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CuH-Catalyzed Olefin Functionalization: from Hydroamination to Carbonyl Addition

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CONSPECTUS:

In organic synthesis, ligand-modified copper(I) hydride (CuH) complexes have become well-known reagents and catalysts for selective reduction, particularly toward Michael acceptors and carbonyl compounds. Recently, our group and others have found that these hydride complexes undergo migratory insertion (hydrocupration) with relatively unactivated and electronically unpolarized olefins, producing alkylcopper intermediates that can be leveraged to forge a variety of useful bonds. The resulting formal hydrofunctionalization reactions have formed the basis for a resurgence of research in CuH catalysis. This Account chronicles the development of this concept in our research group, highlighting its origin in the context of asymmetric hydroamination, evolution to more general C–X bond-forming reactions, and applications in the addition of olefin-derived nucleophiles to carbonyl derivatives.

Hydroamination, the formal insertion of an olefin into the N–H bond of an amine, is a process of significant academic and industrial interest, due to its potential to transform widely available alkenes and alkynes into valuable complex amines. We developed a polarity-reversed strategy for catalytic enantioselective hydroamination relying on the reaction of olefins with CuH to generate chiral organocopper intermediates, which are intercepted by electrophilic amine reagents. By engineering the auxiliary ligand, amine electrophile, and reaction conditions, the scope of this method has since been extended to include many types of olefins, including challenging internal olefins. Further, the scope of amine reagents has been expanded to enable the synthesis of primary, secondary, and tertiary amines, as well as amides, N-alkylated heterocycles, and anilines. All of these reactions exhibit high regio- and stereoselectivity and, due to the mild conditions required, excellent tolerance for heterocycles and polar functional groups.

Though the generation of alkylcopper species from olefins was originally devised as a means to solve the hydroamination problem, we soon found that these intermediates could react efficiently with an unexpectedly broad range of electrophiles, including alkyl halides, silicon reagents, arylpalladium species, heterocycles, and carbonyl derivatives. The general ability of olefins to function as precursors for nucleophilic intermediates has proved particularly advantageous in carbonyl addition reactions because it overcomes many of the disadvantages associated with traditional organometallic reagents. By removing the need for pre-generation of the nucleophile in a separate operation, CuH-catalyzed addition reactions of olefin-derived nucleophiles feature improved step economy, enhanced functional-group tolerance, and the potential for catalyst

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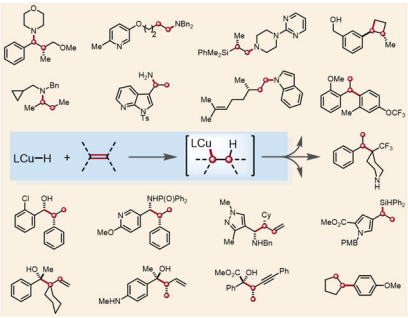
control over regio- and stereoselectivity. Following this paradigm, feedstock olefins such as allene, butadiene, and styrene have been employed as reagents for asymmetric alkylation of ketones, imines, and aldehydes.

Graphical Abstract



BACKGROUND

Discovered in the early 1800s, copper(I) hydride was the earliest known binary metal hydride.[1] Among synthetic organic chemists, however, interest in the reactivity of CuH complexes with organic substrates did not arise until over a century later, sparked by seminal work by Stryker on 1,4-reduction using his now famous Ph3P-modified CuH hexamer.[2] In the decades since, thousands of articles on CuH-promoted reactions have been published, and several excellent reviews and summaries have been compiled.[3] Starting about seven years ago, our group discovered that appropriately ligated CuH catalysts could undergo efficient insertion with a far broader range of unsaturated substrates than had been previously appreciated. Further, the resulting organocopper species could be exploited not only as intermediates to reduction, but toward the construction of many useful bonds. Below, we present an Account of our research on CuH-catalyzed olefin hydrofunctionalization,[4] from its origins as an approach for hydroamination to our continuing efforts in extending the mechanistic concept to problems beyond C–N coupling.

Hydroamination, defined as the addition of a hydrogen and an amino group across a π-bond, has been the subject of extensive research, as the overall transformation represents a highly economical means to prepare complex amines. A diversity of approaches have been studied, including those promoted by rare-earth and noble metals, Bronsted acids, strong bases, free radicals, pericyclic reactions, and photocatalysis.[5] Our motivation to develop an alternative solution to this problem stemmed from a longstanding interest in C–N bond-forming reactions,[6] as well as prior work on asymmetric copper-catalyzed reductions.[7] In traditional processes, the amine nitrogen predominantly reacts in a nucleophilic manner – in contrast, our proposal was based on a polarity-reversed (*umpolung*) mechanism: the hydrogen atom would be derived from a hydridic reagent and the amino group from an electrophilic reagent (Figure 1).[8]

After initial formation of a ligated copper(I) hydride (LCuH), stereoselective migratory insertion of an olefin would produce a chiral alkylcopper complex. We planned to intercept

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this intermediate with an *N*-electrophile, which might produce the desired hydroamination product, as well as LCuX, with X depending on the leaving group on the amine reagent. In the presence of silane and possibly other additives, the initial hydride complex could then be regenerated. The net chemical transformation is equivalent to sum of a traditional hydroamination reaction (olefin + amine → substituted amine) with the reduction of an electrophilic amination reagent by silane ($R_2N–X + [Si]–H \rightarrow R_2N–H + [Si]–X$). Accordingly, the roughly thermoneutral traditional hydroamination is modified into a strongly exothermic process by dividing the R_2N and H components into separate, high-energy reagents. This affords a significant driving force for each of the steps, rendering them irreversible, and thus might provide better chances for kinetically controlled, catalyst-induced selectivity.

Each of the three constituent steps of the hypothetical mechanism had in fact been well precedented in the literature. Although the bulk of catalytic reactions involving hydrocupration had operated on α,β-unsaturated carbonyl compounds and other electron-deficient substrates, a few important reports featuring hydrocupration of less activated olefins were known.[9] Of particular relevance, Yun and co-workers had demonstrated in 2009 that a bisphosphine-ligated CuH catalyst could effect the enantioselective hydroboration of vinylarenes.[9a] Likewise, several well-known results also substantiated the plausibility of the second proposed step, the conversion of an organocopper intermediate into an amine product using an electrophilic reagent. Building on discoveries from Boche concerning the amination of Grignard and organolithium reagents,[10] Johnson had shown that copper salts could catalyze C–N bond formation from diorganozinc compounds and hydroxylamine *O*-benzoates, through the intermediacy of an organocopper(I) intermediate.[11,12] Finally, the regeneration of the starting hydride complex from LCuOR complexes was an extremely well-established process involved in practically every reaction involving CuH catalysis.

Despite the apparent plausibility of these steps, an obvious obstacle remained. Our proposed conditions involved the simultaneous presence of an excellent reductant (LCuH) and a relatively reactive oxidant ($R_2N–X$)! Somehow, the latter must not rapidly annihilate the former, but wait patiently while a comparatively unreactive olefin inserts into the LCu–H bond. Yet, given considerable room for tuning the reactivity of both the reducing and oxidizing species, through the ligand (L) and leaving group (X), respectively, we were hopeful that we might arrive empirically at a solution.

COPPER-CATALYZED HYDROAMINATION: DISCOVERY

In 2013, we reported the CuH-catalyzed hydroamination of styrene (Figure 2) and terminal olefin substrates (Figure 3).[13] Contemporaneously, the same transformation of styrenes was also published by Miura and Hirano.[14,15] As precatalysts, either copper(II) acetate, which reduces to copper(I) *in situ*, or copper(I) *tert*-butoxide, produced from copper(I) chloride and lithium *tert*-butoxide, could be used, in combination with chiral phosphine ligands such as (*R*)-DTBM-SEGPHOS, (*S*,*S*)-Ph-BPE, or (*S*,*S*)-MeDuPhos. Hydroxylamine esters were found to be effective electrophilic amine sources, while the hydride could be supplied by silanes, such as the inexpensive and environmentally benign poly(methylhydrosiloxane) (PMHS) or its monomeric analogues diethoxymethylsilane (DEMS) and

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dimethoxymethylsilane (DMMS). Under these conditions, the hydroamination of a variety of styrenes proceeded in high yield, excellent enantioselectivity, and exclusive Markovnikov regioselectivity, the latter presumably due to preferential formation of a benzylic alkylcopper complex upon hydrocupration over the unstabilized alternative. In stark contrast, the hydroamination of terminal alkenes occurs with full anti-Markonikov selectivity, presumably due to steric interactions that destabilize the secondary alkylcopper complex that would result from Markovnikov-selective hydrocupration.

HYDROAMINATION: EXPANDING THE OLEFIN SCOPE

We quickly found that, using DTBM-SEGPHOS as the supporting ligand for Cu, numerous other classes of olefins could efficiently undergo hydroamination with minimal modification of the reaction conditions. Consistent with the regiochemical observations described above, unactivated olefins reacted to form the anti-Markovnikov isomer of the amine product (Figure 3). As an example, 1,1-disubstituted olefins could be converted enantioselectively to β-chiral amines.[16] Even internal olefins, which are extremely deactivated relative to alkenes typically used in CuH chemistry, participated in hydrocupration and highly stereoselective C–N bond formation.[17] For instance, the feedstock olefin, *trans*-2-butene, could be employed to synthesize useful products with a Me,Et-stereocenter in nearly perfect optical purity.

With regard to Markovnikov-selective hydroamination, several activating olefin substituents other than arenes were found to be suitable for directing the hydrocupration process toward the branched alkylcopper intermediate (Figure 4). For instance, starting from vinyl silanes, we synthesized a collection of highly enantioenriched α-aminosilanes, compounds which are of topical interest as peptide bioisosteres.[18] Similarly, others have reported highly enantioselective hydroaminations of vinylboron compounds[19] and trifluoromethyl alkenes.[20] In the latter case, the use of (*R*)-DTBM-BINAP instead of (*R*)-DTBM-SEGPHOS provided superior results, mainly by suppressing β-fluoride elimination from the key alkylcopper intermediate.

We also investigated several special classes of substrates that exhibited unique or notable reactivity. For instance, alkynes, depending on the reaction conditions, could either undergo selective hydroamination to enamines or tandem hydrogenation–hydroamination to alkylamines (Figure 5).[21] Mechanistic data revealed an intriguing selectivity phenomenon: while the vinylcopper intermediate preferentially reacted with the alcohol over the electrophilic amine reagent, the alkylcopper intermediate reacted with the opposite selectivity, thereby allowing hydrogenation and hydroamination to occur in the intended order.

Another valuable class of methods includes the synthesis of chiral 1,2-diamines (Figure 6A), which are valuable both in biological applications and as chiral ligands, through the hydroamination of allylic amines.[22] These reactions involve the intermediacy of alkylcopper complexes bearing potential leaving groups at the β-position. Thus, β-elimination poses a major problem, consuming the starting material through a net S_N2' reduction to generate

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alkene products that could interfere. To address this obstacle, careful selection of the nitrogen-protecting group for the starting material proved to be essential.[23]

In attempts to achieve the hydroamination of allylic alcohol derivatives to generate 1,2-aminoalcohols, the aforementioned β-elimination process was found to be unavoidably rapid. We were, however, able to capitalize on this tendency to design a cascade process in which one or more allylic reduction reactions could be intentionally performed prior to a terminal hydroamination process (Figure 6B).[24a] After an initial stereocenter-setting hydrocupration, the ligated copper is thus "relayed" to a more distal position, where it participates in C–N bond-formation. This choreographed sequence, dubbed "reductive relay hydroamination," supplied an effective means to access amines with γ- or δ-stereocenters.

As the CuH-catalyzed hydroamination process could be combined with allylic reduction reactions, it could also be performed in sequence with 1,2-reductions (Figure 7). In 2016, we reported that starting from enones, 1,3-aminoalcohols could be synthesized through reduction of the carbonyl group and hydroamination of the styrenic fragment.[24b] Taking advantage of the *syn*-stereospecificity of the hydroamination, we obtained all possible stereoisomers of the aminoalcohol products, through selection of the appropriate starting alkene geometry and enantiomer(s) of catalyst.

HYDROAMINATION: EXPANDING THE AMINE SCOPE

Concurrently with our exploration of the olefin scope associated with CuH-catalyzed hydroamination, our group undertook efforts to systematically expand the types of amine reagents that could be employed. Unlike the alkene substrate, the amination agent is readily tunable in terms of structure, including variation of the leaving group. The ability to tailor electrophilicity proved quite essential, as successful catalysis depends on the reagent being resilient to direct reduction by copper hydride, but active toward reaction with copper alkyl complexes. Thus, a recurring theme in this subsection is the search for the "Goldilocks" amination reagent for each class of amines, possessing a delicate balance of reactivity and stability.

Following our initial reports on hydroamination, which mainly addressed the enantioselective synthesis of tertiary amines, we naturally considered whether secondary and primary amines could be constructed as well. In the case of secondary amine reagents, which are significantly less sterically hindered than the tertiary amine reagents, those bearing the original benzoate leaving group were reduced rapidly in an unproductive pathway.[25] Instead, switching to a modified amine-transfer reagent with a more electron-rich, and hence less labile, leaving group recovered the desired chemoselectivity and enabled the synthesis of many chiral secondary amines, including those derived from fairly complex substrates (Figure 8).

As for primary amines, the most effective reagent turned out not to be a hydroxylamine ester, but the inexpensive heteroarene 1,2-benzisoxazole.[26] Reactions of both styrenes and terminal alkenes worked well to produce the corresponding primary amine in either free or

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salicylimine-protected form. This method was also applied to the synthesis of several pharmaceuticals, including the antiretroviral Maraviroc.[27]

Compared to N(sp^3)-transfer reagents, sources of N(sp^2), including amides and anilines, had been only described rarely in the literature. However, α-chiral anilines and amides are very common substructures in small-molecule drugs and natural products. In designing a synthesis of anilines by CuH-catalyzed hydroamination, the use of an electron-rich benzoate leaving group was again essential to achieving high yields (Figure 9A).[28] Further, while a mechanistic rationale is less apparent, the addition of triphenylphosphine and *tert*-butanol to the reaction mixture was shown to inhibit direct reduction of the electrophile. For the hydro*amidation* problem, however, an entirely different class of electrophiles was needed: 1,4,2-dioxazol-5-ones, previously employed in applications such as Ir-catalyzed C–H amination, proved to be a suitable amide-transfer reagent, albeit only with styrenes (Figure 9B).[29]

A somewhat unusual class of N(sp^2) electrophiles, *N*-benzoyloxy indoles attracted our attention because of the significance of enantioenriched indoles in natural products and pharmaceutical compounds (Figure 10). With the Baik laboratory, we discovered an interesting ligand-controlled regiodivergence in the CuH-catalyzed hydroindolation reaction.[30] Specifically, when the "standard" bis(triarylphosphine) ligand (*R*)-DTBM-SEGPHOS was used, high yields of *N*-alkylated indole products could be obtained, with excellent enantioselectivity where applicable; however, when the bis(trialkylphosphine) ligand (*S,S*)-Ph-BPE was added instead, exclusive alkylation at the C3 position was observed, with useful levels of enantioselectivity as well. DFT calculations suggested that the regioselectivity in both cases is dictated by the site of oxidative addition: while insertion of Cu at the N–O bond is intrinsically favored, when (*S,S*)-Ph-BPE is the modifying ligand, this pathway is disfavored by several steric interactions and oxidative addition at C3 dominates instead.

Finally, in systematically evaluating the scope of the CuH-catalyzed hydroamination reaction, we also developed several highly enantio- and regioselective intramolecular processes (Figure 11). For instance, by using *N*-allylic hydroxylamine ester reagents, enantioenriched *N*-alkyl aziridines, which had been particularly challenging to access in a catalytic, enantioselective manner, could now be synthesized under mild conditions.[31] Using very similar conditions, some five-membered and larger rings (up to nine-membered) could also be generated.[32]

HYDROAMINATION: MECHANISM AND IMPROVED CONDITIONS

In parallel with the synthetic investigations outlined above, our group conducted mechanistic studies with the dual aims of illuminating fundamental aspects of the hydroamination process and of uncovering ways to improve the catalyst or reaction conditions to achieve yet more practical methods. Early work on styrene hydroamination found that the turnover-limiting step does not include the substrate but rather, involves regeneration of the CuH catalyst from a copper(I) benzoate resting state.[33] Consequently, by modifying the amination reagent to the effect of replacing the benzoate leaving group with a more nucleophilic pivalate, we attained an improved procedure (Figure 12A) featuring short (<30 min) reaction

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times and various operational enhancements (air-stable precatalyst, no glovebox required, and open-flask conditions).[34]

Besides enhanced reaction conditions, we were interested in the rational design of better catalysts. Clearly, the use of bulky ligands such as (*R*)-DTBM-SEGPHOS was critical in enabling very challenging hydrocupration processes involving unactivated terminal and internal alkenes. In collaboration with Professor Peng Liu and his group (University of Pittsburgh), we sought to explain this ligand effect at a more fundamental level, through a multifaceted analysis involving reaction kinetics, DFT modeling, and catalyst synthesis. Most notably, we provided substantial evidence that the unique effect of the bulky *tert*-butyl substituents did not originate primarily from a steric influence nor inductive electron-donation to phosphorus, but rather attractive London-dispersion interactions between these hydrocarbon groups and the olefin substrate (Figure 12B).[35] Following this conclusion, it seemed logical that modifying these *tert*-butyl groups could bring about more efficient catalysis. Continuing our synergistic experimental–computational approach, only a few candidate ligands needed to be synthesized before we found that a SEGPHOS derivative bearing perfluorinated isopropyl groups could form a very active, but rather unstable, catalyst. However, a half-and-half mixture of this design with the original DTBM-SEGPHOS structure provided a hybrid ligand “SEGFAST” (Figure 12C), the use of which provided a sustained 62-fold rate increase over previous systems in the anti-Markovnikov hydroamination reaction.[36]

EXPANSION OF THE ELECTROPHILE SCOPE BEYOND HYDROAMINATION

At the outset, it would have been difficult to foresee that the formal hydroamination strategy we developed could encompass so many olefin classes and such a variety of amine electrophiles. All the more unexpectedly, we also learned that olefin functionalization through this sequential hydrocupration–trapping mechanism could extend to a multitude of non-nitrogen-centered reactive partners, including carbon electrophiles. An early example was disclosed in 2015, when we reported the highly enantio- and diastereoselective addition of benzylcopper intermediates in an intramolecular fashion to produce indolines (Figure 13).[37] Besides imines, alkyl bromides were also suitable *C*-electrophiles in this type of cyclization process.[38] By tethering a primary alkyl bromide to a styrenic substrate, saturated carbo- and heterocycles could be synthesized with high stereoselectivity, including the serotonin-reuptake inhibitor (−)-paroxetine.

Though *intermolecular* C–C couplings were generally more challenging to realize, we published a few successful examples, mostly using vinyl (hetero)arene substrates (Figure 14). One effective strategy was to use activated substrates, such as allylic electrophiles.[39] In these asymmetric hydroallylation reactions, isotope-labeling experiments showed that trapping of the benzylcopper intermediate takes place through an S$_N$2’-like substitution on the allylic phosphate. An alternate strategy was to intercept the organocopper intermediate through transmetallation with another metal, such as palladium, that could facilitate the C–C bond-forming step better than copper. In 2016, our group,[40] along with Semba, Sakaki, and Nakao,[41a] independently reported the use of Cu/Pd co-catalysis in the hydroarylation of styrene derivatives with aryl bromides and activated aryl chlorides. We were also able to

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demonstrate high enantioselectivity in this process, which required stereospecific Cu-to-Pd transmetallation and careful rate-matching between the two operative catalytic cycles. We subsequently extended the dual catalysis concept to anti-Markovnikov hydroarylation.[42]

Attempts to engage the benzylcopper intermediates with pyridine-based electrophiles led us to the strange discovery that pyridine (and other nitrogen-containing heterocycles) could undergo direct dearomative 1,4-addition of a chiral benzyl fragment derived from styrene (Figure 15).[43] This was a rare example of such a process requiring neither stoichiometric preactivation of the pyridine nor the nucleophile, and notably, one of the few available asymmetric methods for 1,4-dearomatization. Following this reaction with an oxidation or reduction in the same pot delivered enantioenriched pyridines or piperidines, respectively.

Finally, in reactions with no external electrophile added, the organocopper intermediate can only slowly undergo σ-bond metathesis with the silane, producing a hydrosilylation product. With some optimization, we arrived at a general procedure for the highly asymmetric Markovnikov-selective hydrosilylation of vinyl (hetero)arenes, with optionally a subsequent direct Tamao oxidation to provide chiral alcohols.[44]

OLEFINS AS SURROGATES FOR NUCLEOPHILIC REAGENTS

At this point, the “olefin + CuH = organocopper” equivalence had proved so general and robust that we wondered if, within this catalytic manifold, olefins could be thought of as useful reagents, not just as substrates. From this perspective, reactions that require unstable, difficult-to-access, dangerous, or otherwise non-ideal carbanionic reagents could potentially be improved by replacement of stoichiometric organometallics with relatively more stable, more readily available, and safer olefin surrogates.

Within this concept, our investigations have focused mainly on the reactions involving carbonyl compounds and derivatives such as imines. The addition of organometallic reagents, including organomagnesium (Grignard), boron, silicon, or tin compounds, to C=X bonds is among the most reliable and routinely employed tools for the assembly of C–C bonds in chemical synthesis. These transformations can proceed either in a direct manner or with the aid of acidic, basic, nucleophilic, or organometallic catalysts that can impart control over the product distribution in terms of stereo- or regiochemistry. In either case, pre-formation of an organometallic precursor is usually required, creating issues related to safety, air- and moisture-sensitivity, added operational complexity, functional-group compatibility, and/or the formation of inseparable mixtures of isomeric reagents.

Starting in the 2000s, the use of olefinic compounds, which are very abundant and easily handled, as latent carbanion equivalents in the context of asymmetric carbonyl addition has emerged as a promising alternative. By the time we started our work in this area, several important precedents involving other metal catalysts had already been reported in the literature. Foremost, Krische had reported a multitude of noble metal–catalyzed (transfer) hydrogenative olefin–carbonyl reductive coupling reactions, which were exceedingly atom-economical and often highly stereoselective.[45] Moreover, Montgomery and Jamison devised several reductive alkyne–aldehyde coupling processes based on Ni-derived catalysts.[46]

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Finally, related pioneering Cu-catalyzed methods described by Hoveyda involving the generation of chiral organocopper species through the borylcupration of olefins[47] are mechanistically relevant to the approach we devised (see below).

In 2016, we first reported a highly enantioselective propargylation of ketones using a class of activated alkenes, 1,3-enynes, as surrogates for propargylmetal reagents. The postulated mechanism, displayed in Figure 16, also serves as a prototype for many of the reactions described in the later sections. Initially, stereoselective hydrocupration of the 1,3-enyne would generate a chiral propargylcopper complex, which might exist in fast equilibrium with one or more isomeric species. By analogy to the hydroamination reactions, we recognized that the key question in this step was one of chemoselectivity: could this C=C migratory insertion be encouraged to take place over typically very rapid C=O insertion processes involving the ketone electrophile? Assuming that the propargyl metal species could be efficiently produced, we envisioned that it might be directly intercepted by a ketone electrophile via a six-membered Zimmerman–Traxler-like transition state,[48] forming the desired C–C bond. The resultant copper alkoxide, upon σ-bond metathesis with the silane, should release the silyl-protected product and close the catalytic cycle. A smaller alcohol such as *t*-butanol could also be added to promote this process if necessary. Overall, an organometallic nucleophile would thus be generated and captured by its reactive partner within the same catalytic cycle and with catalyst-controlled stereoinduction.

Using an (*S*,*S*)-Ph-BPE-modified copper catalyst, an extensive range of ketones and 1,3-enynes could be coupled in the reductive propargylation process, all in high yields and with excellent diastereo- and enantioselectivities. The reaction could be conducted on at least 50-mmol scale and required only commercially available reagents and ambient conditions.

STYRENES AS BENZYL ANION EQUIVALENTS

Based on our experience with hydroamination, we reasoned that it might be logical to explore whether styrenes might serve more generally as chiral benzyl anion equivalents. Using imines as electrophiles and (*S*,*S*)-Ph-BPE-ligated CuH as the catalyst, we showed that enantioenriched amines can be synthesized bearing two stereocenters, one derived from the styrene and the other from the imine (Figure 17A).[49] The choice of supporting ligand was crucial, as the use of alternatives such as (*R*)-DTBM-SEGPHOS, which featured prominently in the hydroamination chemistry, resulted in primarily reduction of the imine. Although the diastereoselectivity was modest, both diastereomers were typically formed in very high enantioselectivity, and as is often the case in CuH chemistry, the reaction showed exceptional tolerance for heterocycles, polar functional groups, and even protic substituents.

Styrene-derived nucleophiles also reacted successfully with aryl carboxylic anhydrides to yield α-chiral carbonyl compounds, which could either undergo a subsequent CuH-catalyzed reduction in the same flask to an alcohol or, if the reaction is performed and quenched under low-temperature reaction conditions, be isolated with the ketone intact (Figure 17B).[50] Unfortunately, the same methodology was ineffective for *alkyl* carboxylic anhydrides, and an alternative needed to be devised. We found that α,β-unsaturated acids, presumably after *in situ* silylation of the -OH, can undergo asymmetric addition of a styrene-

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derived nucleophile followed by conjugate reduction of the C=C double bond to access the desired chiral α-aryl dialkyl ketones.[51]

ALLENES AS ALLYL ANION EQUIVALENTS

The asymmetric addition of allylic nucleophiles to carbonyl compounds has been a subject of particular interest to synthetic chemists. Accordingly, we considered whether our olefin-derived nucleophile strategy could be adapted to provide more general, effective, or otherwise advantageous methods for catalytic allylation. The coupling of a ketone with the parent allyl group, the simplest and most commonly encountered synthon of this class, served as a convenient model for the development of this concept. Existing methods for this transformation, though numerous and frequently employed, suffered from several prominent disadvantages. For instance, popular reagents such as allylmagnesium halides are very basic and exhibit poor tolerance for functional groups. As demonstrated by Woerpel, the uniquely high reactivity of allylic organometallic reagents also raises problems with chemoselectivity: for instance, allylmagnesium chloride reacts indiscriminately with mixtures containing esters, ketones, and aldehydes.[52] Moreover, the exothermicity of Grignard formation, along with the generation of stoichiometric quantities of insoluble metal salts, hinders the large-scale applicability of these protocols.[53] Finally, relative to reactions of aldehydes, achieving high enantioselectivity in ketone addition is generally challenging.

Our approach would involve generating an allylcopper intermediate *in situ* and engaging a ketone in a stereoselective addition process within the same catalytic cycle. In order for a parent allylcopper complex to result from hydrocupration, the appropriate olefin precursor would need to be 1,2-propadiene, or allene. As it turns out, allene gas is a million ton/year byproduct of hydrocarbon cracking that was considered to be an undesired contaminant in the propylene feedstock with essentially no productive chemical application.[54] We showed that, in fact, allene or allene-containing crude gas mixtures could function as an efficient, mild, and economical allylation reagent when combined with inexpensive silanes (PMHS or DMMS) and copper catalysts (Figure 18A).[55] In particular, using (*S*,*S*)-QuinoxP* as an ancillary ligand, highly enantioselective additions to aryl, alkyl, and vinyl ketones could be achieved. If catalyst control over stereochemistry was not required, as little as 0.5 mol% of practically any chelating bisphosphine ligand could be employed instead, including the very inexpensive *rac*-BINAP.

The addition of more complex allylic fragments could similarly be accomplished by starting from substituted allenes (Figure 18B), although additional complexities relating to regioselectivity and diastereoselectivity emerged: for instance, hydrocupration of a monosubstituted allene might produce either the more substituted *branched* allylcopper or the less substituted *linear* isomer, the latter with either *cis* or *trans* geometry at the olefin. Likewise, upon electrophilic interception of one or more of these complexes by a ketone, many isomeric allylation products could result. Experimentally, however, we found that the CuH-catalyzed coupling of substituted allenes and ketones could be optimized to provide only the branched isomers of homoallylic alcohol products, with generally very high diastereo- and enantioselectivities.[56]

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As for the mechanistic origin of the regioselectivity, we gathered some important clues through analogous studies on allene–imine reductive coupling (Figure 18C).[57] In the allylation of *N*-alkyl imines, we again observed exclusive formation of the branched product; however, when employing electron-deficient *N*-substituents on the imine, such as diphenylphosphinoyl (DPP), we instead found only the linear allylation product. This useful regiodivergence could be explained by a simple DFT-based model. First, initial hydrocupration of an allene would produce a rapidly equilibrating mixture of allylcopper species, in which the linear *E*-allyl predominates thermodynamically. This isomer is also the most reactive with imines, adding through a six-membered pericyclic transition state structure. In one scenario, wherein the Cu coordinates to the imine nitrogen (for *N*-alkyl substrates), the imine would serve as the two-atom component and the allylcopper the four-atom component, giving the branched product. Conversely, in the case that the Cu could coordinate to the protecting group instead, the imine would instead play the four-atom component and the allylcopper the two-atom component. It is this role-reversal that led to the observed regioselectivity swap. Further, it was also clear that reactions of ketones, which could only perform the duty of the two-atom component, mechanistically resembled the former case.

DIENES AS ALLYL ANION EQUIVALENTS

Allenes are not the only possible precursor to allylcopper intermediates. 1,3-dienes are comparatively more stable and common reagents, which can be particularly useful in some situations. Certain dienes, such as butadiene, isoprene, and myrcene, are industrial feedstocks and important raw materials for commercial manufacturing.[58] On the other hand, since 1,3-dienes are less reactive toward hydrocupration than allenes, the risk of undesired direct reduction of the carbonyl compound is increased. In the case of ketone allylation, we were able to find suitable reaction conditions for the enantio- and diastereoselective addition of nucleophiles derived from either cyclic or acyclic dienes (Figure 19A).[59,60] Some closely related reactions involving 2-aza-1,3-diene pronucleophiles were also reported by the Malcolmson group.[61]

A recent direction for our research has been toward more electrophilic, and thus, more rapidly reduced electrophiles, such as aldehydes. The absence of aldehyde substrates from the Cu-catalyzed reductive addition toolbox was not surprising: the reduction of aldehydes by CuH is known to be extremely rapid,[62] which means that most unpolarized olefin substrates would not have a chance to undergo hydrocupration. The solution to this problem involved adding the aldehyde slowly over the course of several hours, which maintains a large steady-state ratio of the olefin concentration to carbonyl concentration. This allowed for high-yielding allylation of both aryl and alkyl aldehydes with 1,3-diene pronucleophiles with excellent stereoselectivity (Figure 19B).[63] Importantly, this strategy is only effective because the allylcopper intermediate is relatively stable and can therefore “wait” for an aldehyde to intercept it.

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OUTLOOK

CuH-catalyzed hydrofunctionalization continues to be a central topic of interest in our group. Looking forward, some immediate challenges and broad avenues for progress are highlighted in Figure 20. First, with regard to the starting materials, several important classes of olefins (*e.g.*, trisubstituted, tetrasubstituted, *cis*-disubstituted, and those bearing electron-donating substituents) are still challenging substrates for CuH-catalyzed hydrofunctionalization. In these cases, current mechanistic evidence suggests that the difficult hydrocupration step is limiting and must be accelerated.

As a result, the design of improved ligands and (pre)catalysts is projected to play a significant and enabling role in the search for novel reactivity. Besides merely enhancing the activity of CuH catalysts, increasing their stability and compatibility with non-participating functional groups is an important goal. These next-generation catalysts might also allow for known reactions to proceed more quickly, in milder environments, using lower catalyst loadings, with less rigorous exclusion of air or moisture, and in complex, late-stage settings.

Lastly, although numerous mild and selective C–N and C–C bond-forming reactions have now been reported using CuH catalysis, analogous methods for many other couplings such as C–O, C–S, C–P, C–F, and C–CF_3 remain unknown, despite their potential significance for synthetic applications. An obstacle common to all of these transformations is high reactivity of the electrophiles under reducing conditions: for instance, most electrophilic oxygenation and fluorination reagents instantly undergo reduction by CuH and/or decompose the catalyst through the formation of inactive Cu(II) species. Thus, as was the case in the context of hydroamination reactions, the development of precisely tuned reagents will likely be a crucial focus in the future.

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Biography

Richard Y. Liu received his bachelor’s degree in chemistry and physics from Harvard University in 2015, supervised by Prof. Eric N. Jacobsen and Prof. Theodore A. Betley. In 2019, he completed his doctoral studies at MIT, where he worked with Prof. Stephen L. Buchwald on reactions catalyzed by Cu, Pd, and Ni complexes.

Stephen L. Buchwald is the Camille Dreyfus Professor and Associate Head of Chemistry at MIT. He is the recipient of several honors, including recently the Wolf Prize in Chemistry and the Roger Adams Award (ACS).

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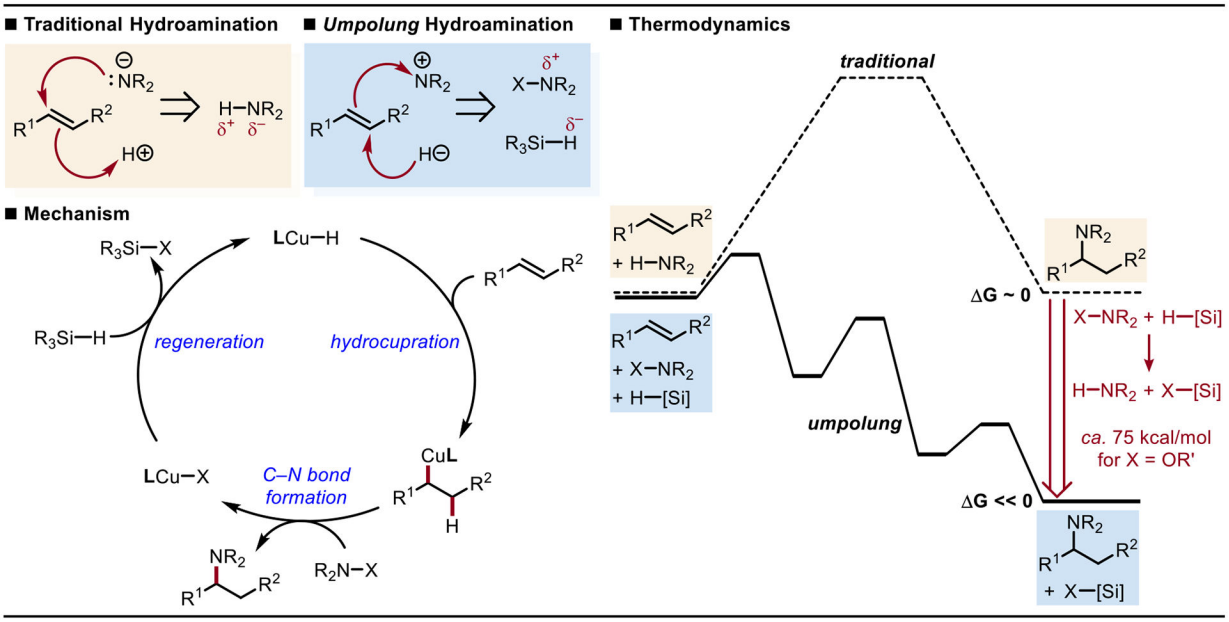

Figure 1.
CuH-Catalyzed Hydroamination.

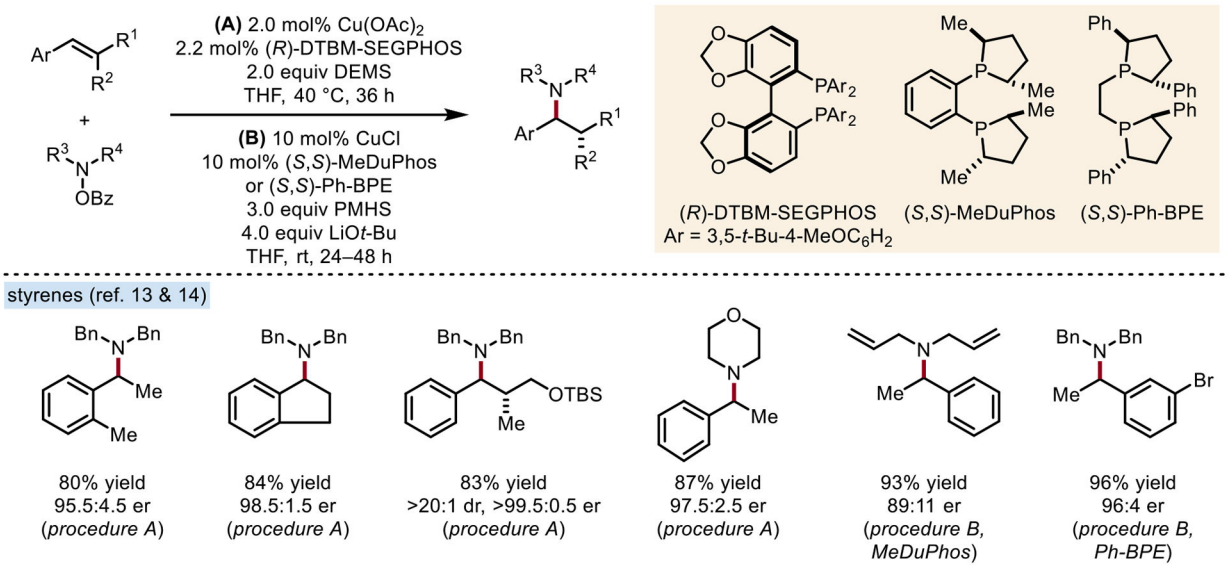

Figure 2.
Asymmetric Hydroamination of Styrenes.

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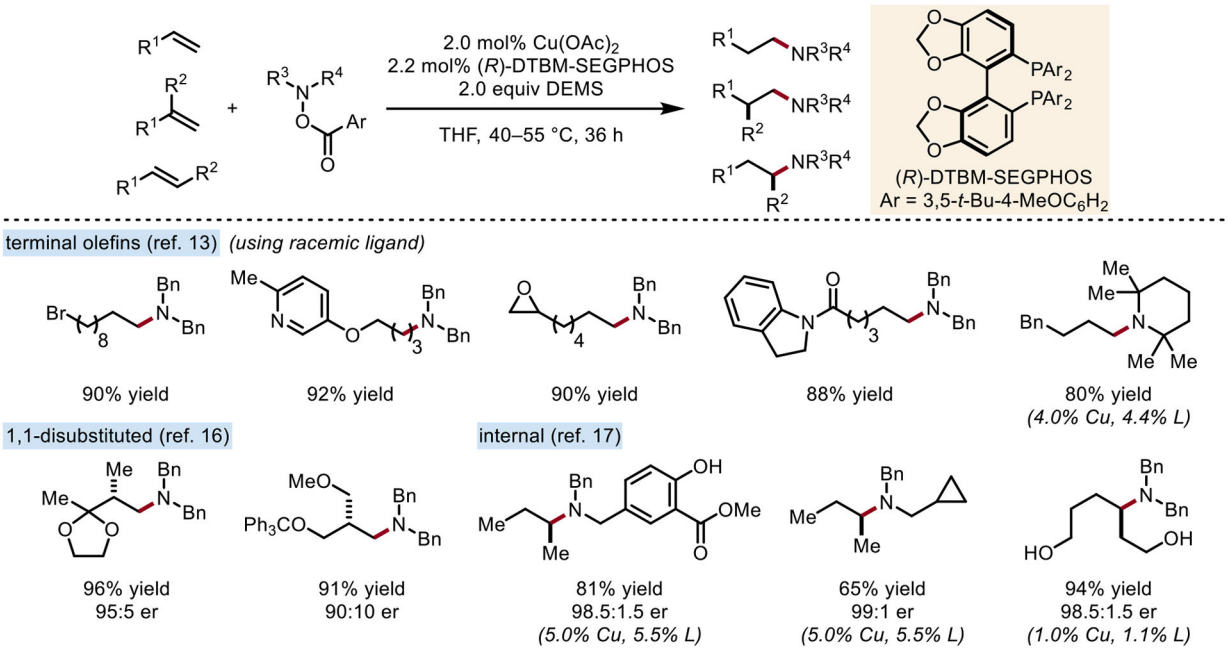

Figure 3.
Hydroamination of Unactivated Olefins.

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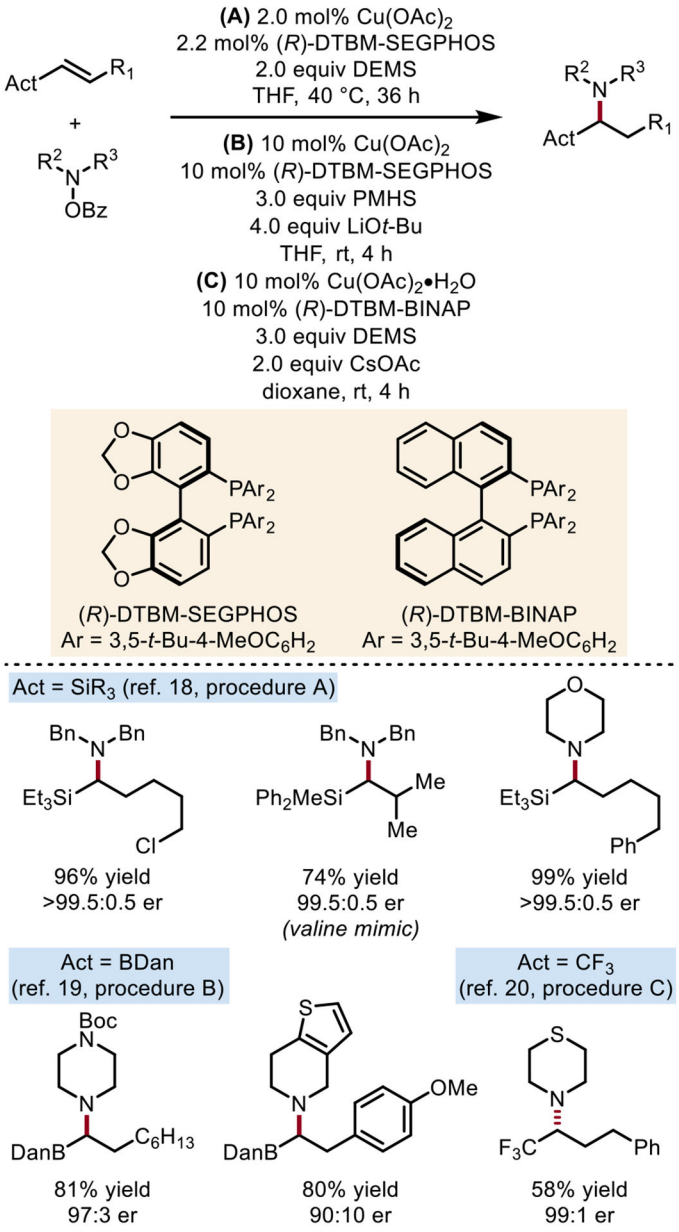

Figure 4.
Hydroamination of Activated Olefins.

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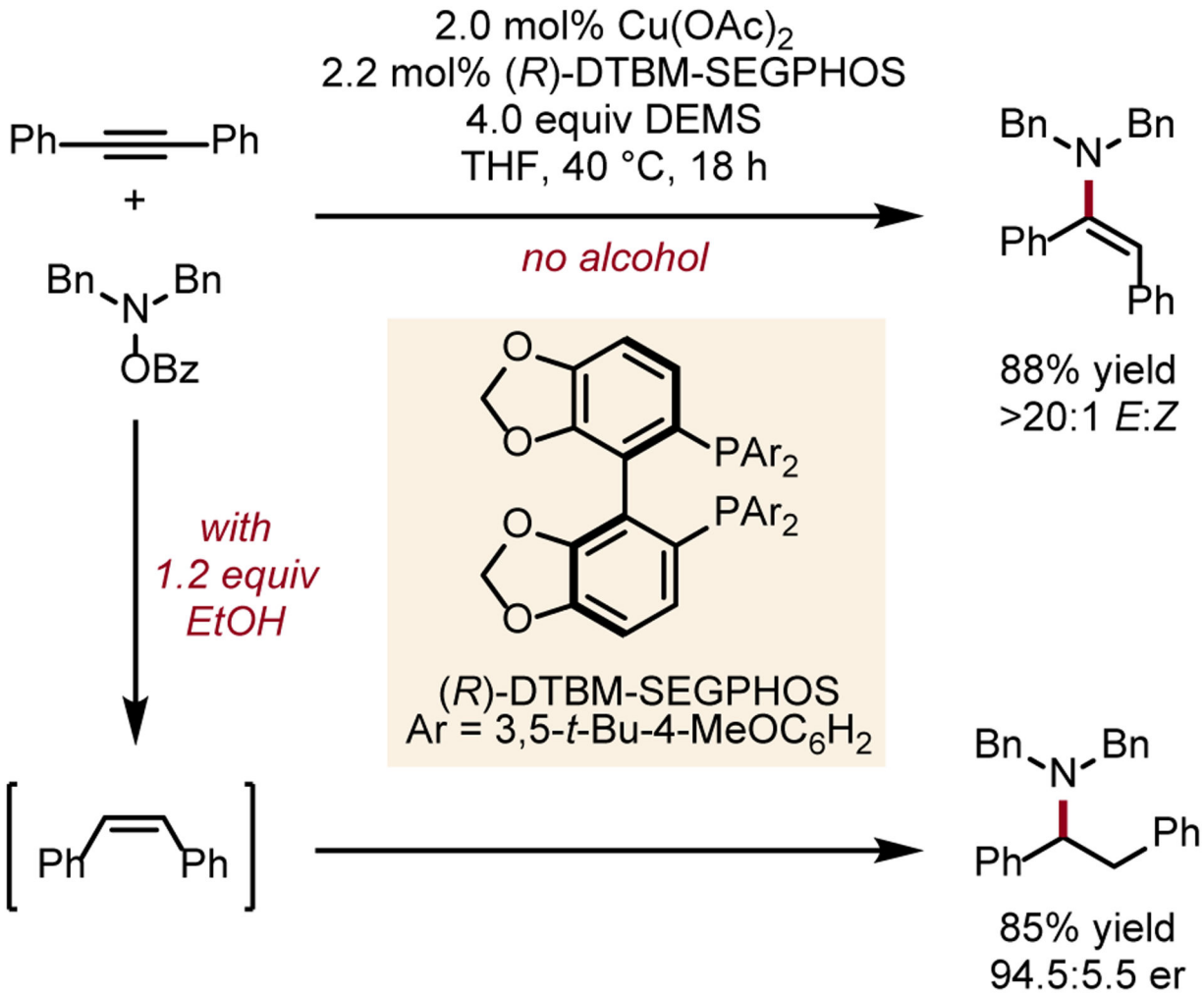

Figure 5.
Hydroamination of Alkynes.

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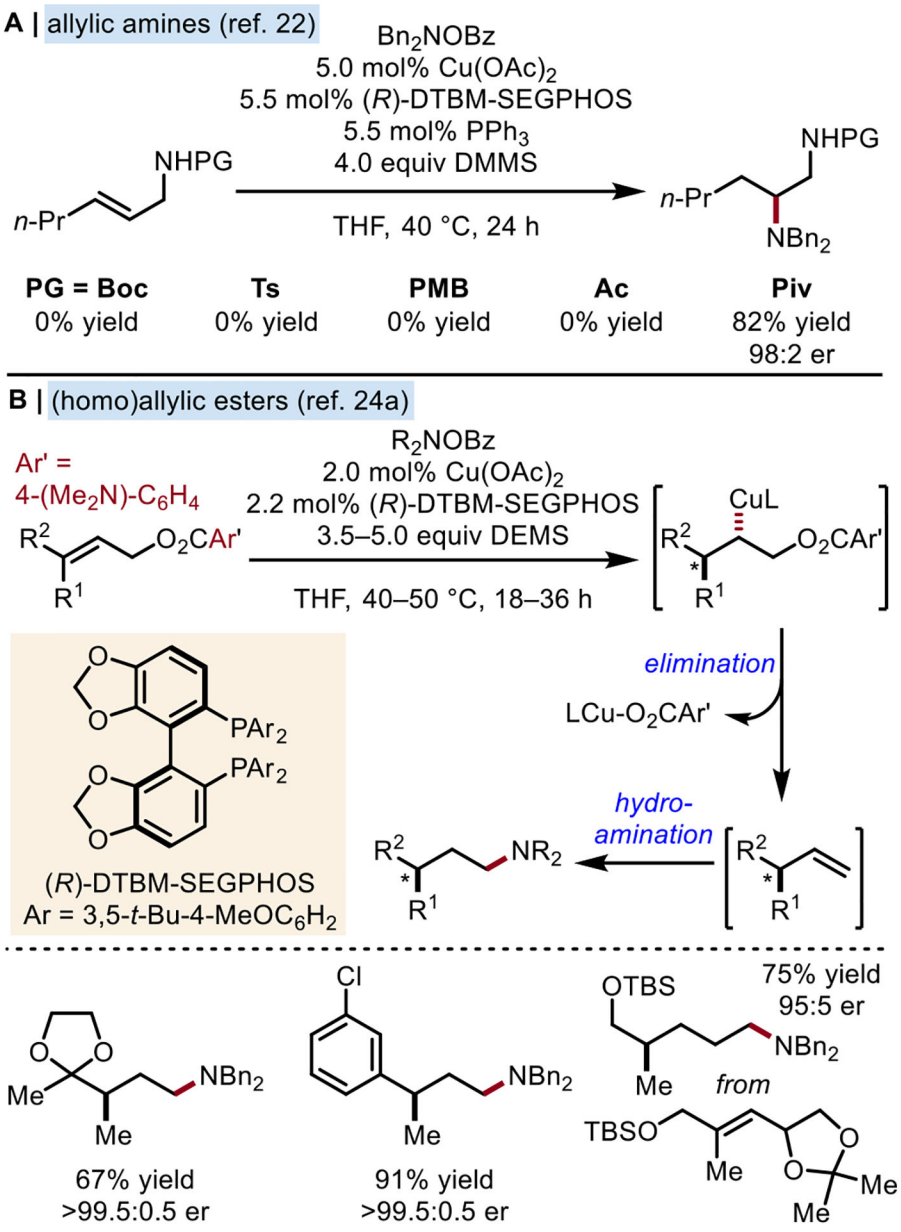

Figure 6.
Hydroamination of Allylic Amine and Alcohol Derivatives.

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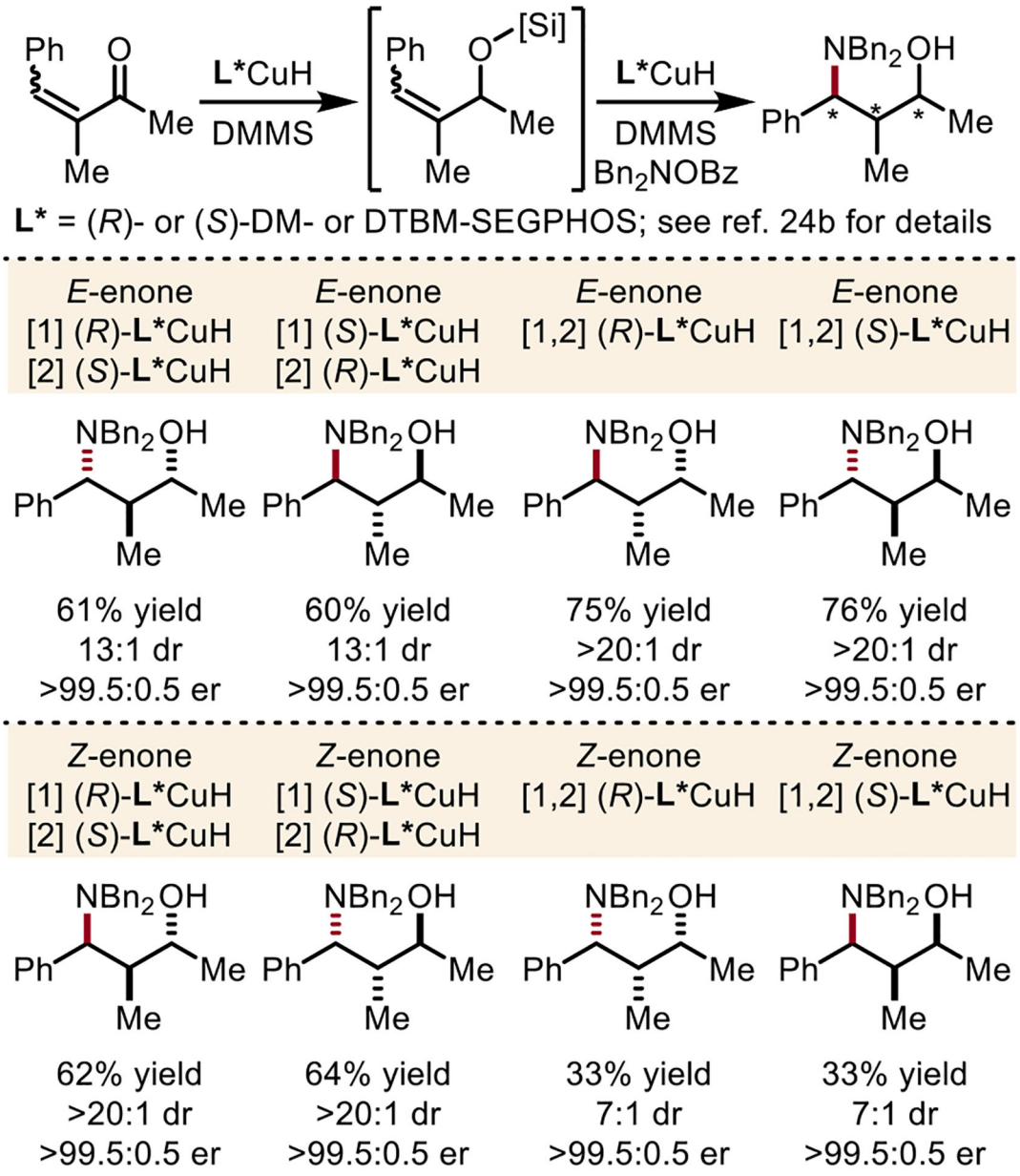

Figure 7.
CuH-Catalyzed Stereodivergent Synthesis of 1,3-Aminoalcohols.

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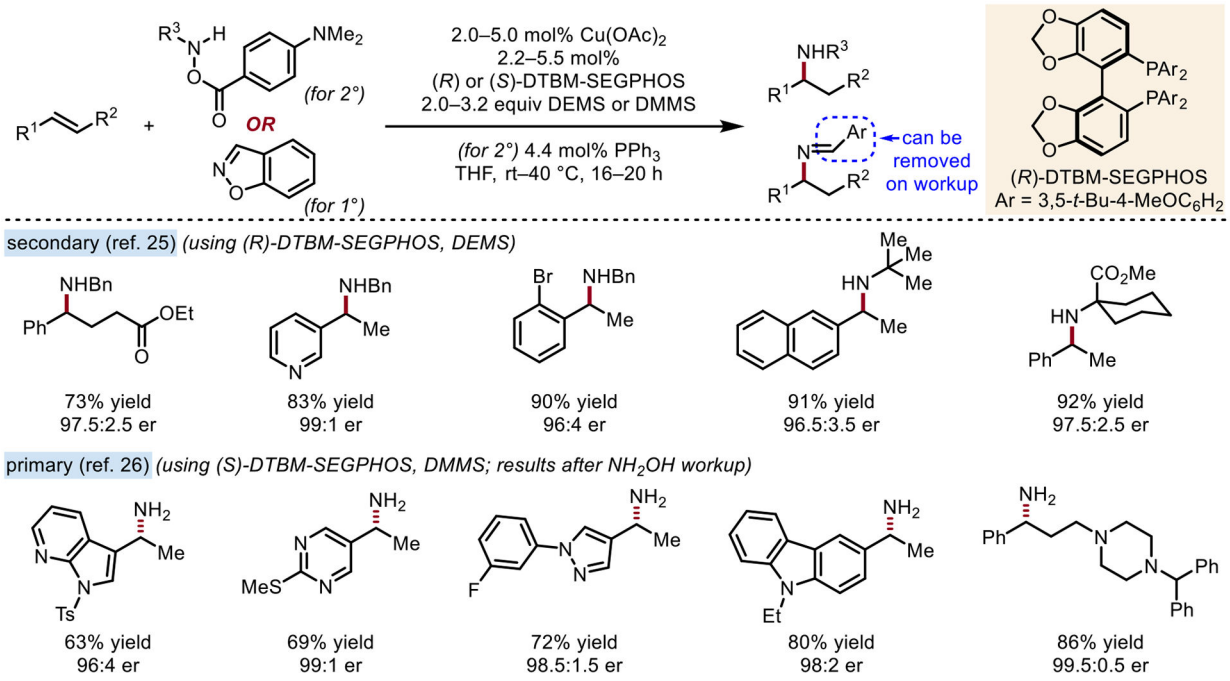

Figure 8.
CuH-Catalyzed Synthesis of Primary and Secondary Amines.

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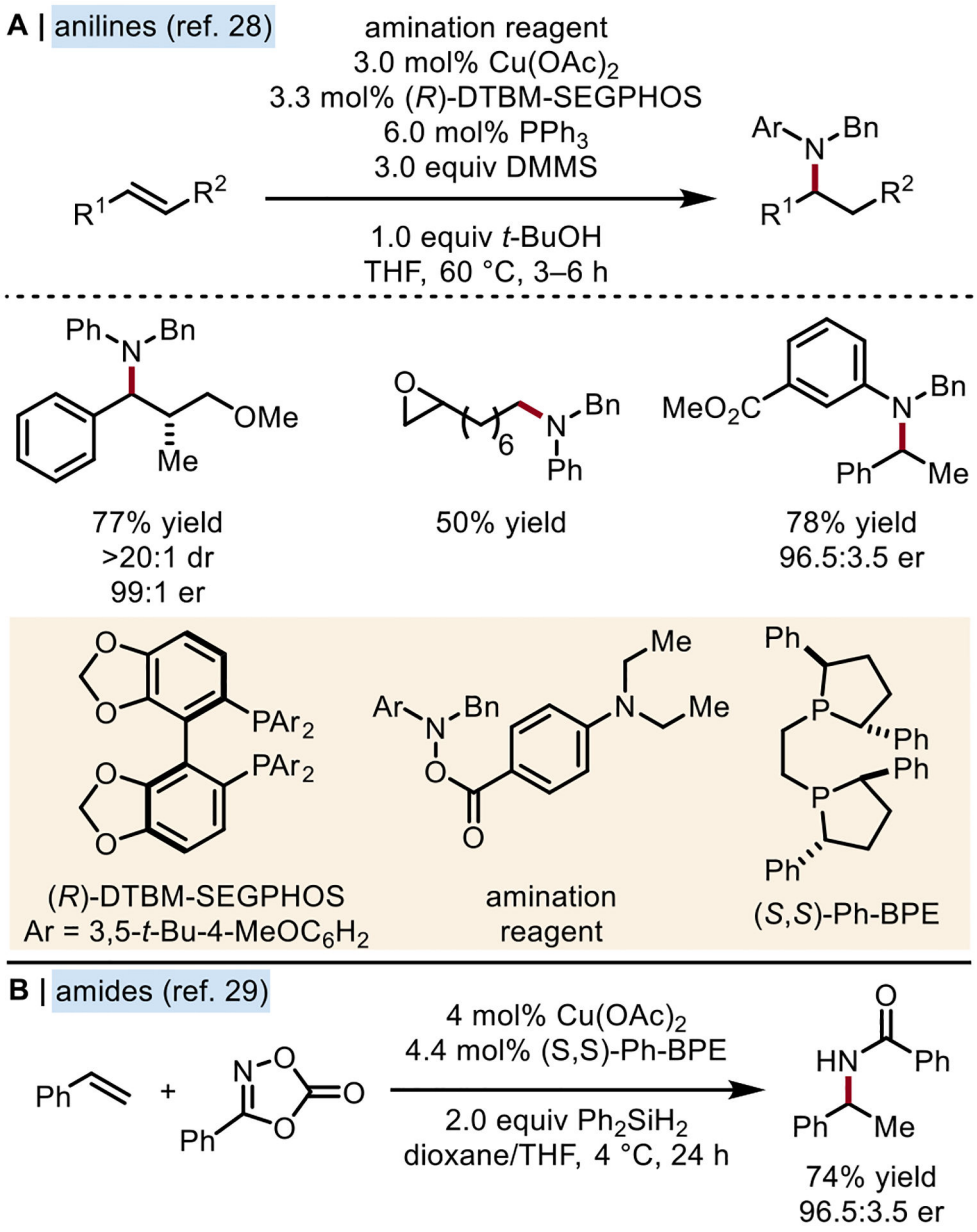

Figure 9.
CuH-Catalyzed Synthesis of Anilines and Amides.

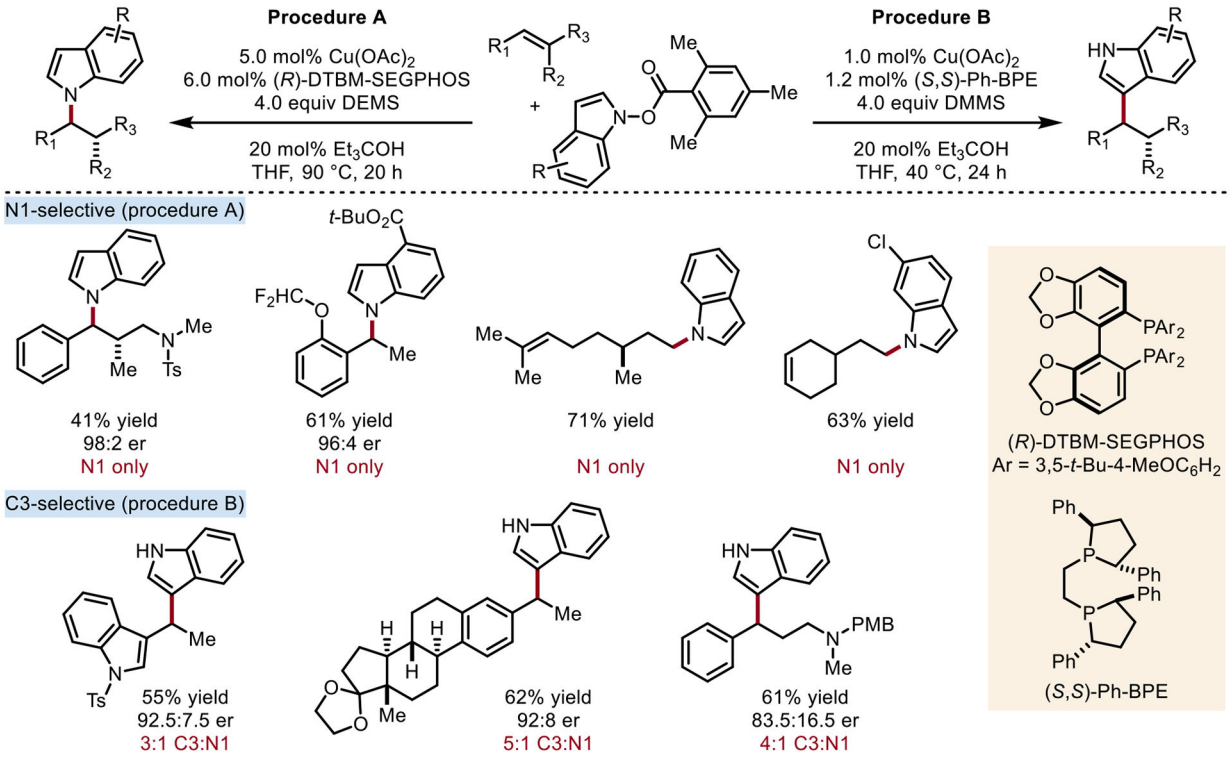

Figure 10.
CuH-Catalyzed Regiodivergent Indole Alkylation.

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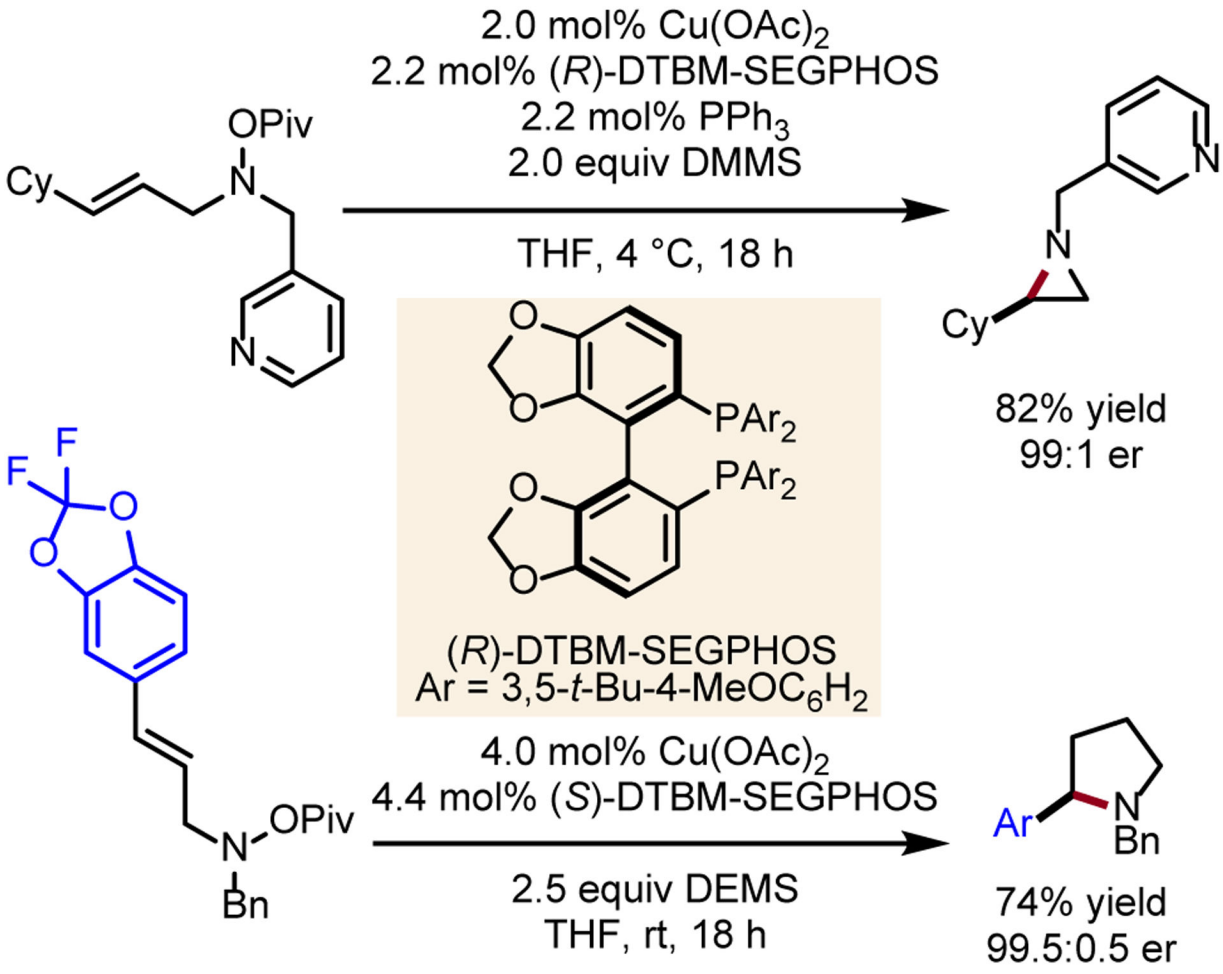

Figure 11.
Examples of CuH-Catalyzed Intramolecular Hydroamination.

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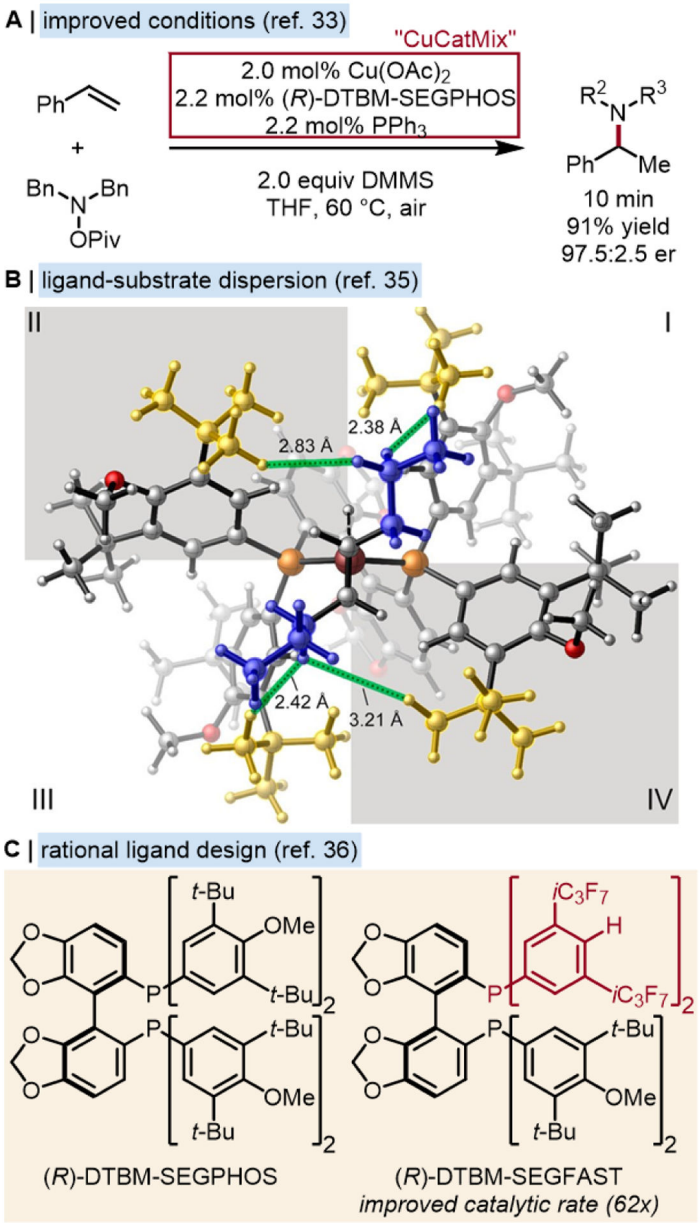

Figure 12.
Mechanistic Aspects of CuH-Catalyzed Hydroamination.

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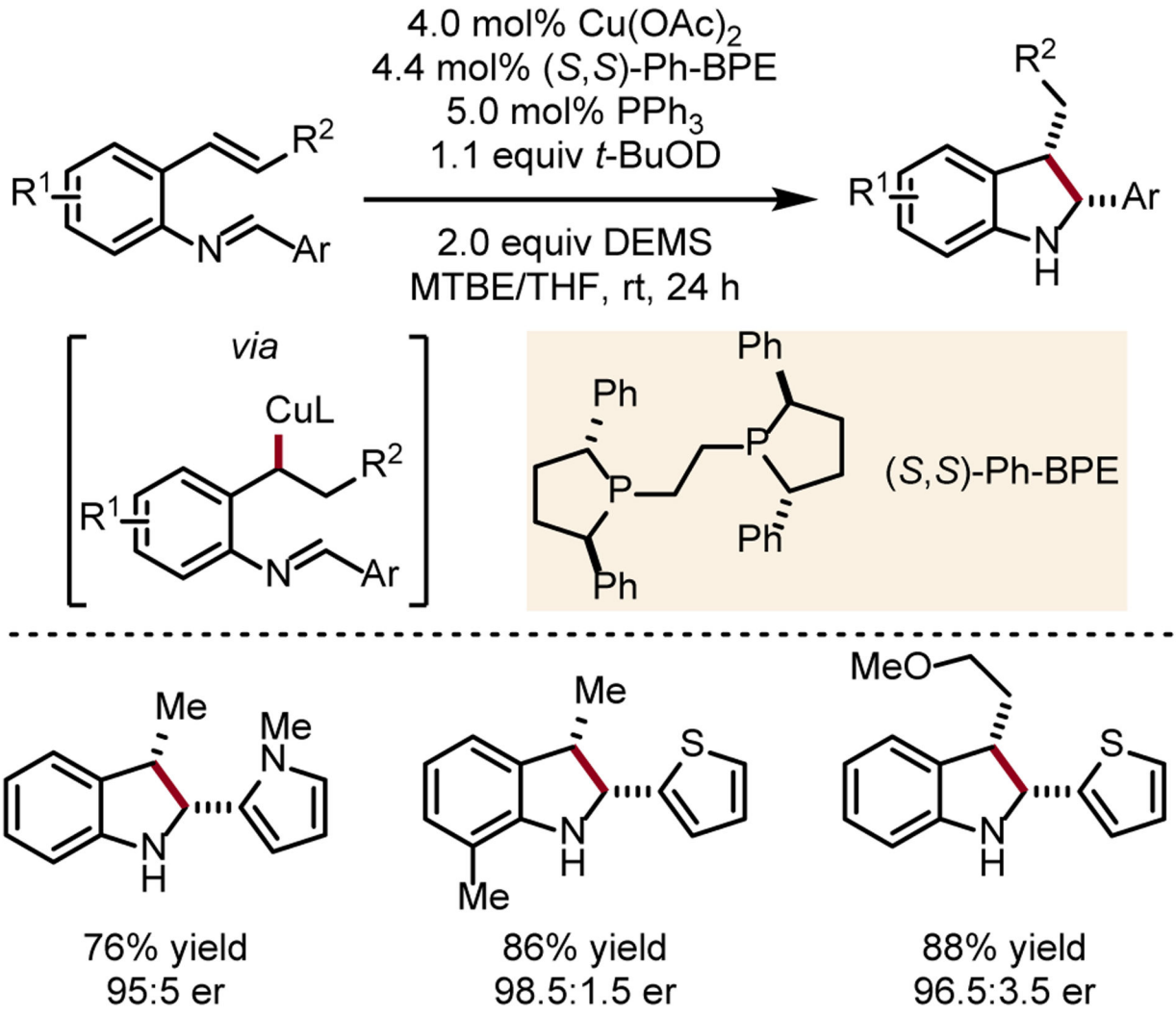

Figure 13.
Early Example of CuH-Catalyzed C–C Coupling.

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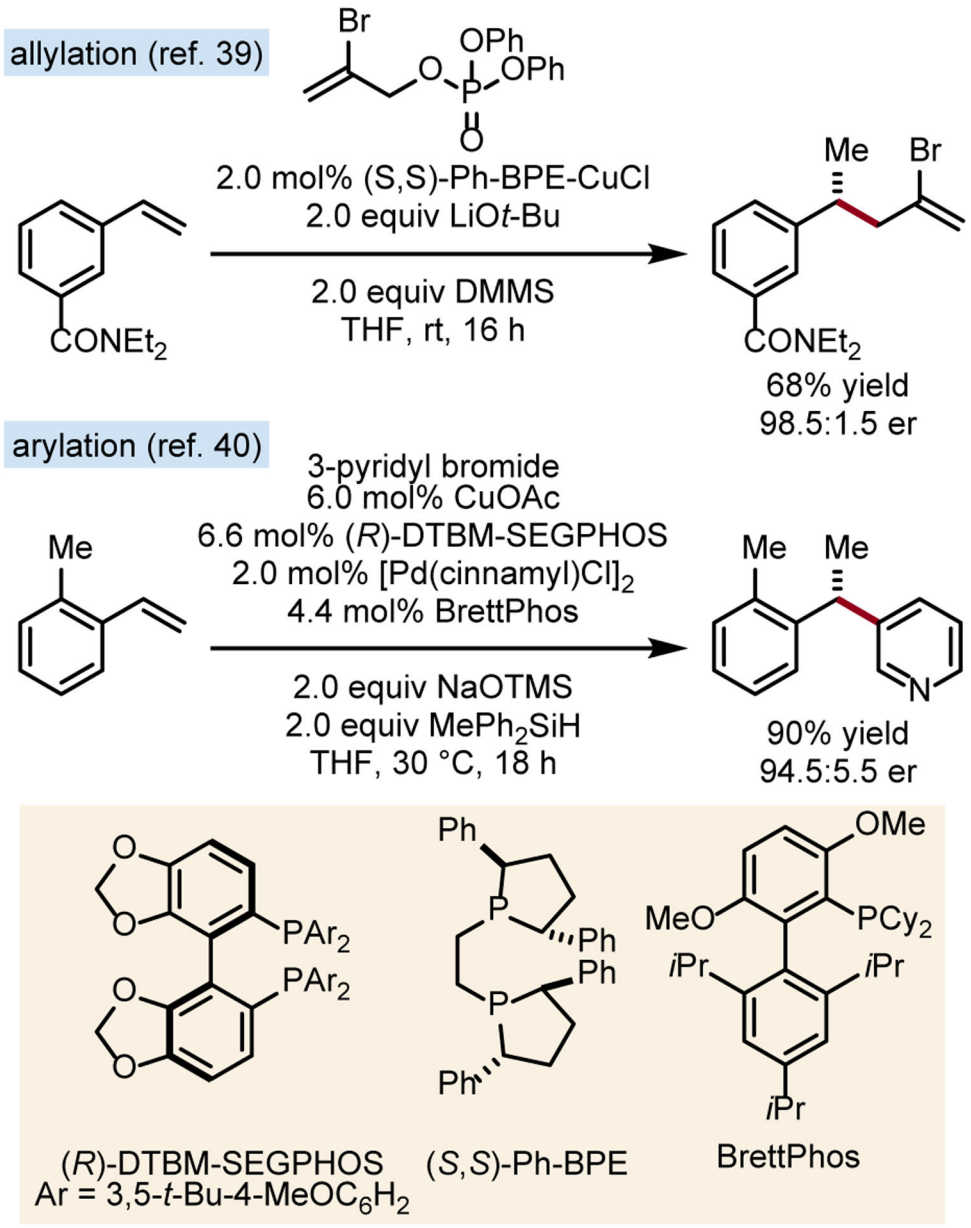

Figure 14.
Examples of Intermolecular C–C Couplings.

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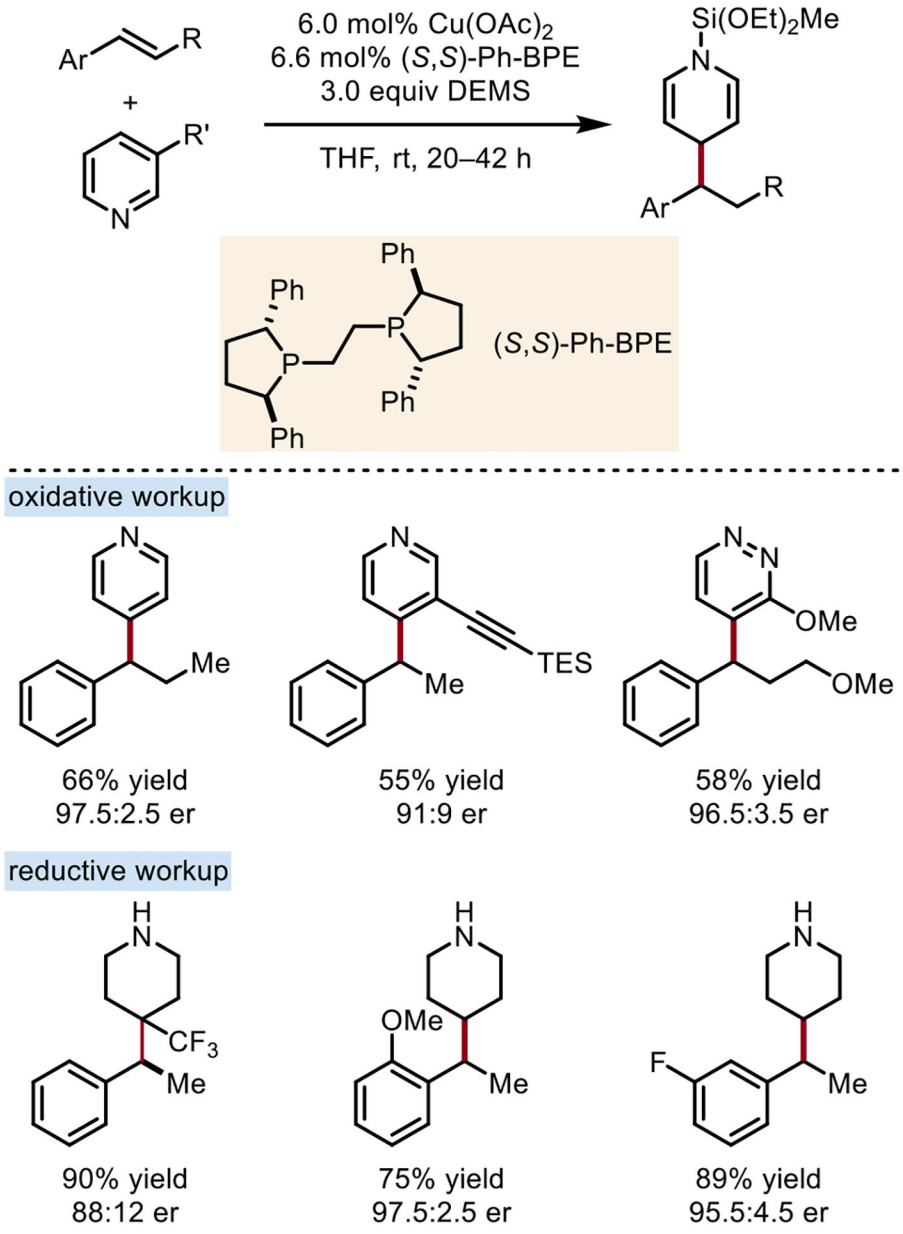

Figure 15.
CuH-Catalyzed Direct 1,4-Dearomative Hydrofunctionalization.

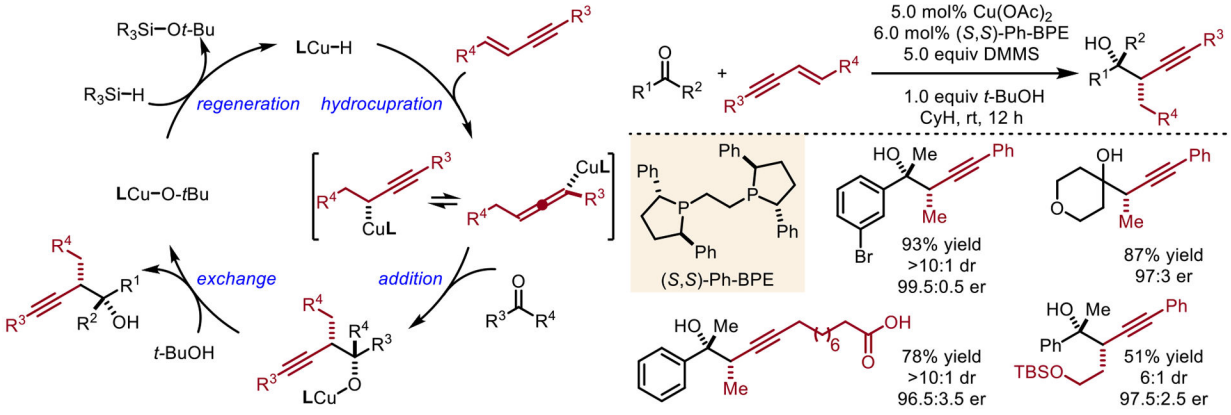

Figure 16.
CuH-Catalyzed Propargylation of Ketones.

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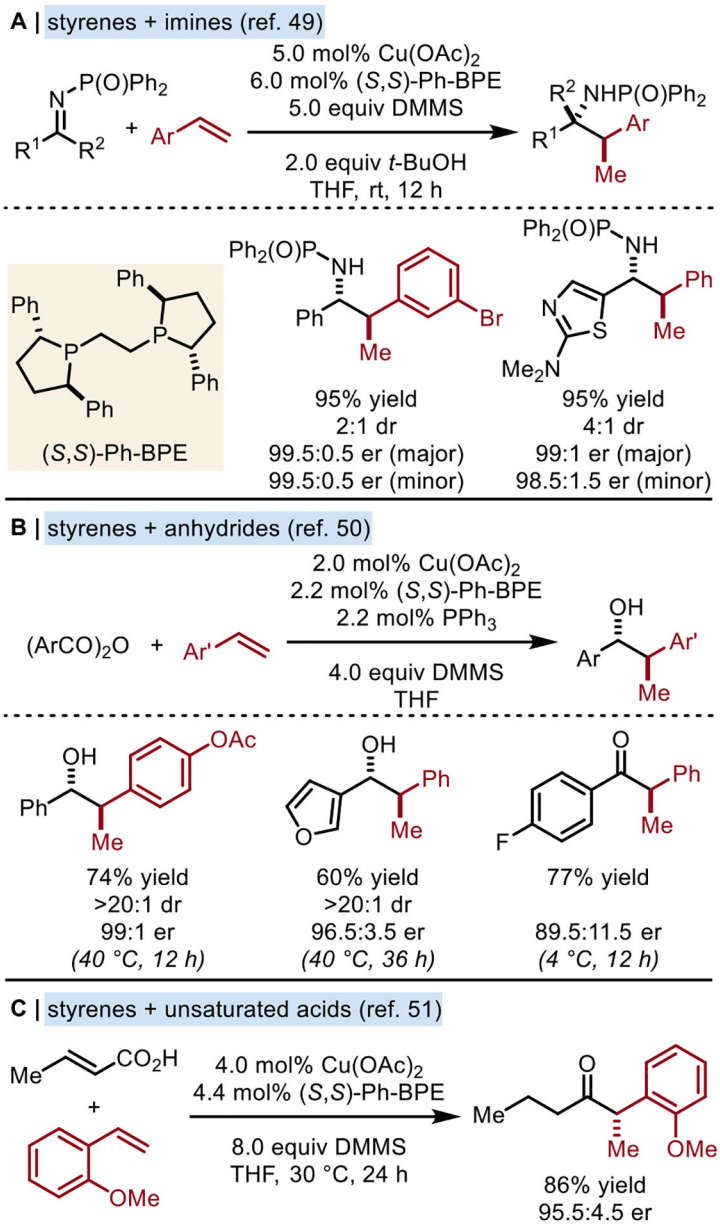

Figure 17.
CuH-Catalyzed Addition of Styrene-Derived Nucleophiles.

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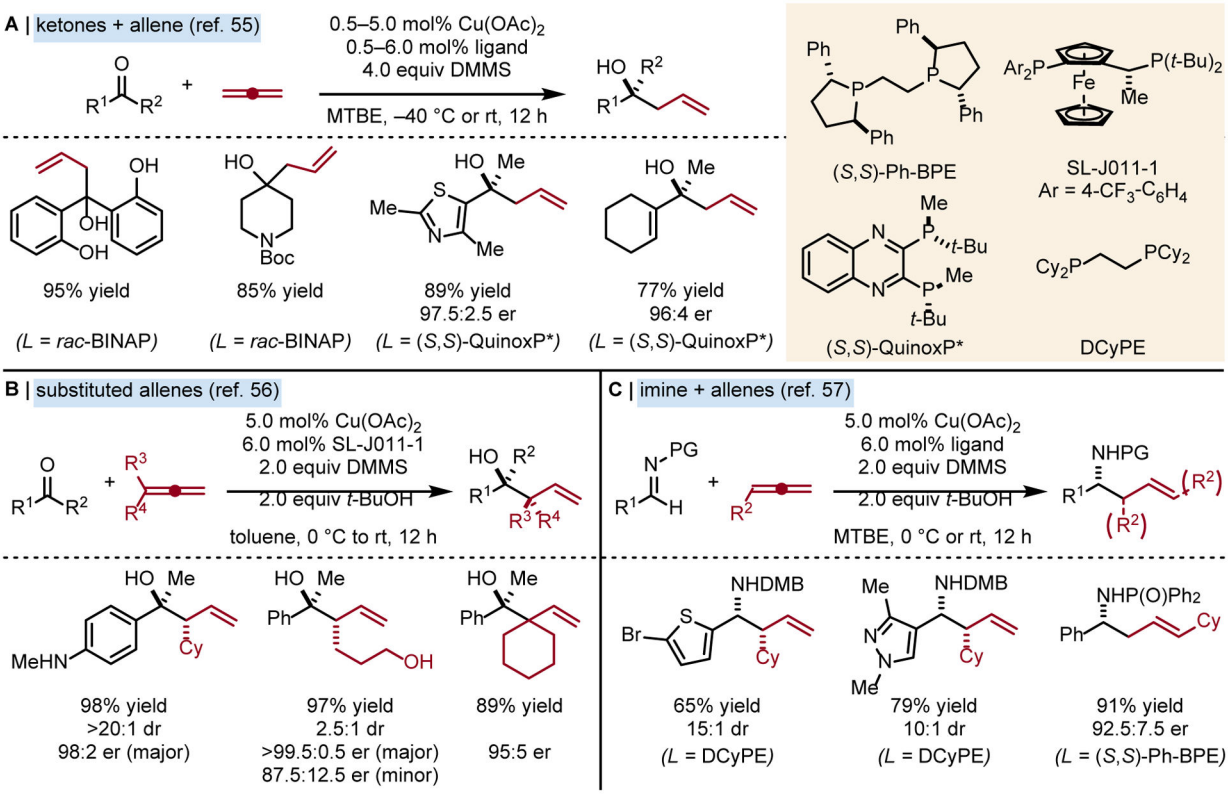

Figure 18.
CuH-Catalyzed Allylation Using Allenes.

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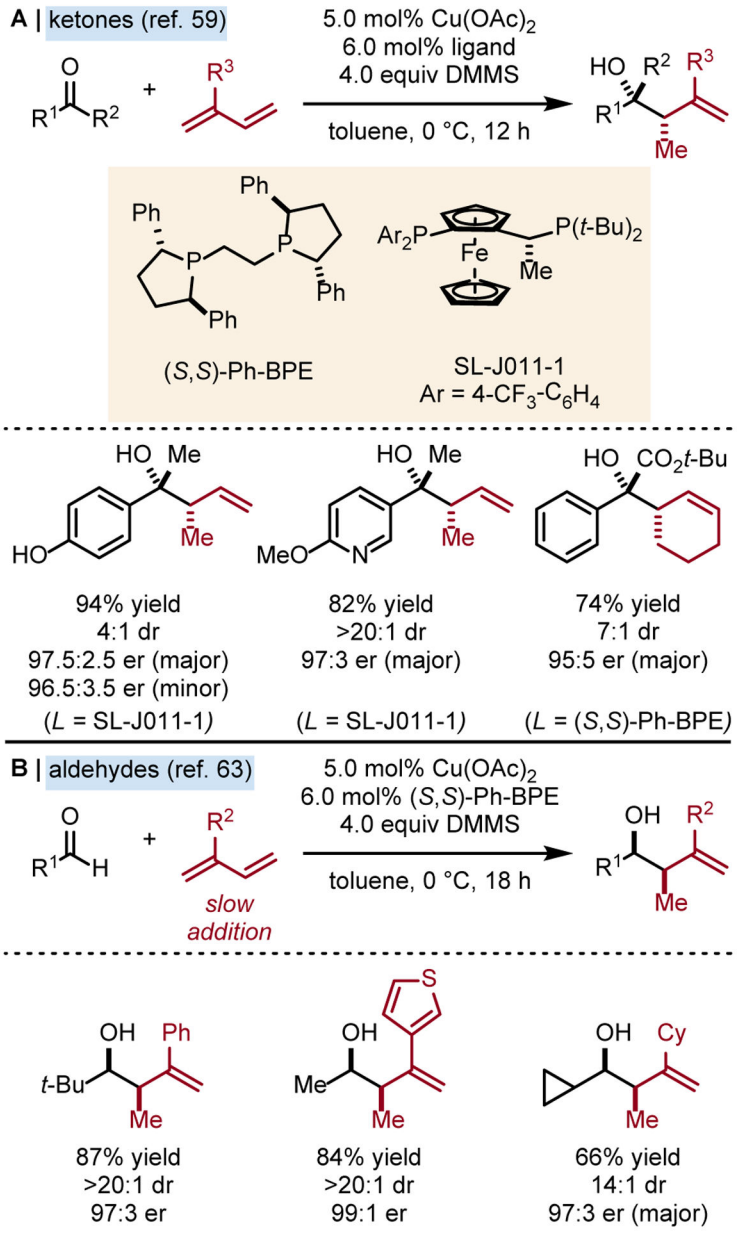

Figure 19.
CuH-Catalyzed Allylation Using Dienes.

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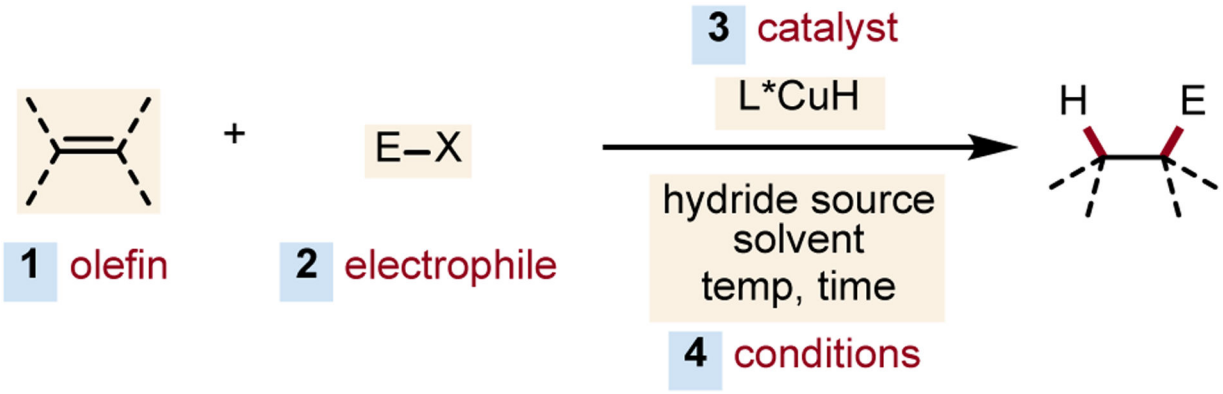

Figure 20.
Future Directions in CuH-Catalyzed Hydrofunctionalization: (1) Broader Olefin Scope, (2) New Types of Electrophiles, (3) Better Catalysts, (4) More Practical and Milder Conditions.