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Design of Modified Amine Transfer Reagents Allows the Synthesis of α-Chiral Secondary Amines via CuH-Catalyzed Hydroamination

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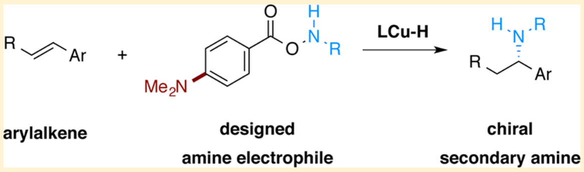
Ⓢ *Supporting Information*

ABSTRACT: The CuH-catalyzed hydroamination of alkenes and alkynes using a silane and an amine transfer reagent represents a simple strategy to access chiral amine products. We have recently reported methods to prepare chiral amines with high efficiency and stereoselectivity using this approach. However, the current technology is limited to the synthesis of trialkylamines from dialkylamine transfer reagents (R_2NOBz). When monoalkylamine transfer reagents [RN(H)OBz] were used for the synthesis of chiral secondary amines, competitive, nonproductive consumption of these reagents by the CuH species resulted in poor yields. In this paper, we report the design of a modified type of amine transfer reagent that addresses this limitation. This effort has enabled us to develop a CuH-catalyzed synthesis of chiral secondary amines using a variety of amine coupling partners, including those derived from amino acid esters, carbohydrates, and steroids. Mechanistic investigations indicated that the modified amine transfer reagents are less susceptible to direct reaction with CuH.



■ INTRODUCTION

Chiral amines are ubiquitous structural motifs found in many pharmaceutical agents, natural products, and catalysts for asymmetric synthesis (see Figure 1 for selected examples).

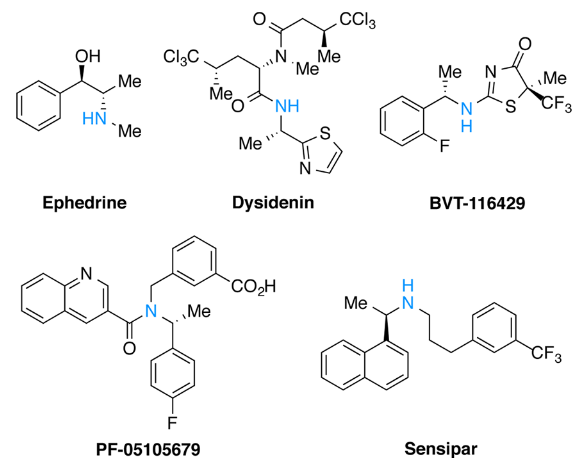


Figure 1. Representative natural products and pharmaceutical agents that feature a chiral amine motif.

As a result, general and selective methods for their synthesis have long been pursued.[1] Methodologies using resolution[2] or chiral auxiliaries[3] have been established as reliable ways to procure these compounds. Significant progress has also been made in the development of catalytic, asymmetric methods for their preparation. Many of these reported catalytic methods are based on asymmetric transformations of imine, enamine, or enamide intermediates.[4] Other strategies, such as asymmetric allylation of amine nucleophiles[5] and direct C−H bond insertion by a nitrenoid species,[6] are important alternatives.

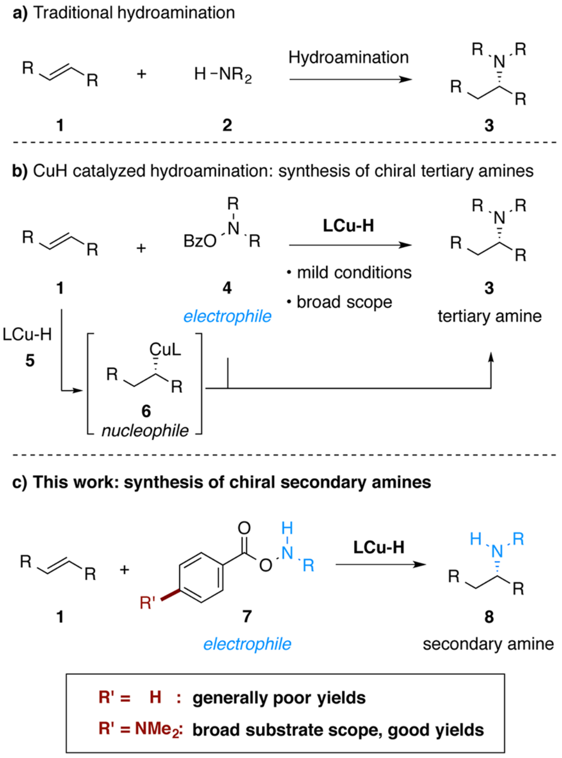


Figure 2. Hydroamination approaches to make α-chiral amines.

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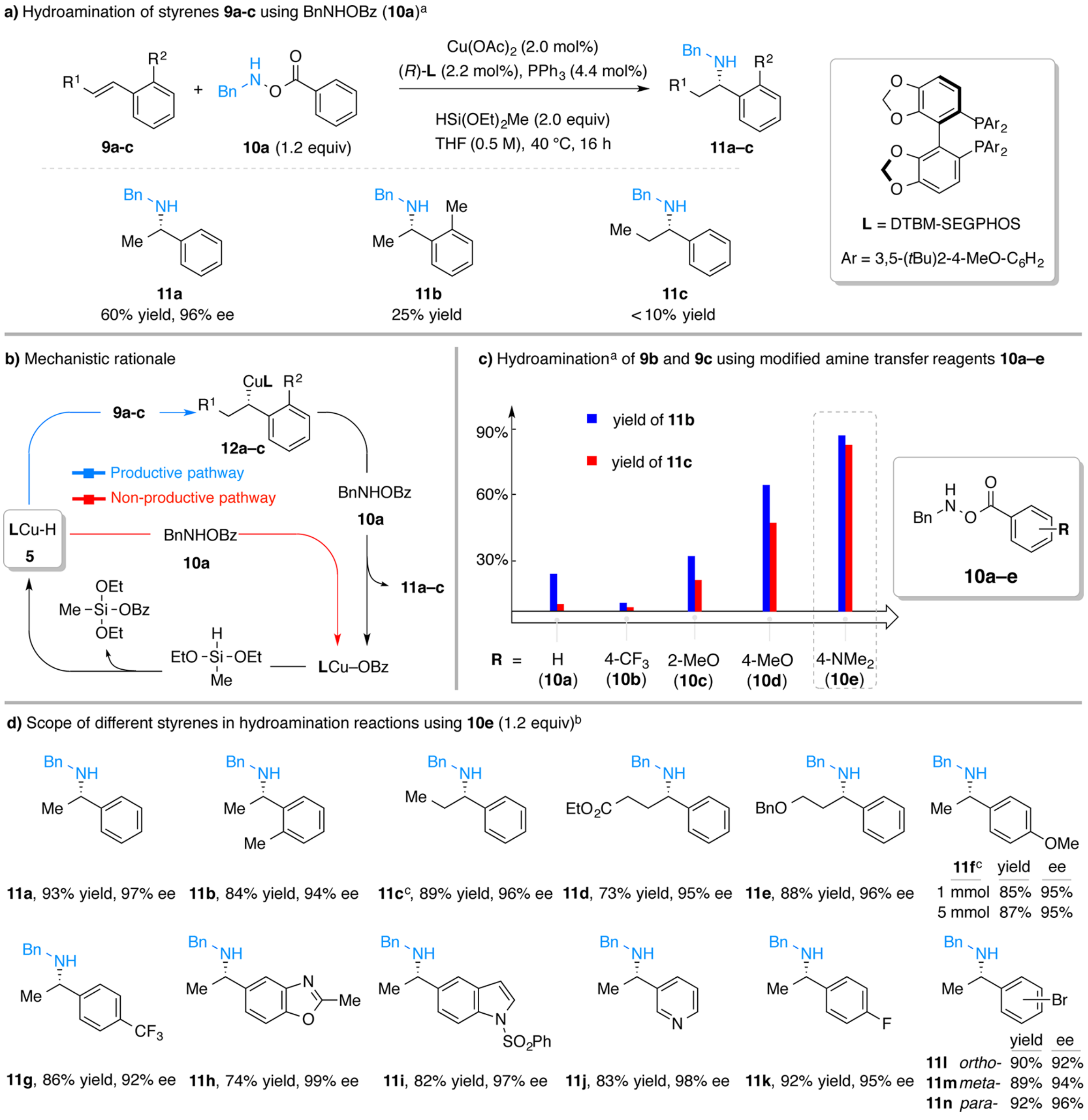

Figure 3. CuH-catalyzed hydroamination of styrenes for the formation of chiral secondary amines. [a]Yields are determined using GC with dodecane as an internal standard; unless otherwise noted, CuH solution used in this study was prepared in a nitrogen-filled glovebox. [b]Isolated yields on 1 mmol scale (average of two runs); enantiomeric excesses (ee) were determined by chiral HPLC analysis; see Supporting Information for experimental details. [c]Three equivalents of $HSi(OEt)_2Me$ was used, and **10e** was added over 1.5 h.

Asymmetric hydroamination,[7] the net stereoselective addition of a hydrogen atom and an amino group directly across a double bond, represents a particularly appealing strategy to prepare chiral amines. Typically, a hydroamination reaction entails the direct union of an alkene **1** with a primary or secondary amine nucleophile **2** in the presence of a catalyst (Figure 2a).[7] Based on catalytic copper(I) hydride chemistry[8] and recent developments in the copper-mediated amination of carbon-based nucleophiles,[9] our group recently reported a mechanistically distinct approach toward asymmetric hydroamination[10] (Figure 2b). In this technique, an olefin first undergoes asymmetric hydrocupration to provide an alkylcopper intermediate, which is then intercepted by a suitable electrophilic amine transfer reagent. Our laboratory has applied this hydroamination strategy to the synthesis of chiral tertiary alkylamines from styrenes,[10a] 1,1-disubstituted alkenes,[10b] vinylsilanes,[10c] and alkynes.[10d] Independently, Miura and co-workers have reported a similar approach for the hydroamination of styrenes[11a] and strained internal alkenes.[11b]

To date, this approach to hydroamination[10,11] has been limited to the synthesis of tertiary alkylamines with *O*-benzoyl-*N*,*N*-dialkylhydroxylamines (R_2NOBz, R = alkyl) as the dialkylamine transfer reagents. The expansion of this method to monoalkylamine transfer reagents to allow the direct preparation of chiral secondary amines would be of considerable interest. Herein we report the development of a copper-catalyzed hydroamination process to directly generate chiral, branched secondary amines **8** from styrenes (Figure 2c). One key factor in the development of this method is the design and use of a modified class of amine transfer reagents **7**, which improved the efficiency and generality of the transformation. Mechanistic studies indicate that use of the modified amine transfer reagent suppresses nonproductive consumption of the reagent by the copper hydride intermediate.

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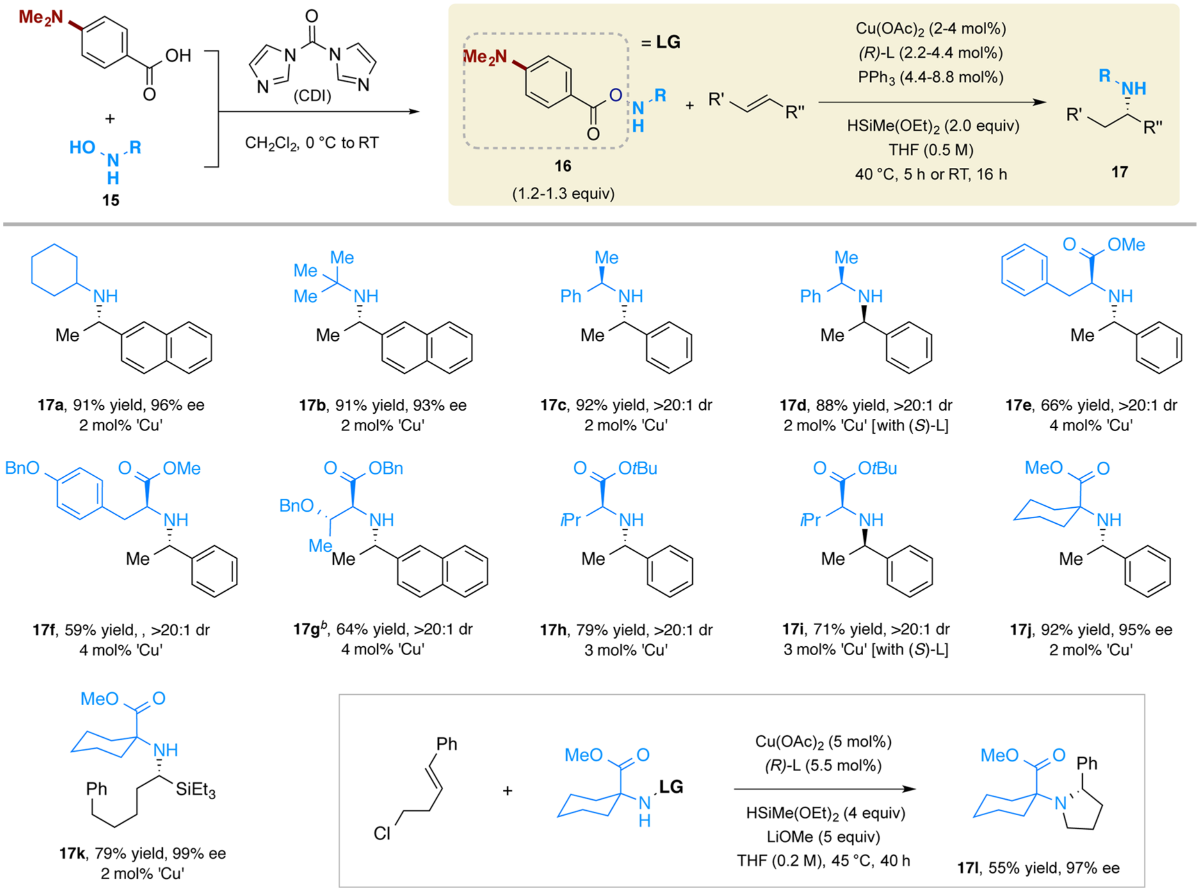
Table 1. Scope of Amine Transfer Reagents in Hydroamination Reactions[a]



[a]Reactions performed on 1 mmol scale for **17a−d** and 0.5 mmol scale for **17e−l**. Isolated yields are reported (average of two runs). Enantiomeric excesses (ee) were determined by chiral HPLC analysis or ^{1}H NMR analysis. Diastereomeric ratios (dr) were determined by ^{1}H NMR or gas chromatography analysis. [b]Toluene was used as the solvent, and amine transfer reagent with a pivolate leaving group was used as the substrate (see Supporting Information).

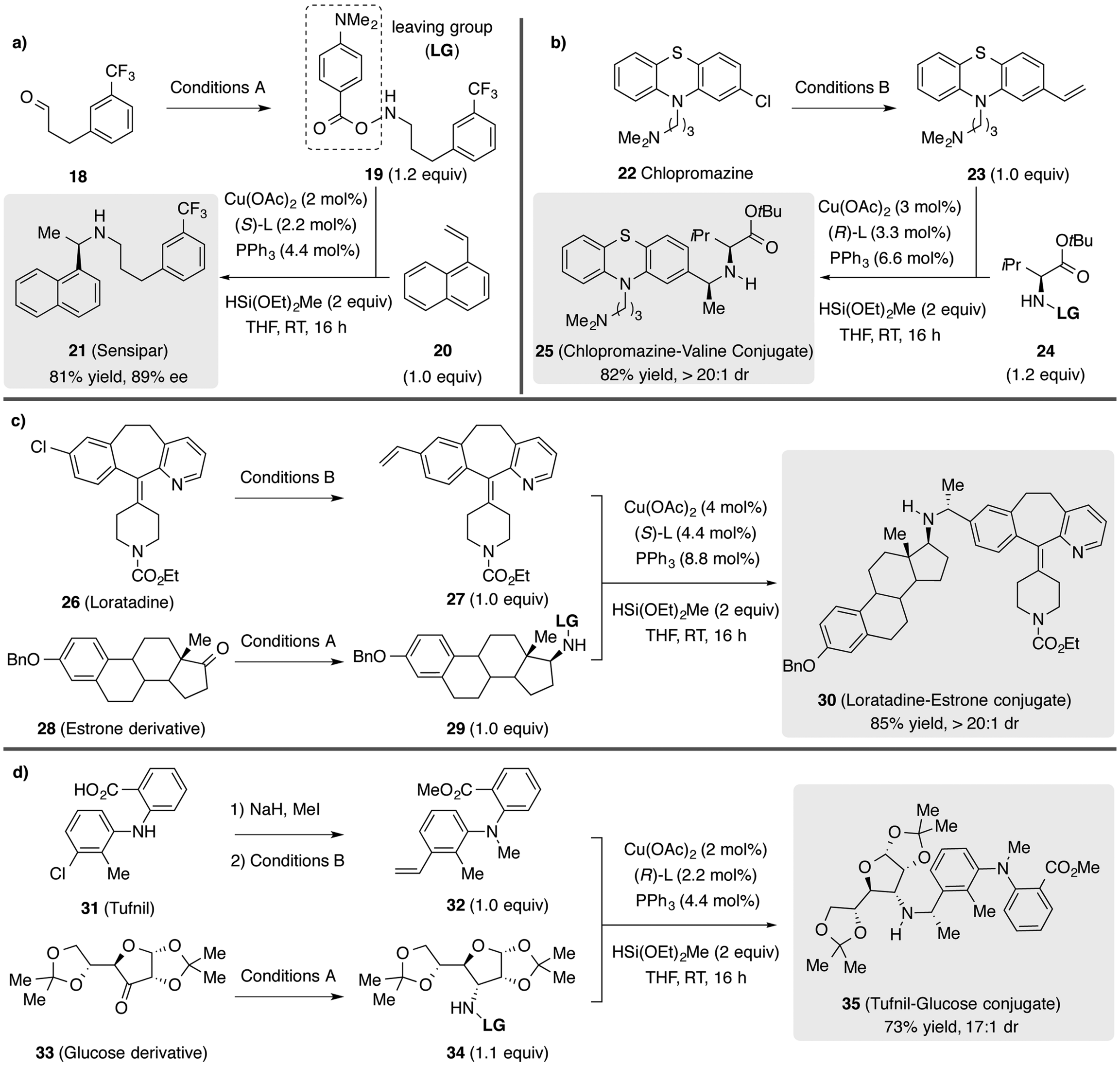
■ RESULTS AND DISCUSSION

We began our work by studying the reaction between styrene (**9a**) and *O*-benzoyl-*N*-benzylhydroxylamine[12] [BnN(H)OBz, **10a**] utilizing our previously reported conditions[10,13] (Figure 3a). It was found that the desired secondary amine **11a** was produced in moderate yield (60%) and excellent enantioselectivity. This result suggested the compatibility between the copper hydride and alkylcopper species with the N−H bond contained in both the amine transfer reagent **10a** and the secondary amine product **11a**. However, we found that this transformation had a limited substrate scope: either *ortho*- or *β*-substitution on the styrene substrate led to a dramatic drop in reaction efficiency (**11b** and **11c**, 25 and <10% yield, respectively). We reasoned that the poor yields of **11b** and **11c** might be caused by the more challenging hydrocupration of the substituted styrenes (**9b** and **9c**). In these cases, the (relatively rapid) nonproductive consumption of amine transfer reagent **10a** by LCuH (Figure 3b, red arrow) would diminish the overall yields of the respective secondary amine products.

We postulated that the use of an amine transfer reagent that is less susceptible to direct reaction with LCuH **5** would change the relative rates of the desired (hydrocupration) versus the undesired [BnN(H)OBz decomposition] pathway, thus expanding the substrate scope for the synthesis of secondary amines. We hypothesized that perturbation of the electronic properties of the benzoyl group of the electrophilic amine source **10** might lead to such an effect.[14] Thus, we prepared amine transfer reagents **10b−e** (Figure 3c) by coupling commercially available *N*-benzyl hydroxylamine hydrochloride with various carboxylic acids and tested these new amine transfer reagents for the hydroamination of styrenes **9b** and **9c** under the same conditions as depicted in Figure 3a. As summarized in Figure 3c, we found that the use of more electron-rich amine transfer reagents **10c−e** was beneficial to the reaction efficiency. Specifically, the use of **10e**, an amine transfer reagent bearing a 4-(dimethylamino)benzoate group, provided the highest yields of **11b** and **11c**. In contrast, **10b**, bearing the electron-deficient 4-(trifluoromethyl)benzoate group, gave poorer yields than the parent benzoate **10a**.[15]

With 4-(dimethylamino)benzoate **10e** as the amine transfer reagent, we found that a variety of styrene derivatives could be converted to the corresponding chiral secondary amines in good to excellent yield and with excellent enantioselectivity (Figure 3d). All these reactions proceeded to completion within 5 h at 40 °C or 16 h at room temperature under the reaction conditions shown in Figure 3a. For example, *β*-substituted styrenes and styrenes with *ortho*-substitution are suitable substrates (**11b−e**).[16] Additionally, styrenes bearing both electron-donating and electron-withdrawing substituents are tolerated as well (**11f−g**), and the reaction efficiency is not reduced when performed on a 5 mmol scale (**11f**). Further, styrenes containing heterocyclic rings are effective reaction partners (**11h−j**).

Scheme 1. Hydroamination Reaction in the Synthesis and Derivatization of Drugs[a]



[a]Reactions performed on 0.5 mmol scale. Isolated yields are reported (average of two runs). Enantioselectivities and diastereoselectivities were determined by chiral HPLC or ^{1}H NMR analysis. Conditions A: (1) $NH_2OH·HCl$, pyridine; (2) $NaBH_3CN$, HCl in MeOH, MeOH/THF; (3) 4-(dimethylamino)benzoic acid, CDI, CH_2Cl_2. Conditions B: $Pd(OAc)_2$, SPhos, potassium vinyltrifluoroborate, K_2CO_3, dioxane/H_2O.

Use of 4-fluorostyrene yielded **11k**, which resembles the core structure of PF-05105679 (Figure 1), in 92% yield and 95% ee. Lastly, this process also permits the preparation of **11l–n**, which contain synthetically versatile aryl bromide. The successful formation of **11l** was somewhat surprising since related alkylcopper intermediates had been shown to undergo rearrangement to afford the arylcopper species.[17]

We next investigated the scope of the amine transfer reagents that could be employed (Table 1). The amine transfer agents used in this study were prepared from the corresponding primary hydroxylamine **15** and 4-(dimethylamino)benzoic acid via condensation effected by 1,1′-carbonyldiimidazole (CDI).[18] As summarized in Table 1, amine transfer reagents with secondary or tertiary alkyl group substituents are competent substrates, delivering products **17a–d** in high yields and enantioselectivities. The use of chiral amine transfer agents afforded products with a high level of diastereoselectivity. The configuration of the newly generated stereocenter was determined by ligand employed (**17c** and **17d**). When either racemic ligand or racemic electrophile was used, a near unity ratio of diastereomers was formed (see Supporting Information). These results are consistent with the diastereoselectivity of the hydroamination process being under catalyst control.

We found that amine transfer reagents prepared from α-amino esters[19] were competent substrates as well, and gave the *N*-monoalkylated amino esters with high levels of stereocontrol (**17e–l**, Table 1). Amino esters spanning a range of steric and electronic properties could be utilized (**17e–j**). Importantly, the protecting groups on the amino esters could be methyl (**17e**,**f** and **17j**), benzyl (**17g**), or *tert*-butyl (**17h**,**i**), allowing a variety of choices for the selection of downstream deprotection methods. No epimerization of the labile stereocenter adjacent to the carbonyl group was observed, reflecting the overall mildness of the reaction system. Not surprisingly, use of different enantiomers of the ligand led to the formation of different diastereomers (**17h** and **17i**), again supporting a catalyst-controlled stereodetermining step. Furthermore, an amine transfer reagent derived from a quaternary α-amino ester could also be employed, giving **17j** in excellent yield and enantioselectivity. This method could also transform a vinylsilane[10c] to the α-aminosilane (**17k**), a class of

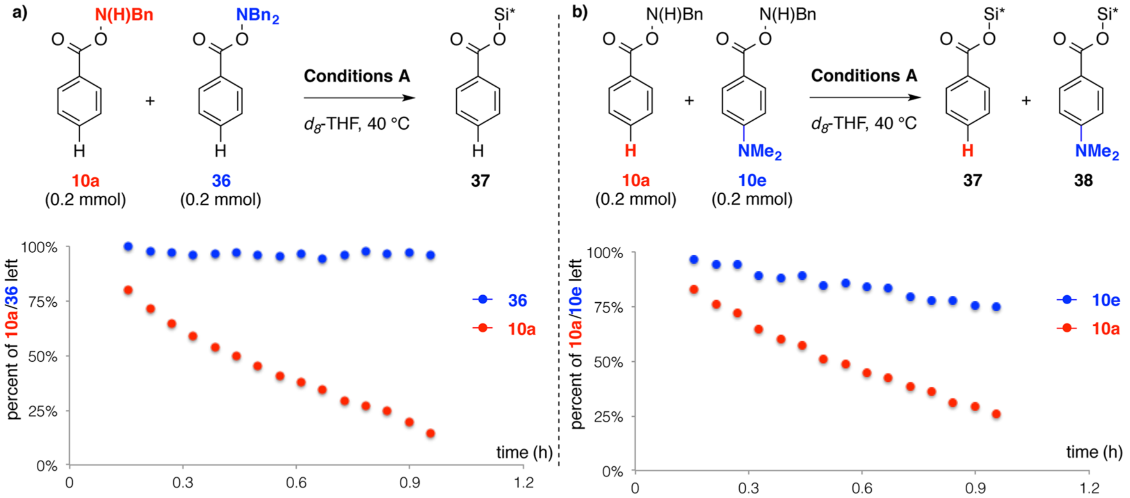


Figure 4. Relative rates of the reactions between LCuH and different amine transfer agents. Si* = $Si(OEt)_2Me$. **Conditions A**: a 0.6 mL of a stock solution made from $Cu(OAc)_2$ (3.6 mg), (*R*)-DTBM-SEGPHOS (26 mg), PPh_3 (11.6 mg), $HSi(OEt)_2Me$ (0.32 mL, 2.0 mmol), and THF-d_8 (1.0 mL) is used. The progress of these experiments was monitored by ^1H NMR.

building blocks often employed for the synthesis of peptidomimetics.[20] Finally, this hydroamination reaction can be integrated into a cascade sequence, delivering cyclic product **17l** after in situ alkylation of the intermediate secondary amine.

To further demonstrate the utility of this methodology, we applied it in the context of drug molecule synthesis (Scheme 1). For example, this method was applied to the synthesis of Sensipar (**21**), a drug used to treat secondary hyperparathyroidism. Commercially available aldehyde **18** was converted to amine transfer reagent **19** and then subjected to hydroamination conditions in the presence of 1-vinylnaphthalene (**20**) to give **21** in 81% yield and 89% ee (Scheme 1a). This methodology was also applied to the derivatization of commercial pharmaceuticals. For instance, chlorpromazine (**22**), an antipsychotic, could be converted to vinylarene **23**,[21] which then underwent hydroamination with L-valine-derived amine transfer reagent **24** to yield **25** (Scheme 1b). In a similar fashion, loratadine (**26**), an antihistamine drug, could be converted to **27** and then coupled with **29**, an amine transfer reagent derived from an estrone derivative **28**, to afford the conjugated product **30** in 85% yield and >20:1 dr (Scheme 1c). Lastly, vinylarene **32** made from tufnil (**31**), a nonsteroid anti-inflammatory drug, could successfully couple with **34**, an amine transfer reagent prepared from a glucose derivative **33**, to afford **35** in 73% yield and 17:1 dr (Scheme 1d).

MECHANISTIC STUDIES

Competition experiments were performed to investigate the role of the modified amine transfer reagents used in this study. We had hypothesized that the narrow substrate scope of the CuH-catalyzed hydroamination reaction using monoalkylamine transfer agents [e.g., BnN(H)OBz] was due to the susceptibility of these reagents toward direct, nonproductive reduction by LCuH. To address this, we conducted a competition experiment by exposing a 1:1 mixture of a pair of mono- and dialkylamine transfer reagents, **10a** and **36**, to $HSi(OEt)_2Me$ and copper catalyst in THF-d_8 *in the absence of styrene* and monitored the consumption of these two reagents by ^1H NMR spectroscopy (Figure 4a). We found that LCuH was capable of directly reacting with the amine transfer reagents, and over 80% of the monoalkylamine transfer agent **10a** was consumed within 1 h to give $BnNH_2$ and the corresponding silylated benzoyl ester (**37**).[22] In contrast, only a trace (<5%) of the dialkylamine transfer agent **36** was consumed during the same period of time.[23] We then subjected a 1:1 mixture of a pair of monoalkylamine transfer reagents, **10a** (parent benzoate) and **10e** [4-(dimethylamino)-benzoate], to identical conditions as described above (Figure 4b). In this case, both **10a** and **10e** were gradually consumed in the reaction system, giving the corresponding silylated esters (**37** and **38**) as products. Importantly, we found that the modified amine transfer reagent **10e** was consumed at a considerably slower rate than was **10a**. The higher stability of the modified monoalkylamine transfer reagents toward direct reaction with LCuH reaction is consistent with the increased substrate scope seen using the 4-(dimethylamino)benzoate-derived amine transfer reagents.

CONCLUSION

In conclusion, we have designed a new type of amine transfer reagent that possesses a 4-(dimethylamino)benzoate group. The use of these reagents enabled the development of a general method to directly convert styrenes to chiral secondary amines. This process was applicable to mono- and disubstituted styrenes and allowed the use of a variety of functionalized, structurally diverse amine transfer reagents, including those derived from carbohydrates, steroids, and amino acid esters. The utility of this reaction was highlighted by its application to the synthesis of pharmaceutically important drugs as well as the conjugation of other ones. Competition experiments have revealed that, relative to the corresponding *O*-benzoyl-*N*-alkyl hydroxylamines, the modified amine transfer reagents (*O*-[4-(dimethylamino)-benzoyl]-*N*-alkyl hydroxylamines) are less susceptible to direct reaction with LCuH. The information gained from this study should prove useful in the design and development of other CuH-catalyzed processes.[24]

ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data for all compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b05446.

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Notes

The authors declare no competing financial interest.

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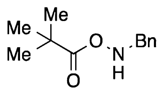
(15) (a) Alkyl carboxylate-based amine transfer reagents **13** and **14** were also tested. Reagent **14** containing a bulky adamantyl group provided yields of **11b** and **11c** similar to that of 4-(dimethylamino)benzoate **10e**. Due to the availability of the 4-(dimethylamino)benzoic acid and its ease of removal after reaction,[15b] 4-(dimethylamino)benzoates were used for most of this work. (b) 4-(Dimethylamino)benzoic acid is sparingly soluble in Et_2O, EtOAc, or CH_2Cl_2 but readily soluble in 2 M aqueous K_2CO_3.



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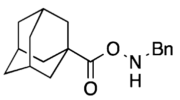

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(22) Formation of $BnNH_2$ and the silylated ester **37** could be detected by GC/MS and ^1H NMR analysis.

(23) Reduction of the dialkylamine transfer agent **36** is much slower. Approximately, 60% of **36** was consumed after 20 h under described conditions.

(24) A manuscript detailing the use of related modified amine transfer reagents to effect hydroamination of unactivated internal alkenes is in press.