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COMMUNICATION

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Copper-Catalyzed Asymmetric Formal Hydroaminomethylation of Alkenes with N,O-Acetals to Access Chiral β-Stereogenic Amines: Dual Functions of the Copper Catalyst

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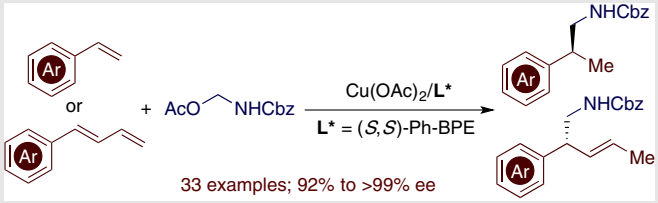
Chiral amines are synthetically versatile intermediates used for the preparation of a wide range of biologically active compounds and drugs. Compared with the well-developed synthesis of α-stereogenic amines, the establishment of enantioselective protocols to access β-stereogenic amines are very limited. Herein, we report an asymmetric synthesis of β-stereogenic amines through copper-catalyzed enantioselective formal aminomethylation of alkenes with N,O-acetals of formaldehyde. We carried out series of reactions using a variety of vinylarenes and 1,3-dienes with N,O-acetals of formaldehyde to generate the corresponding chiral β-branched alkylamines and (*E*)-homoallylamines in high yields, and with excellent enantioselectivity. The copper catalyst promoted not only the formation of alkylcopper nucleophiles from alkenes but also the generation of methylene imine electrophiles from N,O-acetals of formaldehyde. Our experimental design provides an attractive approach for the synthesis of chiral β-stereogenic amines from readily available alkenes and N,O-acetals with a base-metal catalyst under mild conditions.



Keywords: alkene, aminomethylation, asymmetric catalysis, N,O-acetal, amine, copper

Introduction

β-Stereogenic chiral amines are privileged structures found in a variety of bioactive and pharmaceutically relevant molecules and drugs (Figure 1).[1–8] Among numerous methods used to prepare chiral amines, the majority has focused on the synthesis of α-stereogenic amines,[9–11] while attempts to prepare chiral β-stereogenic amines are rather limited.[12–19] Asymmetric hydroamination of 1,1-disubstituted alkenes is an atom-economic approach to synthesize β-stereogenic amines, but the enantioselectivity of this reaction largely depends on the steric difference between two substituents on alkenes.[14,17] Catalytic hydroformylation of alkenes with H_2/CO, followed by enantioselective reductive amination of aldehydes with amines,[13] also yields β-stereogenic amines.[18] However, this sequential reaction requires toxic CO gas and noble metal catalysts. Therefore, developing a practical enantioselective protocol, which could combine high enantioselectivity, base-metal catalysts, and easily

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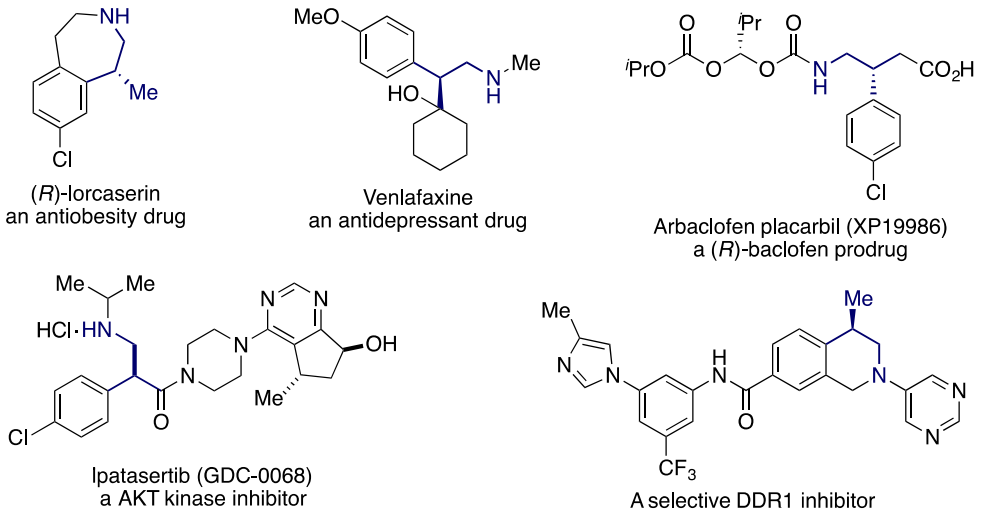

Figure 1 | *Examples of drugs and biologically active compounds containing a β-stereogenic amine moiety.*

accessible starting materials to prepare chiral β-stereogenic amines remains a challenge.

Recently, chiral Cu–H complexes have been emerging as catalysts to convert alkenes to chiral amines via C–N or C–C bond-forming reactions.[20–36] For example, chiral alkylcopper species, formed from alkenes, could react with ketimines and aldimines, derived from ketones or aryl-substituted aldehydes to yield chiral amines containing α,β-stereogenic carbons.[37–39] Due to their high reactivity toward polymerization and oligomerization, methylene imines have not been isolated in pure forms. Therefore, the reactions of chiral organometallic nucleophiles with formaldehyde imines, which could afford synthetically versatile amines bearing only β-stereogenic centers, have not been studied. Very recently, Yu reported a Cu-catalyzed synthesis of β-stereogenic primary alcohols from alkenes[40] and utilization of CO_2 as a C1 building block as a key measure in achieving this transformation. In view of the synthetic importance of β-stereogenic amines, we took an interest to develop an enantioselective protocol for the synthesis of these β-stereogenic amines from alkenes. To study this asymmetric reaction, we rationalized that identifying a suitable N-containing C1 building block would be a critical step.

N,O-Acetals of formaldehyde are readily accessible via the reactions between paraformaldehyde and carbamates in the presence of acetic anhydride and acetic acid.[41] Recently, Luo and co-workers[42] used these N,O-acetals as C1 imine surrogates in Mannich reaction to prepare chiral β-amino carbonyl compounds. However, their applications as methylene imine surrogates in transition-metal-catalyzed C–C bond-forming reactions remain largely unexplored. During our efforts, in search to develop Cu-catalyzed hydrofunctionalization of olefins,[43–45] we found that copper catalysts could promote the conversion of these N,O-acetals to carbamate methylene imines. Herein, we report the reactions between these in-situ-generated carbamate methylene imines and chiral alkylcopper species derived from vinylarenes and 1,3-dienes, which supported a practical and novel highly enantioselective approach to access synthetically versatile chiral β-stereogenic amines from readily available olefinic substrates.

Experimental Method

In an argon (Ar)-filled dry box, cupric acetate [$Cu(OAc)_2$] (1.8 mg, 10.0 μmol), (+)-1,2-Bis((2S,5S)-2,5-diphenylphospholano)ethane [(*S,S*)-Ph-BPE] (6.1 mg, 12.0 μmol), vinylarene (0.200 mmol), N,O-acetal (0.400 mmol), CH_3CN (0.2 mL), and ^{t}BuOH (29.6 mg, 0.400 mmol) were added to a 4 mL screw-capped vial and stirred with a magnetic stirring bar for 10 min, followed by addition of dimethoxymethyl silane [$(MeO)_2MeSiH$] (106 mg, 1.00 mmol). Then, the vial was sealed with a cap containing a polytetrafluoroethylene (PTFE) septum and removed from the dry box, after which the reaction mixture was stirred at room temperature (RT) for 12 h, and the resultant solution was concentrated in vacuum. Subsequently, the crude product was purified by column chromatography on silica gel with a mixture of ethyl acetate (EtOAc) and hexane (1:9) as eluent. The enantiopurity of the purified products was analyzed by chiral high-performance liquid chromatography (HPLC). See the Supporting Information for more detailed experimental procedures and the characterization data of all the products.

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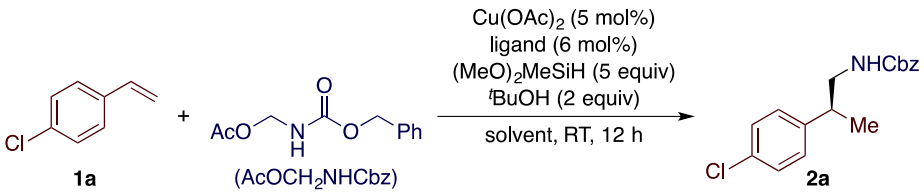
Results and Discussion

We initiated our studies by identifying selective copper catalysts and optimal conditions for the reaction between 4-chlorostyrene (**1a**) and methyl 2-(acetylamino)benzoate ($AcOCH_2NHCbz$), which is an N,O-acetal derived from formaldehyde. Copper catalysts, generated in situ by the combination of $Cu(OAc)_2$ and various bisphosphine ligands were employed in the reaction to test their effectiveness. The results from selected experiments are summarized in Scheme 1. In general, these reactions were conducted in acetonitrile (CH_3CN) at RT with **1a** as a limiting reagent, $(MeO)_2MeSiH$ was used as a hydride source and *tert*-butanol [$(CH_3)_3C$-OH] as a proton source in the presence of 5 mol % copper catalyst. We identified β-stereogenic amine **2a** as the major product for these reactions, by our established optimal reaction conditions indicated below:

Reaction conditions: **1a** (0.100 mmol), $AcOCH_2NHCbz$ (0.150 mmol), $(MeO)_2MeSiH$ (0.500 mmol), $Cu(OAc)_2$ (5.0 μmol), bisphosphine ligand (6.0 μmol), solvent (0.2 mL), RT, 12 h; [a]Isolated yields; [b]ee was determined by chiral HPLC analysis; [c]**1a** (0.200 mmol) and $AcOCH_2NHCbz$ (0.100 mmol) were employed; [d]$AcOCH_2NHCbz$ (0.200 mmol); $(MeO)_2MeSiH$ was added after all other reagents were stirred in acetonitrile (CH_3CN) at RT for 10 min.

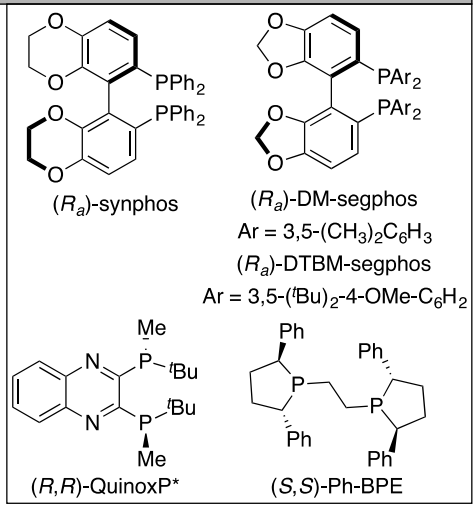
Our results showed that (1) the copper catalysts generated from $Cu(OAc)_2$ and (R_a)-synphos, and (R_a)-DM-segphos were marginally active for this reaction (entries 1 and 2, Scheme 1). (2) The reactions catalyzed by the combination of $Cu(OAc)_2$ and (R_a)-DTBM-segphos or (*R*,*R*)-QuinoxP* occurred at low conversions of **1a**, and the desired product **2a** was obtained in low yields with modest enantioselectivity (entries 3 and 4 in Scheme 1). (3) To our delight, the reaction conducted with 5 mol % of $Cu(OAc)_2$ and 6 mol % (*S*,*S*)-Ph-BPE proceeded with high conversion of **1a**, affording amine **2a** in modest isolated yield, but with excellent enantioselectivity (97% ee, entry 5, Scheme 1).

Subsequently, we tested this catalytic reaction in various solvents, such as cyclohexane, toluene, and tetrahydrofuran (THF). Nonetheless, these reactions proceeded with low conversions of **1a**, with very low isolated yields (<5% to 21%) of **2a** (entries 6–8, Scheme 1). In addition, when we performed the reaction with $AcOCH_2NHCbz$, as a limiting reagent, we found that the process occurred with a higher yield (72%), but with a slightly diminished enantioselectivity (92% ee; entry 9, Scheme 1). Thus to further improve the reaction conditions, we conducted the experiment by stirring $Cu(OAc)_2$, the ligand, **1a**, N,O-acetal, and ^{t}BuOH for 10 min to allow ligand coordination, prior to the addition of $(MeO)_2MeSiH$. This reaction proceeded with a full conversion of **1a** to **2a**, obtaining



1a (AcOCH$_2$NHCbz) **2a**

Entry	Ligand	Solvent	Yield (%)[a]	ee (%)[b]
1	(R_a)-synphos	CH_3CN	<5	--
2	(R_a)-DM-segphos	CH_3CN	<5	--
3	(R_a)-DTBM-segphos	CH_3CN	17	54
4	(*R*,*R*)-QuinoxP*	CH_3CN	32	78
5	(*S*,*S*)-Ph-BPE	CH_3CN	59	97
6	(*S*,*S*)-Ph-BPE	toluene	<5	--
7	(*S*,*S*)-Ph-BPE	cyclohexane	11	--
8	(*S*,*S*)-Ph-BPE	THF	21	--
9[c]	(*S*,*S*)-Ph-BPE	CH_3CN	72	92
10[d]	(*S*,*S*)-Ph-BPE	CH_3CN	78	97



Scheme 1 | *Evaluation of optimal conditions for formal aminomethylation of **1a**.*

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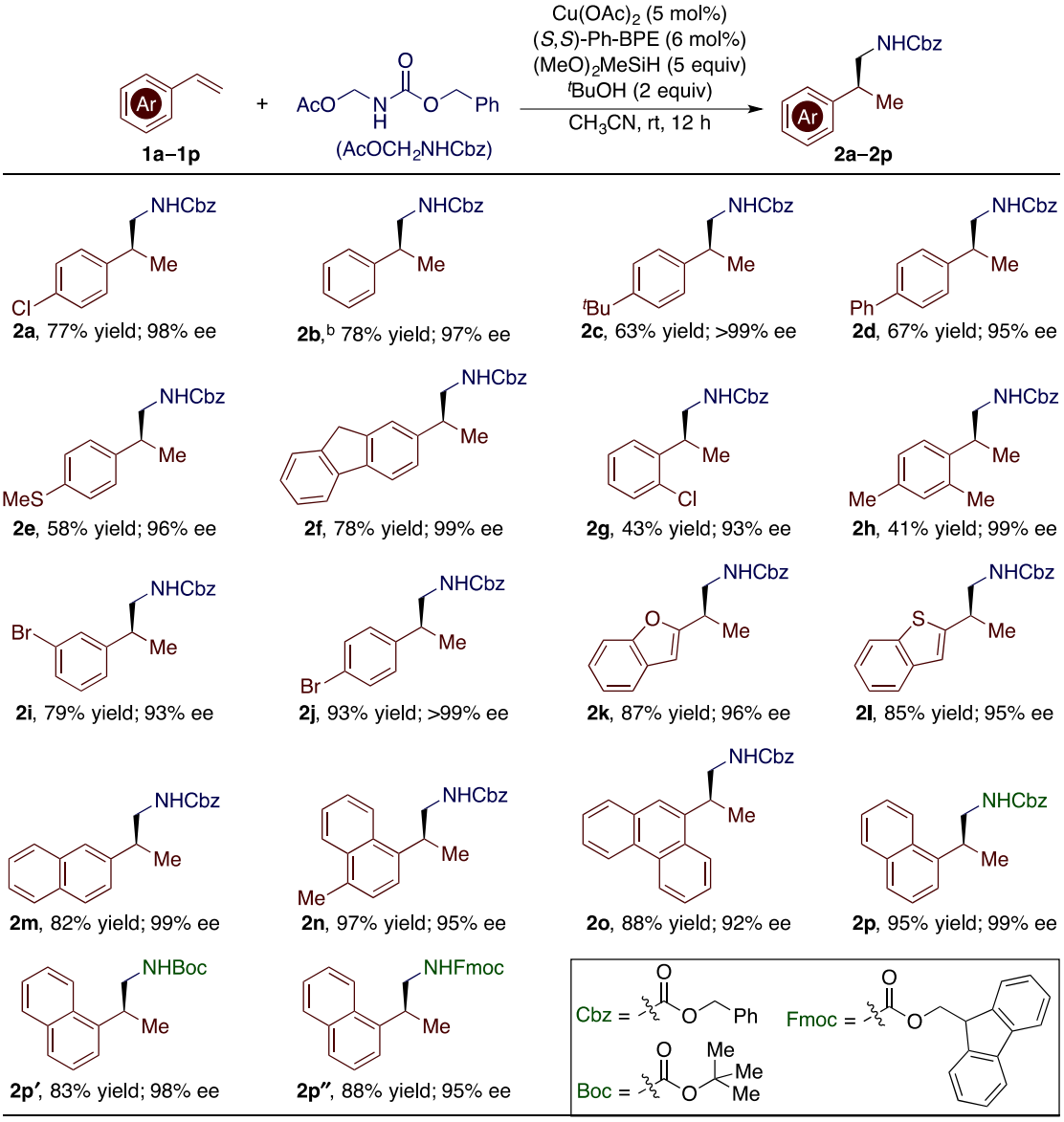
a 79% yield with excellent enantioselectivity (97%; entry 10, Scheme 1).

With the identified copper catalyst and optimal conditions in hand, we studied the scope of vinylarenes that undergo this Cu-catalyzed asymmetric transformation. The results of these reactions are summarized in Scheme 2. In general, we observed that a wide range of vinylarenes containing various substituted phenyl groups (**1c**–**1j**) or polyaromatic groups (**1m**–**1p**) reacted with $AcOCH_2NHCbz$ readily in the presence of 5 mol % $Cu(OAc)_2$ and 6 mol % (*S,S*)-Ph-BPE at RT, yielding the corresponding enantioenriched-β-stereogenic amines (**2a**–**2p**) in moderate to high yields (55–97%) with high enantioselectivities (92% to >99% ee). Noticeably, vinylarenes containing *ortho*-substituted aryl groups (**1g** and **1h**) reacted to give amine products **2g** and **2h** in relatively lower yields (41–43%), but with high enantioselectivity (93–99% ee). These low yields occurred, possibly due to the incomplete conversions of vinylarenes **1g** and **1h** as we were able to recover the unreacted substrates. Besides, Boc- and Fmoc-protected N,O-acetals reacted with **1p** under our standard conditions, affording the desired amines **2p′** and **2p″** in high yields (95% and 83%) with excellent enantioselectivity (99% and 98%), respectively (Scheme 2).

(1) Reaction conditions with lower N,O-acetal derivative but higher ^{t}BuOH concentrations: Vinylarene (0.200 mmol), $AcOCH_2NHR$ (0.400 mmol), $(MeO)_2MeSiH$ (1.00 mmol), ^{t}BuOH (0.400 mmol), $Cu(OAc)_2$ (10.0 μmol), (*S,S*)-Ph-BPE (12.0 μmol), CH_3CN (0.2 mL),



Scheme 2 | *Scope of vinylarenes for the Cu-catalyzed formal aminomethylation.*

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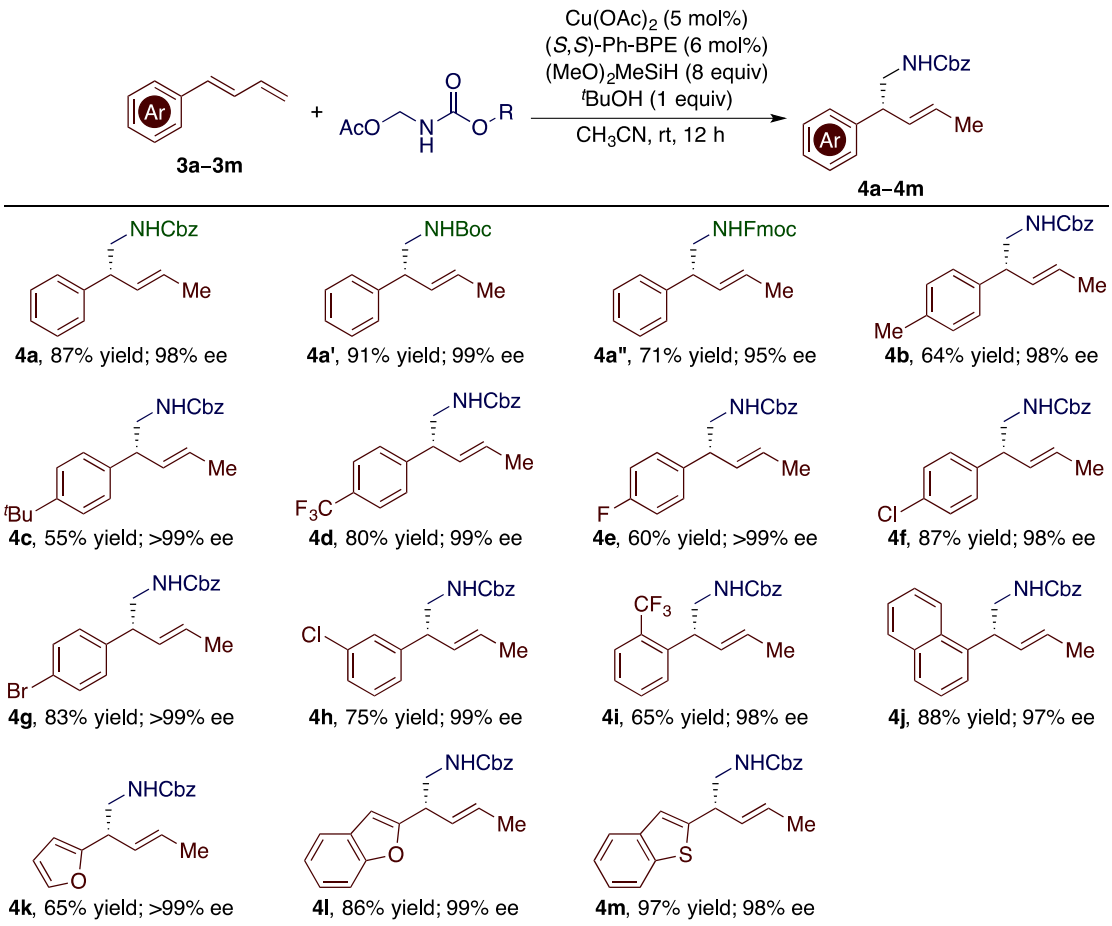
RT, 12 h, yields of isolated products; ee was determined by chiral HPLC analysis. [b]The absolute configuration of 2b was assigned as (*S*), see the Supporting Information for the details.

(2) Reaction conditions with higher N,O-acetal derivative but lower ^{t}BuOH concentrations: Vinylarene (0.200 mmol), $AcOCH_2NHR$ (0.400 mmol), $(MeO)_2MeSiH$ (1.60 mmol), ^{t}BuOH (0.200 mmol), $Cu(OAc)_2$ (10.0 μmol), (*S,S*)-Ph-BPE (12.0 μmol), CH_3CN (0.2 mL), RT, 12 h, yields of isolated products; ee was determined by chiral HPLC analysis.

Subsequently, we tested 1,3-dienes for this Cu-catalyzed asymmetric reaction. Different from vinylarenes, the presence of two double bonds in 1,3-dienes poses additional challenges to the study of formal hydroaminomethylation of 1,3-dienes, such as the control over 1,2-/1,4-regioselectivity and *Z*-/*E*-stereochemistry of the remaining double bond. After modifying reaction conditions (entry 10 in Scheme 1) with 8-gram, instead of 5-gram equivalent of $(MeO)_2MeSiH$, we found that aryl-substituted 1,3-dienes reacted with N,O-acetals to yield chiral homoallylic amines with excellent 1,4-regioselectivity, *E*-selectivity, and enantioselectivity. Scheme 3 summarizes the scope of 1,3-dienes that undergo this Cu-catalyzed formal hydroaminomethylation reaction. Typically, a variety of 1,3-dienes containing electronically varied aryl groups reacted to afford the corresponding (*E*)-homoallylic amines (**4a**–**4m**) in high isolated yields with high enantioselectivity (95% to >99% ee). Our standardized reaction tolerated various aryl groups with substituents at *para* (**4b**–**4g**), *meta* (**4h**), and *ortho* (**4i** and **4j**) positions, as well as oxygen- and sulfur-containing heteroaryl groups (**4k**–**4m**). The absolute configuration of **4b**′ was assigned as (*R*) by comparison of optical rotation with a reported value.[46]

The formal hydroaminomethylation reactions of vinylarene **1p** and 1,3-diene **3a** with $AcOCH_2NHCbz$ were run on a gram scale with 1–2 mol % of $Cu(OAc)_2$/(*S,S*)-Ph-BPE, which occurred in good yields with excellent enantioselectivity (Scheme 4a,b). Thus these reactions could also be conducted on a scale that allows practical applications in synthesis. We also showed that the Cbz, Boc, and Fmoc groups in **2a**, **2p**′, and **2p**″ could be readily removed under neutral, acidic, and basic conditions,[47–53]



Scheme 3 | *Scope of 1,3-dienes for the Cu-catalyzed formal aminomethylation.*

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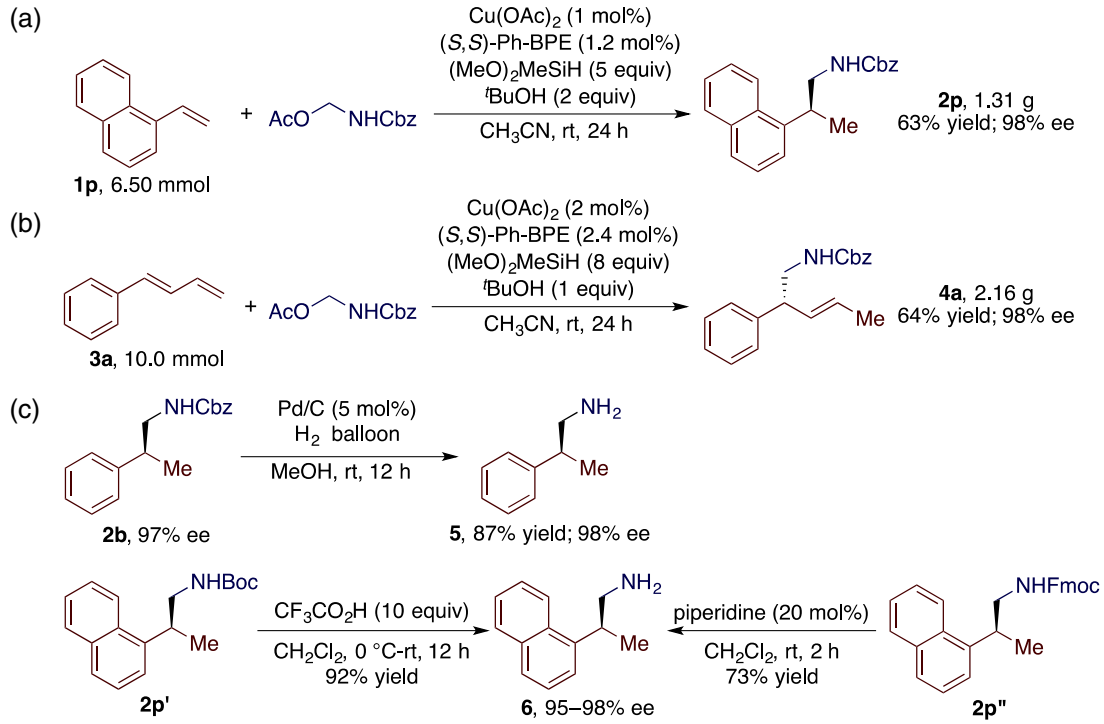

Scheme 4 | *Gram-scale reactions and deprotection of carbamates to access β-stereogenic primary amines.*

respectively, yielding β-stereogenic primary amines **5** and **6** in high yields (87% and 92%), while maintaining excellent enantiopurity (95% and 98% ee), respectively (Scheme 4c).

Further, we conducted several experiments to elucidate the mechanism of this Cu-catalyzed reaction (Scheme 5). First, we showed that the *N*-Cbz methylene imine **6** was generated from $AcOCH_2NHCbz$ in the presence of the copper catalyst, as indicated by gas chromatography–mass spectrometry (GC-MS) and high-resolution mass spectrometry (HRMS) analysis (Scheme 5a). Second, we demonstrated that in contrast to copper catalyst reaction, the corresponding reaction in the absence of the copper catalyst failed to yield the imine **6**. Indeed, our results are consistent with previous studies which showed that N,O-acetals of formaldehyde could form imines in the presence of Lewis acids.[41] Third, our study revealed that formal hydroaminomethylation of vinylarene **1p** in the presence of biphenylhydrosilane (Ph_2SiD_2), instead of $(MeO)_2MeSiH$ yielded the chiral amine **2p**-d_1 in 51% yield with 98% ee, and the deuterium label localized in the methyl group of **2p** (Scheme 5b). Similarly, deuterium incorporation was observed for **4a**-d_1 when the reaction of 1,3-diene **3a** was run with Ph_2SiD_2 (Scheme 5c).

Based on the results of the aforementioned experiments on imine detection, deuterium labeling, and previous studies on Cu–H-catalyzed reactions of alkenes,[23] we proposed a plausible catalytic cycle for this Cu-catalyzed hydroaminomethylation of alkenes (Scheme 5d), as follows: Activation of $Cu(OAc)_2$ with hydrosilane in the presence of (*S,S*)-Ph-BPE (**L***) generates a chiral Cu–H species, (**L***)Cu–H. Insertion of alkenes into (**L***)Cu–H, in turn, formed chiral alkylcopper species **A**.[54] Intermediate **A** reacted with the *N*-Cbz imine **6**, generated in situ from N,O-acetal, in the presence of a copper catalyst, to produce an amido-copper complex **B**. Consequently, **B** was protonated by ^{t}BuOH to yield the chiral β-stereogenic amine product **2** and copper *tert*-butoxide (**L***)CuO^tBu, which was reacted with hydrosilane to regenerate the catalytically active Cu–H species, (**L***)Cu–H.

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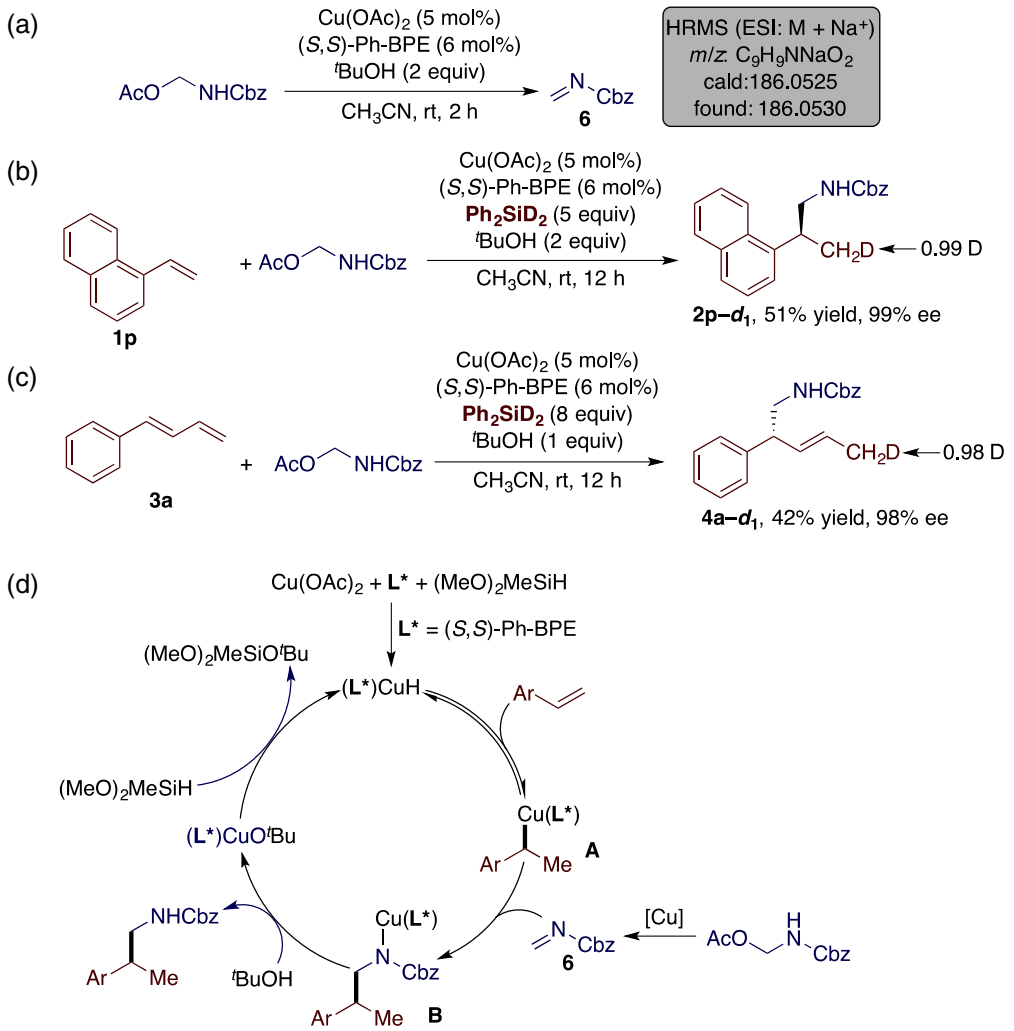

Scheme 5 | *Deuterium-labeling experiments and the proposed catalytic pathway for the Cu–H-catalyzed hydroaminomethylation of alkenes.*

Conclusion

We have developed an effective and highly enantioselective protocol for the synthesis of chiral β-stereogenic amines through Cu-catalyzed asymmetric formal hydroaminomethylation of alkenes with N,O-acetals. A wide range of vinylarenes and 1,3-dienes reacted with N,O-acetals of formaldehyde to afford the corresponding alkylamines and homoallylic amines in high yields with excellent enantioselectivity in the presence of a chiral copper catalyst generated in situ from $Cu(OAc)_2$ and (*S,S*)-Ph-BPE ligand. Mechanistic studies revealed dual functions of the copper catalyst, involving the formations of both the chiral alkylcopper nucleophile from alkenes and the *N*-Cbz imine electrophile from N,O-acetals of formaldehyde. Further studies to determine the detailed mechanism of this transformation and to expand the scope of this aminoalkylation reaction is the focus of future work in our laboratory.

Supporting Information

Supplemental Information is available online.

Conflict of Interest

There is no conflict of interest to report.

Acknowledgment

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