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A Practical Electrophilic Nitrogen Source for the Synthesis of Chiral Primary Amines by Copper-Catalyzed Hydroamination

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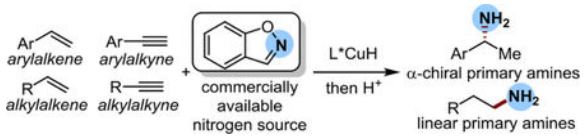
Abstract

A mild and practical method for the catalytic installation of the amino group across alkenes and alkynes has long been recognized as a significant challenge in synthetic chemistry. As the direct hydroamination of olefins using ammonia requires harsh conditions, the development of suitable electrophilic aminating reagents for formal hydroamination methods is of importance. Herein, we describe the use of 1,2-benzisoxazole as a practical electrophilic primary amine source. Using this heterocycle as a new amino group delivery agent, a mild and general protocol for the copper-hydride-catalyzed hydroamination of alkenes and alkynes to form primary amines was developed. This method provides access to a broad range of chiral α-branched primary amines and linear primary amines, as demonstrated by the efficient synthesis of the antiretroviral drug Maraviroc and the formal synthesis of several other pharmaceutical agents.

Graphical Abstract



INTRODUCTION

Chiral primary amines play an essential role in the preparation of natural products, active pharmaceutical ingredients, and other important derivatives because of their synthetic flexibility (Figure 1a).[1] Consequently, synthetic organic chemists have a long-standing interest in general methods for the synthesis of chiral primary amines.[1–2] Important methods for the enantioselective synthesis of chiral primary amines include the reduction of imines and enamines,[3–7] addition of nucleophiles to imines,[8] particularly Ellman's sulfonamide,[9] the reaction of a nitrogen nucleophile to allylic electrophiles,[10] and biocatalytic processes.[11–13] Although various methods exist, they typically require a pre-existing carbon–heteroatom bond or ketone group as the handle for functionalization. In comparison, hydroamination reactions provide a direct approach to access amines from readily available

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alkene and alkyne precursors. Specifically, copper(I) hydride complexes have been shown to catalyze hydroamination reactions between alkenes and hydroxylamine esters.[14] Despite the number of electrophilic aminating reagents that have been developed for the synthesis of chiral secondary[15] and tertiary amines[16–25] as well as amides[26], there have not been any reports of enantioselective transformations that allow for the direct synthesis of primary amines from olefins, in part due to the lack of a suitable electrophilic amine source.

Current electrophilic primary amine reagents that provide a direct approach for the synthesis of primary amines typically suffer from instability (in the case of haloamines) or have been reported to be hazardous upon purification and isolation (in the case of *O*-(mesitylenesulfonyl)hydroxylamine, MSH).[27] Moreover, reagents such as methoxyamine are stable as the corresponding hydrochloride salt, but require a minimum of two equivalents of strongly basic organometallic reagents to access the active form (through neutralization and further deprotonation),[28] which is capable of forming the desired C-N bond. Although protected NH_3 surrogates such as oxime derivatives[29] or creatively designed oxaziridines[30] may circumvent the problems of competitive amine deprotonation and difficult deprotections, most of these electrophiles require multistep synthesis (Figure 1b).[31] Thus, a simple, stable, and commercially available electrophilic amine source is highly desirable.

In this work, we describe the fortuitous discovery that isoxazole can be used as a suitable electrophilic nitrogen source providing a solution to the synthesis of primary amines via the copper-hydride-catalyzed hydroamination. Previously, we reported the copper-hydride-catalyzed enantioselective 1,4-dearomatization of pyridines with styrene-derived nucleophiles (Figure 1c(i)).[32] While attempting to extend this method to other nitrogen-containing heterocycles, the isoxazole unexpectedly provided the Schiff base product, instead of the anticipated dihydroisoxazole product (Figure 1c(ii)). The nucleophilic substitution of isoxazole via the cleavage of the N-O bond, upon imine hydrolysis, provided a new approach for synthesis of primary amines via an unknown mode of reactivity. Based on this result coupled with the high stability and commercial availability of isoxazole, we envisioned that isoxazole and its derivatives might function as electrophilic primary amine sources.

Herein, we demonstrate the generality of this initial result and describe the preparation of primary amines (or equivalents) via the hydroamination of alkenes and alkynes using isoxazole electrophiles as new commercially available electrophilic nitrogen sources. Under mild reaction conditions, a wide range of chiral α-branched (from aryl alkenes or alkynes) and linear primary amines (from alkyl-substituted terminal alkenes or alkynes) are afforded in good-to-excellent yields with high levels of enantioselectivity (Figure 1d). Additionally, the synthetic utility of this transformation is demonstrated by the preparation of several important pharmaceuticals, as well as the one-step conversion of low-cost readily available starting materials into valuable synthetic intermediates.

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RESULTS AND DISCUSSION

Effect of substitution patterns of isoxazole derivatives.

To arrive at the optimal isoxazole reagent for the CuH-catalyzed hydroamination of alkenes, styrene was allowed to react with a series of commercial isoxazole derivatives with varying electronic and steric properties under typical CuH catalysis conditions.[18] In the presence of 5.0 mol% copper acetate, 5.5 mol% (*S*)-DTBM-SEGPHOS, 3.2 equivalents of dimethoxymethylsilane, and 2.0 equivalents of isoxazole, the Schiff base product was afforded in moderate yield and with excellent enantioselectivity. Evaluation of other isoxazole derivatives revealed that the 3-substituted isoxazoles could not be used for the hydroamination process regardless of their steric and electronic properties (**2b**, **2c**). Furthermore, a comparison between the 4- (**2d**, **2e**) and 5- (**2f, 2g)** substituted isoxazoles showed that, although substituents at these positions are reported to promote the undesired ring-opening decomposition of the electrophile,[33] extension of the **π**-conjugation at the 5 position proved to be beneficial for overall reaction efficiency. The use of 1,2-benzisoxazole, **2h**, proved to be optimal, affording the chiral Schiff base product in excellent yield and enantiopurity. Additional experiments confirmed that 3-substituted 1,2-benzisoxazole (**2i**) was also not a suitable electrophile for this system. In addition to isoxazole derivatives, we have found that the *O*-benzoyl oxime derivative **2j** also provided the desired protected primary amine under similar conditions, albeit in reduced levels of yield and enantioselectivity (see Supporting Information). Due to the lower reactivity of **2j**, higher reaction temperatures and lower reaction concentrations were required to achieve high yields and enantioselectivity.

The effectiveness of **2h** as an electrophilic amine source was benchmarked against *N,N*-dibenzyl-*O*-pivaloylhydroxylamine (Bn_2NOPiv), which was previously found to be an excellent electrophilic amine reagent for CuH-catalyzed hydroamination reactions.[34–35] In separate reactions, the overall rate of reaction with Bn_2NOPiv was found to be about twice as fast as that with 1,2-benzisoxazole (Figure 2a, entry 1,2). However, because previous mechanistic studies indicated that the rate-determining-step of CuH-catalyzed hydroamination of styrene was the regeneration of LCuH catalyst (Figure 2b, **III** → **I**),[34] we speculated that the slower relative rate of reaction with 1,2-benzisoxazole was due to the slower regeneration of active LCuH species from Cu-phenolate **IIIb** relative to the analogous regeneration of LCuH from the copper pivalate **IIIa** in the reaction employing Bn_2NOPiv as the electrophile. In agreement with this hypothesis, a one-pot competition between **2h** and Bn_2NOPiv revealed that the alkyl-copper species **II** reacts preferentially with **2h** over Bn_2NOPiv (Figure 2a, Entry 3). These collective results indicate that, while **2h** is more reactive toward substitution with the Cu-alkyl intermediate (**II**), the resulting Cu-phenolate **IIIb** is less reactive toward reaction with the silane. The latter effect causes reactions employing **2h** to display reaction rates that are slower than reactions using Bn_2NOPiv as aminating reagents. The slower regeneration of LCuH in the isoxazole-based system has an important implication for the hydroamination of complex substrates, which is discussed below.

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Hydroamination of alkenes and alkynes to form primary amines.

Having identified 1,2-benzisoxazole as the optimal electrophilic nitrogen source, we set out to examine the scope of the alkene coupling partners of this hydroamination protocol (Table 2). The chiral Schiff base products can be quantitatively converted, in a one-pot procedure, to the corresponding primary amine without erosion of enantiomeric purity. Both the Schiff base products (**3a-l**) and the primary amines (**4a-f**) derived from this protocol can be obtained in good yields and high enantioselectivity (≥93% ee). Styrenes bearing electron-withdrawing (**3g**) and electron-donating (**3h**) substituents were converted to products with good efficiency. Similarly, substrates with an electronically diverse set of *ortho*-substituents (**3b**, **3c**) were also suitable. Due to the mild reaction conditions, a variety of functional groups such as aryl chlorides (**3d**) and bromides (**3e**), esters (**3j**), sulfonamides (**4a**), carbamates (**4b**), and a thiomethyl group (**4c**) were tolerated. The reaction conditions also accommodated a wide range of vinyl-substituted heteroarenes, including those containing an electron-deficient heterocycles, such as pyridine (**3k**), 7-azaindole (**4a**), pyrimidine (**4c**), electron-rich indazole (**4b**), pyrazole (**4d**), and carbazole (**4e**) ring, providing α-chiral primary amines with high levels of enantioselectivity. This approach was applied to the hydroamination of complex aryl alkenes such as estrone to provide rapid access to the structurally complex Schiff base **3l**.

Previously, we have demonstrated that increased steric hindrance at the β-position may negatively influence the efficiency of hydroamination.[15] Although sterically less-hindered β-substituted styrenes (**3i**, **3j**) provided the desired product with good yield, a significant amount of alkene reduction (~50%) was observed when the more sterically hindered substrate, cinnarizine (**4f**), was subjected to our standard hydroamination conditions. The observation of salicylonitrile as a major byproduct led us to postulate that Kemp elimination of 1,2-benzisoxazole (Figure 3a) had emerged as a competing, non-productive pathway when the rate of CuH regeneration (i.e., **II'** → product, Figure 3b) is reduced by the steric hinderance of the large β-substituent. Due to the slowed rate of CuH regeneration, the copper-phenolate (**II'**) can catalyze the Kemp elimination of **2** to form **III'**. This copper-phenolate can catalyze further Kemp elimination of 1,2-benzisoxazole to give salicylonitrile (see Supporting Information for details), which in turn serves as a proton source (**IV'**) for the reduction of the alkene. The issue of alkene reduction due to competitive Kemp elimination was addressed by employing solvents of lower polarity, which are known to slow the rate of Kemp elimination,[36–37] as well as by using a syringe pump for the slow addition of 1,2-benzisoxazole (see Supporting Information for details). Presumably, the slow addition of 1,2-benzisoxazole reduces the rate of Kemp elimination versus the rate of productive catalyst turnover by keeping the concentration of 1,2-benzisoxazole low. Under these reaction conditions, cinnarizine was successfully converted to the chiral primary amine **4f** in high yield and excellent levels of enantioselectivity. This simple modification of the reaction system later proved to be crucial during our subsequent synthesis of Maraviroc.

Having confirmed the effectiveness of our method for the synthesis of chiral Schiff bases and primary amines using styrene substrates, we continued by investigating the anti-Markovnikov hydroamination of unactivated alkenes (Table 3). Due to the higher energy barrier for the hydrocupration of terminal alkenes,[38] slightly elevated temperatures (45 °C)

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and slow addition of the electrophile using a syringe pump were required to obtain good yields and high levels of enantioselectivity. This protocol was successfully applied to terminal alkenes (**4g**-**4k**). As before, the protocol manifested excellent functional group tolerance, as acetals (**4g**), sulfonamides (**4h**), epoxy groups (**3n**), and silyl groups (**3o**) were tolerated under the reaction conditions. Both electron-rich and electron-deficient heterocycles, such as benzothiazole (**4i**) and quinoline (**4j**), were also readily accommodated. Furthermore, the one-pot synthesis of primary amine **4k** provided an alternative route for the preparation of bifemelane, a cerebral activator used for the treatment of senile dementia and glaucoma.[39] The hydroamination of 1,1-disubstituted alkenes also worked well with this protocol providing the a silicon-substituted stereogenic center (**3o**), as well as demonstrating the chemoselectivity for the reaction of 1,1-disubstituted alkenes over trisubstituted ones (**3p**). The regioselectivity and enantioselectivity of hydroamination of 1,1-dialkyl substituted alkenes (**3o**, **3p** in Table 3) are in accord with the results previously reported by our lab.[19]

We next explored the hydroamination of alkynes. Previous work in our lab demonstrated that alkynes may be converted into alkyl amines via a sequence involving semireduction of the alkyne and hydroamination of the resultant alkene.[40] With a modified reductive hydroamination protocol, including *i*PrOH as the proton source and **2h** as the aminating reagent, we found that the aryl-substituted terminal alkynes undergo the Markovnikov hydroamination to access the corresponding chiral Schiff base products (Table 4). The reaction conditions tolerated the electron-withdrawing (**3e**) and electron-donating (**3h**) substituents on the arene as well as the electron-rich heterocycles, such as thiophene (**3q**). Additionally, the terminal aliphatic alkynes undergo anti-Markovnikov hydroamination to access the linear primary amine product (**4l**) with the one-pot operation. The regioselectivity is in accord with the results previously reported by our lab.[40] The reductive hydroamination of alkynes to primary amines provides an alternative approach for the synthesis of the valuable primary amines.

Application to the synthesis of pharmaceutical agents.

An important advantage of this mild enantioselective hydroamination process using 1,2-benzisoxazole as an ammonia surrogate lies in its ability to install a chiral primary amine unit onto highly functionalized late-stage synthetic intermediates. To illustrate this, a convergent strategy for the three-step synthesis of the antiretroviral drug Maraviroc, which is used for the treatment of HIV infections, is described. All three previous asymmetric synthetic routes that have been reported in the literature call for early-stage installation of the amino group,[41–44] therefore limiting the tunability of the arene fragment. As a complementary approach, our strategy introduced the amino group via copper-catalyzed asymmetric hydroamination of styrene **5c**, which can be accessed in high yield from reductive amination of cinnamyl aldehyde **5a** and the complex secondary amine **5b**. Using similar conditions to those developed for the hydroamination of cinnarizine, the core chiral primary amine fragment **5d** was isolated in 73% yield and 94% ee after hydrolytic workup. Subsequent acylation then provided Maraviroc in 59% yield over three steps (Figure 4a). This approach provides an alternative route that allows for the diversification of the arene component of drug analogs.

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As another application of this method, we converted a simple hydrocarbon feedstock, indene, to 1-aminoindane (**4m**), a highly valuable synthetic precursor for important pharmaceuticals such as Rasagiline.[45] By following the slow addition protocol developed for unactivated alkenes and increasing the reaction temperature to 70 °C, 1-aminoindane (**4m**) was obtained in 69% yield and 92% ee (Figure 4b). To evaluate the scalability of this method, we have also synthesized (*S*)-3-amino-3-phenyl-1-propanol hydrochloride (**4n**), an important intermediate for the synthesis of Dapoxetine[46] from the hydroamination of cinnamyl acetate on a 10 mmol scale. This gram-scale reaction provided the Schiff base product in 94% NMR yield and 99% ee. After the hydrolysis of the imine and the ester, the hydrochloride (**4n**) can be obtained by acidification of the corresponding primary amine in good isolated yield (78%, Figure 4c). Finally, the chiral Schiff base product **3r** can also be obtained in exceptional levels of enantiopurity under our standard conditions, and this intermediate can be further hydrolyzed to the valuable chiral primary amine product for the synthesis of human leukocyte elastase inhibitor, DMP 777 (Figure 4d).[47]

CONCLUSION

In conclusion, we have discovered that 1,2-benzisoxazole is effective as a practical electrophilic ammonia equivalent in CuH-catalyzed hydroamination. We described the first enantioselective hydroamination of alkenes and alkynes to primary amines that occurs by asymmetric substitution of 1,2-benzisoxazole through the N–O bond cleavage. This approach provides an efficient method to access chiral α-branched and linear primary amines under very mild conditions. During the exploration of the scope of alkenes and alkynes, a series of primary amines were prepared in excellent enantio-, regio- and chemoselectivity. Furthermore, we developed a highly convergent route to prepare anti-HIV drug Maraviroc, and demonstrated the preparation of precursors of Rasagiline mesylate, Dapoxetine hydrochloride, and DMP 777.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

(1). Nugent TC, Chiral Amine Synthesis: Methods, Developments and Applications. Wiley-VCH, 2010.

(2). Morandi B; Legnani L; Bhawal B, Recent Developments in the Direct Synthesis of Unprotected Primary- Amines. Synthesis 2016, 49, 776–789.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

(3). Tan X; Gao S; Zeng W; Xin S; Yin Q; Zhang X, Asymmetric Synthesis of Chiral Primary Amines by Ruthenium-Catalyzed Direct Reductive Amination of Alkyl Aryl Ketones with Ammonium Salts and Molecular H2. J. Am. Chem. Soc 2018, 140, 2024–2027. [PubMed: 29377687]

(4). Gallardo-Donaire J; Hermsen M; Wysocki J; Ernst M; Rominger F; Trapp O; Hashmi ASK; Schafer A; Comba P; Schaub T, Direct Asymmetric Ruthenium-Catalyzed Reductive Amination of Alkyl-Aryl Ketones with Ammonia and Hydrogen. J. Am. Chem. Soc 2018, 140, 355–361. [PubMed: 29195041]

(5). Zhao Q; Wen J; Tan R; Huang K; Metola P; Wang R; Anslyn EV; Zhang X, Rhodium-catalyzed asymmetric hydrogenation of unprotected NH imines assisted by a thiourea. Angew. Chem., Int. Ed 2014, 53, 8467–8470.

(6). Nugent TC; El-Shazly M, Chiral amine synthesis. Recent developments and trends for enamide reduction, reductive amination, and imine reduction. Adv. Synth. Catal 2010, 352, 753–819.

(7). Li K; Shao X; Tseng L; Malcolmson SJ, 2-Azadienes as Reagents for Preparing Chiral Amines: Synthesis of 1,2-Amino Tertiary Alcohols by Cu-Catalyzed Enantioselective Reductive Couplings with Ketones. J. Am. Chem. Soc 2018, 140, 598–601. [PubMed: 29272124]

(8). Jang H; Romiti F; Torker S; Hoveyda AH, Catalytic diastereo- and enantioselective additions of versatile allyl groups to N-H ketimines. Nat. Chem 2017, 9, 1269–1275. [PubMed: 29168479]

(9). Robak MT; Herbage MA; Ellman JA, Synthesis and Applications of tert-Butanesulfinamide. Chem. Rev 2010, 110, 3600–3740. [PubMed: 20420386]

(10). Roggen M; Carreira EM, Stereospecific substitution of allylic alcohols to give optically active primary allylic amines: unique reactivity of a (P,alkene)Ir complex modulated by iodide. J. Am. Chem. Soc 2010, 132, 11917–9. [PubMed: 20698515]

(11). Kroutil W; Fischereder E-M; Fuchs CS; Lechner H; Mutti FG; Pressnitz D; Rajagopalan A; Sattler JH; Simon RC; Siirola E, Asymmetric Preparation of prim-, sec-, and tert-Amines Employing Selected Biocatalysts. Org. Process Res. Dev 2013, 17, 751–759. [PubMed: 23794796]

(12). Savile CK; Janey JM; Mundorff EC; Moore JC; Tam S; Jarvis WR; Colbeck JC; Krebber A; Fleitz FJ; Brands J; Devine PN; Huisman GW; Hughes GJ, Biocatalytic asymmetric synthesis of chiral amines from ketones applied to sitagliptin manufacture. Science 2010, 329, 305–9. [PubMed: 20558668]

(13). Paetzold J; Backvall JE, Chemoenzymatic dynamic kinetic resolution of primary amines. J. Am. Chem. Soc 2005, 127, 17620–1. [PubMed: 16351088]

(14). Pirnot MT; Wang Y-M; Buchwald SL, Copper Hydride-Catalyzed Hydroamination of Alkenes and Alkynes. Angew. Chem., Int. Ed 2016, 55, 48–57.

(15). Niu D; Buchwald SL, Design of Modified Amine Transfer Reagents Allows the Synthesis of α-Chiral Secondary Amines via CuH-Catalyzed Hydroamination. J. Am. Chem. Soc 2015, 137, 9716–9721. [PubMed: 26144542]

(16). Miki Y; Hirano K; Satoh T; Miura M, Copper-Catalyzed Intermolecular Regioselective Hydroamination of Styrenes with Polymethylhydrosiloxane and Hydroxylamines. Angew. Chem., Int. Ed 2013, 52, 10830–10834.

(17). Nishikawa D; Hirano K; Miura M, Asymmetric Synthesis of α-Aminoboronic Acid Derivatives by Copper-Catalyzed Enantioselective Hydroamination. J. Am. Chem. Soc 2015, 137, 15620–15623. [PubMed: 26653275]

(18). Zhu S; Niljianskul N; Buchwald SL, Enantio- and Regioselective CuH-Catalyzed Hydroamination of Alkenes. J. Am. Chem. Soc 2013, 135, 15746–15749. [PubMed: 24106781]

(19). Zhu S; Buchwald SL, Enantioselective CuH-Catalyzed Anti-Markovnikov Hydroamination of 1,1-Disubstituted Alkenes. J. Am. Chem. Soc 2014, 136, 15913–15916. [PubMed: 25339089]

(20). Niljianskul N; Zhu S; Buchwald SL, Enantioselective synthesis of α-aminosilanes by copper-catalyzed hydroamination of vinylsilanes. Angew. Chem., Int. Ed 2015, 54, 1638–1641.

(21). Yang Y; Shi S-L; Niu D; Liu P; Buchwald SL, Catalytic asymmetric hydroamination of unactivated internal olefins to aliphatic amines. Science 2015, 349, 62–66. [PubMed: 26138973]

(22). Shi S-L; Wong ZL; Buchwald SL, Copper-catalysed enantioselective stereodivergent synthesis of amino alcohols. Nature 2016, 532, 353–356. [PubMed: 27018656]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

(23). Xi Y; Butcher TW; Zhang J; Hartwig JF, Regioselective, Asymmetric Formal Hydroamination of Unactivated Internal Alkenes. Angew. Chem., Int. Ed 2016, 55, 776–780.

(24). Zhu S; Niljianskul N; Buchwald SL, A direct approach to amines with remote stereocentres by enantioselective CuH-catalyzed reductive relay hydroamination. Nat. Chem 2016, 8, 144–150. [PubMed: 26791897]

(25). Wang H; Yang JC; Buchwald SL, CuH-Catalyzed Regioselective Intramolecular Hydroamination for the Synthesis of Alkyl-Substituted Chiral Aziridines. J. Am. Chem. Soc 2017, 139, 8428–8431. [PubMed: 28594548]

(26). Zhou Y; Engl OD; Bandar JS; Chant ED; Buchwald SL, CuH-Catalyzed Asymmetric Hydroamidation of Vinylarenes. Angew. Chem., Int. Ed 2018, 57, 6672–6675.

(27). Mendiola J; Rincón JA; Mateos C; Soriano JF; de Frutos Ó; Niemeier JK; Davis EM, Preparation, Use, and Safety of O-Mesitylenesulfonylhydroxylamine. Org. Process Res. Dev 2009, 13, 263–267.

(28). Mlynarski SN; Karns AS; Morken JP, Direct Stereospecific Amination of Alkyl and Aryl Pinacol Boronates. J. Am. Chem. Soc 2012, 134, 16449–16451. [PubMed: 23002712]

(29). Kitamura M; Suga T; Chiba S; Narasaka K, Synthesis of primary amines by the electrophilic amination of Grignard reagents with 1,3-dioxolan-2-one O-sulfonyloxime. Org. Lett 2004, 6, 4619–21. [PubMed: 15548090]

(30). Gao H; Zhou Z; Kwon DH; Coombs J; Jones S; Behnke NE; Ess DH; Kurti L, Rapid heteroatom transfer to arylmetals utilizing multifunctional reagent scaffolds. Nat. Chem 2017, 9, 681–688. [PubMed: 28644470]

(31). Gosmini C; Corpet M, Recent Advances in Electrophilic Amination Reactions. Synthesis 2014, 46, 2258–2271.

(32). We note that a related paper appeared while our paper was in revision: REFERENCE DOI: 10.1021/acs.orglett.8b03093.It involves ring opening of anthranils as a source of electrophile for Cu-catalyzed asymmetric hydroamination processes. It does not appear to allow for the easy introduction of a primary amino group.Gribble MW; Guo S; Buchwald SL, Asymmetric Cu-Catalyzed 1,4-Dearomatization of Pyridines and Pyridazines without Preactivation of the Heterocycle or Nucleophile. J. Am. Chem. Soc 2018, 140, 5057–5060. [PubMed: 29609461]

(33). De Munno A; Bertini V; Lucchesini F, On the base catalysed ring opening of 3-unsubstituted isoxazoles. Derivatives of 4- and 5-phenylisoxazole. J. Chem. Soc., Perkin Trans 2 1977, 1121–1124.

(34). Bandar JS; Pirnot MT; Buchwald SL, Mechanistic Studies Lead to Dramatically Improved Reaction Conditions for the Cu-Catalyzed Asymmetric Hydroamination of Olefins. J. Am. Chem. Soc 2015, 137, 14812–14818. [PubMed: 26522837]

(35). In principle, Bn2NOPiv could provide the same products (primary amines) that are synthesized in this paper by hydrogenolysis of the benzyl groups. However, because of the possibility of hydrogenating the benzyl amines we are synthesizing, we did not pursue this approach.

(36). Casey ML; Kemp DS; Paul KG; Cox DD, Physical organic chemistry of benzisoxazoles. I. Mechanism of the base-catalyzed decomposition of benzisoxazoles. J. Org. Chem 1973, 38, 2294–301.

(37). D'Anna F; La Marca S; Lo Meo P; Noto R, A Study of the Influence of Ionic Liquids Properties on the Kemp Elimination Reaction. Chem. Eur. J 2009, 15, 7896–7902. [PubMed: 19562783]

(38). Lu G; Liu RY; Yang Y; Fang C; Lambrecht DS; Buchwald SL; Liu P, Ligand-Substrate Dispersion Facilitates the Copper-Catalyzed Hydroamination of Unactivated Olefins. J. Am. Chem. Soc 2017, 139, 16548–16555. [PubMed: 29064694]

(39). Kikumoto R; Tobe A; Tonomura S, Synthesis and antidepressant activity of substituted (ω-aminoalkoxy)benzene derivatives. J. Med. Chem 1981, 24, 145–8. [PubMed: 7205881]

(40). Shi S-L; Buchwald SL, Copper-catalyzed selective hydroamination reactions of alkynes. Nat. Chem 2015, 7, 38–44. [PubMed: 25515888]

(41). Zhao G-L; Lin S; Korotvicka A; Deiana L; Kullberg M; Cordova A, Asymmetric Synthesis of Maraviroc (UK-427,857). Adv. Synth. Catal 2010, 352, 2291–2298.

(42). Lou S; Moquist PN; Schaus SE, Asymmetric Allylboration of Acyl Imines Catalyzed by Chiral Diols. J. Am. Chem. Soc 2007, 129, 15398–15404. [PubMed: 18020334]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

(43). Ahman J; Birch M; Haycock-Lewandowski SJ; Long J; Wilder A, Process Research and Scale-up of a Commercializable Route to Maraviroc (UK-427,857), a CCR-5 Receptor Antagonist. Org. Process Res. Dev 2008, 12, 1104–1113.

(44). Haycock-Lewandowski SJ; Wilder A; Ahman J, Development of a Bulk Enabling Route to Maraviroc (UK-427,857), a CCR-5 Receptor Antagonist. Org. Process Res. Dev 2008, 12, 1094–1103.

(45). Ma G; Xu Z; Zhang P; Liu J; Hao X; Ouyang J; Liang P; You S; Jia X, A Novel Synthesis of Rasagiline via a Chemoenzymatic Dynamic Kinetic Resolution. Org. Process Res. Dev 2014, 18, 1169–1174.

(46). Torre O; Gotor-Fernandez V; Gotor V, Lipase-catalyzed resolution of chiral 1,3-amino alcohols: application in the asymmetric synthesis of (S)-dapoxetine. Tetrahedron: Asymmetry 2006, 17, 860–866.

(47). Storace L; Anzalone L; Confalone PN; Davis WP; Fortunak JM; Giangiordano M; Haley JJ, Jr.; Kamholz K; Li H-Y; Ma P; Nugent WA; Parsons RL, Jr.; Sheeran PJ; Silverman CE; Waltermire RE; Wood CC, An efficient large-scale process for the human leukocyte elastase inhibitor, DMP 777. Org. Process Res. Dev 2002, 6, 54–63.

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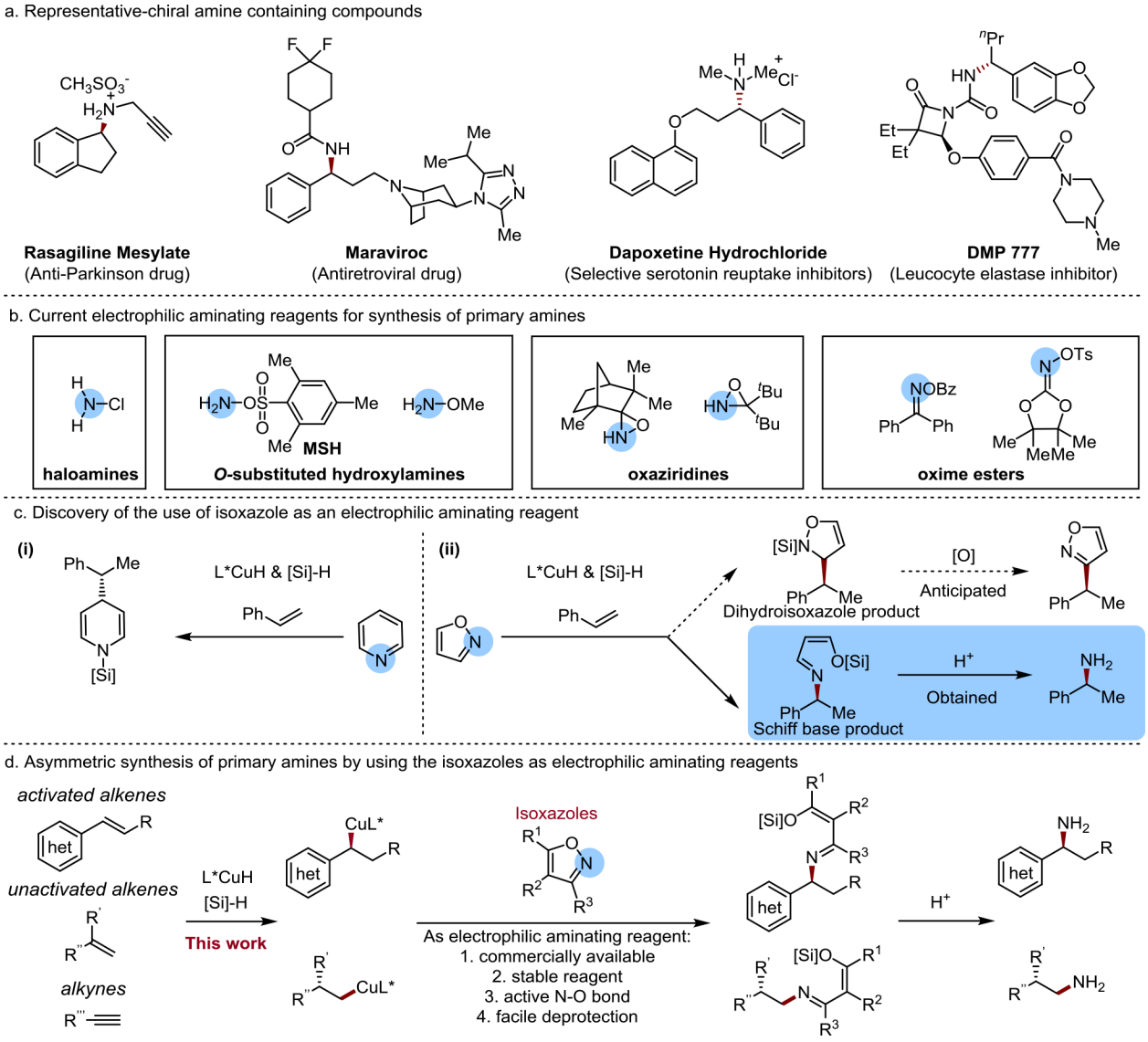
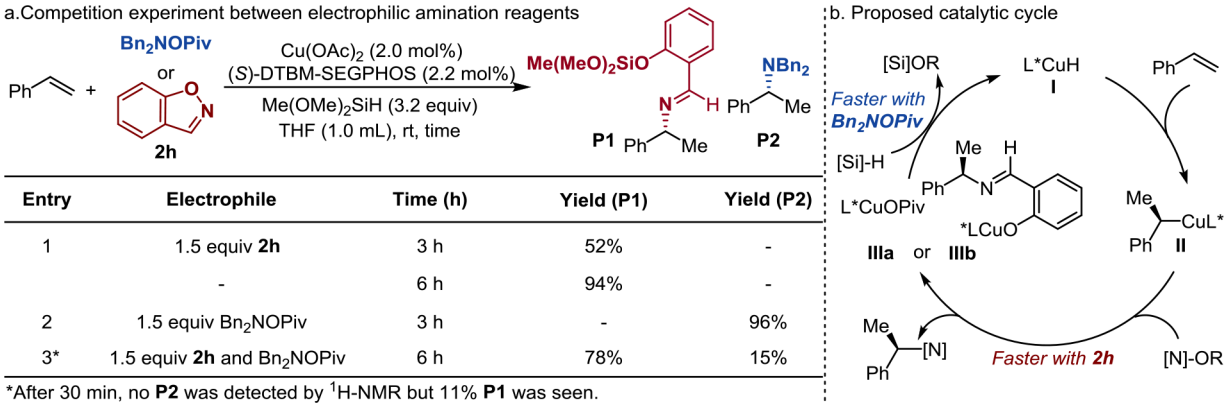


Figure 1.

a) Representative pharmaceuticals prepared from chiral primary amines. b) Current electrophilic aminating reagents used for the synthesis of primary amines. c) The discovery of isoxazole as an electrophilic aminating reagent. d) Asymmetric synthesis of primary amines by using the isoxazoles as electrophilic aminating reagents.



Entry	Electrophile	Time (h)	Yield (P1)	Yield (P2)
1	1.5 equiv **2h**	3 h	52%	-
	-	6 h	94%	-
2	1.5 equiv Bn_2NOPiv	3 h	-	96%
3*	1.5 equiv **2h** and Bn_2NOPiv	6 h	78%	15%

*After 30 min, no **P2** was detected by ^{1}H-NMR but 11% **P1** was seen.

Figure 2.

a) Competition experiment between electrophilic amination reagents. b) Proposed catalytic cycle

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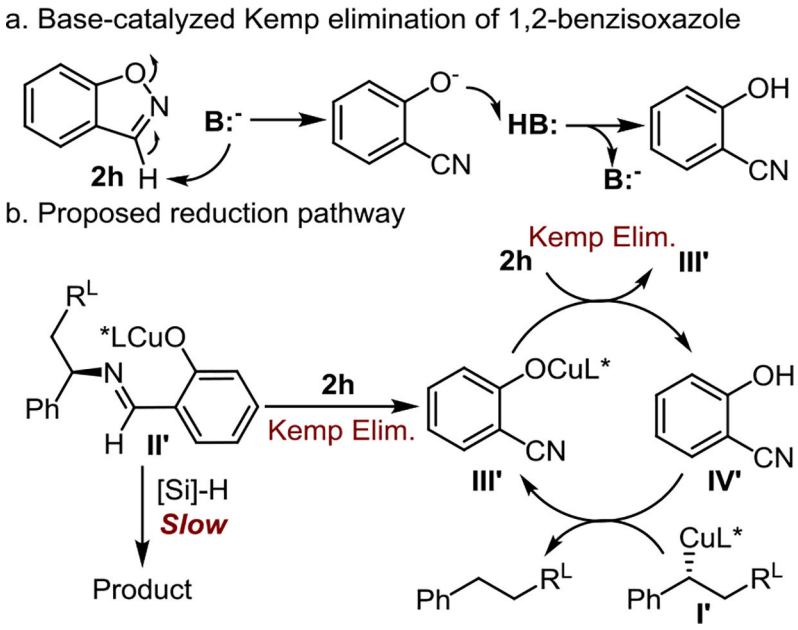

Figure 3.

a. Base-catalyzed Kemp elimination of 1,2-benzisoxazole. b. The proposed mechanism for alkene reduction in the hydroamination of β-sterically hindered styrenes.

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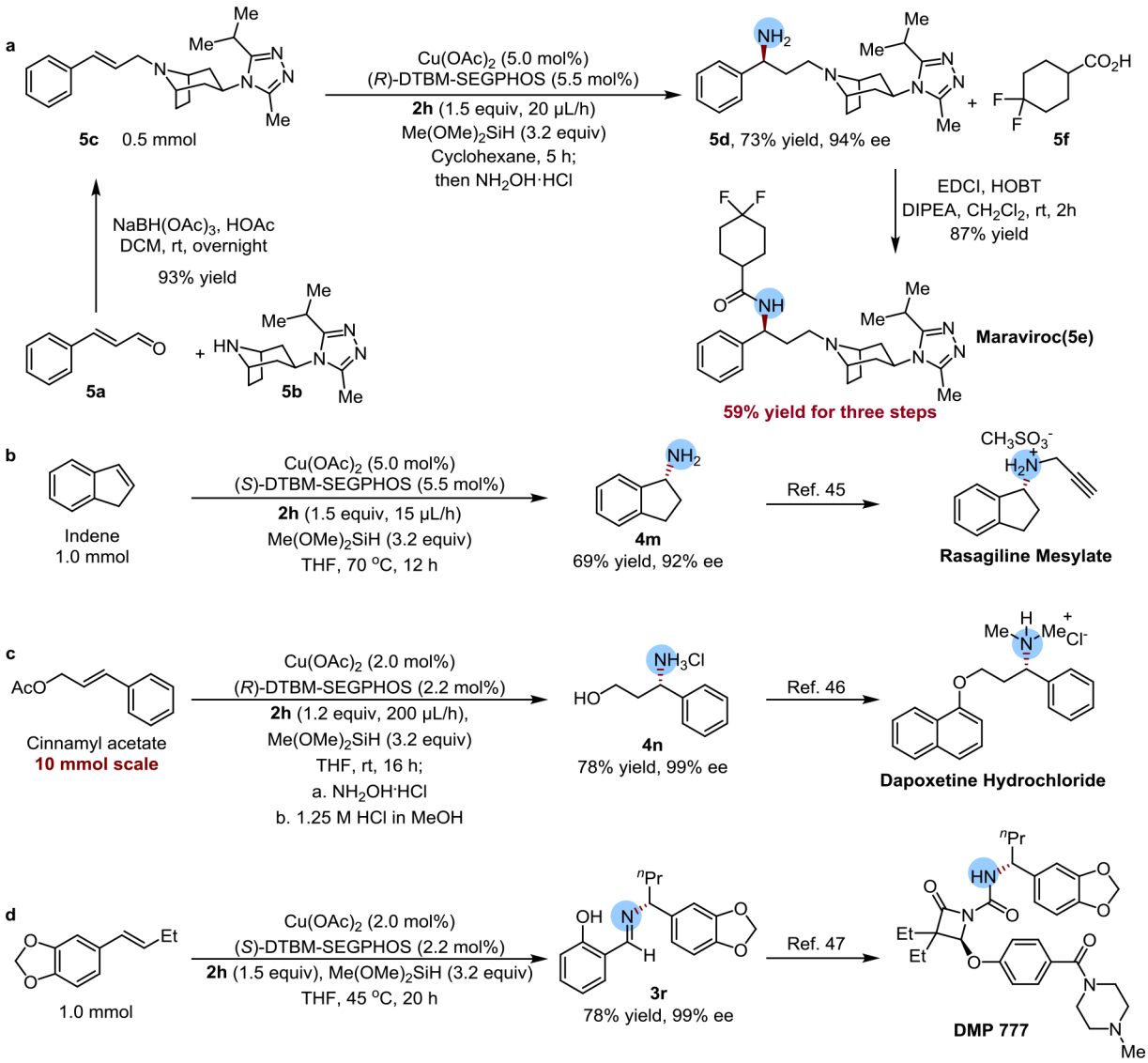

Figure 4.

Application of the hydroamination reaction in the synthesis of some pharmaceutical agents: (a) Maraviroc, (b) Rasagiline mesylate, (c) Dapoxetine hydrochloride, (d) DMP 777

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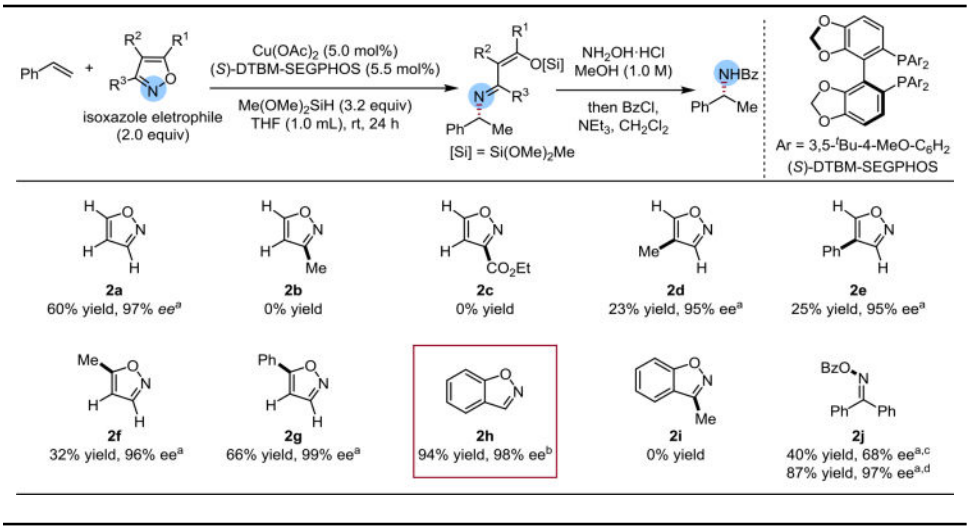
Table 1.

Effect of substitution pattern of isoxazole derivatives



a)(5.0 mol%) $Cu(OAc)_2$, (5.5 mol%) (*S*)-DTBM-SEGPHOS, styrene (0.50 mmol), electrophile (2.0 equiv), rt, 24 h. The yield and ee were determined based on the benzamide product.

*b)*The yield and ee were determined based on the Schiff base product.

*c)*40 °C, 0.5 M in THF. d) 85 °C, 0.05 M in THF, see supporting information for optimization.

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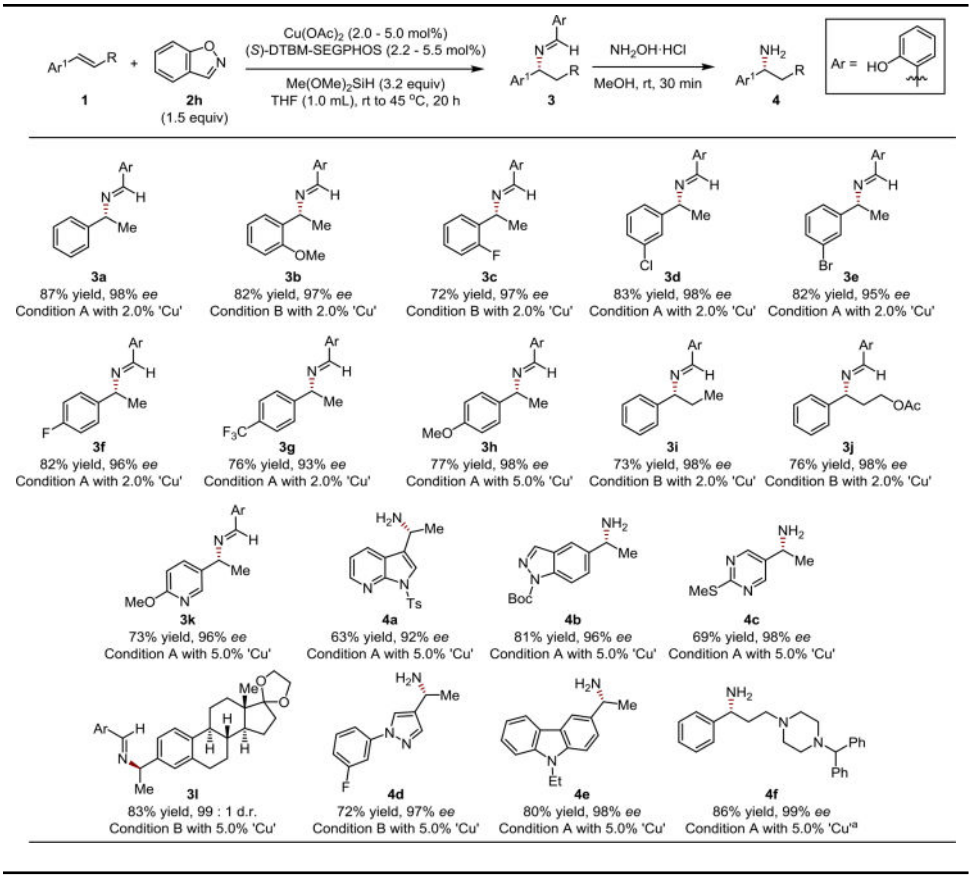
Table 2.

Using 1,2-benzisoxazole as an electrophilic aminating reagent for the hydroamination of aryl alkenes to primary amines



Condition A: (2.0 – 5.0 mol%) $Cu(OAc)_2$, (2.2 – 5.5 mol%) (*S*)-DTBM-SEGPHOS, **2h** was added in one portion, rt.

Condition B: (2.0 – 5.0 mol%) $Cu(OAc)_2$, (2.2 – 5.5 mol%) (*S*)-DTBM-SEGPHOS, **2h** (0.5 equiv.) was added every 2 h, 45 °C. Yield refers to isolated yield of purified product (1.0 mmol scale, average of two runs) and the ee was determined on the Schiff base product. a. cyclohexane as solvent and **2h** was added via syringe pump (30 μL/h).

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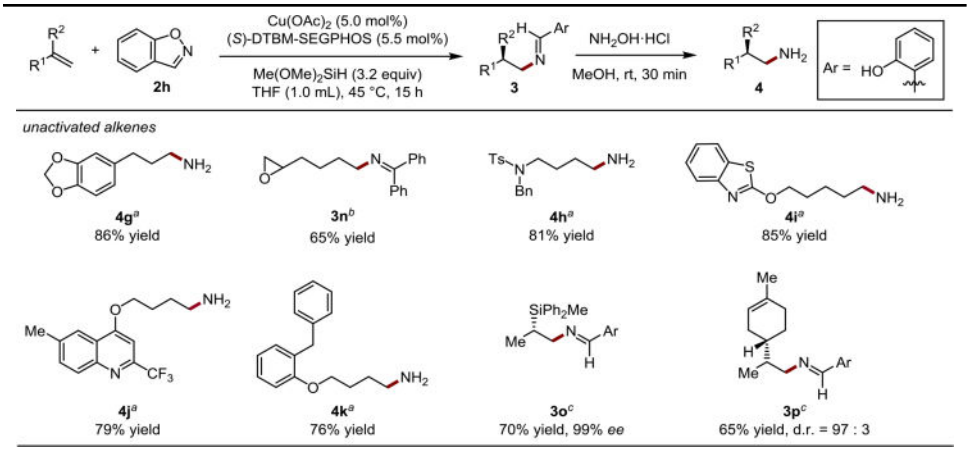
Table 3.

Using 1,2-benzisoxazole as an electrophilic aminating reagent for the hydroamination of unactivated alkenes to primary amines



Yield refers to isolated yield of purified product (1.0 mmol scale, average of two runs).

a) 1.5 equiv 2h was added via syringe pump (15 μL/h).

b) 1.05 equiv 2j was used. The use of the oxime ester 2j as the electrophile for the synthesis of 3n did not require slow addition or excess aminating reagent to achieve a moderate yield, presumably due to its comparatively higher stability at elevated temperatures.

c) 1.5 equiv 2h was added via syringe pump (10 μL/h).

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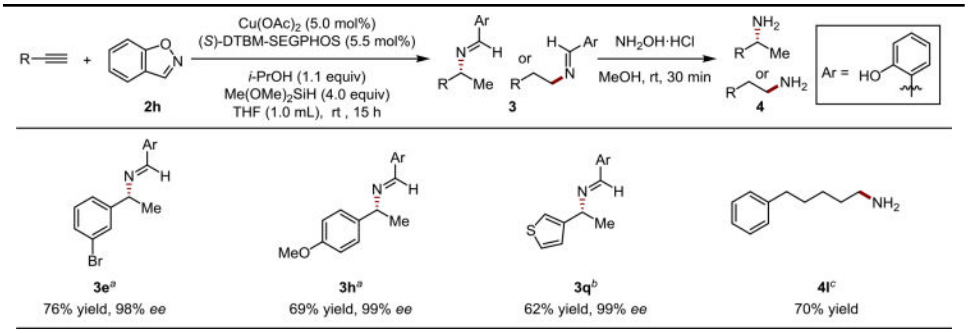
Table 4.

Using 1,2-benzisoxazole as an electrophilic aminating reagent for the reductive hydroamination of alkynes to primary amines



Yield refers to isolated yield of purified product (1.0 mmol scale, average of two runs).

a) 1.5 equiv **2h** was added in one portion.

b) 1.5 equiv **2h** was added via syringe pump (30 μL/h) at rt.

c) 1.5 equiv **2h** was added via syringe pump (15 μL/h) at 45 °C