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Enantioselective CuH-Catalyzed Anti-Markovnikov Hydroamination of 1,1-Disubstituted Alkenes

Shaolin Zhu and Stephen L. Buchwald*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States

Ⓢ *Supporting Information*

ABSTRACT: Enantioselective synthesis of β-chiral amines has been achieved via copper-catalyzed hydroamination of 1,1-disubstituted alkenes with hydroxylamine esters in the presence of a hydrosilane. This mild process affords a range of structurally diverse β-chiral amines, including β-deuterated amines, in excellent yields with high enantioselectivities. Furthermore, catalyst loading as low as 0.4 mol% could be employed to deliver product in undiminished yield and selectivity, demonstrating the practicality of this method for large-scale synthesis.

As a privileged structural subclass, β-chiral amines are found in a broad range of bioactive molecules, including a number of widely employed medicinal agents (Figure 1A).[1] Although several strategies have been devised to access β-chiral amines in an enantioselective manner,[2] catalytic hydroamination constitutes a potentially powerful yet unexplored direct approach for their construction.[3] In particular, we recognized that if asymmetric anti-Markovnikov hydroamination could be achieved, enantioenriched β-chiral amines would be directly accessible from readily available 1,1-disubstituted alkenes (Figure 1B).

The ability to access β-chiral amines through catalytic hydroamination would offer increased flexibility and generality compared to existing approaches for their preparation. To date, there are only a handful of reports describing the enantioselective hydroamination of unactivated olefins,[4] and although several transition-metal-mediated[5] and metal-free[6] approaches have recently been reported for anti-Markovnikov hydroamination, an enantioselective process remains elusive.

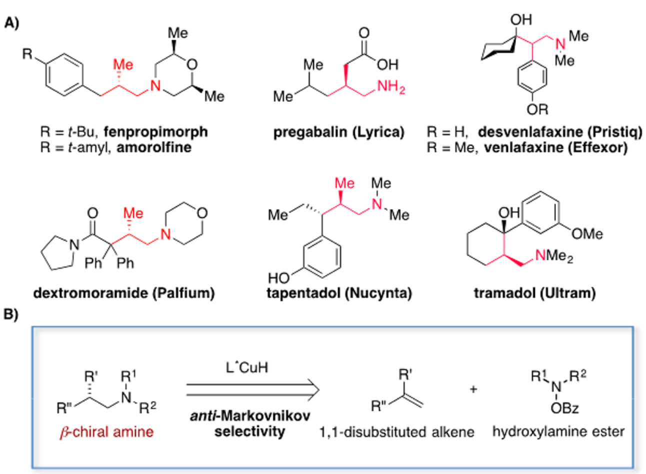

Figure 1. (A) Representative β-chiral amines. (B) Hydroamination strategy for their preparation.

Recently, we reported a catalytic protocol for the hydroamination of styrene derivatives and monosubstituted alkenes initiated by the hydrocupration of olefin double bonds.[7] Interception of the thus-generated alkylcopper species by a hydroxylamine ester furnished the formal hydroamination product.[8] The copper hydride species was regenerated *in situ* by a stoichiometric amount of a hydrosilane to achieve a net catalytic hydroamination reaction. We wondered whether this process could be extended to 1,1-disubstituted alkene substrates to produce β-chiral amines in an enantioselective manner (Figure 2). We anticipated that hydroamination of 1,1-disubstituted olefins would proceed with exclusive anti-Markovnikov regioselectivity, in analogy to the regioselectivity previously observed for monosubstituted olefins.[7a] However, successful implementation of this strategy would require a catalyst capable of efficient hydrocupration of these unactivated and sterically encumbered substrates, as well as the effective discrimination of olefin substituents well-removed from the Cu center and its chiral ligand. Indeed, the enantioselective functionalization of 1,1-disubstituted olefins has been cited as a major challenge for asymmetric synthesis,[9] and only a few highly enantioselective catalytic transformations of these substrates have been reported.[10] Herein we report the regio- and enantioselective hydroamination of 1,1-disubstituted olefins as a practical and general method for the synthesis of β-chiral amines.

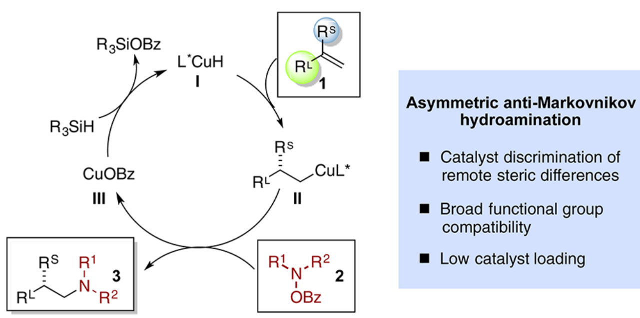

Figure 2. Proposed mechanism of CuH-catalyzed anti-Markovnikov hydroamination.

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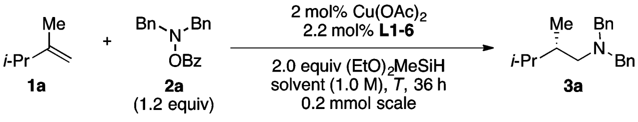
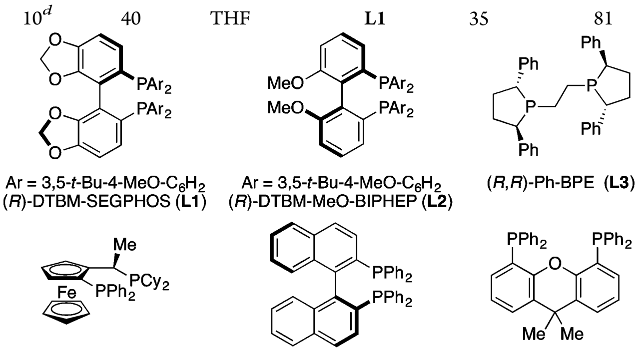
We began our investigation by examining the enantioselective hydroamination of 2,3-dimethyl-1-butene (**1a**), a 1,1-disubstituted alkene substrate with moderately differentiated substituents (Table 1). An evaluation of ligands revealed (*R*)-DTBM-SEGPHOS to be superior to all others tested (entry 1 vs entries 2−6). The use of (*R*)-DTBM-MeO-BIPHEP as ligand afforded product with good enantioselectivity but in moderate yield (entry 2). Cu catalysts based on other ligands, including (*R*,*R*)-Ph-BPE, (*R*)-(*S*)-Josiphos, (*S*)-BINAP, and Xantphos, exhibited little or no activity (entries 3−6). Although varying the solvent had minimal impact on enantioselectivity, THF was found to give the highest reactivity (entry 1 vs entries 7, 8). The enantiomeric excess was essentially unchanged when the reaction was conducted at room temperature instead of 40 °C. However, the reaction did not proceed to full conversion after 36 h (entry 9). Likewise, reduction of catalyst loading to 0.4 mol% led to incomplete conversion (entry 10). Hence the reaction conditions shown in entry 1 were chosen for subsequent examination of the substrate scope of this transformation.[11a]

Table 1. Variation of Reaction Parameters



entry	T (°C)	solvent	L	yield (%)[a]	ee (%)[b]
1	40	THF	**L1**	91	83
2	40	THF	**L2**	67	82
3[c]	40	THF	**L3**	7	−12
4[c]	40	THF	**L4**	0	
5[c]	40	THF	**L5**	0	
6[c]	40	THF	**L6**	0	
7	40	toluene	**L1**	60	82
8	40	cyclohexane	**L1**	74	82
9	rt	THF	**L1**	64	84
10[d]	40	THF	**L1**	35	81

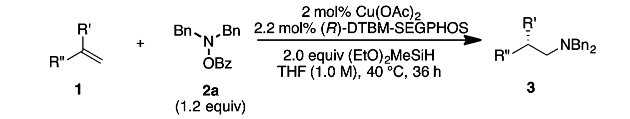


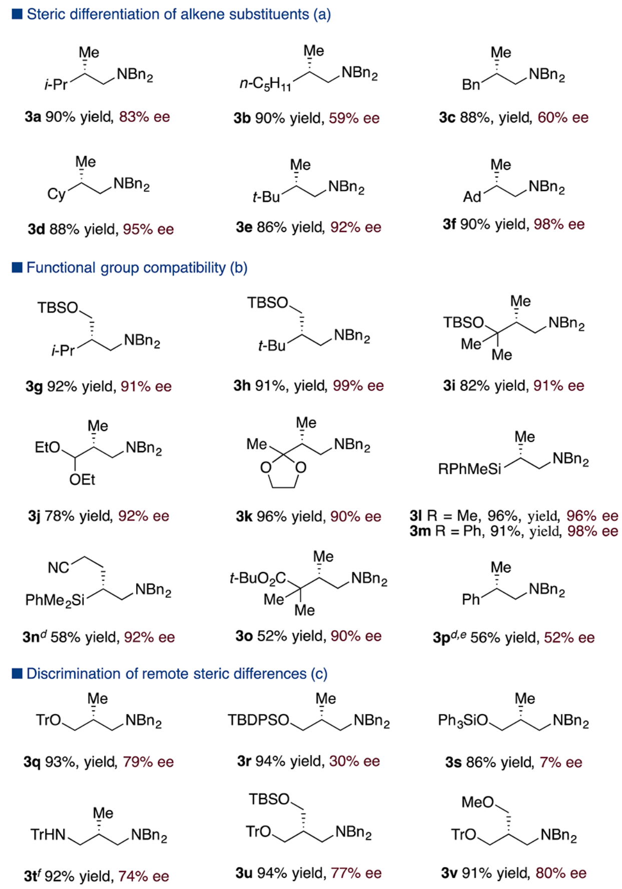
Ar = 3,5-*t*-Bu-4-MeO-C_6H_2 (*R*)-DTBM-SEGPHOS (**L1**)
Ar = 3,5-*t*-Bu-4-MeO-C_6H_2 (*R*)-DTBM-MeO-BIPHEP (**L2**)
(*R*,*R*)-Ph-BPE (**L3**)
(*R*)-(*S*)-JOSIPHOS (**L4**)
(*S*)-BINAP (**L5**)
Xantphos (**L6**)

[a]Yields were determined by GC using dodecane as the internal standard. [b]Enantioselectivities were determined by chiral HPLC analysis. [c]10 mol% $Cu(OAc)_2$ and 11 mol% L used. [d]0.4 mol% $Cu(OAc)_2$ and 0.44 mol% (*R*)-DTBM-SEGPHOS used.

Under these optimized conditions, we first examined the steric effect of substituents on the alkene on enantioselectivity. As illustrated in Table 2a, we found that hydroamination generally proceeded with levels of enantioselectivity that correlated with the steric difference between the 1,1-substituents. High levels of enantioselectivity were observed when one of the alkene substituents was *α*-branched (**3a**,**d**−**f**). Nevertheless, moderately enantioselective hydroamination could still be achieved for more challenging substrates bearing methyl and primary alkyl substituents (**3b**,**c**).

Table 2. Substrate Scope of 1,1-Disubstituted Alkenes[a,b,c]





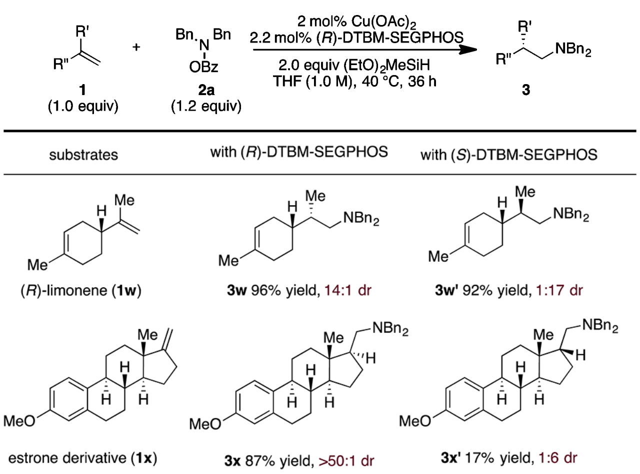
[a]Isolated yields on 1 mmol scale (average of two runs). [b]Absolute configuration was assigned by chemical correlation or analogy. [c]Enantioselectivities were determined by chiral HPLC or chiral SFC analysis. [d]$Cu(OAc)_2$ (5 mol%) and (*R*)-DTBM-SEGPHOS (5.5 mol %) used. [e]Isolated as a 7:1 mixture of anti-Markovnikov and Markovnikov regioisomers, respectively. Enantioselectivity refers to that of the anti-Markovnikov regioisomer. [f]$Cu(OAc)_2$ (4 mol%) and (*R*)-DTBM-SEGPHOS (4.4 mol%) used.

Hydroamination of 1,1-disubstituted alkenes demonstrated broad functional group compatibility (Table 2b). Under these base-free and exceptionally mild reaction conditions, a variety of functional groups were readily accommodated, including an acetal (**3j**), a ketal (**3k**), a nitrile (**3n**), an ester (**3o**), ethers (**3g**−**i**), and silanes (**3l**−**n**).[12] In particular, vinylsilanes underwent hydroamination to afford highly enantioenriched amines containing stereogenic silicon substituents (**3l**−**n**). Moreover, silyl-protected allylic alcohols proved to be excellent substrates for this transformation, furnishing protected 1,3-amino alcohols in excellent yields and enantioselectivities (**3g**−**i**). Surprisingly, subjecting *α*-methylstyrene to hydroamination conditions provided a 7:1 mixture of anti-Markovnikov and Markovnikov products, though enantioselectivity was only moderate (**3p**). The observed regioselectivity for this substrate is presumably due to preferential formation of the less crowded alkylcopper species during the hydrocupration step, which overcomes the preference for benzylic cupration that we previously observed for α-unsubstituted styrenes.[7]

In some cases, a judicious choice of protecting group allowed good enantioselectivity to be achieved in substrates with remote or otherwise ineffective steric differentiation (Table 2c). For β-methallyl alcohol, we found that installation of a trityl protecting group allowed good enantioselectivity to be achieved (**3q**), while the use of bulky silyl protecting groups was ineffective (**3r**,**s**). This strategy could be extended to the corresponding amine to generate the diamine product in comparable enantioselectivity (**3t**). The presence of an unprotected N−H group in this case did not adversely affect reactivity or selectivity of the hydroamination. The catalyst system was also able to effectively differentiate between two remote alcohol protecting groups installed onto 2-methylene-1,3-propanediol: hydroamination proceeded with high efficiency and good enantioselectivity to afford the orthogonally protected aminodiol products (**3u**,**v**). Finally, an additional benefit of employing the trityl protecting group in some cases is the high crystallinity of the resulting hydroamination products. Thus, the enantiopurity of both **3q** and **3t** could be upgraded to >90% ee upon a single recrystallization (see the Supporting Information).

We next explored the ability of the catalyst to control diastereoselectivity in reactions of enantiopure chiral olefins. As shown in Table 3, the hydroamination of (*R*)-limonene proceeded with excellent catalyst control (**3w**,**w′**). However, in the case of conformationally rigid estrone-derived substrate **1x**, a substrate−catalyst matching and mismatching effect was observed. In the matched case, the substrate was transformed to the product with high efficiency and outstanding diastereoselectivity (>50:1 dr, **3x**). In contrast, the mismatched case furnished product with poor conversion and low diastereoselectivity (**3x′**).

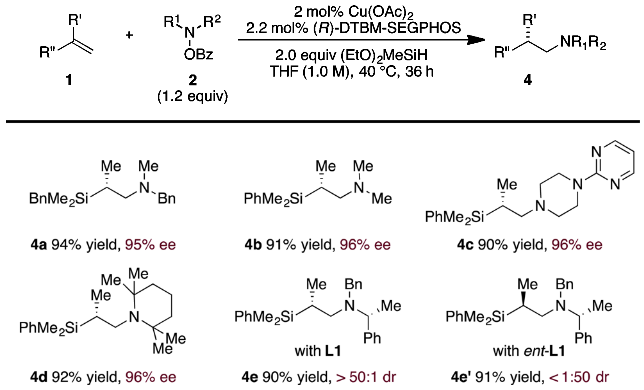
Table 3. Hydroamination of Chiral 1,1-Disubstituted Alkenes[a]



[a]Isolated yields on 1 mmol scale (average of two runs). Absolute configuration assigned by chemical correlation or analogy. Diastereoselectivities determined by ^{1}H NMR analysis of the crude reaction mixture.

A survey of hydroxylamine esters revealed that a range of amino groups could be installed under these hydroamination conditions (Table 4). The use of dimethyl *O*-benzoylhydroxylamine was successful (**4b**),[11b] allowing for the enantioselective synthesis of dimethylamine derivatives, which are prevalent in pharmaceutical agents. Furthermore, 4-(pyrimidin-2-yl)-piperazin-1-yl benzoate (**4c**) and the sterically hindered reagent derived from tetramethylpiperidine (**4d**) were well tolerated by our system. Finally, a stereocenter adjacent to the nitrogen atom of the electrophilic aminating reagent could be accommodated, with the hydroamination reaction proceeding in a completely catalyst-controlled manner (**4e**,**e′**).

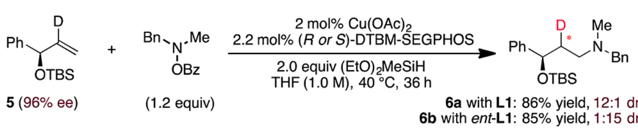
Table 4. Scope of Hydroxylamine Electrophiles[a]



[a]Isolated yields on 1 mmol scale (average of two runs). Enantioselectivities determined by chiral HPLC analysis. Absolute configuration assigned by chemical correlation or analogy.

The anti-Markovnikov hydroamination could be extended to the synthesis of amines with stereogenic deuterium substituents, which may find utility in chemical or biological labeling studies.[13] An enantioenriched deuterated alkene with an adjacent stereocenter was prepared to permit determination of stereoselectivity by NMR spectroscopy. Deuterated alkene **5** was readily prepared by deuteroalumination of the corresponding enantioenriched alkyne. Subjecting **5** to hydroamination conditions selectively afforded either diastereomer of the expected β-deuterated amine product, depending on the antipode of ligand employed (Scheme 1). The observation of catalyst-controlled selectivity in this example suggests that the catalyst can achieve effective facial discrimination for monosubstituted aliphatic alkenes as well as for 1,1-disubstituted alkenes and styrenes.

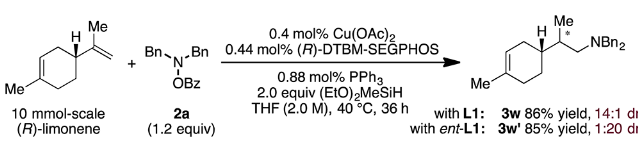
Scheme 1. Practical Synthesis of β-Chiral Deuterated Amines[a]



[a]Isolated yields on 1 mmol scale (average of two runs). Absolute configuration assigned by chemical correlation or analogy. Diastereoselectivities determined by ^{1}H NMR analysis.

Finally, as previously observed by Lipshutz and coworkers in related CuH-based systems,[14] it was found that the addition of triphenylphosphine as a secondary ligand improved catalyst

Scheme 2. Large-Scale Hydroamination with Lower Catalyst Loading



turnover numbers without significantly impacting the reaction rate or enantioselectivity of hydroamination, thereby allowing a reduced loading of Cu precatalyst and chiral ligand to be used. Thus, we developed a slightly modified protocol for practical hydroamination reactions conducted on large scale. A catalyst loading of 0.4 mol% proved sufficient for reactions performed on 10 mmol scale using commercially available (*R*)-limonene as the substrate (Scheme 2).

In conclusion, we have described a mild catalytic process for the synthesis of β-chiral amines by asymmetric anti-Markovnikov hydroamination of 1,1-disubstituted alkenes. This versatile method tolerated a wide range of functional groups on the alkene component and was compatible with heterocycle-containing and sterically hindered aminating reagents. This approach was further applied to the stereoselective synthesis of β-deuterated amines. The amount of catalyst required could be reduced by the addition of triphenylphosphine as an inexpensive secondary ligand, further enhancing the practicality of this system for large-scale synthesis. The application of this protocol toward the synthesis of pharmaceutical agents and natural products is currently underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data for all compounds, and crystallographic data of **3x** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

sbuchwal@mit.edu

Notes

The authors declare no competing financial interest.

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(11) The crude R_2NOBz can be used directly in the hydroamination reaction after simple aqueous workup, although the yield was somewhat lower. (a) Using crude Bn_2NOBz, **3a** was obtained in 87% isolated yield, 83% ee. (b) Using crude Me_2NOBz, **4b** was obtained in 70% isolated yield, 95% ee.

(12) (a) Only poor to moderate conversion to the hydroamination products was observed for unactivated 1,2-disubstituted alkenes. No hydroamination products were observed for either unactivated trisubstituted alkenes or α-substituted acrylates. (b) Free alcohols will undergo silylation, while aldehydes and ketones are hydrosilylated under the current reaction conditions.

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