Hydroamination, Aminoboration, and Carboamination with Electrophilic Amination Reagents: Umpolung-Enabled Regio- and Stereoselective Synthesis of *N*-Containing Molecules from Alkenes and Alkynes

Koji Hirano*, † and Masahiro Miura*, ‡

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

‡ Innovative Catalysis Science Division, Institute for Open and Transdisciplinary Research Initiatives (ICS-OTRI), Osaka University, Suita, Osaka 565-0871, Japan

Abstract: Nitrogen (N) is ubiquitously found in bioactive molecules, pharmaceutical agents, and organic functional materials. Accordingly, development of new C–N bond-forming catalysis has been one of the long-standing research subjects in synthetic organic chemistry. In this Perspective, recent advances in highly selective amination reactions with electrophilic amination reagents are described: by taking advantage of the concept of nitrogen umpolung, otherwise challenging aminofunctionalizations, such as hydroamination, aminoboration, and carboamination, of readily available feedstock-like alkenes and alkynes are possible, giving densely functionalized complex and often chiral alkylamines with high selectivity. The scope, limitations, and reaction mechanism are briefly summarized.

INTRODUCTION

Nitrogen (N) is ubiquitously found in important organic molecules such as pharmaceutical agents[1] and functional materials[2] and thus, is an indispensable element to induce unique biological activity as well as physical/chemical properties. Accordingly, to introduce the amino group (R_2N) into organic skeletons, development of C–N bond forming reactions has been one of the long-standing research subjects in synthetic organic chemistry. Among them, transition-metal-catalyzed addition-type reactions of the R_2N group across C–C multiple bonds, such as the hydroamination,[3] are particularly attractive, because relatively simple and abundant alkenes and alkynes can be readily converted to highly valuable *N*-containing molecules. However, the catalytic hydroamination reaction is still restricted in scope and generality: the reaction is often kinetically difficult due to high activation barriers associated with combining two nucleophilic amine and alkene components as well as catalyst deactivation by overcoordination of the amine. Moreover, the overall reaction is sometimes the uphill, thermodynamically unfavored process.[4]

Meanwhile, an umpolung[5] amination strategy with electrophilic amination reagents of type $R_2N–X$ (X = leaving group)[6] has recently received significant attention. The nitrogen has one lone pair and relatively high electronegativity (3.0; Pauling), and thus the parent amine ($R_2N–H$) is inherently nucleophilic. However, by introducing the suitable leaving group X on nitrogen, the innate polarity is inverted, and $R_2N–X$ can work as the nitrogen electrophile (Figure 1). The concept of the umpolung amination can address the aforementioned problems in the conventional hydroamination with the parent $R_2N–H$; combined with suitable external nucleophilic hydride sources, the three-component-coupling-type net hydroamination of various alkenes and alkynes proceeds efficiently (Scheme 1a). Moreover, rational design of catalysts and substrates successfully controls the regio- and stereoselectivity in the reaction. In this Perspective, recent advances of the umpolung-enabled net hydroamination reactions are categorized according to transition metal catalysts employed, and their scope, limitations, and mechanism are briefly summarized. Additionally, we also describe related aminoboration (Scheme 1b) and carboamination (Scheme 1c) reactions with boron and carbon nucleophiles, respectively, to deliver structurally complex and densely functionalized alkylamines from readily available feedstock-like hydrocarbon starting materials.[7] Notably, some reactions, particularly, fully intermolecular aminoborations of simple alkenes, are possible only by using the umpolung amination strategy.[8] Here, N-centered aminyl and/or amidyl radical cascade reactions involving $R_2N–X$ homolysis or related SET process are not covered (Scheme 2a), and only the reactions directly involving electrophilic amination with $R_2N–X$ (Scheme 2b) are demonstrated.

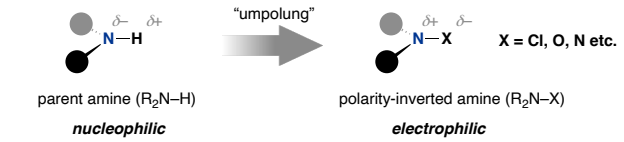
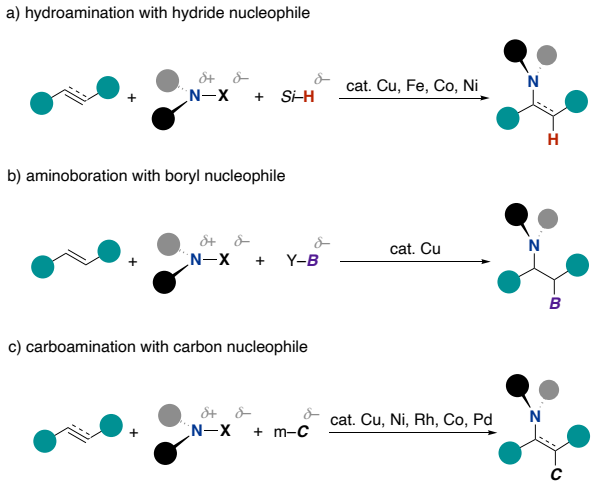
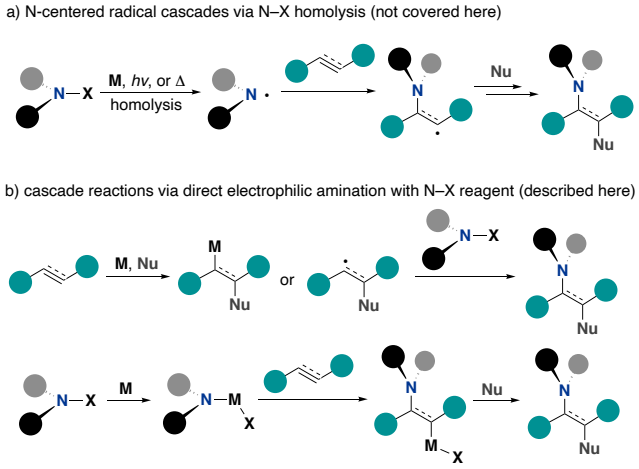


Figure 1. An umpolung (polarity inversion) concept of amines.

Scheme 1. Umpolung-Enabled Three-Component-Coupling-Type Aminofunctionalizations of Alkenes and Alkynes



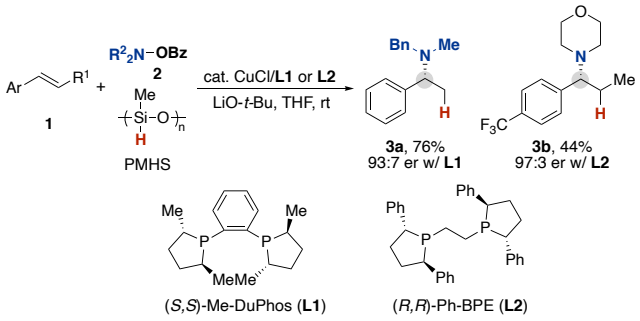
Scheme 2. Scope of This Perspective



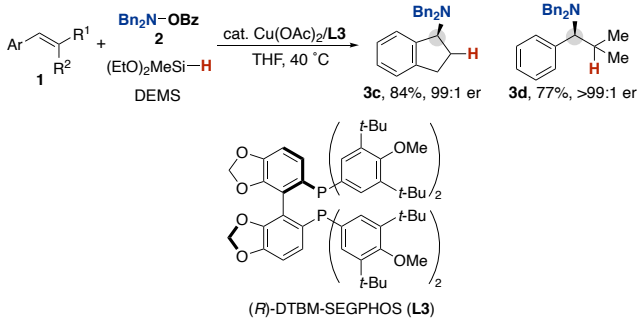
HYDROAMINATION

Copper Catalysts. The umpolung-amination-enabled net hydroamination of alkenes with hydroxylamines and hydrosilanes was first reported, independently, by Hirano/Miura (Scheme 3)[9] and Buchwald (Scheme 4).[10] Under conditions developed by Hirano and Miura, terminal and *trans*-β-substituted styrenes **1** were coupled with *O*-benzoyl-*N,N*-dialkylhydroxylamine **2** and polymethylhydrosiloxane (PMHS) in the presence of CuCl/(*S,S*)-Me-DuPhos (**L1**) or (*R,R*)-Ph-BPE (**L2**) chiral catalyst and LiO-*t*-Bu base to form the corresponding benzylic amines **3** regioselectively and enantioselectively. On the other hand, Buchwald demonstrated the broader substrate scope, including more challenging *cis*-β-substituted and β,β-disubstituted styrenes, by using Cu(OAc)$_2$/(*R*)-DTBM-SEGPHOS (**L3**) catalyst and diethoxymethylsilane (DEMS) even under external base-free conditions.

Scheme 3. Umpolung-Enabled Regio- and Enantioselective Hydroamination of Styrenes by Hirano and Miura

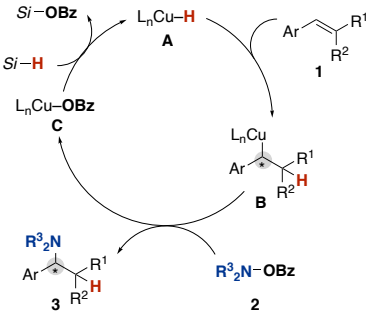


Scheme 4. Umpolung-Enabled Regio- and Enantioselective Hydroamination of Styrenes by Buchwald



A generally proposed reaction mechanism is shown in Scheme 5. The starting catalytically active species is L$_n$Cu–H **A**,[11] which is initially generated in situ from copper salt and hydrosilane (initiation step). Subsequent insertion of **1** into the Cu–H bond of **A**[12] is followed by the electrophilic amination of the resulting alkylcopper intermediate **B** with the hydroxylamine **2** to produce the observed hydroaminated product **3** and copper benzoate **C**. Final σ-bond metathesis with the hydrosilane regenerates the starting copper hydride **A** to complete the catalytic cycle. The regio- and enantioselectivity is determined in the insertion step (**A** to **B**), and the C–N bond forming process occurs with retention of configuration.[13] The external base such as LiO-*t*-Bu is believed to accelerate the formation of the copper hydride species **A** (initiation step and/or **C** to **A**).

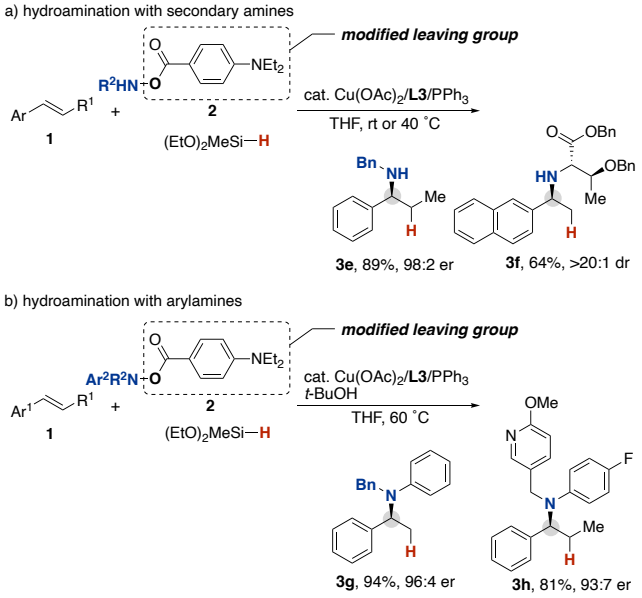
Scheme 5. General Mechanism of Cu-Catalyzed Umpolung-Enabled Hydroamination with Hydroxylamine and Hydrosilane



The initially applicable hydroxylamines were limited to *N,N*-dialkylamine derivatives, but appropriate modification of the leaving group successfully expanded their scope. In particular, introduction of the *para*-diethylamino (Et$_2$N) group into the benzoate leaving moiety dramatically improved the stability and reactivity to allow secondary amines (**3e** and **3f**; Scheme 6a)[14] and

tertiary arylamines (**3g** and **3h**; Scheme 6b)[15] to be constructed in the net hydroamination. Without the modification, nonproductive rapid decomposition of the hydroxylamine derivative **2** with the copper hydride species mainly occurred.

Scheme 6. Et_2N-Modification of Leaving Group that Expands Scope of Amines



In addition to relatively simple styrenes, cinnamyl alcohol/amine (**3i**)[16] and its cyclic variants (**3j** and **3k**)[17,18] were also viable substrates (Figure 2, top). Biologically important chiral α-aryl-*N*-heterocycles could be readily constructed by the rational design of substrate (Figure 2, middle).[19] The intramolecular hydroamination of *N*-arylalkenyl-substituted hydroxylamines proceeded to form the corresponding five-membered pyrrolidine (**3l**) and six-membered piperidine (**3m**) with high enantioselectivity. This methodology was also amenable to preparation of medium to large sized ring systems (**3n** and **3o**), which are difficult to synthesize by other means. Moreover, copper/bisphosphine catalyst systems were effective for a variety of aliphatic alkenes (Figure 2, bottom), including monosubstituted terminal alkenes (**3p**),[10] 1,1-disubstituted terminal alkenes (**3q**),[20] 1,2-disubstituted internal alkenes (**3r** and **3s**),[21] bicyclic alkenes (**3t**),[22] methylenecycloproanes (**3u**),[23] and cyclobutenes (**3v**).[24] Particularly in the synthesis of **3r** and **3s**, the aforementioned leaving group modification with the *para*-Et_2N group was indispensable to obtain the desired hydroaminated products, thus indicating that judicious choice of the leaving group can expand the scope of not only amines but also alkenes. In the case of sterically less biased unsymmetrical internal alkenes, the regioselectivity was generally poor to moderate (e.g., **3s**.) However, several directing groups at the suitable position can increase the regioselectivity, as exemplified by allylic and homoallylic amines (**3w** and **3x**) and homoallylic alcohol (**3y**).[25,26] This strategy was also applicable to the intramolecular reaction, giving the chiral aziridine (**3z**).[27] The origin of the directing group effect is considered to be an electronic (inductive) and/or a steric effect rather than coordination to the copper center.[26]

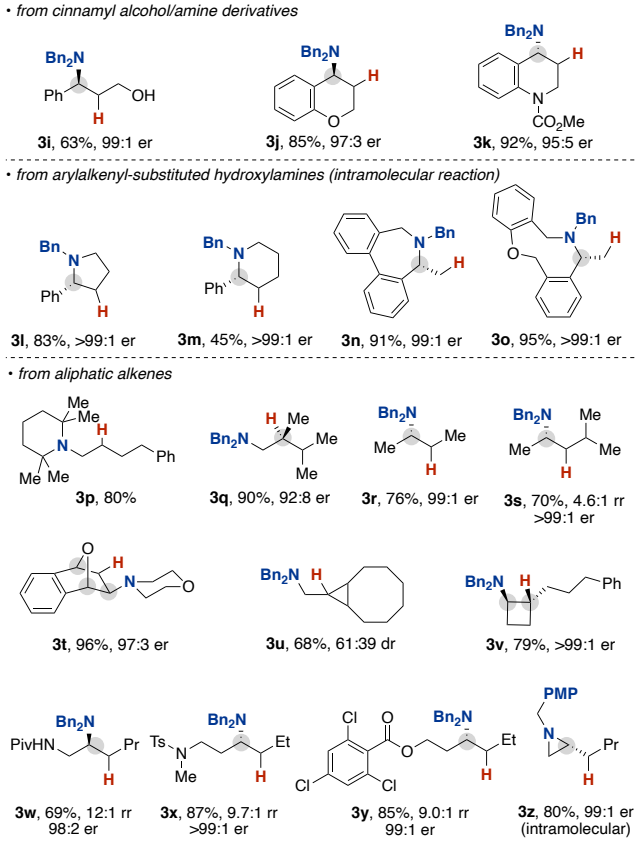
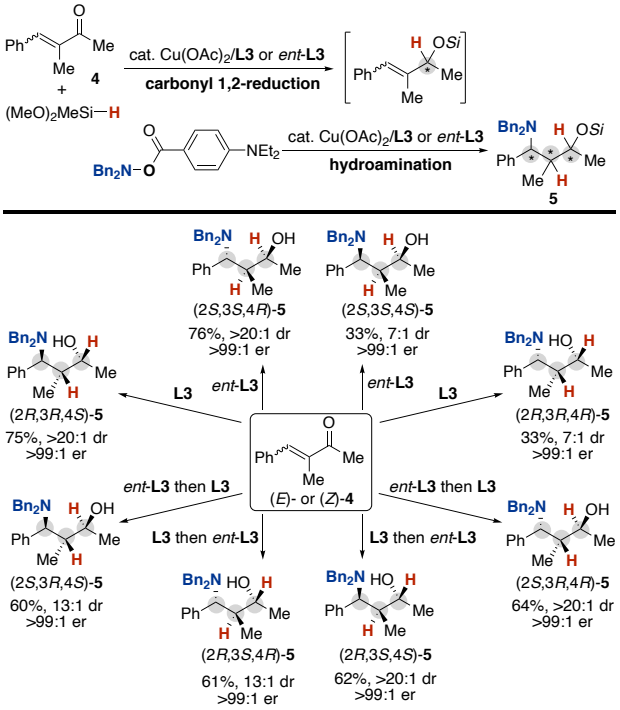


Figure 2. Representative examples of alkylamines synthesized by umpolung-enabled Cu-catalyzed hydroamination of cinnamyl alcohol/amine derivatives (top), arylalkenyl-substituted hydroxylamines (middle), and aliphatic alkenes (bottom).

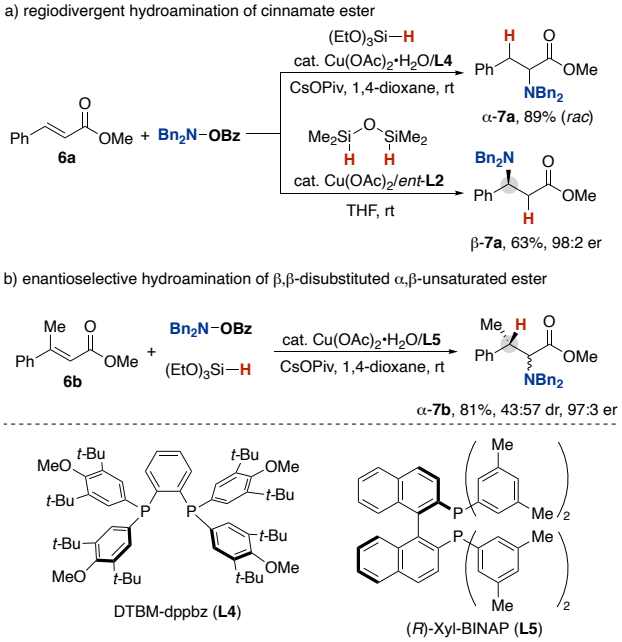
The asymmetric copper catalysis also accommodates alkenes that are directly conjugated with carbonyl functions. One significant example is the stereodivergent synthesis of 1,3-aminoalcohol **5** with three successive stereocenters from α,β-unsaturated ketone **4** via copper hydride-catalyzed enantioselective carbonyl 1,2-reduction/umpolung-enabled enantioselective hydroamination cascade (Scheme 7).[28] With proper choice of an ancillary chiral ligand in each step, (*E*)-α-methylbenzalacetone (*E*)-**4** was divergently transformed to four stereoisomers (2*S*,3*S*,4*R*)-, (2*R*,3*R*,4*S*)-, (2*S*,3*R*,4*S*)-, and (2*R*,3*S*,4*R*)-**5**. From the geometrical isomer (*Z*)-**4**, four complementary stereoisomers (2*S*,3*S*,4*S*)-, (2*R*,3*R*,4*R*)-, (2*S*,3*R*,4*R*)-, and (2*R*,3*S*,4*S*)-**5** were obtained. Thus, all possible eight stereoisomers can be easily accessible with high stereoselectivity.

Scheme 7. Stereodivergent Synthesis of 1,3-Aminoalcohols

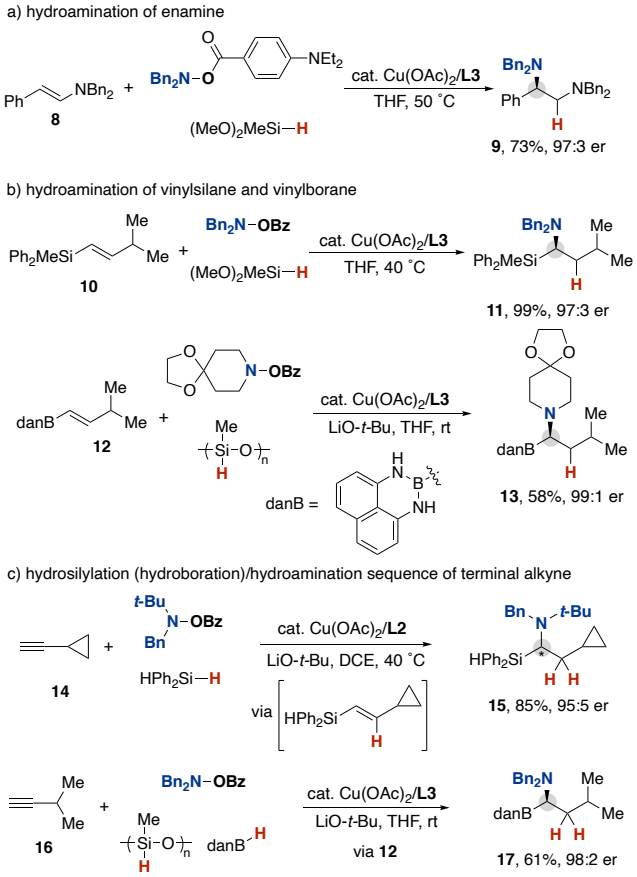


In the net hydroamination of α,β-unsaturated ester **6a**, condition-dependent regiodivergency was observed: the $Cu(OAc)_2.H_2O$/DTBM-dppbz (**L4**) catalyst system delivered the corresponding α-amino acid α-**7a** exclusively,[29] whereas the regioisomeric β-amino acid β-**7a** was selectively formed in the presence of $Cu(OAc)_2$/(*S,S*)-Ph-BPE (*ent*-**L3**; Scheme 8a).[30] In the latter case, the point chirality at the β-position was well controlled. Unfortunately, in the former case attempts of asymmetric induction at the α-position remained unsuccessful. However, with the (*R*)-Xyl-BINAP chiral ligand (**L5**), the β,β-disubstituted substrate **6b** was converted to the optically active α-**7b** with high enantioselectivity but with moderate diastereoselectivity, thus indicating that effective asymmetric induction occurs at the β-position in the olefin insertion step but the formed copper enolate undergoes the electrophilic amination at the α position with poor diastereocontrol (Scheme 8b).

Scheme 8. Regiodivergent and Enantioselective Hydroamination of α,β-Unsaturated Esters



Scheme 9. Hydroamination of Heteroatom-Substituted Alkenes



Heteroatom-substituted alkenes are valuable platforms for preparation of functionality-rich chiral amines. The enamine substrate **8** underwent the copper-catalyzed regio- and enantioselective hydroamination to produce the chiral 1,2-diamine **9** with a high enantiomeric ratio (Scheme 9a).[31] In the reaction of vinylsilane (**10**) and vinylborane (**12**), the corresponding α-aminosilane (**11**)[32] and α-aminoborane (**13**)[33] were obtained, respectively, which are Si- and B-mimics of the α-amino acid and

known to be pharmacophores in bioactive molecules such as the proteasome inhibitor and serine protease human neutrophil elastase (HNE) inhibitor[34] (dan = 1,8-diaminonaphthyl; Scheme 9b). Recently, these important compounds were more readily accessible from the simple terminal alkynes **14** and **16** by the hydrosilylation (hydroboration)/hydroamination sequence using a single copper catalyst component (**15** and **17**; Scheme 9c).[35,36] Additionally, $Ph_2P(BH_3)$-[37] and CF_3-substituted alkenes[38] are also viable substrates. Representative product structures are shown in Figure 3 (**18a**, **b**, and **19**).

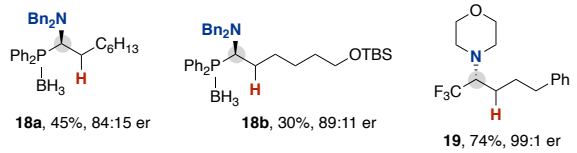
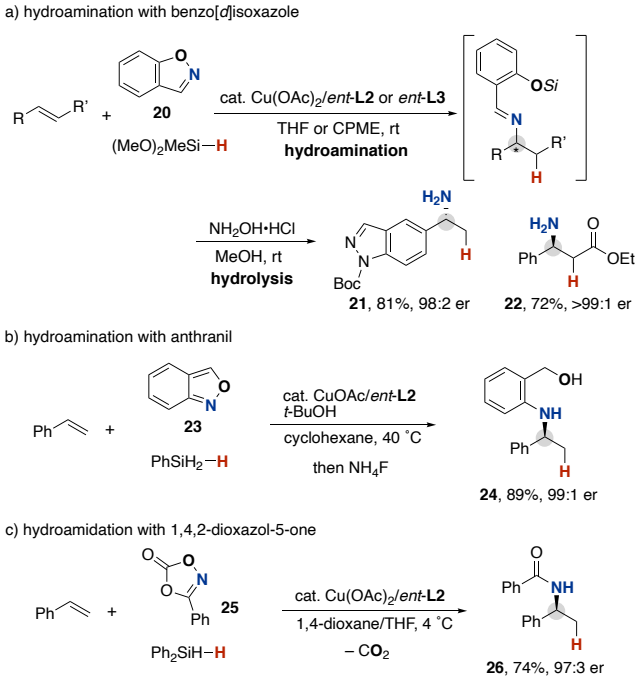


Figure 3. Representative examples of enantioselective hydroamination of $Ph_2P(BH_3)$- and CF_3-substituted alkenes.

As mentioned above, the most frequently employed electrophilic amination reagent in the copper-catalyzed net hydroamination is *O*-acylated hydroxylamine, but some N-O containing heterocycles can work as nitrogen electrophiles. Particularly notable is benzo[*d*]isoxazole (**20**), which is an equivalent of H_2N^+: after hydrolysis workup, the optically active primary amines (**21** and **22**) were obtained with high enantioselectivity (Scheme 10a).[39,40] Its constitutional isomer, anthranil (**23**), was also used, giving the corresponding secondary arylamine (**24**; Scheme 10b).[41] Additionally, otherwise difficult hydro*amidation* was possible by using 1,4,2-dioxazol-5-one (**25**; Scheme 10c),[42] which was originally developed for catalytic aromatic C–H amidation reactions.[43]

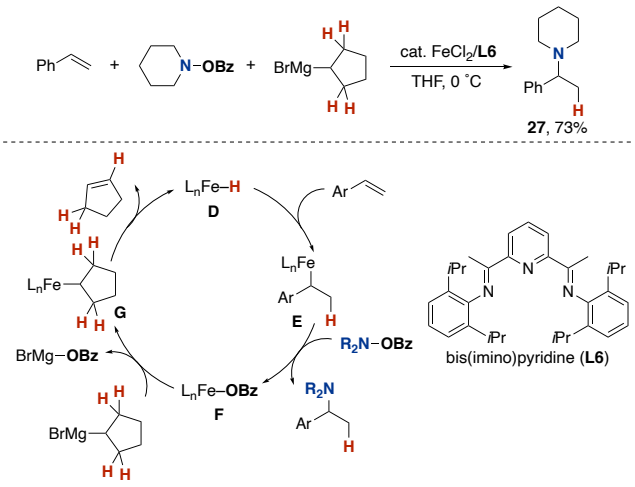
Scheme 10. Hydroamination with N-O Heterocycles as Electrophilic Amination Reagents



Since seminal work by Hirano/Miura and Buchwald in 2013, the copper-catalyzed enantioselective net hydroamination of alkenes has greatly and rapidly progressed. However, there are still some challenges to be solved; for example, (1) improvement in regioselectivity in the case of sterically and electronically less biased internal alkenes and (2) expansion of the scope of electrophilic amination reagents. In particular, the direct use of the electrophilic primary amino source, that is, H_2N–X, is strongly awaited, because the resulting chiral primary amines are most frequently occurring alkylamines in bioactive molecules and pharmaceuticals.

Iron Catalysts. The Fe(II)/bis(imino)pyridine ligand (**L6**) also catalyzed the net hydroamination of styrene with *O*-benzoyl-*N,N*-dialkylhydroxylamine (Scheme 11).[44] A proposed reaction mechanism is similar to that catalyzed by the copper (Scheme 5): (1) insertion of styrene into the Fe–H bond of the initially formed iron hydride **D**, (2) electrophilic amination of the benzyliron intermediate **E**, and (3) conversion from the concurrently formed iron benzoate **F** back to the starting **D** via transmetalation with the cyclopentylmagnesium reagent (**F** to **G**) and β-hydride elimination (**G** to **D**). Thus, the cyclopentylmagnesium reagent works as the external hydride source instead of the hydrosilane in the aforementioned Cu-based hydroamination system.

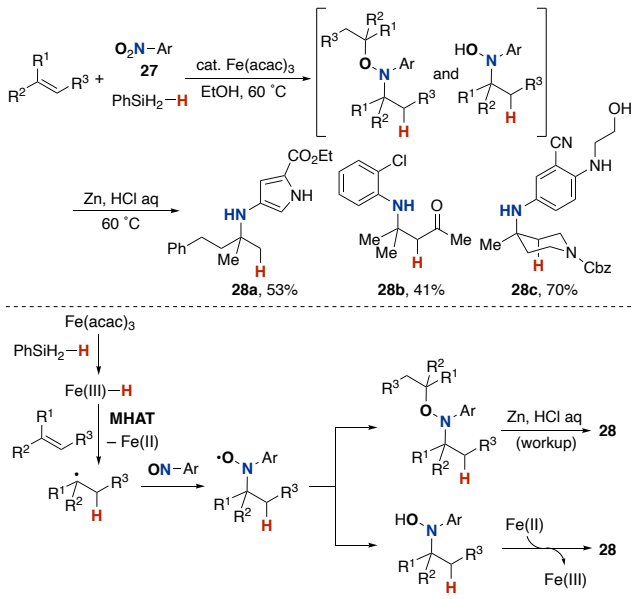
Scheme 11. Fe-Catalyzed Hydroamination with Hydroxylamines and Alkyl Grignard Reagents



Baran reported a totally mechanistically distinct iron hydride-catalyzed net hydroamination of alkenes with nitroarenes **27** and hydrosilanes as the electrophilic amino sources and nucleophilic hydrides, respectively (Scheme 12).[45] The electronically and sterically diverse aliphatic alkenes reacted under mild conditions to form the sterically congested Markovnikov hydroaminated products **28** in good yields. The initially formed compounds are ArRN-OR and ArRN-OH.The former is reduced with Zn and HCl aq upon workup to finally deliver the corresponding secondary arylamines **28**. The latter is directly reduced with the in situ generated iron hydride species to form **28** with concomitant turnover of the Fe catalyst. The iron catalysis involves the Fe(III)H-mediated metal hydride H atom transfer (MHAT) process of alkenes to generate the alkyl radical intermediate, which then undergoes addition reaction across the nitrosoarene derived from the nitroarene, the prototype of which was originally reported by Mukaiyama.[46]

The iron-based catalyst system is particularly effective for the synthesis of sterically hindered α-branched aniline derivatives, which are generally difficult to prepare by other means. However, asymmetric catalysis still remains to be developed.

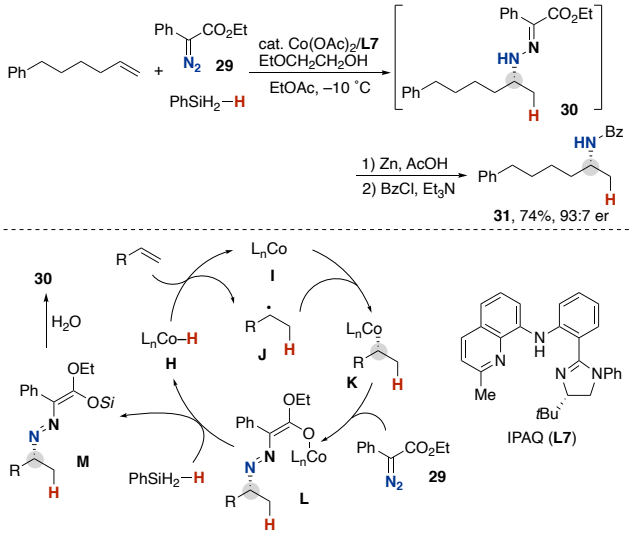
Scheme 12. Fe-Catalyzed Hydroamination with Nitroarenes and Hydrosilanes via MHAT



Cobalt Catalysts. Cobalt complexes are also known to promote MHAT-type hydrofunctionalizations of alkenes, but in some cases formed alkyl radicals are rapidly recombined with Co species to form alkylcobalt intermediates, thus enabling asymmetric induction by using suitable chiral ligands. Actually, Lu reported the Co(II)/IPAQ (**L7**)-catalyzed asymmetric net hydroamination of aliphatic alkenes with the diazo compound **29** as the electrophilic amination reagent (Scheme 13).[47] Afterreductive workup and benzoylation with BzCl of the initially observed hydrazine **30**, the corresponding chiral amide **31** was isolated in a good overall yield with acceptable enantioselectivity. The key to success is the use of redox-active, noninnocent *N,N,N*-tridentate chiral ligand **L7**, which facilitates the radical rebound to the Co center (from **I** and **J** to **K**). Subsequent insertion of the N≡N bond of **29** into the C–Co bond of the alkylcobalt (**K** to **L**) is followed by σ-bond metathesis with the hydrosilane to form the starting cobalt hydride **H** and intermediate **M**, en route to **30**.

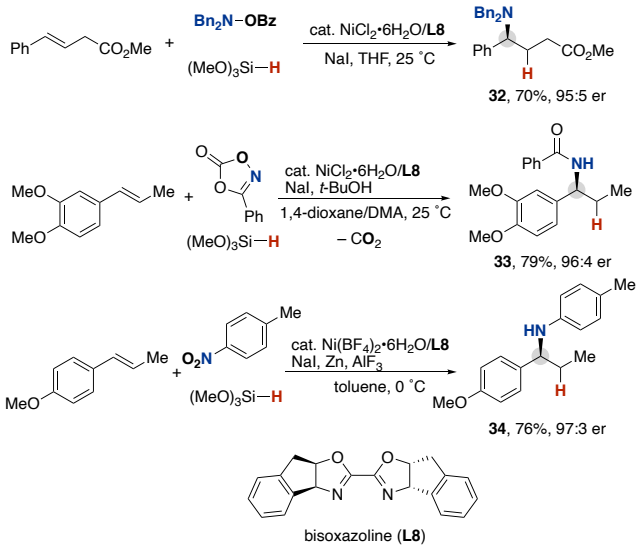
One disadvantage of the Co-based catalyst system is the narrow scope of the electrophilic amination reagent; now only the diazo compounds of type **29** are suitable. Additional expansion of amine coupling partners is strongly desired.

Scheme 13. Co-Catalyzed Enantioselective Hydroamination with Diazo Compounds via MHAT and Radical Rebound



Nickel Catalysts. The enantioselective net hydroamination of styrene with electrophilic amination reagent and hydrosilane efficiently occurred also in the presence of nickel catalysts ligated with the chiral bisoxazoline **L8** (Scheme 14).[48] One advantage of the nickel-based catalyst system is the broader scope of the electrophilic amination reagent: hydroxylamine, 1,4,2-dioxazol-5-one, and nitroarene all were successfully coupled with styrenes under almost the same conditions to afford the corresponding benzylic amines **32–34** with high enantiomeric ratios. A proposed reaction mechanism is similar to that shown in Scheme 5, in which a nickel hydride is the active species and enantioselectivity is determined in a styrene insertion step.

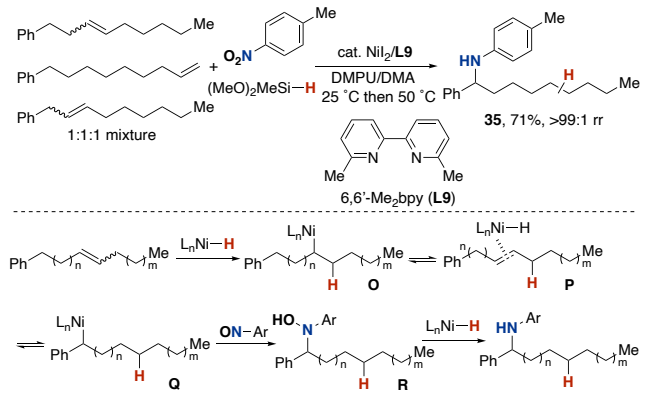
Scheme 14. Ni-Catalyzed Enantioselective Hydroamination and -amidation of Styrenes with Various Electrophilic Amination Reagents



The significant feature of nickel-catalyzed net hydroamination is the chain-walking event, which is observed in the reaction of aliphatic alkenes (Scheme 15).[49] Even from a complicated regio- and stereomixture of alkenes, the single benzylic amine **35** was convergently obtained via iterative insertion/β-hydride elimination with the nickel hydride (**O** to **P** to **Q**). The benzylnickel **Q**

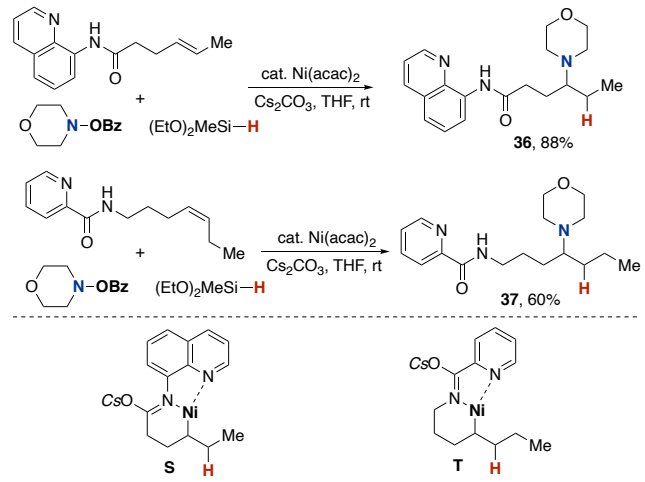
irreversibly reacts with the in situ generated nitrosoarene to form the benzylic C–N bond regioconvergently (**Q** to **R**). The final product is produced by additional reductive cleavage of N–O of **R** with the nickel hydride.

Scheme 15. Ni-Catalyzed Regioconvergent Hydroamination with Nitroarenes via Chain-Walking



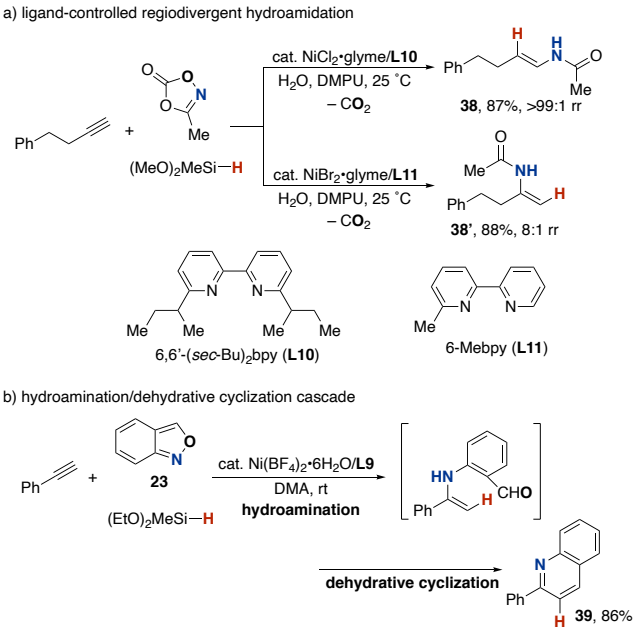
The regioselective hydroamination of internal alkenes without the chain-walking is also possible by using suitable directing groups (Scheme 16).[50] The 8-aminoquinoline and picolinamide were promising auxiliaries[51] to furnish the corresponding hydroaminated products **36** and **37** with controllable regioselectivity. The *N,N*-bidentate coordination in the nickelacycles **S** and **T** is considered to be a key to control the regioselectivity in a step of the alkene insertion into a nickel hydride.

Scheme 16. Ni-Catalyzed Directed Regioselective Hydroamination of Internal Aliphatic Alkenes



The NiH-based catalyst system also showed high performance in the hydroamidation of alkynes with 1,4,2-dioxazol-5-one, where the regioselectivity could be controlled by judicious choice of supporting bipyridine-type ligands (Scheme 17a).[52] While 6,6'-(*sec*-Bu)$_2$bpy (**L10**) afforded the *anti*-Markovnikov hydroamidated product **38** exclusively, the opposite Markovnikov-type regioisomer **38'** was mainly formed with 2-Mebpy ligand (**L11**). With anthranil **23** instead of 1,4,2-dioxazol-5-one, the initially formed Markovnikov hydroaminated product spontaneously underwent the intramolecular dehydrative cyclization to furnish the corresponding 2-phenylquinoline (**39**) in one synthetic operation (Scheme 17b).[53]

Scheme 17. Ni-Catalyzed Hydroamidation and Hydroamination of Alkynes



The NiH catalysis accommodated both alkenes and alkynes as unsaturated starting substrates with high regio- and stereocontrols, which is a significant advantage compared to the aforementioned CuH, FeH, and CoH catalysis. However, in the reaction of the unactivated internal alkenes, the specially designed bidentate auxiliaries are still inevitable (Scheme 16). Their attachment and detachment require additional synthetic steps, which is somewhat tedious and decreases overall synthetic efficiency. Application of ubiquitous functional groups such as carboxylic acid and amine is more attractive.

AMINOBORATION

In the proposed catalytic cycle of the copper-catalyzed umpolung-enabled hydroamination (Scheme 5), if the hydrosilane is replaced with other external nucleophiles, aminative difunctionalizations of styrene are possible. Bis(pinacolato)diboron (pinB–Bpin) seems to be a good candidate (Scheme 18); *syn*-addition of in situ generated borylcopper species **A'** across styrene generates the borylated alkylcopper intermediate **B'**.[54,55] By proper choice of supporting ligands, the enantioselectivity is determined in this step. Subsequent stereoretentive electrophilic amination with **2** delivers the corresponding chiral aminoborated product **40** with generation of the copper benzoate **C**. The catalytic cycle is closed by LiO-*t*-Bu-assisted σ-bond metathesis with pinB–Bpin (**C** to **A'**). Actually, in 2013, Hirano and Miura reported the catalytic and regio-/enantioselective intermolecular aminoboration of styrene with hydroxylamine and pinB–Bpin in the presence of CuCl/(*S,S*)-Me-DuPhos (**L1**) catalyst and LiO-*t*-Bu base to deliver β-aminoalkylborane **40a** of potentially biological importance.[56,57] This is the first example of simultaneous addition of amino group and boryl group to alkene π bonds in a fully intermolecular manner. Subsequently, the broader substrate scope and better enantioselectivity were achieved by using the ^{Piv}ZPhos ligand (**L12**).[58] The oxidation with $NaBO_3$ following the aminoboration can provide efficient access to the enantioenriched 1,2-aminoalcohol (**40b**).

The umpolung-enabled aminoboration catalysis was applicable to a wide range of alkenes (Figure 4). Strained alkenes such as methylenecyclopropane (**41**),[59] benzylidenecyclopropane (**42**),[60] and cyclopropene (**43**)[61] were highly reactive templates, giving the corresponding stereodefined cyclopropane-containing alkylamines frequently occurring in pharmaceutical agents. Bicyclic alkenes were also viable substrates (**44**).[62] Similar to the net hydroamination (Scheme 9b), the vinylsilane and vinylborane were transformed to the β-borylated α-aminosilane (**45**)[63] and -borane (**46**)[64] with good to high stereochemical control.

Scheme 18. Copper-Catalyzed Umpolung-Enabled Aminoboration of Styrenes

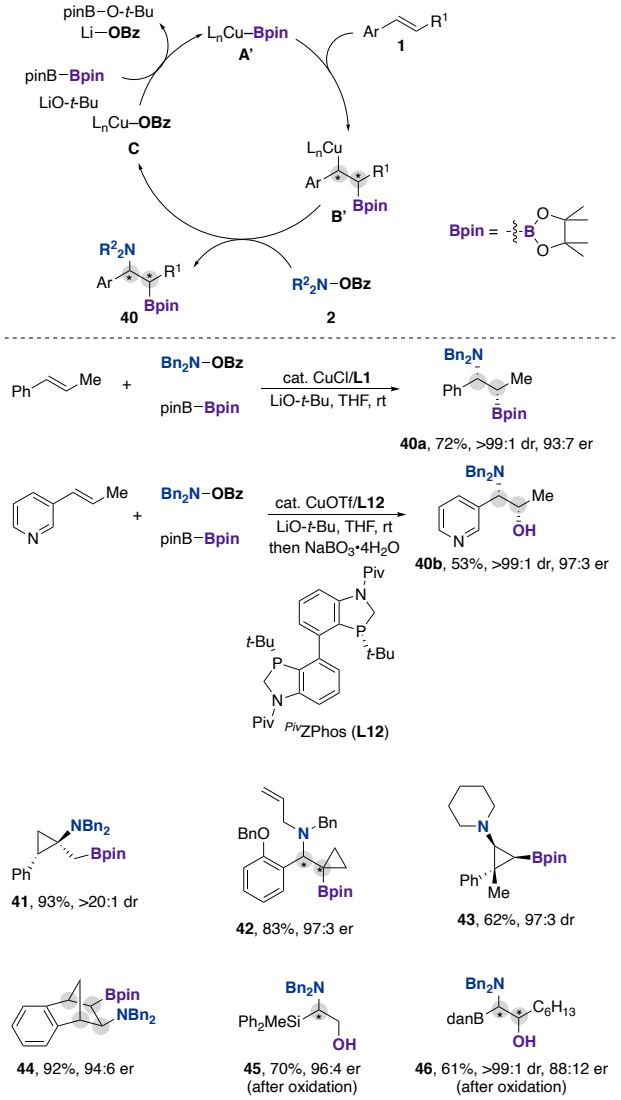
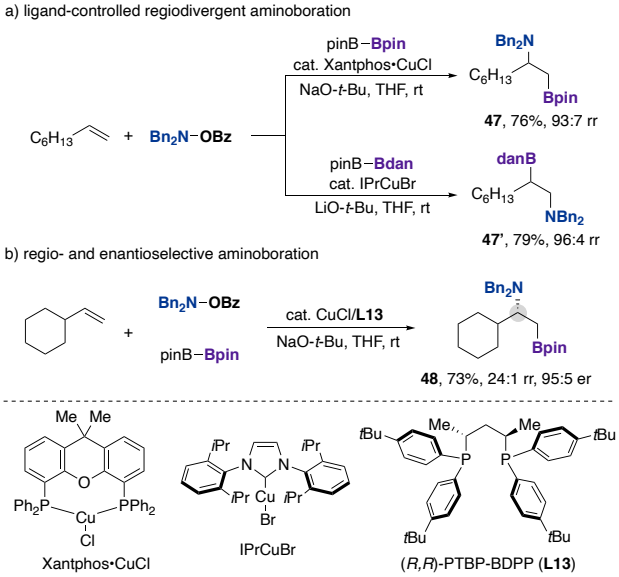


Figure 4. Representative examples of umpolung-enabled copper-catalyzed aminoboration of strained alkenes, vinylsilane, and vinylborane.

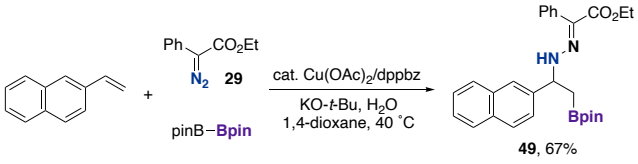
In the reaction of simple terminal alkenes, the ligand-controlled rediodivergent aminoboration was possible (Scheme 19a).[65] The Xantphos•CuCl complex guided the amino group and boryl group at the internal position and terminal position (**47**), respectively, while the opposite internally borylated aminoboration product **47'** was selectively formed under IPrCuBr catalysis. It should be noted that suitable choice of the alkoxide base and boron source was necessary to maximize the regioselectivity and yield. The regioselectivity is determined in the alkene insertion step (from **A'** and **1** to **B'** in Scheme 18), where steric factors play pivotal roles. Moreover, the regioselective and enantioselective aminoboration was also feasible by using the chiral (*R,R*)-PTBP-BDPP ligand (**L13**; Scheme 19b).[66]

In almost all reported copper-catalyzed umpolung-enabled aminoboration reactions, *O*-acylated hydroxylamines of the type **2** were employed as the electrophilic amination reagents. Only one exception was shown in Scheme 20: the diazo ester **29** was successfully combined with pinB–Bpin, although alkene substrates were limited to electronically activated and sterically accessible terminal styrenes.[67]

Scheme 19. Regio- and Enantioselective Aminoboration of Simple Aliphatic Terminal Alkenes



Scheme 20. Copper-Catalyzed Aminoboration with Diazo Ester as Electrophilic Amination Reagent



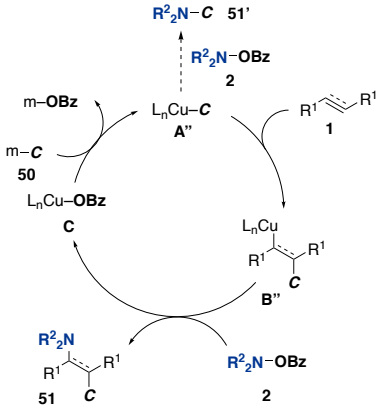
As mentioned in this section, the fully intermolecular aminoboration of simple alkenes is now possible only by copper catalysts. Development of mechanistically distinct aminoboration catalysis with other transition metals might be necessary to expand the scope and overcome unsolved challenges, e.g., an internally borylated enantioselective aminoboration of terminal alkenes (vs Scheme 19b).

CARBOAMINATION

Copper Catalysts. Compared to the above copper-catalyzed hydroamination and aminoboration, a three-component-coupling-type carboamination is relatively difficult (Scheme 21), because the organocopper species **A"** generated from the carbon nucleophile **50** is prone to react directly with the electrophilic amination reagent (from **A"** and **2** to **51'**) over the desired alkene or alkyne C–C

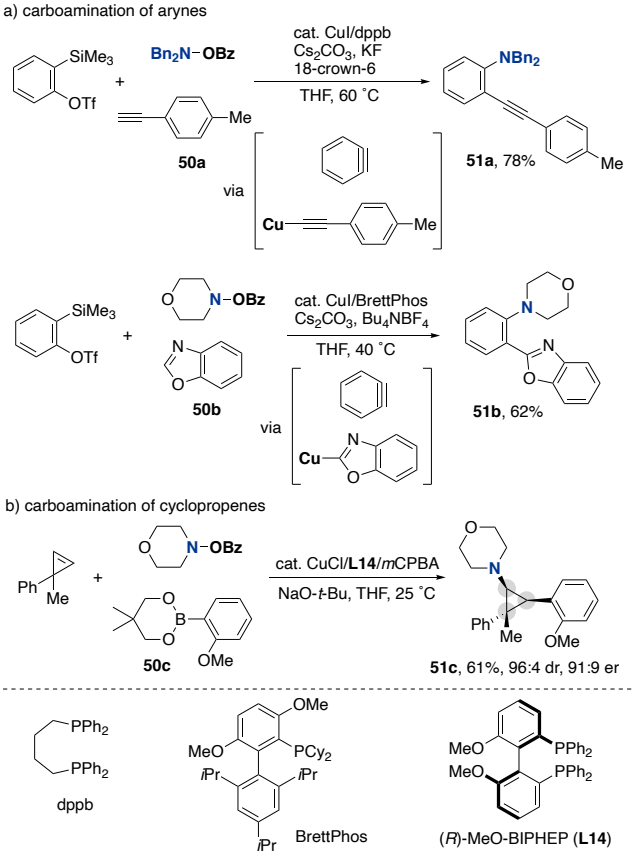
multiple bond of **1** (from **A"** and **1** to **B"**).[6b,68] Thus, the suitable choice of alkene/alkyne substrate is critical for success.

Scheme 21. Plausible Mechanism of Copper-Catalyzed Umpolung-Enabled Carboamination of Alkenes or Alkynes



While somewhat specific, one solution is the use of highly strained thus reactive π-components. Indeed, in-situ generated arynes from the *o*-silylaryl triflates underwent the catalytic carboamination with the hydroxylamine and terminal alkyne **50a** (Scheme 22a).[69] Under modified conditions, 1,3-azole **50b** could also be used as the carbon nucleophile. In these cases, external base-assisted C–H abstraction of **50a** and **50b** occurred to form the corresponding organocopper species corresponding to the intermediate **A"** in Scheme 21. Similarly, cyclopropenes showed promise in the chemoselective coupling of the hydroxylamine and arylboronate **50c** with high diastereo- and enantioselectivity (Scheme 22b).[70]

Scheme 22. Copper-Catalyzed Umpolung-Enabled Carboamination of Arynes and Cyclopropenes

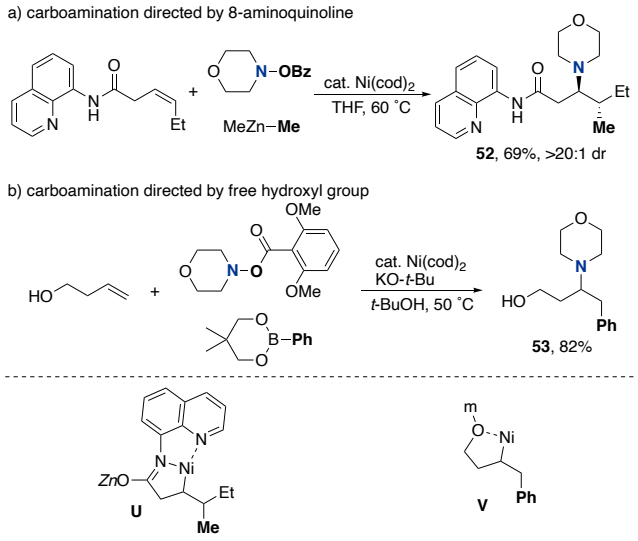


Apparently, the copper-based carboamination reaction suffers from the limited scope of alkene and alkyne substrates; only highly reactive strained alkenes and benzynes are amenable. To address the chemoselectivity problem discussed in Scheme 21 (**A"** to **B"** vs **A"** to **51'**), it is necessary to design supporting ligands and/or electrophilic amination reagents to induce a strong affinity of organocopper **A"** for the alkene/alkyne **1**.

Nickel Catalysts. Another approach to the chemoselective three-component-coupling-type carboamination of alkenes is a directing group-assisted strategy. Engle reported the 8-aminquinoline-directed nickel-catalyzed regio- and diastereoselective carboamination of aliphatic internal alkenes with hydroxylamines and organozinc reagents (Scheme 23a).[71] More recently, much simpler unsaturated free alcohols were also adopted in this type of transformation, where *o,o'*-$(MeO)_2$ modification of the leaving group in the hydroxylamine was essential for obtaining satisfactory chemoselectivity (Scheme 23b).[72] In both cases, formation of chelated five-membered nickelacycles **U** and **V** is proposed to be the key to success.

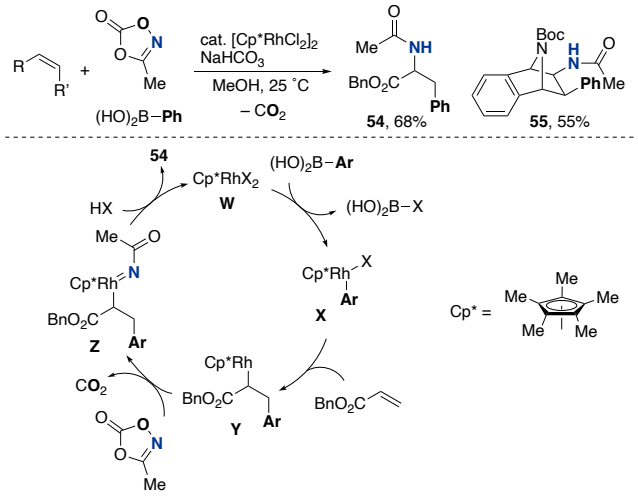
As seen in the nickel-catalyzed hydroamination section, the use of the 8-aminoquinoline auxiliary is generally essential for obtaining the promising regioselectivity, but now the free alcohol can serve as a good directing group for several alkene substrates. Successful use of more ubiquitous and productive functional groups as directing groups can further increase the synthetic utility of this process. Additionally, development of asymmetric catalysis is strongly appealing.

Scheme 23. Nickel-Catalyzed Directed Carboamination of Alkenes



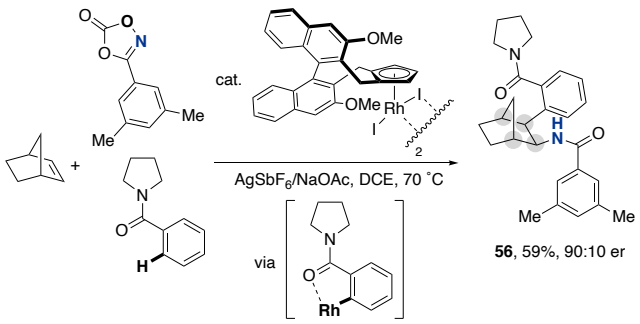
CpM-Type (M = Rh, Co) Catalysts. The chemoselective fully intermolecular carboamination of electronically activated acrylate esters was achieved by the $[Cp^*RhCl_2]_2$ catalyst (Scheme 24).[73] With arylboronic acid and 1,4,2-dioxazol-5-one as the carbon nucleophile and nitrogen electrophile, respectively, the targeted phenylglycine derivative **54** was obtained in a synthetically useful yield. A similarly highly reactive strained alkene such as bicyclic alkene was also amenable to the reaction (**55**). A generally proposed reaction mechanism with the acrylate involves (1) formation of Ar-Rh(III) via transmetalation with the arylboronic acid (**W** to **X**), (2) alkene insertion into the Ar–Rh bond (**X** to **Y**), (3) Rh-nitrene generation with removal of CO_2 (**Y** to **Z**), and (4) productive reductive elimination/protodemetalation (**Z** to **W**).

Scheme 24. Cp*Rh-Catalyzed Carboamination of Acrylate and Strained Alkene



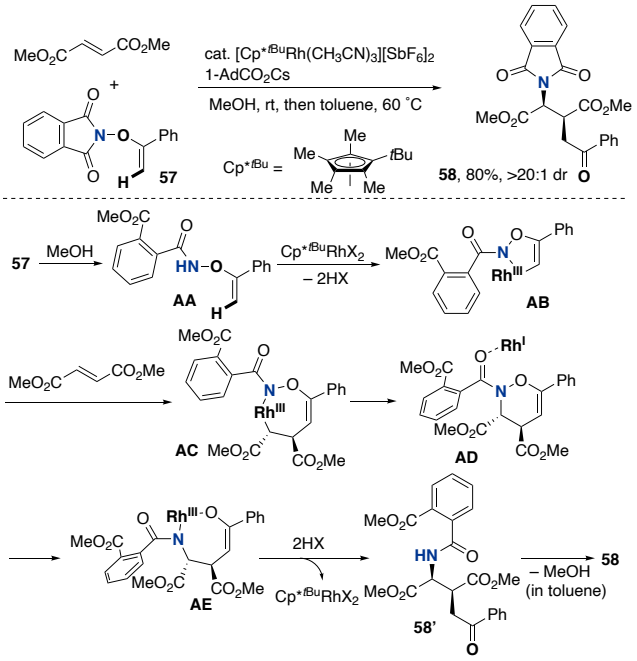
Several Cp*Rh-type complexes are well-known to promote directed C–H activation of aromatic compounds.[74] Thus, rational design of substrates enables the carboamination reaction directly with simple aromatic C–H as the carbon nucleophile. Ellman reported the reaction with 1,4,2-dioxazol-5-one and benzamide (Scheme 25); the alkene substrate was limited to the strained bicyclic alkene, but suitable Cramer-type chiral cyclopentadienyl Rh catalysts[75] also induced good enantioselectivity.[76,77]

Scheme 25. Enantioselective Carboamination of Bicyclic Alkene with Simple Aromatic C–H Nucleophile Catalyzed by Chiral CpRh-Type Complex



The well-designed enoxyphthalimide (**57**) contains both the nucleophilic carbon part and electrophilic nitrogen part in one molecule and thus works as a carboamination reagent for fumarate under $Cp^{*t\mathrm{Bu}}Rh(III)$ catalysis, which was originally developed by Rovis (Scheme 26).[78] The phthalimide moiety of **57** initially undergoes partial alcoholysis with solvent MeOH to form the transient **AA**. Directed C–H activation with $Cp^{*t\mathrm{Bu}}Rh(III)$ (**AA** to **AB**) is followed by insertion of dimethyl fumarate to afford the seven-membered rhodacycle **AC**. Subsequent reductive elimination, N–O bond cleavage by the in situ generated $Cp^{*t\mathrm{Bu}}Rh(I)$ species, and protodemetalation initially deliver the open-form carboaminated product (**AC** to **AD** to **AE** to **58'**). Additional heating in toluene (60 °C) finally furnishes **58**. Overall, the N–O bond of **57** was cleaved, and both fragments were added across the alkene moiety as the *C*-enolate carbon nucleophile and phthalimide nitrogen electrophile.

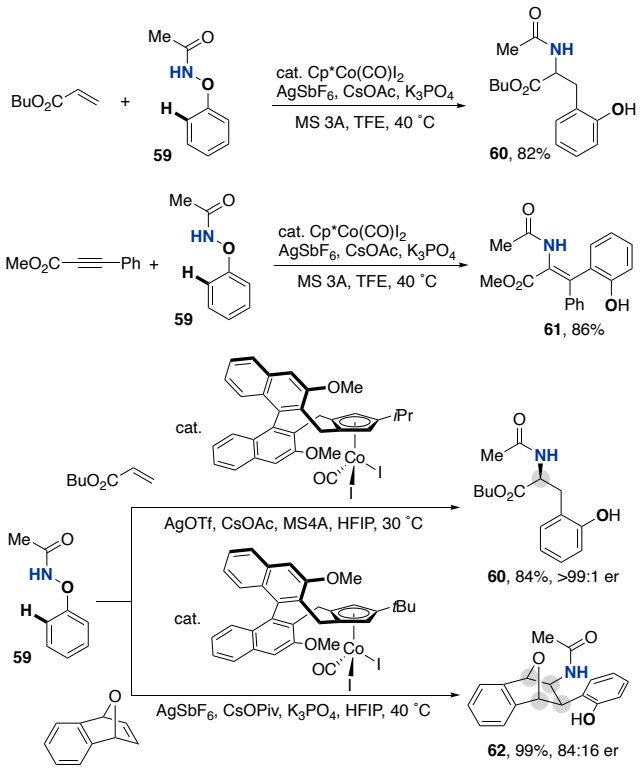
Scheme 26. Carboamination of Fumarate with Enoxyphthalimide Catalyzed by CpRh-Type Complex



Related carboamination reactions of acrylate[79] and propiolate[80] with phenoxyamide (**59**) were possible by using Cp*Co(III)[81] catalyst (**60** and **61**; Scheme 27). Notably, under Cp*Rh(III) catalysis, the N–O moiety in **59** just worked as a traceless internal oxidant, giving a simply oxidative alkenylated product over the

carboamination product. These results clearly demonstrate the unique and distinct catalytic activity of Co-based catalyst systems. Very recently, Cramer succeeded in asymmetric induction in the carboamination of acrylate and bicyclic alkene (**60** and **62**) with originally developed chiral cyclopentadienyl cobalt catalysts.[82]

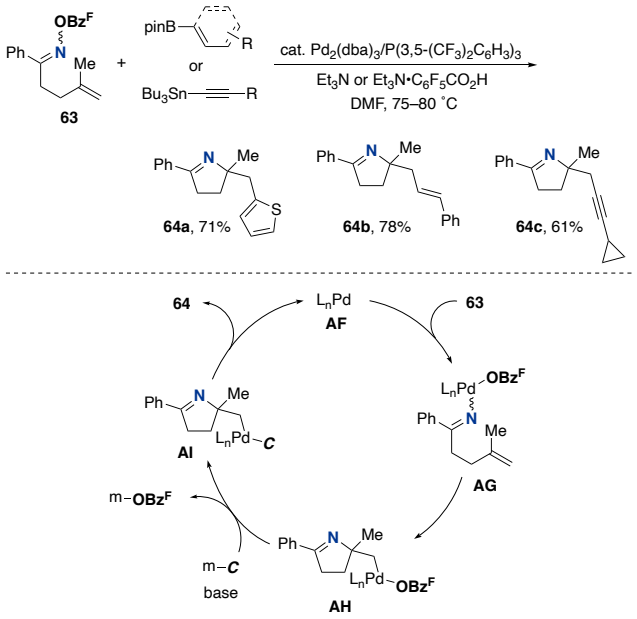
Scheme 27. Carboamination of Alkenes and Alkynes with Phenoxyamide Catalyzed by CpCo-Type Complexes



The feature of CpM-type catalysts is the successful combination of C–H activation and electrophlic amination process, which enables the direct use of relatively simple aromatic and vinylic C–Hs as the carbon nucleophiles. However, C–C unsaturated components are still limited to relatively activated carbonyl-conjugated substrates or strained bicyclic alkenes. Applications of more general alkene/alkyne substrates are strongly awaited.

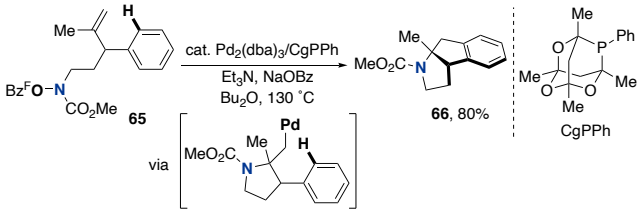
Palladium Catalysts. A totally distinct approach to the alkene carboamination is mediated by the palladium-catalyzed aza-Heck-type reaction (Scheme 28).[83] Bower developed the semi-intermolecular carboamination of *O*-pentafluorobenzoyl (Bz^F) oxime ester **63** with a pendant olefinic moiety. In conjunction with external carbon nucleophiles such as arylboronate, vinylboronate, and alkynyl stannane, the corresponding carboaminated products, 3,4-dihydro-2*H*-pyrrole derivatives **64**, were obtained in good yields.[84] The reaction is proposed to be initiated by oxidative addition of the N–O bond in **63** to the palladium(0) **AF**. Intramolecular alkene insertion into the Pd–N bond generates the alkylpalladium intermediate **AH**, which is then intercepted with the external carbon nucleophile (**AH** to **AI**). Productive reductive elimination furnishes **64** with regeneration of the starting **AF** to complete the catalytic cycle.

Scheme 28. Palladium-Catalyzed aza-Heck Reaction-Enabled Carboamination



Additionally, in the case with 4-pentenylamine derivative **65**, the intramolecular aromatic C–H serves as the internal carbon nucleophile to afford the complex *N*-heterocycle **66** under similar conditions (Scheme 29).[85] Following N–O oxidative addition and alkene insertion, the formed alkylpalladium is trapped with the intramolecular aromatic C–H to finally deliver the tricyclic system **66**.

Scheme 29. Synthesis of Complex *N*-Heterocycle by aza-Heck-Triggered Palladium-Catalyzed Intramolecular Carboamination



The palladium-catalyzed aza-Heck reaction-enabled carboamination can provide a powerful tool for rapid assembly of multiply substituted, complex *N*-heterocycles. On the other hand, a fully intermolecular three-component-coupling process is still challenging.

CONCLUSION

In this Perspective, we have briefly summarized recent advances in the catalytic aminative functionalization of alkenes and alkynes with electrophilic amination reagents. By taking advantage of the concept of nitrogen umpolung, the inherently nucleophilic amino group can work as the nitrogen electrophile to realize otherwise challenging aminofunctionalizations such as hydroamination, aminoboration, and carboamination, in conjunction with the hydride, boryl, and carbon external nucleophiles, respectively. Moreover, suitable design of catalysts and supporting ligands successfully induces the enantioselectivity, thus, from readily available hydrocarbon materials, giving optically active complex alkylamines of high value in medicinal and pharmaceutical chemistry. In principle, all other nucleophilic components can be employed as external nucleophiles. For example, the successful use of an oxygen nucleophile enables an oxyamination reaction. Actually, the rhodium-catalyzed fully intermolecular three-

component-coupling-type oxyamination of 1,3-dienes with alcohols and 1,4,2-dioxazol-5-ones was recently reported.[86] Expansion of the scope to relatively simple alkenes as well as development of asymmetric catalysis can provide a complementary method to the classical Os-based oxyamination process.[87] With suitable Si and F external nucleophiles, otherwise difficult enantioselective silylamination and fluoroamination of alkenes are expected. They are still unmet challenges but believed to be achieved by additional rational design of catalysts, electrophilic amination reagents, and external nucleophiles. We postulate that further development of umpolung-enabled aminative difunctionalization reactions can open the door to the discovery of new *N*-containing drug molecules and functional organic materials.

AUTHOR INFORMATION

Corresponding Authors

Koji Hirano – *Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan;* orcid.org/0000-0001-9752-1985; Email: k_hirano@chem.eng.osaka-u.ac.jp.

Masahiro Miura – *Innovative Catalysis Science Division, Institute for Open and Transdisciplinary Research Initiatives (ICS-OTRI), Osaka University, Suita, Osaka 565-0871, Japan;* orcid.org/0000-0001-8288-6439; Email: miura@chem.eng.osaka-u.ac.jp.

Complete contact information is available at: https://pubs.acs.org/10.1021/xxxx.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

Our finding in this work was supported by JSPS KAKENHI Grant Nos. JP 25620084 (Grant-in-Aid for Challenging Exploratory Research) and JP 15H05485 (Grant-in-Aid for Young Scientists (A)) to K.H. and JP 24225002 (Grant-in-Aid for Scientific Research (S)) and JP 17H06092 (Grant-in-Aid for Specially Promoted Research) to M.M.. K.H. also acknowledges The Uehara Memorial Foundation and Toyota Riken Scholar for financial supports. The authors thank all of the students listed in our papers.

REFERENCES

(1) (a) Hili, R.; Yudin, A. K. Making carbon-nitrogen bonds in biological and chemical synthesis. *Nat. Chem. Biol.* **2006**, *2*, 284–287. (b) Ricci, A. *Amino Group Chemistry: From Synthesis to the Life Sciences*; Wiley-VCH: Weinheim, Germany, **2007**.

(2) (a) Shirota, Y.; Kageyama, H. Charge Carrier Transporting Molecular Materials and Their Applications in Devices. *Chem. Rev.* **2007**, *107*, 953. (b) Li, L.-L.; Diau, E. W.-G. Porphyrin-sensitized solar cells. *Chem. Soc. Rev.* **2013**, *42*, 291.

(3) (a) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. Hydroamination: Direct Addition of Amines to Alkenes and Alkynes. *Chem. Rev.* **2008**, *108*, 3795–3892. (b) Hesp, K. D.; Stradiotto, M. Rhodium- and Iridium-Catalyzed Hydroamination of Alkenes. *ChemCatChem* **2010**, *2*, 1192–1207. (c) Huang, L.; Arndt, M.; Gooβen, K.; Heydt, H.; Gooβen, L. Late Transition Metal-Catalyzed Hydroamination and Hydroamidation. *Chem. Rev.* **2015**, *115*, 2596–2697. (d) Coman, S. M.; Parvulescu, V. I. Nonprecious Metals Catalyzing Hydroamination and C–N Coupling Reactions. *Org. Process Res. Dev.* **2015**, *19*, 1327–1355.

(4) (a) Müller, T. E.; Beller, M. Metal-Initiated Amination of Alkenes and Alkynes. *Chem. Rev.* **1998**, *98*, 675–704. (b) Johns, A. M.; Sakai, N.; Hartwig, J. F. Direct Measurement of the Thermodynamics of Vinylarene Hydroamination. *J. Am. Chem. Soc.* **2006**, *128*, 9306–9307. (c) Musacchio, A. J.; Lainhart, B. C.; Zhang, X.; Naguib, S. G.; Sherwood, T. C.; Knowles, R. R. Catalytic intermolecular hydroaminations of unactivated olefins with secondary alkyl amines. *Science* **2017**, *355*, 727–730.

(5) For a concept and an application of umpolung in organic synthetic chemistry, see: (a) Seebach, D.; Corey, E. J. Generation and Synthetic Applications of 2-Lithio-1,3-dithianes. *J. Org. Chem.* **1975**, *40*, 231–237. (b) Seebach, D. Methods of Reactivity Umpolung. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239–258.

(6) For pioneering work on the electrophilic amination, see: (a) Tsutsui, H.; Hayashi, Y.; Narasaka, K. Preparation of Primary Amines by the Copper(I) Catalyzed Reaction of 4,4'-Bis(trifluoromethyl)benzophenone *O*-Methylsulfonyloxime and Alkyl Grignard Reagents. *Chem. Lett.* **1997**, *26*, 317–318. (b) Berman, A. M.; Johnson, J. S. Copper-Catalyzed Electrophilic Amination of Diorganozinc Reagents. *J. Am. Chem. Soc.* **2004**, *126*, 5680–5681. (c) Liu, S.; Liebeskind, L. S. A Simple, Modular Synthesis of Substituted Pyridines. *J. Am. Chem. Soc.* **2008**, *130*, 6918–6919. Representative reviews: (d) Erdik, E.; Ay, M. Electrophilic amination of carbanions. *Chem. Rev.* **1989**, *89*, 1947–1980. (e) Narasaka, K.; Kitamura, M. Amination with Oximes. *Eur. J. Org. Chem.* **2005**, *2005*, 4505–4519. (f) Ciganek, E. Electrophilic Amination of Carbanions, Enolates, and Their Surrogates. *Org. React.* **2009**, *72*, 1. (g) Barker, T. J.; Jarvo, E. R. Developments in Transition-Metal-Catalyzed Reactions Using Electrophilic Nitrogen Sources. *Synthesis* **2011**, *2011*, 3954–3964. (h) Corpet, M.; Gosmini, C. Recent Advances in Electrophilic Amination Reactions. *Synthesis* **2014**, *46*, 2258–2271. (i) Dong, X.; Liu, Q.; Dong, Y.; Liu, H. Transition-Metal-Catalyzed Electrophilic Amination: Application of *O*-Benzoylhydroxylamines in the Construction of the C−N Bond. *Chem.–Eur. J.* **2017**, *23*, 2481–2511.

(7) For related recent reviews, see: (a) Pirnot, M. T.; Wang, Y.-M.; Buchwald, S. L. Copper Hydride Catalyzed Hydroamination of Alkenes and Alkynes. *Angew. Chem., Int. Ed.* **2016**, *55*, 48–57. (b) Sorádová, Z.; Šebesta, R. Enantioselective Cu-Catalyzed Functionalizations of Unactivated Alkenes. *ChemCatChem.* **2016**, *8*, 2581–2588.

(8) For the selected intramolecular aminoboration reactions by the nucleophilic amination strategy, see: (a) Chong, E.; Blum, S. A. Aminoboration: Addition of B–N σ Bonds across C–C π Bonds. *J. Am. Chem. Soc.* **2015**, *137*, 10144–10147. (b) Yang, C.-H.; Zhang, Y.-S.; Fan, W.-W.; Liu, G.-Q.; Li, Y.-M. Intramolecular Aminoboration of Unfunctionalized Olefins. *Angew. Chem., Int. Ed.* **2015**, *54*, 12636–12639. (c) Yang, C.-H.; Han, M.; Li, W.; Zhu, N.; Sun, Z.; Wang, J.; Yang, Z.; Li, Y.-M. Direct Intramolecular Aminoboration of Allenes. *Org. Lett.* **2020**, *22*, 5090–5093. (d) Voss, T.; Chen, C.; Kehr, G.; Nauha, E.; Erker, G.; Stephan, D. W. Cyclizations via Frustrated Lewis Pairs: Lewis Acid Induced Intramolecular Additions of Amines to Olefins and Alkynes. *Chem.–Eur. J.* **2010**, *16*, 3005–3008.

(9) 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.

(10) Zhu, S.; Niljianskul, N.; Buchwald, S. L. Enantio- and Regioselective CuH-Catalyzed Hydroamination of Alkenes. *J. Am. Chem. Soc.* **2013**, *135*, 15746–15749.

(11) For leading work on the copper hydride chemistry, see: (a) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. Selective hydride-mediated conjugate reduction of α,β-unsaturated carbonyl compounds using $[(Ph_3P)CuH]_6$. *J. Am. Chem. Soc.* **1988**, *110*, 291–293. Review: (b) Deutsch, C.; Krause, N.; Lipshutz, B. H. CuH-Catalyzed Reactions. *Chem. Rev.* **2008**, *108*, 2916–2027.

(12) (a) Mankad, N. P.; Laitar, D. S.; Sadighi, J. P. Synthesis, Structure, and Alkyne Reactivity of a Dimeric (Carbene)copper(I) Hydride. *Organometallics* **2004**, *23*, 3369–3371. (b) Jordan, A. J.; Wyss, C.

M.; Bacsa, J.; Sadighi, J. P. Synthesis and Reactivity of New Copper(I) Hydride Dimers. *Organometallics* **2016**, *35*, 613–616.

(13) For recent computational studies on the electrophilic amination of organocopper species with the hydroxylamine, see: (a) Tobisch, S. CuH-Catalysed Hydroamination of Styrene with Hydroxylamine Esters: A Coupled Cluster Scrutiny of Mechanistic Pathways. *Chem.–Eur. J.* **2016**, *22*, 8290–8300. (b) Tobisch, S. Copper-Catalysed Aminoboration of Vinylarenes with Hydroxylamine Esters—A Computational Mechanistic Study. *Chem.–Eur. J.* **2017**, *23*, 17800–17809. (c) Tobisch, S. CuH-catalysed hydroamination of arylalkynes with hydroxylamine esters – a computational scrutiny of rival mechanistic pathways. *Chem. Sci.* **2017**, *8*, 4410–4423.

(14) Niu, D.; Buchwald, S. L. 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.

(15) Ichikawa, S.; Zhu, S.; Buchwald, S. L. A Modified System for the Synthesis of Enantioenriched N-Arylamines through Copper-Catalyzed Hydroamination. *Angew. Chem., Int. Ed.* **2018**, *57*, 8714-8718.

(16) Ichikawa, S.; Buchwald, S. L. Asymmetric Synthesis of γ-Amino Alcohols by Copper-Catalyzed Hydroamination. *Org. Lett.* **2019**, *21*, 8736–8739.

(17) Yang, Q.; Li, S.; Wang, J. Asymmetric Synthesis of Chiral Chromanes by Copper- Catalyzed Hydroamination of 2H-Chromenes. *ChemCatChem.* **2020**, *12*, 3202–3206.

(18) Xu-Xu, Q.-F.; Zhang, X.; You, S.-L. Enantioselective Synthesis of 4-Aminotetrahydroquinolines via 1,2-Reductive Dearomatization of Quinolines and Copper(I) Hydride-Catalyzed Asymmetric Hydroamination. *Org. Lett.* **2019**, *21*, 5357–5362.

(19) Dai, X.-J.; Engl, O. D.; León, T.; Buchwald, S. L. Catalytic Asymmetric Synthesis of α-Arylpyrrolidines and Benzo-fused Nitrogen Heterocycles. *Angew. Chem., Int. Ed.* **2019**, *58*, 3407–3411.

(20) Zhu, S.; Buchwald, S. L. Enantioselective CuH-Catalyzed Anti-Markovnikov Hydroamination of 1,1-Disubstituted Alkenes. *J. Am. Chem. Soc.* **2014**, *136*, 15913–15916.

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

(22) Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. Copper-Catalyzed Enantioselective Formal Hydroamination of Oxa- and Azabicyclic Alkenes with Hydrosilanes and Hydroxylamines. *Org. Lett.* **2014**, *16*, 1498–1501.

(23) Nishikawa, D.; Sakae, R.; Miki, Y.; Hirano, K.; Miura, M. Copper-Catalyzed Regioselective Ring-Opening Hydroamination of Methylenecyclopropanes. *J. Org. Chem.* **2016**, *81*, 12128–12134.

(24) Feng, S.; Hao, H.; Liu, P.; Buchwald, S. L. Diastereo- and Enantioselective CuH-Catalyzed Hydroamination of Strained Trisubstituted Alkenes. *ACS Catal.* **2020**, *10*, 282–291.

(25) Ichikawa, S.; Buchwald, S. L. Regio- and Enantioselective Synthesis of 1,2-Diamine Derivatives by Copper-Catalyzed Hydroamination. *Org. Lett.* **2019**, *21*, 4370–4373.

(26) Xi, Y.; Butcher, T. W.; Zhang, J.; Hartwig, J. F. Regioselective, Asymmetric Formal Hydroamination of Unactivated Internal Alkenes. *Angew. Chem., Int. Ed.* **2016**, *55*, 776–780.

(27) Wang, H.; Yang, J. C.; Buchwald, S. L. CuH-Catalyzed Regioselective Intramolecular Hydroamination for the Synthesis of Alkyl-Substituted Chiral Aziridines. *J. Am. Chem. Soc.* **2017**, *139*, 8428–8431.

(28) Shi, S.-L.; Wong, Z. L.; Buchwald, S. L. Copper-catalysed enantioselective stereodivergent synthesis of amino alcohols. *Nature* **2016**, *532*, 353–356.

(29) Nishino, S.; Miura, M.; Hirano, K. An umpolung-enabled copper-catalysed regioselective hydroamination approach to α-amino acids. *Chem. Sci.* **2021**, *12*, 11525–11537.

(30) Zhang, G.; Liang, Y.; Qin, T.; Xiong, T.; Liu, S.; Guan, W.; Zhang, Q. Copper-Catalyzed Asymmetric Hydroamination: A Unified Strategy for the Synthesis of Chiral β-Amino Acid and Its Derivatives. *CCS Chem.* **2021**, *3*, 1737–1745.

(31) Yu, L.; Somfai, P. Regio- and Enantioselective Formal Hydroamination of Enamines for the Synthesis of 1,2-Diamines. *Angew. Chem., Int. Ed.* **2019**, *58*, 8551–8555.

(32) Niljianskul, N.; Zhu, S.; Buchwald, S. L. Enantioselective Synthesis of α-Aminosilanes by Copper-Catalyzed Hydroamination of Vinylsilanes. *Angew. Chem., Int. Ed.* **2015**, *54*, 1638–1641.

(33) 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.

(34) (a) Smoum, R.; Rubinstein, A.; Dembitsky, V. M.; Srebnik, M. Boron Containing Compounds as Protease Inhibitors. *Chem. Rev.* **2012**, *112*, 4156–4220. (b) Franz, A. K.; Wilson, S. O. Organosilicon Molecules with Medicinal Applications. *J. Med. Chem.* **2013**, *56*, 388–405.

(35) Nishino, S.; Hirano, K.; Miura, M. Cu-Catalyzed Reductive *gem*-Difunctionalization of Terminal Alkynes via Hydrosilylation/Hydroamination Cascade: Concise Synthesis of α-Aminosilanes. *Chem.–Eur. J.* **2020**, *26*, 8725–8728.

(36) Gao, D.-W.; Gao, Y.; Shao, H.; Qiao, T.-Z.; Wang, X.; Sanchez, B. B.; Chen, J. S.; Liu, P.; Engle, K. M. Cascade CuH-catalysed conversion of alkynes into enantioenriched 1,1-disubstituted products. *Nat. Catal.* **2020**, *3*, 23–29.

(37) Takata, T.; Nishikawa, D.; Hirano, K.; Miura, M. Synthesis of α-Aminophosphines by Copper-Catalyzed Regioselective Hydroamination of Vinylphosphines. *Chem.–Eur. J.* **2018**, *24*, 10975–10978.

(38) Takata, T.; Hirano, K.; Miura, M. Synthesis of α-Trifluoromethylamines by Cu-Catalyzed Regio- and Enantioselective Hydroamination of 1-Trifluoromethylalkenes. *Org. Lett.* **2019**, *21*, 4284–4288.

(39) Guo, S.; Yang, J. C.; Buchwald, S. L. A Practical Electrophilic Nitrogen Source for the Synthesis of Chiral Primary Amines by Copper-Catalyzed Hydroamination. *J. Am. Chem. Soc.* **2018**, *140*, 15976–15984.

(40) Guo, S.; Zhu, J.; Buchwald, S. L. Enantioselective Synthesis of β-Amino Acid Derivatives Enabled by Ligand-Controlled Reversal of Hydrocupration Regiochemistry. *Angew. Chem., Int. Ed.* **2020**, *59*, 20841–20845.

(41) Xie, F.; Shen, B.; Li, X. Enantioselective Copper-Catalyzed Hydroamination of Vinylarenes with Anthranils. *Org. Lett.* **2018**, *20*, 7154–7157.

(42) Zhou, Y.; Engl, O. D.; Bandar, J. S.; Chant, E. D.; Buchwald, S. L. CuH-Catalyzed Asymmetric Hydroamidation of Vinylarenes. *Angew. Chem., Int. Ed.* **2018**, *57*, 6672–6675.

(43) Park, Y.; Park, K. T.; Kim, J. G.; Chang, S. Mechanistic Studies on the Rh(III)-Mediated Amido Transfer Process Leading to Robust C–H Amination with a New Type of Amidating Reagent. *J. Am. Chem. Soc.* **2015**, *137*, 4534–4542.

(44) Huehls, C. B.; Lin, A.; Yang, J. Iron-Catalyzed Intermolecular Hydroamination of Styrenes. *Org. Lett.* **2014**, *16*, 3620–3623.

(45) Gui, J.; Pan, C.-M.; Jin, Y.; Qin, T.; Lo, J. C.; Lee, B. J.; Spergel, S. H.; Mertzman, M. E.; Pitts, W. J.; La Cruz, T. E.; Schmidt, M. A.; Darvatkar, N.; Natarajan, S. R.; Baran, P. S. Practical olefin hydroamination with nitroarenes. *Science* **2015**, *348*, 886–891.

(46) Isayama, S.; Mukaiyama, T. A New Method for Preparation of Alcohols from Olefins with Molecular Oxygen and Phenylsilane by the Use of Bis(acetylacetonato)cobalt(II). *Chem. Lett.* **1989**, *18*, 1071–1074.

(47) Shen, X.; Chen, X.; Chen, J.; Sun, Y.; Cheng, Z.; Lu, Z Ligand-promoted cobalt-catalyzed radical hydroamination of alkenes. *Nat. Commun.* **2020**, *11*, 783–790.

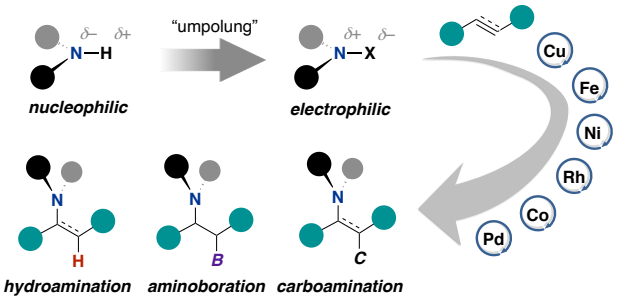
(48) Meng, L.; Yang, J.; Duan, M.; Wang, Y.; Zhu, S. Facile Synthesis of Chiral Arylamines, Alkylamines and Amides by Enantioselective NiH-Catalyzed Hydroamination. *Angew. Chem., Int. Ed.* **2021**, *60*, 23584–23589.

(49) Xiao, J.; He, Y.; Ye, F.; Zhu, S. Remote sp3 C–H Amination of Alkenes with Nitroarenes. *Chem.* **2018**, *4*, 1645–1657.

(50) Jeon, J.; Lee, C.; Seo, H.; Hong, S. NiH-Catalyzed Proximal-Selective Hydroamination of Unactivated Alkenes. *J. Am. Chem. Soc.* **2020**, *142*, 20470–20480.

(51) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. Highly Regioselective Arylation of sp3 C−H Bonds Catalyzed by Palladium Acetate. *J. Am. Chem. Soc.* **2005**, *127*, 13154–13155.
(52) Lyu, X.; Zhang, J.; Kim, D.; Seo, S.; Chang, S. Merging NiH Catalysis and Inner-Sphere Metal-Nitrenoid Transfer for Hydroamidation of Alkynes. *J. Am. Chem. Soc.* **2021**, *143*, 5867–5877.
(53) Gao, Y.; Yang, S.; Huo, Y.; Chen, Q.; Li, X.; Hu, X.-Q. NiH-Catalyzed Hydroamination/Cyclization Cascade: Rapid Access to Quinolines. *ACS Catal.* **2021**, *11*, 7772–7779.
(54) Laitar, D. S.; Müller, P.; Sadighi, J. P. Efficient Homogeneous Catalysis in the Reduction of CO_2 to CO. *J. Am. Chem. Soc.* **2005**, *127*, 17196–17197.
(55) Laitar, D. S.; Tsui, E. Y.; Sadighi, J. P. Copper(I) β-Boroalkyls from Alkene Insertion: Isolation and Rearrangement. *Organometallics* **2006**, *25*, 2405–2408.
(56) Matsuda, N.; Hirano, K.; Miura, M. Regioselective and Stereospecific Copper-Catalyzed Aminoboration of Styrenes with Bis(pinacolato)diboron and *O*-Benzoyl-*N,N*-dialkylhydroxylamines. *J. Am. Chem. Soc.* **2013**, *135*, 4934–4937.
(57) Li, X.; Hall, D. G. Synthesis and Applications of β-Aminoalkylboronic Acid Derivatives. *Adv. Synth. Catal.* **2021**, *363*, 2209–2223.
(58) Wu, L.; Zatolochnaya, O.; Qu, B.; Wu, L.; Wells, L. A.; Kozlowski, M. C.; Senanayake, C. H.; Song, J. J.; Zhang, Y. Cu-Catalyzed Asymmetric Aminoboration of *E*-Vinylarenes with ^{piv}ZPhos as the Ligand. *Org. Lett.* **2019**, *21*, 8952–8956.
(59) Sakae, R.; Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. Highly Stereoselective Synthesis of (Borylmethyl)cyclopropylamines by Copper-Catalyzed Aminoboration of Methylenecyclopropanes. *Org. Lett.* **2014**, *16*, 1228–1231.
(60) Jiang, H.-C.; Tang, X.-Y.; Shi, M. Copper-catalyzed regio- and enantioselective aminoboration of alkylidenecyclopropanes: the synthesis of cyclopropane-containing β-aminoalkylboranes. *Chem. Commun*. **2016**, *52*, 5273–5276.
(61) Parra, A.; Amenós, L.; Guisán-Ceinos, M.; López, A.; Ruano, J. L. G.; Tortosa, M. Copper-Catalyzed Diastereo- and Enantioselective Desymmetrization of Cyclopropenes: Synthesis of Cyclopropylboronates. *J. Am. Chem. Soc.* **2014**, *136*, 15833–15836.
(62) Sakae, R.; Hirano, K.; Satoh, T.; Miura, M. Copper-Catalyzed Stereoselective Aminoboration of Bicyclic Alkenes. *Angew. Chem., Int. Ed.* **2014**, *54*, 613–617.
(63) Kato, K.; Hirano, K.; Miura, M. Synthesis of β-Boryl-α-Aminosilanes by Copper-Catalyzed Aminoboration of Vinylsilanes. *Angew. Chem., Int. Ed.* **2016**, *55*, 14400–14404.
(64) Nishikawa, D.; Hirano, K.; Miura, M. Copper-Catalyzed Regio- and Stereoselective Aminoboration of Alkenylboronates. *Org. Lett.* **2016**, *18*, 4856–4859.
(65) Sakae, R.; Hirano, K.; Miura, M. Ligand-Controlled Regiodivergent Cu-Catalyzed Aminoboration of Unactivated Terminal Alkenes. *J. Am. Chem. Soc.* **2015**, *137*, 6460–6463.
(66) Kato, K.; Hirano, K.; Miura, M. Copper-Catalyzed Regio- and Enantioselective Aminoboration of Unactivated Terminal Alkenes. *Chem.–Eur. J.* **2018**, *24*, 5775–5778.
(67) Huo, J.; Xue, Y.; Wang, J. Regioselective copper-catalyzed aminoborylation of styrenes with bis(pinacolato)diboron and diazo compounds. *Chem. Commun.* **2018**, *54*, 12266–12269.
(68) (a) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. Copper-Catalyzed Amination of Arylboronates with N,N-Dialkylhydroxylamines. *Angew. Chem., Int. Ed.* **2012**, *51*, 3642–3645. (b) Rucker, R. P.; Whittaker, A. M.; Dang, H.; Lalic, G. Synthesis of Hindered Anilines: Copper-Catalyzed Electrophilic Amination of Aryl Boronic Esters. *Angew. Chem., Int. Ed.* **2012**, *51*, 3953–3956. (c) Rucker, R. P.; Whittaker, A. M.; Dang, H.; Lalic, G. Synthesis of Tertiary Alkyl Amines from Terminal Alkenes: Copper-Catalyzed Amination of Alkyl Boranes. *J. Am. Chem. Soc.* **2012**, *134*, 6571–6574.
(69) Niu, S.-L.; Hu, J.; He, K.; Chen, Y.-C.; Xiao, Q. Copper-Catalyzed Three-Component Carboamination of Arynes: Expeditious Synthesis of *o*-Alkynyl Anilines and *o*-Benzoxazolyl Anilines. *Org. Lett.* **2019**, *21*, 4250–4254.
(70) Li, Z.; Zhang, M.; Zhang, Y.; Liu, S.; Zhao, J.; Zhang, Q. Multicomponent Cyclopropane Synthesis Enabled by Cu-Catalyzed Cyclopropene Carbometalation with Organoboron Reagent: Enantioselective Modular Access to Polysubstituted 2-Arylcyclopropylamines. *Org. Lett.* **2019**, *21*, 5432–5437.
(71) van der Puyl, V. A.; Derosa, J.; Engle, K. M. Directed, Nickel-Catalyzed Umpolung 1,2-Carboamination of Alkenyl Carbonyl Compounds. *ACS Catal.* **2019**, *9*, 224–229.
(72) Kang, T.; Kim, N.; Cheng, P. T.; Zhang, H.; Foo, K.; Engle, K. M. Nickel-Catalyzed 1,2-Carboamination of Alkenyl Alcohols. *J. Am. Chem. Soc.* **2021**, *143*, 13962–13970.
(73) Lee, S.; Rovis, T. Rh(III)-Catalyzed Three-Component Syn-Carboamination of Alkenes Using Arylboronic Acids and Dioxazolones. *ACS Catal.* **2021**, *11*, 8585–8590.
(74) Satoh, T.; Miura, M. Oxidative Coupling of Aromatic Substrates with Alkynes and Alkenes under Rhodium Catalysis. *Chem.–Eur. J.* **2010**, *16*, 11212–11222.
(75) Newton, C. G.; Kossler, D.; Cramer, N. Asymmetric Catalysis Powered by Chiral Cyclopentadienyl Ligands. *J. Am. Chem. Soc.* **2016**, *138*, 3935–3941.
(76) Brandes, D. S.; Sirvent, A.; Mercado, B. Q.; Ellman, J. A. Three-Component 1,2-Carboamidation of Bridged Bicyclic Alkenes via RhIII-Catalyzed Addition of C–H Bonds and Amidating Reagents. *Org. Lett.* **2021**, *23*, 2836–2840.
(77) For a related 1,1-carboamination reaction, see: Maity, S.; Potter, T. J.; Ellman, J. A. α-Branched amines by catalytic 1,1-addition of C–H bonds and aminating agents to terminal alkenes. *Nat. Catal.* **2019**, *2*, 756–762.
(78) Piou, T.; Rovis, T. Rhodium-catalysed *syn*-carboamination of alkenes via a transient directing group. *Nature* **2015**, *527*, 86–90.
(79) Lerchen, A.; Knecht, T.; Daniliuc, C. G.; Glorius, F. Unnatural Amino Acid Synthesis Enabled by the Regioselective Cobalt(III)-Catalyzed Intermolecular Carboamination of Alkenes. *Angew. Chem., Int. Ed.* **2016**, *55*, 15166–15170.
(80) Zhu, Y.; Chen, F.; Zhao, X.; Yan, D.; Yong, W.; Zhao, J. Cobalt(III)-Catalyzed Intermolecular Carboamination of Propiolates and Bicyclic Alkenes via Non-Annulative Redox-Neutral Coupling. *Org. Lett.* **2019**, *21*, 5884–5888.
(81) For pioneering work on Cp*Co(III) catalysis in C–H activation, see: Yoshino, T.; Ikemoto, H.; Matsunaga, S.; Kanai, M. A Cationic High-Valent Cp*CoIII Complex for the Catalytic Generation of Nucleophilic Organometallic Species: Directed C-H Bond Activation. *Angew. Chem., Int. Ed.* **2013**, *52*, 2207–2211.
(82) Ozols, K.; Onodera, S.; Woźniak, Ł.; Cramer, N. Cobalt(III)-Catalyzed Enantioselective Intermolecular Carboamination by C−H Functionalization. *Angew. Chem., Int. Ed.* **2021**, *60*, 655–659.
(83) For pioneering work by Narasaka, see: (a) Tsutsui, H.; Narasaka, K. Synthesis of Pyrrole Derivatives by the Heck-Type Cyclization of γ,δ-Unsaturated Ketone O-Pentafluorobenzoyloximes. *Chem. Lett.* **1999**, *28*, 45–46. Selected recent review and examples: (b) Race, N. J.; Hazelden, I. R.; Faulkner, A.; Bower, J. F. Recent developments in the use of aza-Heck cyclizations for the synthesis of chiral N-heterocycles. *Chem. Sci.* **2017**, *8*, 5248–5260. (c) Shuler, S. A.; Yin, G.; Krause, S. B.; Vesper, C. M.; Watson, D. A. Synthesis of Secondary Unsaturated Lactams via an Aza-Heck Reaction. *J. Am. Chem. Soc.* **2016**, *138*, 13830–13833. (d) Ma, X.; Hazelden, I. R.; Langer, T.; Munday, R. H.; Bower, J. F. Enantioselective Aza-Heck Cyclizations of *N*-(Tosyloxy)carbamates: Synthesis of Pyrrolidines and Piperidines. *J. Am. Chem. Soc.* **2019**, *141*, 3356–3360.
(84) Faulkner, A.; Scott, J. S.; Bower, J. F. An Umpolung Approach to Alkene Carboamination: Palladium Catalyzed 1,2-Amino-Acylation, -Carboxylation, -Arylation, -Vinylation, and -Alkynylation. *J. Am. Chem. Soc.* **2015**, *137*, 7224–7230.
(85) Jones, B. T.; García-Cárceles, J.; Caiger, L.; Hazelden, I. R.; Lewis, R. J.; Langer, T.; Bower, J. F. Complex Polyheterocycles and the Stereochemical Reassignment of Pileamartine A via Aza-Heck Triggered Aryl C–H Functionalization Cascades. *J. Am. Chem. Soc.* **2021**, *143*, 15593–15598.
(86) Burg, F.; Rovis, T. Diastereoselective Three-Component 3,4-Amino Oxygenation of 1,3-Dienes Catalyzed by a Cationic

Heptamethylindenyl Rhodium(III) Complex. *J. Am. Chem. Soc.* **2021**, *143*, 17964–17969.
(87) Muñiz, K. Imido-osmium(VIII) compounds in organic synthesis: aminohydroxylation and diamination reactions. *Chem. Soc. Rev.* **2004**, *33*, 166–174.


δ− δ+
N—H
nucleophilic
"umpolung"
δ+ δ−
N—X
electrophilic
Cu
Fe
Ni
Rh
Co
Pd
N
H
hydroamination
N
B
aminoboration
N
C
carboamination

TOC Graphic