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Regio- and Enantioselective Synthesis of 1,2-Diamine Derivatives by Copper-Catalyzed Hydroamination

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Citation: Ichikawa, Saki et al., "Regio- and Enantioselective Synthesis of 1,2-Diamine Derivatives by Copper-Catalyzed Hydroamination." *Organic Letters* 21, 11 (June 2019): p. 4370–4373 doi. 10.1021/acs.orglett.9b01592 ©2019 Authors

As Published: <https://dx.doi.org/10.1021/ACS.ORGLETT.9B01592>

Publisher: American Chemical Society (ACS)

Persistent URL: <https://hdl.handle.net/1721.1/126008>

Version: Author's final manuscript: final author's manuscript post peer review, without publisher's formatting or copy editing

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Published in final edited form as:

Org Lett. 2019 June 07; 21(11): 4370–4373. doi:10.1021/acs.orglett.9b01592.

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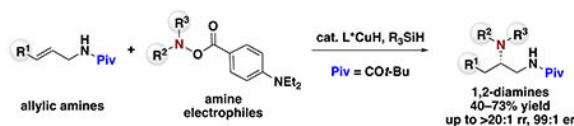
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Abstract

A highly regio- and enantioselective synthesis of 1,2-diamine derivatives from γ -substituted allylic pivalamides using copper-catalyzed hydroamination is reported. The *N*-pivaloyl group is essential, both in facilitating the hydrocupration step and suppressing an unproductive β -elimination from the alkylcopper intermediate. This approach enables an efficient construction of chiral differentially protected vicinal diamines under mild conditions with broad functional group tolerance.

Graphical Abstract



Chiral 1,2-diamines are common structural elements in pharmaceuticals, natural products, and chiral ligands.^[1] Due to their prevalence, a number of methods have been developed for their preparation (Figure 1a), including the addition of amines to aziridines,^[2] nucleophilic addition to α -aminoimines,^[3] Mannich^[4] and nitro-Mannich reactions,^[5] and alkene diamination.^[6] Although many approaches exist,^[7] each is associated with significant practical limitations. For example, aziridine-opening processes and nucleophilic addition to α -aminoimines require substrates containing preinstalled stereocenters. In Mannich and nitro-Mannich reactions, an electron-withdrawing group is necessary for stabilizing the carbanion generated in situ. Finally, alkene diamination often only allows for the introduction of identical amine groups; the regioselective addition of two different amines remains difficult.^[8]

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data, preparation of starting materials, copies of ¹H, ¹³C, and ¹⁹F NMR spectra for compounds, copies of GC and chiral SFC traces for the products (PDF)

The authors declare no competing financial interest.

We sought to develop a complementary method that would (1) easily differentiate the two amine groups in the products and (2) tolerate a broad range of functional groups. To fulfill these requirements, the asymmetric hydroamination^[9] of alkenes is an attractive strategy. Recently, Hull, Schultz, and coworkers reported the Rh-catalyzed hydroamination of allylamines. This pioneering work represented the first enantioselective variant of vicinal diamine synthesis by a metal-catalyzed hydroamination (Figure 1b).^[10] Although this process tolerated a wide variety of amine nucleophiles, the alkene partner was limited to those bearing an unsubstituted allyl group. We considered whether our recent work on CuH-catalyzed asymmetric hydroamination^[11] could be extended to provide a complementary method for the synthesis of chiral 1,2-diamines from allylic amines (Figure 1c). We note that while we were preparing this manuscript, a related method for synthesis of 1,2-diamines via the CuH-catalyzed hydroamination of enamines was reported by Yu and Somfai.^[12]

The mechanism proposed for the CuH-catalyzed hydroamination process is shown in Figure 2.^[13–15] First, the allylic amine undergoes hydrocupration to form a chiral alkylcopper species, **II**, which is then trapped by hydroxylamine benzoate, **IV**, to generate the corresponding chiral amine product, **V**, and copper(I) benzoate, **III**. The active catalyst, **I**, can be regenerated after σ -bond metathesis with a hydrosilane. A possible side reaction is the β -elimination of the amine group (i.e., NHPG) after hydrocupration (**II** \rightarrow **VI**, Figure 2), a process that would compete with the desired C–N bond forming process (**II** \rightarrow **V**).^[16] β -Elimination would produce the terminal alkene, **VI**, which could then undergo hydroamination to yield **VII** as a side product. In order to maximize the selectivity for the desired pathway (**II** + **IV** \rightarrow **III** + **V**, Figure 2) over the undesired β -elimination (**II** \rightarrow **VI**), we examined reactions of a series of γ -substituted allylic amines,^[17] differing in the protecting group on the allylic amine nitrogen.

We began our investigation using *N*-protected derivatives of (*E*)-hex-2-en-1-amine as the substrate (Scheme 1). In the presence of Cu(OAc)₂/(*R*)-DTBM-SEGPHOS/PPh₃ (a mixture known as CuCatMix*^[13a]), (MeO)₂MeSiH, and **2a** as the electrophilic amine source, the reactions of substrates bearing *t*-butoxycarbonyl (Boc, entry 1), tosyl (entry 2), and *p*-methoxy benzyl (PMB, entry 3) groups afforded neither the desired product **3** nor the side product **4**. The low reactivity of these substrates is consistent with the previous experimental^[13, 14] and computational studies,^[15] showing that hydrocupration is typically challenging for internal alkenes. When the protecting group was switched to an acetyl group (Ac, entry 4), no desired product was seen, but the formation of moderate amount of side product **4** was observed (41%). This indicated that through the use of an appropriate *N*-protecting group, hydrocupration of the alkene could take place. Encouraged by this result, we investigated the use of related protecting groups including isobutyryl (entry 5) and pivaloyl (entry 6) groups. In the case of the *N*-pivaloyl^[18] substrate, we obtained the desired 1,2-diamine product in 82% yield with a high level of enantioselectivity (entry 6).

We next explored the substrate scope of this asymmetric hydroamination process (Scheme 2). Allylic amines bearing primary (**3a**), secondary (**3b** and **3c**), and tertiary alkyl substituents (**3d**) on the γ -carbon afforded the corresponding products in good to moderate yields with excellent levels of regio- and enantioselectivity. In addition, a benzothiazole-containing product (**3e**) could be prepared using this protocol. The relatively lower

regioisomeric ratio of **3e** (3:1 rr), compared to the other examples, reflects more facile formation of the minor regioisomer during hydrocupration. This is possibly due to the coordination of the sp² nitrogen of the benzothiazole to L*CuH.

We also investigated the scope of the reaction with respect to the amine electrophile component (Scheme 3). Amine electrophiles bearing a variety of heterocycles, including pyrimidine (**4b**), carbazole (**4c**), pyridine (**4d**), and pyrazole (**4e**) were all compatible substrates. Other functional groups such as a thioether (**4f**) and an acetal (**4g**) were also accommodated under the reaction conditions.

To evaluate the scalability and practicality of this method, we performed a gram-scale reaction using (*E*)-*N*-(hex-2-en-1-yl)pivalamide (Scheme 4). We obtained 1.32 g of the desired vicinal diamine product with high levels of both regio- and enantioselectivity (64% yield, 10:1 rr, and 98:2 er).

In conclusion, we have developed a method for the copper-catalyzed hydroamination of γ -substituted allylic amines for the synthesis of enantioenriched 1,2-diamines. Two major challenges in this transformation were (1) slow hydrocupration of γ -substituted allylic amines and (2) unproductive β -elimination after the hydrocupration. By utilizing a pivaloyl protecting group for the allylic amine nitrogen, the asymmetric hydroamination proceeded with high levels of regio- and enantioselectivity. Various functional groups, including heterocycles, were well tolerated in this protocol. Finally, a gram-scale reaction was conducted to demonstrate the scalability and practicality of this method.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

Research reported in this publication was supported by the National Institutes of Health (R01-GM58160 and R35-GM122483). The authors further thank the NIH for a supplemental grant for a supercritical fluid chromatography instrument (SFC) under grant GM58160-17S1. The content of this publication is solely the responsibility of the authors and does not claim to represent the official views of the National Institutes of Health. S.I. thanks the Japan Student Services Organization (JASSO) for a graduate fellowship. X.-J.D. thanks the Canadian National Science and Engineering Research Council (NSERC) for a postdoctoral fellowship. We are grateful to Dr. Christine Nguyen (MIT), Dr. Scott McCann (MIT), Dr. Andy Thomas (MIT), and Richard Liu (MIT) for their advice on the preparation of this manuscript.

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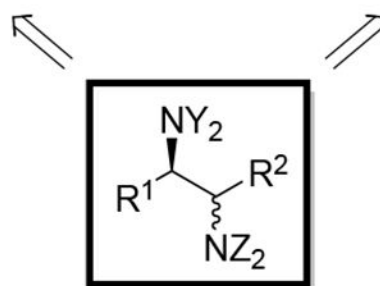
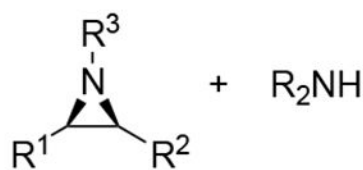
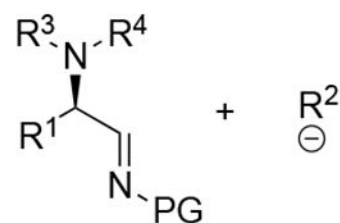
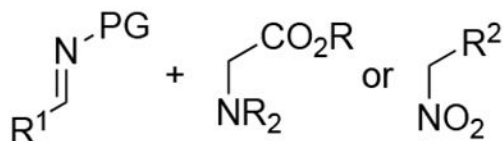
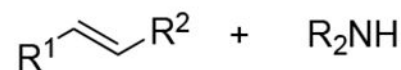
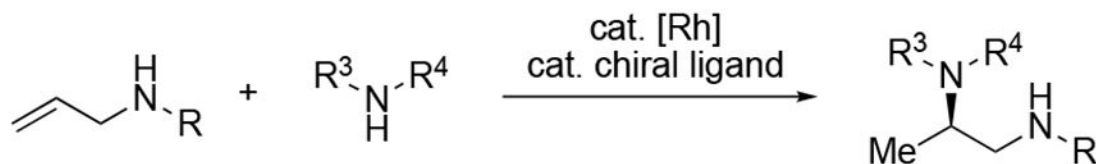
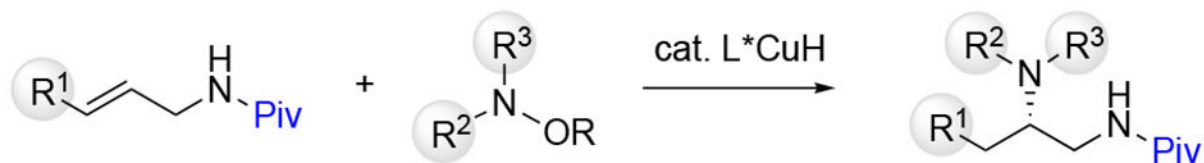
(a) Synthetic methods to access chiral 1,2-diaminesAsymmetric aziridine openingNucleophilic addition into α -aminoiminesMannich & nitro-MannichAlkene diamination**(b) Traditional hydroamination for the synthesis of chiral 1,2-diamines (Hull)****(c) This work: CuH-catalyzed asymmetric hydroamination**

Figure 1.
Strategies for the Asymmetric Synthesis of 1,2-Diamine Derivatives.

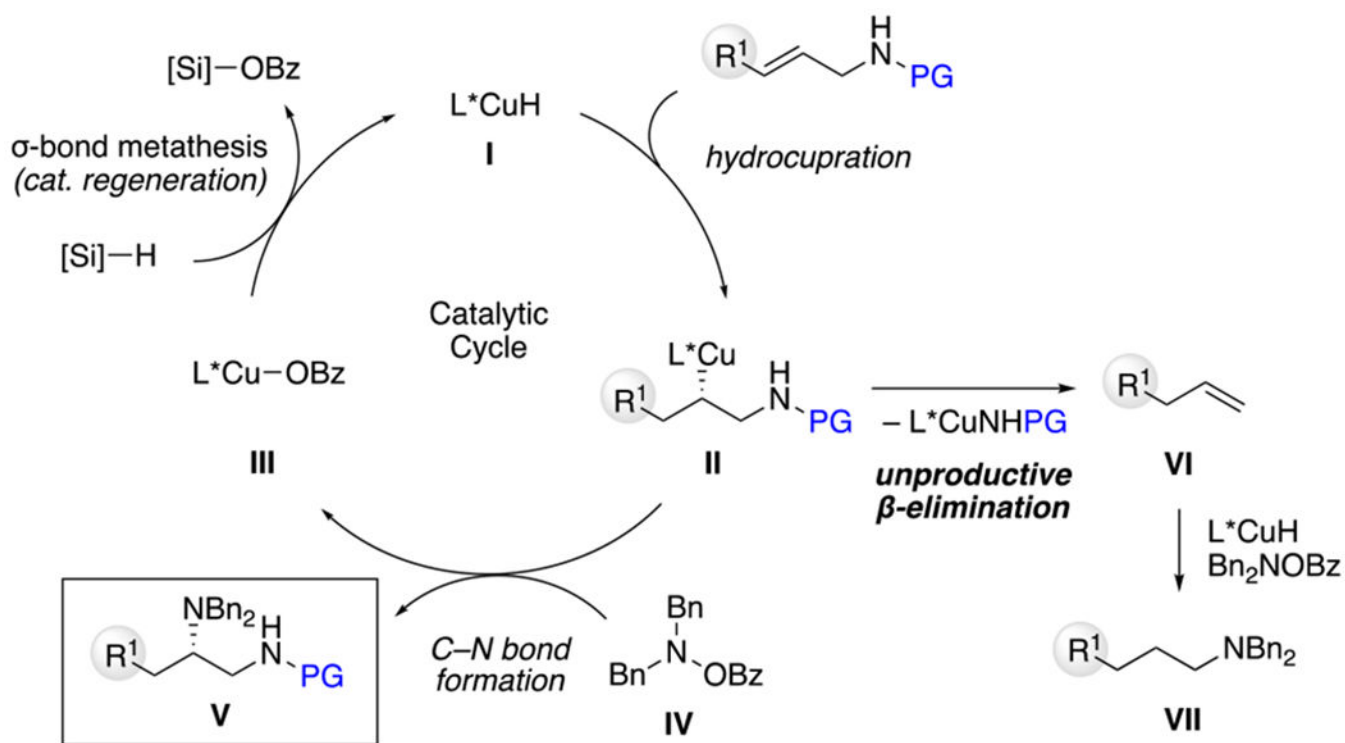
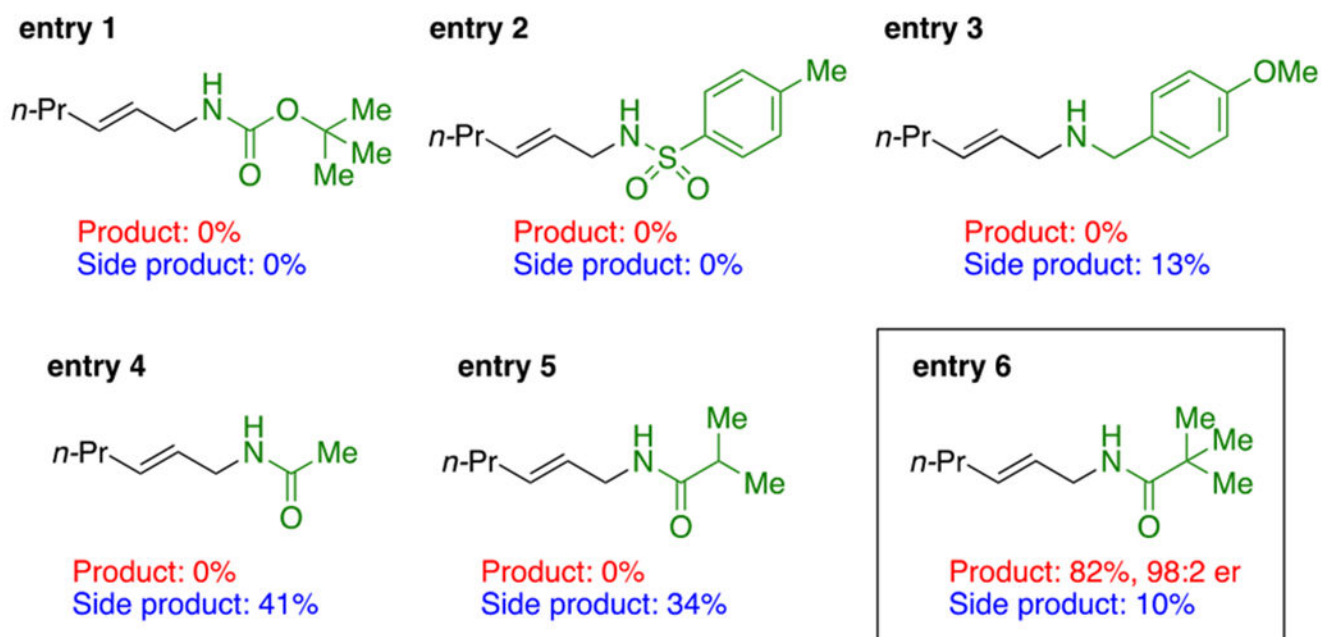
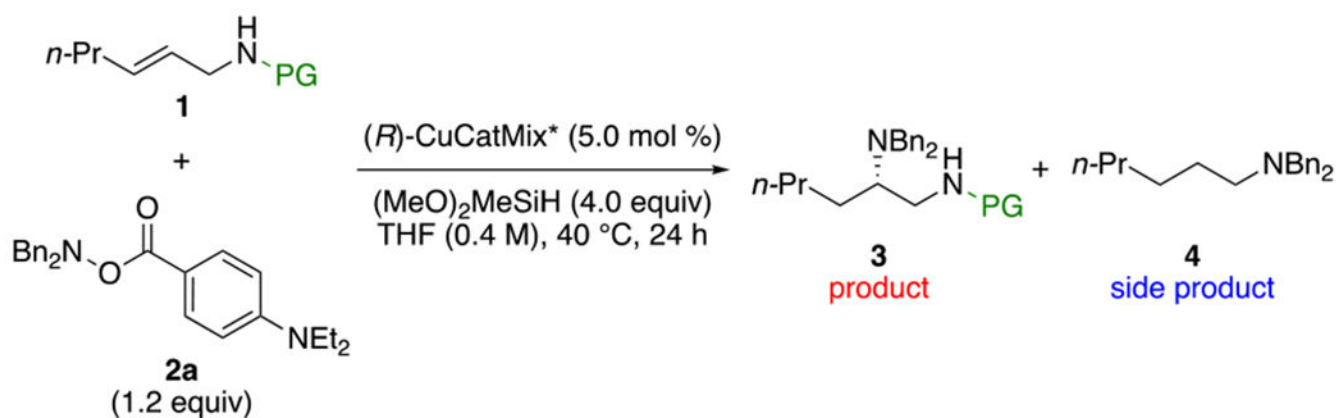
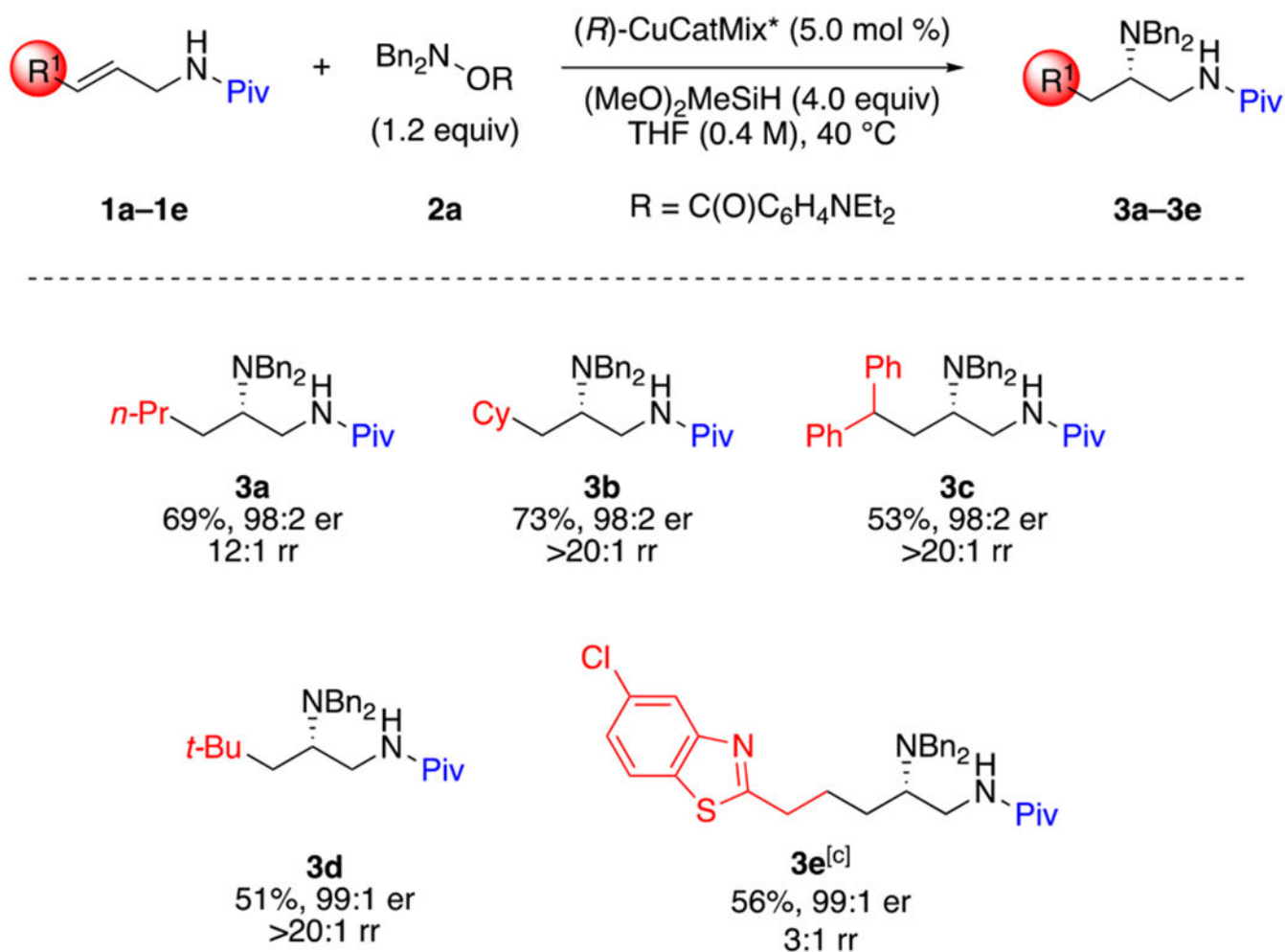


Figure 2. Possible Catalytic Cycle and Unproductive β -Elimination. R¹ = alkyl groups.

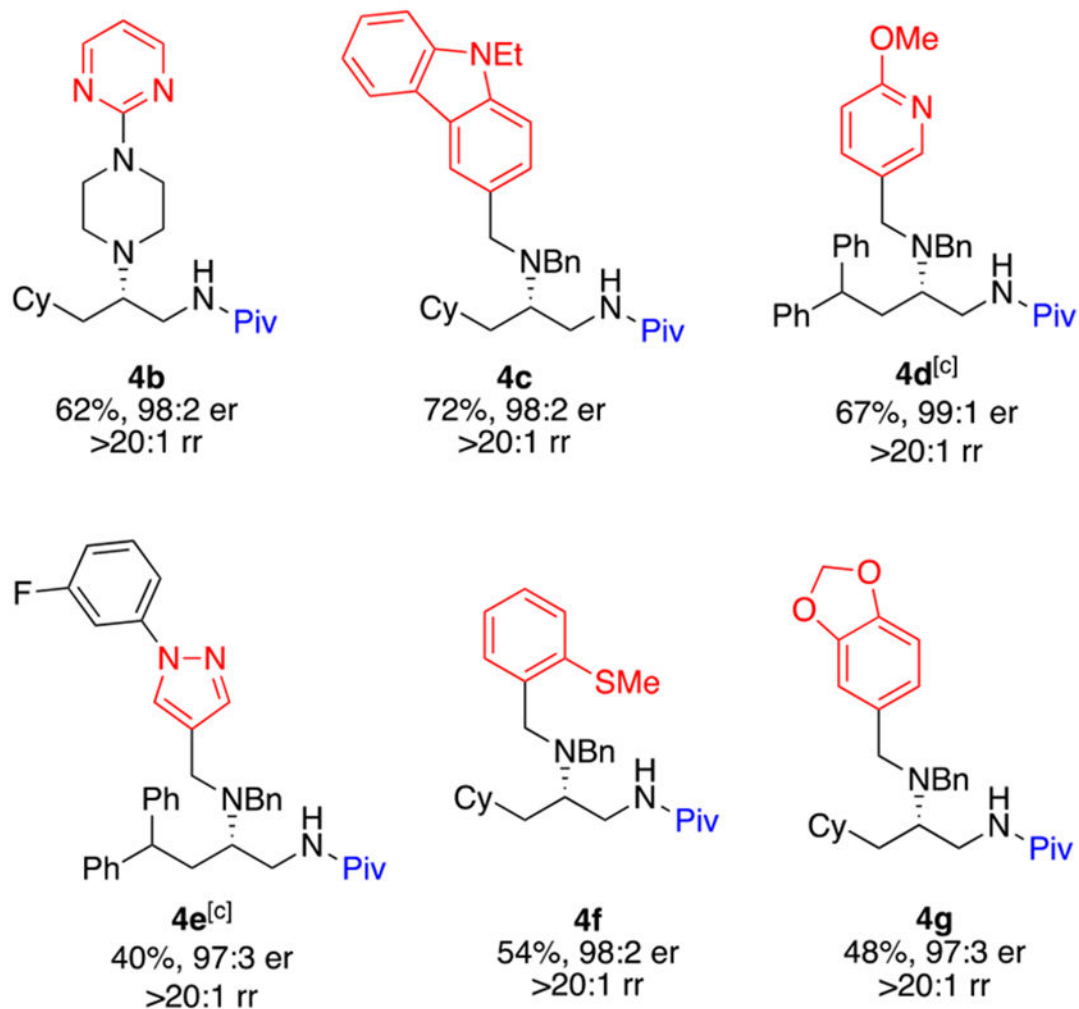
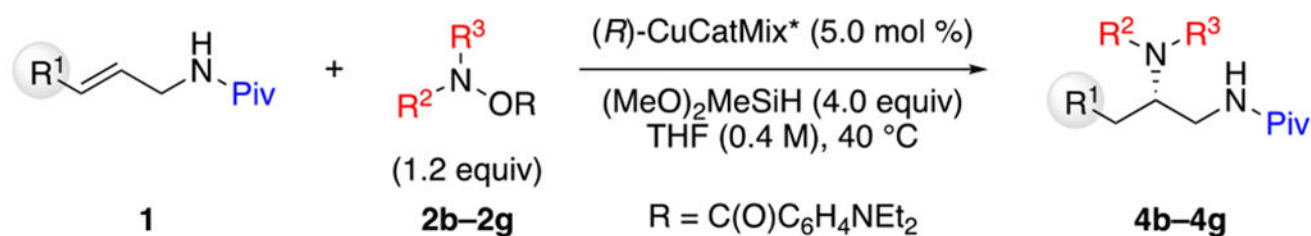
**Scheme 1.**

Protecting Group Screening to Facilitate Hydrocupration and Suppress β -Elimination.^[a, b, c]

[a] Reaction conditions: 0.1 mmol **1** (1.0 equiv), **2a** (1.2 equiv), (*R*)-CuCatMix* (Cu(OAc)₂/*R*-DTBM-SEGPHOS/PPh₃ = 1/1.1/1.1, 5.0 mol % [Cu]), (MeO)₂MeSiH (4.0 equiv) in THF (0.25 mL, 0.4 M) at 40 °C; see the Supporting Information for details. [b] The yield was determined by ¹H NMR spectroscopy of the crude reaction mixture, using 1,1,2,2-tetrachloroethane as an internal standard. [c] The enantiomeric ratio was determined by chiral SFC analysis on commercial chiral columns.

**Scheme 2.**Scope of γ -Substituted Allylic Amines.^[a, b, c]

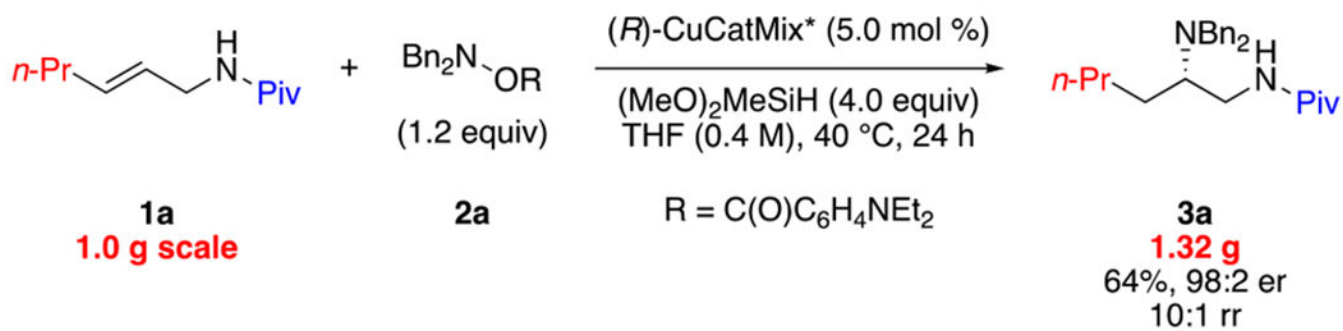
[a] Reaction conditions: 0.5 mmol **1a–1e** (1.0 equiv), **2a** (1.2 equiv), (*R*)-CuCatMix* (Cu(OAc)₂/*R*-DTBM-SEGPHOS/PPh₃ = 1/1.1/1.1, 5.0 mol % [Cu]), (MeO)₂MeSiH (4.0 equiv) in THF (1.25 mL, 0.4 M) at 40 °C; see the Supporting Information for details. [b] The regioisomeric ratio of **3a** was determined by GC analysis of the crude reaction mixture, using *n*-dodecane as an internal standard. The regioisomeric ratios of **3b–3e** were determined by ¹H NMR spectroscopy of the crude reaction mixture, using 1,1,2,2-tetrachloroethane as an internal standard. [c] 10 mol % of (*R*)-CuCatMix* was used.



Scheme 3.

Scope of Amine Electrophiles.^[a, b, c]

[a] Reaction conditions: 0.5 mmol **1** (1.0 equiv), **2b–2g** (1.2 equiv), (*R*)-CuCatMix* (Cu(OAc)₂/*R*-DTBM-SEGPHOS/PPh₃ = 1/1.1/1.1, 5.0 mol % [Cu]), (MeO)₂MeSiH (4.0 equiv) in THF (1.25 mL, 0.4 M) at 40 °C; see the Supporting Information for details. [b] The regioisomeric ratio was determined by ¹H NMR spectroscopy of the crude mixture, using 1,1,2,2-tetrachloroethane as an internal standard. [c] 10 mol % of (*R*)-CuCatMix* was used.



Scheme 4.
Gram-Scale Reaction.