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Direct Conversion of *N*-Alkylamines to *N*-Propargylamines Through C–H Activation Promoted by Lewis Acid/Organocopper Catalysis: Application to Late-Stage Functionalization of Bioactive Molecules

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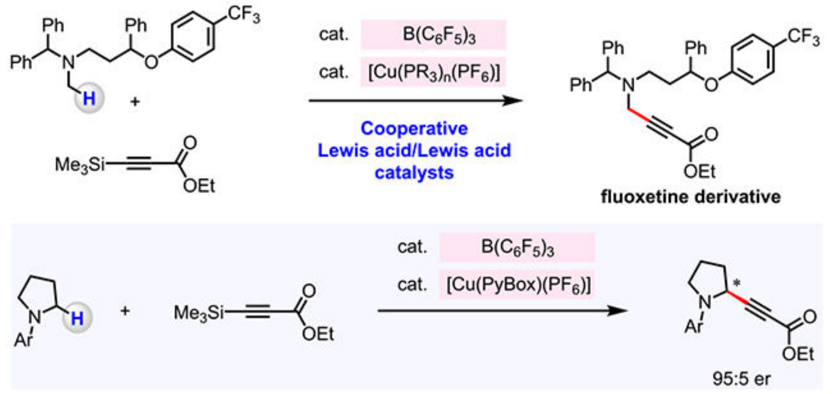
Abstract

An efficient catalytic method to convert an α-C–H bond of *N*-alkylamines into an α-C–alkynyl bond was developed. In the past, such transformations were carried out under oxidative conditions, and the enantioselective variants were confined to tetrahydroisoquinoline derivatives. Here, we disclose a method for union of *N*-alkylamines and trimethylsilyl alkynes, without the presence of an external oxidant, and promoted through cooperative actions of two Lewis acids, $B(C_6F_5)_3$ and a Cu-based complex. A variety of propargylamines can be synthesized in high diastereo- and enantioselectivity. The utility of the approach is demonstrated by late-stage site-selective modification of bioactive amines. Kinetic investigations that shed light on various mechanistic nuances of the catalytic process are presented.

Graphical Abstract



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Supporting Information **Available:** Experimental procedures and spectral data for all new compounds (PDF). This material is available free of charge *via* the Internet at http://pubs.acs.org.

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1. INTRODUCTION

Propargylamines are prevalent in pharmaceuticals and are commonly used intermediates in synthesis of bioactive amines (Figure 1a).[1] Enantiomerically enriched propargylamines have been prepared by addition of an alkynylmetal compound to an imine.[2–4] An attractive alternative would entail the conversion of an α-amino C(sp^3)–H bond into a α-C–alkynyl bond. One way to accomplish this would be through in situ generation of an iminium ion intermediate formed from the corresponding amine under oxidative conditions.[5–6] An illustrative case is enantioselective Cu–PyBOX-catalyzed coupling of a benzylic α-amino C–H bond of *N*-phenyl tetrahydroisoquinoline **1a** with ethynylbenzene **2a** to afford propargylamine **3a** (Figure 1b).[6] Still, development of a precious transition metal- and oxidant-free catalytic C–H functionalization process represents a compelling research objective.[5–7] Particularly noteworthy would be the direct conversion of α-C–H bonds contained in bioactive *N*-alkylamines into α-C–alkynyl bonds because these entities constitute over 50% of the top-selling drugs; the resulting derivatives of these pharmaceuticals possessing the alkyne unit can serve as modifiable intermediates for late-stage structural diversification that could lead to new leads and/or more effective therapeutics.[8]

In contemplating ways to design a possible method for the reaction of an *N*-alkylamine **1** with trimethylsilylacetylene **2**,[9–10] which can be easily prepared, we envisioned utilizing the combination of two Lewis acid catalysts, an organoborane and a Cu-based complex, so that they might function cooperatively (Figure 1c).[11–14] Specifically, we surmised that $B(C_6F_5)_3$ might receive a hydride from an amine (**1**), generating a borohydride and an iminium ion (**I**).[15–21] Subsequently, Cu-based catalyst might undergo transmetalation with alkynyl silane **2** with the aid of an alcohol additive (R–OH) to afford a L_nCu–alkynyl complex (**II**) and trimethylsilanol **4**.[22] An ensuing C–C bond formation (**III**) between in situ generated L_nCu–alkynyl complex and iminium ion would afford the desired propargylamine **3**. Hydride transfer from borohydride to R–OH-derived cationic species (**IV**→ **5**) would then regenerate $B(C_6F_5)_3$, thereby closing the cycle. Here, we report the development of a cooperative Lewis acid/Lewis acid catalyst system for the transformation of α-amino C–H bonds of *N*-alkylamines into C–alkyne bonds and its utility in synthesis, including late-stage incorporation of alkynyl units into bioactive amines.

2. RESULTS AND DISCUSSION

2.1. Method Development

2.1.1. Identification of optimal conditions.—

To begin, we set out to identify a suitable combination of catalysts (Table 1). We probed the ability of $B(C_6F_5)_3$ and various Cu-based complexes to catalyze the reaction between **1b** and **2b**, generating α-alkynyl amines **3b** and **6b**. Treatment of **1b** (0.10 mmol) and **2b** (0.15 mmol) with $B(C_6F_5)_3$, $(MeCN)_4CuPF_6$, Xantphos (10 mol % of each) afforded **3b** in 7% yield ($C_2H_4Cl_2$, 60 °C, 24 h; entry 1, Table 1).[23] Use of an alcohol as an additive improved efficiency (entries 3–7), likely by accelerating the transmetalation between **2b** and $(MeCN)_4CuPF_6$/Xantphos complex, releasing trimethylsilanol **4** as byproduct. Whereas the use of *i*-PrOH was ineffective (entry 2), addition of the more hindered *t*-BuOH resulted in the formation of **3b** in 17% yield (entry 3). With Ph_3COH as the hydroxyl source, a mixture of **3b** (52% yield) and **6b** (34% yield) was formed (entry 4) and Ph_3C–H was obtained as a byproduct (i.e., **5**, R = Ph_3C; Figure 1c). When less Ph_3COH was used (1.0 equiv.), **3b** (83% yield) was formed more selectively (vs **6b** in 15% yield; entry 5), and the desired product **3b** was isolated in 90% yield when the reaction time was shortened to 12 h (vs 24 h; entry 6). The transformation was efficient with less $B(C_6F_5)_3$ (5.0 mol %), affording **3b** in 81% yield (entry 7). There was no transformation in the absence of $B(C_6F_5)_3$ or when the less hindered BF_3 or less Lewis acidic BPh_3 were used (entries 8–10, Table 1).

2.1.2. Scope.—An assortment of cyclic and acyclic *N*-alkylanilines (**1b**–**1g**) may be used in reaction with 3-(trimethylsilyl)propiolate **2b** to generate the corresponding propargylamines (**3b**–**3g**, Figure 2). With $B(C_6F_5)_3$ and L_nCu–Xantphos complex as catalysts, *N*-aryl pyrrolidines (**1b**, **1c**), and *N*-aryl azepane (**1d**) were converted to **3b**–**3d** in 77–90% yield. In a number of instances there was efficient hydride abstraction at the *N*-methyl site (cf. **1e**–**1j**). 4-Methoxy-*N*,*N*,2,6-tetramethylaniline **1e** reacted with **2b** to afford **3e** (90% yield) along with minimal amounts of the byproduct containing two propargyl amine moieties (<5%). With **1f** and **1g**, C–C bond formation occurred predominantly at the *N*-methyl site to furnish **3f** (42% yield) and **3g** (70% yield), respectively; there was <10% reaction at the α-amino C–H bonds of *N*-ethyl and *N*-benzyl groups. Tertiary amines **1h**–**1j**, which lack the fused *N*-aryl group, readily underwent transformation to afford **3h**–**3j** in 76%–97% yield. For synthesis of propargylamines **3h**–**3j** the use of the less hindered and conformationally more flexible 1,2-bis(diphenylphosphino)ethane (dppe) ligand was optimal (vs <30% conv. with Xantphos).[23] Furthermore, the more sizeable benzhydryl moiety was identified as a superior *N*-substituent as benzhydryl-substituted **3j** was obtained in higher yield than benzyl-substituted **3i** (97% vs 86% yield).

The method is applicable to late-stage modification of *N*-containing bioactive molecules that possess an array of Lewis acid-sensitive functional groups (**1k**–**1p**; Figure 2). In addition to the *N*-alkylamine moieties of **1k**–**1p**, an ester (**1l**), an ether (**1l**, **1m**, **1o**), a thienyl (**1o**) and an aryl chloride (**1p**) were tolerated, affording **3k**–**3p** in 56–76% yield. The structures of antifungal compounds bearing a tertiary amine, such as butenafine **1k** and trimebutine **1l**, were readily altered (**3k**, **3l**). For secondary amines, such as atomoxetine (used for treatment of ADHD), as well as antidepressants nortriptyline, duloxetine, and sertraline, incorporation of *N*-benzhydryl group was necessary for efficient generation of **3m**–**3p**.

The catalytic protocol may involve the use of trimethylsilylacetylenes containing different alkynyl substituents (**2b**–**2i**, Figure 3). The reactions of fluoxetine derivative **1q** with trimethylsilylacetylenyl esters (**2b**, **2c**) and amide (**2d**) afforded **7b**–**7d** in 76–82% yield. A series of phenyl-, *para*-(trifluoromethyl)phenyl-, *para*-chlorophenyl- or 3-thiophenyl-substituted trimethylsilylacetylenes were coupled with **1q** to furnish **7e**–**7h** in 74–82% yield. Whereas the transformation involving **1q** and trimethylsilylacetylene (X = H) was inefficient (<10% yield),[23] 1,2-bis(trimethylsilyl)ethyne **2i** proved to be a suitable reaction partner, affording **7i** in 87% yield.

2.1.3. Diastereo- and Enantio-selective Processes.—To develop a stereoselective version of the catalytic C–alkynyl bond forming process, we chose to use $B(C_6F_5)_3$ in combination with an appropriate chiral organocopper complex, with *N*-arylpyrrolidine **1b** and 3-(trimethylsilyl)propiolate **2b** as model substrates. Accordingly, we performed systematic evaluation of catalyst systems comprised of $(MeCN)_4CuPF_6$ and a chiral ligand (Figure 4). The effectiveness of various bis-phosphine ligands (e.g., **L1**–**L2**) were evaluated in the presence of 10 mol % of $B(C_6F_5)_3$.[23] These transformations afforded **8b** with minimal enantiomeric purity. We then explored the suitability of bis-oxazoline ligands (e.g., **L3**–**L7**), leading us to establish that with (*S*)-Ph–PyBOX (**L3**), **8b** can be obtained in 84% yield and 82:18 er. Enantioselectivity improved when more sizeable 2,6-bis((*S*)-4-(*m*-tolyl)-4,5-dihydrooxazol-2-yl)pyridine (**L4**) and 2,6-bis((*S*)-4-(3,5-dimethylphenyl)-4,5-dihydrooxazol-2-yl)pyridine (**L5**) were used: **8b** was isolated in 53% yield and 90:10 er, and 75% yield and 95:5 er, respectively. Neither efficiency nor enantioselectivity improved when **L6** and **L7** were used.

2.1.4. Stereoselective Synthesis and Functionalization of Propargylamines. —Reactions with an array of *N*-alkylamines were carried out in the presence of $B(C_6F_5)_3$ and $(MeCN)_4CuPF_6$, **L5** and **2b** (Figure 5). *N*-Arylpyrrolidines ((*S*)-**8b**, **8c**, **8d**) as well as *N*-arylazepane (**8e**) bearing α-alkynyl group were thus synthesized in 64–75% yield and 83:17–95:5 er; there was minimal double-alkynyl byproduct formed (<5% yield). When *rac*-2-methyl-1-arylpyrrolidine was reacted with **2b**, ***trans*-8c** was produced preferentially in 83:17 er. The reaction with 3,3-dimethyl-1-arylpyrrolidine and **2b** furnished **8d** as the sole regioisomer (vs the isomer formed through the formation of more sterically hindered iminium ion). An α-benzylic C–H bond of (*E*)-*N,N*-dibenzyl-4,4,4-trifluorobut-2-en-1-amine was functionalized to give propargylamine **8f** in 45% yield and 84:16 er. Additionally, a range of enantiomerically enriched pyrrolidine substrates underwent transformation in the presence of $B(C_6F_5)_3$ and $(MeCN)_4CuPF_6$/**L5** to afford **8g–8i**. With (*S*)-3-methyl- or (*S*)-3-phenyl-substituted pyrrolidine as substrate, reaction occurred at the less hindered α-amino C–H bond, affording **8g** and **8h** in 64% yield (11.8:1 *trans*:*cis*) and 68% yield (10.1:1 *trans*:*cis*), respectively. The union of a α-amino carbonyl compound[19] and **2b** resulted in the formation of **8i** in 93% yield and 7.7:1 *trans*:*cis* ratio. The use of **L5** was crucial in these latter processes, as **8g–8i** were obtained in notably lower dr with an achiral ligand (e.g., Xantphos).[23]

A benzhydryl group can be removed, as illustrated by the reaction of **1j** and **2e** with Et_3SiH and trifluoroacetic acid, which afforded **9** in 64% yield (Figure 6a). The silyl moiety of fluoxetine derivative **7i** (Figure 3) was excised by its treatment with $(n\text{-}Bu)_4NF$, furnishing terminal alkyne **10** in >95% yield.[23] Subjection of **10** with biotin-PEG3-azide to $CuSO_4$/*L*-ascorbic acid and K_2CO_3 afforded heterocyclic derivative **11** in 70% yield (Figure 6b).[24]

1.4. Scalability.

The catalytic method is scalable. For example, treatment of 1.0 g (2.1 mmol) of *N*-benzhydryl fluoxetine **1q** and **2b** with 10 mol % $B(C_6F_5)_3$, 10 mol % $(MeCN)_4CuPF_6$/dppe, 2.0 equivalents of Ph_3COH ($C_2H_4Cl_2$, 48 h, 80 °C) afforded **7b** in 93% yield (1.12 g; Figure 6c). Furthermore, enantioselective coupling of *N*-arylpyrrolidine **1b** (0.21 g, 1.0 mmol) with

2b in the presence of 5.0 mol % $B(C_6F_5)_3$, 5.0 mol % $(MeCN)_4CuPF_6$/**L5**, and 1.0 equivalent of Ph_3COH (*t*-BuOMe, 72 h, 60 °C) gave **(*S*)-8b** in 85% yield (0.26 g) and 95:5 er (Figure 6d). Hydrogenation of **(*S*)-8b** delivered *Z*-alkene **12a** in 96% yield and reduction of **(*S*)-8b** furnished propargyl alcohol **12b** in >99% yield.

2.2. Mechanistic Investigations

We designed and performed studies aimed at shedding light on the mechanism of the catalytic process (a revised catalytic cycle, based on the investigations described below, is illustrated in Figure 7).

2.2.1. Kinetic studies.

These investigations revealed that the rate of the reaction of 4-methoxy-*N*,*N*,2,6-tetramethylaniline **1e** with ethyl 3-(trimethylsilyl)propiolate **2b** is independent of the concentration of **1e**, $(MeCN)_4CuPF_6$/Xantphos complex, and Ph_3COH (Figure 8).[23] However, there were 0.5-order dependence on the $B(C_6F_5)_3$ concentration (Figure 8a),[25] and 1.0-order dependence on the concentration of **2b** (Figure 8b). These data imply that C–H bond cleavage through $(F_5C_6)_3B$-catalyzed hydride abstraction (Figure 7, **1** → **IX**) occurs after the turnover-limiting step (energetic span).[26,27] They further suggest that the transformation has a resting state that consists of two $B(C_6F_5)_3$ units, such as an ionic complex containing a borate anion $[(F_5C_6)_3B(\mu\text{-OH})B(C_6F_5)_3]^-$ (**VI**, $[X]^+ = H^+$ and/or Ph_3C^+).[28] The ^{11}B NMR spectra acquired for the reaction mixture under the standard catalytic conditions (Figure 8) are in agreement with the formation of the borate anion **VI**.[23, 28] In the presence of Ph_3COH and/or H_2O, two molecules of $[(F_5C_6)_3B\text{–}OH]^-[X]^+$ (**V**) may be produced from **VI**.[28] Ensuing reaction of **V** and trimethylsilylacetylene **2** to afford $[(F_5C_6)_3B\text{–alkyne}]^-\ [X]^+$ (**VII**) is turnover-limiting. Treatment of preformed $[(F_5C_6)_3B\text{–}C{\equiv}C\text{–}CO_2Et]^-[H\text{–}NR_3]^+$ (NR_3 = **1e**)[29] with 100 mol % of $(MeCN)_4CuPF_6$/Xantphos complex was found to give propargylamine product **3e** in 24% yield, thereby demonstrating the competency of intermediate **VII** in the alkyne incorporation process.[23] Subsequent to the turn-over limiting step (**V** → **VII**), $[(F_5C_6)_3B\text{–alkynyl}]^-\ [X]^+$ undergoes transmetalation with $(MeCN)_4CuPF_6$/Xantphos complex to afford a L_nCu–alkynyl complex and $B(C_6F_5)_3$, latter of which converts amine **1** into iminium ion through hydride abstraction (**VII** → **VIII** → **IX**). C–C bond formation between in situ generated L_nCu–alkynyl complex and iminium ion would afford the desired propargylamine (**IX** → **3**). The reaction between borohydride and Ph_3COH would then produce $Ph_3C\text{–}H$ **5** and regenerate **V**, thereby closing the cycle.

2.2.2. Kinetic Isotope Effect Studies.

To shed light on the hydride abstraction step (Figure 7, **1** → **IX**), deuterium-labeled methylaniline **1g-*d*** was prepared, and its reaction with **2b** was studied (Figure 9). Based on the aforementioned rate studies (Figure 8), which suggested that C–H bond cleavage might not be turnover-limiting, the overall rate of the reaction should be unaffected for a reaction involving **1g-*d***, and, indeed, there was no significant kinetic isotope effect with independent rate measurements (Figure 9a).[26] On the other hand, with competition rate measurements, there could be an observable KIE if $(F_5C_6)_3B$-catalyzed C–H bond cleavage step were irreversible (Figure 9b), as these experiments measure a change in product distribution that results from a difference in the rate of an irreversible C–H bond cleavage event.[26] That is, these experiments should provide a product ratio that reflects a primary KIE, despite the C–H bond cleavage not being turnover-limiting.[26] In the event, independent rate measurements (Figure 9a) involving **1g** and **1g-*d*** was found to have k_H/k_D = 1.02 ± 0.02 (average of 2 measurements;).[23] What is more, intermolecular competition rate measurements (Figure 9b) showed that **1g** reacts 4.4 times faster than **1g-*d*** (k_H/k_D = 4.4). These isotope effect experiments support the notion that the turnover-limiting step is before the $(F_5C_6)_3B$-catalyzed hydride abstraction, and that C–H bond cleavage step is irreversible.

2.2.3. Origin of Regioselectivity.—Next, we chose to investigate why an *N*-methyl C–H bond of an *N*-methyl-*N*-benzylamine moiety is preferentially activated (e.g., Figure 9b, **1g**) while *N*-benzyl and *N*-benzhydryl groups remain intact (c.f., Figures 2, 3). We considered two possible scenarios. In one, $B(C_6F_5)_3$ activation cannot convert an *N*-benzyl or an *N*-benzyhydryl group to the corresponding iminium intermediate ($[ArMeN{=}CHPh]^+$ (e.g., Figure 10a, **XI** and **XII**), and in the other, the C-phenyl iminium intermediates are formed but are too hindered and/or not sufficiently electrophilic to react with a L_nCu–alkynyl complex. To establish whether a C-phenyl iminium intermediate can be formed, we prepared **1g-*d*** and subjected it to 10 mol % $B(C_6F_5)_3$ at 60 °C for 16 hours (in $C_2H_4Cl_2$; Figure 10a). The ^1H NMR spectrum of purified **13g-*d*** (>95% yield) indicated that 63% of benzylic C–H bonds were converted to C–D bonds, while 37% of *N*-methyl C–D bonds were transformed to C–H bonds. The finding that deuterium incorporation takes place at the benzylic site indicates that $B(C_6F_5)_3$ is capable of generating a C-phenyl iminium ion (**XI**), which might occur through $(F_5C_6)_3B$-catalyzed deuteride abstraction at the $N{-}CD_3$ moiety of **1g-*d*** to afford iminium ion **X** followed by isomerization to the lower energy intermediate **XI**.[30] Subsequent reduction of C-phenyl iminium then furnishes a benzylic C–D bond (**13g-*d***). Nonetheless, direct formation of C-phenyl iminium intermediate by $(F_5C_6)_3B$-catalyzed benzylic C–H abstraction cannot be ruled out (**1g-*d*** → **XII**; Figure 10a).[31]

Alternatively, intermolecular H/D exchange between two **1g-*d*** molecules, promoted by $B(C_6F_5)_3$, might generate **13g-*d***. That is, iminium/borohydride complexes **X** and **XII** (Figure 10a) could exchange their anionic and cationic components, after which hydride or deuteride iminium reduction might produce **13g-*d***. To probe whether H/D exchange is intermolecular, we treated a mixture of **1e** and **1g-*d*** in the presence of 10 mol % $B(C_6F_5)_3$ (Figure 10b). Analysis of the corresponding ^1H NMR spectrum and HRMS data of the resulting products **13e-*d*** and **13g-*d*** (both were obtained in >95% yield) revealed that 28% of *N*-methyl C–H bonds in **1e** was converted to C–D bonds and 27% of *N*-benzylic C–H bonds in **1g-*d*** was transformed to C–D bonds. This intermolecular H/D exchange reaction might proceed through formation of iminium complexes **XIV** and **XV,** generated by $(F_5C_6)_3B$-catalyzed hydride or deuteride abstraction from **1e** and **1g-*d***, respectively. The iminium/borohydride complexes **XIV** and **XV** could then exchange their anionic and cationic components followed by hydride or deuteride reduction of **XVI** to furnish **13e-*d*** and **13g-*d***. These results (Figure 10) imply that in the absence of $(MeCN)_4CuPF_6$/Xantphos and **2b**, the iminium/borohydride complexes are sufficiently long-lived to undergo isomerization and/or intermolecular anion/cation exchange.

To determine whether the H/D exchange reaction is possible under the standard reaction conditions, we performed the reaction involving 0.10 mmol **1g-*d***, 0.15 mmol of 3-

(trimethylsilyl)propiolate **2b** and 0.10 mmol Ph_3COH (Figure 11a); this allowed us to isolate propargylamine product **3g-*d*** in 31% yield. However, <5% of the benzylic C–H bonds in **3g-*d*** were converted to C–D bonds, whereas the propargylic position of **3g-*d*** retained >98% of C–D bonds from **1g-*d***. Additionally, there was no detectable H/D exchange in the recovered **1g-*d*** (0.067 mmol of **1g-*d*** was isolated); namely, there was no H/D exchange under the catalytic conditions (vs H/D exchange processes shown in Figure 10). The above findings indicate that the in situ generated $[ArBnN{=}CD_2]^+[D{-}B(C_6F_5)_3]^-$ is short-lived and rapidly consumed by its reaction with L_nCu–alkynyl complex and Ph_3COH to afford propargylamine **3g-*d*** and Ph_3C–D **5-*d*** (**1** → **IX** → **3**, Figure 7); thus, it neither undergoes intra- and/or intermolecular H/D exchange (vs the pathway in Figure 10) nor does borodeuteride reduction generate $B(C_6F_5)_3$ and **1g-*d***.

We examined the structure of byproducts to determine the fate of deuteride from amines **1g-*d*** and **1e-*d*** as well as trimethylsilyl group from **2b** (Figure 11a–b). Based on our proposed mechanism (Figure 7), the expected byproducts generated by the reaction between **1g-*d*** and **2b** (to give **3g-*d*** in 31% yield; Figure 11a) would be Ph_3C–D (**5-*d***) and Me_3Si–OH (**4**). Although the formation of Ph_3C–D (**5-*d***) could be confirmed by ^2H NMR spectroscopy of the unpurified mixture (24% yield), we were unable to detect any Me_3Si–OH (**4**). To confirm that **4** is formed, we reacted **1e-*d*** and **2b**, which led to the formation of **3e-*d*** (together with other byproducts; Figure 11b). Spectroscopic analysis indicated that when the latter mixture was heated at 60 °C for 7 hours, **3e-*d*** (37% yield), Ph_3C–D (**5-*d***, 39% yield) and Me_3SiO–$SiMe_3$ (**14**, 14% yield) are generated; Me_3Si–O–$SiMe_3$ is likely produced by $(F_5C_6)_3B$-catalyzed condensation between two molecules of Me_3Si–OH (**4**) to afford **14** and H_2O.[32]

3. CONCLUSIONS

In summary, we have developed an efficient and diastereo- and enantio-selective method for activation of α-amino C–H bonds to generate propargyl amines. We find that by using a blend of $B(C_6F_5)_3$ and an organocopper complex, it is possible to generate an iminium from an *N*-alkylamine and a L_nCu–alkynyl complex from an alkynylsilane. The catalyst system tolerates a wide variety of Lewis acid-sensitive functional groups and is therefore applicable to late-stage transformation of a complex (and bioactive) trialkyl amine molecule to its derived propargylamine. Mechanistic investigations indicate that the turnover-limiting step occurs prior to $(F_5C_6)_3B$-catalyzed C–H abstraction, and that $(F_5C_6)_3B$-catalyzed C–H abstraction is an irreversible process under the reaction conditions for alkyne incorporation. The principles outlined here demonstrate that proper combination of an achiral organoborane and a chiral organometallic catalyst can be used for chemo- and enantioselective C–H bond activation, providing a rational framework for further development of processes involving the late-stage stereoselective α-functionalization of bioactive amines. Studies aimed at achieving these objectives are currently underway.

Supplementary Material

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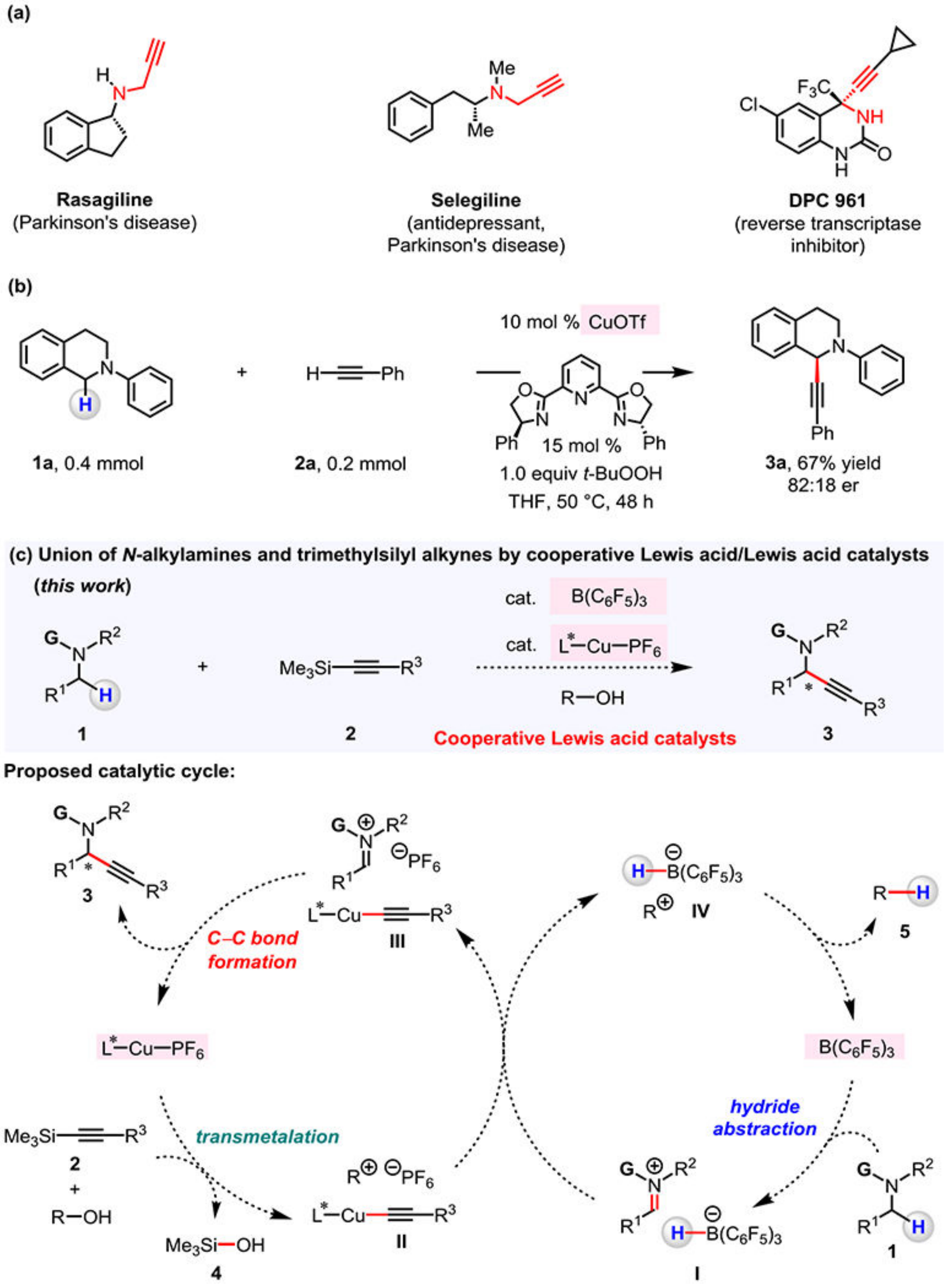


Figure 1. Representative bioactive compounds containing *N*-propargylamines and the synthesis strategy to be pursued.

(a) Examples of pharmaceutical agents that contain a propargylamine unit. (b) Enantioselective organocopper-catalyzed transformation of an α-amino C–H bond of tetrahydroisoquinolines into C–alkyne bond under oxidative conditions. (c) Coupling of *N*-alkylamines with trimethylsilylacetylenes by cooperative Lewis acid/Lewis acid catalysis. A possible mechanism might involve enantioselective C–C bond formation between an iminium ion and a chiral alkynylcopper complex via reactive intermediates that are generated in situ by cooperative functions of a chiral and an achiral Lewis acid co-catalyst.

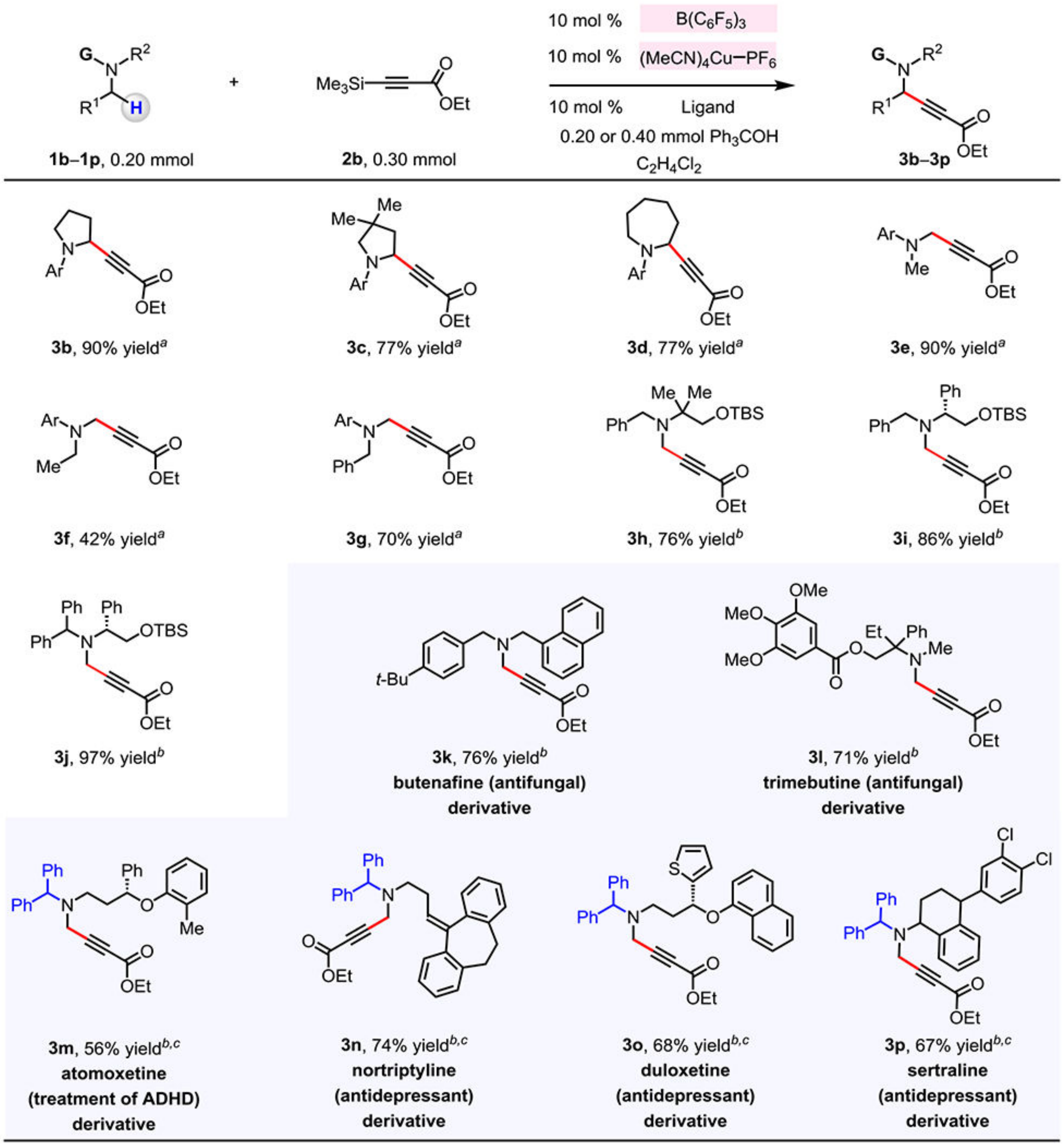


Figure 2. Incorporation of an alkyne unit into various *N*-alkylamines with 3-(triemthylsilyl)propiolate.

The values correspond to yields of isolated and purified products. [a] Conditions: *N*-alkylamine (**1**, 0.20 mmol), 3-(trimethylsilyl)propiolate (**2b**, 0.30 mmol), $B(C_6F_5)_3$ (10 mol %), $(MeCN)_4CuPF_6$ (10 mol %), Xantphos (10 mol %), triphenylmethanol (0.20 mmol), $C_2H_4Cl_2$ (0.4 mL), under N_2 atmosphere, 60 °C, 12 h. [b] 1,2-Bis(diphenylphosphino)ethane (10 mol %) was used as a ligand, 0.40 mmol of triphenylmethanol was used, and the reaction mixture was allowed to stir at 80 °C for 24 h. [c] Blue color indicates protecting groups. See the Supporting Information for details.

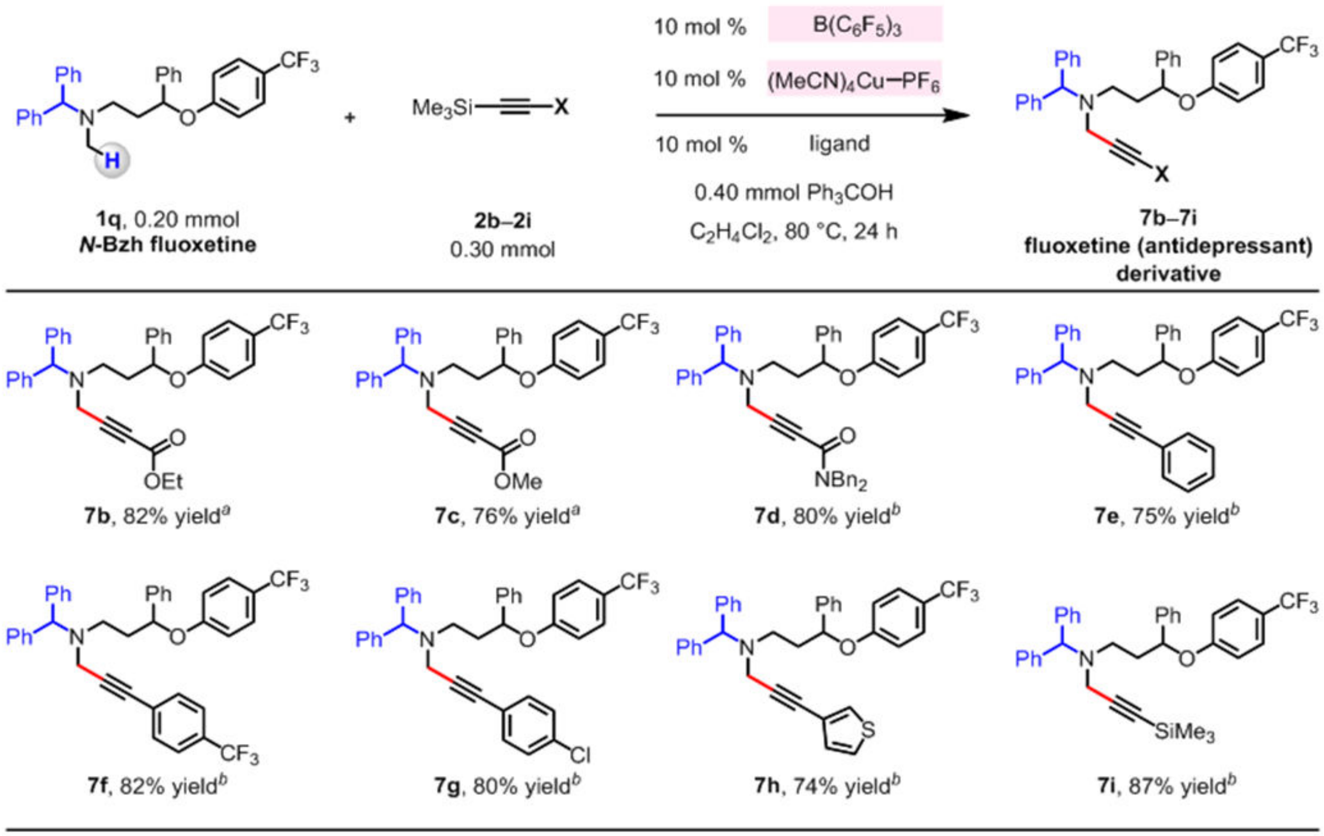


Figure 3. Reactions of *N*-Bzh fluoxetine with triemthylsilylacetylenes.

The values correspond to yields of isolated and purified products. The reaction conditions are identical to those in Figure 2, aside from the ligands used. Blue color indicates protecting groups. [a] 1,2-bis(diphenylphosphino)ethane was used as a ligand. [b] (*S*)-Ph–PyBOX was used as ligand. See the Supporting Information for details.

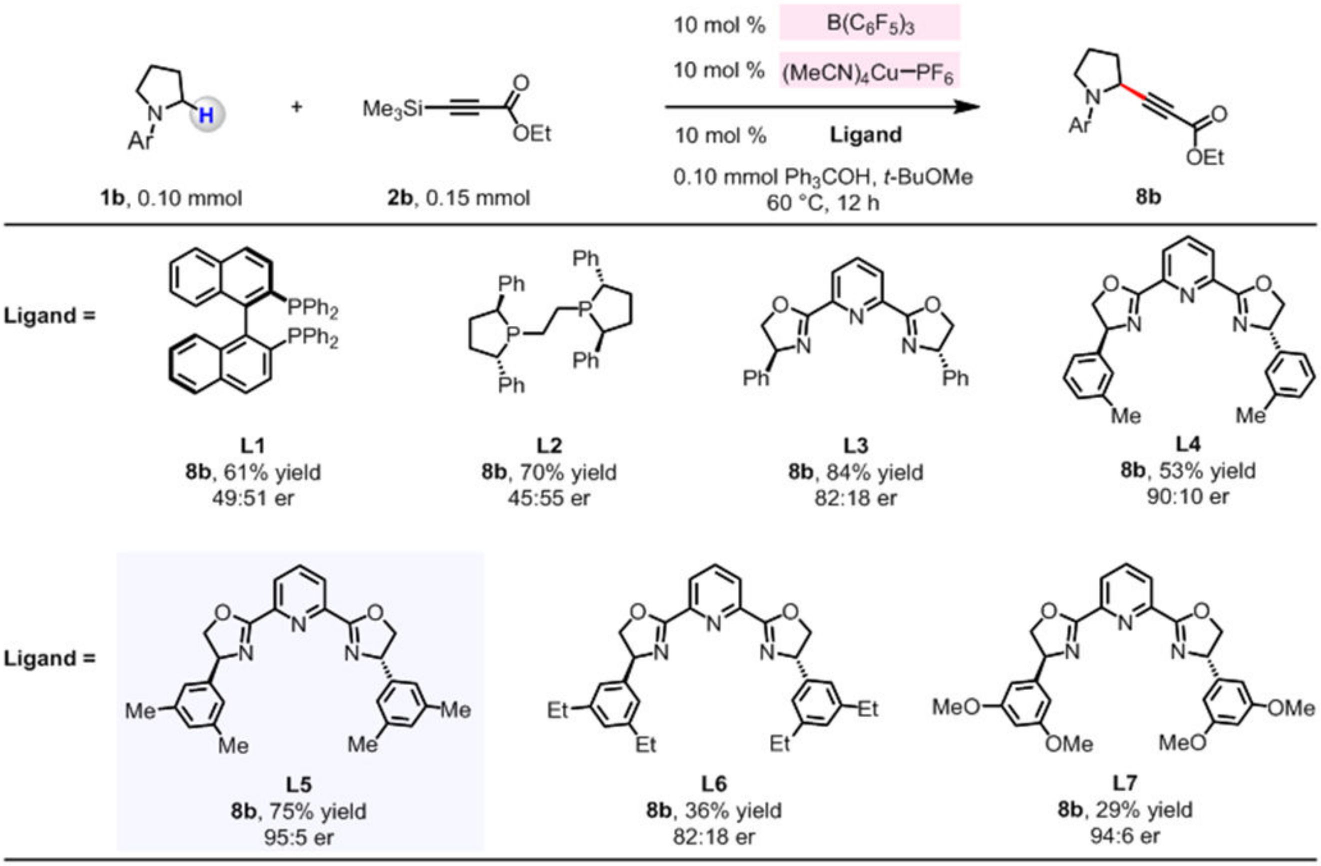


Figure 4. Evaluation of chiral ligands.

Yield values were determined by the ^{1}H NMR analysis of unpurified reaction mixtures with mesitylene as the internal standard. Enantiomeric ratio (er) values were determined by the HPLC analysis of isolated and purified product. Conditions: *N*-arylpyrrolidine (**1b**, 0.10 mmol), 3-(trimethylsilyl)propiolate (**2b**, 0.15 mmol), $B(C_6F_5)_3$ (10 mol %), $(MeCN)_4CuPF_6$ (10 mol %), ligand (10 mol %), triphenylmethanol (0.20 mmol), $C_2H_4Cl_2$ (0.4 mL), under N_2 atmosphere, 60 °C, 12 h. See the Supporting Information for details.

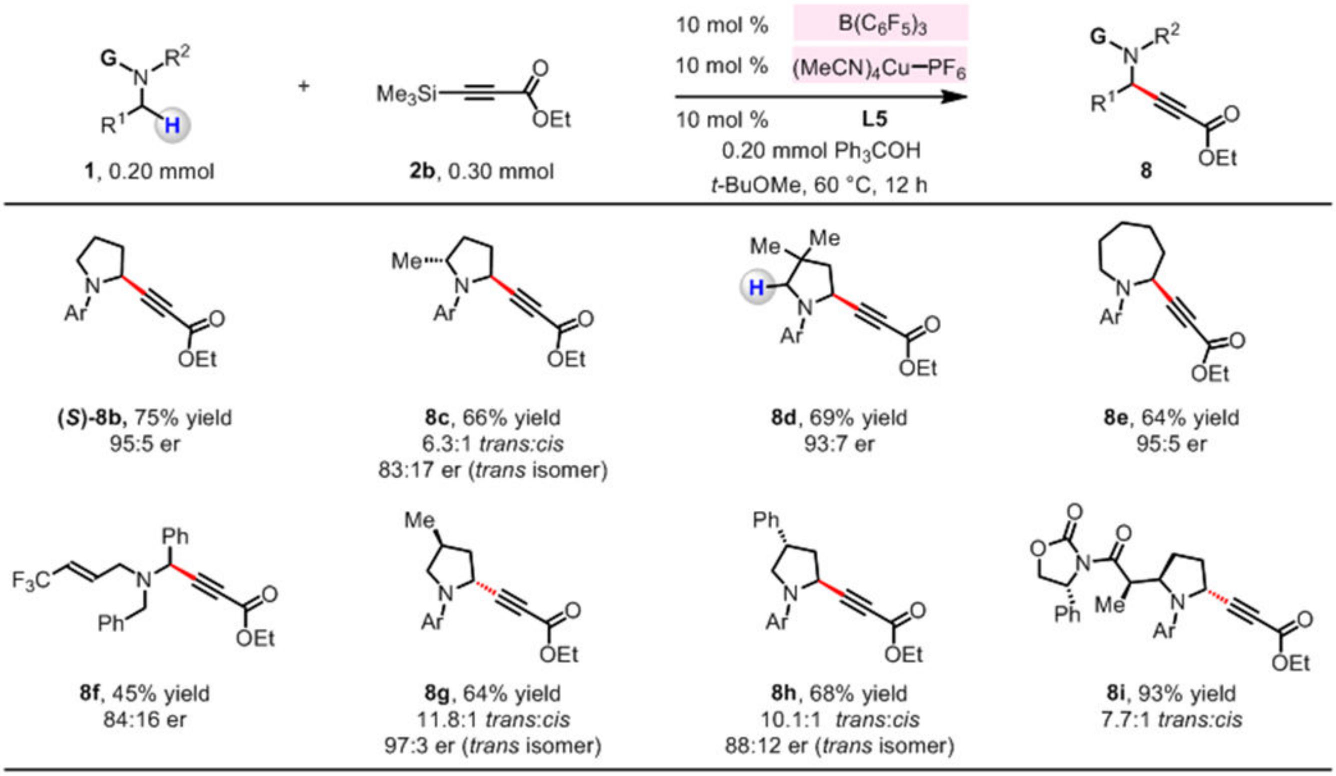


Figure 5. Diastereo- and enantio-selective processes.

Cooperative functions of B(C_6F_5)$_3$ and (MeCN)$_4$CuPF$_6$/**L5** catalysts promote stereoselective conversion of *N*-alkylamines to the corresponding dialkyl propargylamines. Conditions: *N*-alkylamine (**1**, 0.20 mmol), 3-(trimethylsilyl)propiolate (**2b**, 0.30 mmol), B(C_6F_5)$_3$ (10 mol %), (MeCN)$_4$CuPF$_6$ (10 mol %), **L5** (10 mol %), triphenylmethanol (0.20 mmol), $C_2H_4Cl_2$ (0.4 mL), under N_2 atmosphere, 60 °C, 12 h. See the Supporting Information for details.

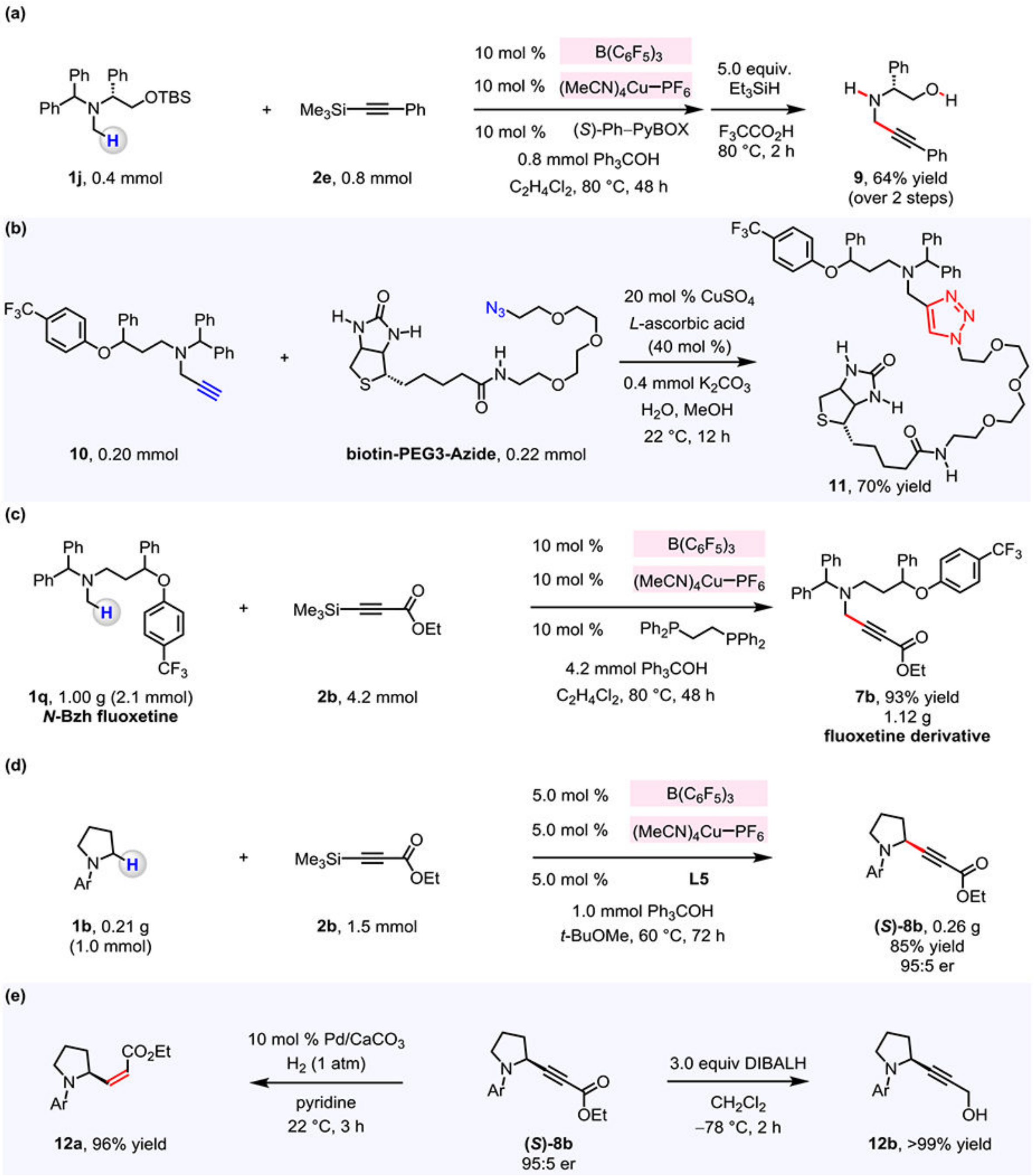


Figure 6. Modification of propargyl amine products and scalability.

(a) Sequential conversion of C–H bond into C–alkynyl bond and removal of *N*-benzhydryl and *O*-TBS protecting groups can be achieved to afford propargylamine **9**. (b) The fluoxetine derivative **10** can undergo organocopper-catalyzed Click reaction with biotin-PEG3-azide to give **11**. (c) The method is amenable to gram-scale operations. (d) Enantioselective reactions may be carried out on 1.0 mmol scale. (e) The versatility of **(*S*)-8b** was demonstrated by its transformation to a *Z*-alkene **12a** and a propargyl alcohol **12b**. See the Supporting Information for details.

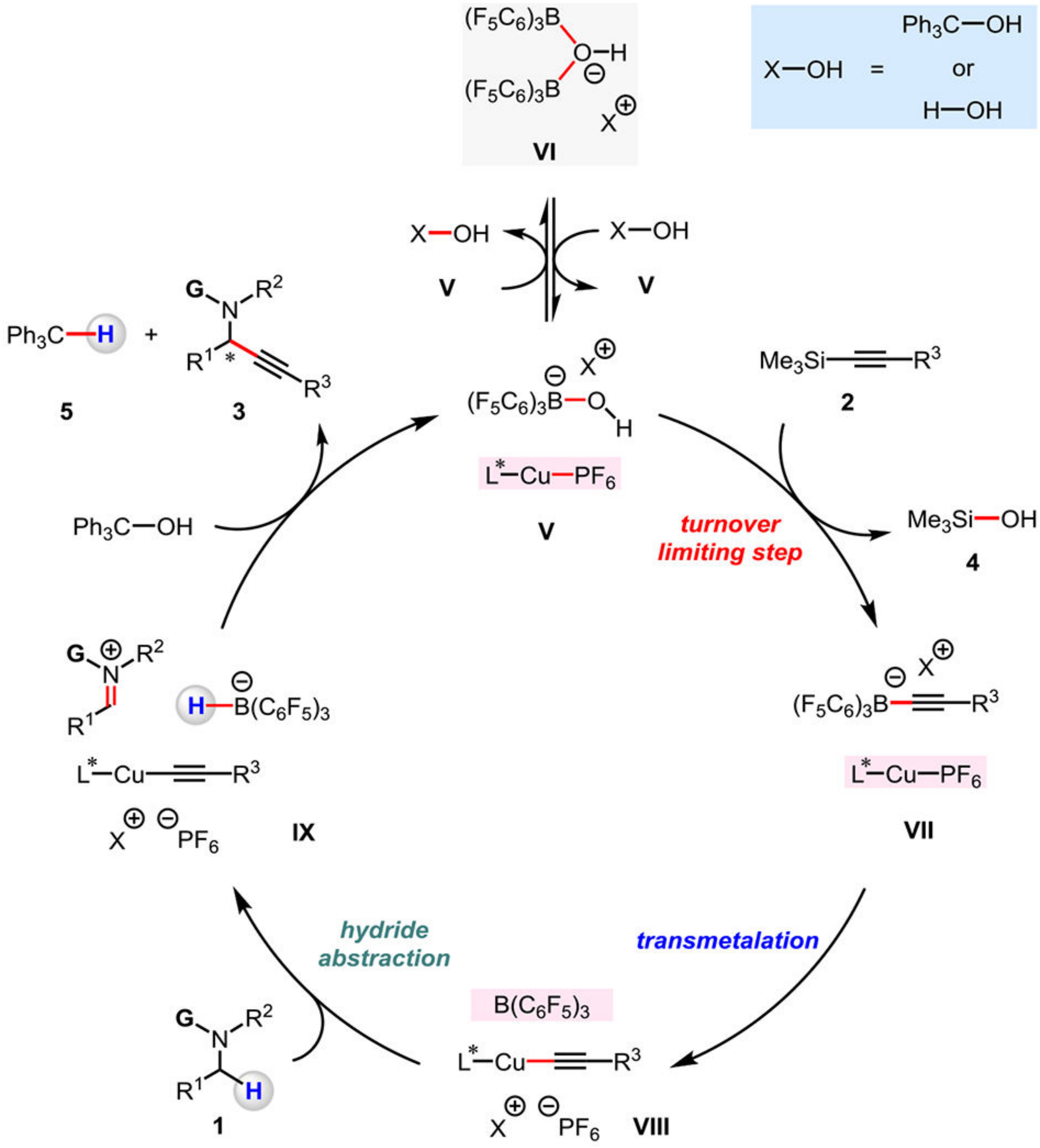


Figure 7. A catalytic cycle consistent with the results of mechanistic investigations.

Kinetic and NMR studies indicate that the turnover-limiting step occurs prior to the $(F_5C_6)_3B$-catalyzed hydride abstraction, and that the C–H bond cleavage step is irreversible.

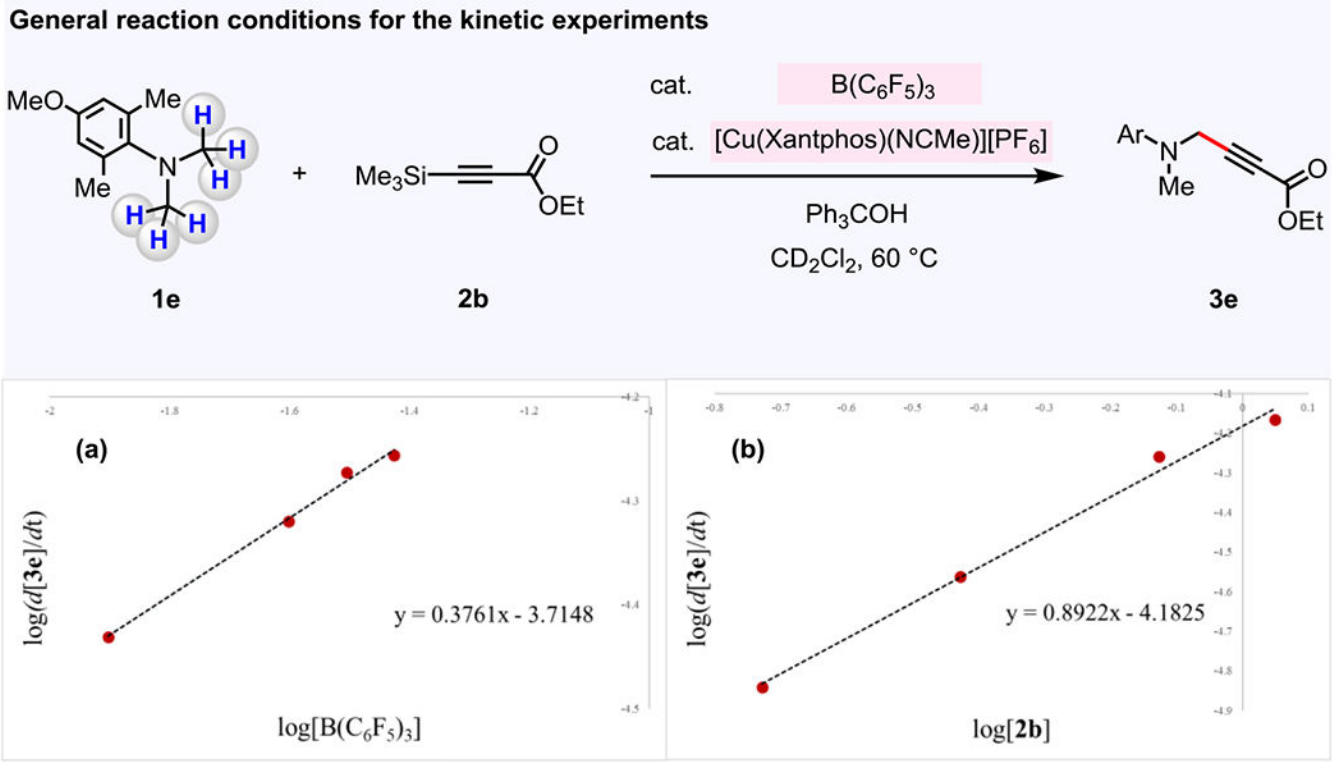


Figure 8. Kinetic studies.

The reaction of **1e** and **2b** to afford propargylamine **3e** was found to be 0.5-order in $B(C_6F_5)_3$ and 1.0-order in alkyne, suggesting that the resting state of $B(C_6F_5)_3$ contains two $B(C_6F_5)_3$ units and that the turnover-limiting involves the reaction of **2b** with in situ generated $[(F_5C_6)_3B–OH]^-$ to give $[(F_5C_6)_3B–\text{alkynyl}]^-$ and TMS–OH. (a) Log(rate) vs Log[$B(C_6F_5)_3$] plot is employed to determine the reaction order for $B(C_6F_5)_3$. (b) Log(rate) vs Log[**2b**] plot is employed to determine the reaction order for **2b**. See the Supporting Information for details.

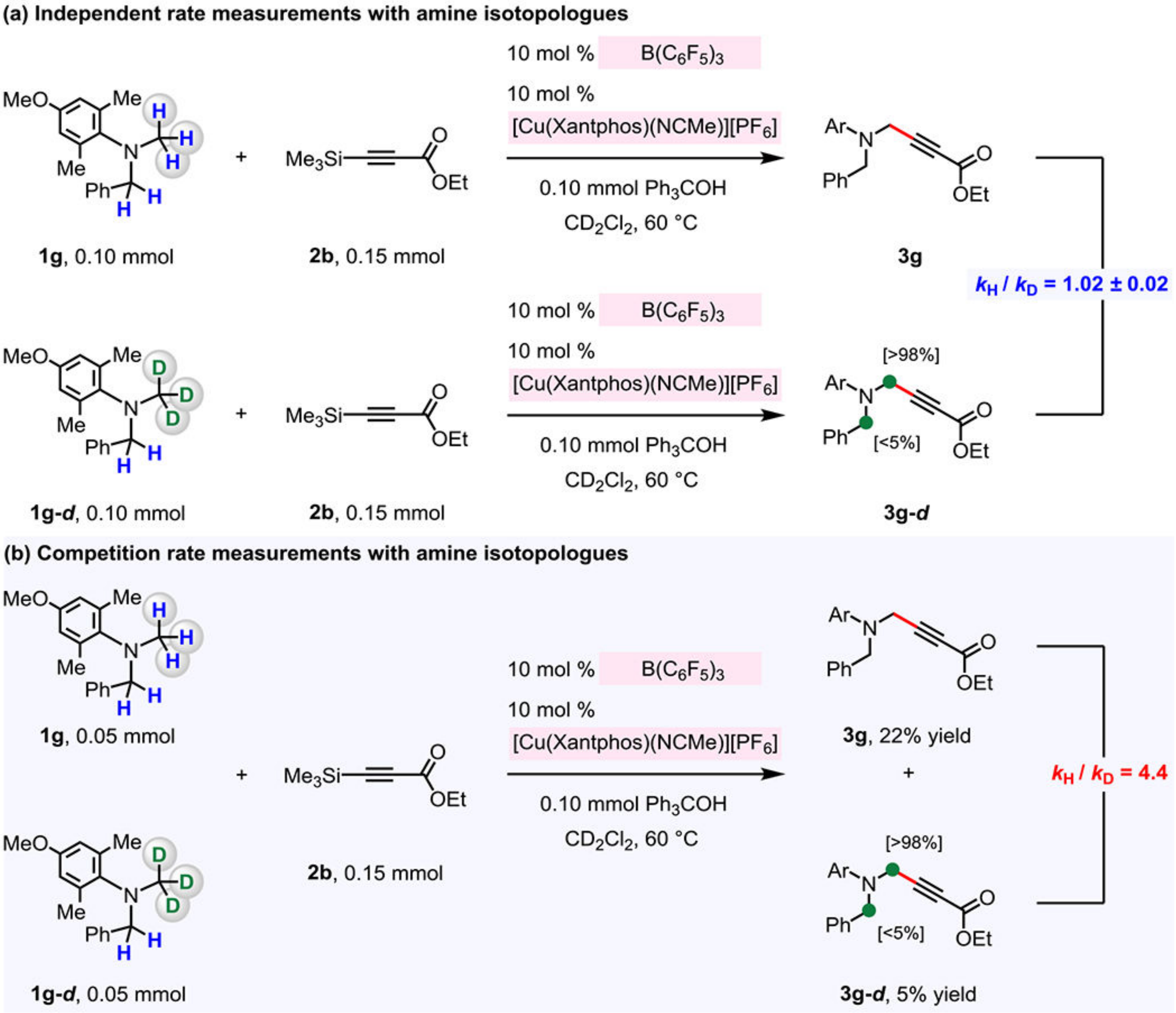


Figure 9. Kinetic isotope effect studies.

These studies indicate that hydride abstraction is not the turnover-limiting step, and yet the deuterium-labeling caused an amine to react 4.4 times slower in the competition rate measurement studies. See the Supporting Information for details.

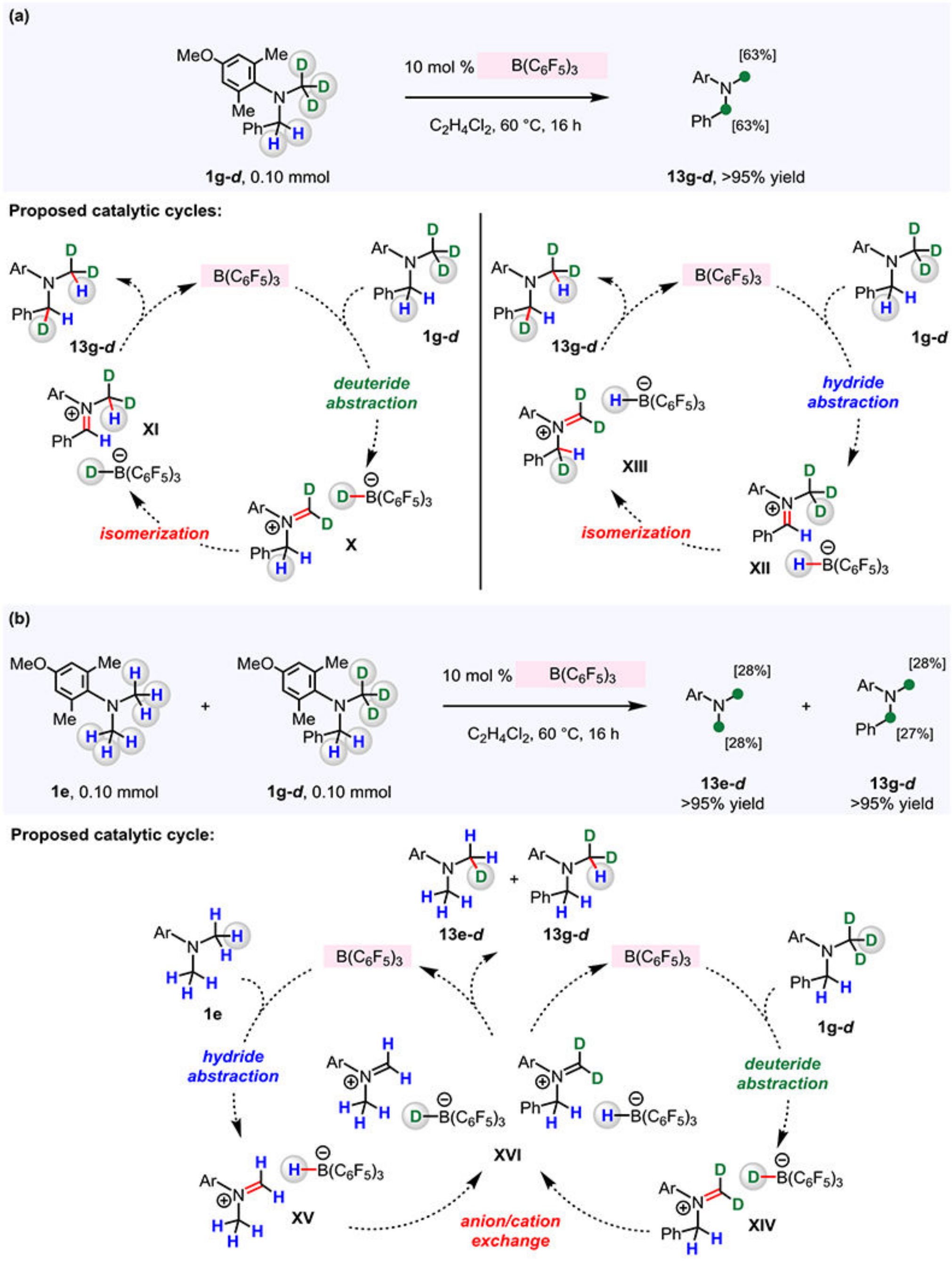


Figure 10. $B(C_6F_5)_3$ promotes intramolecular and intermolecular H/D exchange.

(a) $(F_5C_6)_3B$-catalyzed H/D exchange occurs within *N*-benzyl-4-methoxy-2,6-dimethyl-*N*-(methyl-*d_3*)aniline. (b) Intermolecular H/D exchange was shown to take place between **1e** and **1g-*d***. See the Supporting Information for details.

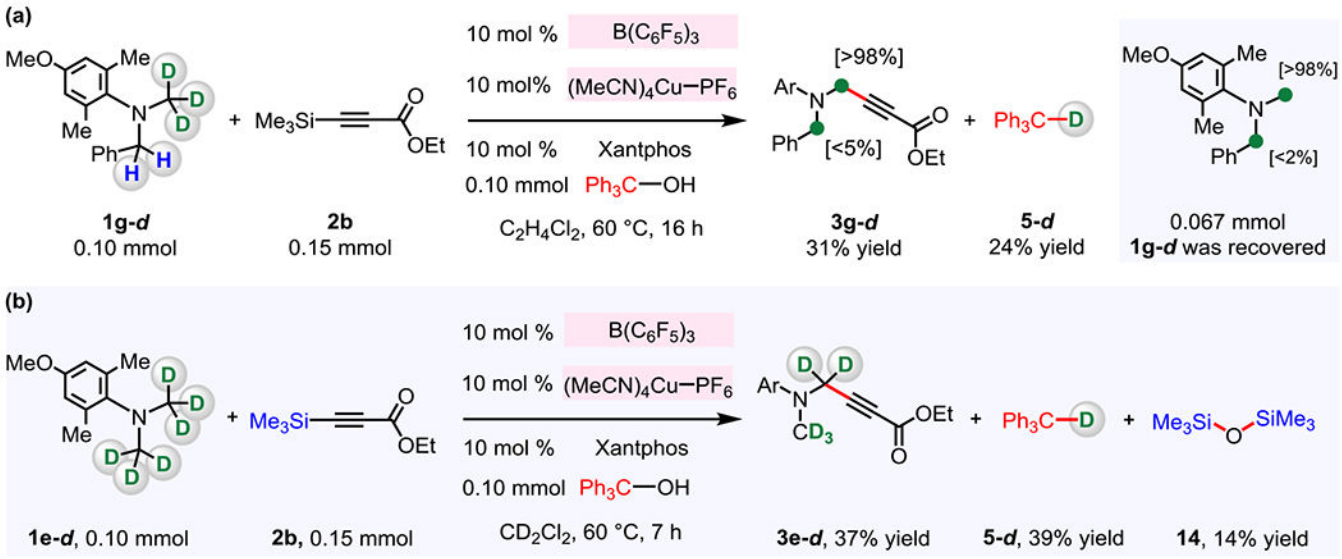
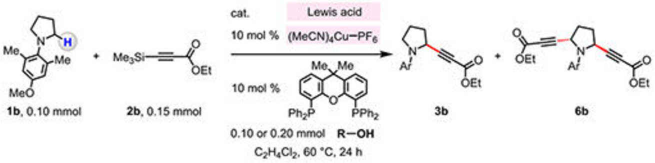


Figure 11. Structure Determination of Products.

(a) Under the standard reaction conditions for installation of the alkyne unit, no intra- and/or intermolecular H/D exchange was observed between *N*–CD_3 and *N*–CH_2Ph groups, indicating that in situ generated iminium salt is rapidly consumed through C–alkynyl bond forming reaction vs H/D scrambling. (b) Spectroscopic studies (^1H and ^2H NMR) involving pure compounds revealed that $Ph_3C–D$ and $Me_3Si–O–SiMe_3$ are the stable byproducts. See the Supporting Information for details.

Table 1.

Evaluation of Various Reaction Parameters[a,b].



entry	Lewis acid (mol %)		R–OH (mmol)	yield (%)	
				3b	**6b**
1	$B(C_6F_5)_3$	(10)	none	7	0
2	$B(C_6F_5)_3$	(10)	*i*-PrOH (0.20)	0	0
3	$B(C_6F_5)_3$	(10)	*t*-BuOH (0.20)	17	0
4	$B(C_6F_5)_3$	(10)	Ph_3COH (0.20)	52	34
5	$B(C_6F_5)_3$	(10)	Ph_3COH (0.10)	83	15
6[c]	$B(C_6F_5)_3$	(10)	Ph_3COH (0.10)	90	<5
7	$B(C_6F_5)_3$	(5.0)	Ph_3COH (0.10)	81	<5
8	none		Ph_3COH (0.10)	0	0
9	$BF_3{\cdot}OEt_2$	(10)	Ph_3COH (0.10)	0	0
10	BPh_3	(10)	Ph_3COH (0.10)	0	0

[a] Conditions: Reactions were performed under N_2 atmosphere. *N*-arylpyrrolidine (**1b**, 0.10 mmol), 3-(trimethylsilyl)propiolate (**2b**, 0.15 mmol), B-based Lewis acid, $(MeCN)_4CuPF_6$ (10 mol %), Xantphos (10 mol %), alcohol additive, $C_2H_4Cl_2$ (0.4 mL), 60 °C, 24 h.

[b] Yield values were determined by analysis of the ^1H NMR spectra of unpurified mixtures with mesitylene as the internal standard.

[c] Reaction mixture was allowed to stir for 12 h. See the Supporting Information for details.