Regio- and Diastereoselective Synthesis of *E*-Allylic Amines Through Hydroalkylation of Terminal Alkynes.

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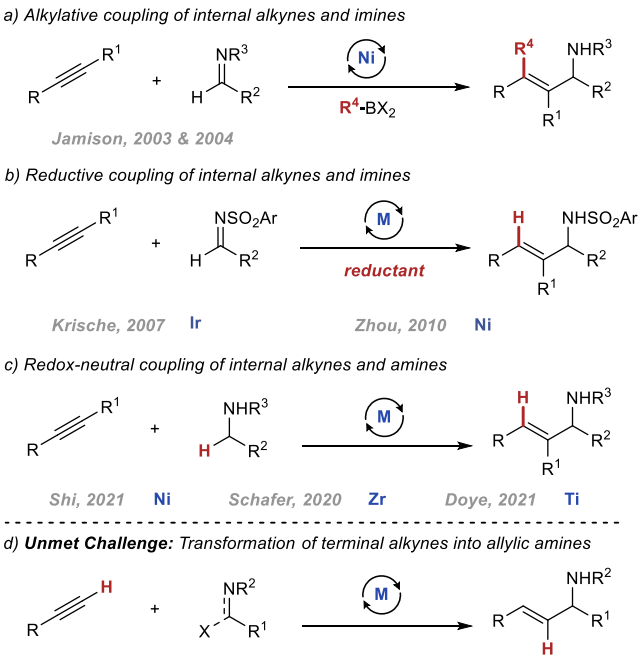
ABSTRACT: Allylic amines are an important class of organic compounds that have inspired the development of numerous methods for their synthesis. One of the most effective transformations involves coupling of internal alkynes with appropriate nitrogen-containing electrophiles in the presence of a transition metal catalyst. We have developed a method that allows transformation of terminal alkynes into allylic amines through a copper-catalyzed reductive cross coupling with α-chloro phthalimides. The method has a broad substrate scope and results in the highly selective formation of the *E*-isomer of the anti-Markovnikov hydroamination product. A preliminary mechanistic study supports a mechanism that involves hydrocupration of the alkyne and the formation of a solvent caged radical pair.

Allylic amines are common among natural products and biologically active molecules[1] and can serve as versatile synthetic intermediates.[2] As a result, numerous methods have been developed for their synthesis.[3] The most common synthetic strategy involves forming a new C-N bond to the preexisting carbon skeleton. Notable examples of this approach include amination of allylic electrophiles[4] (Tsuji-Trost reaction) and allylic C-H amination.[5]

Another strategy for making allylic amines involves creating a new C-C bond. While various C-C bond-forming reactions have been explored, one of the most general and commonly used transformations is the alkenylation of nitrogen-based electrophiles, such as imines, in reactions with organometallic reagents.[6] Recent advances in transition metal catalysis have allowed non-functionalized unsaturated compounds to replace preformed organometallic reagents in such alkenylation reactions.[7] Particularly impactful have been catalytic reactions of alkynes with imines, pioneered by Jamison and Krische (Scheme 1). In 2003 and 2004, Jamison reported alkylative coupling of alkynes and imines (Scheme 1a).[8] The first reductive coupling of alkynes and imines was reported by Krische in 2007 using an iridium catalyst,[9] while Zhou reported a nickel-catalyzed variant of the reaction in 2010 (Scheme 1b).[10] More recently, a redox-neutral variant of the reaction that involves in situ transformation of amines to imines and their coupling with alkynes has been developed by Shi (Scheme 1c).[11] The same transformation has been achieved through a different mechanistic pathway[12] using zirconium[13] and titanium catalysts.[14]

Using alkynes instead of alkenyl metal reagents offers well documented advantages,[15] but also narrows the scope of allylic amines that can be accessed using this approach. The various iterations of the alkyne-imine coupling reactions have been limited to reactions of *internal alkynes* (Scheme 1d). In this article we describe a new method for the transformation of *terminal alkynes* into allylic amines with excellent anti-Markovnikov and *E*-selectivity.

Scheme 1. Alkynes in the Synthesis of Allylic Amines.



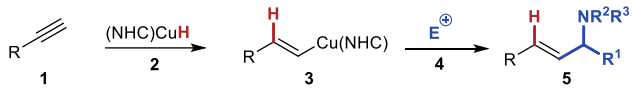
Our approach to the synthesis of allylic amines was based on a general approach to transformation of terminal alkynes into *E*-alkenes outlined in Scheme 2a.[16] The key component of the approach is the hydrocupration of an alkyne (**1**).[17] The addition of NHC-supported copper hydride complexes (**2**) to terminal alkynes is highly selective[18] and sets the anti-Markovnikov regioselectivity and *E*-diastereoselectivity of the overall transformation. The *E*-alkenyl copper intermediate (**3**) formed in the hydrocupration then reacts with an electrophilic coupling partner (**4**) to afford the final allylic amine (**5**). The challenge in using this approach to the synthesis of allylic amines was to identify an electrophilic coupling partner **4** that would provide the allylic amine

without interfering with the formation of the copper hydride or alkenyl copper intermediates.

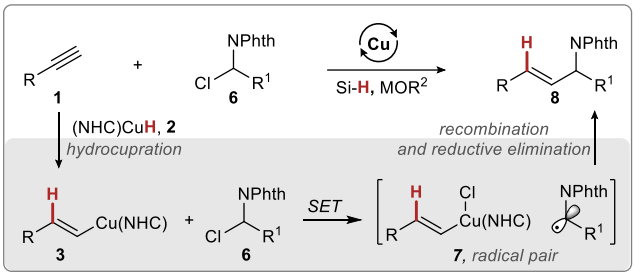
Initially, we explored reactions with imines as electrophiles. Buchwald[19] and Malcolmson[20] used them successfully in related copper-catalyzed reductive cross coupling reactions. However, in our attempts to achieve copper-catalyzed reductive coupling of terminal alkynes with various imines, under a wide range of reaction conditions, we observed the direct reduction of imines to amines as the dominant reaction pathway.

Scheme 2. Hydrofunctionalization of Terminal Alkynes and the Synthesis of Allylic Amines.

a) Synthesis of allylic amines through hydrofunctionalization



b) Reductive cross coupling of terminal alkynes with α-chloro phthalimides[a]

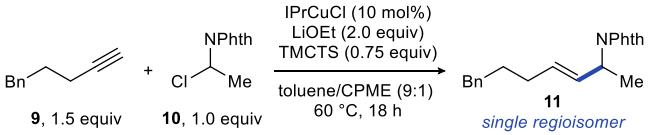


[a]NPhth = Phthalimido

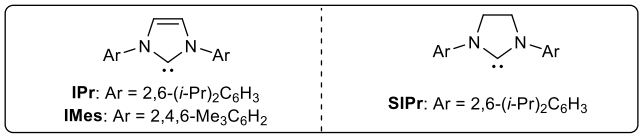
To avoid the direct reduction of electrophilic coupling partners by NHC copper hydride, we focused our attention on σ-electrophiles. α-Bromo esters,[21] alkyl iodides,[22] and α-chloro boronates,[16d] are all compatible with the hydrocupration of alkynes. Their reactions with NHC copper hydride complexes, when occur, are relatively slow two-electron processes.[16d, 23] Based on these considerations, and inspired by Fu's recent report,[24] we chose α-chloro phthalimides as coupling partners for the reductive transformation of terminal alkynes into allylic amines (Scheme 2b). We anticipated that α-chloro phthalimides (**6**) would couple with the alkenyl copper intermediate through a radical pathway initiated by inner-sphere single electron transfer (SET) (see **7**).[25] Similar mechanism has been documented in other transformations of alkenyl copper complexes[21] and in nickel-catalyzed cross coupling of α-chloro phthalimides with alkyl zinc reagents.[24] Another consideration in favor of α-chloro phthalimides as coupling partners is that the phthalimide group could be easily removed after the reaction to afford primary (*E*)-allylic amines.[26]

The proposed reactivity outlined in Scheme 2b prompted us to explore the catalytic reductive coupling of terminal alkynes with α-chloro phthalimides promoted by a copper catalyst in the presence of a silane and a turnover reagent. We found that the best results in the reaction of alkyne **9** with α-chloro phthalimide **10** were achieved using conditions shown in Table 1 (entry 1). The desired allylic amine **11** was obtained in 83% yield, as a single regioisomer and with greater than 70 to 1 E/Z selectivity (see SI for details). During the reaction development, we identified factors that were important for the success of the reaction. Among the NHC supported catalysts, only IPrCuCl and the closely related SIPrCuCl performed well (entries 1 and 2). Even the catalyst supported by the closely related IMes ligand gave a significantly lower yield of the desired product (entry 3). Similarly, catalysts prepared in situ from CuCl and various nitrogen-based or phosphine ligands provided no desired product (see SI). We also found that alkoxy silanes other than TMCTS (tetramethylcyclotetrasiloxane) gave lower yields (entries 4 and 5), while still outperforming a variety of alkyl or aryl silanes (see SI). Turnover reagents closely related to LiOEt, including LiOMe, LiO*t*-Bu, NaOEt, and KOEt, provided **11** in significantly diminished yields (entries 6-9). A mixture of toluene and cyclopentyl methyl ether (CPME) in a 9:1 ratio emerged as the best solvent. Using CPME or toluene individually or varying their ratio in the mixture led to diminished yields (entries 10-12). Notably, polar aprotic solvents, like DMA and THF, were not suitable as reaction solvents (entries 13 and 14).

Table 1. Reaction Development.



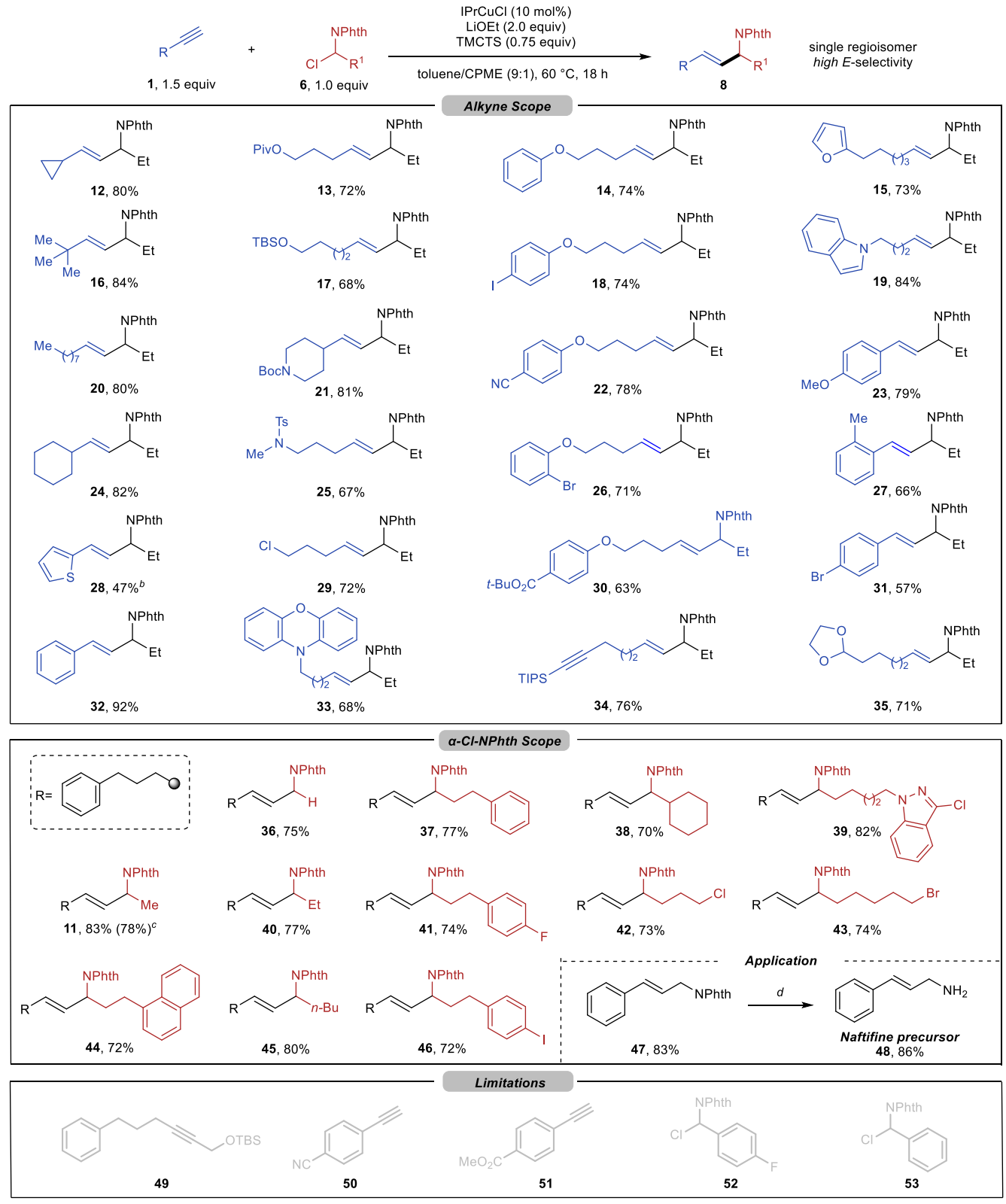
Entry	Change from standard conditions	Yield (%)[a]
1	none	83[b]
2	SIPrCuCl instead of IPrCuCl	80
3	IMesCuCl instead of IPrCuCl	7
4	PMHS instead of TMCTS	73
5	$(EtO)_3SiH$ instead of TMCTS	67
6	LiOMe instead of LiOEt	0
7	LiO*t*-Bu instead of LiOEt	55
8	NaOEt instead of LiOEt	7
9	KOEt instead of LiOEt	42
10	toluene instead of toluene/CPME (9:1)	75
11	CPME instead of toluene/CPME (9:1)	49
12	toluene/CPME (1:1) instead of toluene/CPME (9:1)	56
13	DMA instead of toluene/CPME (9:1)	0
14	THF instead of toluene/CPME (9:1)	21



[a]Yields determined by GC using an internal standard. [b]E:Z>70:1 determined by GC analysis using authentic samples of isomers.

With the optimized reaction conditions in hand, we explored the reaction scope and found that a variety of terminal alkynes and α-chloro phthalimides gave the desired products in moderate to high yields (Scheme 3). The allylic phthalimide products were obtained with excellent regio- and diastereoselectivity as only the anti-Markovnikov *E*-isomers of the products were detected by ^1H NMR spectroscopy. We also found that alkynes containing primary (**20**), secondary (**12**, **24**), and tertiary (**16**) alkyl substituents performed well. The reaction could be successfully performed in the presence of oxygen and nitrogen heterocycles (**15**, **19**, **21**, **33**), protected amines (**21**, **25**), protected alcohols (**13**, **17**), alkyl chlorides (**29**), esters (**30**), nitriles (**22**), and acetals (**35**).

Scheme 3. Substrate Scope.[a]



[a]Reactions performed on 0.5 mmol scale. Yields of isolated products are reported. [b]Two equivalents of the alkyne were used. [c]The reaction was performed on 3 mmol scale. [d]Conditions: $N_2H_4{\cdot}H_2O$ (1.1 equiv), MeOH.

Ortho and para substituted aryl halides (**18**, **26**, and **31**) afforded products in yields exceeding 70%. Even the substrate containing an additional internal alkyne (**34**) performed well, underscoring a preference for terminal alkynes in the hydrocupration step. One limitation of the reaction is that internal alkynes, such as **49**, fail to provide the desired allylic phthalimide products. Interestingly, our investigation unveiled substantial disparity in the reactivity

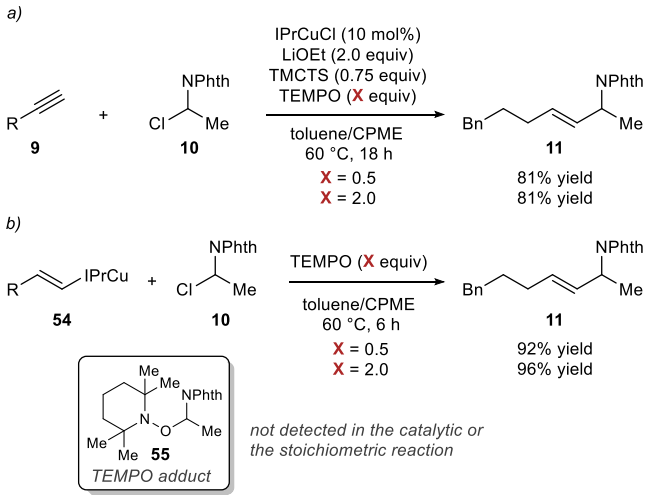
of conjugated alkynes. Electron-rich aryl alkynes (**23**, **32**) delivered high yields, aryl alkynes with moderately electron-withdrawing groups (**28**, **31**) gave moderate yields of the allylic amine products, while the electron-deficient aryl alkynes (**50**, **51**) afforded the desired product in about 10% yield. Intriguingly, the introduction of a single methyl group at the ortho position (**27**) caused a notable 26% reduction in yield (compared to **32**). We postulate that the lower yield in this case could be attributed to the effects of steric hinderance on the hydrocupration step.

We also explored the reactivity of different α-chloro phthalimide electrophiles and observed that alkyl halides (**42**, **43**), aryl halides (**41**, **46**), naphthalene (**44**), and chloroindazole (**39**) are well tolerated. Unfortunately, the α-aryl substituted α-chloro phthalimide yielded less than 40% of the expected product (**52**, **53**).

To illustrate the practical applicability of our method, we prepared **11** in 78% yield on a gram scale using standard conditions. Furthermore, we prepared Naftifine[27] precursor **48**[28] from phenyl acetylene through hydroalkylation and phthalimide deprotection in 71% overall yield (see SI for details).

Next, we explored the reaction mechanism. Our initial hypothesis was that the reaction proceeds through a SET mechanism similar to the one established for the reductive coupling of terminal alkynes and α-bromo esters.[21] This hypothesis was also consistent with Fu's observations of the TEMPO adduct of an α-phthalimide radical in the nickel catalysed cross coupling of α-chloro phthalimides with alkyl zinc reagents.[24] Surprisingly, we found that the addition of two equivalents of TEMPO did not inhibit the reaction (Scheme 4a). Furthermore, the stoichiometric reaction of alkenyl copper with α-chloro phthalimide also proceeded successfully in the presence of two equivalents of TEMPO (Scheme 4b). No TEMPO adducts were detected in either experiment, suggesting the absence of free radical intermediates.

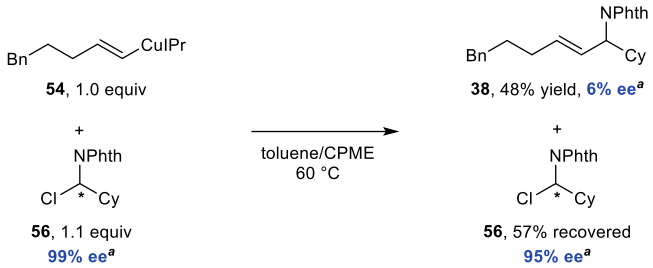
Scheme 4. Radical Trap Experiments.



[a]R = $Bn(CH_2)_2$

A plausible alternative mechanism consistent with the results of TEMPO experiments involves the formation of a radical pair followed by the radical recombination that is faster than the diffusion from the solvent cage.[29] To investigate this possibility, we explored the stereochemistry of the reaction (Scheme 5). A stoichiometric reaction with enantioenriched α-chloro phthalimide **56** provided a nearly racemic product **38** (6% ee). Additionally, the recovered starting material remained highly enantioenriched (95% ee). The loss of ee% in the allylic amine product is attributed to the equilibrium between two configurations of the α-phthalimide radical. The highly enantioenriched α-chloro phthalimide recovered after the reaction provides supporting evidence for the rapid and irreversible radical recombination step. It also eliminates the possibility of starting material racemization through a process unrelated to the formation of the allylic amine product. Similar results were obtained when enantioenriched **56** was used in a catalytic reaction (see SI).

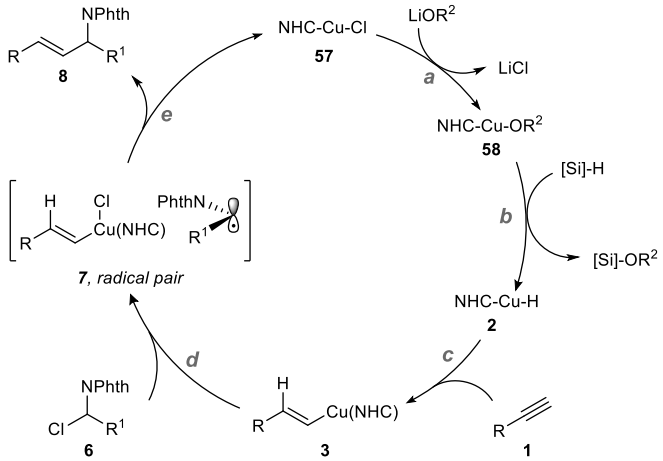
Scheme 5. Stereochemical Probe Experiment.



[a]Absolute configurations of enantioenriched compounds were not established.

Based on our experiments and literature precedents, we propose a reaction mechanism shown in Scheme 6. Alkenyl copper intermediate **3** is formed through a sequence that involves transmetalation of the NHC-supported copper alkoxide (**58**) with a silane (*step b)* and the subsequent hydrocupration of the alkyne (*step c*).[17a]

Scheme 6. Proposed Reaction Mechanism.



An inner-sphere electron transfer[25, 30] from alkenyl copper intermediate (**3**) ($E_{p,a}$ = 0.90 V vs. SCE in THF) to an α-chloro phthalimide ($E_{p,c}$ = -2.19 V vs. SCE in THF, (see SI)) results in C-Cl bond dissociation and the formation of a radical pair (**7**) (*step d*). The rapid radical recombination within a solvent cage, followed by the reductive elimination from a

copper(III) intermediate yields allylic amine **8** (*step e*).[30-31] Finally, the catalyst turnover is achieved by the recovery of copper alkoxide **58** in a reaction with lithium alkoxide.

In conclusion, we have developed a new method for transformation of terminal alkynes into allylic amines. The transformation is accomplished through the reductive coupling of terminal alkynes with α-chloro phthalimides promoted by a copper catalyst in the presence of a silane as the hydride source. The overall transformation is highly regioselective and affords anti-Markovnikov product with excellent *E*-selectivity (>70:1). The transformation is also compatible with a wide range of functional groups, including esters, nitriles, alkyl chlorides, aryl bromides and iodides, and a variety of heterocycles. Preliminary mechanistic investigation supports a mechanism that involves hydrocupration of the alkyne, followed by the cross coupling of the resulting alkenyl copper intermediate with an α-chloro phthalimide. We found evidence that the cross coupling involves the formation of a solvent caged radical pair through the initial inner-sphere SET followed by a rapid radical recombination.

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ASSOCIATED CONTENT

Supporting Information. Experimental procedures, results of mechanistic experiments, and product characterization (pdf). This material is available free of charge via the Internet at http://pubs.acs.org.

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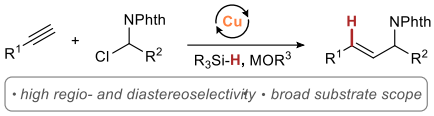
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• high regio- and diastereoselectivity • broad substrate scope