OUKA
Osaka University Knowledge Archive

Title	Copper-Catalyzed Electrophilic Amination: An Umpolung Strategy for New CN Bond Formations
Author(s)	Hirano, Koji
Citation	Bulletin of the Chemical Society of Japan. 2023, 96(3), p. 198-207
Version Type	AM
URL	https://hdl.handle.net/11094/92800
rights	© 2023 The Chemical Society of Japan.
Note	

Osaka University Knowledge Archive : OUKA

https://ir.library.osaka-u.ac.jp/

Osaka University

Copper-catalyzed Electrophilic Amination: An Umpolung Strategy for New C–N Bond Formations

Koji Hirano*

Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

E-mail: k_hirano@chem.eng.osaka-u.ac.jp

Koji Hirano

Koji Hirano studied chemistry at Kyoto University where he obtained his B. Eng. (2003), M. Eng. (2005), and Dr. Eng. (2008) degrees under the supervision of Professor Koichiro Oshima. He subsequently worked as a postdoctoral fellow with Professor Tamio Hayashi at Kyoto University from April to September 2008. He then joined the research group of Professor Masahiro Miura at Osaka University as an assistant professor in October 2008, and was promoted to an associate professor in April 2015 and a full professor in May 2022.

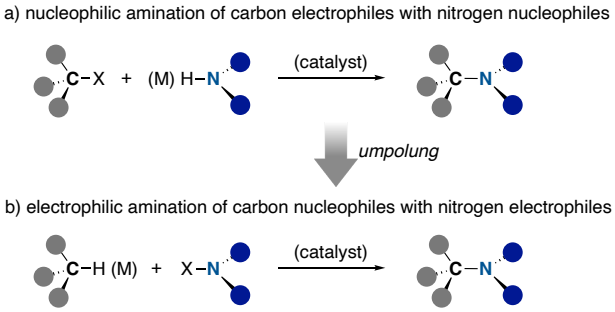
Abstract

The nitrogen atom is ubiquitous in bioactive molecules and functional materials, and the development of new C–N bond forming strategies is thus one of the long-standing research subjects in the synthetic community. This account describes the nitrogen-umpolung-enabled copper-catalyzed highly chemo- and stereoselective amination protocols developed by the author's research group. Starting from the C–H amination, electrophilic amination of stable organoboron and organosilicon compounds, aminoboration/hydroamination of alkenes, and their applications to the synthesis of functionality-rich alkylamines are shown. The reaction design, concept, and substrate scope are briefly summarized.

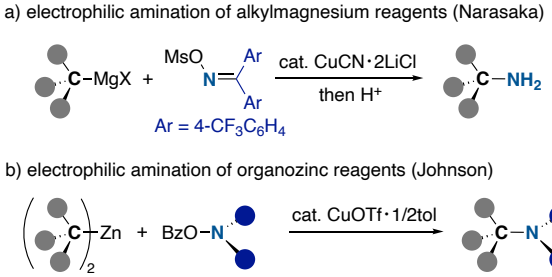
Keywords: Amination, Copper, Umpolung

1. Introduction

Nitrogen (N) is a main group 15 element that is ubiquitously found in natural products, biologically active compounds, and pharmaceutical agents.[1] Additionally, many recently reported aromatic functional organic materials contain N as the key element because of the effective n-π conjugation.[2] Accordingly, the development of C–N bond forming reactions that introduce N into organic skeletons has been one research area of long-standing interest to the synthetic community. The nitrogen is a relatively electronegative element; its electronegativity on Pauling scale is 3.04. In addition, the amino group (R_2N), which is the most common N-containing organic functional group, has one lone pair and thus generally works as the nucleophile. Therefore, to form the targeted C–N bond, synthetic chemists have developed the nucleophilic amination strategy, that is, the reaction of carbon electrophiles with nitrogen nucleophiles of the type (M) H–NR_2 (Scheme 1a). The well-known examples of the nucleophilic amination include the text-book S_N2 reaction of alkyl halides with amines[3] and Pd-catalyzed Buchwald-Hartwig amination of aryl halides with amines.[4] On the other hand, umpolung (polarity inversion), electrophilic amination using carbon nucleophiles and nitrogen electrophiles of the type X–NR_2 (X = leaving group, e.g., halides and OR') can be a good alternative to the nucleophilic amination (Scheme 1b). The concept of electrophilic amination has a long history, but its synthetic application had been restricted probably due to the relatively low stability of the electrophilic amination reagents, in particular, haloamines.[5] A breakthrough was reported by Narasaka in 1997, where CuCN・2LiCl catalyzed the electrophilic amination of alkylmagnesium reagents with sulfonyloximes (Scheme 2a).[6] Subsequent hydrolysis afforded the corresponding primary alkylamines, some of which are still relatively difficult to prepare by other means. Seven years later, Johnson developed the copper-catalyzed electrophilic amination of organozinc reagents with *O*-benzoyl-*N,N*-dialkylhydroxylamines to furnish tertiary amines (Scheme 2b).[7] Although these seminal works clearly demonstrated the high potential of the electrophilic amination strategy in the synthesis of *N*-containing molecules, viable carbon nucleophiles were still limited to highly reactive organometallic reagents such as RMgX and R_2Zn; their low functional group compatibility hampered wide applications in organic synthesis.



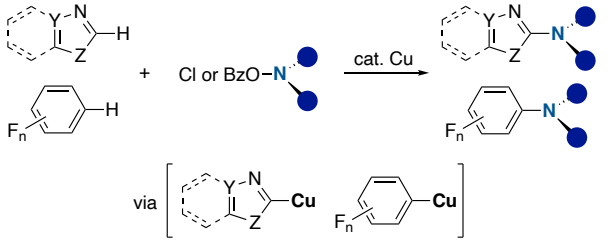
Scheme 1. C–N Bond formations: (a) nucleophilic amination versus (b) electrophilic amination.



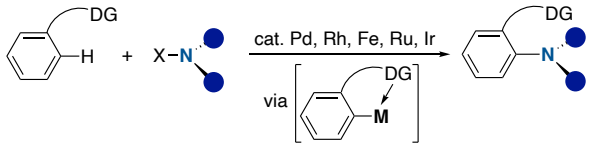
Scheme 2. Pioneering works on electrophilic amination developed by (a) Narasaka and (b) Johnson.

In 2010, we reported the copper-catalyzed C–H amination of 1,3-azoles with the electrophilic amination reagents,

chloroamines, at room temperature, in which the non-metalated simple C–H bonds were directly converted to the corresponding C–N bonds (Scheme 3).[8a] To the best of our knowledge, this was the first successful application of the electrophilic amination strategy in direct (hetero)aromatic C–H amination. Subsequently, the more stable *O*-benzoyl-*N,N*-dialkylhydroxylamines were also found to work well as the electrophilic amination sources and expand the scope of aromatic C–H bonds.[8b] The active species is proposed to be (hetero)aryl-Cu species, which is generated in situ from the (hetero)aryl C–H bond and rapidly coupled with the electrophilic amination reagents to deliver the C–H aminated products. Afterward, several research groups developed the directing-group (DG)-assisted C–H amination of various (hetero)aromatic C–H bonds with electrophilic amination reagents of the type N–O and N–Cl in the presence of Pd, Rh, Fe, Ru, and Ir catalysts (Scheme 4).[9] These findings suggest that the electrophilic amination is a potentially useful protocol to aminate less reactive substrates via catalytically generated organometallic species. This account summarizes our efforts for the development of copper-catalyzed highly chemo- and stereoselective amination reactions uniquely enabled by the umpolung, electrophilic amination strategy.[10]



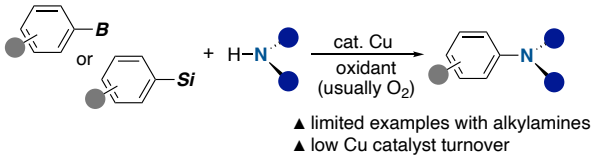
Scheme 3. Our early examples of C–H amination of (hetero)arenes with electrophilic amination reagents.



Scheme 4. Transition-metal-catalyzed directed C–H amination of (hetero)arenes with electrophilic amination reagents.

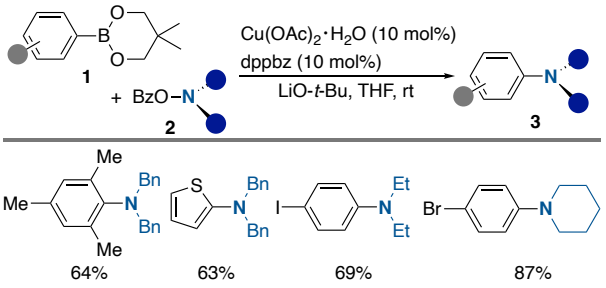
2. Electrophilic Amination of Organoboron, Organosilicon, and Related Compounds

The organoboron and organosilicon compounds are relatively stable and easy-to-handle but sufficiently reactive under specific conditions. Accordingly, these organometallic reagents show unique reactivity and selectivity, compared to highly reactive organomagnesium and -zinc reagents, and are thus indispensable in modern organic synthetic chemistry.[11] Although the Cu-mediated oxidative amination reaction of arylborons and -silanes with simple NH amines, so-called Chan-Lam coupling,[12] is recognized as a powerful alternative to the Pd-catalyzed Buchwald-Hartwig amination of aryl halides in the synthesis of aniline derivatives, its narrow substrate scope of alkylamines and low catalyst turnover of Cu are often problematic (Scheme 5).



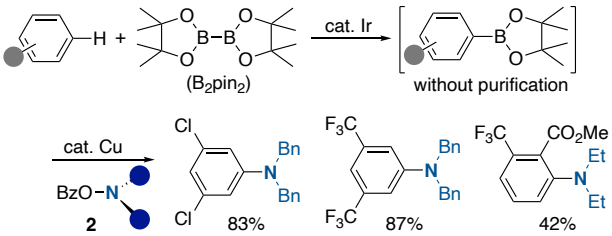
Scheme 5. Cu-mediated Chan-Lam coupling reaction of arylborons and -silanes with simple NH amines.

On the basis of our previous work on the C–H amination of (hetero)arenes (Scheme 3), in 2012 we developed the Cu-catalyzed electrophilic amination of arylboronates **1** with *O*-benzoyl-*N,N*-dialkylhydroxylamines **2** (Scheme 6).[13] The Cu catalysis successfully prepared various tertiary *N,N*-dialkylanilines **3**, which is complementary to the classical Chan-Lam coupling. Additionally, electronically and sterically diverse functional groups were well tolerated. The most salient feature is high compatibility with aryl-Br and -I moieties.



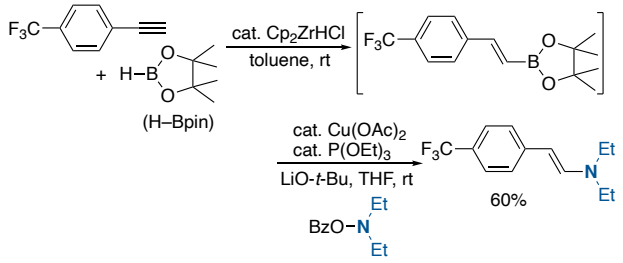
Scheme 6. Cu-catalyzed electrophilic amination of neopentylglycol-derived arylboronates **1** with *O*-benzoyl-*N,N*-dialkylhydroxylamines **2**.

The Cu-catalyzed electrophilic amination strategy could be combined with the Ir-catalyzed C–H borylation with B_2pin_2[14] and thus provide rapid access to functionalized anilines from simple arenes (Scheme 7).



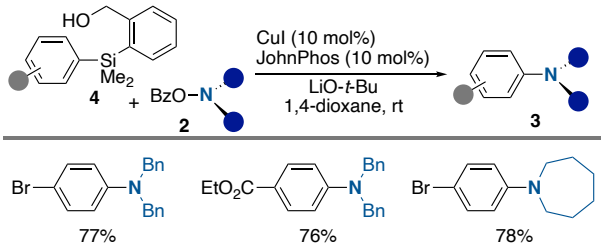
Scheme 7. Direct synthesis of anilines from simple arenes by sequential Ir-catalyzed C–H borylation and Cu-catalyzed electrophilic amination.

The alkenylboronates could also be employed in the Cu-catalyzed electrophilic amination.[15] Combined with Zr-catalyzed regioselective hydroboration with H–Bpin, the formal *anti*-Markovnikov hydroamination of the terminal arylalkyne made possible delivery of the corresponding enamine in a sequential manner (Scheme 8).



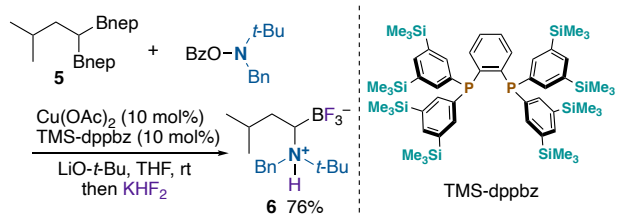
Scheme 8. Formal *anti*-Markovnikov hydroamination of terminal arylalkyne via sequential Zr-catalyzed hydroboration and Cu-catalyzed electrophilic amination.

Instead of the arylboronates, the arylsilanes **4** also underwent the Cu-catalyzed electrophilic amination with **2** to form the corresponding tertiary anilines **3** (Scheme 9).[16] The (2-hydroxymethyl)phenyl substituent in **4**, which was originally developed by Hiyama,[17] was essential for the successful conversion: Other common arylsilanes such as $ArSi(OMe)_3$ did not provide the targeted anilines at all.[18] Also in this case, the tertiary *N,N*-dialkylanilines were accessible with high halogen compatibility, which significantly expands the substrate scope in the classical Chan-Lam coupling with the arylsilanes.[12]



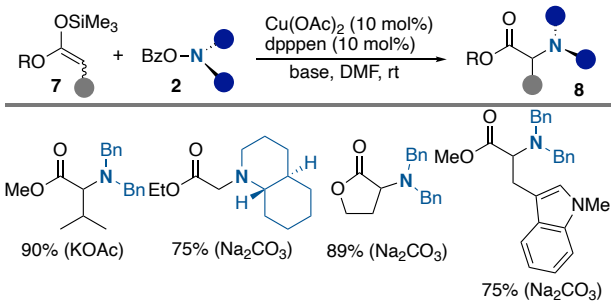
Scheme 9. Cu-catalyzed electrophilic amination of arylsilanes **4** with *O*-benzoyl-*N,N*-dialkylhydroxylamines **2**.

The Cu-catalyzed electrophilic amination strategy is also applied to C–N bond formation with sp^3-hybridized alkylboron[19] and alkylsilane derivatives. The *gem*-diborylalkane **5**[20] was the promising sp^3 carbon nucleophile and selectively mono-aminated with the hydroxylamine to form the biologically important α-aminoboronic acid derivative **6**[21] after treatment with KHF_2 (Scheme 10).[22] The key to success is the use of Me_3Si-modified dppbz-type ligand (TMS-dppbz), which dramatically accelerated the reaction.



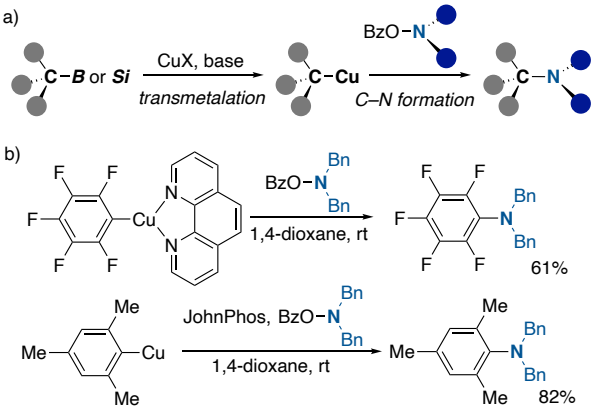
Scheme 10. Cu-catalyzed electrophilic mono-amination of *gem*-diborylalkane **5** with hydroxylamine.

The ketene silyl acetals **7** also worked well as the sp^3 carbon nucleophiles in the Cu-catalyzed electrophilic amination with **2** (Scheme 11).[23] The optimal base was highly dependent on the steric and electronic nature of **7**, but the corresponding α-amino acid derivatives **8** were obtained in good yields.



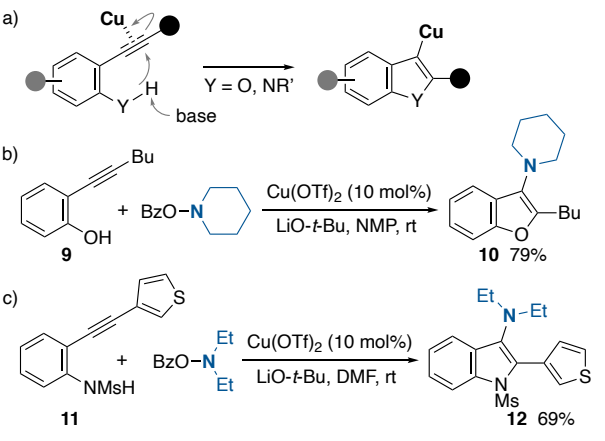
Scheme 11. Cu-catalyzed electrophilic amination of ketene silyl acetals **7** with hydroxylamines **2**. The base employed is indicated in parentheses.

In the aforementioned reactions, base-assisted transmetalation between the Cu salt and organoboron or -silicon compounds occurs to generate the organocopper species, which is responsible for the C–N bond formation with the hydroxylamines (Scheme 12a). Some control experiments with stoichiometric amounts of the isolated ArCu complexes can support the mechanistic hypothesis (Scheme 12b).[8b,16]



Scheme 12. (a) Proposed reaction mechanism and (b) control experiments with isolated ArCu complexes.

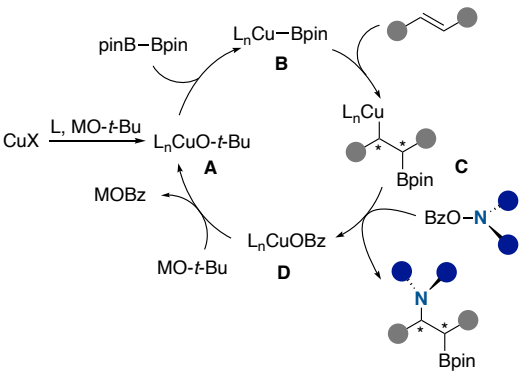
To generate the active organocopper species in situ, we also designed the annulative cupration of *ortho*-alkynylphenols and -anilines (Scheme 13a).[24] Actually, treatment of *ortho*-alkynylphenol **9** with hydroxylamine in the presence of a $Cu(OTf)_2$ catalyst and LiO-*t*-Bu base afforded the 3-aminobenzofuran **10** probably via the annulative cupration–electrophilic amination cascade (Scheme 13b).[25] Under similar conditions, 3-aminoindole **12** was obtained from *ortho*-alkynylaniline **11** (Scheme 13c).[26]



Scheme 13. (a) Reaction design of annulative cupration of *ortho*-alkynylphenols and -anilines and synthesis of (b) 3-aminobenzofuran and (c) 3-aminoindole.

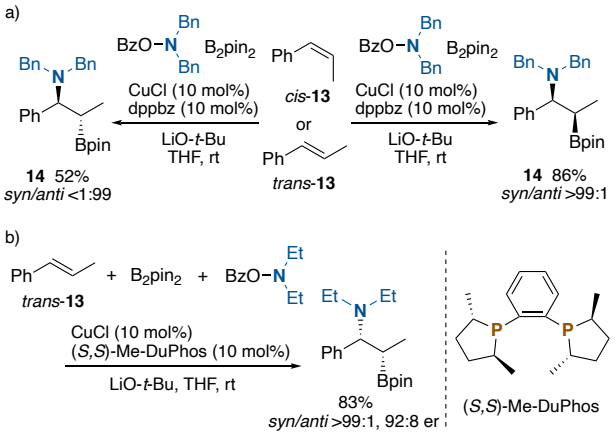
3. Electrophilic Amination-Enabled Aminoboration of Alkenes

Organoboron compounds are now indispensable synthetic reagents in modern organic chemistry because of their high utilities for carbon–carbon and carbon–heteroatom bond forming reactions with high chemoselectivity and stereospecificity. Accordingly, the development of rapid and selective preparative methods for densely functionalized and stereodefined organoboron compounds is an important research subject in synthetic community. Among them, transition-metal-catalyzed borylative difunctionalizations of readily available and simple alkenes have received significant attention owing to their high efficiency and versatility. However, the simultaneous addition of amino group and boryl group across the alkene π bond (aminoboration) remained largely elusive[11a] until our first successful report based on the electrophilic amination strategy: Our scenario for the catalytic aminoboration of alkenes is illustrated in Scheme 14. The initial step is generation of the catalytically competent L_nCuO-*t*-Bu species **A** from the starting CuX salt, ligand L, and MO-*t*-Bu. Subsequent σ-bond metathesis with B_2pin_2 (**A** to **B**)[27] is followed by insertion of alkene into the Cu–B bond in **B** to form the borylated alkylcopper intermediate **C**.[28] The targeted aminoboration product is produced by electrophilic amination with *O*-benzoylhydroxylamine. The concurrently formed L_nCuOBz **D** finally undergoes salt metathesis with MO-*t*-Bu (**D** to **A**) to complete the catalytic cycle. The enantioselectivity can also be induced in the insertion step (**B** to **C**) by the judicious choice of chiral ancillary ligand.



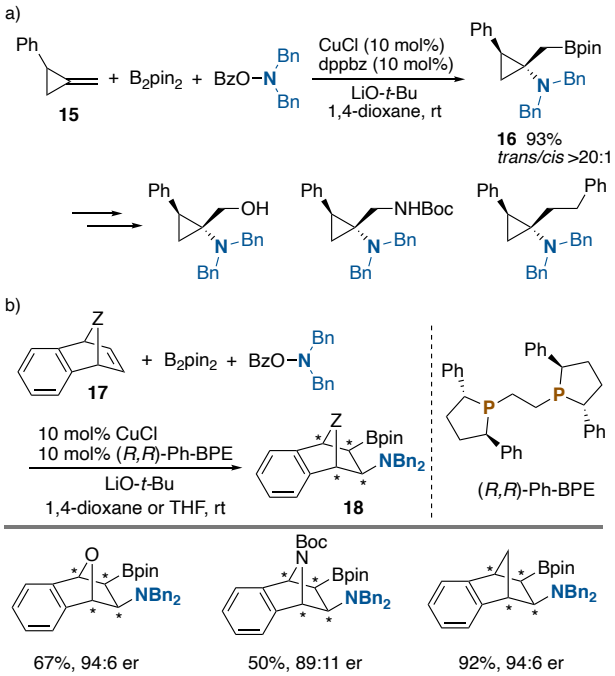
Scheme 14. Working scenario of electrophilic amination-enabled aminoboration of alkenes with B_2pin_2 and hydroxylamines.

The catalytic aminoboration of *trans*-β-methylstyrene (*trans*-**13**) proceeded in the presence of a CuCl/dppbz catalyst and LiO-*t*-Bu base to furnish **14** with high regio- and diastereoselectivity (*syn/anti* >99:1; Scheme 15a, right).[30] On the other hand, the opposite *anti*-diastereomer was selectively obtained from the reaction of *cis*-**13** (Scheme 15a, left). Thus, the aminoboration is stereospecific: The *syn*-addition of the boron and amine functionalities in the overall transformation. Given the *syn*-stereochemistry in the insertion step (**B** to **C** in Scheme 14),[28] the C–N bond formation process (**C** to aminoboration product in Scheme 14) occurs with retention of configuration.[29] Moreover, by using the chiral (*S,S*)-Me-DuPhos ligand, the regio-, diastereo-, and enantioselective aminoboration of *trans*-**13** was possible (Scheme 15b).



Scheme 15. (a) Stereospecific aminoboration of *trans*- and *cis*-β-methylstyrenes and (b) regio-, diastereo-, and enantioselective aminoboration.

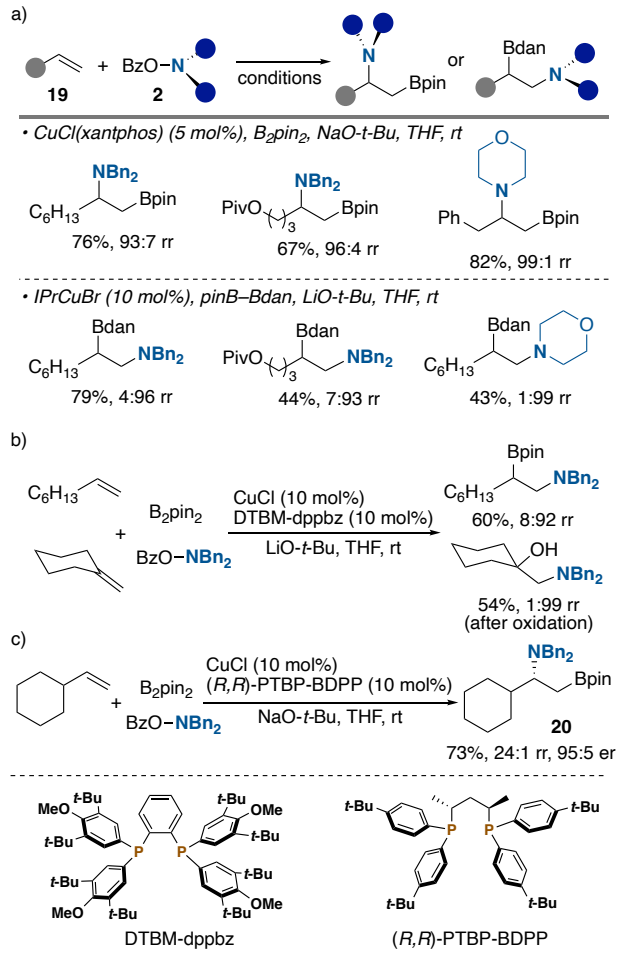
The Cu catalysis also accommodated the strained alkenes, including the methylenecyclopropane **15** (Scheme 16a)[31] and bicyclic alkenes **17** (Scheme 16b).[32] In the former case, the borylmethyl-substituted cyclopropylamine **16** was obtained with high regio- and diastereoselectivity. The post functionalization of the boron moiety can provide access to the biologically interesting functionalized cyclopropylamines. The latter reaction could be conducted in an enantioselective manner by using the (*R,R*)-Ph-BPE ligand, giving the chiral aminoboration products **18** with high enantiomeric ratios.



Scheme 16. (a) Regio- and diastereoselective aminoboration of methylenecyclopropane and post functionalizations of the Bpin moiety and (b) regio-, diastereo-, and enantioselective aminoboration of bicyclic alkenes.

Simple and abundant terminal alkenes **19** are also viable substrates in the aminoboration Cu catalysis (Scheme 17a).[33] Notably, a ligand-controlled regiodivergency was observed: The CuCl(xantphos) complex guided the boron and amino groups to the terminal and internal positions, respectively

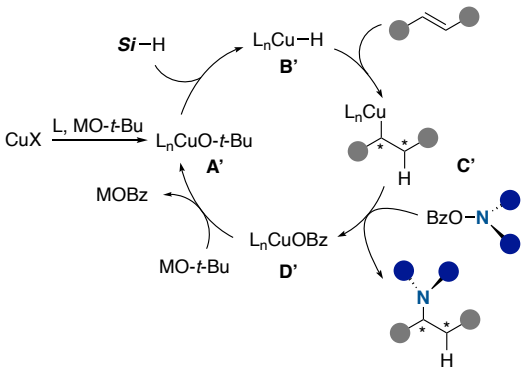
(upper), whereas the internally borylated opposite regioisomers were selectively obtained under IPrCuBr catalysis (bottom). The regioselectivity switching was uniformly possible regardless of the steric and electronic nature of the terminal alkene as well as the hydroxylamine. However, there are some drawbacks in the case of IPrCuBr catalysis: One is the inevitable use of pinB–Bdan[34] (dan = 1,8-diaminonaphthyl) for acceptable conversion, so stable but difficult-to-transform Bdan group is incorporated into the product, which requires additional deprotection steps for further manipulations. Another problem is the sluggish reactivity of more sterically hindered 1,1-disubstituted alkenes. To overcome the above issues, we designed a second generation catalyst system composing a bulky and electron-rich DTBM-dppbz ligand (Scheme 17b).[35] Under modified conditions, B_2pin_2 worked well, and 1-octene was regioselectively converted to the internally borylated aminoboration product with high regioselectivity. Additionally, the otherwise challenging methylenecyclohexane also participated in the reaction, and the corresponding β-aminoalcohol was isolated as the sole regioisomer after oxidative workup with H_2O_2 aq. Moreover, asymmetric induction was also possible by using a (*R,R*)-PTBP-BDPP ligand containing bulky *tert*-butyl groups at the remote para position (Scheme 17c):[36] The regio- and enantioselective aminoboration of vinylcyclohexane proceeded to form the optically active **20** with high regio- and enantioselectivity.



Scheme 17. Aminoboration of simple terminal alkenes. (a) Ligand-controlled regiodivergent aminoboration, (b) modified DTBM-dppbz catalysis, and (c) regio- and enantioselective reaction.

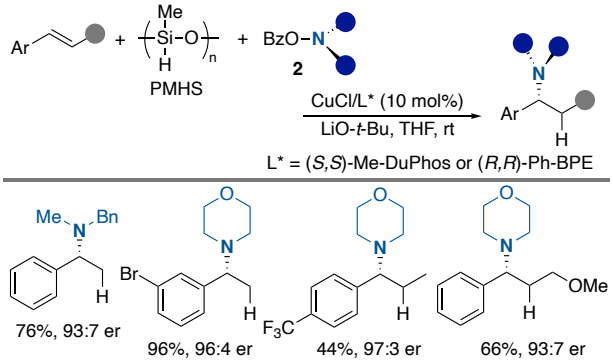
4. Electrophilic Amination-Enabled Hydroamination of Alkenes

The aforementioned success of the umpolung-enabled aminoboration prompted us to design a CuH-catalyzed[37] net hydroamination reaction of alkenes with a hydrosilane external nucleophile instead of B_2pin_2 (Scheme 18). Of course, the direct hydroamination with the parent NH amines[38] is a more atom-economical process, but the reaction is often kinetically difficult due to high activation barriers and catalyst deactivation by overcoordination of the amine. Moreover, the overall reaction is sometimes an uphill, thermodynamically unfavored process.[39] In sharp contrast, the umpolung-enabled net hydroamination is generally exothermic, more thermodynamically favored because cleavage process of the energetically high N–O bond is involved in the catalytic cycle. Additionally, the totally distinct reaction mechanism can provide a chance for kinetically controlled, catalyst-induced regio- and stereoselectivity (**B'** to **C'**).



Scheme 18. Working scenario of electrophilic amination-enabled net hydroamination of alkenes with hydrosilanes and hydroxylamines.

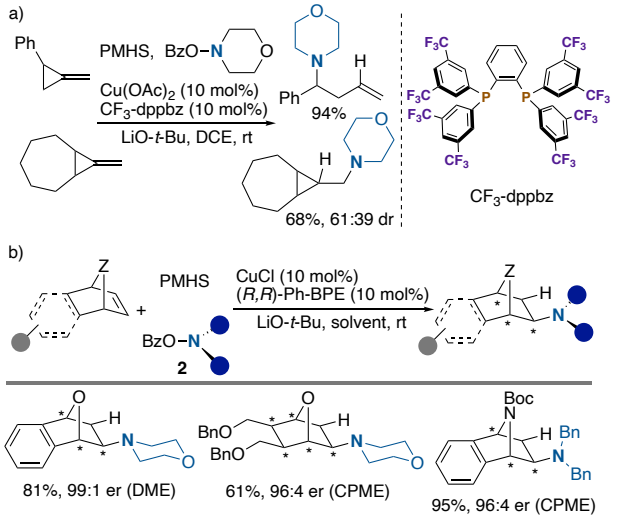
Actually, the regio- and enantioselective net hydroamination of styrenes with PMHS and hydroxylamines **2** was possible by using a CuCl/(*S,S*)-MeDuPhos or (*R,R*)-Ph-BPE catalyst to deliver the chiral benzylic amines with good to high enantiomeric ratios (Scheme 19).[40] Notable is the successful use of the β-substituted styrenes, which are still challenging substrates in the conventional hydroamination with the parent NH amines.



Scheme 19. Umpolung-enabled regio-and enantioselective net hydroamination of styrenes with PMHS and hydroxylamines.

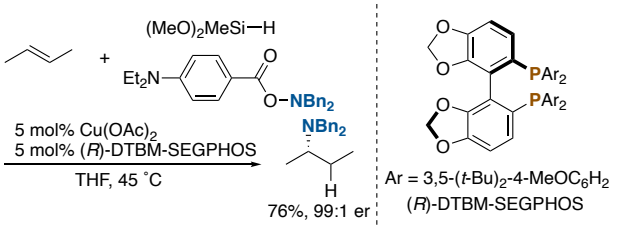
Similar to the aminoboration reaction mentioned above, the hydroamination was also applicable to the strained alkenes. In the case of the methylenecyclopropanes, the substituent-dependent divergent reaction pathways were observed: The mono-substituted substrate underwent the

ring-opening hydroamination probably via β-carbon elimination of a cyclopropylmethylcopper intermediate while the ring-remaining hydroaminated product was exclusively formed from the 2,3-disubstituted methylenecyclopropane (Scheme 20a).[41] Heterobicyclic alkenes are also promising substrates under the enantioselective hydroamination Cu catalysis with (*R,R*)-Ph-BPE to afford the corresponding enantioenriched alkylamines with high enantioselectivity (Scheme 20b).[42]



Scheme 20. Hydroamination of (a) methylenecyclopropanes and (b) bicyclic alkenes.

Contemporaneously, the Buchwald research group also reported the same enantioselective net hydroamination reaction.[43] Notably, the catalyst system composing the DTBM-SEGPHOS ligand accommodated a broader range of alkenes, involving unactivated internal alkenes (Scheme 21).

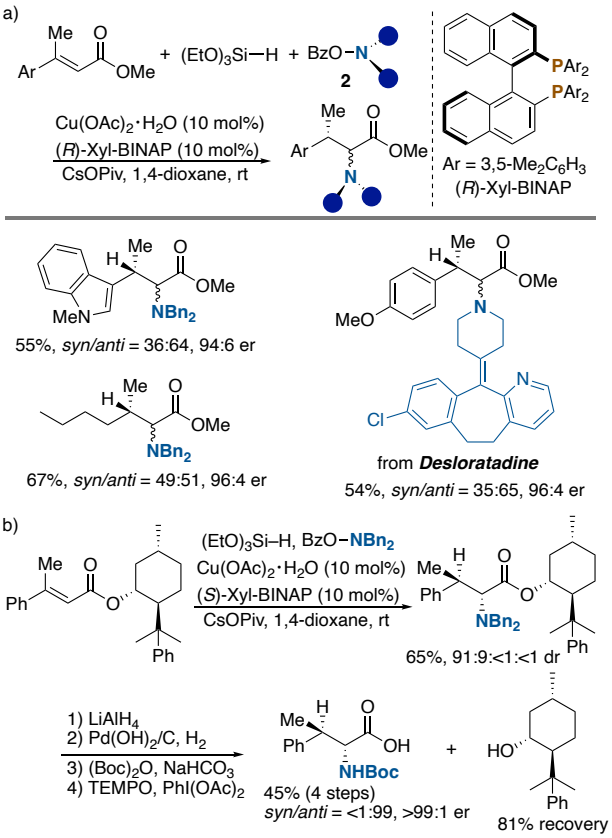


Scheme 21. Enantioselective hydroamination of unactivated internal alkenes under Cu/DTBM-SEGPHOS catalysis reported by Buchwald.

5. Application to Activated Alkenes

The umpolung-enabled hydroamination and aminoboration of functional-group-conjugated activated alkenes can provide rapid access to the functionality-rich alkylamines, which are important building blocks in the synthesis and design of natural products and pharmaceutical agents.

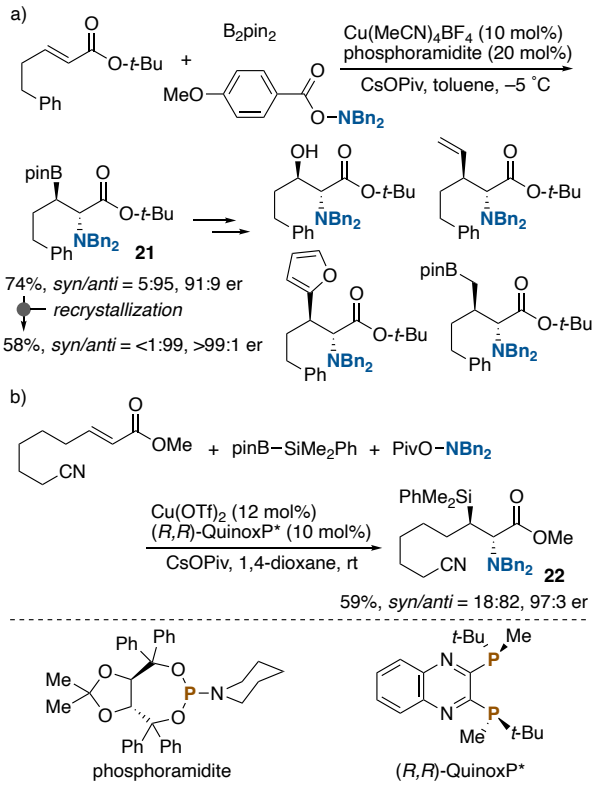
We reported the Cu/Xyl-BINAP-catalyzed regio- and enantioselective hydroamination of α,β-unsaturated esters to form the corresponding α-amino acid derivatives (Scheme 22a).[44] The polarity inversion concept of the amine is key to success for the challenging α-amination selectivity. Otherwise, the inherent polarity of the α,β-unsaturated carbonyl and amine usually leads to the β-amination selectivity. The point chirality at the β-position was successfully controlled by the chiral copper catalyst but not at the α-position, thus giving poor diastereoselectivity. This problem was addressed by the double asymmetric induction strategy using the chiral copper catalyst and (-)-8-Ph-menthol chiral auxiliary (Scheme 22b). Subsequent removal of the auxiliary and protecting group exchange on nitrogen afforded the optically active unnatural β-methylphenylalanine in a stereochemically pure form.



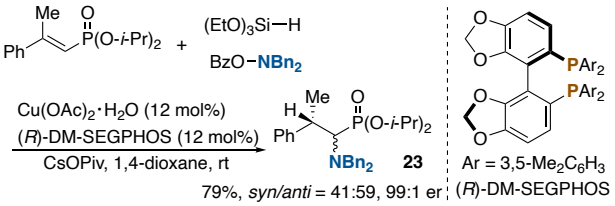
Scheme 22. Synthesis of α-amino acids by umpolung-enabled regio- and stereoselective hydroamination of α,β-unsaturated esters.

The related enantioselective aminoboration of the α,β-unsaturated esters was also possible affording the corresponding β-boryl-α-amino acid **21** (Scheme 23a).[45] Notably, in this case, the diastereoselectivity as well as the enantioselectivity was satisfactory high (*syn/anti* = 5:95). The stereochemically pure β-boryl-α-amino acid **21** obtained by single recrystallization was a useful platform for a variety of β-functionalized α-amino acids via post modifications of the Bpin moiety. We have also developed the aminosilylation reaction with pinB–$SiMe_2Ph$ as the silyl nucleophile to furnish the corresponding β-silyl-α-amino acid **22** (Scheme 23b).[46] The introduction of the silyl substituent at the β-position is known to increase the lipophilicity and metabolic stability of the parent α-amino acid, and the β-silyl-α-amino acids like **22** are thus promising candidates in the peptidomimetic strategy.[47]

The P analogue of ester, that is the α,β-unsaturated phosphonate, is also amenable to the enantioselective net hydroamination to deliver the corresponding enantioenriched α-aminophosphonate **23** albeit with poor diastereoselectivity (Scheme 24).[48]



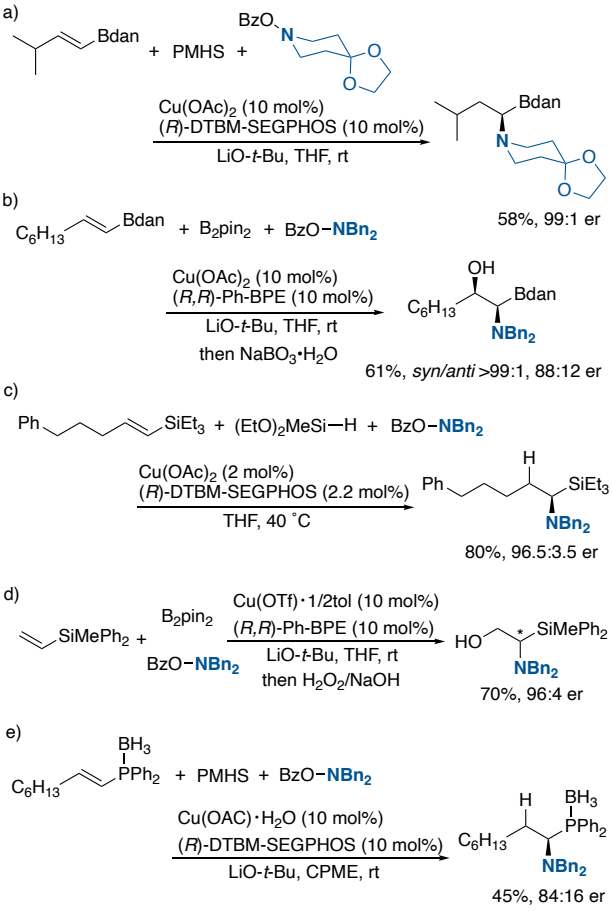
Scheme 23. Regio- and stereoselective (a) aminoboration and (b) silylamination of α,β-unsaturated esters.



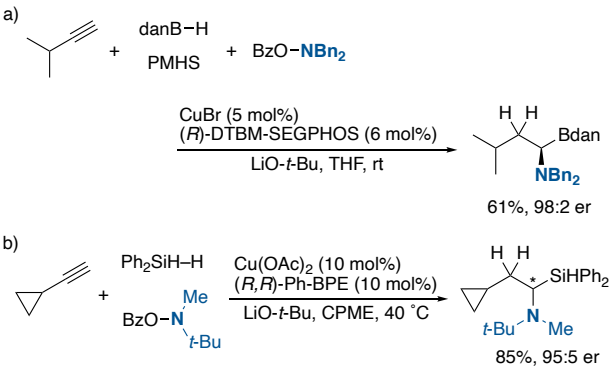
Scheme 24. Enantioselective hydroamination of α,β-unsaturated phosphonate.

The use of directly heteroatom-substituted alkenes, including boryl-, silyl-, and phosphinylalkenes, can provide a stereoselective avenue to the corresponding heteroatom mimics of α-amino acid. Chiral α-aminoboronic acid, which is the pharmacophore in proteasome inhibitors,[21] can be readily constructed by Cu/DTBM-SEGPHOS-catalyzed regio- and enantioselective net hydroamination of the boryl-substituted alkenes (Scheme 25a).[49] The boron-masking group Bdan[34] is indispensable for the successful conversion and product isolation. The related aminoboration was followed by oxidation with $NaBO_3•H_2O$ to produce the β-hydroxy-α-aminoboronic acid (Scheme 25b).[50] Buchwald developed the asymmetric hydroamination of the silylalkene to form the enantioenriched α-aminosilane of important structural motif in angiotensin-converting enzyme (ACE) and serine protease neutrophil elastase (HNE) inhibitors (Scheme 25c).[51,52] We also succeeded in the aminoboration of the same silyl-substituted alkene (Scheme 25d).[53] The follow-up treatment with H_2O_2 afforded the Si mimic of the naturally occurring serine with high enantioselectivity. The enantioselective net hydroamination of the alkenylphosphine borane delivered the chiral α-aminophosphine of potent interest as the supporting ligand under transition metal catalysis (Scheme 25e).[54]

Boryl- and silylalkenes are generally prepared by hydroboration and hydrosilylation, respectively, of the corresponding alkynes. If the hydroboration/hydrosilylation-hydroamination cascade is catalyzed by a single Cu component, the simple terminal alkynes can be directly converted into the α-aminoboronic acids/α-aminosilanes in one synthetic operation. Actually, Engle and coworkers reported sequential hydroboration-hydroamination of a terminal alkyne under Cu/DTBM-SEGPHOS catalysis (Scheme 26a).[55] The combined use of PMHS and danB–H was key to success, and the targeted α-aminoboronic acid derivative was obtained with a high enantiomeric ratio. Around the same time, our group also developed an enantioselective hydrosilylation-hydroamination cascade with Ph_2SiH_2 as both the hydride and silyl sources to form an optically active α-aminosilane (Scheme 26b).[56]

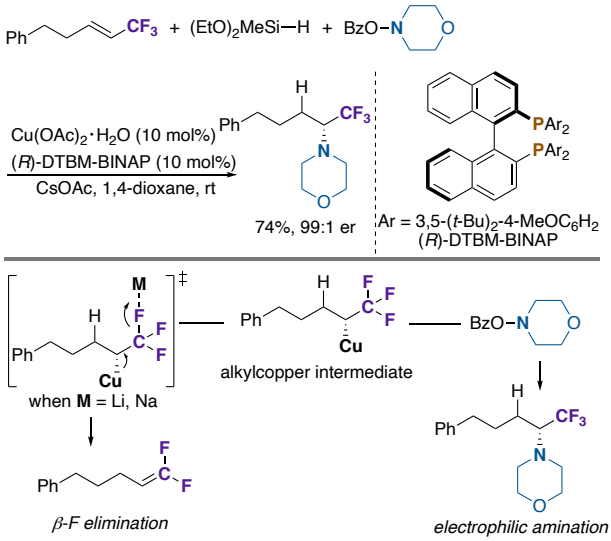


Scheme 25. Regio- and stereoselective hydroamination and/or aminoboration of (a,b) borylalkenes, (c,d) silylalkenes, and (e) phosphinylalkenes.



Scheme 26. Cu-catalyzed sequential (a) hydroboration-hydroamination and (b) hydrosilylation-hydroamination of terminal alkynes.

Organofluorine compounds have now received significant attention in the design of new drug candidates and agrochemicals because, associated with the unique steric and electronic nature of fluorine atom, the introduction of fluorine into the parent organic molecules can increase lipophilicity and metabolic stability to increase the biological activity.[57] Among them, α-trifluoromethylamines are amide isosteres and frequently observed in biologically active compounds.[58] Thus, their preparation, particularly the catalytic asymmetric synthesis, is in high demand. The umpolung-enabled regio- and enantioselective hydroamination of 1-trifluoromethylalkene is a promising path to enantioenriched α-trifluoromethylamine (Scheme 27).[59] The CsOAc additive is crucial; when using Li- and Na-based basic additives instead, the predominant β-F elimination from an alkylcopper intermediate occurs to afford the *gem*-difluoroalkene as the major product.[60]



Scheme 27. Regio- and enantioselective hydroamination of 1-trifluoromethylalkenes.

4. Conclusion

By taking advantage of the concept of nitrogen umpolung, we have developed the electrophilic amination-based, copper-catalyzed highly chemo- and stereoselective C–N bond forming reactions. One feature of the chemoselectivity is the halogen compatibility, which is complementary to the precedented nucleophilic amination reaction. Moreover, some transformations are impossible under the conventional amination conditions using the nucleophilic parent amines. The electrophilic amination-promoted catalytic aminoboration is such a case, and there is no other general protocol that enables the simultaneous addition of amino and boryl groups across the simple alkene in a fully intermolecular manner, to the best of our knowledge. The umpolung-based strategy also allows a wider range of alkenes to be adopted in the stereoselective hydroamination reaction, thus giving the densely functionalized, enantioenriched alkylamines of great importance in the synthesis of natural products and biologically active compounds. We believe that the electrophilic amination reactions described here can streamline the synthesis of complex *N*-containing molecules and find wide applications in the synthesis and discovery of drug candidates.

Now, our group focuses on the conceptual extension of the nitrogen umpolung to other heteroatom species. One of ongoing research projects is the phosphorus umpolung: Generation and use of highly electrophilic phosphenium cations arising from phosphine oxides or phosphinic acids by the action of Tf_2O.[61] Further development of the "heteroatom umpolung" is believed to revolve the synthetic technologies in organic chemistry.

Acknowledgement

The author appreciates coworkers listed in his papers. Mr. Tsuyoshi Kawano started the umpolung-enabled C–H amination research project together with the author. Mr. Naoki Matsuda, Mr. Ryosuke Sakae, and Mr. Kodai Kato developed the umpolung-enabled regio- and stereoselective aminoboration of alkenes. Mr. Yuya Miki and Mr. Daiki Nishikawa achieved the net hydroamination of relatively simple alkenes. Mr. Tatsuaki Takata, Mr. Soshi Nishino, and Mr. Shogo Nakamura successfully applied the aminoboration and hydroamination protocols to the activated alkenes, giving the functionality-rich alkylamines. In addition, Mr. Naoki Matsuda, Mr. Yuya Miki, Mr. Ryosuke Sakae, and Mr. Soshi Nishino developed the electrophilic amination reactions of organoborns, organosilanes, and related compounds. The author is also grateful to Prof. Masahiro Miura for his insightful advice and guidance. The author acknowledges JSPS KAKENHI Grant Nos. JP 25620084 (Grant-in-Aid for Challenging Exploratory Research), JP 15H05485 (Grant-in-Aid for Young Scientists (A)), JP 22H02077 (Grant-in-Aid for Scientific Research (B)), JST FOREST Program Grant No. JPMJFR 211X, Uehara Memorial Foundation, and Toyota Riken Scholar for the financial supports.

References

1. (a) R. Hili, A. K. Yudin, *Nat. Chem. Biol.* **2006**, *2*, 284. (b) A. Ricci, *Amino Group Chemistry: From Synthesis to the Life Sciences*, Wiley-VCH, Weinheim, Germany, **2007**.
2. (a) Y. Shirota, H. Kageyama, *Chem. Rev.* **2007**, *107*, 953. (b) L.-L. Li, E. W.-G. Diau, *Chem. Soc. Rev.* **2013**, *42*, 291.
3. For example, see: J. McMurry, *Organic Chemistry*, 9th edition, Brooks/Cole Pub Co, **2015**, pp. 313–322.
4. For a recent short review, see; P. A. Forero-Cortés, A. M. Haydl, *Org. Process Res. Dev.* **2019**, *23*, 1478.
5. E. Erdik, M. Ay, *Chem. Rev.* **1989**, *89*, 1947.
6. H. Tsutsui, Y. Hayashi, K. Narasaka, *Chem. Lett.* **1997**, 317.
7. A. M. Berman, J. S. Johnson, *J. Am. Chem. Soc.* **2004**, *126*, 5680.
8. (a) T. Kawano, K. Hirano, T. Satoh, M. Miura, *J. Am. Chem. Soc.* **2010**, *132*, 6900. (b) N. Matsuda, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2011**, *13*, 2860.
9. For selected examples, see: (a) E. J. Yoo, S. Ma, T.-S. Mei, K. S. L. Chan, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *137*, 7652. (b) C. Grohmann, H. Wang, F. Glorius, *Org. Lett.* **2012**, *14*, 656. (c) C. Grohmann, H. Wang, F. Glorius, *Org. Lett.* **2013**, *15*, 3014. (d) M. Shang, S.-H. Zeng, S.-Z. Sun, H.-X. Dai, J.-Q. Yu, *Org. Lett.* **2013**, *15*, 5286. (e) Y. Park, K. T. Park, J. G. Kim, S. Chang, *J. Am. Chem. Soc.* **2015**, *137*, 4534.
10. For selected reviews and perspectives, see: (a) K. Narasaka, M. Kitamura, *Eur. J. Org. Chem.* **2005**, 4505.

(b) E. Ciganek, *Org. React.* **2009**, *72*, 1. (c) T. J. Barker, E. R. Jarvo, *Synthesis* **2011**, 3954. (d) M. Corpet, C. Gosmini, *Synthesis* **2014**, *46*, 2258. (e) X. Dong, Q. Liu, Y. Dong, H. Liu, *Chem. Eur. J.* **2017**, *23*, 2481. (f) K. Hirano, M. Miura, *J. Am. Chem. Soc.* **2022**, *144*, 648.

11. (a) D. G. Hall, *Boronic Acids*, 2nd ed. Wiley-VCH, Weinheim, Germany, **2011**. (b) T. Hiyama, M. Oestreich, *Organosilicon Chemistry: Novel Approaches and Reactions*, Wiley-VCH, Weinheim, **2020**.
12. (a) S. V. Ley, A. W. Thomas, *Angew. Chem. Int. Ed.* **2003**, *42*, 5400. (b) J. X. Qiao, P. Y. S. Lam, *Synthesis* **2011**, 829.
13. (a) N. Matsuda, K. Hirano, T. Satoh, M. Miura, *Angew. Chem., Int. Ed.* **2012**, *51*, 3642. Around the same time, Lalic also reported the Cu-catalyzed electrophilic amination of arylboronates with hydroxylamines for the synthesis of hindered anilines; (b) R. P. Rucker, A. M. Whittaker, H. Dang, G. Lalic, *Angew. Chem., Int. Ed.* **2012**, *51*, 3953.
14. (a) T. Ishiyama, J. Takagi, K. Ishida, N. Miyaura, N. R. Anastasi, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 390. (b) J. M. Murphy, X. Liao, J. F. Hartwig, *J. Am. Chem. Soc.* **2007**, *129*, 15434. (c) T. Ishiyama, H. Isou, T. Kikuchi, N. Miyaura, *Chem. Commun.* **2010**, *46*, 159.
15. R. Sakae, K. Hirano, T. Satoh, M. Miura, *Chem. Lett.* **2013**, *42*, 1128.
16. Y. Miki, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2013**, *15*, 172.
17. Y. Nakao, H. Imanaka, A. K. Sahoo, A. Yada, T. Hiyama, *J. Am. Chem. Soc.* **2005**, *127*, 6952.
18. Recently, Shimokawa and Yorimitsu reported the successful electrophilic amination of $ArSi(OEt)_3$ in the presence of the IPrCuCl catalyst and AgF activator; Q. Zhang, K. Hitoshio, H. Saito, J. Shimokawa, H. Yorimitsu, *Eur. J. Org. Chem.* **2020**, 4018.
19. Lalic reported the Cu-catalyzed electrophilic amination of highly reactive alkyl-9-BBNs. R. P. Rucker, A. M. Whittaker, H. Dang, G. Lalic, *J. Am. Chem. Soc.* **2012**, *134*, 6571.
20. A recent review on synthetic applications of *gem*-diborylalkanes: R. Nallagonda, K. Padala, A. Masarwa, *Org. Biomol. Chem.* **2018**, *16*, 1050. For seminal work, see: (b) K. Endo, T. Ohkubo, M. Hirokami, T. Shibata, *J. Am. Chem. Soc.* **2010**, *132*, 11033. (c) C. Sun, B. Potter, J. P. Morken, *J. Am. Chem. Soc.* **2014**, *136*, 6534.
21. (a) R. Smoum, A. Rubinstein, V. M. Dembitsky, M. Srebnik, *Chem. Rev.* **2012**, *112*, 4156. (b) F. Yang, M. Zhu, J. Zhang, H. Zhou, *MedChemComm* **2018**, *9*, 201.
22. S. Nishino, K. Hirano, M. Miura, *Org. Lett.* **2019**, *21*, 4759.
23. N. Matsuda, K. Hirano, T. Satoh, M. Miura, *Angew. Chem., Int. Ed.* **2012**, *51*, 11827.
24. K. Hiroya, S. Itoh, T. Sakamoto, *J. Org. Chem.* **2004**, *69*, 1126.
25. K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2011**, *13*, 2395.
26. N. Matsuda, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2012**, *77*, 617.
27. (a) H. Ito, H. Yamanaka, J.-i. Tateiwa, A, Hosomi, *Tetrahedron Lett.* **2000**, *41*, 6821. (b) H. Ito, C. Kawakami, M. Sawamura, *J. Am. Chem. Soc.* **2005**, *127*, 16034.
28. D. S. Laitar, E. Y. Tsui, J. P. Sadighi, *Organometallics* **2006**, *25*, 2405.
29. M. J. Campbell, J. S. Johnson, *Org. Lett.* **2007**, *9*, 1521.
30. N. Matsuda, K. Hirano, T. Satoh, M. Miura, *J. Am. Chem. Soc.* **2013**, *135*, 4934.
31. R. Sakae, N. Matsuda, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2014**, *16*, 1228.
32. R. Sakae, K. Hirano, T. Satoh, M. Miura, *Angew. Chem., Int. Ed.* **2015**, *54*, 613.
33. R. Sakae, K. Hirano, M. Miura, *J. Am. Chem. Soc.* **2015**, *137*, 6460.
34. (a) H. Noguchi, K. Hojo, M. Suginome, *J. Am. Chem. Soc.* **2007**, *129*, 758. (b) N. Iwadate, M. Suginome, *J. Am. Chem. Soc.* **2010**, *132*, 2548.
35. K. Kato, K. Hirano, M. Miura, *J. Org. Chem.* **2017**, *82*, 10418.
36. K. Kato, K. Hirano, M. Miura, *Chem. Eur. J.* **2018**, *24*, 5775.
37. (a) W. S. Mahoney, D. M. Brestensky, J. M. Stryker, *J. Am. Chem. Soc.* **1988**, *110*, 291. (b) C. Deutsch, N. Krause, B. H. Lipshutz, *Chem. Rev.* **2008**, *108*, 2916.
38. For selected reviews, see: (a) L. Huang, M. Arndt, K. Gooβen, H. Heydt, L. Gooβen, L. *Chem. Rev.* **2015**, *115*, 2596. (b) S. M. Coman, V. I. Parvulescu, *Org. Process Res. Dev.* **2015**, *19*, 1327.
39. (a) T. E. Müller, M. Beller, *Chem. Rev.* **1998**, *98*, 675. (b) A. M. Johns, N. Sakai, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 9306. (c) A. J. Musacchio, B. C. Lainhart, X. Zhang, S. G. Naguib, T. C. Sherwood, R. R. Knowles, *Science* **2017**, *355*, 727.
40. Y. Miki, K. Hirano, T. Satoh, M. Miura, *Angew. Chem., Int. Ed.* **2013**, *52*, 10830.
41. D. Nishikawa, R. Sakae, Y. Miki, K. Hirano, M. Miura, *J. Org. Chem.* **2016**, *81*, 12128.
42. Y. Miki, K. Hirano, M. Miura, *Org. Lett.* **2014**, *16*, 1498.
43. For an account, see: R. Y. Liu, S. L. Buchwald, *Acc. Chem. Res.* **2020**, *53*, 1229.
44. S. Nishino, M. Miura, K. Hirano, *Chem. Sci.* **2021**, *12*, 11525.
45. S. Nishino, Y. Nishii, K. Hirano, *Chem. Sci.* **2022**, *13*, 14387.
46. T. Kobayashi, S. Nishino, M. Miura, K. Hirano, *Org. Lett.* **2022**, *24*, 1418.
47. R. Tacke, M. Merget, R. Bertermann, M. Bernd, T. Beckers, T. Reissmann, *Organometallics* **2000**, *19*, 3486.
48. S. Nakamura, S. Nishino, K. Hirano, *J. Org. Chem.* **2023**, *88*, 1270.
49. D. Nishikawa, K. Hirano, M. Miura, *J. Am. Chem. Soc.* **2015**, *137*, 15620.
50. D. Nishikawa, K. Hirano, M. Miura, *Org. Lett.* **2016**, *18*, 4856.
51. N. Niljianskul, S. Zhu, S. L. Buchwald, *Angew. Chem., Int. Ed.* **2015**, *54*, 1638.
52. (a) N. A. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529. (b) A. K. Franz, S. O. Wilson, *J. Med. Chem.* **2013**, *56*, 388. (c) R. Ramesh, D. S. Reddy, *J. Med. Chem.* **2018**, *61*, 3779.
53. K. Kato, K. Hirano, M. Miura, *Angew. Chem., Int. Ed.* **2016**, *55*, 14400.
54. T. Takata, D. Nishikawa, K. Hirano, M. Miura, *Chem. Eur. J.* **2018**, *24*, 10975.
55. D.-W. Gao, Y. Gao, H. Shao, T.-Z. Qiao, X. Wang, B. B. Sanchez, J. S. Chen, P. Liu, K. M. Engle, *Nat. Catal.* **2020**, *3*, 23.
56. S. Nishino, K. Hirano, M. Miura, *Chem. Eur. J.* **2020**, *26*, 8725.
57. (a) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881. (b) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315.
58. (a) I. Ojima, J. C. Slater, *Chirality* **1997**, *9*, 487. (b) G.

Bringmann, D. Feineis, R. Brueckner, M. Blank, K. Peters, E. M. Peters, H. Reichmann, B. Janetzky, C. Grote, H. W. Clement, W. Wesemann, *Bioorg. Med. Chem.* **2000**, *8*, 1467. (c) W. C. Black, C. I. Bayly, D. E. Davis, S. Desmarais, J.-P. Falgueyret, S. Leger, C. S. Li, F. Masse, D. J. McKay, J. T. Palmer, M. D. Percival, J. Robichaud, N. Tsou, R. Zamboni, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4741. (d) L. J. Holsinger, K. Elrod, J. O. Link, M. Graupe, I. J. Kim, WO-2009/055467 A2, 2009. (e) B. W. Trotter, K. K. Nanda, C. S. Burgey, C. M. Potteiger, J. Z. Deng, A. I. Green, J. C. Hartnett, N. R. Kett, Z. Wub, D. A. Henze, K. Della Penna, R. Desai, M. D. Leitl, W. Lemaire, R. B. White, S. Yeh, M. O. Urban, S. A. Kane, G. D. Hartman, M. T. Bilodeau, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2354.

59. T. Takata, K. Hirano, M. Miura, *Org. Lett.* **2019**, *21*, 4284.

60. For related Cu-catalyzed CF_3-compatible functionalizations of 1-trifluoromethylalkenes, see: (a) P. H. S. Paioti, J. del Pozo, M. S. Mikus, J. Lee, M. J. Koh, F. Romiti, S. Torker, A. H. Hoveyda, *J. Am. Chem. Soc.* **2019**, *141*, 19917. (b) Y. Kojima, M. Miura, K. Hirano, *ACS Catal*. **2021**, *11*, 11663. (c) Y. Kojima, Y. Nishii, K. Hirano, *Org. Lett*. **2022**, *24*, 7450.

61. (a) Y. Unoh, K. Hirano, M. Miura, *J. Am. Chem. Soc.* **2017**, *139*, 6106. (b) K. Nishimura, Y. Unoh, K. Hirano, M. Miura, *Chem. Eur. J.* **2018**, *24*, 13089. (c) K. Nishimura, K. Hirano, M. Miura, *Org. Lett.* **2019**, *21*, 1467. (d) K. Nishimura, K. Hirano, M. Miura, *Org. Lett.* **2020**, *22*, 3185.

Graphical Abstract

<Title> Copper-catalyzed Electrophilic Amination: An Umpolung Strategy for New C–N Bond Formations

<Authors' names> Koji Hirano

<Summary>
Nitrogen-umpolung-enabled, copper-catalyzed highly chemo- and stereoselective C–N bond forming reactions have been developed. By taking advantage of electrophilic amines, otherwise challenging halogen-compatible amination of organoboron, organosilicon, and related compounds is achieved. Moreover, the catalytic regio- and enantioselective aminoboration/hydroamination of various alkenes are also realized.

<Diagram>