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Review

Recent Advances in Nonprecious Metal Catalysis

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ABSTRACT: This Perspective is part of a continuing review series that is published within the alliance among AbbVie, Boehringer Ingelheim, and Pfizer. The purpose of this article is to highlight the myriad of applications for nonprecious metal catalysts, specifically highlighting copper, cobalt, iron, and nickel. The utility of these metals, alongside their low cost and sustainable feedstocks, makes them ideal reagents. To underscore the advantages of nonprecious metal catalysis, we have highlighted transformations that are of interest to synthetic chemists.

KEYWORDS: *iron, cobalt, nickel, copper, nonprecious metals, catalysis*

INTRODUCTION

The generality and cost-effectiveness of nonprecious metal catalysis (NPMC) make it an alluring field of study for synthetic chemists in both academia and industry. This review showcases various transformations that were carried out using copper, cobalt, iron, and nickel catalysts. The highlighted examples were published during July−October 2024. It is the hope of the authors that this review series helps stimulate further advancement and utilization of NPMC.

RECENT REPORTS ON FE-CATALYZED REACTIONS

Iron catalysis is appealing to synthetic chemists because it is inexpensive and readily found in biological systems, making it an ideal choice for sustainable process development.[1] Because iron belongs to the *d*-block of the periodic table, with a plethora of formal oxidation states, it can tackle many synthetic challenges. Indeed, iron has been employed to catalyze Aldol reactions, substitutions, cross-couplings, cycloadditions, etc.[2] This portion of the review highlights contemporary additions to the field of iron catalysis, whereby iron continues to prove itself as a versatile promoter of chemical transformations.

Chang and co-workers prepared an enantioselective α-amidation of aldehydes via organo-iron dual photocatalysis.[3] The iron catalyst contributes to the amide activation through ligand-to-metal charge transfer (LMCT), while chiral enamine catalysis facilitates facial selectivity. This reaction was reported alongside a varied substrate scope, including aliphatic aldehydes, benzyl aldehydes, and varied dioxazolone substrates (Scheme 1a). It is significant that alkene- and alkyne-containing substrates were tolerated well. The authors expanded their scope to include biologically relevant aldehydes, which highlighted the potential to use this reaction in discovery programs. It should be noted that while the published conditions and scope employ diethyl ether, a solvent that is not considered safe on scale, the Supporting Information in ref 3 indicates that similar results were obtained with a THF or ethyl acetate substitution. This improves the potential for industrial application. To further support the utility of this chemistry in industrial applications, the authors prepared nateglinide, a non-natural amino acid derivative used to treat type II diabetes, on a 3 mmol scale without column chromatography in >99:1 er.

The authors conducted various mechanistic studies, both experimental and computational (Scheme 1b). While $FeCl_2$ and $FeCl_3$ showcased dioxazolone reactivity, various experimental studies clearly indicated that $[FeCl_3]^-$ was the primary source of catalytic activity. This is clearly shown in Scheme 1b, where $FeCl_3$ and TBACl were employed in dark conditions to generate $[FeCl_4]^-$ in situ; this resulted in less than 5% yield. However, when $FeCl_2$ and TBACl were employed to generate $[FeCl_3]^-$, a 41% yield and 99:1 er were observed under dark conditions. Additionally, when the $[FeCl_4]^-$ conditions were irradiated with light, a 71% yield with a 99:1 er was obtained. This highlights that $FeCl_3$ forms the active $[FeCl_4]^-$ via LMCT. Notably, DFT calculations supported the Fe(III)-imidyl radical and were consistent with a previous characterization of an iron-nitrenoid.[4] In summary, this enantioselective α-amidation of aldehydes is a useful reaction that also highlights an interesting visible-light-promoted LMCT to activate dioxazolones to afford iron-acylnitrenoid radical intermediates.

Wang and co-workers reported a homolytic aromatic substitution (HAS) reaction, where an iron catalyst selectively aminates indoles at the C-7 location.[5] The HAS pathway enables this C−H metalation to tolerate various functional groups that otherwise may exhibit undesired interceptions via

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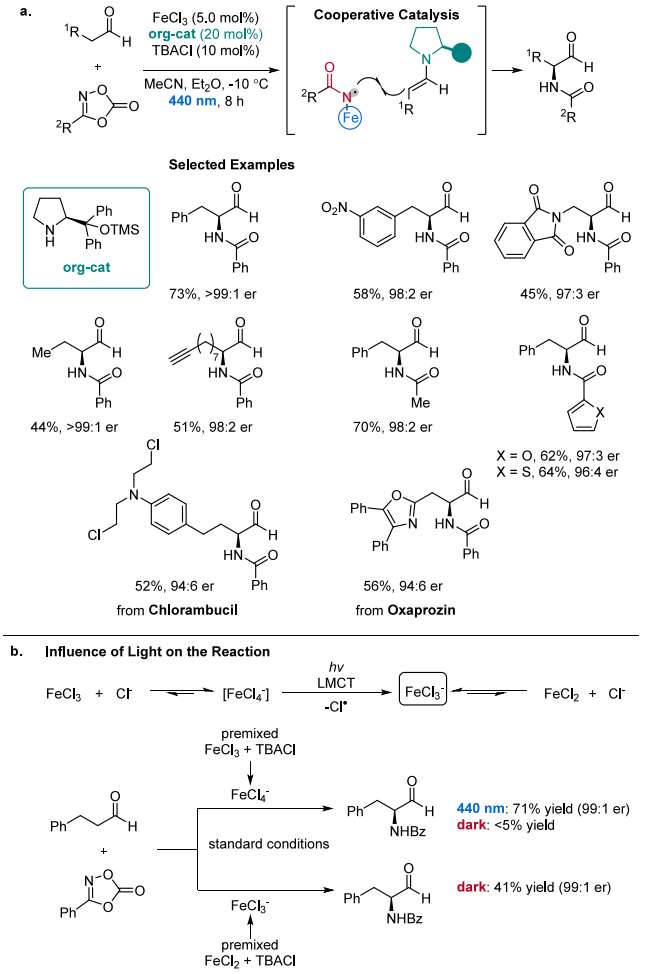
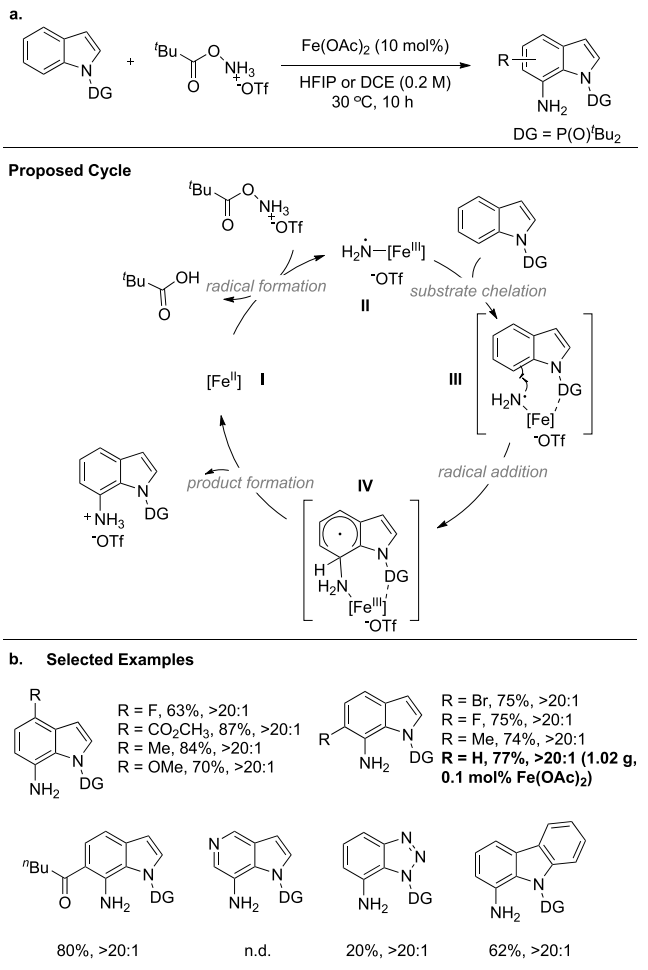
Scheme 1. (a) Scope of a Visible-Light-Promoted Enantioselective α-Amidation of Aldehydes via Organo-Iron Dual Catalysis; (b) Mechanistic Studies Considering the Effect of Light on Conversion



Scheme 2. (a) Mechanistic Cycle of an Iron-Catalyzed C−7 Selective Amination of Indoles; (b) Selected Examples of Indole Aminations



carbon−metal intermediates. Indoles are a notoriously difficult substrate class, as amination at the C-2 site is common and the electron-rich nature of the ring could lead to nondirected HAS. For this reason, the authors employed an N−P(O)^{t}Bu$_2$ (TBPO) indole, using the directing group to promote the desired C-7 activation. A varied substrate scope was examined, with functional group tolerance shown for substrates containing halide, ester, ether, cyanide, ketone, alcohol, olefin, and terminal alkyne (Scheme 2a). The tolerance of olefins in these conditions is notable, as these functional groups have been shown to effectively intercept nitrogen-centered radicals.[6,7] Electron-rich and electron-deficient indoles were aminated in good yields and high regioselectivity (most >20:1). Introducing heteroatoms to the indole motif, such as azaindoles or benzotriazoles, showed limited success. The authors note that this process is likely scalable, as they successfully prepared over a gram of aminated indole on 10 mmol scale at 0.1 mol % iron catalyst loading. The proposed mechanistic cycle is illustrated below (Scheme 2b), where the iron(II) catalyst and electrophilic aminating reagent afford the key iron(III)-aminyl radical (**IV**).[8] The C−H activation chemistry is always a welcome addition to heterocycle functionalization, making this an interesting use of an earth-abundant iron catalyst.

Nagib and co-workers reported an iron-catalyzed cyclopropanation reaction with nonstabilized carbenes via ketyl radicals, as shown in Scheme 3.[9] In their previous work,[10] they employed α-acyloxy halides as iron carbene precursors via a multistep activation procedure. The organozinc intermediates associated with α-acyloxy halide activation resulted in protodemetalation issues. Therefore, acidic motifs were not tolerated and anhydrous conditions were necessary. In this new and improved ketyl radical approach, the halides were activated in a single step. Furthermore, the authors were able to employ a one-pot procedure from α-acyloxy halide precursors, enabling a one-pot transformation of the aldehyde to a cyclopropane ring on a 2.5 mmol scale.

In developing this reaction, the authors noted that $FeCl_2$ or $FeCl_3$ were significantly less reactive than FeTPPCl (<10% yield vs >99% yield, respectively). Both zinc and manganese were viable reductants. Under standard conditions, the olefin scope was broad, tolerating heteroaromatics, esters, amines, etc. More importantly, both electron-rich and electron-poor olefins were viable carbene traps. The carbene scope tolerated alkyl and aryl acyloxy chlorides well. The authors went on to study the mechanism of the reaction, concluding a non-concerted (2 + 1) cycloaddition reaction. Stereochemical probes supported this mechanistic proposal as both *E*- and *Z*-styrene yielded the *anti*-product (Scheme 3b). Synthetic chemists will surely appreciate this robust cyclopropanation

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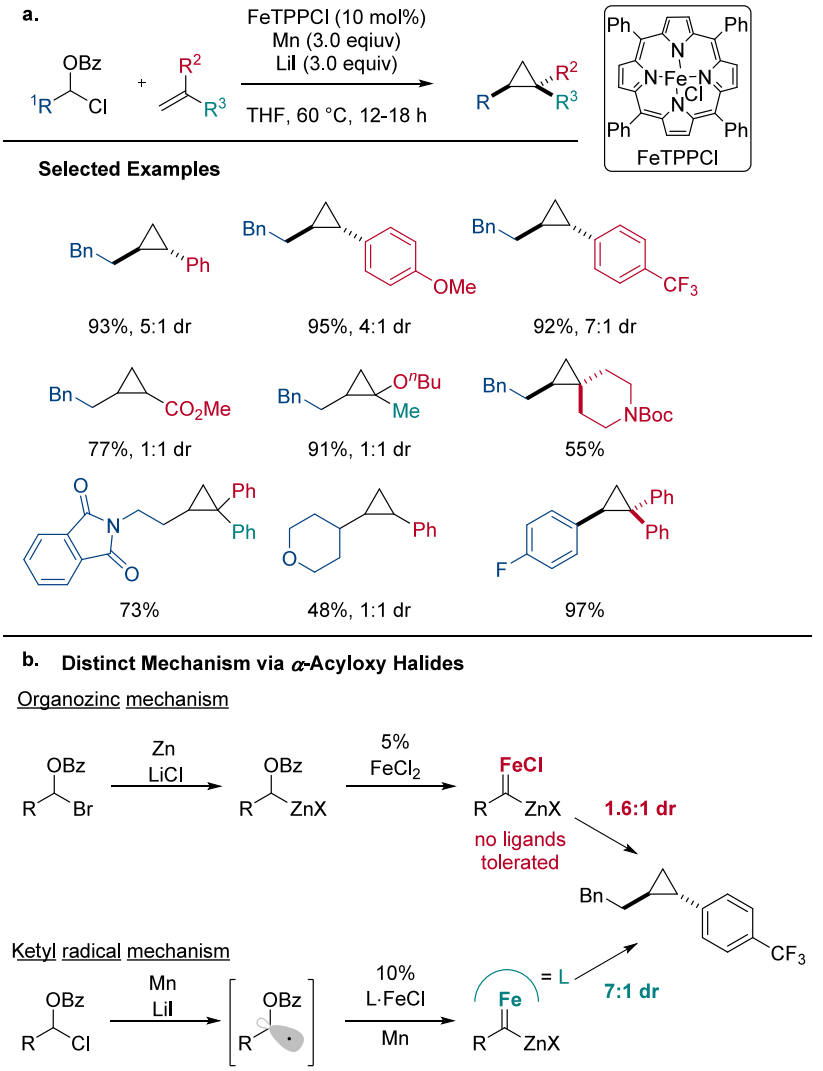
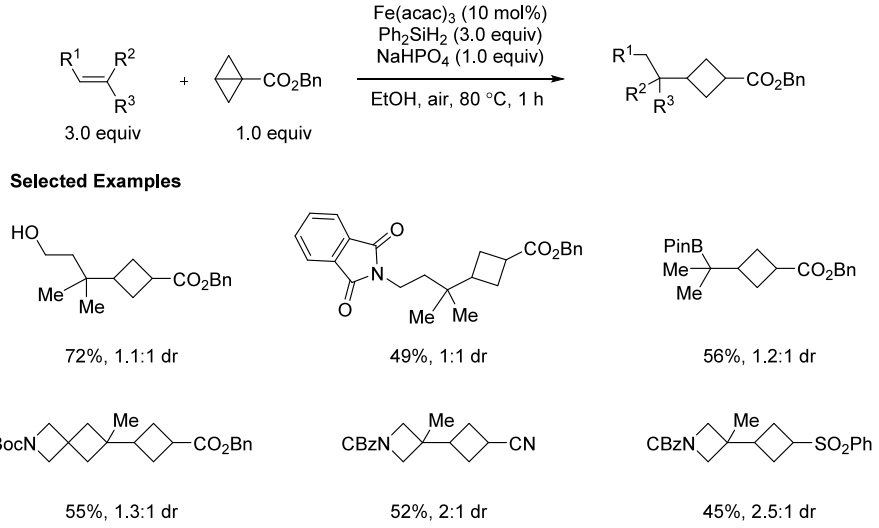
Scheme 3. (a) Selected Examples of a Cyclopropanation with Nonstabilized Carbenes via Ketyl Radical Intermediates; (b) Distinct Mechanism via α-Acyloxy Halides versus Organozinc Intermediates



Scheme 4. Reductive Olefin Coupling Enabled by Iron Hydride HAT



reaction, in part due to the simplicity of the starting materials. However, future work to address moderate diastereoselectivity issues would make this chemistry more impactful.

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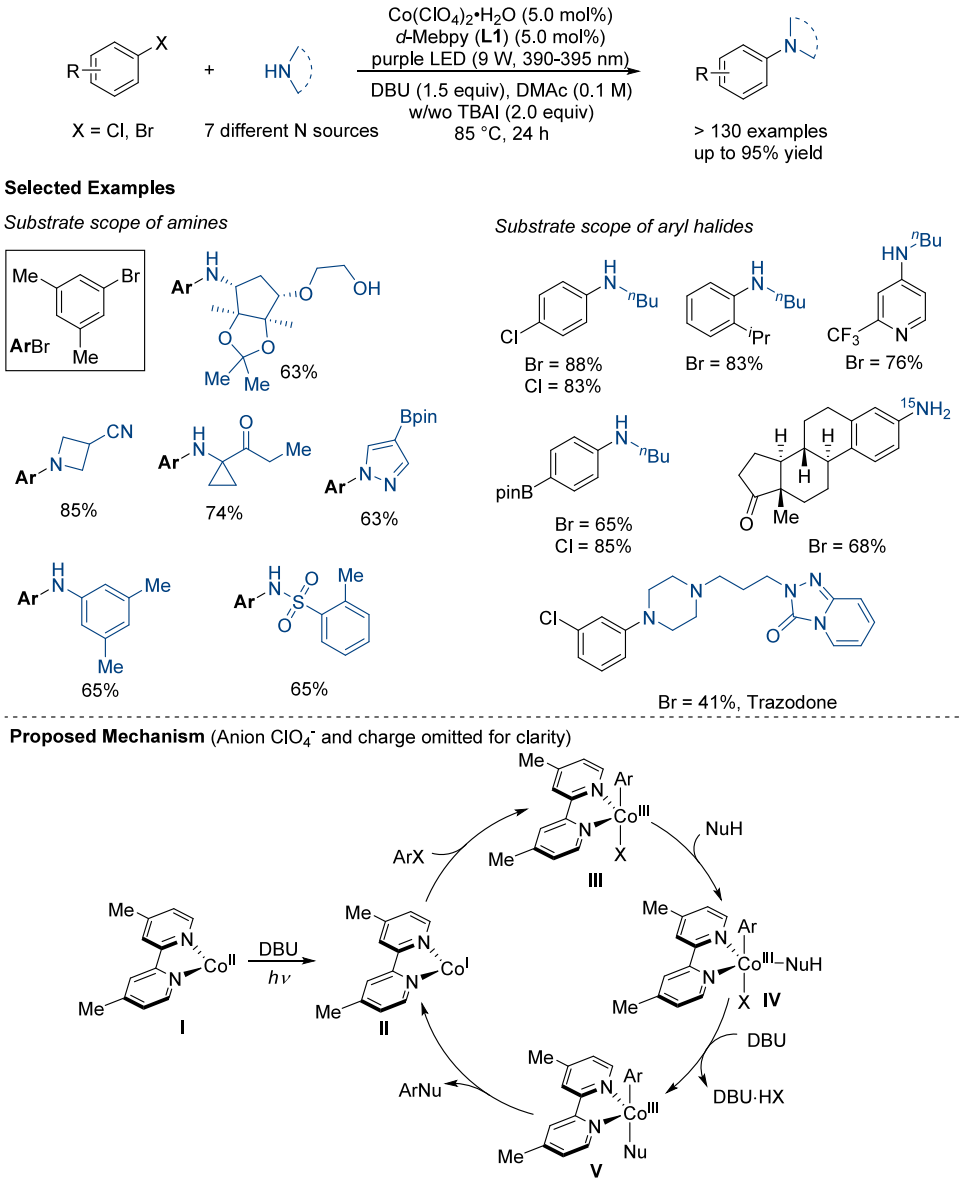
Scheme 5. Cobalt-Catalyzed Photochemical C−N Cross-Coupling



A novel reductive olefin coupling to bicyclo[1.1.0]butanes (BCB) was reported by Zhang and co-workers.[11] This reaction is an interesting surrogate for the corresponding Michael additions and Giese reactions. The coupling was enabled by an iron hydride hydrogen atom transfer (HAT) under ambient conditions. Only a restricted number of radical precursors have been found to couple with BCBs bearing electron-withdrawing groups, most being highly nucleophilic radical precursors.[12] The authors note two significant obstacles to develop this chemistry: (1) some metal hydrides react preferentially with BCBs over olefins,[13] and (2) the addition of radical species to BCBs requires overcoming a much higher energy barrier compared to Michael acceptors.[12]

In developing this chemistry, the authors observed strong reactivity only with iron catalysts, with cobalt and manganese furnishing the desired product in trace amounts. When the olefin equivalents were reduced from three equiv to only two, the isolated yield dropped from 85 to 64%. Consistent with previous reports on the addition of C(sp^3)-centered radicals to BCBs, practically no diastereoselectivity was observed.[12,13] The substrate scope illustrated that terminal olefins exhibited higher yields compared to internal olefins, presumably due to steric hindrance (Scheme 4). A variety of functional groups were well tolerated for both olefins and BCBs, such as alcohols, sulfones, boronic esters, and ketals. Alkyl halides, styrenes, and sterically encumbered olefins were not amenable to the current conditions. The authors showcased this chemistry on a variety of biologically relevant scaffolds as well on a 3 mmol scale. The results obtained on 3 mmol scale were comparable to the substrate scope, which indicated that this process is likely scalable. Overall, this work would be more scalable if the equivalents of olefin were reduced and diastereoselectivity was improved. However, this interesting cyclobutane alkylation will certainly assist drug discovery programs.

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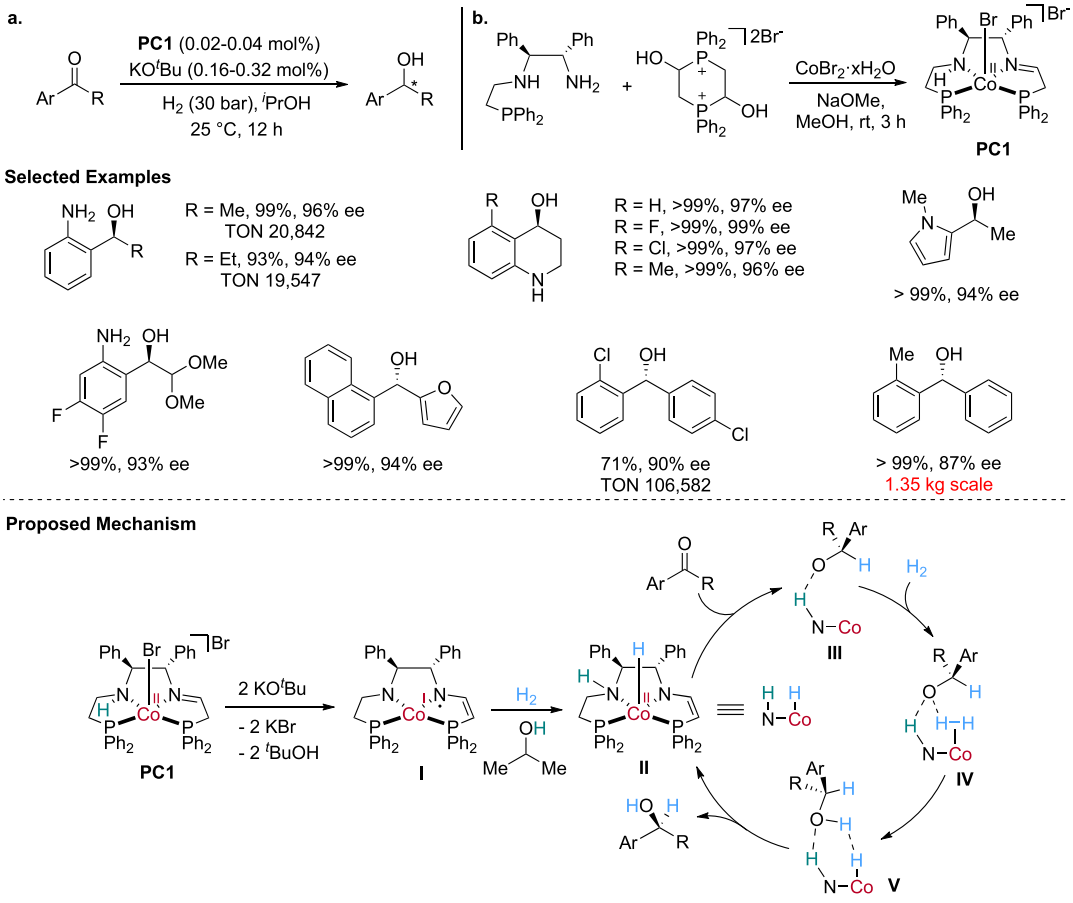
Scheme 6. (a) Cobalt-Catalyzed Symmetric Hydrogenation of Ketones; (b) Synthesis of Precatalyst PC1



RECENT REPORTS ON CO-CATALYZED REACTIONS

As an inexpensive and earth-abundant transition metal, cobalt retains its attractiveness in organic synthesis over the past decades.[14] Several representative advances in cobalt-catalyzed reactions, including C−N cross-coupling, AH, dehydrogenation, reductive addition, and hydrothiolation, are covered in this review. These examples were selected because they are applicable to drug discovery and process chemistry programs.

C−N cross-coupling has been established as a fundamental technology to construct aromatic amines. Despite significant advancements in this field, practical implementation necessitates the ligand/precatalyst design and condition diversification; therefore, a universal and reliable protocol is in increasing demand.[15,16] The Xue group reported a Co-catalyzed C−N coupling under identical photochemical conditions (Scheme 5), wherein cobalt served as a dual catalyst for both sensitization and organometallic process.[17] A broad substrate scope, containing 69 examples of amines that possess a wide range of functional groups and 54 examples of aryl halides with steric and electronic variants, was investigated and demonstrated to proceed in excellent yields. Additionally, the method was successfully applied in the synthesis of pharmaceutical molecules such as Q203 and trazodone. It is worth noting that five-membered heterocyclic compounds, except pyrazole and acidic aryl bromides, were not compatible with the amination method. Mechanistically, $Co(ClO_4)_2·6H_2O$ coordinated with 4,4′-dimethyl-2,2′-bipyridyl (d-Mebpy, **L1**), and was irradiated to Co(I) complex **II** upon exposure to light in the presence of DBU. Oxidative addition with the aryl halide generated Co(III)−Ar intermediate **III**, which underwent substitution by the amine with the assistance of DBU to deliver Co(III)−Nu intermediate **V**. The subsequent reductive amination afforded *N*-arylated adducts and Co(I) species **II**.

Synthesis of chiral alcohols via asymmetric hydrogenation (AH) is commonly enabled by precious metal catalysts.[18,19] In terms of cost efficacy and sustainability, a nonprecious-metal-catalyzed AH with a high turnover number (TON) is preferable for manufacturing.[20] Zuo and co-workers designed a cobalt AH catalyst **PC1** that assisted the reduction of ketones with a comparable TON with precious metal catalysts and high enantioselectivity (Scheme 6a).[21] The precatalyst does not require any π-acidic ligands such as CO and could be simply prepared from inexpensive $CoBr_2·xH_2O$, the shelf-stable chiral tridentate ligand (*S*,*S*)−P−NH−NH_2, and the phosphonium salt (Scheme 6b).[22] Ketones featuring alkyl, cycloalkyl, acetal, and aryl substituents accommodated the developed condition effectively, and the corresponding alcohols were achieved in excellent yields and high ee with TONs of up to 150,000. In particular, 2-amino-benzenemethanols and 1,2,3,4-tetrahydroquinolin-4-ols were widely utilized as pharmaceutical building blocks. Remarkably, 1.35 kg of (*R*)-phenyl(*o*-tolyl)methanol was synthesized with 0.02 mol % cobalt catalyst, demonstrating its feasibility for scale-up.

By experimental studies and quantum calculation, the Zuo group hypothesized that low-spin Co(II) complex **II** arose from isopropanol-assisted H_2 activation of Co(I) complex **I**

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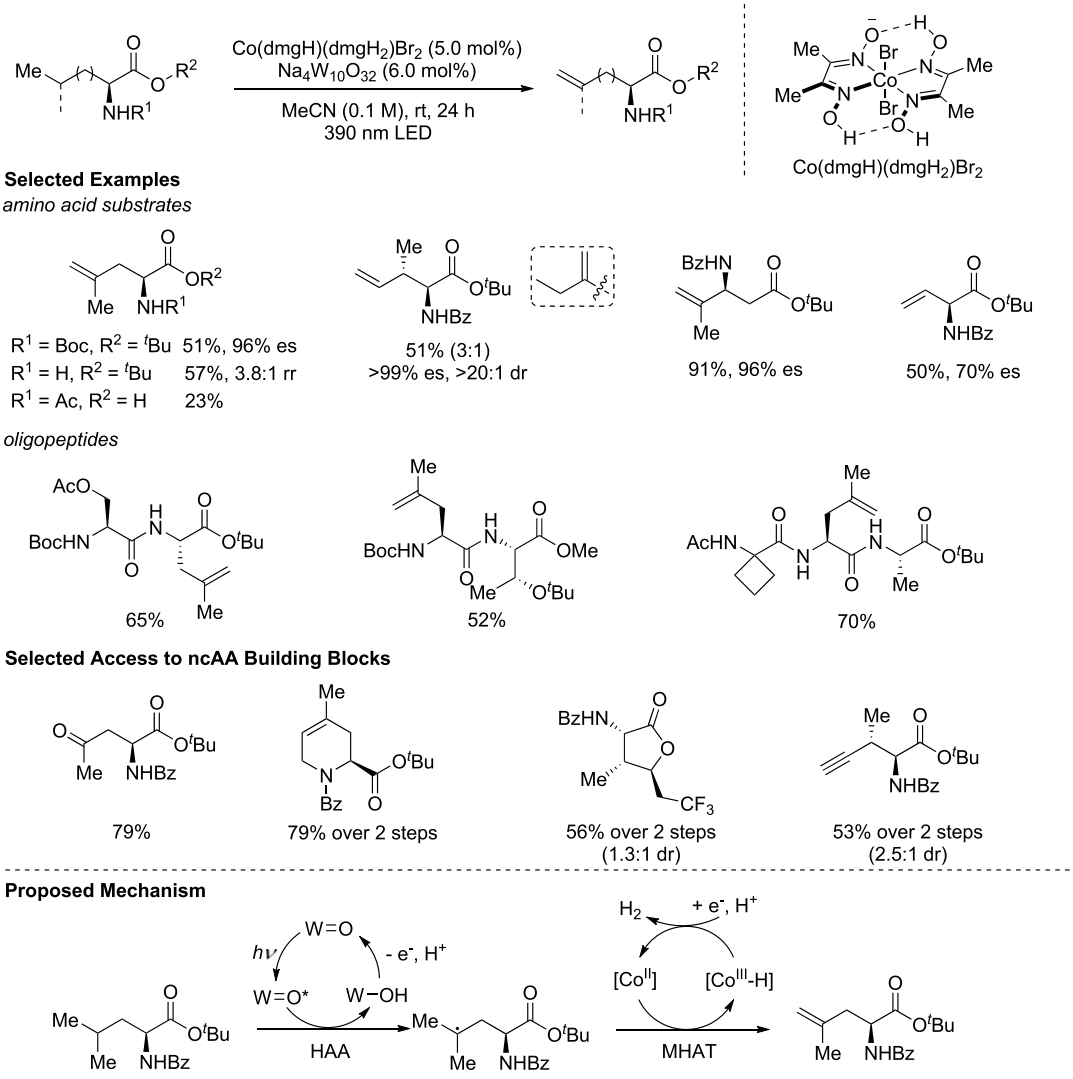
Scheme 7. Terminal-Selective Dehydrogenation of Aliphatic Amino Acids



that originated from precatalyst **PC1**. After approaching **II** by hydrogen bonding between the O and NH functionality, the ketone was reduced via an outer-sphere hydride transfer through an enantiodetermining transition state. The enantioselectivity is attributed to the steric repulsion between the phenyl substituent of the phosphorus donor and the substituent of ketone. The ion pair **III** coordinated with H_2 to furnish the η^2-H_2 cobalt complex **IV**, subsequent dihydrogen splitting and proton transfer delivered intermediate **V**, and the chiral alcohol and intermediate **II** were then released to close the catalytic cycle.

As a chiral module widely used in organic synthesis, noncanonical amino acids (ncAAs) could be readily accessed from a few proteinogenic amino acids, and aliphatic amino acids lacking reactive functional groups are rarely explored.[23,24] The Wendlandt group developed a photocatalytic terminal-selective dehydrogenation of aliphatic amino acids with the assistance of $Na_4W_{10}O_{32}$ (NaDT) and Co(dmgH)-($dmgH_2$)Br_2 catalysts, whereby the resultant terminal alkenes enabled their extensions to ncAAs (Scheme 7).[25] Mechanistic studies revealed that the irradiated decatungstate anion predominantly abstracted the H atom at the methine γ-position to generate the alkyl radical. The subsequent metal-hydride hydrogen atom transfer (MHAT) preferably occurred at the terminal δ-H by cobaloxime, contributing to the site selectivity of the dehydrogenation. Single-electron transfer between reduced decatungstate and oxidized cobaloxime regenerated both catalysts and released H_2. Moreover, the cocatalyst-assisted internal-to-terminal isomerization further increased the terminal selectivity.

The dehydrogenation proceeded effectively with protected α- and β-amino acid derivatives and provided moderate yields with oligopeptides, whereas attenuated yields were presented for unprotected substrates and dipeptides bearing histidine, tryptophan, and lysine residues. Erosion of enantiospecificity (es) was observed for the (L)-homoalanine and (L)-homoglutamic acid derivative. The synthetic application was further illustrated by modifying the dehydrogenated product containing established terminal olefins and fixed stereospecific amines, such as cyclization, dihydroxylation, ozonolysis, thio-ene reaction, etc., to access ncAA building blocks. Additionally, dehydrogenation followed by Kwon hydrodealkenylation of the leucine-containing tripeptide to the alanine analogue enabled the late-stage modification.

To approach the unnatural α-amino acid (UAA) subset, Chen and co-workers leveraged a cobalt-catalyzed enantioselective aza-Barbier reaction between dehydroglycine and unactivated alkyl halide (Scheme 8).[26] Initial condition

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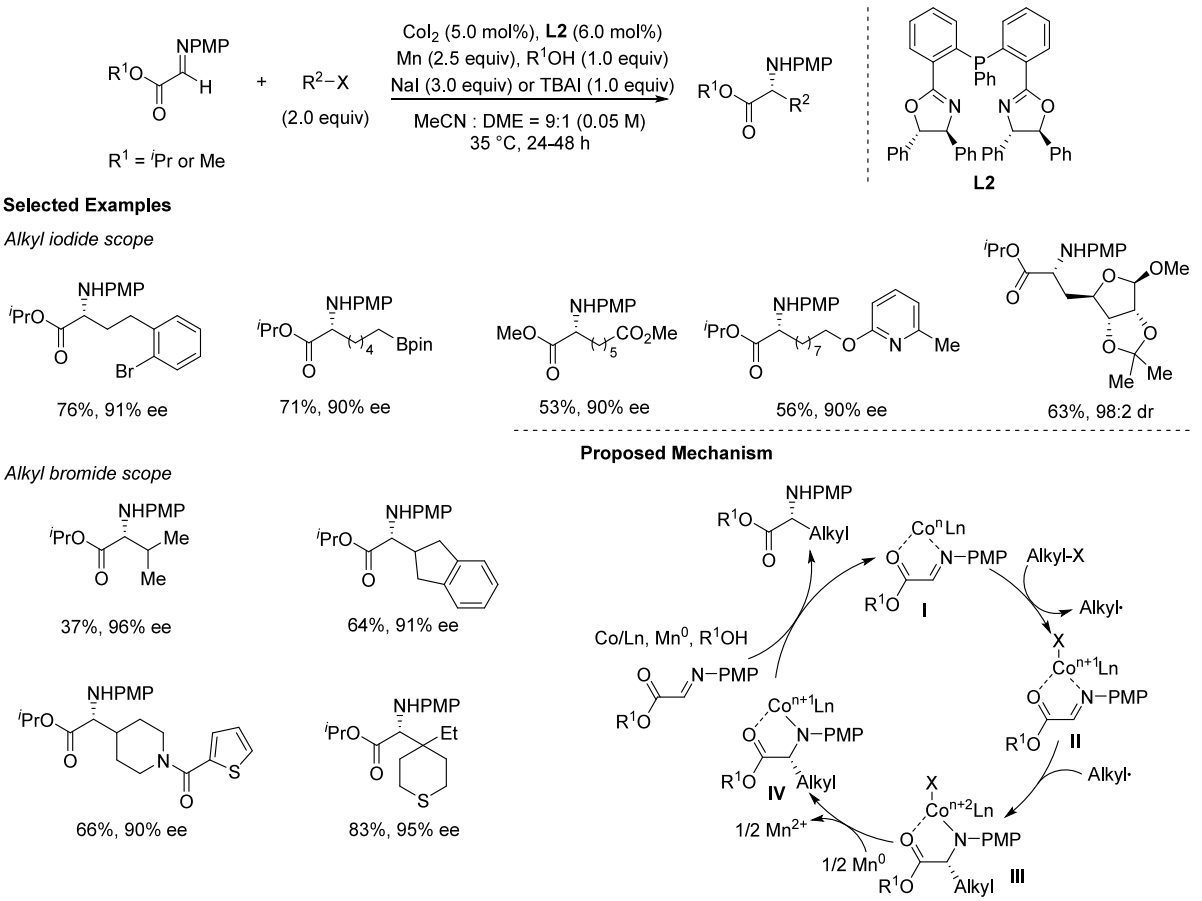
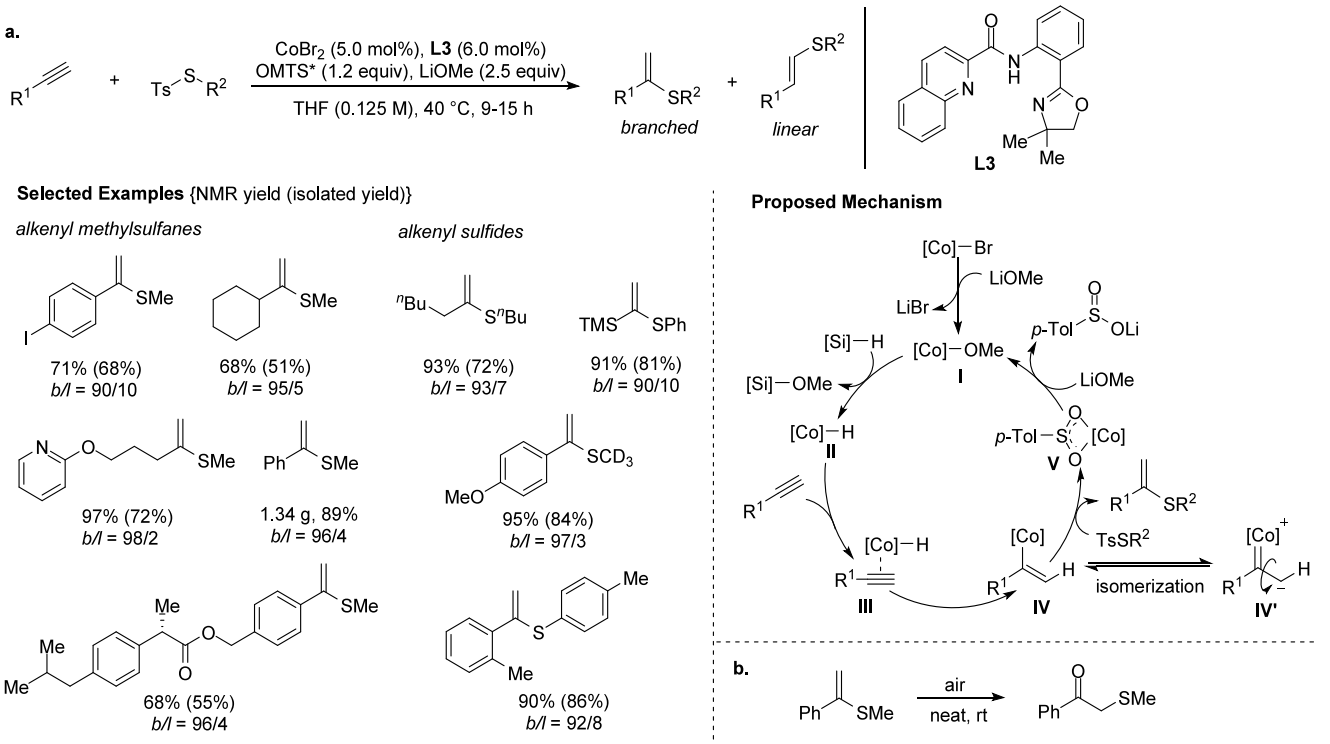
Scheme 8. Enantioselective Aza-Barbier Reaction via Cobalt Catalyst



Scheme 9. (a) Cobalt -Catalyzed Hydrothiolation of Alkynes; (b) Aerobic Oxidation of Alkenyl Sulfide



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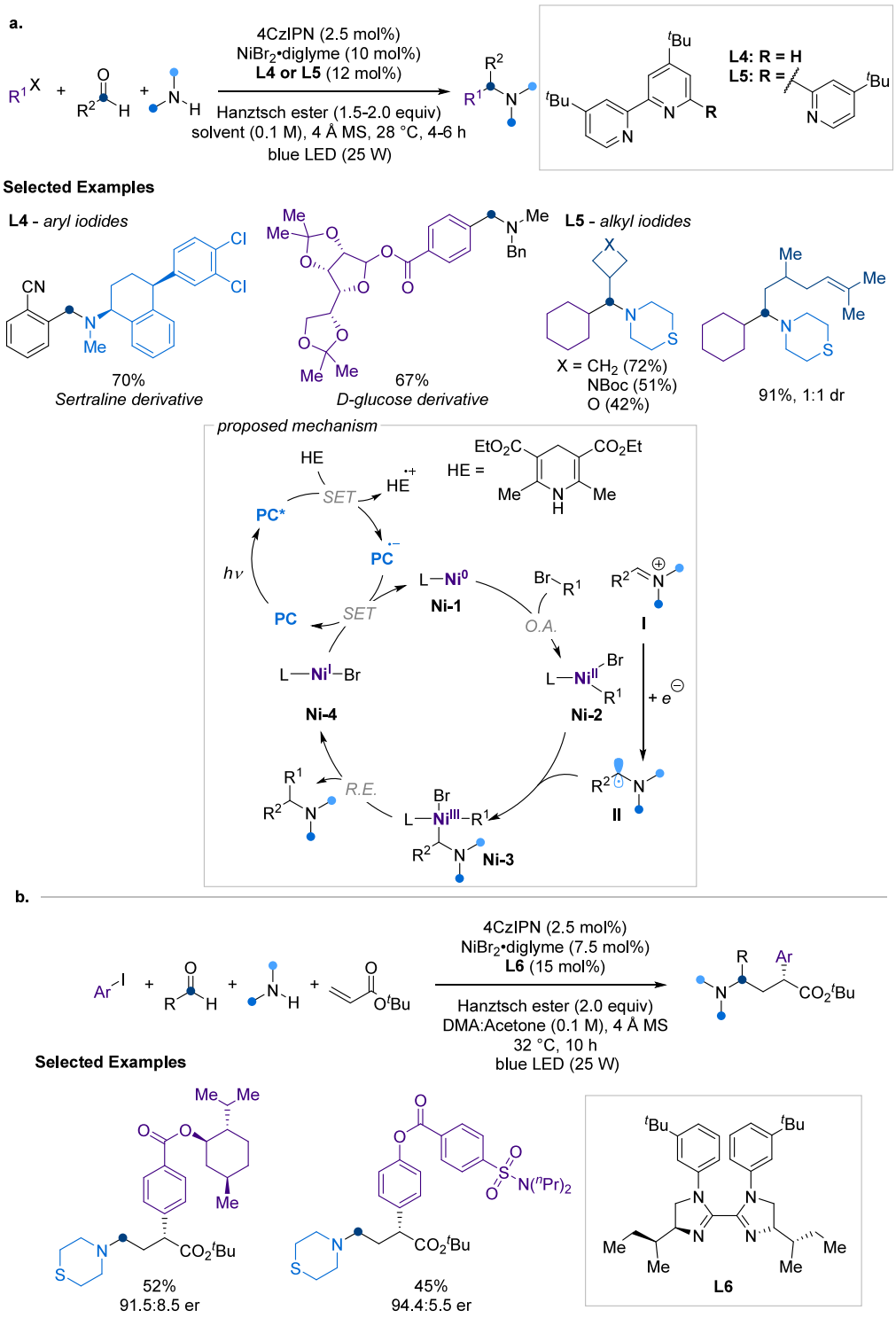
Scheme 10. (a) Nickel-Metallaphotoredox-Catalyzed, Three-Component Aminoalkylation of Aryl and Alkyl halides; (b) Asymmetric, Four-Component Cross-Coupling of Medicinally Relevant Molecules



screening found that the *trans* diphenyl substituents of bisoxazolinephosphine (NPN) ligand, NaI additive, and DME/MeCN cosolvent played a critical role in achieving high reactivity, and the primary alkyl iodide provided a higher yield than bromide despite the same enantioselectivity. Various functionalities of primary alkyl iodides, including alkene, cyanide, carbonyl group, acetal, *N*-containing heterocycle, boronic ester, and carbohydrate, were compatible with the reductive addition. Secondary and tertiary alkyl bromides also delivered amino esters in moderate yield and high stereoselectivity. However, aryl halide or triflate was not suitable for the coupling. This method could be further extended to a one-pot condensation/reductive addition from isopropyl 2-oxoacetate to prepare UAAs. Radical trapping experiments suggested that a low-valent Co(n) and dehydroglycine complex **I** reacted with an alkyl halide to form an alkyl radical and Co(n + 1) intermediate **II**. The radical was trapped in situ to acquire cobalt and amino ester

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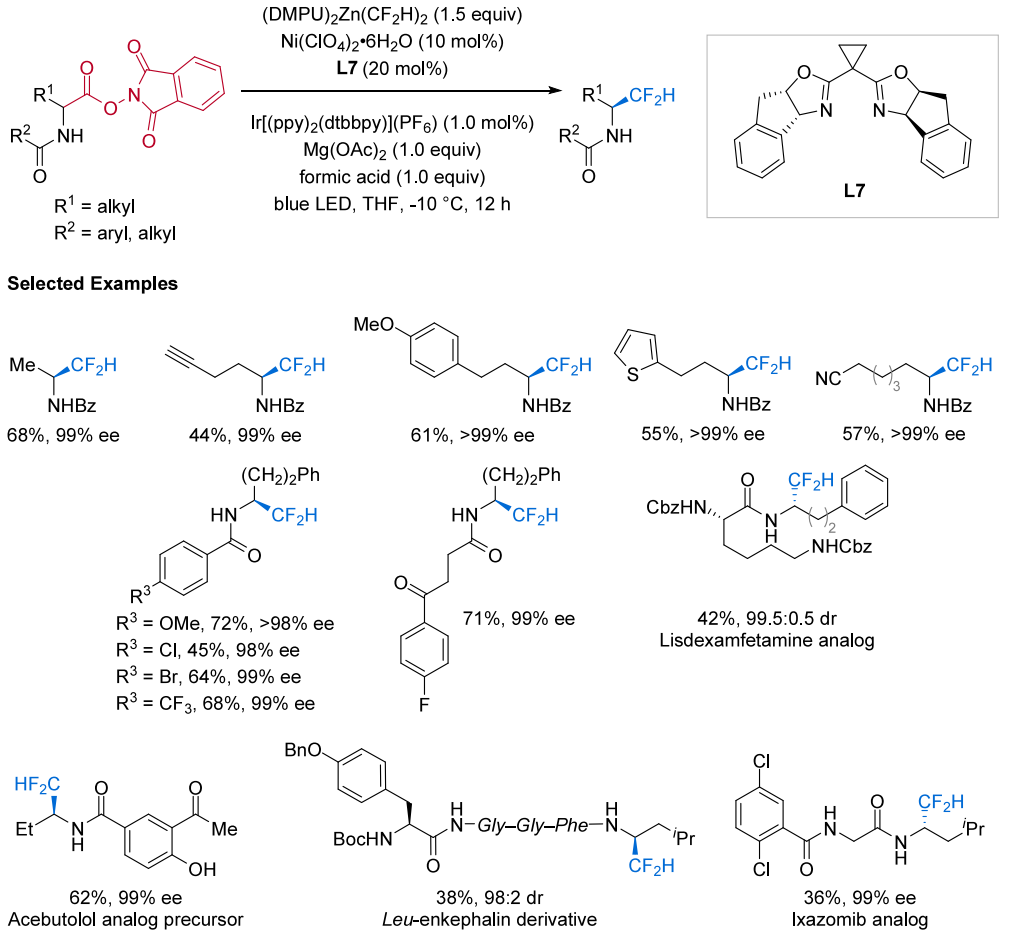
Scheme 11. Nickel/Photoredox-Catalyzed Enantioselective Decarboxylative Difluoromethylation



complex **III** asymmetrically, which was reduced to the Co(n + 1) complex **IV** by Mn powder. The following reduction, protonation, and ligand exchange delivered α-amino ester with the regeneration of intermediate **I**.

Sulfur-containing compounds play important roles in drug discovery and material science. Methodologies for the synthesis of branched alkenyl sulfides and hydromethylthiolation of alkynes are limited in the literature.[20] Lu and coworkers exploited a cobalt-catalyzed Markovnikov hydrothiolation of alkynes to form branched alkenyl sulfides (Scheme 9a).[27] Aryl and aliphatic alkynes bearing various functional groups delivered alkenyl methylsulfanes in 46−83% yield with up to >99/1 regioselectivity. Diverse sulfurizing reagents such as deuterated methyl, cyclopropylmethyl, benzyl, and phenyl derivatives were well-adapted in the conditions, affording the branched alkenyl sulfides in decent yields. A gram-scale synthesis of methyl(1-phenylvinyl)sulfane was demonstrated, whereby the alkenyl sulfide was air sensitive and could be oxidized to the ketone (Scheme 9b), hypothetically through a radical process with oxygen. Experiments were conducted to investigate the mechanism of regioselective hydrothiolation. It is suggested that cobalt bromide reacted with lithium methoxide and silane to generate cobalt hydride intermediate **II**. After coordination with the terminal alkyne, the subsequent cobalt hydride insertion mainly led to α-selective alkenyl cobalt intermediate **IV**, which equilibrated with cobalt carbene zwitterion **IV'** through isomerization. The branched alkenyl sulfide was furnished between the alkenyl cobalt intermediate **IV** and the sulfurizing reagent, and the simultaneous liberation of cobalt p-toluenesulfinate **V** delivered cobalt methoxide **I** to close the catalytic cycle.

RECENT REPORTS ON NI-CATALYZED REACTIONS

Nickel, a group 10 transition metal, is often at the forefront of NPMC by virtue of its similar properties with respect to palladium while participating in new, untapped reactivity.[28] Indeed, many efforts have shown the use of nickel catalysts in typical palladium cross-coupling reactions, as evidenced by its efficiency in the Kumada−Corriu, Suzuki−Miyaura, and Negishi reactions[29,30] along with the Mizoroki−Heck[31] and Buchwald−Hartwig[32] reactions. While nickel participates in the typical 2-electron processes expected of palladium catalysis, new reactivity has also been explored because nickel species can traverse through several oxidation states through a 1-electron process. With an increased stability of Ni−alkyl bonds against β-hydride elimination[33,34] compared to their palladium congeners, nickel has also been at the forefront of $C(sp^3)-C(sp^2)$ and $C(sp^3)-C(sp^3)$ cross-couplings and has been coupled with photoredox catalysis to achieve reactivity with new coupling partners. As such, this inexpensive metal is indeed one of the most useful and exciting first-row transition metals for its chemical properties and earth-abundance.

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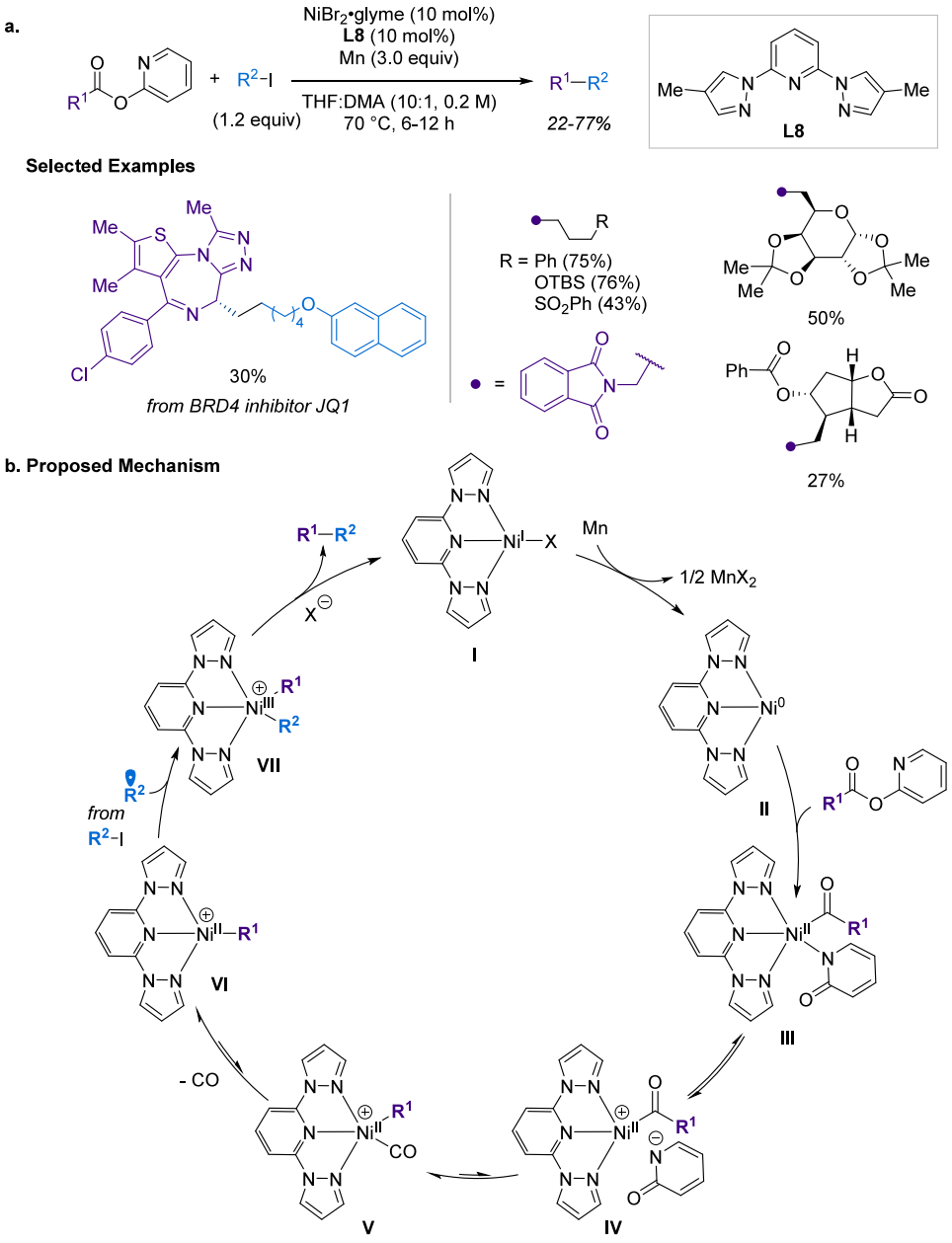
Scheme 12. (a) Nickel-Catalyzed, Reductive C(sp^3)−C(sp^3) Cross-Coupling between 2-Pyridyl Esters and Alkyl Iodides; (b) The Proposed Mechanism Demonstrates a 2-Electron Process to Generate Ni-Alkyl Species



The merger of nickel and photoredox catalysis has led to advances in C(sp^3)−C(sp^2), C−X, and the coveted C(sp^3)−C(sp^3) coupling with a wide variety of partners that are typically inert in thermal cross-coupling (carboxylic acids, alcohols, amines, etc.).[35−37] As such, exciting frontiers in nickel metallaphotoredox research involve rendering these transformations asymmetric or discovering new, multicomponent reactions, with focus on the tolerance toward a wide range of pharmaceutical-like scaffolds for practical use. Yang et al. recently described a multicomponent aminoalkylation of organohalides through nickel metallaphotoredox chemistry.[38] The generated iminium **I** between a secondary alkylamine and an aldehyde is proposed to be reduced (either by Hantzch ester (HE) or by photocatalyst) to the corresponding α-amino radical **II**. Upon oxidative addition of the organohalide into Ni(II)-bipyridyl species **Ni-1** to yield complex **Ni-2**, radical trapping of **II** generates the Ni^{III} species (**Ni-3**), bringing all of the components together and furnishing the desired product upon reductive elimination. Overall, this process is a reductive process; thus, turning over the catalytic cycles requires a Hantzsch ester as the terminal reductant (Scheme 10a). Synthetically useful yields using aryl and alkyl iodides were obtained (32−93% yield) with no observed decrease in efficiency at 1 mmol scale, and great functional group tolerance including trifluoromethyl groups, sulfones, alkenes, etc., was observed. Importantly, bioactive molecules were successfully prepared, such as derivatives of sertraline and D-glucose (Scheme 10a). The use of a terpyridyl ligand expanded the scope to alkyl iodides, which the authors proposed is due to an increased rate of oxidative addition (Scheme 10b). Finally, a four-component reaction with a Michael acceptor was explored with synthetically

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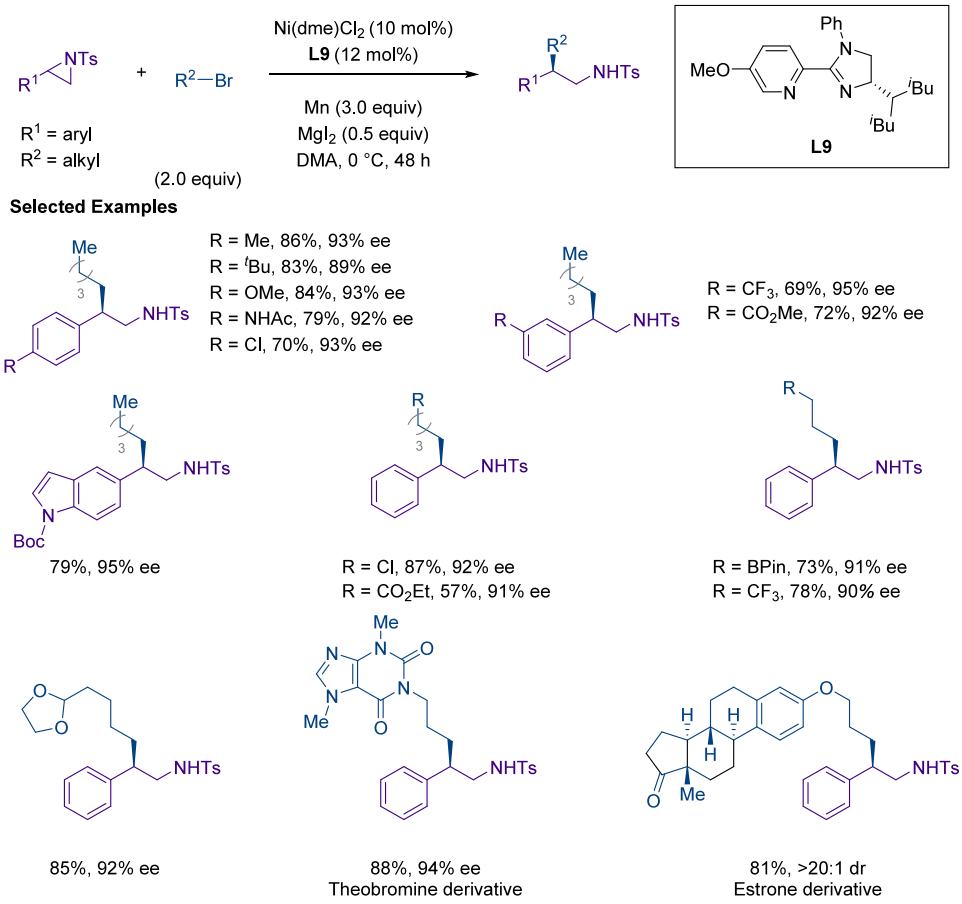
Scheme 13. Cross-Electrophile-Coupling of *N*-Sulfonyl Styrenyl Aziridines and Alkyl Bromides via Nickel Catalysis



useful yields (42−61% yield) and high enantioselectivity (>89:11 er) with a bis-imidazole (BiIM) chiral ligand, tolerating various functional groups and medicinally interesting moieties such as that of a menthol derivative (Scheme 10c). Indeed, the ability to synthesize and modulate complex molecules with simple building blocks in an enantioselective manner renders this method highly enabling and exciting to synthetic organic chemists.

Zhao et al. developed a highly enantioselective decarboxylative difluoromethylation (Scheme 11).[39] *N*-hydroxyphthalimide esters, readily derived from racemic carboxylic acids, were reacted with a nucleophilic difluoromethyl source, $(DMPU)_2Zn(CF_2H)_2$,[40−42] under dual nickel/photoredox catalytic conditions. Interestingly, initial attempts for this transformation utilizing copper catalysts resulted in a moderate yield but poor enantioselectivity. However, when $Ni(ClO_4)_2{\cdot}6H_2O$ and chiral cyclopropyl-containing bisoxazoline (BOX) ligand were employed, high enantioselectivity was achieved. Thorough optimization of the reaction conditions revealed that the addition of $Mg(OAc)_2$ and formic acid led to increased reaction yields, presumably by facilitating transmetalation between the Zn reagent and Ni catalyst. Although the use of 1 mol % $Ir(ppy)_2(dtbbpy)(PF_6)$ resulted in an optimal yield and enantioselectivity, this transformation is possible with an inexpensive organic dye, 4CzIPN (1 mol %), which is more amenable for scale-up. The authors investigated this transformation on over 50 substrates with varying alkyl and amide substituents, highlighting broad functional group tolerance and synthetically useful yields. However, a limitation of this reaction was its sensitivity to bulky substituents at the R^1 position. Notably, the methodology was applied to multiple bioactive compounds including acebutolol and pentapeptide *Leu*-enkephalin. Given that the introduction of fluorine atoms to drug candidates can modulate pharmacological properties, this metallaphotoredox-catalyzed synthetic method will be a useful addition to drug discovery campaigns.

The thermal counterpart to $C(sp^3)−C(sp^3)$ coupling lies in the powerful involvement of nickel in reductive cross-electrophile-coupling, using stoichiometric reductants such as Zn or Mn to reach low-valent Ni species for productive catalysis.[43] Weix and co-workers demonstrated the decarbonylation of an alkyl 2-pyridyl ester (from its respective carboxylic acid) and 1.2 equiv of an alkyl iodide (Scheme 12).[44] The small excess of the coupling partner contrasts with radical−radical coupling methods, which typically require a high excess of one reactant over the other (>2.5 equiv). The authors point out that this method does not proceed through a dual-radical process; instead, the oxidative addition of Ni(0) species **II** into the 2-pyridyl ester generates a Ni-acyl species **III** that decarbonylates to generate the desired Ni-alkyl species **VI**. Expectedly, carbon monoxide must dissociate to prevent catalyst poisoning, which the authors mitigated through the ligand design. By using the tridentate 2,6-bis(pyrazol-1-yl)pyridine ligand (**L8**), the authors hypothesized that the redox activity of the ligand allows for faster associative substitution and release of CO, preventing catalyst death. Upon radical trapping (by the reduction of the

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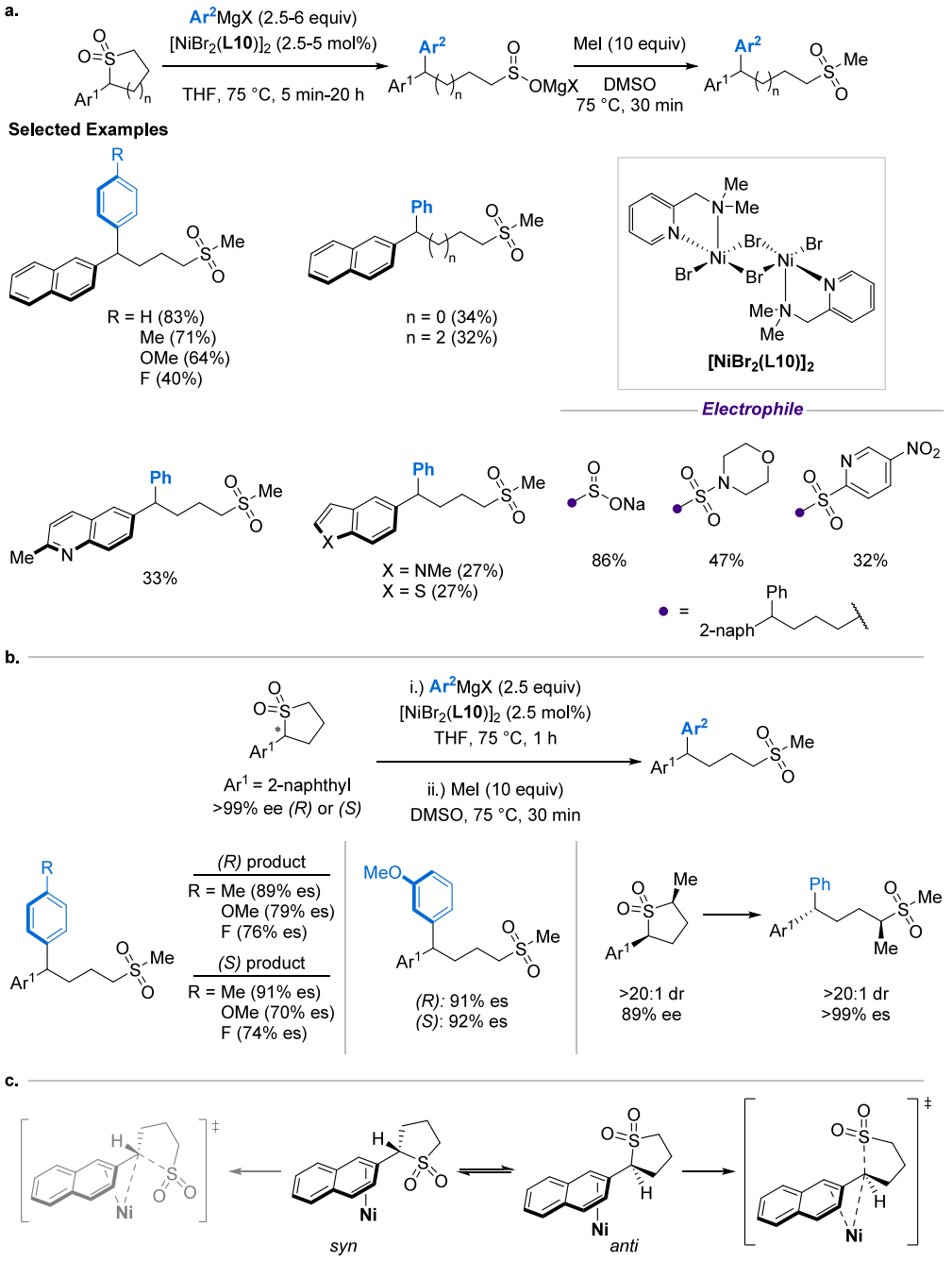
Scheme 14. (a) Nickel-Catalyzed, Enantiospecific, C(sp^3)−SO_2 Activation and Cross-Coupling with Grignards; (b) High Recovery of Enantiomeric Excess with Net Stereoinversion; (c) Proposed Mechanism to Enantiospecificity



alkyl iodide) of **VII** and reductive elimination, the desired product is extruded in synthetically useful yields (27−77% yield). A wide variety of functional groups were compatible (protected alcohols, sulfones, etc.) with this method, and the authors explored bioactive moieties such as sugars (α-D-galactose) and those of interest to pharmaceutical chemists such as the Corey lactone. Finally, complex carboxylic acids, such as that of BRD4 inhibitor JQ1, were explored with synthetically useful yields, indicating that this method can be used for the elaboration of complex molecules. As one of the main challenges in dual-radical cross-coupling is the need for a large excess of coupling partners, this is an excellent step toward the practical use of C(sp^3)−C(sp^3) coupling in synthesis. With new discoveries in ligand properties, preventing deleterious pathways such as CO poisoning improves the already wide scope of reactions in which nickel participates.

An enantioselective nickel-catalyzed C(sp^3)−C(sp^3) cross-electrophile-coupling was reported by Lan et al. (Scheme 13).[45] The alkylative aziridine ring-opening utilized a new chiral pyridine-imidazoline ligand featuring bulky isobutyl arms to establish high enantiocontrol. The authors showcased their methodology with various racemic *N*-sulfonyl styrenyl aziridines and primary alkyl bromides. A wide array of substituents on the aromatic ring of the *N*-sulfonyl aziridines was tolerated, including electron-donating and -withdrawing groups. Investigation of the alkyl bromide scope revealed that this method was limited to primary alkyl bromides. Notably,

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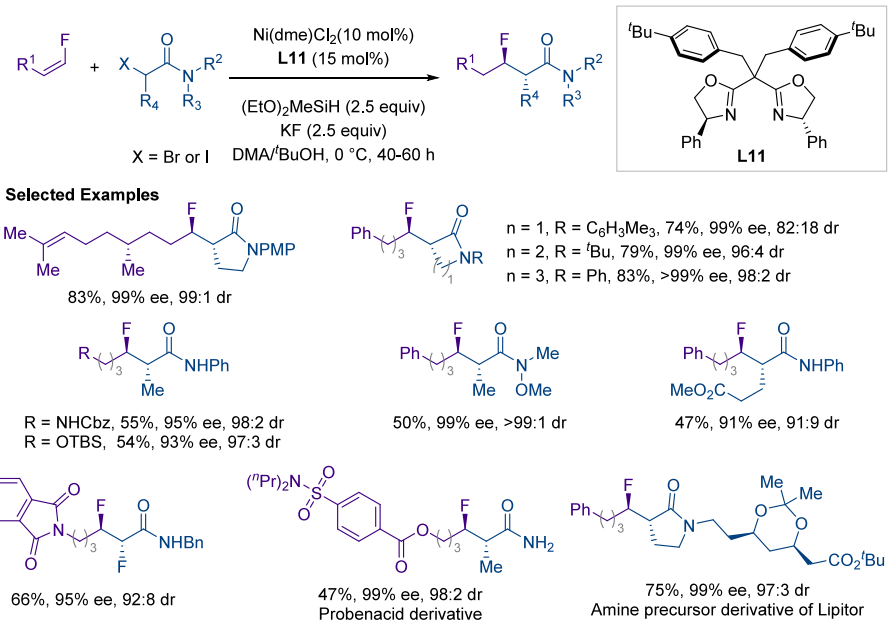
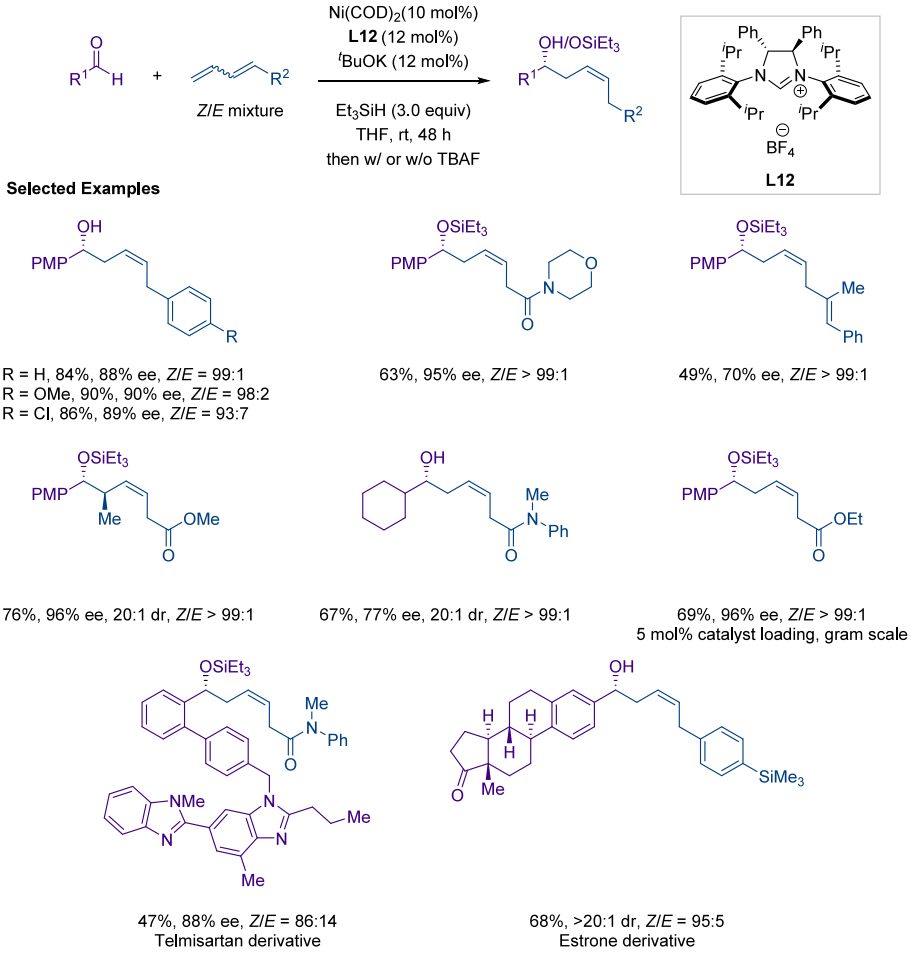
Scheme 15. Stereoselective Synthesis of Fluorine-Containing Vicinal Chiral Centers via Nickel-Catalyzed Hydroalkylation



Scheme 16. Nickel-Catalyzed Reductive Coupling of Aldehydes and 1,3-Dienes for the Stereoconvergent and Enantioselective Synthesis of *Z*-Homoallylic Alcohols



alkyl bromides derived from theobromine and estrone were asymmetrically converted to their cross-coupling products. To further showcase the synthetic utility of their methodology, derivatizations of cross-coupling products involving sulfonamide or phenyl transformations were investigated. Preliminary mechanistic studies support the proposed mechanism, which

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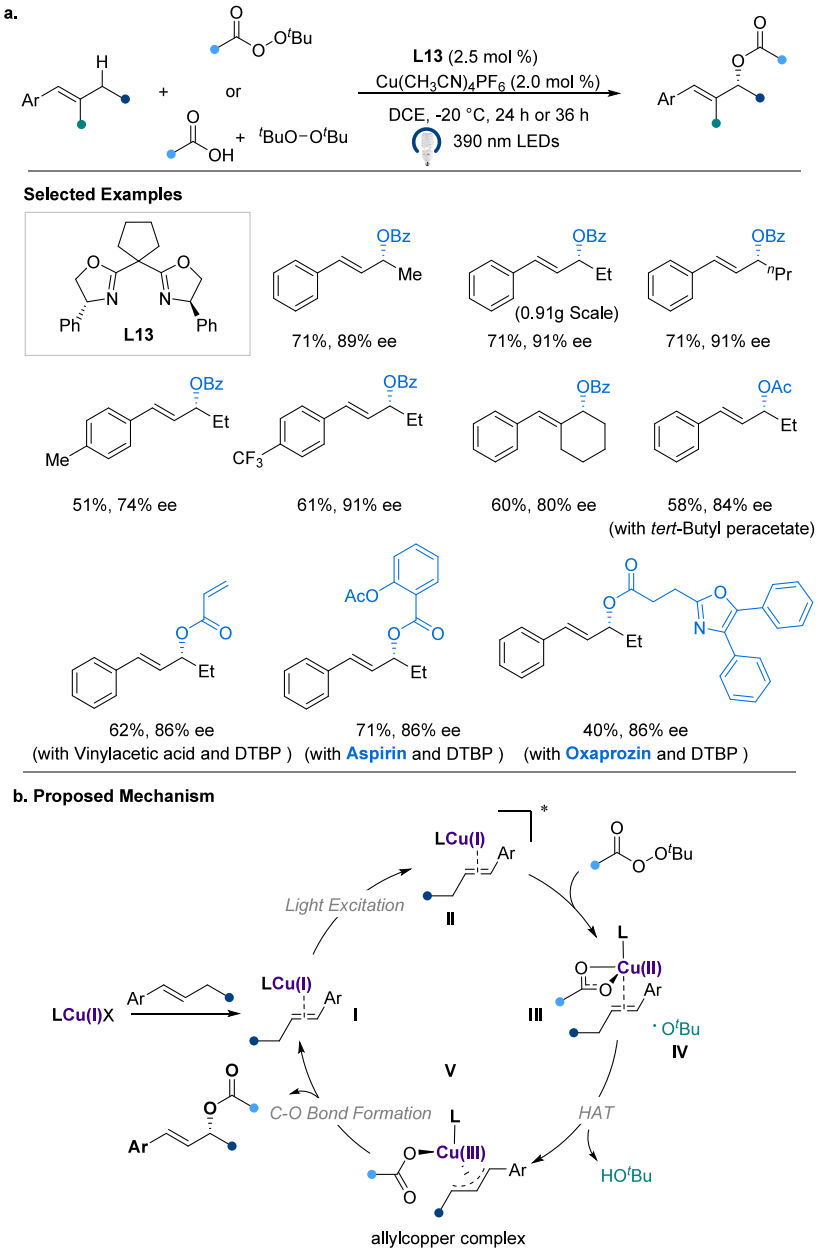
Scheme 17. Photoexcited Copper-Catalyzed Enantioselective Allylic C(sp^3)−H Acyloxylation of Acyclic Internal Alkenes



entails regioselective iodolysis of *N*-sulfonyl styrenyl aziridines followed by nickel-catalyzed enantioconvergent cross-electrophile-coupling between the benzyl iodides formed in situ and alkyl bromides.

The use of cross-coupling is indeed an enduring strategy in synthetic organic chemistry; as such, employing previously unstudied electrophiles in cross-coupling allows for new opportunities in creative synthetic design and greatly impacts the current synthetic toolbox. Sulfones have been newly exploited as electrophiles with great stability, but they can be activated and engage in cross-coupling with various coupling partners such as boronic esters/acids and zincates using typical metal catalysts. Nolla-Saltiel et al. employed nickel catalysis to undergo an enantiospecific cross-coupling of cyclic alkyl sulfones with Grignards. This resulted in an enantio-enriched, acylic sulfone or sulfonamide upon trapping with an electrophile (Scheme 14).[46] Therein, they employed a precomplexed $[NiBr_2(\mathbf{L10})]_2$ catalyst (which can also be generated in situ) to yield the products in useful yields (16−75% yield) with a wide range of Grignard reagents and sulfones that include heterocycles. Throughout the reaction, the sulfinate was retained and trapped with a myriad of partners to yield sodium sulfinate salts (conducted on a gram scale), sulfonamides, sulfones, etc., in decent yields (32−86% yield). One of the key findings in this work is the *net inversion* upon using an enantioenriched substrate with high retention of enantiomeric excess (calculated as % es), which was probed computationally. Therein, it was observed that the transition state upon C(sp^3)−SO_2 activation favored the *anti*-conformer, generating the necessary π-benzyl to generate the inverted product (Scheme 14). The ability to activate new electrophiles with control of stereochemistry is indeed a boon to the synthetic community, and in this case functional

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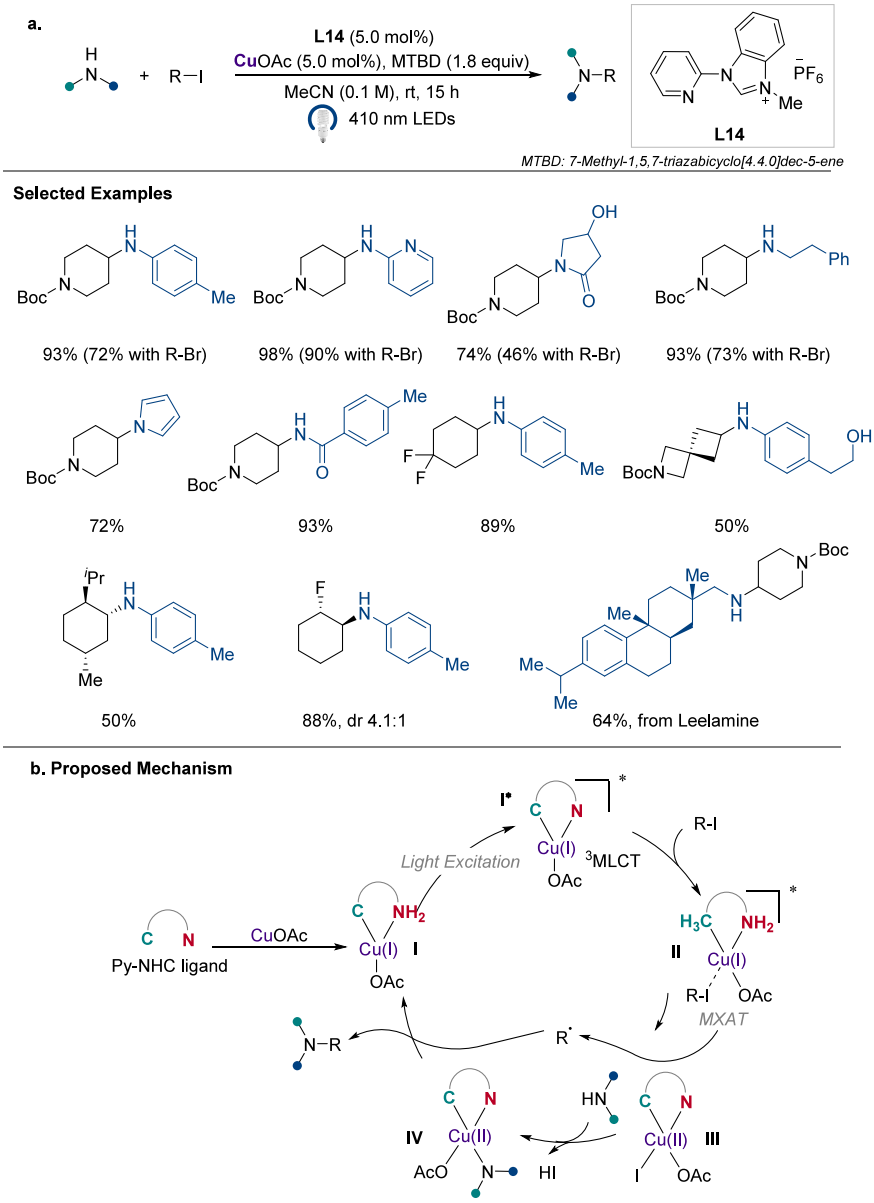
Scheme 18. Photoexcited Copper-Catalyzed C(sp^3)−N Coupling with Unactivated Alkyl Halides



groups of interest such as sulfones and sulfonamides are retained, bringing great relevance to pharmaceutical chemists.

Dhawa et al. published the enantioselective and diastereoselective hydroalkylation of fluoroalkenes with α-haloamides (Scheme 15).[47] This nickel-hydride-catalyzed method established two adjacent chiral centers without the use of directing groups. The *tert*-butyl groups on the ligand backbone were required for high enantioselectivity; however, the lower temperature and cosolvent system were crucial for improving diastereoselectivity. This method tolerated a variety of lactams as well as acyclic amides. Furthermore, this method was extended to the stereoselective synthesis of vicinal difluorides. Various substituents on the fluoroalkene were tolerated as well as on the bromofluoroamide. The synthetic applicability of this methodology was exemplified by the derivatization of probenacid and Lipitor amine precursor. Indeed, the stereoselective construction of vicinal fluorine-containing chiral centers will be a valuable addition to the repertoire of existing asymmetric methods to synthesize bioactive organofluorine molecules.

Zhang et al. developed a nickel-catalyzed method to enantioselectively synthesize *Z*-homoallylic alcohols from *Z*/*E*-1,3-dienes and aldehydes (Scheme 16).[48] Mixtures of *Z*/*E*-olefins were readily converted to *Z*-homoallylic alcohols with high stereocontrol enabled by a *N*-heterocyclic carbene ligand with a C_2-symmetric backbone and bulky isopropyl substituents. Notably, reactions proceeded with excellent *Z*-selectivity independent of the *Z*/*E* ratio of the 1,3-diene starting material used. This stereoconvergent reductive coupling was demonstrated for over 40 examples. A wide range of substituents on the 1,3-diene and aldehyde were well tolerated, resulting in yields up to 91%, greater than 99:1 *Z*/*E*, and up to 97% ee. To highlight the synthetic applicability of their protocol, a gram-scale synthesis, using half their normal catalyst loading, was executed, maintaining a synthetically useful yield (69%) and stereoselectivity (96% ee, *Z*/*E* > 99:1). Moreover, the method was applied to various

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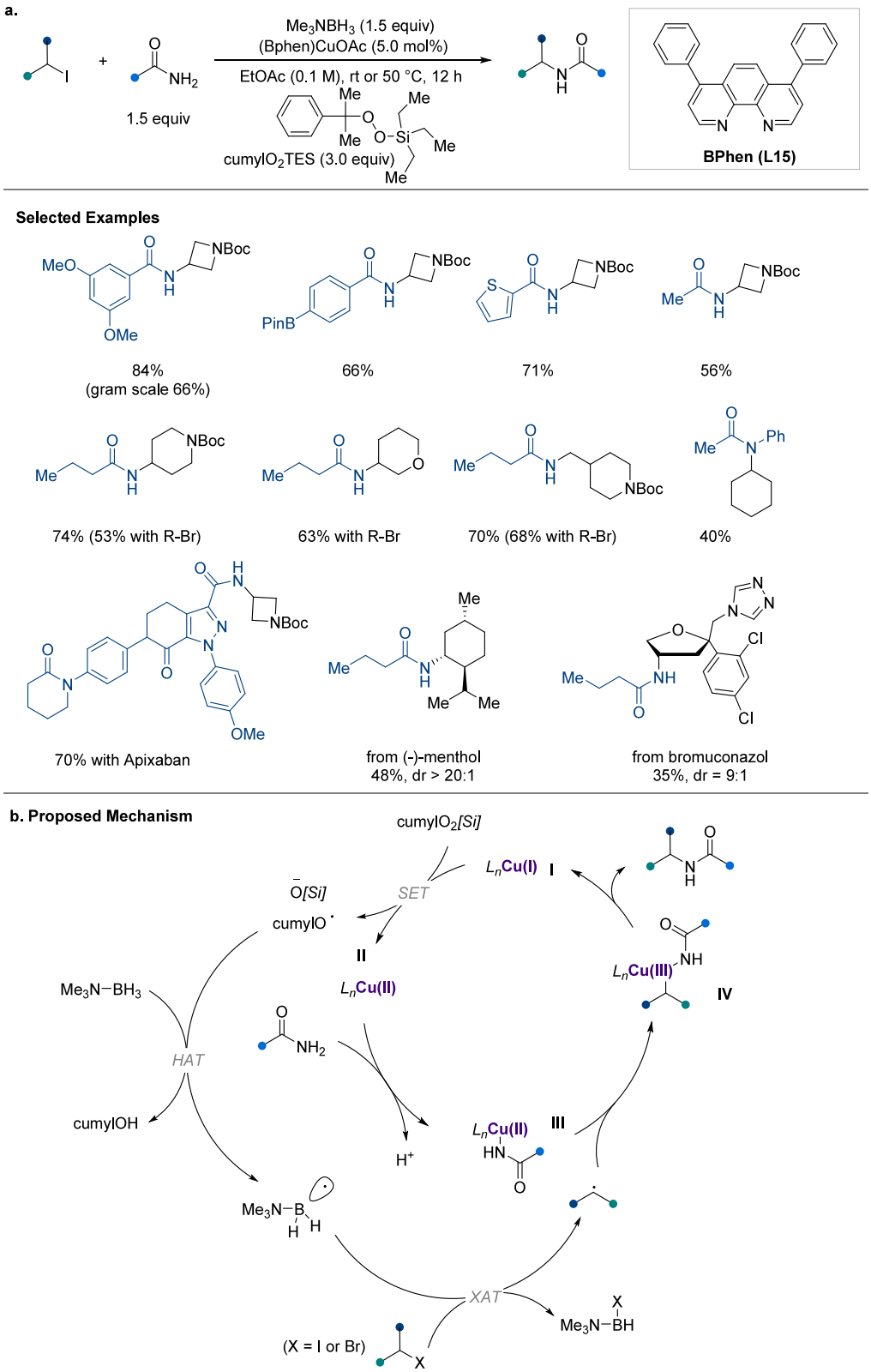
Scheme 19. Copper-Catalyzed Amide Alkylation with Alkyl Halides



biologically relevant compounds, including telmisartan and estrone.

RECENT REPORTS ON CU-CATALYZED REACTIONS

Copper is a multifaceted transition metal that has been used by mankind since ancient times. The diversity of copper chemistry stems from its (a) variable and interchangeable

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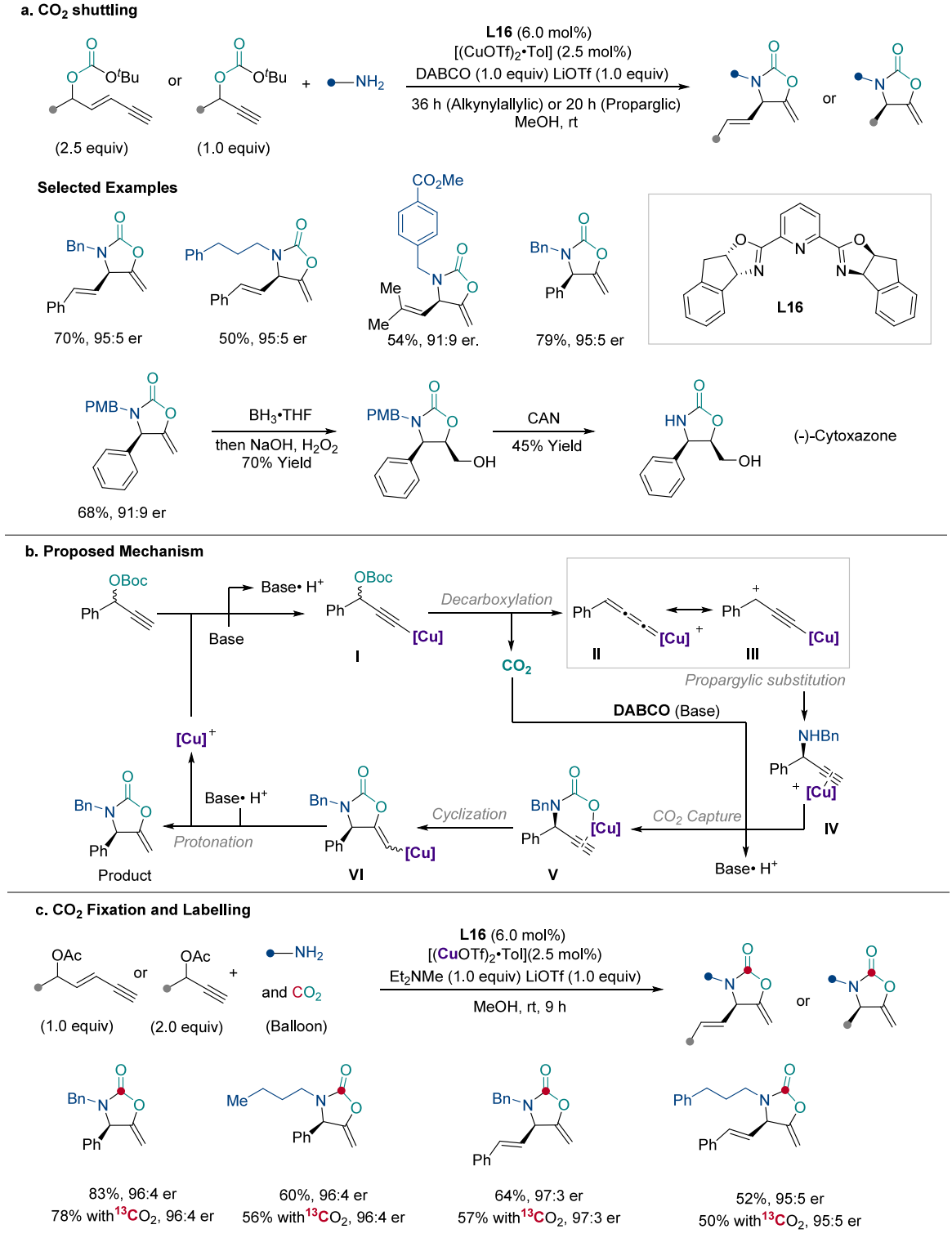
Scheme 20. Copper Catalyzed Asymmetric Multicomponent Propargylations via Carbon Dioxide Shuttling and Fixation



oxidation states, (b) ability to coordinate with heteroatoms, and (c) capacity to activate terminal alkynes.[49] These distinctive properties of copper have been leveraged in a variety of renowned name reactions, such as the Ullmann coupling, Ullmann diaryl ether formation,[50] Cadiot−Chodkiewicz reaction,[51] and Chan−Lam reaction,[52−54] among others. The formation of C−C and C−N bonds serves as the backbone of these reactions, while other modes of bond formation, such as C−O and C−S, have also been explored extensively. A wide array of contemporary copper-catalyzed reactions, including their asymmetric variants, has become invaluable methodologies for organic synthesis.

The Kharasch−Sosnovsky reaction is a cornerstone of Cu-catalyzed C(sp^3)−H functionalization, traditionally used for oxidizing allylic C−H bonds to produce allylic esters. Its asymmetric version using cyclic olefins has been reported with high yields and good enantioselectivity.[55] Yet, previous reports with acyclic olefins has only led to moderate

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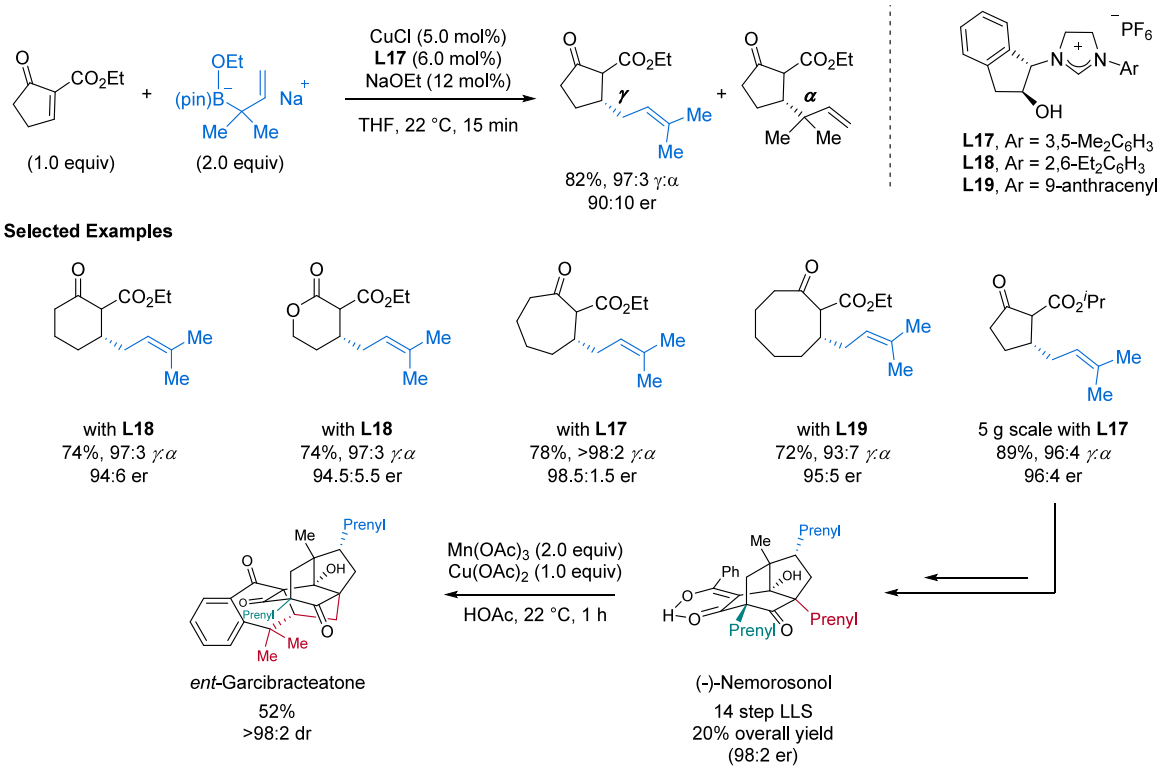
Scheme 21. Cu-Catalyzed Enantioselective Prenyl Conjugate Addition and Application to Enantioselective Total Synthesis of Nemorosonol and Garcibracteatone



enantioselectivity.[56] Tang et al. recently made progress in this area by introducing a photoexcited copper-catalyzed asymmetric Kharasch−Sosnovsky reaction for acyclic olefins, achieving of up to 82% yields, greater than 95:5 rr, and up to 95% ee.[57] The method was scaled up to the gram scale and showed tolerance to trisubstituted alkenes. Furthermore, a diverse array of carboxylic acids, including bioactive carboxylic acids aspirin and oxaprozin, were successfully employed as coupling partners, with di-*tert*-butyl peroxide (DTBP) serving as the external oxidant (Scheme 17a). After extensive mechanism studies, a mechanism was proposed, as shown in Scheme 17b, which begins with the LCu(I)X complex binding to the alkene to form the active Cu(I)−alkene catalyst complex (**I**). Photoexcitation elevates complex **I** to its excited state (**II**), which then undergoes single-electron oxidation by the perester, generating the LCu(II) species (**III**) and the *tert*-butoxy radical (**IV**). The *tert*-butoxy radical (**IV**) initiates a HAT process with complex **III**, leading to the π-allyl Cu(III) intermediate (**V**). This intermediate then undergoes enantioselective reductive elimination to yield the allylic ester, simultaneously regenerating the LCu(I) complex (**I**) for the next catalytic cycle.

Nitrogen-containing compounds are essential in natural products, pharmaceuticals, and agrochemicals.[58] The C−N coupling reaction is a key method for synthesizing nitrogen-rich compounds. On the other hand, to create C(sp^3)−N bonds, nucleophilic substitution reactions (S_N1 or S_N2) are identified as direct and efficient methods, yet electrophiles are mainly limited to activated alkyl halides and related derivatives.

Luo et al. recently developed a pyridylcarbene-ligated copper(I) catalyst that can abstract a halide atom and generate alkyl radicals for general C(sp^3)−N couplings under visible light (Scheme 18).[59] This approach accommodates a broad spectrum of *N*-nucleophiles, achieving moderate to high yields. However, secondary amines were ineffective. Furthermore, amides were effectively transformed into C(sp3)−N coupled products. Substrates with vicinal fluoro- or bulky isopropyl groups preferentially undergo amination on the less hindered side. Couplings with alkyl bromides typically show lower yields compared with their alkyl iodide counterparts. The methodology also provides synthetically valuable coupling yields for complex alkyl iodides or *N*-nucleophiles (Scheme 18a). Following a series of mechanistic studies, a proposed mechanism (Scheme 18b) involves the in situ formation of the [CuI(Py-NHC)OAc] complex **I**, which upon excitation by 410 nm LEDs transitions to the ^{3} metal-to-ligand charge transfer excited state, complex **I***. This excited complex **I*** forms an exciplex **II** with an alkyl iodide, leading to a halide atom transfer through an inner-sphere single-electron transfer (SET) to result in an alkyl radical and Cu(II) complex **III**. The Cu(II) complex (**III**) then undergoes ligand exchange to yield the Cu(II)-amido complex (**IV**). Finally, complex **IV** engages in radical coupling with the alkyl radical to produce the final product and concurrently regenerate complex **I**.

Shortly after Luo et al.'s work, Leonori and co-workers reported a copper-catalyzed alkylation of amides with alkyl halides featuring a boryl radical-mediated halogen-atom transfer mechanism.[60] A broad range of alkyl halides and amides could be employed, delivering the desired products in moderate to good yields. The *N*-alkylation of several bioactive molecules, such as Apixaban and Bromuconazol, were also demonstrated (Scheme 19a). In the proposed mechanism, a [Cu(I)/(II)/(III)] catalytic cycle is designed to

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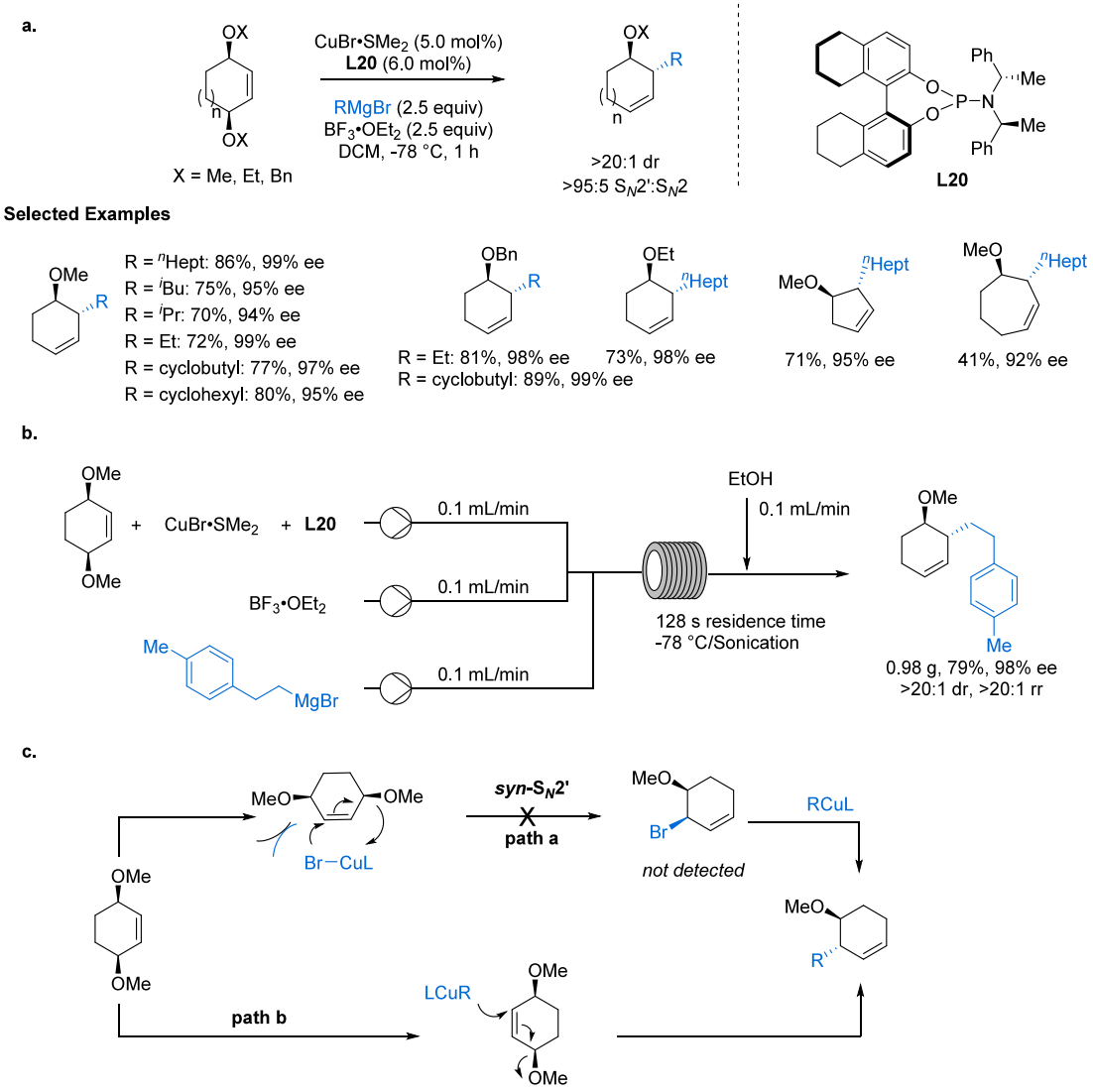
Scheme 22. (a) Cu-Catalyzed Desymmetrization of *meso*-Diethers; (b) Gram-Scale Continuous Flow Application; (c) Plausible Reaction Pathway



consecutively generate the boryl radical. Upon formation of the boryl radical, halogen atom transfer (XAT) with both alkyl iodides and bromides is expected to proceed readily. Subsequently, the alkyl radical is anticipated to intercept the [Cu(II)]−amide complex **III**, forming an alkyl, amide−[Cu(III)] intermediate **IV**. This species should then undergo a smooth reductive elimination to yield the product while simultaneously regenerating catalytically active [Cu(I)] **I** (Scheme 19b).

He and co-workers recently unveiled a copper-catalyzed, asymmetric propargylic substitution reaction utilizing chiral PyBox-type ligands.[61] As illustrated in Scheme 20a, interestingly, employing OBoc as the leaving group enables the CO_2 gas released from the carbonate leaving group to be recaptured and reused in the formation of the oxazolidinone product. The reaction accommodates alkynes and conjugated enynes bearing a *tert*-butyl carbonate leaving group (-OBoc) and various aryl substitutions, achieving moderate to high yields and exhibiting good enantioselectivity. This CO_2 recapture strategy has been adeptly applied to the total synthesis of (−)-cytoxazone, which is a potent cytokine modulator. A plausible mechanism was proposed after a series of kinetic studies (Scheme 20b), beginning with the Cu catalyst, which reacts with the terminal alkyne in the presence of a base to form intermediate **I**. Subsequently, the electrophilic Cu-allenylidene species (**II**) is formed through the cleavage of the carbonate group, coinciding with the release of CO_2 gas. The enantioselective propargylic substitution with a primary amine then yields **IV**, which captures the released CO_2 to form **V**. Species **VI** arises from the intramolecular cyclization of **V**, and the catalytic circle concludes with the protonation of **VI**, delivering the final product and regenerating the Cu catalyst. Additionally, when using an acetoxy leaving group, the methodology allows for the smooth incorporation of external CO_2 and $^{13}CO_2$ into an enantioenriched product, showcasing its potential in isotopic labeling (Scheme 20c).

Polycyclic polyprenylated acylphloroglucinols (PPAPs) are an important class of natural products. PPAPs exhibit a broad spectrum of biological activity such as antimicrobial, anti-inflammatory, antiobesity, antidepressant, and anticancer.[62] They contain several prenyl groups; thus, a method for the catalytic enantioselective addition of the prenyl group would allow direct access to enantiomerically enriched PPAPs. Ng et

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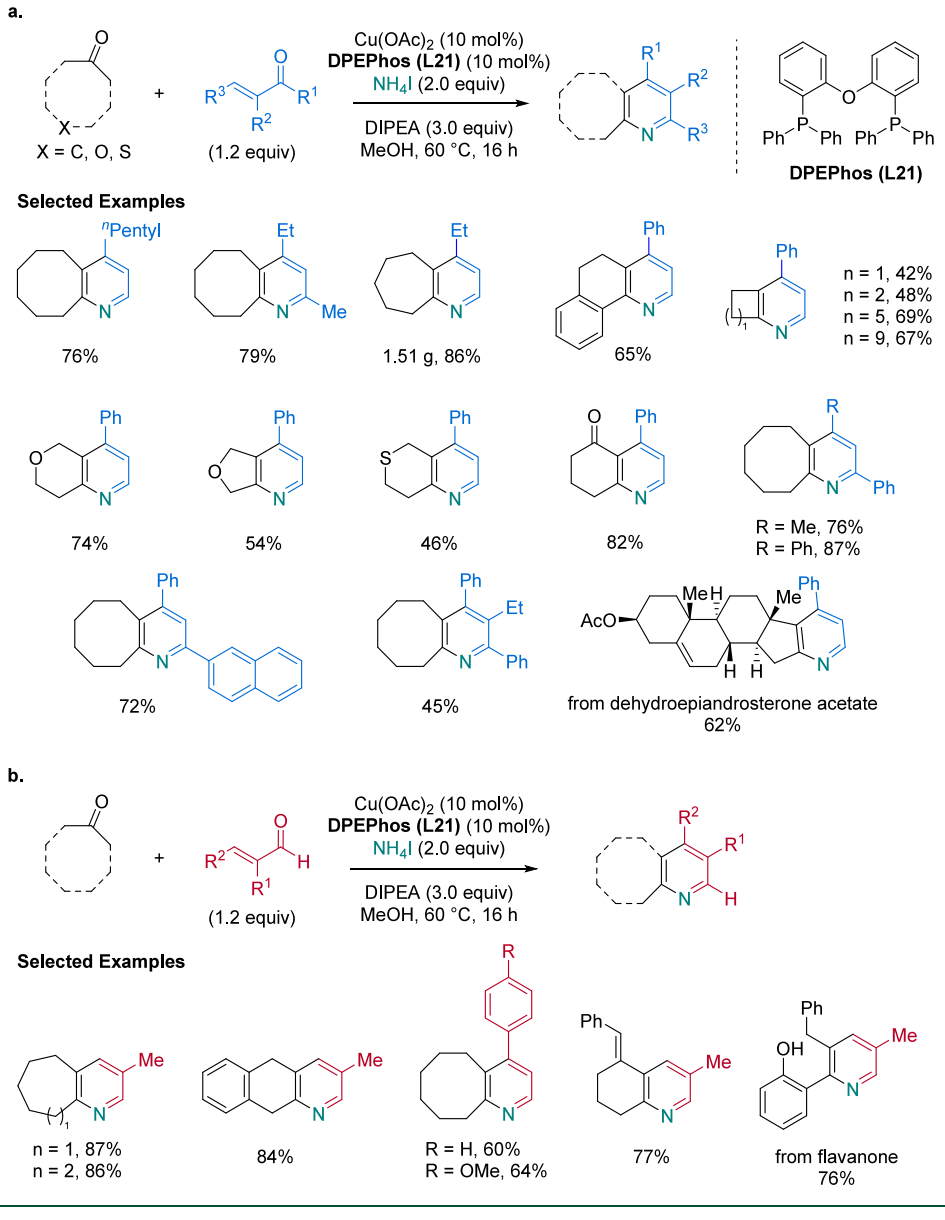
Scheme 23. Cu(II)-Catalyzed Three-Component [2 + 1 + 3] Cyclization of Cyclic Ketones with α,β-Unsaturated Carbonyls: (a) Scope of α,β-Unsaturated Ketones; (b) Scope of α,β-Unsaturated Aldehydes



al. developed a copper-catalyzed enantioselective conjugate addition of a prenyl group to cyclic α,β-unsaturated carbonyl compounds (Scheme 21).[63] The corresponding β-prenyl carbonyl products were obtained in good yields with high regio- and enantioselectivity, regardless of the ring size. A bulkier ester substituent (^{i}Pr vs Et) could lead to a higher enantioselective outcome (96:4 er vs 90:10 er). The synthetic utility was elegantly demonstrated in the enantioselective total synthesis of PPAPs such as (−)-nemorosonol and *ent*-garcibracteatone, where the prenyl addition was performed on a 5 g scale, showcasing the possibility for larger scale synthesis. In this transformation, the use of a preformed borate was key to achieve higher yields. When the preformed borate was used, less excess metal alkoxide was needed in the reaction, which resulted in minimal side product formation from enone decomposition when exposed to a metal alkoxide. The preformed borate could easily be prepared and isolated as a solid on the multigram scale in one step from the corresponding reverse-prenyl-Bpin and sodium ethoxide.

The desymmetrization of racemic or *meso* compounds via a catalytic enantioselective transformation is an attractive approach for C−C bond-forming reactions to access enantioenriched molecules.[64,65] Li et al. reported a Cu-catalyzed asymmetric allylic alkylation (AAA) using Grignard reagents for the desymmetrization of inert *meso*-diethers.[66] This approach is applicable to a wide range of Grignard nucleophiles, including sterically hindered secondary alkyl Grignard such as ^{i}Pr and cyclohexyl Grignard reagents. The *meso* diether starting materials were not limited to only the less hindered methyl diethers, but ethyl and benzyl diethers were well tolerated (Scheme 22a).

Moreover, a gram-scale reaction was demonstrated under continuous flow conditions, showing a larger scale synthesis potential that could offer higher safety and efficiency (Scheme 22b).[67] With 128 s residence time, the product was obtained in similar yield and enantioselectivity compared to the batch process (flow: 79% yield, 98% ee; batch: 81% yield, 99% ee). The flow system was shown to operate for

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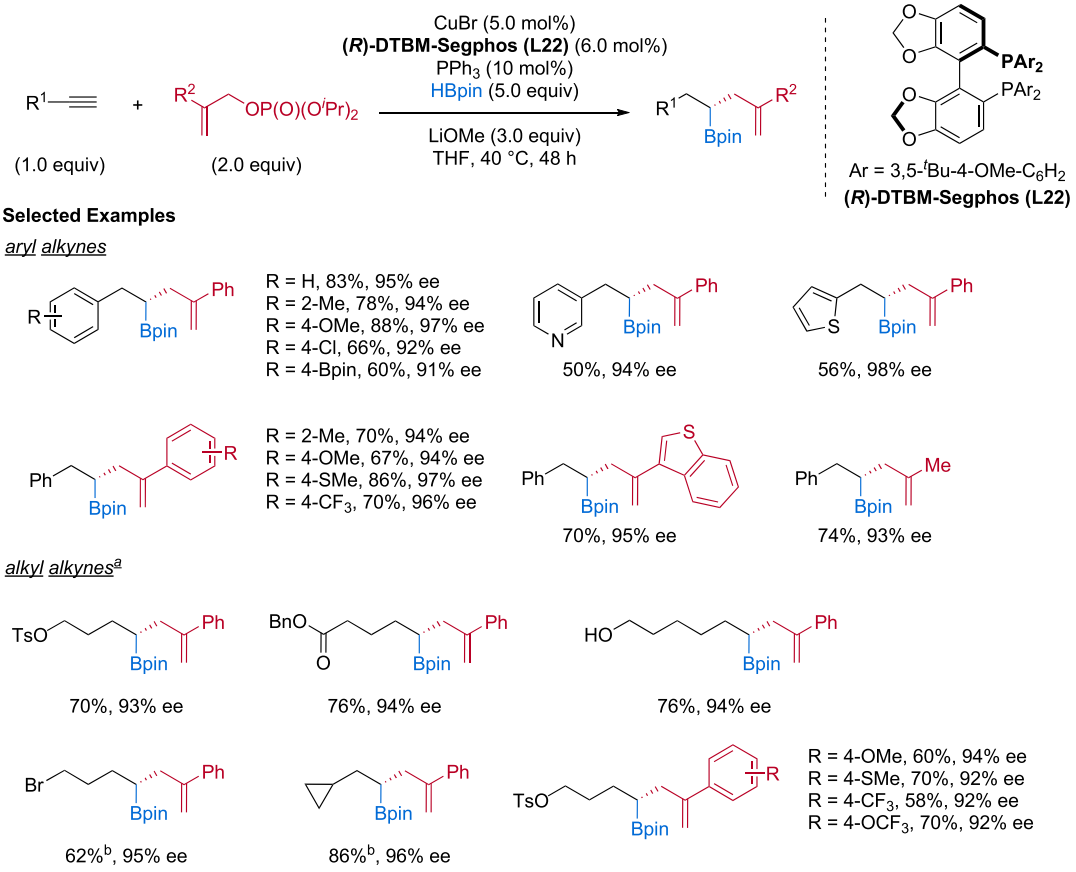
Scheme 24. Cu-Catalyzed Asymmetric Synthesis of 1,1-Difunctionalized Aryl and Alkyl Alkynes



[a]1.0 equiv alkyne, 1.5 equiv allylic phosphate, 4.0 equiv HBpin. [b]1.0 equiv allylic phosphate, 3.0 equiv alkyne, 4.0 equiv HBpin.

>540 min without any decrease in the reaction efficiency or enantioselectivity. The detailed mechanistic study revealed that the reaction is unlikely to occur via an in situ-generated allylic bromide intermediate since no formation of allylic bromide was observed (Scheme 22c, path a). A plausible mechanism is rather a direct *anti*-S_N2' pathway with the alkoxy group participating in the process directly (Scheme 22c, path b). The present method allows the use of the more stable *meso*-diethers compared to those *meso*-bisphosphates or *meso*-dibromides, which are often prone to decomposition and will decrease complications in the preparation and storage of the substrates, especially on a large scale.

Fused pyridines can be found in several applications in the pharmaceutical and agricultural industry. Thanks to their unique electronic properties and structural rigidity, they exhibit a broad range of biological properties such as antiviral,[68] anticancer,[69] antioxidant activity,[70] and other properties.[71] Lu et al. reported an efficient Cu(II)-catalyzed three-component [2 + 1 + 3] cyclization of various cyclic ketones with α,β-unsaturated carbonyls and NH_4I as an ammonia surrogate (Scheme 23).[72] The reactions between cyclic ketones with different ring sizes and α,β-unsaturated alkyl or aryl ketones afforded fused pyridine products in moderate to good yields. The cyclization was demonstrated on a gram scale using cycloheptanone and ethyl vinyl ketone, and the desired product was obtained in 86% yield. Notably, the fused pyridine product derived from dehydroepiandrosterone acetate could be synthesized in 62% yield (Scheme 23a). α,β-Unsaturated aldehydes also reacted efficiently, generating the desired products in satisfactory yields (Scheme 23b). Interestingly, when flavanone was used, a C−O bond cleavage product was isolated in 76% yield, instead of the expected fused pyridine. This C−O bond cleavage was also observed when 4-chromanone was used with an unsaturated ketone. This three-component cyclization approach provides a practical method to access a wide array of fused pyridines from simple starting materials. The use of ammonium iodide as a nitrogen source instead of ammonia or hydroxylamine is also attractive.

Alkynes are ubiquitous raw materials and widely used in various applications of organic synthesis thanks to their versatile reactivity.[73] Wang et al. developed a ligand-controlled Cu-catalyzed asymmetric difunctionalization of terminal alkynes through a cascade hydroboration and hydroallylation process.[74] In the system where (*R*)-DTBM-Segphos (**L22**) was used as a ligand, 1,1-difunctionalization of aryl or alkyl alkynes could be achieved in good yield with high enantioselectivity (Scheme 24). A broad spectrum of substrates was reported, where electron-donating and -withdrawing substituents on the aryl group of either alkynes or allylic phosphates were efficient and selective. Notably, alkyl alkynes bearing an unprotected alcohol, a bromide, or a cyclopropyl group were well tolerated.

By switching the ligand to (*S*,*S*)-Ph-BPE (**L23**), 1,2-difunctionalized products were obtained exclusively (Scheme 25a). Interestingly, lowering the amount of HBpin, while adding hydrosilane (PMHS), improved the yield (~20%) without a negative impact on the enantioselectivity. While a

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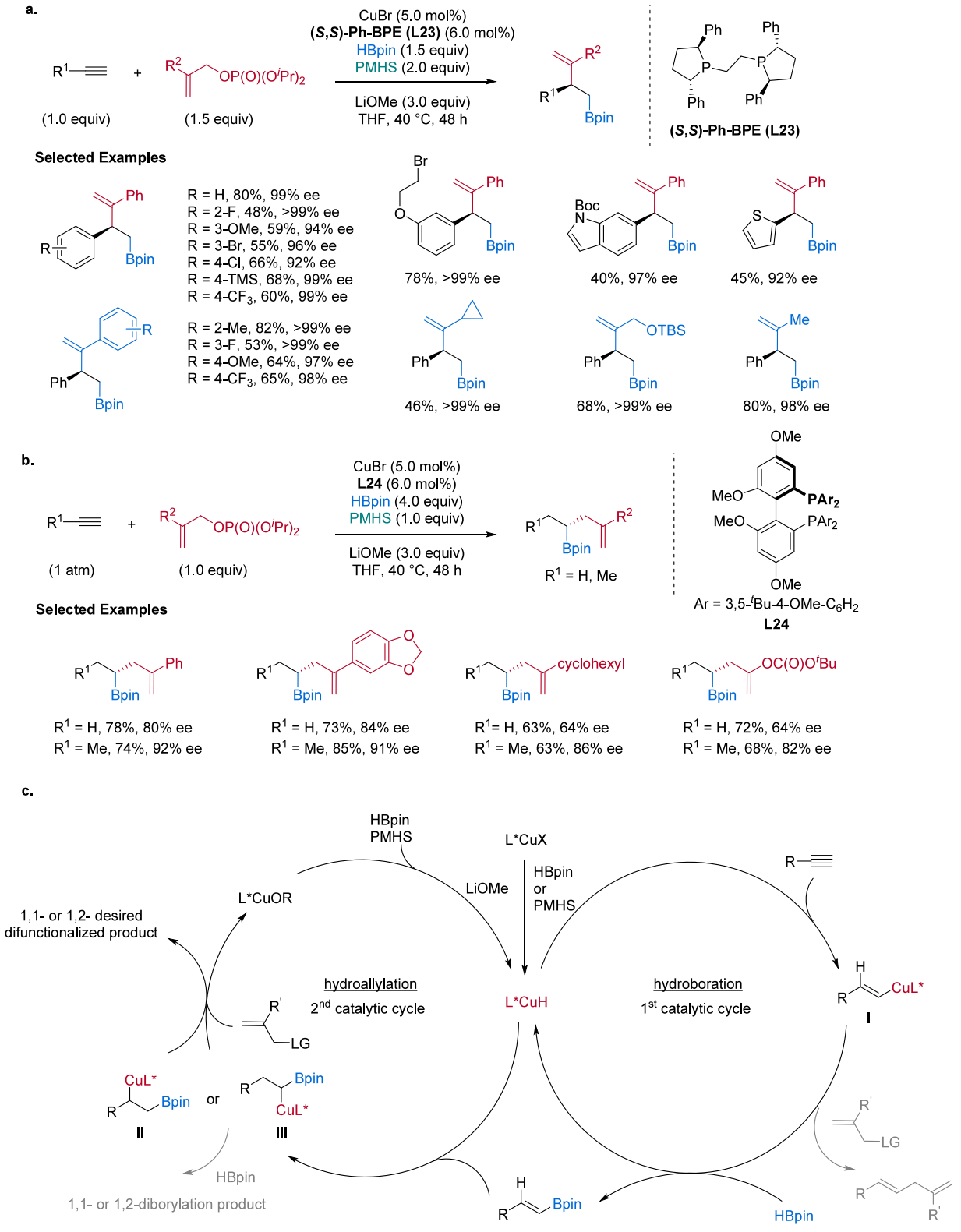
Scheme 25. Cu-Catalyzed Asymmetric Difunctionalization of Terminal Alkynes: (a) Synthesis of 1,2-Difunctionalized Aryl Alkynes; (b) Reactions with Acetylene and Propyne; (c) Proposed Catalytic Cycles



broad scope of substrates was achieved, alkyl-substituted terminal alkynes were not efficient under the present conditions, most likely due to a less stable alkylcuprate intermediate. To further broaden the industrial implications of this transformation, acetylene and propyne gas were investigated (Scheme 25b). In both cases, 1,1-difunctionalized products were obtained in moderate to good yield in the presence of PMHS. Moderate levels of enantioselectivity were obtained when acetylene was used, while reactions with propyne provided high enantioselectivity. Of note, reactions with internal alkynes such as 1-phenyl propyne and 1-phenyl pentyne were examined; however, no desired difunctionalized

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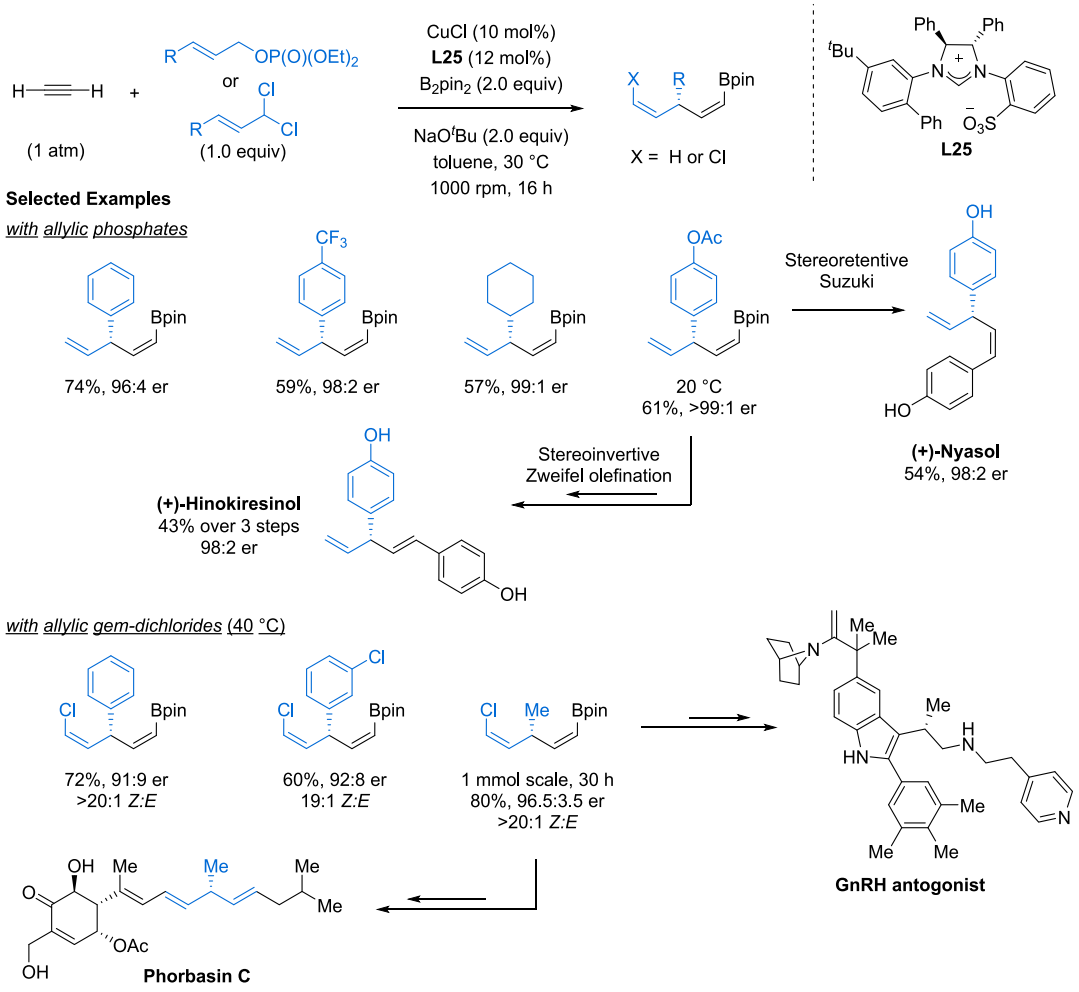
Scheme 26. Cu-Catalyzed Enantioselective Allylboration of Acetylene



(1,1- nor 1,2-) products were detected. The authors conducted mechanistic studies and proposed a cascade hydroboration and hydroallylation process, as shown in Scheme 25c. The first catalytic cycle involved a hydroboration reaction of an alkyne, affording a vinyl boronate intermediate. Then, a ligand-controlled regio- and enantioselective hydroallylation of the vinyl boronate generated 1,1- or 1,2-difunctionalized products with remarkable selectivities despite several possible side reactions.

Acetylene gas is a simple and abundant chemical feedstock. Thus, catalytic, enantioselective transformations using this raw material directly have great industrial implications.[75,76] Fañanás-Mastral and co-workers developed a Cu-catalyzed enantioselective allylboration of acetylene, generating skipped dienes in moderate to good yield with high enantiopurity (Scheme 26).[77] A chiral sulfonate-containing *N*-heterocyclic carbene (**L25**) was found to be an optimal ligand for the transformation.[78] In addition to allylic phosphates, which were shown to be crucial for reaction efficiency and enantioselectivity of the products compared to allylic halides, allylic *gem*-dichlorides could be used to access orthogonally difunctionalized *Z*,*Z*-stereodefined chiral skipped dienes in good yield and high enantioselectivity. Interestingly, the authors found that increasing the reaction stirring rate improved the isolated yield. This is likely because the improved mass transfer of acetylene between the gas and liquid phases was achieved. The synthetic utility of the present protocol was highlighted in the synthesis of several bioactive molecules and natural products, such as (+)-nyasol, (+)-hinokiresinol, GnRH antagonist, and Phorbasin C. The present method should expand the use of acetylene gas as an inexpensive and versatile feedstock in the synthetic community.

CONCLUSIONS

Nonprecious metals have proven themselves to be effective catalysts for a wide variety of transformations. Because they are sustainable nonprecious metals, it is important that the scientific community continues to create new synthetic transformations with them. This review highlights a variety of NPMC reactions, including cross-couplings, borylations, cyclizations, aminations, etc. The broad applicability of these catalysts emphasizes the importance of these studies, which is why Boehringer Ingelheim engages in this continuing review series alongside Abbvie and Pfizer.

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Notes

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