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Exploration of New Reaction Tools for Late-Stage Functionalization of Complex Chemicals

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Abstract

Chemistry has always had as a target the conversion of molecules into valuable materials. Nevertheless, the aim of past synthesis has primarily focused on achieving a given transformation, regardless of the environmental impact of the synthetic route. Given the current global situation, the demand for sustainable alternatives has substantially increased. Our group focuses on developing selective chemical transformations which benefit from mild conditions, improved atom economy, and that can make use of renewable feedstocks as starting materials. This account summarizes our work over the past two decades specifically regarding the selective removal, conversion, and addition of functional groups which can, later on, be applied at a late stage for the modification of complex molecules.

Keywords:

Late-stage modification, selective conversion, functional group removal, A^3-coupling, phenol coupling, hydrogen borrowing, amino acid modification, CDC reaction, trifluoromethylation, difluoromethylthiolation, photochemistry, catalysis

Introduction

The ability to synthesize complex molecules from simple building blocks is an important manifestation of modern chemistry, representing power and skills of organic synthesis.[1] As most modern organic chemicals are based on petroleum as the ultimate feedstock, bearing no or little functional groups, most classical reactions developed were focused on reactivity/conversion rather than functional group selectivity.[2] Thus, generally highly reactive reagents, such as the Grignard reagents,[3] and forcing conditions, such as refluxing, were often employed to ensure the completion of the specific reaction. Considering the recent emphasis on synthetic efficiency and increased interest on sustainability and green

chemistry,[4-5] the use of renewable biomass as a potential future chemical feedstocks, the selective direct transformation of complex molecules becomes highly essential. Thus, mild and selective modifications of biomolecules such as nucleotides, peptides, carbohydrates, and various natural products play an essential role for chemical biology and synthetic biology, and can drastically speed up the drug discovery process.

However, unlike petroleum-based feedstock, biomass-based materials (carbohydrates, lignins, amino acids, fatty acids) and natural products are generally over-functionalized. Unfortunately, these functional groups are not compatible with the standard classical reactions.[6-7] Consequently, in order to utilize these renewable feedstocks or to make selective changes on such molecules, extensive functional group protections and maskings are required to make these highly functionalized molecules petroleum-like, in order to apply the classical reactions developed.[8] As a result, most total syntheses of biological compounds and modification of bio-based molecules are very lengthy, which are not only man-power intensive but also slow down the availability and increase the cost of target structures in drug discovery and other applications.[9]

An alternative strategy to overcome such a fundamental scientific challenge is to develop new reaction tools that can selectively and directly change a specific site in these complex structures, tolerating existing functional groups with no need for protection, under mild conditions. Such kind of transformations include three major types: a) selective removal of functional groups, b) selective conversion of functional groups, and c) selective addition of functional groups. In this account, we will describe selected examples exploring new reaction tools towards these three types of transformations which have been developed in our laboratory over the past two decades.

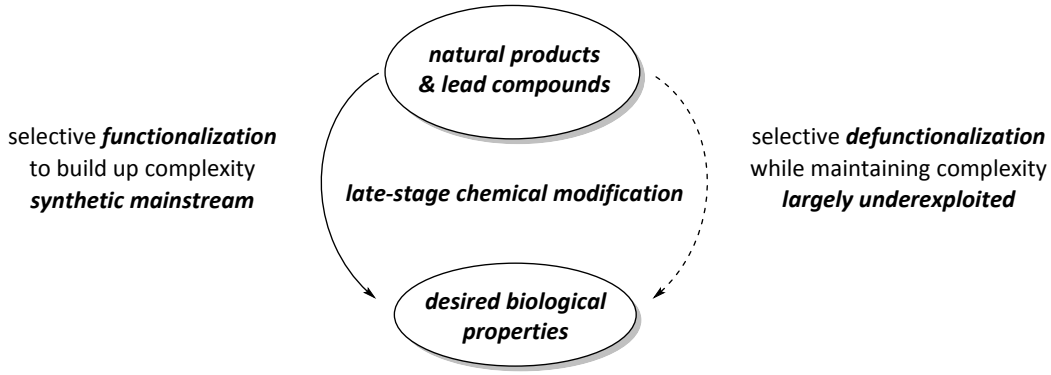
Selective removal of functional groups

Throughout the history of contemporary synthetic chemistry, the focus has been on how to functionalize organic compounds.[10-11] Very little attention has been given to the opposite direction: how to selectively defunctionalize a specific functional group without affecting others. The availability of such methods would provide unprecedented tools for chemists to convert natural products readily into analogs and to diversify lead compounds rapidly for various applications. In this respect, it is a great challenge to selectively and efficiently remove a primary hydroxyl group in the presence of other hydroxyl groups and amines widely present in complex natural products and lead compounds (i.e., steroids and alkaloids). All previous methods require extensive functional group transformations, with the most well-known one being the Barton-McCombie deoxygenation, due to its widespread synthetic applications (Scheme 1).[12-14] Thus, the direct catalytic deoxygenation of alcohols that are highly selective and efficient, especially in the presence of other functionalities, has been a long-standing scientific challenge.[15]

To pursue such a direct alcohol deoxygenation protocol, we conceived a catalytic late-transition-metal-catalyzed redox design, combining dehydrogenative oxidation[16-19] with Wolff-Kishner (WK) reduction, to simultaneously tackle the challenges regarding step economy and selectivity. The early development of our hypothesis focuses on an iridium-catalyzed process efficient mainly with activated alcohols, which dictates harsh reaction conditions and thus limits its synthetic utility.[20] Later, a significant advancement was made on aliphatic primary alcohol deoxygenation by employing a ruthenium complex, with good functional group tolerance and exclusive selectivity under practical reaction conditions.[21] Synthetic utility using molecules with varying degrees of complexity and with a number of different functional groups has been illustrated. Unprecedented highly chemoselective deoxygenation of aminoalcohols and alkaloids, as well as regioselective monodeoxygenation of steroids with multiple hydroxyl groups, has been achieved. Mechanistic insight of the reaction was also investigated. Overall, our current method provides a practical redox-based approach to the direct sp^3 C-O defunctionalization of aliphatic primary alcohols.

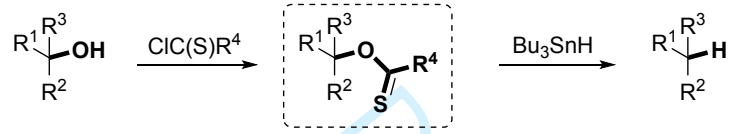
Scheme 1. Overview of the late-stage chemical modification of alcohols

A. Synthetic Toolbox for Late-Stage Chemical Modification



B. Classical Alcohol Deoxygenation

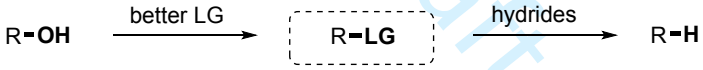
a) Barton-McCombie Radical Pathway



1975, ***multi-step*** *aliphatic 2° & 3°* alcohols

R^1, R^2 = alkyl; R^3 = H or alkyl; R^4 = H, SCH_3, OPh, etc.

b) Ionic S_N2-Based Pathway



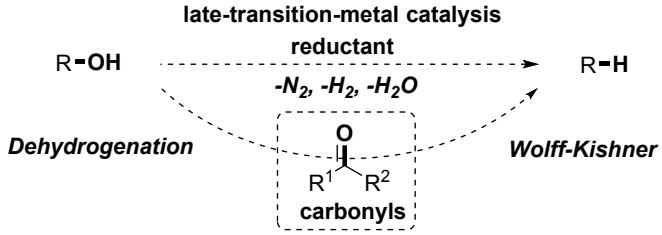
1970s, ***multi/single-step*** *aliphatic 1°* alcohols

LG = OTs, OMs, X, etc.

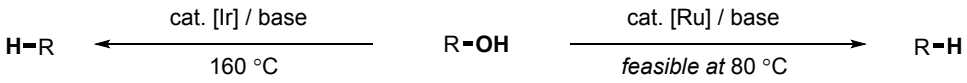
Unsolved Challenge: direct *deoxygenation with* ***high selectivity and efficiency****?*

C. This Work: Redox-Based, Catalytic, Direct Alcohol Deoxygenation

a) Design Principle



b) Key Features



Part I. Early Development

- ***Proof-of-concept*** discovery
- efficient mainly with ***benzylic*** & ***allylic*** alcohols
- ***harsh*** conditions, less synthetically applicable
- ***stoichiometric innocuous*** byproducts

Part II. Practical Advancement

- ***practical*** reaction conditions
- free ***hydroxyl*** groups & ***amines*** compatibility
- complete ***chemo-*** & ***regio-selectivity***
- ***single-step*** with ***high selectivity*** on aliphatic 1° alcohols

Selective Conversion of Functional Groups

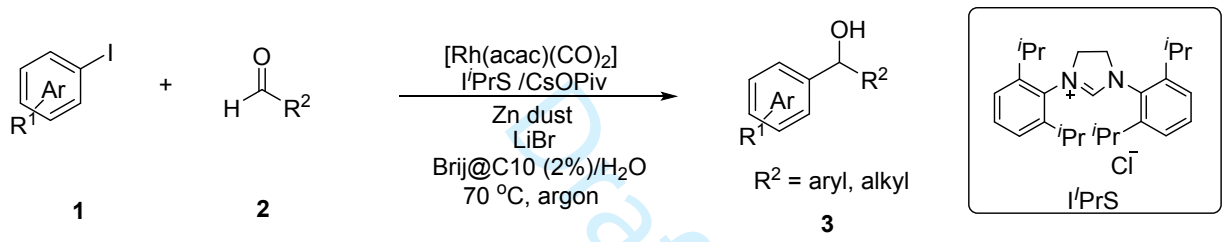
Grignard-type reactions in water

The Grignard reaction has been undoubtedly one of the most powerful and useful reactions for the formation of C-C bonds since its discovery over 100 years ago.[22-24] The intrinsically highly polarized C-Mg bond present in the Grignard reagent is endowed with strong nucleophilicity towards nucleophilic addition. However, this inherent attribute also limits its practical applications owing to the issues associated with the stringent anhydrous conditions as well as functional group compatibility.[25] To overcome these limitations and improve synthetic efficiency, many Grignard-type reactions have been successfully developed by using softer nucleophiles, which either directly utilize pre-formed organometallic reagents such as organotin reagents or generated *in situ* with metals such as Zn and In.[26-32]

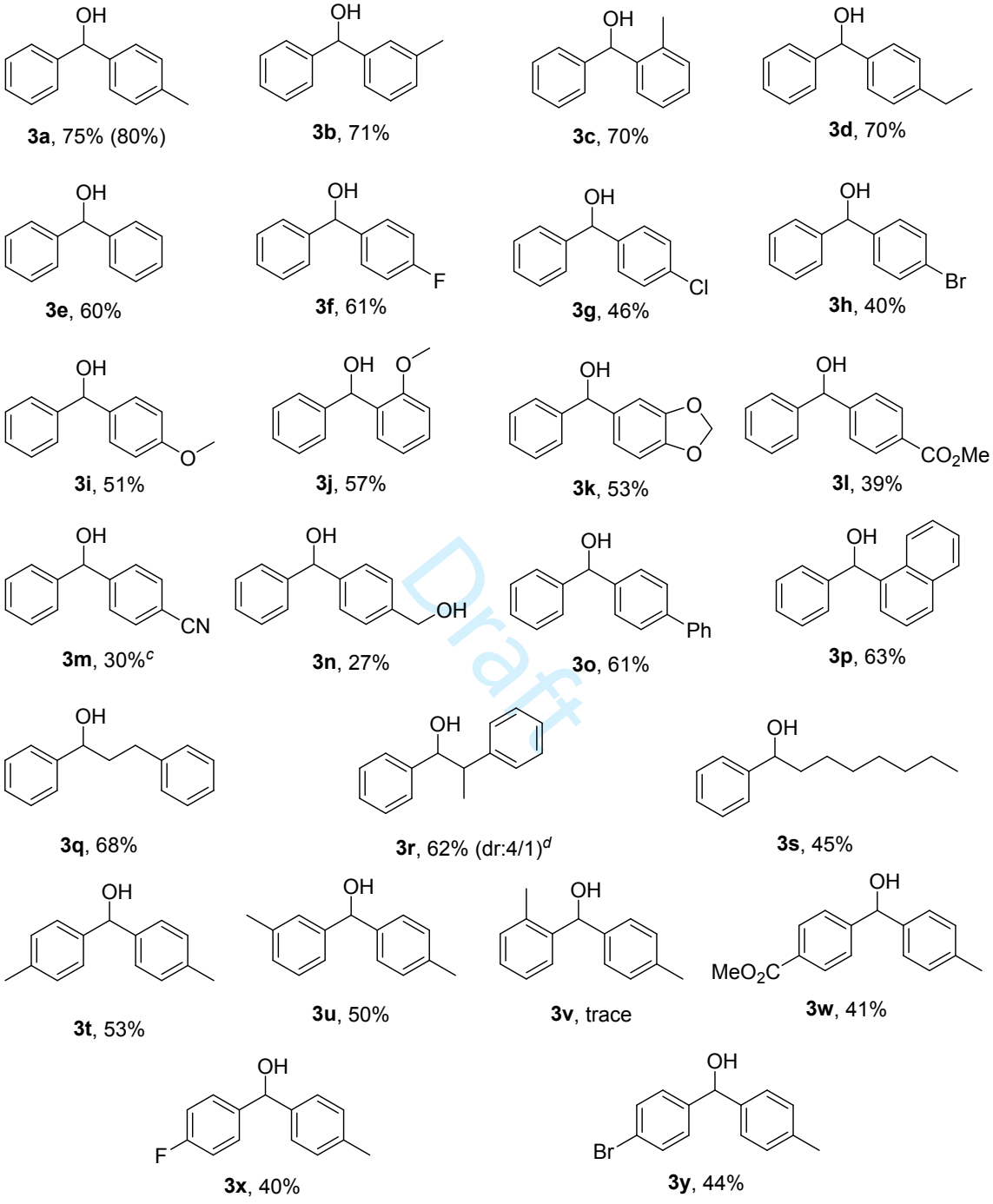
Environmental concerns and resource depletion have raised full attention in developing more sustainable chemical syntheses,[33] among which, the development of organic reactions using water as a solvent has gained increased attention. There have been significant advances in the catalysis of organometallic reactions in aqueous media, one of which has been the Grignard-type reaction.[26-32] Previously, our group reported the successful allylation,[34-35] allenylation,[36] propargylation,[36] alkynylation,[37, 38] phenylation[39] and alkylation[40] of carbonyl or imine compounds mediated by various metals in water. Recently, as the last and most difficult challenge towards Grignard-type reactions in aqueous media, we developed a direct arylation of aldehydes using unactivated aryl iodides in water[41] (Scheme 2). This breakthrough has successfully achieved the transition from the conventional two-step anhydrous conditions to a one-pot Rh-catalyzed reaction in water. The appropriate combination of a Rh catalyst and an NHC ligand along with the fine-tuning of the electronic properties of the catalyst, are key for this transformation. The reaction tolerates various functional groups, such as halogens, alkoxyl, ester,

cyano and free alcohols (Scheme 3). Notably, the optimal conditions can be applied to both aromatic and aliphatic aldehydes. Preliminary mechanistic analysis of this transformation was performed by conducting several control experiments. The reaction could not proceed in the absence of either the rhodium complex or metal zinc, demonstrating that each plays a crucial role in the catalytic cycle. Upon understanding the synergy between the rhodium catalyst and the zinc, the reaction was able to proceed smoothly without the need of a surfactant (Scheme 4).

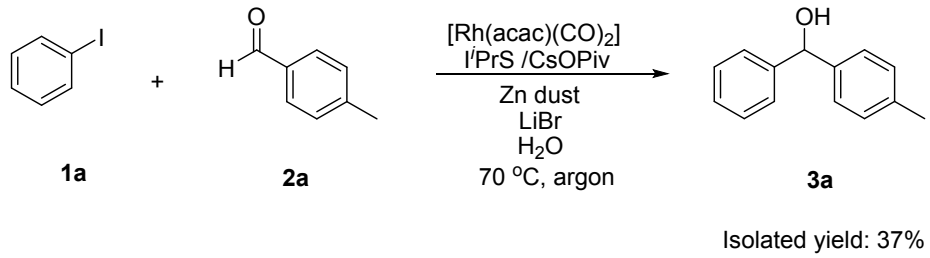
Scheme 2. Reaction conditions for the arylation of aldehydes using unactivated aryl iodides in water



Scheme 3. Scope for the arylation of aldehydes with unactivated aryl iodides in water



Scheme 4. Reaction conditions for the arylation of aldehydes without surfactant



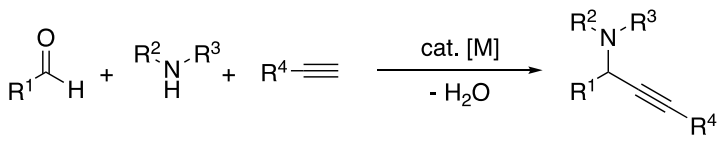
1a **2a** **3a**

Isolated yield: 37%

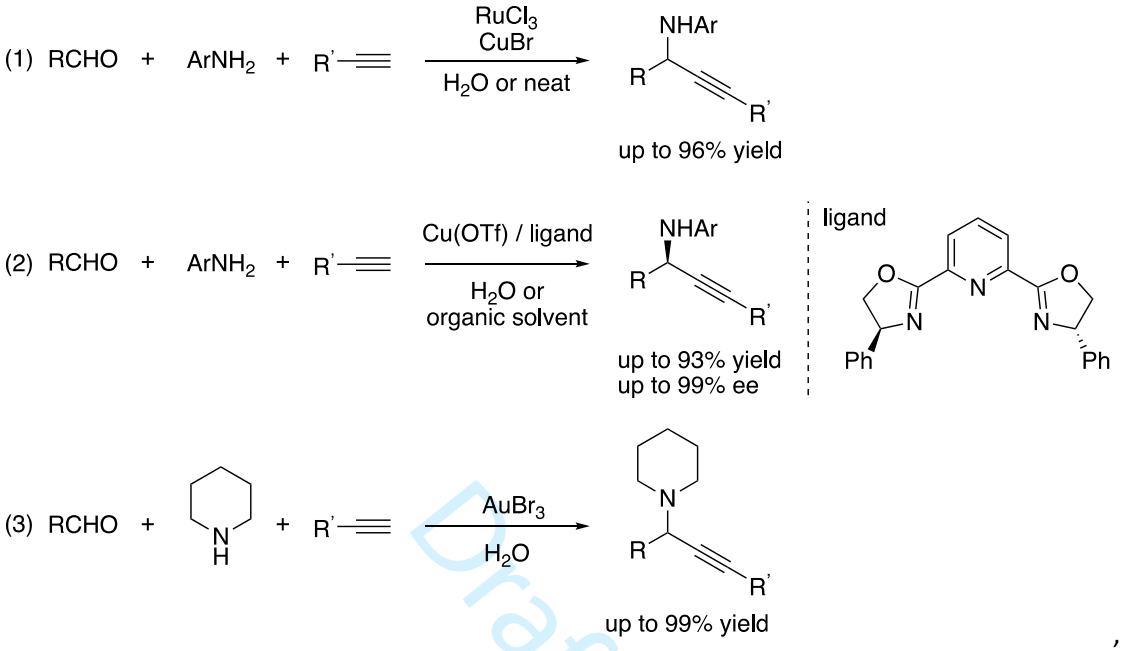
A^3-coupling and amino acid modification

The catalytic conversion of classical functional groups, such as aldehydes, amines, and terminal alkynes into valuable compounds is a relatively modern development in organic chemistry. From our interest in maximizing atom economy, working under ambient atmosphere, using benign solvents, and adhering to the principles of green chemistry, our group has discovered and developed the aldehyde-amine-alkyne coupling (A^3 coupling) (Scheme 5).[42] Over the years, this methodology has been used to prepare propargylamines with an extremely high tolerance to functional groups and reaction conditions. This reaction proceeds through a Mannich-type condensation to form an electrophilic imine or iminium species, extruding water as the sole by-product of the reaction. Subsequently, a nucleophilic metal acetylide intermediate is generated and adds to the C=N electrophilic partner, producing the corresponding propargylamine.

Scheme 5. General equation for the synthesis of propargylamines through A^3 coupling

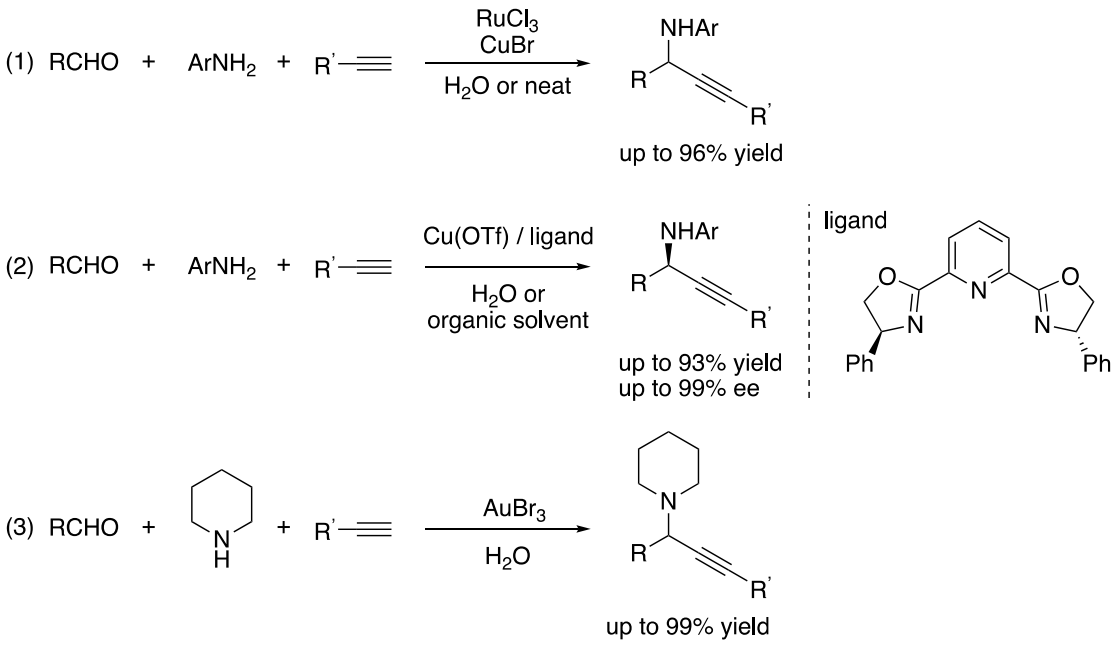


Initially, our first discovery was made in early 2001 when the A^3-coupling was performed in the presence of a two-metal Ru/Cu catalyst system under aqueous or neat conditions (Scheme 6. Early development of A^3 coupling using (1) ruthenium/copper, (2) copper, and (3) gold catalysts

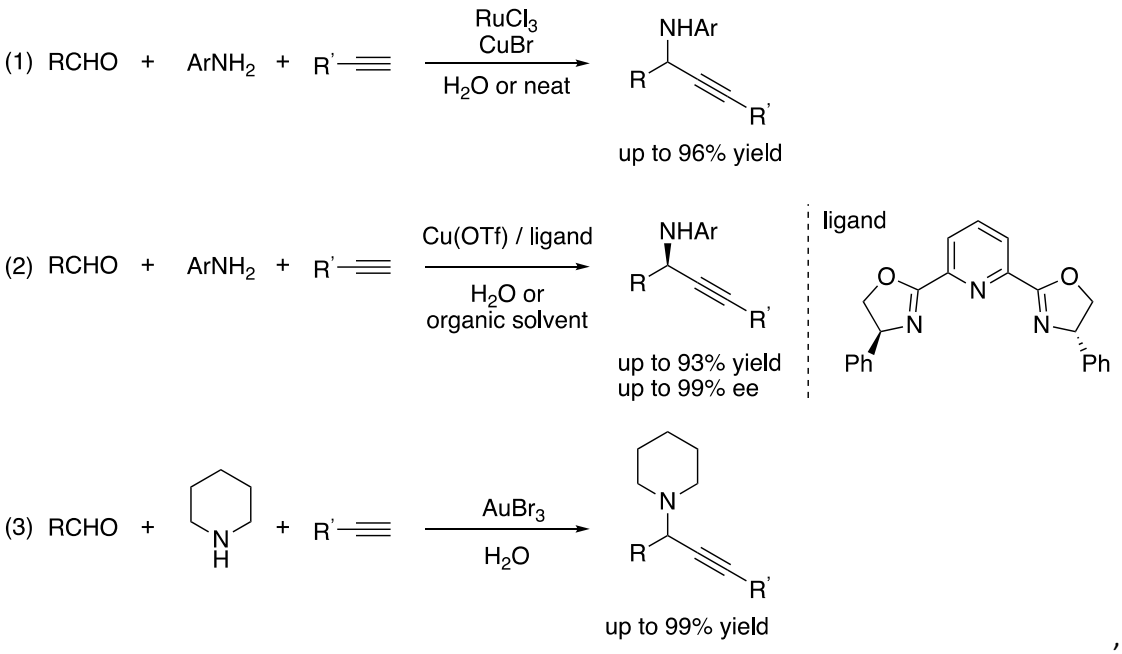


Eq.1).[37] Investigating this reaction, we observed that copper could solely catalyze the reaction towards the formation of the propargylamine in low yields. This observation oriented our interest to develop a copper-catalyzed asymmetric A^3-coupling.

Scheme 6. Early development of A^3 coupling using (1) ruthenium/copper, (2) copper, and (3) gold catalysts



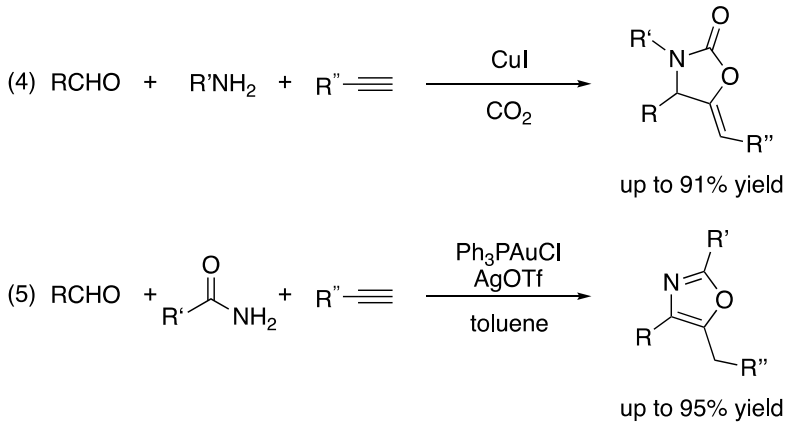
We found that when using Cu(OTf) and a chiral pyridine bis-oxazoline (pybox) ligand, alkynes could be enantioselectively added to imines pre-generated or via three-component (Scheme 6, Eq.2).[43, 44] The reaction was shown to give the best enantiomeric excess in chloroform (99.6% *ee*). Shortly after our original discovery, we found that a gold(III) catalyst was efficient for this transformation in the presence of secondary amines. Under organic or aqueous conditions, the alkyl-iminium addition could be performed by $AuBr_3$ achieving the desired transformation in quantitative yields (Scheme 6. Early development of A^3 coupling using (1) ruthenium/copper, (2) copper, and (3) gold catalysts



,

Eq.3).[45] Similarly, we evaluated the efficiency of other catalysts and found that silver,[46-49] iron,[50] copper,[51, 52] gold,[51, 53] and ruthenium[54] transition metal catalysts show significant activities. Subsequently, various modifications to the original A^3-coupling were reported by our group.[55, 56] We developed magnetic iron-nanoparticles, a robust and magnetically recoverable catalyst as well as a chiral copper catalyst supported on magnetic iron nanoparticles for the synthesis of enantioenriched propargylamines.[57, 58] Moreover, we benefited from the propargylamine structure to explore novel cyclization reactions. Catalyzed by copper, the tandem A^3-coupling/carboxylative cyclization reaction with CO_2 occurs to generate the corresponding oxazolidinones (Scheme 7, Eq.4).[59]

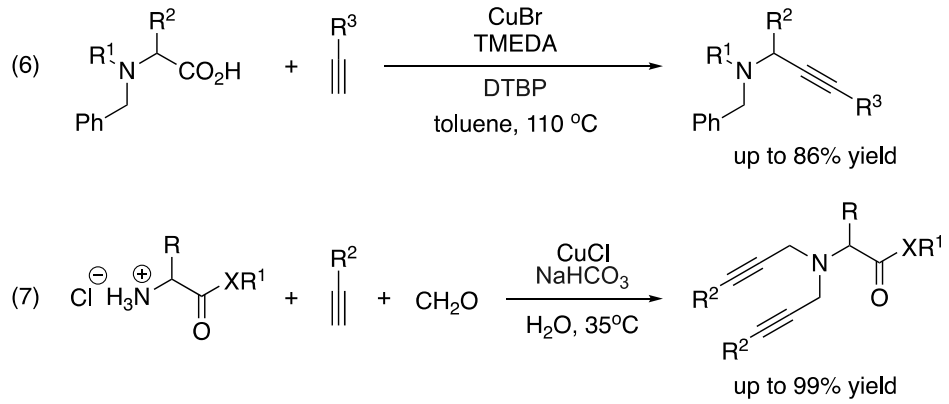
Scheme 7. Modified A^3-coupling with (4) copper and (5) gold



More recently, our group has investigated the reaction with amides (Scheme 7, Eq. 5).[60] We found that cationic gold was the most efficient catalyst to perform both the A^3-coupling and the cyclization reaction simultaneously, leading to the formation of highly substituted oxazole compounds. We also evaluated other deactivated amines, such as the reaction of *t*-butyl carbamates with aldehydes and alkynes.[61]

Methods for the selective modification of amino acids and peptidic structures are highly useful in chemical biology and biochemistry. Selective post-synthetic addition of the alkyne functionality to peptide derivatives represents an exciting route to these compounds. During our initial investigation, the reactivity of primary amines was poor due to the low stability and reactivity towards water and carbon nucleophiles. By using *N*-acyliminium ions, the reactivity of the C=N bond is radically increased. Indeed, we discovered that copper bromide can catalyze the decarboxylative coupling of an alkyne with different amino acids (Scheme 8, Eq.6).[62]

Scheme 8. Amino acid modification employing A^3-coupling



Using highly reactive imines, formed from formaldehyde and amines, amino acids and dipeptides can be functionalized. Thus, copper(I) could catalyze the alkynylation of amino acid derivatives at their *N*-terminus or at the lysine ξ-amino functionality under concentrated conditions (

Scheme 8, Eq.7).[63] Our reaction system serves as a proof of concept for the use of the A^3-coupling as an orthogonal tool for rapid modification of amino acids and biomolecules.[64-66] Indeed, the A^3-coupling in water allows the selective modification of glyderaldehydes,[49] sugars,[66] and oligosaccharides.[67]

Considered as a powerful chemical tool, the A^3-coupling features a great tolerance to aqueous media and air, possesses a high efficiency with excellent applicability towards enantioselective or tandem reactions and has a broad and tunable substrate scope.

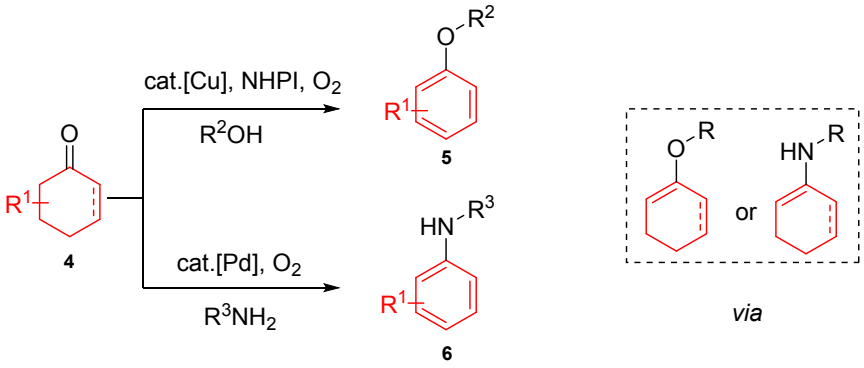
Phenol Coupling

Phenols comprise lignocellulosic biomass as one of the basic units and can be easily obtained from the coal, as well as the pulp and paper industries. Therefore, phenols are considered as widely available, economical, sustainable aromatic feedstocks. Based on this, phenols are ideal aromatic coupling partners compared to the well-known aromatic halides.[68-70] In the past decades, the research on the cross-coupling

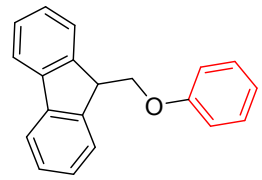
of phenols (C-O bond cleavage) has mainly focused on phenol derivatives, such as the corresponding triflates, tosylates, mesylates, esters, ethers, etc., led by Shi,[71-72] Chatani,[73] Martin[74] and others.[75]

However, utilizing the unprotected phenols for cross-coupling reactions had remained extremely challenging, due to the highly reactive acidic hydroxyl group and the strong C–O bond with a high-dissociation-energy due to p-π conjugation. To explore the cross-coupling of unprotected phenols, our group initially developed a catalytic oxidative-dehydrogenative aromatization process in 2012, to synthesize aromatic ethers and amines from the cyclohexanones or cyclohexenones (the reduced form of phenols) with alcohols or amines as nucleophiles, using copper or palladium as the catalyst (Scheme 9).[76-77] Other notable studies have also been reported by Lemaire, Deng, Yoshikai, and Stahl.[78-82]

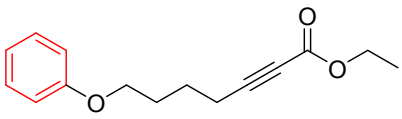
Scheme 9. Oxidative catalytic dehydrogenative aromatization



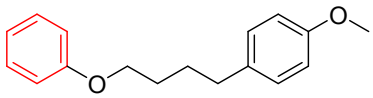
Representative examples:
Aromatic ethers:
cat. [Cu]



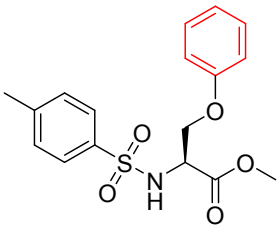
5a, 64%



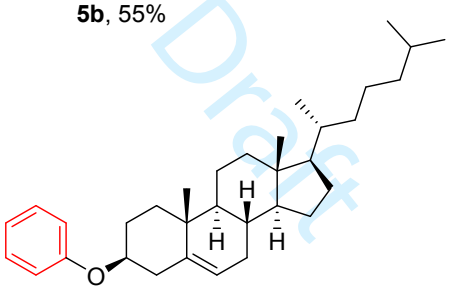
5b, 55%



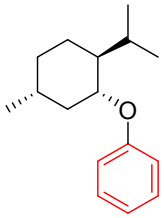
5c, 100%



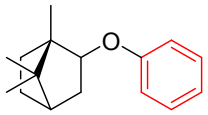
5d, 33%



5e, 58%

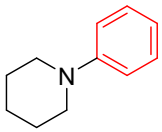


5f, 61%

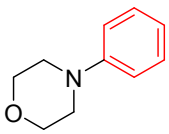


5g, 67%

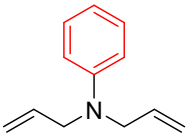
Representive examples:
Aromatic amines:
cat. [Pd]



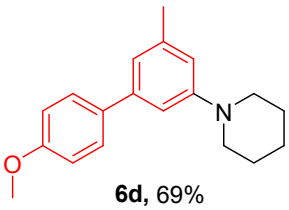
6a, 82%



6b, 66%



6c, 82%



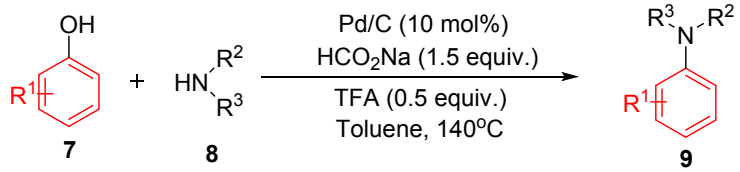
6d, 69%

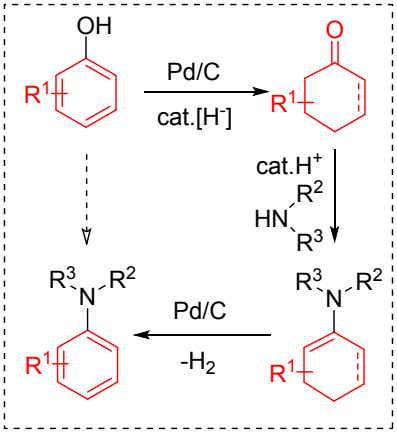
In 2015, with the successful coupling results of the cyclohexanones and cyclohexenones with amines under oxidative conditions, we proceeded to make use of the unique redox properties of phenols. That is, through the redox-couple of phenol and cyclohexanones or cyclohexenones, using a 'hydrogen-

borrowing' strategy via a catalytic reductive dearomatization-condensation-rearomatization sequence to achieve the direct cross-coupling of phenol with amines (Scheme 10, A).[83] This transformation proceeded efficiently and tolerated a broad scope of phenols, catechols and naphthols with primary, secondary, aliphatic and aromatic amines as nucleophiles. It is important to mention that by increasing the sodium formate amount to 6 equivalents, phenols could be used as cyclohexyl synthons to couple with amines and to generate cyclohexylamines in high yields (Scheme 10, B).[84] In addition, this transformation can be successfully performed in a flow reactor.

Scheme 10. Direct cross-coupling of phenols with amines

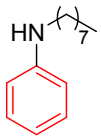
A. Formally direct coupling of phenol with amines



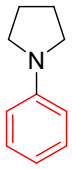


via
dearomatization-condensation-rearomatization strategy

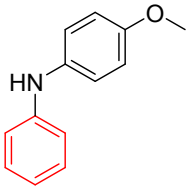
Representative examples:



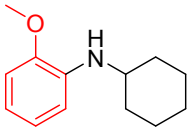
9a, 81%



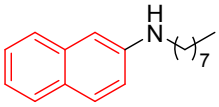
9b, 63%



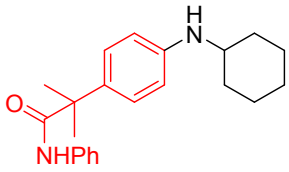
9c, 74%



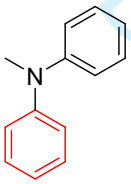
9d, 68%



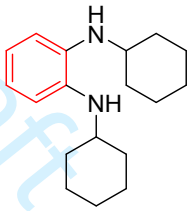
9e, 90%



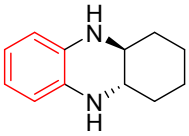
9f, 84%



9g, 40%

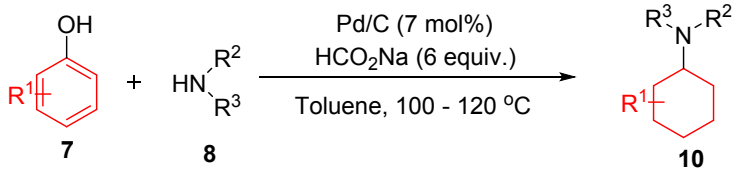


9h, 83%

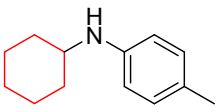


9i, 75%

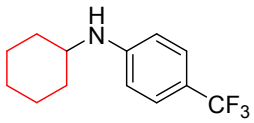
B. Phenols as cyclohexyl synthons to couple with amines



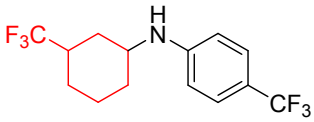
Representative examples:



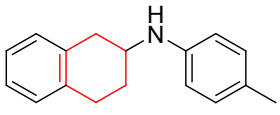
10a, 92%



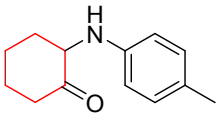
10b, 67%



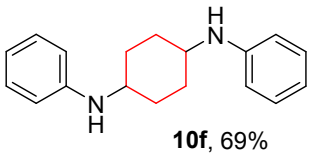
10c, 57%



10d, 73%



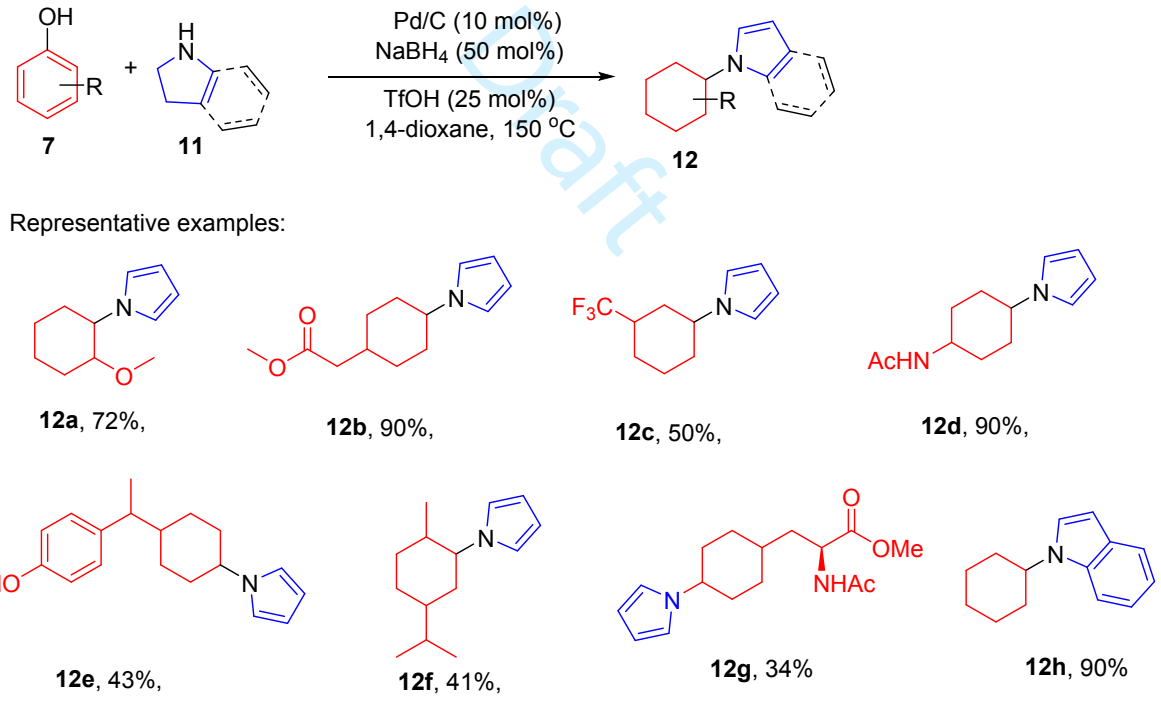
10e, 77%



10f, 69%

Inspired by the success of the direct coupling of phenols with amines, we developed in 2017 a formal aromaticity-transfer reaction between phenols and pyrrolidines or indolines to afford the corresponding *N*-cyclohexyl pyrrole/indole. In this case, the amine moiety (pyrrolidine or indoline) rearomatized, as opposed to the phenol moiety (Scheme 11).[85] To improve the yield, a potent reducing agent, in this case sodium borohydride, and TfOH were required. This transformation worked well with various substituents, phenols and some protected bio-active phenols such as tyramine, tyrosine and carvacrol.

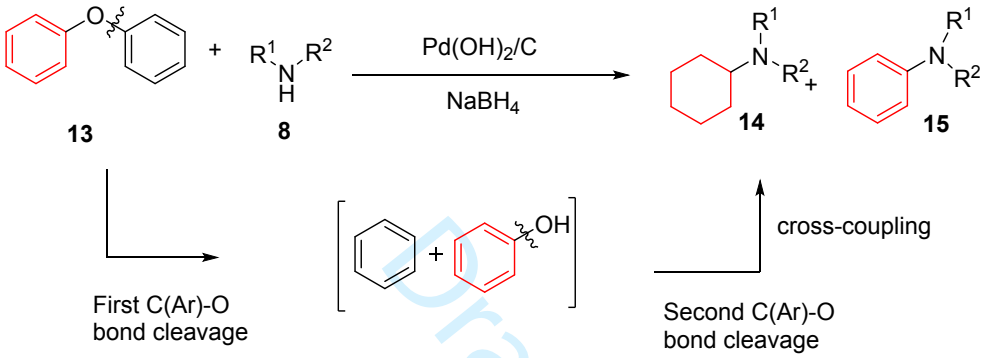
Scheme 11. Formal aromaticity-transfer coupling of phenols with pyrrolidines/indolines



Following this work, we developed in 2018 a novel method to cross-coupling diary ethers, which is a key type of linkage found in lignin, with amines. This transformation involved two C-O bond cleavage

processes and worked well with various diary ethers, generating the corresponding aromatic amines, cyclohexylamines and aromatic transfer *N*-cyclohexylpyrrole products. Interestingly, to obtain high conversions and yields, $Pd(OH)_2/C$, $NaBH_4$, and a trace amount of water were necessary to effectively promote this transformation (Scheme 12).[86]

Scheme 12. Cross-coupling of diaryl ethers with amines



Amino Acid Modification with Phenol

Amino acids are bio-renewable, C-chiral nitrogen sources with important applications in chemistry[87-90] and biology.[91-93] Our laboratory has developed novel methodologies through which these building blocks can be arylated or cylohexylated by using 2-cyclohexen-1-one or phenol, respectively.[94] By using a phenolic compound as the *N*-alkylating reagent, we can circumvent the need of halogen derivatives and protecting groups, while generating water as the sole by-product. In addition, phenol represents a sustainable alternative to current alkylating reagents due to its wide availability as the main constituent of lignin.[94]

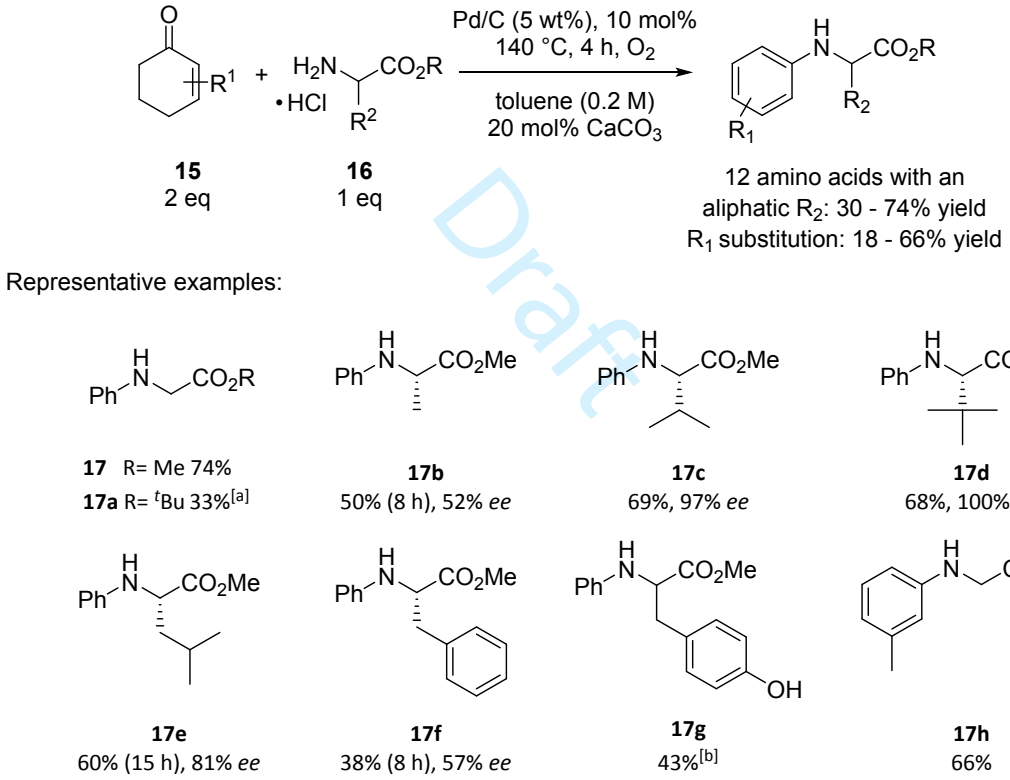
As previously discussed, our laboratory had already achieved the amine coupling and re-aromatization of cyclohexanone and 2-cyclohexen-1-one,[95] as well as in the activation of phenol through hydrogen borrowing strategies.[95] While these procedures proved successful for anilines,[75, 84] secondary amines,[77, 85] primary alkyl amines,[83] and hydrazine;[96] it was not possible to perform the desired *N*-modification on amino acids under these conditions. We presumed that this was due to the amino acid's inherent low nucleophilicity, pH sensitivity, and diverse functionalization at the α-position. Thus, the primary challenge is to find a widely applicable one-pot method for activating the phenolic compound and the amino acids' *N*-terminal simultaneously.

Previous literature reports for *N*-arylation of α-amino acids describe modified versions of the Ullman[97] or the Buchwald-Hartwig[98] coupling reactions. On the other hand, *N*-mono-alkylation of α-amino acids has been achieved through reductive amination using boron or transition metal catalysts as the reducing reagents.[99,100] Remarkably, some examples of hydrogen borrowing strategies for using aliphatic alcohols as *N*-alkylating reagents have also emerged.[100-102] While these methods provide versatile methodologies for the desired transformations, the use of organic halides, protecting groups, and low selectivity remained to be addressed.

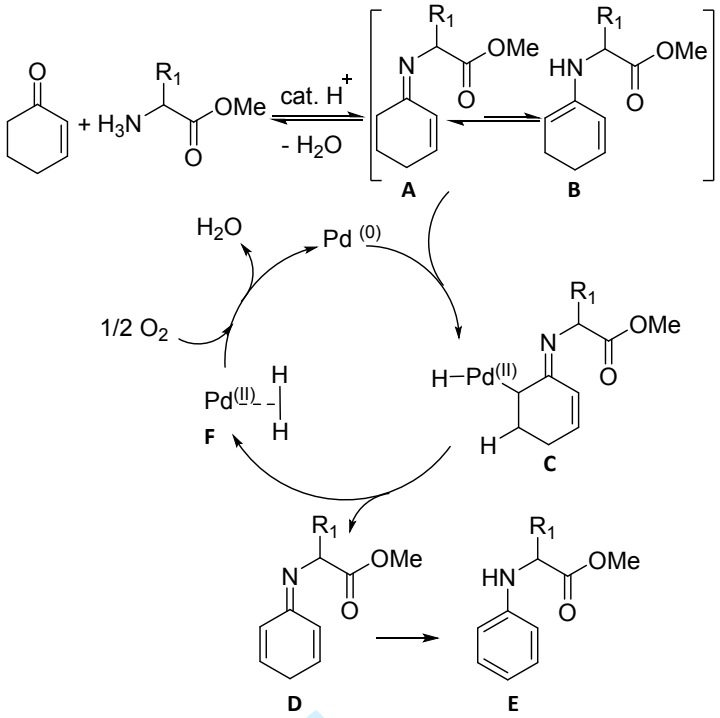
Glycine ethyl ester hydrochloride was employed as the model substrate for the *N*-arylation with 2-cyclohexen-1-one, since using amino acids in their free carboxylic form led to decomposition through decarboxylation.[93] The transformation was found to work best using 10 mol% of palladium on charcoal (5 wt%) and 20 mol% of calcium carbonate in toluene at 140 °C under an oxygen atmosphere (Scheme 13). The catalytic amount of base was necessary to buffer the reaction and promote amine condensation with the ketone. Regarding scope, aliphatic amino acids proved effective under the reaction conditions, with large α-substituents (Scheme 13). On the other hand, the phenolic scope was restricted to aliphatic substituents at the meta-position. Bi-arylation of the amine was also achieved in 55% to 65% yield with each 2-cyclohexen-1-one and cyclohexanone respectively, by modifying the reaction conditions. We

propose that upon imine formation (A), the palladium catalyst inserts to an sp^3 C-H bond of the 2-cyclohexen-1-one (C) which upon β-hydride elimination leads to the desired arylated (E) product and to the formation of a palladium dihydride species (F). However, if the concentration of PdH_2 builds up the ketone is reduced to its alcohol form and is ineffective as an alkylating reagent. We found that employing an oxygen atmosphere, the release of H_2 from the catalyst and prevented reduction (Scheme 14).

Scheme 13. Reaction conditions and scope overview for the *N*-arylation of amino acids using 2-cyclohexen-1-one

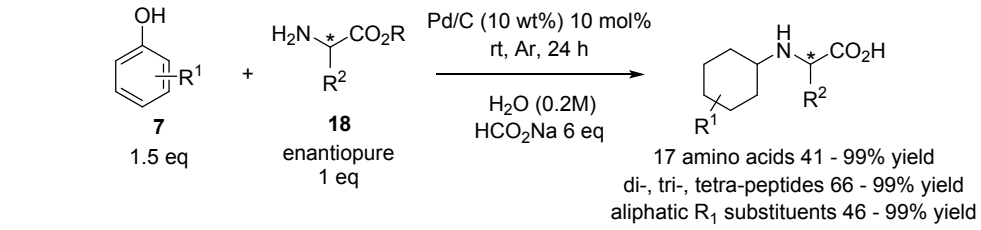


Scheme 14. Proposed mechanism for the *N*-arylation of α-amino acids using cyclohexenone

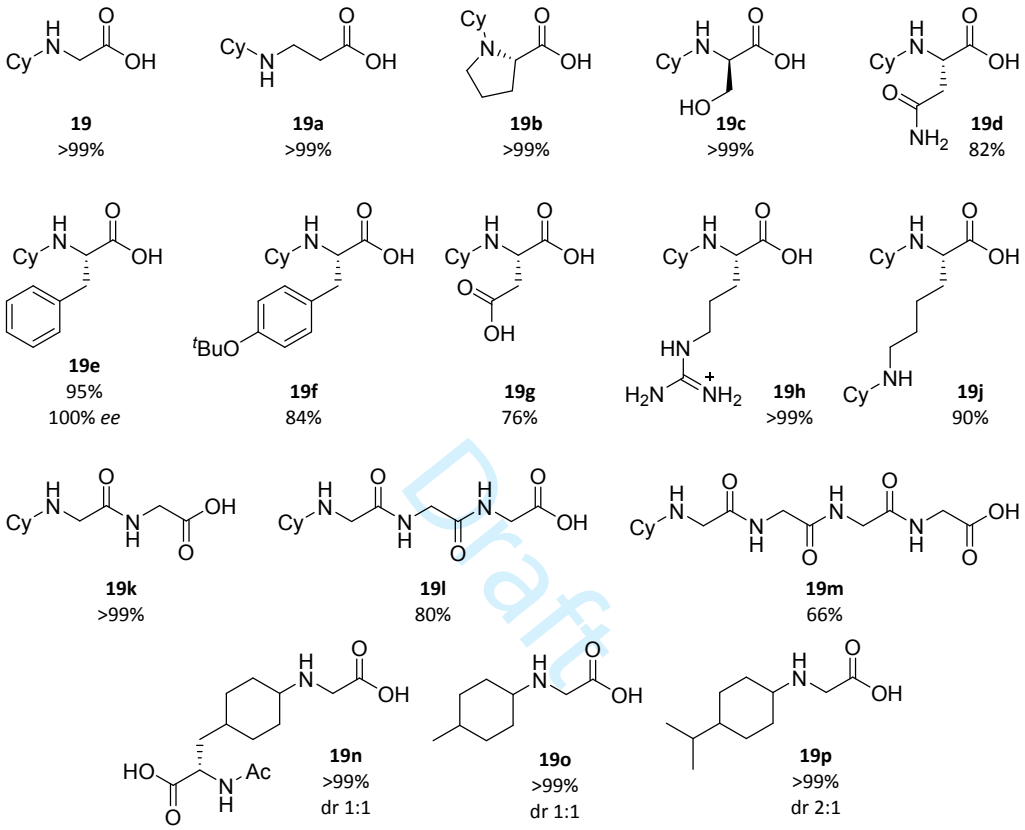


Due to the high energetic cost for re-aromatization, we reckoned that simple cyclohexylation would require milder reaction conditions. Based on previous work from our group[85] and that of Vaccaro,[104] we developed a reaction under bio-compatible conditions with phenol as the coupling partner. Upon a brief screening, it was found that by employing 10 mol% of Pd/C (10 wt%), with HCO_2Na as a hydride source, it was possible to cyclohexylate amino acids at room temperature in water. Furthermore, it was possible to recycle the catalyst up to three times while maintaining quantitative conversion. Except for sulfur-containing amino acids and tryptophan, all natural amino acids were successful substrates, as were di- tri- and tetra-peptides (Scheme 14). Regarding the phenolic scope, alkyl para-substituents were well tolerated and meta-substituents less so. Exceptionally, the enantiomeric purity of the amino acids was completely preserved under the reaction conditions (Scheme 15).

Scheme 15. Reaction conditions and scope overview for the *N*-cyclohexylation of amino acids using phenol



Representative examples:



Cross Dehydrogenative Coupling strategies on amino acid and peptide derivatives

Building molecular complexity through the formation of carbon-carbon bonds always has been a prime concern amongst organic chemists. Classical ways to achieve the construction of new C-C bonds include nucleophilic substitution or additions, as well as Friedel-Crafts type reactions. However, these reactions all require *a priori* functionalizations of the substrates generating an additional series of

protection and deprotection steps to control the regioselectivity. More recently, the development of metal catalyzed cross-coupling reactions and metathesis techniques has proved to be an outstanding solution to address these problems.[105-107] Despite these unprecedented accomplishments, cross-coupling reactions are still highly dependent on pre-functionalized coupling partners, such as halogenated substrates, which increment the total number of steps in the synthesis and lead to the generation of chemical waste. One way to circumvent this would be to construct C-C bonds directly from two C-H bonds in the presence of an oxidant, leading to the formal loss of an H_2 molecule (Scheme 16). Our group has formulated this concept and coined this general strategy as the "Cross-Dehydrogenative Coupling" (CDC) reaction.[108-109]

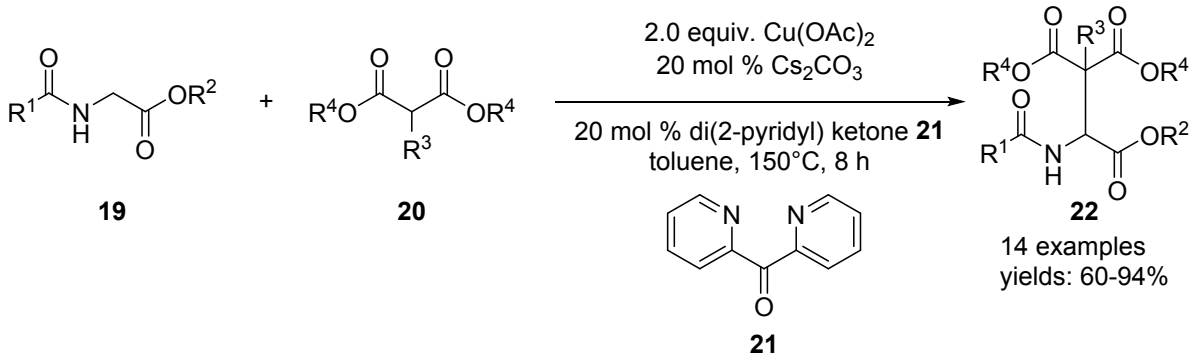
Scheme 16. Overview of the Cross-Dehydrogenative Coupling (CDC) reaction

Most of our work has focused on the cross-coupling between an sp^3 C-H bond situated at the α position to heteroatoms such in N,N-dimethylaniline derivatives,[110] tetrahydroisoquinolines[111-114] and isochromans,[115-116] coupled to an sp, sp^2 or sp^3 hybridized C-H bond from pro-nucleophiles such as terminal alkynes, malonates, nitroalkanes or dialkyl phosphites. In addition, we have also reported the direct cross-coupling of cycloalkanes,[117] as well as asymetric variants of the CDC reaction.[118] Noteworthy is the direct modification of α-amino acids through a CDC type reaction. Currently, there is an increasing demand in proteomics for modified amino acids.[119] The structure and biological activities of peptides can thus be tuned according to the modifications incorporated and the discovery of new peptide-based drugs can be pursued. Aryl glycines, like phenyl glycines and p-hydroxyphenyl glycines, are also common patterns found

amidst popular ß-lactam antibiotics such as in ampicillin or amoxicillin.[120] The traditional routes to access α-modified amino acids include Claisen rearrangements,[121-122] radical-based functionalization (by UV photolysis[123] or by bromination with NBS[124-125]), alkylations of α-carbanions pre-formed by the use of a strong base,[126-129] or palladium catalyzed arylations.[130] However, a direct and selective α-modification of glycine derivatives would be highly desirable.

Our group started investigating the addition of malonates to glycine derivatives through an oxidative C-H/C-H coupling. Malonates have a relatively reactive sp^3 C-H bond that can readily react with electrophiles. By employing diester alkylmalonates (**20**), we were able to modify glycine derivatives (**19**) using $Cu(OAc)_2$, Cs_2CO_3 and di(2-pyridyl) ketone (**21**) as a ligand at 150 °C in toluene[131] (Scheme 17). We suspect that the copper salt acts as a stoichiometric oxidant to yield the imino intermediate, which is subsequently attacked by the malonate in a copper (II) catalyzed Mannich-type reaction.

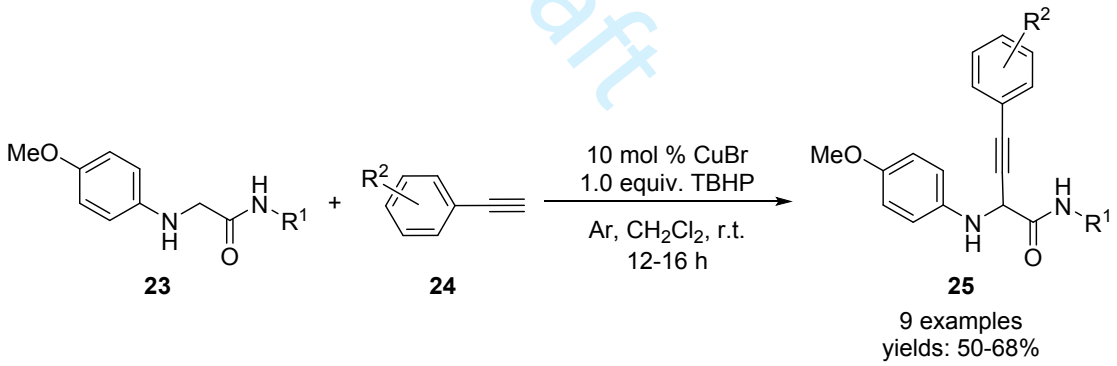
Scheme 17. Reaction of glycine derivatives with dialkyl malonates *via* CDC



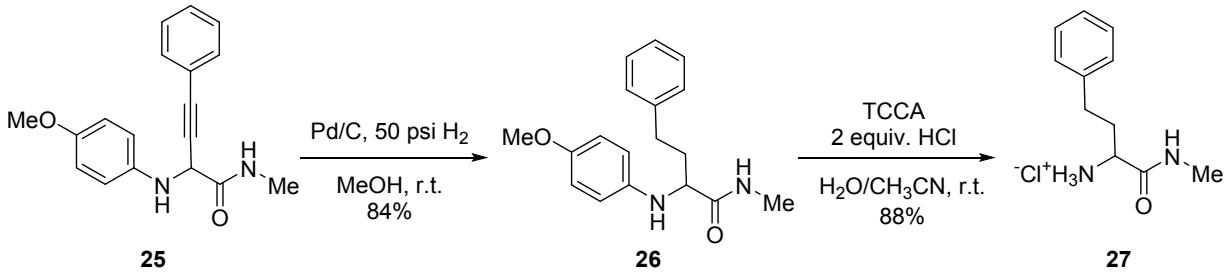
By switching the protecting group at the *N*-terminus from an amide to a *para*-methoxyphenyl (PMP) group, we discovered that α-alkynylation reactions were possible. Various alkynes were reacted with *p*-methoxyphenyl glycine amides at room temperature using a combination of copper (I) bromide

and *tert*-butyl hydroperoxide (TBHP) as a terminal oxidant at room temperature (Scheme 18). The PMP protecting group decreases the oxidation potential of the substrate by stabilizing the imine intermediate, making it possible for the reaction to proceed under milder conditions. It is also important to note that the C-terminus must be an amide for the reaction to proceed, as replacing it by an OEt or a phenyl did not yield the desired product. We hypothesize that the amide moiety also plays a role in reducing the oxidation potential of the substrate and that the imino-amide intermediate tautomerizes to the iminol form before the alkynylation occurs. This alkynylation strategy also provides a versatile way to access homophenylalanine derivatives **27**, which are important synthons for many angiotensin-converting enzyme inhibitors (Scheme 19).[132]

Scheme 18. Direct alkynylation of glycine amides *via* CDC

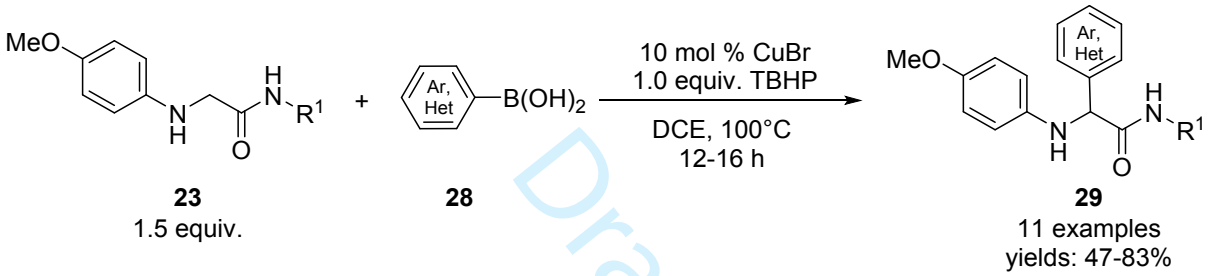


Scheme 19. Synthesis of homophenylalanine derivatives



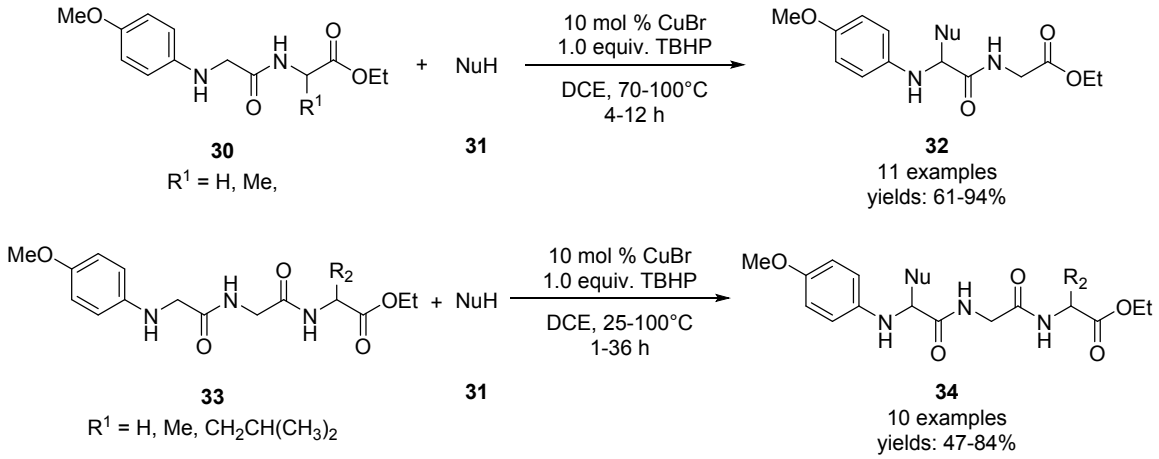
We found that it was also possible to use arylboronic acids as pro-nucleophiles for the α-arylation of the PMP-protected glycine amides in 1,2-dichloroethane at 100 °C (Scheme 20). Heterocyclic boronic acids and vinyl boronic acids were also successful substrates for the reaction. It noteworthy to mention that the reaction is shut down when secondary amides are used.[133]

Scheme 20. Direct arylation/heteroarylation of glycine amides *via* CDC



After achieving the α-functionalization of glycine amides, we were motivated to pursue peptide chains as substrates. To our delight, we found that our method could successfully achieve site-specific modifications of di- and tri-peptides (Scheme 21). Furthermore, the reaction proceeded smoothly without any racemization of the pre-existing stereocenters.

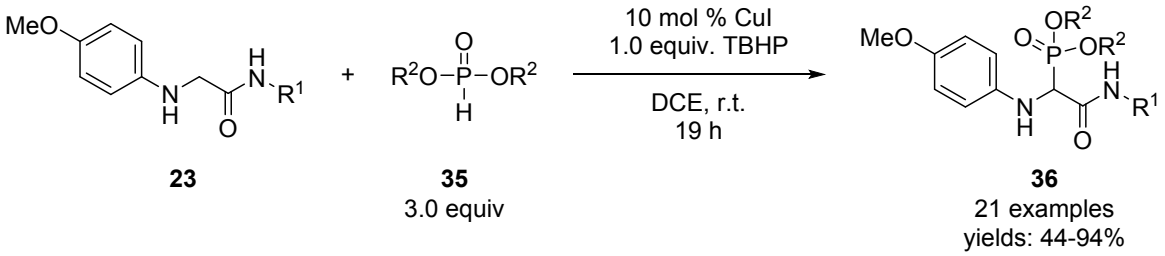
Scheme 21. Site-specific α-modification of peptides *via* CDC



31 = aryl, heteroaryl or vinyl boronic acid, phenylacetylene, indole

α-Amino phosphonates show remarkable biological properties in medicinal chemistry.[134] Thus, the prospect of directly phosphonylating amino acids via CDC became quite attractive. We therefore developed a methodology using dialkyl phosphite in the presence of copper (I) iodide and TBHP, to directly phosphonylate glycine amide derivatives (Scheme 22).[135] The reaction proceeds at room temperature in open air when using an excess of the dialkyl phosphite.

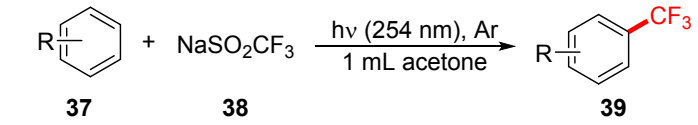
Scheme 22. Direct phosphonylation of glycine amides *via* CDC



Light promoted innate trifluoromethylation

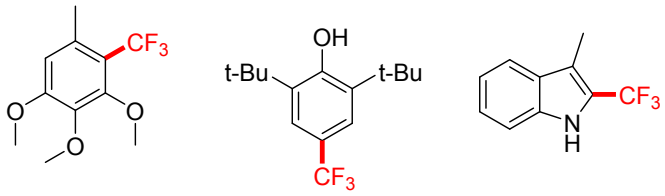
Introducing fluorine atoms to drug candidates can significantly alter their physical and metabolic properties by increasing their lipophilicity and metabolic stability. Based on this, appending trifluoromethyl (-CF_3) groups onto (hetero)aromatic rings has attracted broad attention. Various strategies which rely on different types of trifluoromethylation reagents have been previously established. A well-recognized strategy is the use of CF_3 radicals generated by employing energy intensive peroxides, to directly functionalize aromatic C-H bonds via radical addition. In this context, we envisioned a simple and efficient protocol using a readily available CF_3 reagent, such as $NaSO_2CF_3$. Considering the similarities between triplet ketone and an oxygen radical, we developed a light-induced trifluoromethylation reaction using acetone as the promoter without any strong oxidants or photo-redox catalysts. Under light irradiation (254 nm), acetone can be excited to the oxidative triplet state. Through a single electron transfer process, $NaSO_2CF_3$ is oxidized to trifluoromethylsulfinate radical, which further fragments to the CF_3 radical. The generated CF_3 radical can subsequently add to the electron-rich (hetero)aromatic compounds. This simple and efficient protocol can trifluoromethylate various (hetero)aromatic compounds in modest to good yields (Scheme 23). Moreover, it was found that when diacetyl instead of acetone was employed as the photo-sensitizer, more environmentally friendly visible light can drive this trifluoromethylation, which bears a comparable scope to the acetone protocol (Scheme 24).[136]

Scheme 23. Acetone promoted photo-induced trifluoromethylation



37 **38** **39**

Representative examples:

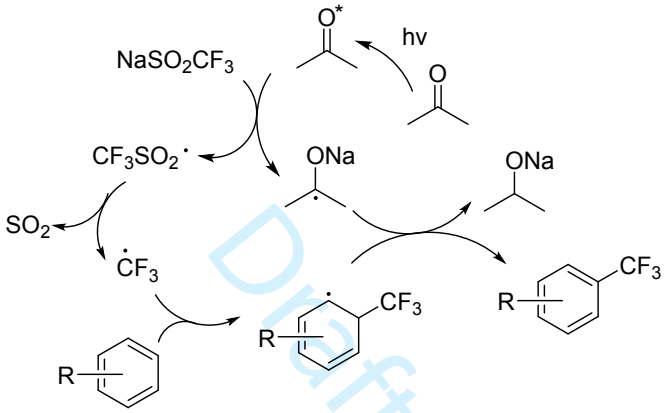


39a 75%

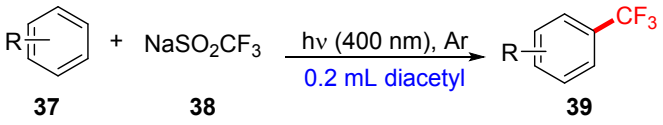
39b 49%

39c 72%

Proposed mechanism:

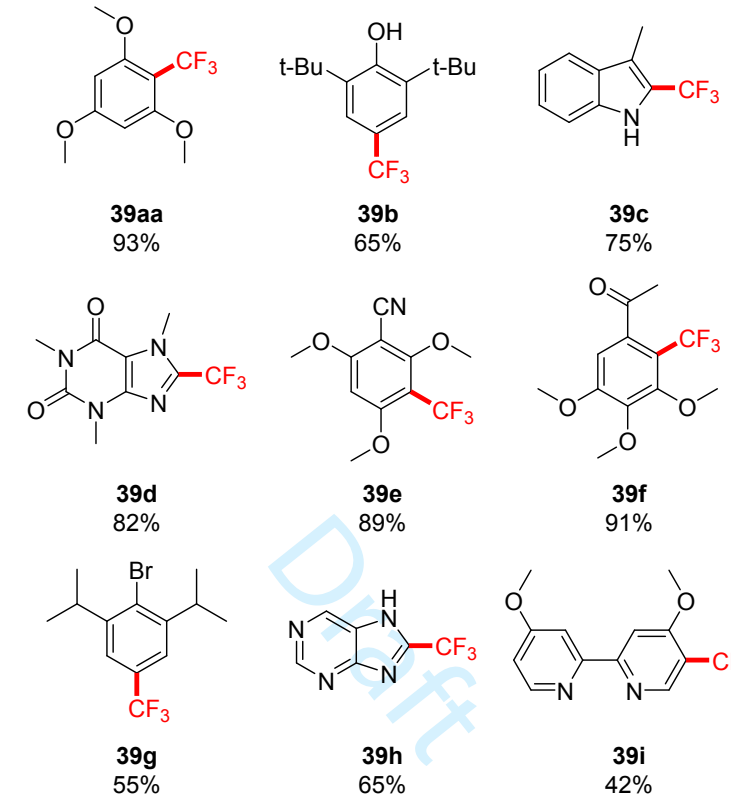


Scheme 24. Diacetyl promoted photo-induced trifluoromethylation



37 **38** **39**

Representative examples:



39aa 93%

39b 65%

39c 75%

39d 82%

39e 89%

39f 91%

39g 55%

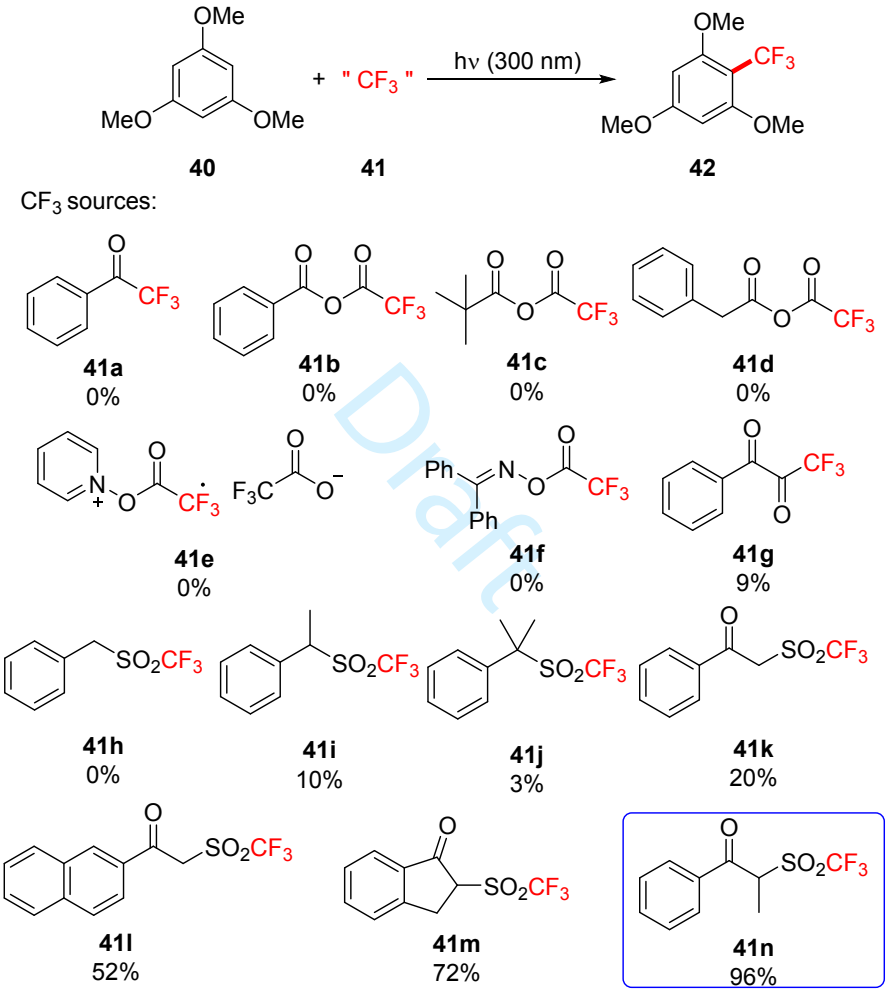
39h 65%

39i 42%

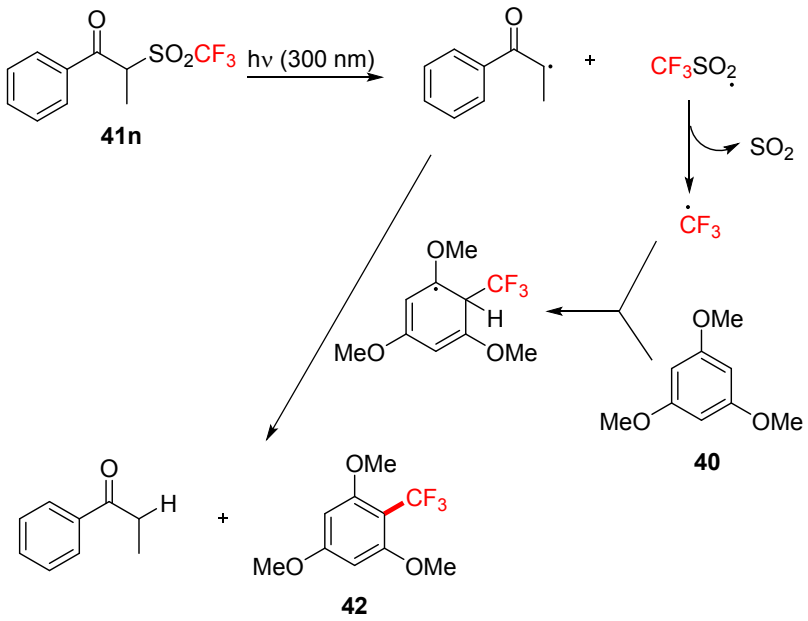
Despite the simplicity and efficiency of the acetone/diacetyl-involved protocol, it still relies on an external reagent to produce the CF_3 radical. This dependence on external photosensitizers carries some limitations. For example, this methodology is not compatible with the presence of amine groups. To circumvent this issue, we designed a brand-new CF_3 reagent which was expected to be photo-active in the absence of any external promoter. Inspired by the Norrish type I reaction, we synthesized a series of CF_3 reagents, among which 1-phenyl-2-((trifluoromethyl)sulfonyl)propan-1-one was the most reactive (Scheme 25). This reagent was proposed to undergo a Norrish I process, which would undergo the alpha-cleavage to produce the trifluoromethylsulfinate radical under the photo-activation. Subsequently, upon

SO_2 extrusion, the desired CF_3 radical was generated, which reacts with the aromatic substrates to yield the desired products (Scheme 26).[137]

Scheme 25. Identification of reactive photo-active CF_3 reagents

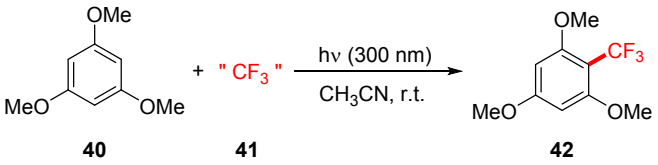


Scheme 26. Proposed mechanism for the trifluoromethylation



Following the identification of the desired CF_3 reagent, the substrate scope was further evaluated, the result of which suggests that various functional groups can be tolerated by using this newly designed CF_3 reagent (Scheme 27).

Scheme 27. Scope of the aromatic compounds using the newly identified CF_3 reagent.



40 **41** **42**

Representative examples:

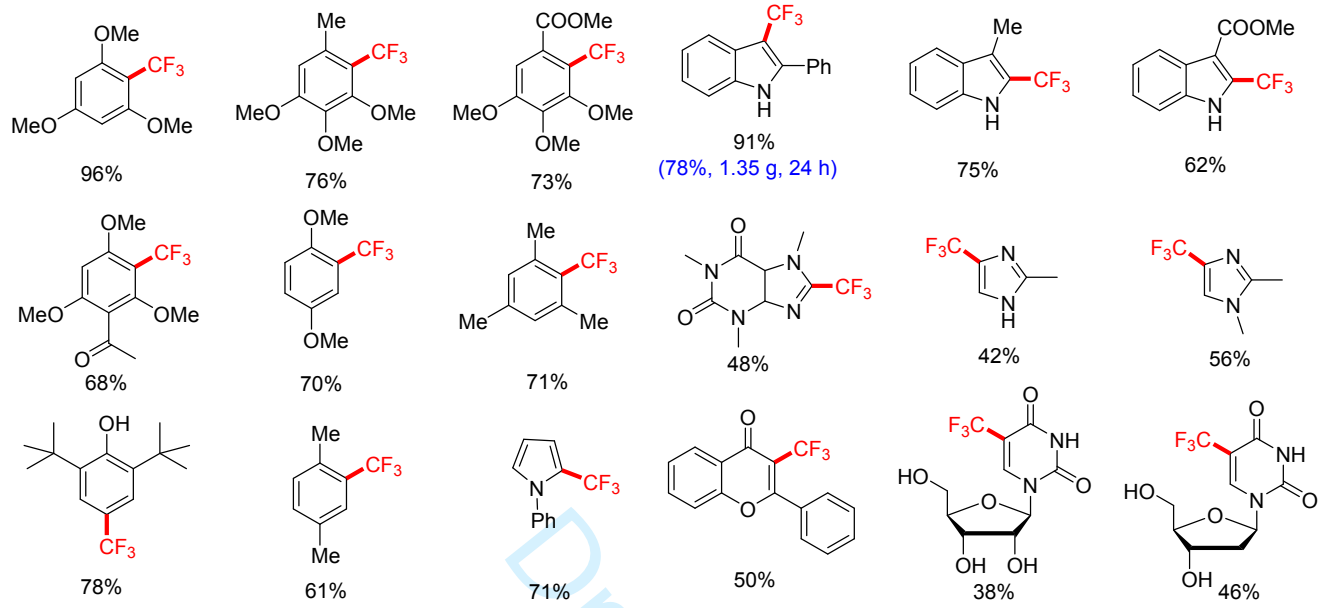
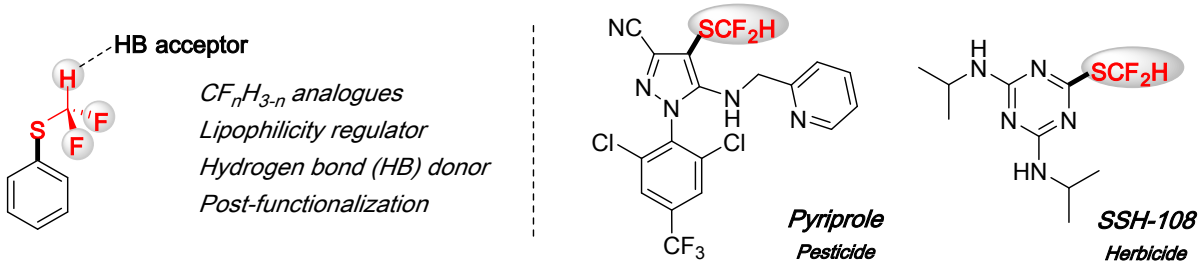


Photo-induced C_{sp2}-H difluoromethylthiolation: synthesis of aromatic difluoromethylthioethers

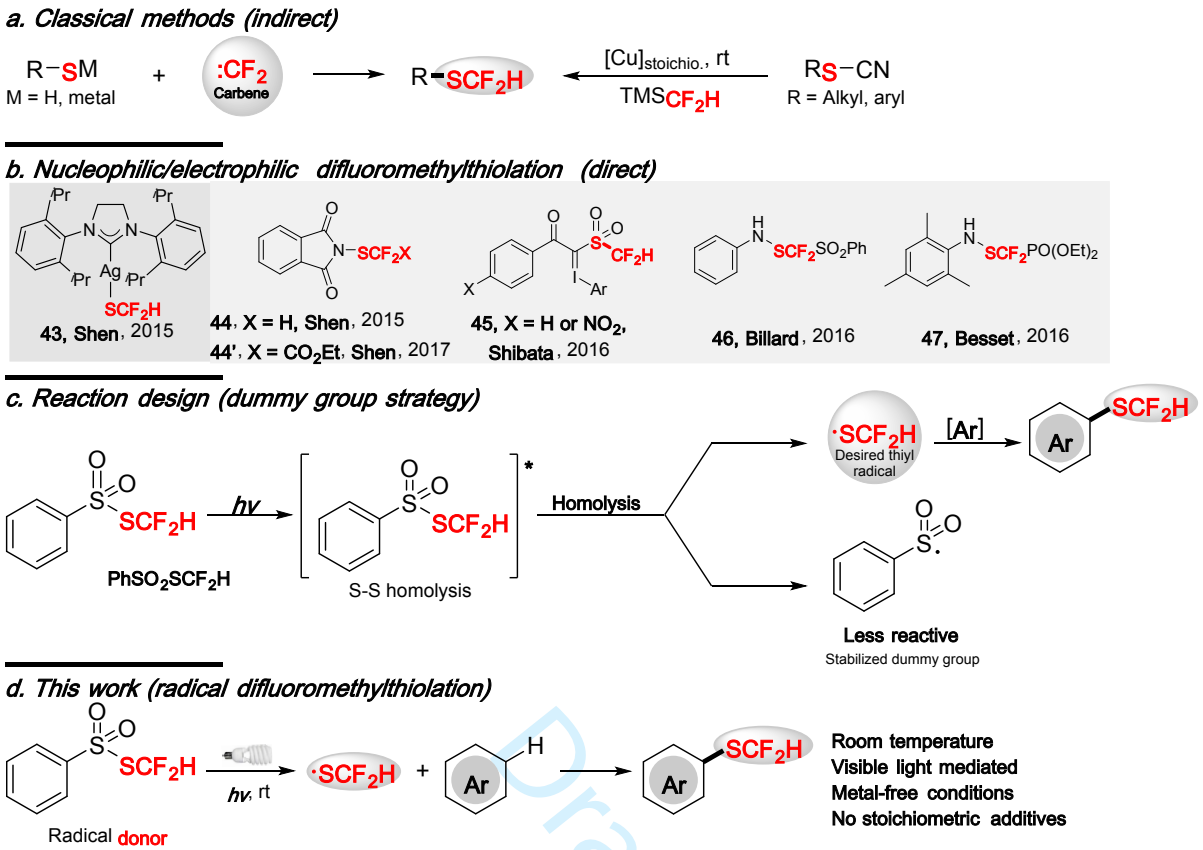
Aryl difluoromethylthioethers have gained an increased interest in academic and industrial settings due to their potential as a novel class of pharmaceuticals.[138-141] Given this interest, the difluoromethylthio group (-SCF_2H) has found its utility in new drug candidate design and discovery.[142-145] This functionality is composed of two instrumental elements, sulfur and fluorine, which give it the following key features: 1) -SCF_2H is a lipophilicity mediator with an intermediate Hansch lipophilicity parameter (π_R = 0.68);[146-147] 2) -SCF_2H features a slightly acidic proton (p*K*a = 35.2), rendering it a weak hydrogen bond donor (hydrogen bond acidity parameter *A* = 0.098) to tune the molecule's binding ability;[139, 148-149] 3) its electron-withdrawing nature could promote the metabolic stability of lead compounds; and 4) the difluoromethylsulfides could be actively engaged in diversification, enriching bio-activity of the host molecules (Figure 1).

Figure 1. Physicochemical properties of aryl difluoromethylthioethers and representative HF_2CS-containing drug molecules.



By virtue of these attractive properties, efficient synthetic methods to access difluoromethylthioethers have become a rewarding target.[150] Classical and routinely used methods to prepare difluoromethylthioethers employ appropriate thiolates and "CF_2" species,[151-153] which is in most cases difluorocarbene (Scheme 28a, left).[154-166] These early methods suffer from a limited substrate scope and low step economy due to the harsh conditions and stepwise assembly of the -SCF_2H moiety. In light of these issues, the Gooβen group took a step forward to extend the scope by employing the Langlosis type nucleophilic displacement of thiocyanates (-SCN) by $TMSCF_2H$ (Scheme 28a, right).[148, 167] However, the step efficiency remained unsolved since it necessitated the pre-formation of the thiocyanates.

Scheme 28. Synthetic routes for difluoromethylthioethers and our reaction design

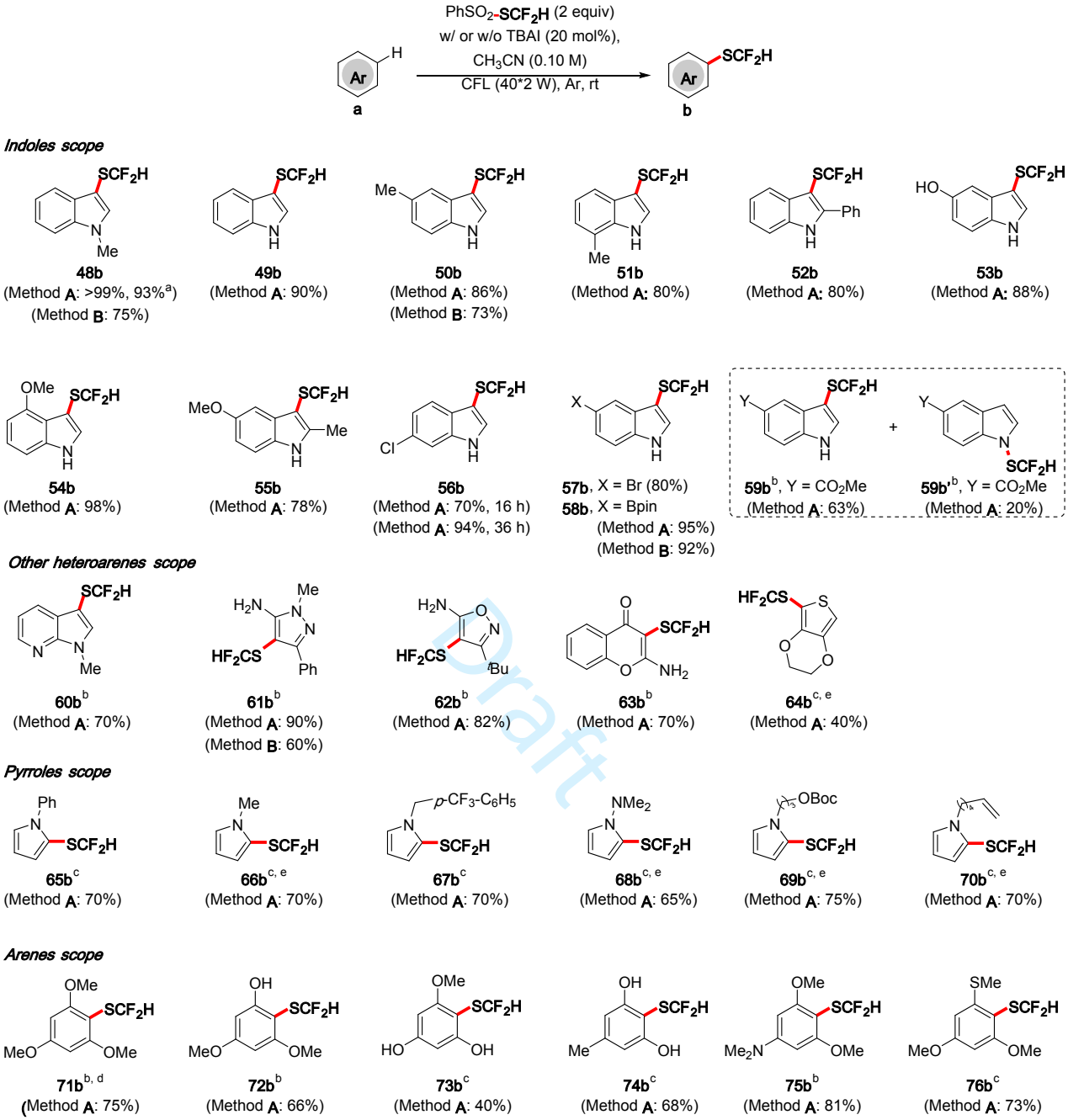


On the other hand, the direct installation of -SCF_2H on arenes represents a promising route to access the aryl difluoromethylthioethers in an atom- and step-efficient manner. As a key contribution, the Shen group disclosed the first nucleophilic difluoromethylthiolating reagent **43**, [(SIPr)Ag(SCF_2H)] and achieved the direct difluoromethylthioether synthesis by coupling **43** and aryl (pseudo)halides *via* transition metal catalysis (M = Pd or Cu) (Scheme 28b).[168-169] Following this pioneering work, several reagents with complementary reactivity **44-47** were described independently by Shen,[170-172] Shibata,[173] Billard[174] and Besset[175] *et al*. Using these reagents under thermal conditions, electron-rich arenes can be difluoromethylthiolated through a Friedel-Craft type reaction. Despite these promising strategies, the preparation of the difluoromethylthioethers still relied on relatively high thermal energy (from 50 to 120 °C) or involved precious metal catalysts and stoichiometric additives. In the case of the -SCF_2FG group

transfer, additional reduction steps were needed to furnish the desired thioether products. A more sustainable synthetic protocol that featured milder conditions and an improved step economy became highly desirable. Based on our group's light-mediated redox-neutral aromatic trifluoromethylation, we envisioned the so-called "dummy group strategy" which could be applicable and implemented as a new technique to achieve radical difluoromethylthiolation (Scheme 28c).[176] Upon light irradiation, *S*-(difluoromethyl)benzenesulfonothioate, $PhSO_2SCF_2H$ undergoes S-S homolysis, facilitated by the weak S-S bond, to engender two radicals.[177-178] The resonance stabilized sulfonyl radical ($PhSO_2\cdot$) has a diminished reactivity, therefore causing less competition towards the achievement of the desired reaction.[179] The twin difluoromethylthiyl ($HF_2CS\cdot$) was expected to complete the difluoromethylthiolation *via* a radical attack on arenes. Based on this concept, we developed a metal-free direct difluoromethylthiolation method which was enabled by visible light at room temperature in the absence of stoichiometric additives (Scheme 28d).[180]

After exploration of the optimal conditions, identified as arene (1.0 equiv), $PhSO_2SCF_2H$ (2.0 equiv), TBAI (20 mol%) in argon atmosphere at room temperature under compact fluorescent lamp (CFL) irradiation for 16 hours, we examined the scope of this radical difluoromethylthiolation protocol (Scheme 29). Initially, the functional group tolerance of different heteroarenes including indoles (**48a** to **60a**, **77a**), pyrazole (**61a**), isoxazole (**62a**), chromone (**63a**), thiophene (**64a**), and pyrroles (**65a** to **70a**) was investigated. They all proved to be active substrates, resulting in good to excellent yields of product formation. This radical difluoromethylthiolation protocol was also found versatile on some arenes as anisole (**71b**), phenol (**72b**), resorcinol (**73b**), aniline (**74b** and **75b**), thioether (**76b**) and their derivatives, which were all difluoromethylthiolated smoothly under our optimal conditions.

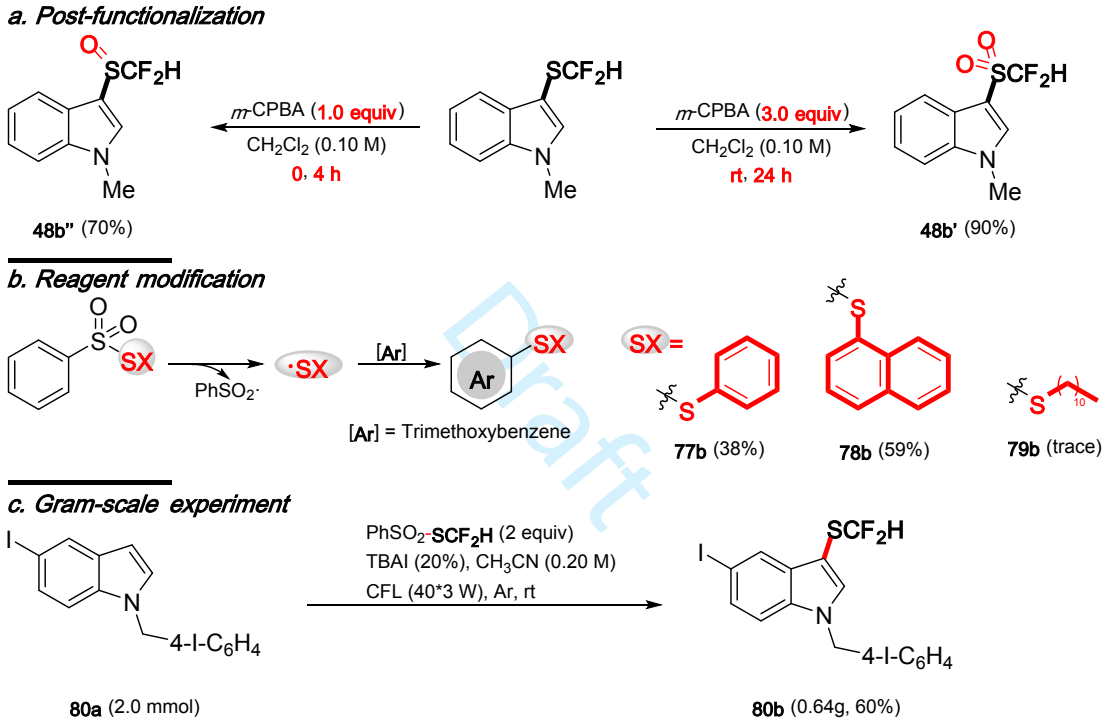
Scheme 29. Scope of arenes. Method **A**: Arene (0.10 mmol), $PhSO_2SCF_2H$ (0.20 mmol), TBAI (0.020 mmol) in 1.0 mL CH_3CN under argon for CFL irradiation at rt for 16 h. Method **B**: Arene (0.10 mmol), $PhSO_2SCF_2H$ (0.20 mmol) in 1.0 mL CH_3CN under argon for CFL irradiation at rt for 16 h. The yields in the parentheses refer to the isolated ones unless otherwise specified. Volatility resulted in the low isolated yield of **69b** and **70b**. [a]Reaction performed in 0.40 mmol scale. [b]The reactions were performed for 24 h. [c]The reactions were performed for 48 h. [d]4 equiv $PhSO_2SCF_2H$ was used. [e]Yields are quantified by GC-MS due to the volatility of target compounds. [a]Reaction performed in 0.40 mmol scale.



To demonstrate the practicality of this method, the late-stage modification was performed to furnish the corresponding difluoromethylsulfoxides (**48b''**) and difluoromethylsulfones (**48b'**), which were both identified as valuable entities in medicinal chemistry (Scheme 30a).[181-182] Other thiolation moieties, e.g., phenyl- (**77b**) and naphthylthiol (**78b**), proceed successfully, endowing this method with appreciable

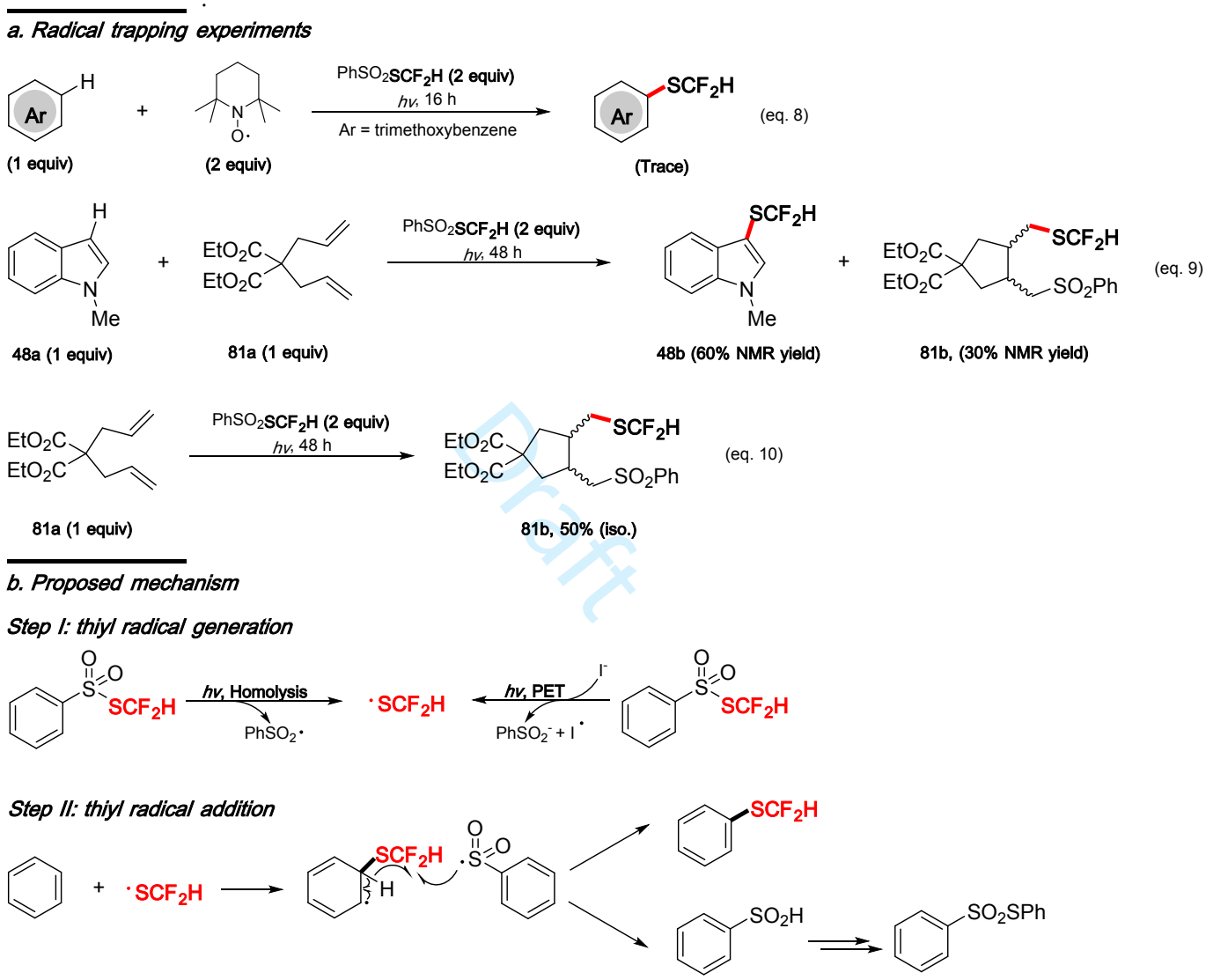
flexibility (Scheme 30b). Moreover, when subjected to a gram-scale experiment, moderate yields could be obtained in the case of **80a** (Scheme 30c).

Scheme 30. Application. a. Controlled oxidation of the thioether to the corresponding sulfoxides and sulfones. b. Modified reagents to afford arylthiolation products. c. Scaled experiment.



With regards to the mechanistic insight, we performed trapping experiments which suggested a radical process (Scheme 31). In the presence of radical-clock type reagent, the ring-closure product was isolated (**81b**). Based on these preliminary results and previous literature,[145, 183-190] we proposed a radical mechanism, in which the difluoromethylthiyl radical was generated from either the homolysis event of $PhSO_2SCF_2H$ or its single electron reduction by iodide. Subsequently, the difluoromethylthiolation was operated *via* the radical substitution on arenes.

Scheme 31. Mechanistic study. a. Termination of the desired reactivity in the presence of radical trappers; b. Plausible mechanism.



Concluding Remarks

We have developed a series of novel strategies which bring us closer to more "benign-by-design" synthetic routes. By being able to finely tune how to selectively remove, convert or add functional groups under

mild conditions with improved atom economy, these reactions provide fundamental tools for the direct late-stage functionalization of complex molecules, which are essential for efficient valorization of biomasses, synthetic biology, and drug discoveries.

Acknowledgments

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Tables and figures captions

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