 0 ºC for 5 min and purified by 10 % EtOAc in cyclohexane as a yellow solid (99 mg, 75%).

M.p. 74 - 76 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (s, 2H), 4.23 (s, 2H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.7, 132.3, 129.5, 108.9, 19.9.

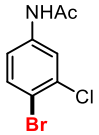
N-(4-bromophenyl)acetamide (169) [34]



The title compound was prepared between N-phenylacetamide (67.5 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at 0 °C for 2 h and purified by 30 % EtOAc in cyclohexane as a white solid (96 mg, 90%).

M.p. 168 - 170 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.05 (s, 1H), 7.54 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 8.7 Hz, 2H), 2.03 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.5, 138.7, 131.5, 120.9, 114.5, 24.0.

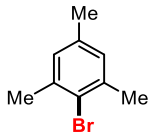
N-(4-bromo-3-chlorophenyl)acetamide (170) [12]



The title compound was prepared between N-(3-chlorophenyl)acetamide (84.5 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at 0 °C for 2 h and purified by 30 % EtOAc in cyclohexane as a white solid (92 mg, 74%).

M.p. 122 - 124 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.21 (s, 1H), 7.96 (s, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.38 (dd, J = 8.8, 2.0 Hz, 1H), 2.05 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.8, 139.9, 133.7, 133.0, 120.0, 119.1, 114.0, 24.1.

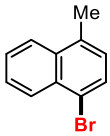
2-bromo-1,3,5-trimethylbenzene (171) [46]



The title compound was prepared between mesitylene (60.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 5 h and purified by pure cyclohexane as a colorless oil (95 mg, 96%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (s, 2H), 2.40 (s, 6H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 136.4, 129.2, 124.3, 23.9, 20.8.

2-bromo-1-methylnaphthalene (172) [46]



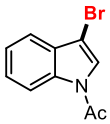
The title compound was prepared between 1-methylnaphthalene (71.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 5 h and purified by pure cyclohexane as a colorless oil (104 mg, 94%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, J = 9.2 Hz, 1H), 8.00 (d, J = 7.4 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.64 – 7.59 (m, 2H), 7.17 (d, J = 7.5 Hz, 1H), 2.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.5, 134.0, 132.0, 129.7, 127.9, 127.1, 127.1, 126.6, 124.7, 120.8, 19.5.

General Procedure for Bromination of Heterocycles with NBS

To a stirred solution of heterocycles (0.5 mmol) in HFIP (2 mL) was added NBS (0.5 mmol) under air. The reaction mixture was stirred at rt for 15 min ~ 1 h. After, the reaction mixture was evaporated under reduce pressure and the crude product was purified by column chromatography on silica gel using cyclohexane: ethyl acetate as the eluent to give the brominated products.

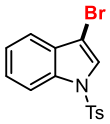
1-(3-bromo-1H-indol-1-yl)ethan-1-one (180) [32]



The title compound was prepared between N-acetylindole (79.5 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP/DCM (4/1) at rt for 15 min and purified by 10 % EtOAc in cyclohexane as a white solid (107 mg, 90%).

M.p. 114 - 116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.49 (s, 1H), 7.44 – 7.33 (m, 2H), 2.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 135.0, 129.5, 126.5, 124.4, 124.3, 119.6, 116.6, 100.2, 24.0.

3-bromo-1-tosyl-1H-indole (181) [33]

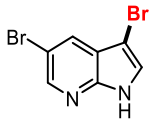


The title compound was prepared between N-tosylindole (135.5 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP/DCM (4/1) at rt for 15 min, and purified by 5 % EtOAc in cyclohexane

as a white solid (164 mg, 94%)

M.p. 124 - 126 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.63 (s, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.41 – 7.28 (m, 2H), 7.23 (d, *J* = 8.3 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.5, 135.0, 134.4, 130.1, 129.9, 127.0, 125.9, 124.9, 124.0, 120.2, 113.7, 99.7, 21.7.

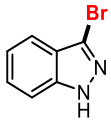
3,5-dibromo-1H-pyrrolo[2,3-b]pyridine (182)



The title compound was prepared between 5-bromo-1H-pyrrolo[2,3-b]pyridine (98.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at 0 ºC for 15 min, and purified by 30 % EtOAc in cyclohexane as a light yellow solid (122 mg, 89%).

M.p. 230 - 232 ºC; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.33 (s, 1H), 8.35 (s, 1H), 8.02 (s, 1H), 7.80 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 145.6, 144.0, 128.4, 127.6, 120.4, 111.5, 86.4; HRMS calcd. for $C_7H_5N_2$ $Br_2[M+H]^+$ m/z 276.8799, found 276.8804.

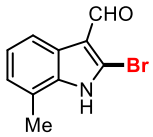
3-bromo-1H-indazole (183) [33]



The title compound was prepared between indazole (59.0 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at 0 ºC for 15 min and purified by 20 % EtOAc in cyclohexane as a white solid (83 mg, 84%).

M.p. 120 - 122 ºC; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.27 (s, 1H), 8.06 (s, 1H), 8.00 (s, 1H), 7.54 (d, *J* = 8.7 Hz, 1H), 7.44 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 138.6, 133.0, 128.6, 124.5, 122.9, 112.5, 112.2.

2-bromo-7-methyl-1H-indole-3-carbaldehyde (184)

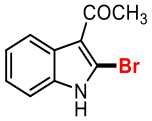


The title compound was prepared between 7-methyl-1H-indole-3-carbaldehyde (72.5 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at 0 ºC for 15 min and purified by 20 %

EtOAc in cyclohexane as a yellow solid (97 mg, 87%).

M.p. 236 - 238 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.33 (s, 1H), 9.93 (s, 1H), 8.33 (d, J = 2.7 Hz, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 2.55 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 185.1, 138.7, 126.1, 123.2, 121.7, 119.7, 118.5, 118.5, 16.9; HRMS calcd. for $C_{10}H_9NOBr[M+H]^+$ m/z 237.9868, found 237.9878.

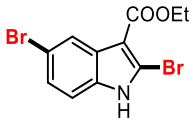
1-(2-bromo-1H-indol-3-yl)ethan-1-one (185)



The title compound was prepared between 1-(1H-indol-3-yl)ethan-1-one (79.5 mg, 0.5 mmol) and NBS (89.0 mg, 0.5 mmol) in HFIP (2 ml) at 0 °C for 15 min and purified by 20 % EtOAc in cyclohexane as a white solid (97 mg, 82%).

M.p. 228 - 230 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.09 (s, 1H), 8.33 (d, J = 14.0 Hz, 2H), 7.44 (d, J = 8.6 Hz, 1H), 7.33 (dd, J = 8.6, 1.5 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 192.7, 135.5, 135.4, 127.0, 125.3, 123.4, 116.2, 114.4, 114.2, 27.2; HRMS calcd. for $C_{10}H_9NOBr$ $[M+H]^+$ m/z 237.9868, found 237.9872.

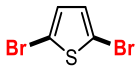
ethyl 2-bromo-1H-indole-3-carboxylate (186)



The title compound was prepared between ethyl-1H-indole-3-carboxylate (94.5 mg, 0.5 mmol) and NBS (178.0 mg, 1.0 mmol) in HFIP (2 ml) at rt for 30 min and purified by 30 % EtOAc in cyclohexane as a yellow solid (130 mg, 75%).

M.p. 226 - 228 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.15 (s, 1H), 8.27 (s, 1H), 8.15 (d, J = 2.9 Hz, 1H), 7.87 (s, 1H), 4.28 (q, J = 7.1 Hz, 2H), 1.32 (t, J = 7.1, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.7, 136.1, 134.6, 126.5, 124.4, 117.2, 116.5, 115.9, 106.3, 59.4, 14.4; HRMS calcd. for C11H10NO279Br81Br [M+H]+ m/z 347.9058, found 347.9055.

2,5-dibromothiophene (187) [47]



The title compound was prepared between thiophene (42.0 mg, 0.5 mmol) and NBS (178.0 mg,

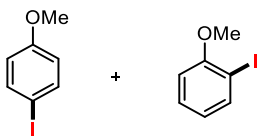
1.0 mmol) in HFIP (2 ml) at rt for 30 min and purified by 5 % EtOAc in cyclohexane as a colorless oil (107 mg, 89%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.52, 111.67.

General Procedure for Iodination and Chlorination of Arenes and Heterocycles

To a stirred solution of arenes or heterocycles (0.5 mmol) in HFIP (2 mL) was added NIS or NCS (0.5 mmol) under air. The reaction mixture was stirred at rt for 0.5 ~ 16 h. After, the reaction mixture was evaporated under reduce pressure and the crude product was purified by column chromatography on silica gel using cyclohexane: ethyl acetate as the eluent to give the iodinated/chlorinated products.

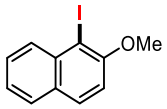
1-iodo-2-methoxybenzene and 1-iodo-4-methoxybenzene (188/188': 9/1) [44]



The title compound was prepared between anisole (54.0 mg, 0.5 mmol) and NIS (112.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 30 min and purified by 5 % EtOAc in cyclohexane as a colorless oil (111 mg, 95%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 7.7 Hz, 0.1 ×1 H), 7.56 (d, J = 8.8 Hz, 0.9 × 2H), 7.31 (t, J = 7.8 Hz, 0.1 ×1 H), 6.83 (d, J = 8.2 Hz, 0.1 × 1H), 6.68 (d, J = 8.8 Hz, 0.9 × 2H), 3.88 (s, 0.1 × 3H), 3.78 (s, 0.9 × 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 158.2, 139.6, 138.3, 129.6, 122.6, 116.5, 111.1, 86.1, 82.8, 56.4, 55.4.

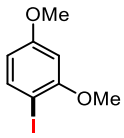
1-iodo-2-methoxynaphthalene (189) [10]



The title compound was prepared between 2-methoxynaphthalene (79.0 mg, 0.5 mmol) and NIS (112.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 30 min and purified by 5 % EtOAc in cyclohexane as a white solid (132 mg, 93%).

M.p. 88 - 90 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, J = 8.6 Hz, 1H), 7.82 (d, J = 8.9 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.55 (t, J = 7.5 Hz, 1H), 7.39 (t, J = 7.5 Hz, 1H), 7.20 (d, J = 8.9 Hz, 1H), 4.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 135.7, 131.3, 130.5, 130.0, 128.3, 128.2, 124.4, 113.0, 87.8, 57.3.

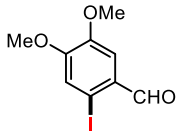
1-iodo-2,4-dimethoxybenzene (190) [10]



The title compound was prepared between 1,3-dimethoxybenzene (69.0 mg, 0.5 mmol) and NIS (112.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 30 min and purified by 5 % EtOAc in cyclohexane as a white solid (127 mg, 96%).

M.p. 38 - 40 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, J = 8.7 Hz, 1H), 6.48 (s, 1H), 6.39 (d, J = 8.7 Hz, 1H), 3.86 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3, 133.2, 106.0, 102.5, 100.1, 56.2, 55.7.

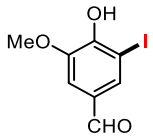
2-iodo-4,5-dimethoxybenzaldehyde (191) [48]



The title compound was prepared between 3,4-dimethoxybenzaldehyde (83.0 mg, 0.5 mmol) and NIS (112.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 30 min and purified by 20 % EtOAc in cyclohexane as a white solid (127 mg, 96%).

M.p. 174 - 176 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.17 (s, 1H), 8.18 (s, 1H), 6.37 (s, 1H), 3.95 (s, 3H), 3.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.1, 164.2, 139.3, 120.5, 94.9, 75.7, 56.8, 56.0.

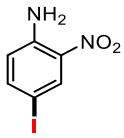
4-hydroxy-3-iodo-5-methoxybenzaldehyde (192) [44]



The title compound was prepared between 3-methoxy-4-hydroxybenzaldehyde (76.0 mg, 0.5 mmol) and NIS (112.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 30 min and purified by 30 % EtOAc in cyclohexane as a white solid (128 mg, 92%).

M.p. 180 - 182 ºC; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.79 (s, 1H), 9.74 (s, 1H), 7.87 (s, 1H), 7.40 (s, 1H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 190.3, 152.3, 147.4, 134.8, 130.1, 110.2, 84.2, 56.3.

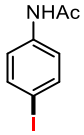
4-iodo-2-nitroaniline (193) [49]



The title compound was prepared between 2-nitroaniline (69.0 mg, 0.5 mmol) and NIS (112.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 2 h and purified by 20 % EtOAc in cyclohexane as a yellow solid (117 mg, 87%).

M.p. 124 - 126 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.59 (d, J = 8.9 Hz, 1H), 7.53 (s, 2H), 6.85 (d, J = 8.9 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 145.5, 143.2, 132.9, 131.4, 121.5, 74.8.

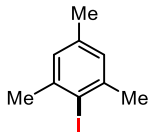
N-(4-iodophenyl)acetamide (194) [23]



The title compound was prepared between N-phenylacetamide (67.0 mg, 0.5 mmol) and NIS (112.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 2 h and purified by 30 % EtOAc in cyclohexane as a white solid (124 mg, 95%).

M.p. 170 - 172 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.01 (s, 1H), 7.61 (d, J = 8.7 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H), 2.03 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.4, 139.1, 137.2, 121.1, 86.2, 24.0.

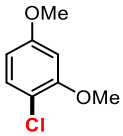
2-iodo-1,3,5-trimethylbenzene (195) [48]



The title compound was prepared between 1,3,5-trimethylbenzene (54.0 mg, 0.5 mmol) and NIS (112.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 16 h and purified by pure cyclohexane as a colorless oil (118 mg, 96%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (s, 2H), 2.47 (d, J = 4.1 Hz, 6H), 2.27 (d, J = 4.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 137.4, 128.1, 104.4, 29.6, 20.8.

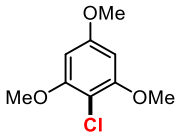
1-chloro-2,4-dimethoxybenzene (198) [50]



The title compound was prepared between 1,3-dimethoxybenzene (69.0 mg, 0.5 mmol) and NCS (66.5 mg, 0.5 mmol) in HFIP (2 ml) at rt for 5 h and purified by 5 % EtOAc in cyclohexane as a colorless oil (82 mg, 95%).

M.p. 36 - 38 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 9.0 Hz, 1H), 6.51 (d, J = 2.6 Hz, 1H), 6.43 (dd, J = 8.7, 2.6 Hz, 1H), 3.87 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 155.8, 130.3, 114.3, 105.3, 100.2, 56.2, 55.7.

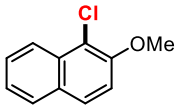
2-chloro-1,3,5-trimethoxybenzene (199) [50]



The title compound was prepared between 1,3,5-trimethoxybenzene (84.0 mg, 0.5 mmol) and NCS (66.5 mg, 0.5 mmol) in HFIP (2 ml) at rt for 2 h and purified by 5 % EtOAc in cyclohexane as a white solid (97 mg, 96%).

M.p. 92 - 94 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.17 (s, 2H), 3.87 (s, 6H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 156.7, 102.8, 91.8, 56.4, 55.7.

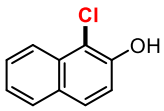
1-chloro-2-methoxynaphthalene (200) [38]



The title compound was prepared between 2-methoxynaphthalene (79.0 mg, 0.5 mmol) and NCS (66.5 mg, 0.5 mmol) in HFIP (2 ml) at rt for 16 h and purified by 5 % EtOAc in cyclohexane as a white solid (88 mg, 92%).

M.p. 68 - 70 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, J = 8.6 Hz, 1H), 7.81 – 7.76 (m, 2H), 7.58 (t, J = 7.5 Hz, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.30 (d, J = 9.0 Hz, 1H), 4.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.0, 129.7, 128.1, 128.1, 127.6, 124.4, 123.6, 113.8, 57.1.

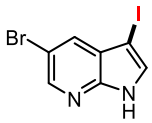
1-chloronaphthalen-2-ol (201) [38]



The title compound was prepared between naphthalen-2-ol (64.0 mg, 0.5 mmol) and NCS (66.5 mg, 0.5 mmol) in HFIP (2 ml) at rt for 16 h and purified by 10 % EtOAc in cyclohexane as a white solid (72 mg, 88%).

M.p. 66 - 68 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 8.2 Hz, 1H), 7.72 (d, J = 8.9 Hz, 1H), 7.58 (t, J = 7.7 Hz, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.27 (d, J = 8.7 Hz, 1H), 5.90 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5, 131.2, 129.6, 128.6, 128.3, 127.7, 124.3, 122.9, 117.4, 113.5.

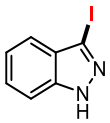
5-bromo-3-iodo-1H-pyrrolo[2,3-b]pyridine (202)



The title compound was prepared between 5-bromo-1H-pyrrolo[2,3-b]pyridine (98.5 mg, 0.5 mmol) and NIS (112.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 0.5 h and purified by 30 % EtOAc in cyclohexane as a white solid (155 mg, 96%).

M.p. 240 - 242 ºC; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.34 (s, 1H), 8.31 (s, 1H), 7.86 (s, 1H), 7.80 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 146.5, 143.8, 132.5, 129.9, 123.8, 111.6, 53.5; HRMS calcd. for $C_7H_5N_2IBr$ $[M+H]^+$ m/z 322.8681, found 322.8675.

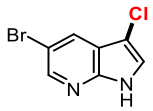
3-iodo-1H-indazole (203)



The title compound was prepared between 1H-indazole (59.0 mg, 0.5 mmol) and NIS (112.0 mg, 0.5 mmol) in HFIP (2 ml) at rt for 0.5 h and purified by 20 % EtOAc in cyclohexane as a yellow solid (104 mg, 85%).

M.p. 134 - 136 ºC; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.51 (s, 1H), 7.56 (d, J = 8.7 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.19 (t, J = 13.5 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 140.4, 127.2, 126.8, 121.2, 120.4, 110.5, 93.5; HRMS calcd. for $C_7H_6N_2I$ $[M+H]^+$ m/z 244.9576, found 244.9572.

5-bromo-3-chloro-1H-pyrrolo[2,3-b]pyridine (204)

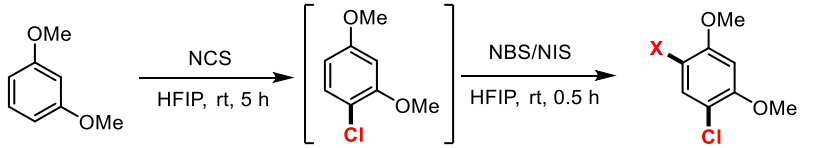


The title compound was prepared between 5-bromo-1H-pyrrolo[2,3-b]pyridine (98.5 mg, 0.5 mmol) and NCS (66.5 mg, 0.5 mmol) in HFIP (2 ml) at rt for 2 h and purified by 30 % EtOAc in cyclohexane as a white solid (108 mg, 94%).

M.p. 206 - 208 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.23 (s, 1H), 8.35 (s, 1H), 8.11 (s, 1H), 7.76 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 145.1, 144.0, 127.7, 125.2, 118.8, 111.4, 101.3; HRMS calcd. for $C_7H_5N_2BrCl$ $[M+H]^+$ m/z 232.9304, found 232.9306.

General Procedure for One-Pot Sequential Halogenation

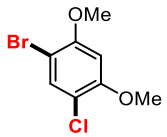
(1)



205, (X = Br) 92%
206, (X = I) 90%

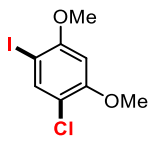
To a stirred solution of 1,3-dimethoxybenzene (69.0 mg, 0.5 mmol) in HFIP (2 mL) was added NCS (66.5 mg, 0.5 mmol). The reaction mixture was stirred at rt for 5 h. Then added NBS (89.0 mg, 0.5 mmol) or NIS (112.0 mg, 0.5 mmol) and the mixture was stirred at rt for another 0.5 h. After, the reaction mixture was evaporated under reduce pressure to get crude product. Then the crude product was purified by column chromatography on silica gel using cyclohexane: ethyl acetate (20: 1) as the eluent to give the sequential halogenated products **205** and **206.**

1-bromo-5-chloro-2,4-dimethoxybenzene (205) [32]



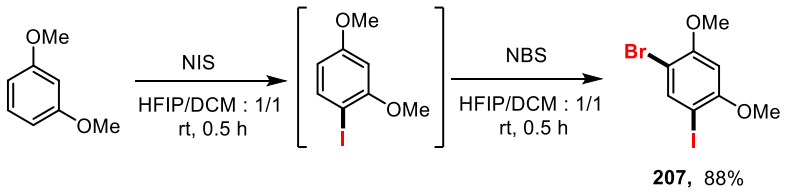
M.p. 116 - 118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (s, 1H), 6.50 (s, 1H), 3.90 (s, 3H), (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 155.3, 133.3, 114.6, 102.0, 97.7, 56.7, 56.6.

1-chloro-5-iodo-2,4-dimethoxybenzene (206) [51]



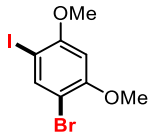
M.p. 128 - 130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (s, 1H), 6.43 (s, 1H), 3.90 (s, 3H), (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 156.3, 138.9, 115.2, 96.8, 73.9, 56.9, 56.5.

(2)



To a stirred solution of 1,3-dimethoxybenzene (69.0 mg, 0.5 mmol) in HFIP/DCM (1/1, 2 mL) was added NIS (112.0 mg, 0.5 mmol). The reaction mixture was stirred at rt for 0.5 h. Then added NBS (89.0 mg, 0.5 mmol) and the mixture was stirred at rt for another 0.5 h. After, the reaction mixture was evaporated under reduce pressure to get crude product. Then the crude product was purified by column chromatography on silica gel using cyclohexane: ethyl acetate as the eluent (20: 1) to give the sequential halogenated product **207.**

1-bromo-5-iodo-2,4-dimethoxybenzene (207) [52]



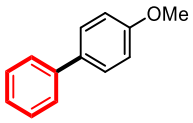
M.p. 168 - 170 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (s, 1H), 6.41 (s, 1H), 3.90 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 157.3, 141.5, 103.2, 96.7, 74.6, 56.8, 56.5.

General Procedure for One-Pot of Halogenation with Suzuki Cross-Coupling Reaction

To a stirred solution of arenes (0.5 mmol) in HFIP (2 mL) was added NBS or NIS (0.5 mmol) under air. The reaction mixture was stirred at rt for 0.25 - 16 h. Afterward added boronic acid derivatives (0.75 mmol), sodium carbonate (1.0 mmol), $PdCl_2(PPh_3)_2$ (0.015 mmol), and H_2O (2.0 mL) under N_2 atmosphere. The mixture was placed in an oil bath and stirred at 100 °C for 16 h. Subsequently the mixture was cooled down to room temperature and treated with DCM (10 mL) and water (20 mL) and then extracted by DCM (20 mL × 3). The combined extraction was washed by brine, dried over anhydrous $NaSO_4$ and concentrated in vacuum. The residue

was purified by silica-gel column chromatography using cyclohexane: ethyl acetate as eluent to give desired products.

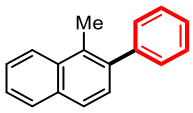
4-methoxy-1,1'-biphenyl (208) [53]



The title compound was prepared as described in the general procedure using anisol (54.0 mg, 0.5 mmol), NBS (89.0 mg, 0.5 mmol) and phenylboronic acid (91.5 mg, 0.75 mmol), and purified by 5 % EtOAc in cyclohexane as a white solid (86 mg, 93%).

M.p. 92 - 94 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 – 7.54 (m, 4H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.34 (d, *J* = 7.3 Hz, 1H), 7.00 (d, *J* = 8.7 Hz, 2H), 3.87 (s, 3H); 13C NMR (75 MHz, $CDCl_3$) δ 159.3, 141.0, 133.9, 128.9, 128.3, 126.9, 126.8, 114.3, 55.5.

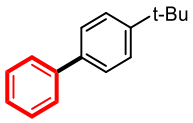
1-methyl-2-phenylnaphthalene (209) [54]



The title compound was prepared as described in the general procedure using 1-methylnaphthalene (71.0 mg, 0.5 mmol), NBS (89.0 mg, 0.5 mmol) and phenylboronic acid (91.5 mg, 0.75 mmol), and purified by pure cyclohexane as a colorless oil (99 mg, 91%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 8.3 Hz, 1H), 7.59 – 7.34 (m, 9H), 2.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 138.8, 133.9, 132.9, 131.8, 130.3, 128.9, 128.3, 127.2, 126.8, 126.8, 126.3, 125.8, 124.5, 19.7.

4-(tert-butyl)-1,1'-biphenyl (210) [55]

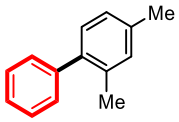


The title compound was prepared as described in the general procedure using *tert*-butylbenzene (67.0 mg, 0.5 mmol), NBS (89.0 mg, 0.5 mmol) and phenylboronic acid (91.5 mg, 0.75 mmol), and purified by pure cyclohexane as a colorless oil (99 mg, 94%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 – 7.54 (m, 4H), 7.49 – 7.41 (m, 4H), 7.38 – 7.31 (m, 1H), 1.38 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.4, 141.2, 138.5, 128.9, 127.2, 127.1, 126.9,

125.9, 34.7, 31.5.

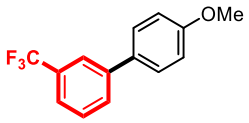
2,4-dimethyl-1,1'-biphenyl (211) [55]



The title compound was prepared as described in the general procedure using *m*-xylene (53.0 mg, 0.5 mmol), NBS (89.0 mg, 0.5 mmol) and phenylboronic acid (91.5 mg, 0.75 mmol), and purified by pure cyclohexane as a colorless oil (81 mg, 89%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, J = 7.2 Hz, 0.14 × 4H), 7.50 – 7.34 (m, 5H + 0.14 × 4H), 7.19 – 7.08 (m, 3H + 0.14 × 2H), 2.40 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.1, 141.4, 139.2, 137.0, 135.3, 131.2, 129.9, 129.4, 128.9, 128.2, 127.4, 127.3, 126.7, 126.6, 21.2, 20.5.

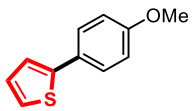
4'-methoxy-3-(trifluoromethyl)-1,1'-biphenyl (212) [53]



The title compound was prepared as described in the general procedure using anisol (54.0 mg, 0.5 mmol), NBS (89.0 mg, 0.5 mmol) and 3-(trifluoromethyl)phenylboronic acid (142.5 mg, 0.75 mmol), and purified by 5 % EtOAc in cyclohexane as a white solid (86 mg, 93%).

M.p. 78 - 80 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.73 (d, J = 7.0 Hz, 1H), 7.56 – 7.50 (m, 4H), 7.01 (d, J = 8.7 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 141.7, 132.3, 130.1, 129.3, 128.4, 123.6 (d, J = 3.7 Hz), 123.4 (q, J = 3.7 Hz), 114.6, 55.5.

2-(4-methoxyphenyl)thiophene (213) [56]

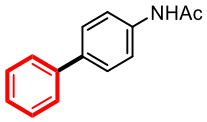


The title compound was prepared as described in the general procedure using anisol (54.0 mg, 0.5 mmol), NBS (89.0 mg, 0.5 mmol) and 2-thienylboronic acid (87.0 mg, 0.75 mmol), and purified by 10 % EtOAc in cyclohexane as a white solid (71 mg, 80%).

M.p. 104 - 106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, J = 8.7 Hz, 2H), 7.23 – 7.20 (m, 2H), 7.06 (t, J = 4.8 Hz, 1H), 6.92 (d, J = 8.7 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

159.3, 144.5, 128.1, 127.4, 127.4, 124.0, 122.2, 114.4, 55.5.

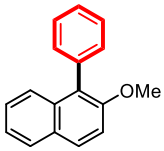
N-([1,1'-biphenyl]-4-yl)acetamide (214) [57]



The title compound was prepared as described in the general procedure using acetanilide (67.5 mg, 0.5 mmol), NIS (112.0 mg, 0.5 mmol) and phenylboronic acid (91.5 mg, 0.75 mmol), and purified by 30 % EtOAc in cyclohexane as a white solid (98 mg, 93%).

M.p. 170 - 172 ºC; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.02 (s, 1H), 7.70 – 7.59 (m, 6H), 7.43 (t, J = 7.5 Hz, 2H), 7.31 (t, J = 7.2 Hz, 1H), 2.07 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.3, 139.7, 138.8, 134.6, 128.8, 126.9, 126.8, 126.2, 119.3, 24.0.

2-methoxy-1-phenylnaphthalene (215) [58]



The title compound was prepared as described in the general procedure using 2-methoxynaphthalene (79.0 mg, 0.5 mmol), NIS (112.0 mg, 0.5 mmol) and phenylboronic acid (91.5 mg, 0.75 mmol), and purified by 5 % EtOAc in cyclohexane as a white solid (111 mg, 95%).

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.63 – 7.34 (m, 10H), 2.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 138.8, 133.9, 132.9, 131.8, 130.3, 128.9, 128.3, 127.2, 126.8, 126.7, 126.3, 125.8, 124.5, 19.7.

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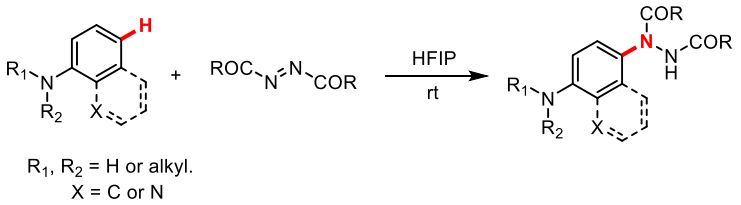
General Conclusion

Over the past few years, we have obtained some valuable results, which proved that fluorinated solvents are excellent solvents for the electrophilic aromatic substitution reactions. At first, several electrophilic aromatic substitution reactions in fluorinated alcohols under mild conditions without the need for any additional catalysts or reagents have been developed.

1. C-H Amination of Free Anilines with Azodicarboxylates

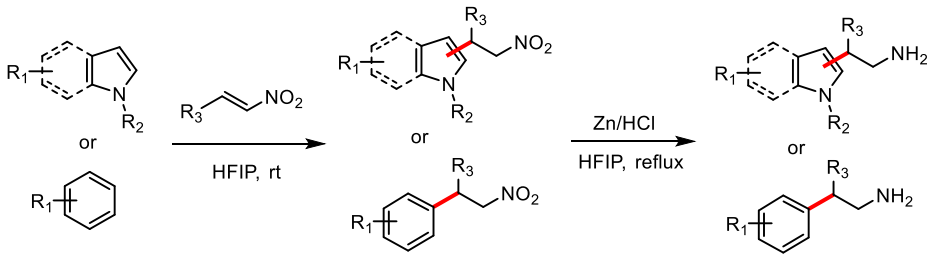
HFIP has proved to be an effective solvent for the *para*-selective C-H amination of free anilines with azodicarboxylate derivatives. a wide range of anilines were well aminated under mild condition and quickly to provide a series of *p*-aminophenylhydrazine derivatives in excellent yields. This method avoided the use of stoichiometric amount of reagents and additional steps for installation/removal of the protecting group due to the high nucleophilicity of the free amino group.



Scheme 1. C-H Amination of Free Anilines with Azodicarboxylates in HFIP

2. FC Alkylation of Indoles and Electron-Rich Arenes with β-Nitroalkenes

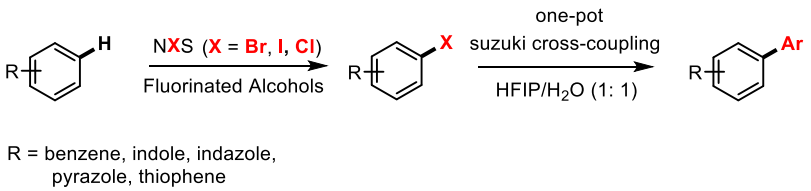
Fluorinated solvents were explored as hydrogen-bond donors and solvents for mild and effective FC alkylation of indoles and electron-rich arenes with β-nitroalkenes. The reaction also worked with secondary anilines in moderate yields which the Aza-Michael products were always the major products in previous reports. This methodology can be applied to one-pot synthesis of biologically active tryptamine derivatives.



Scheme 2. FC Alkylation of Indoles and Electron-Rich Arenes with β-Nitroalkenes

3. C-H Halogenation of Arenes and Heterocycles with NXS

The used of HFIP as solvent for mild, regioselective and high-yielding halogenation of a wide range of arenes and heterocycles was described. Many functionalities such as alcohols, amines, aldehydes, methyl ketone, ester, amide and halo were well tolerated. By taking advantage of the clean reaction profile, the one-pot of the sequential halogenation and the halogenation/Suzuki cross-coupling reaction were demonstrated to occur with good efficiency.



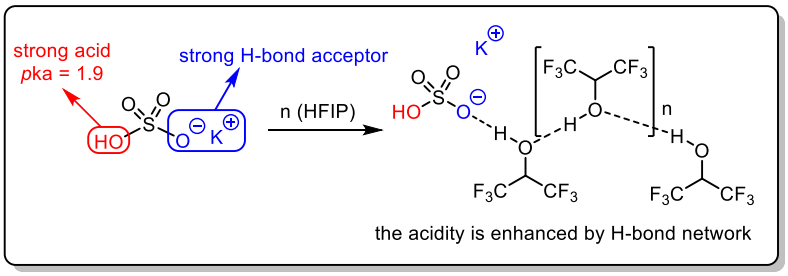
Scheme 3. C-H Halogenation of Arenes and Heterocycles with NXS

All these reactions could be easily scaled up and the solvent could be recycled due to its low boiling point (bp = 59 °C) and low viscosity.

Those works have led to three publications:

1. **Ren-Jin Tang**, Thierry Milcent, Benoit Crousse*, *Eur. J. Org. Chem.* **2017**, *32*, 4753-4757.
2. **Ren-Jin Tang**, Thierry Milcent, Benoit Crousse*. *RSC Adv.* **2018**, *8*, 10314-10317.
3. **Ren-Jin Tang**, Thierry Milcent, Benoit Crousse*, *J. Org. Chem.* **2018**, *83*, 930-938.

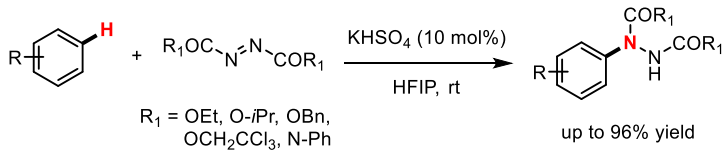
Later in my work, we have disclosed a mild and efficient system using catalytic amount of green, inexpensive and readily available inorganic salt potassium bisulfate ($KHSO_4$) in HFIP. The hydrogen-bonding cluster generated from HFIP formed a hydrogen-bonding complex with $KHSO_4$ and granted the $KHSO_4$ enhanced acidity. An additional advantage of $KHSO_4$ is can be easily removed in just an aqueous workup. This system has been applied to different reactions.



1. Bisulfate Salt-Catalyzed Direct Amination of Arenes with Azodicarboxylates

We reported a mild and efficient amination of simple arenes with azodicarboxylates using

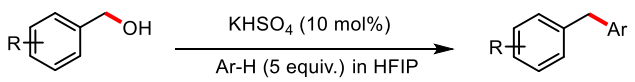
$KHSO_4$ as catalyst in HFIP. This protocol is shown to efficiently aminate a broad range of arenes, including arenes with certain electron-withdrawing groups, generating the corresponding hydrazides in good to excellent yields. In addition, this approach has been carried out effectively on a large scale.



Scheme 4. Bisulfate Salt-Catalyzed Direct Amination of Simple Arenes with Azodicarboxylates

2. Bisulfate Salt-Catalyzed FC Benzylation of Arenes with Benzylic Alcohols

The system of $KHSO_4$/HFIP has also been used for the FC benzylation of a variety of slightly activated and neutral arenes with stable and readily available primary and secondary benzylic alcohols. This methodology employs exceptionally mild conditions to provide a wide variety of unsymmetrical diarylmethanes and other 1,1-diarylalkane products in high yield with good to high regioselectivity. A S_N1 mechanism involving activation of the hydroxy group through hydrogen-bond-network system was proposed.



Scheme 5. Bisulfate Salt-Catalyzed FC Benzylation of Arenes with Benzylic Alcohols

Those works have led to two publications submitted.

université PARIS-SACLAY
ÉCOLE DOCTORALE
Innovation thérapeutique : du fondamental à l'appliqué

Titre : Alcools fluorés: un milieu parfait pour la fonctionnalisation directe d'aromatiques..... ....

Mots clés : Alcools fluorés; Liaison hydrogène; Amination; Alkylation; Halogénation

Résumé : Le trifluoroéthanol (TFE) et l'hexafluoroisopropanol (HFIP) présentent des propriétés physicochimiques particulières comme un fort pouvoir ionisant élevé, une forte capacité à donner des liaisons hydrogène, et une faible nucléophilie. Ces différentes propriétés ont été avantageusement exploitées dans plusieurs réactions sans la présence de catalyseur. Dans un premier temps, l'étude de l'amination électrophile sélective d'aromatiques avec les azodicarboxylates a été réalisée dans l'HFIP pour conduire à une famille d'hydrazines aromatiques. Ensuite l'alkylation de Friedel-Crafts avec des hétéroaromatiques et des β-nitroalcènes a conduit à des dérivées de tryptamines. Ensuite, l'halogénation sélective d'aromatiques et d'hétérocycles en présence de *N*-halosuccinimides (NIS, NBS et NCS) a été développée.

Egalement, nous avons étudié un nouveau système combinant l'HFIP et le $KHSO_4$ qui est un sel inorganique peu coûteux. L'association de l'HFIP et de $KHSO_4$ (10 mol%) est un système catalytique doux et efficace pour promouvoir certaines réactions. En particulier nous avons montré que ce système catalytique a été appliqué avec succès pour l'amination directe d'aromatiques peu activés avec des azodicarboxylates pour conduire à d'autres dérivés hydrazines. Ce système a aussi montré son efficacité dans la réaction directe de benzylation de Friedel-Crafts avec des alcools benzyliques. Ainsi une grande variétés de composés diarylméthanes dissymétriques a pu être obtenue avec une excellente régiosélectivité.

Title: Fluorinated Alcohols: A Perfect Medium for the Direct Functionalization of Aromatics..... ....

Keywords: Fluorinated Alcohols; Hydrogen-bond; Amination; Alkylation; Halogenation

Abstract: Due to the electron-withdrawing character of fluoroalkyl groups, fluorinated alcohols such as trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP) exhibit a nearly unique set of properties that include high ionizing power, strong hydrogen bond donating ability, mild acidity, and low nucleophilicity. All of these properties have been exploited without the need of an external catalyst. At first, the *para*-selective amination of free anilines with azodicarboxylates in HFIP led to hydrazine derivatives. The Friedel-Crafts alkylation of indoles and electron-rich arenes with β-nitroalkenes succeeded to afford tryptamines derivatives. Then the regioselective halogenation of arenes and heterocycles with N-halosuccinimides (NIS, NBS, NCS) have been developed.

Meanwhile, we have disclosed a new mild system between HFIP and KHSO4 which is a green, inexpensive and readily available inorganic salt. The association of HFIP/KHSO4 (10 mol%) is an efficient and mild catalytic system in order to promote some reactions. In particular, we showed that this system allowed the direct amination of slightly activated and neutral arenes with azodicarboxylates in order to give other families of hydrazines. This mild system has been applied successfully for the Friedel-Crafts benzylation with benzylic alcohols. These mild conditions provided a straightforward synthesis of a variety of unsymmetrical diarylmethanes in high yield with good to high regioselectivity.

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