Aromatic Heterocycles as Activating Groups for Asymmetric Conjugate Addition Reactions. Enantioselective Copper-Catalyzed Reduction of 2-Alkenylheteroarenes

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Aromatic Heterocycles as Activating Groups for Asymmetric Conjugate Addition Reactions. Enantioselective Copper-Catalyzed Reduction of 2-Alkenylheteroarenes

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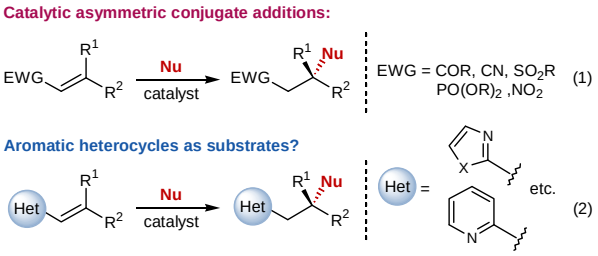
The 1,4-addition of a nucleophile to an alkene conjugated to an electron-withdrawing group is a fundamental reaction in organic chemistry, and numerous catalytic asymmetric variants (eq 1) of this process are now routinely employed in the synthesis of molecules of interest.[1,2] The most common functional groups used to activate alkenes toward asymmetric conjugate additions include carbonyls, nitriles, sulfones, phosphonates, and nitro groups. We recently questioned whether other rarely considered yet common functional groups might also be employed in this capacity, and our attention focused on nitrogen-containing aromatic heterocycles. Given that heteroarenes such as oxazoles, thiazoles, pyridines, and others are ubiquitous in biologically active natural products, pharmaceuticals, and agrochemicals, the ability to functionalize these privileged structures through a diverse set of asymmetric conjugate additions of 2-alkenyl derivatives (eq 2) would open up broad-ranging applications.

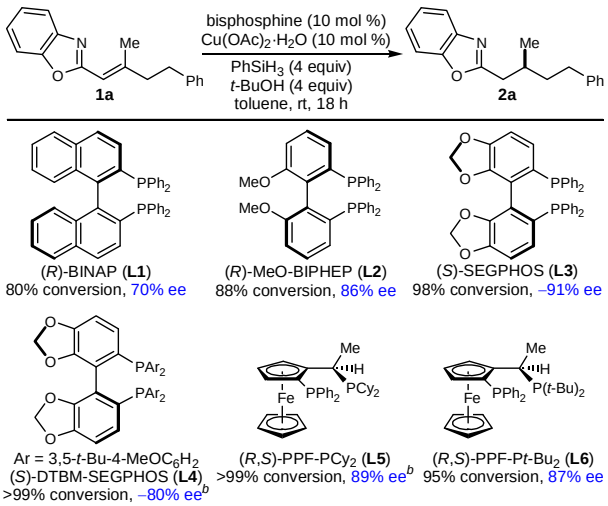


Although conjugate additions to 2-vinylheteroarenes (R^1, R^2 = H in eq 2) are relatively common,[3] the corresponding reactions of substrates containing a β-substituent are much rarer, presumably for steric reasons.[4,5] Furthermore, the only report of a catalytic enantioselective variant is limited to poorly selective (≤15% ee) Grignard additions to 4-alkenylpyridines.[5] Therefore, we recently initiated a program targeted at addressing these deficiencies, and in this Communication, our preliminary findings involving highly enantioselective copper-catalyzed reductions[6] of β,β'-disubstituted 2-alkenylheteroarenes are presented.

The asymmetric copper-catalyzed conjugate reduction of activated alkenes is a well-established method for the synthesis of various useful chiral building blocks.[6,7,8,9,10] Whether a nitrogen-containing heteroarene would provide sufficient activation to an adjacent alkene in an analogous reaction was however, uncertain. In addition, it seemed likely that coordination of the Lewis basic nitrogen of the heteroarene to the copper catalyst would occur in such a process, and whether this interaction would be beneficial, inconsequential, or detrimental, was not easy to predict.

Our investigations began with a survey of chiral bisphosphines **L1–L6** using 2-alkenylbenzoxazole **1a** as a test substrate (Table 1). Using 10 mol % of $Cu(OAc)_2 \cdot H_2O$, 10 mol % of ligand and 4 equivalents each of $PhSiH_3$ and *t*-BuOH in toluene at room temperature, biaryl-based ligands **L1**–**L4** proved competent in promoting conjugate reduction.[11] With (*R*)-BINAP (**L1**), both conversion and enantioselectivity were only moderate. However, improved results were observed using (*R*)-MeO-BIPHEP (**L2**) and the SEGPHOS ligands **L3** and **L4**, with 91% ee obtained using (*S*)-SEGPHOS (**L3**). The Josiphos ligands **L5** and **L6** were also effective, providing **2a** in 89% and 87% ee respectively. Of all the ligands, the highest reaction rates were observed with **L4** and **L5** (reactions were complete in 2 h). However, the superior selectivity provided by **L5** prompted us to select this ligand for further optimization and investigation of reaction scope.

Table 1. Ligand Optimization for the Asymmetric Reduction of **1a**[a]

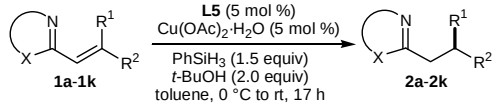


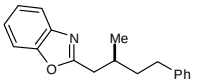
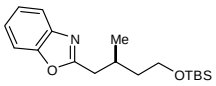
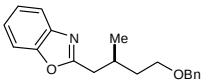
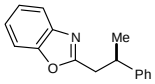
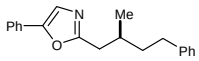
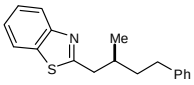
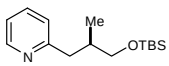
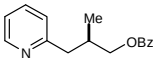
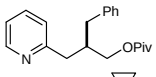
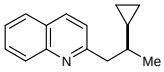
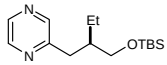
[a] Reactions were conducted using 0.20 mmol of **1a** in toluene (1 mL). Conversions were determined by GC analysis. Enantioselectivities were determined by chiral HPLC analysis. [b] Reactions complete after 2 h.

Using 5 mol % each of $Cu(OAc)_2 \cdot H_2O$ and **L5**, $PhSiH_3$ (1.5 equiv), and *t*-BuOH (2.0 equiv) at an initial temperature of 0 °C, a range of β,β'-disubstituted 2-alkenylheteroarenes underwent conjugate reduction with generally excellent levels of enantioselection (Table 2).[11] In addition to benzoxazole (entries 1–4), other effective nitrogen-containing hetereoarenes in this process included 5-phenyloxazole (entry 5), benzothiazole (entry 6), pyridine (entries 7–9), quinoline (entry 10), and pyrazine (entry 11). Tolerated functionality at the β-positions of the alkene included simple aliphatic groups, a phenyl group (entry 4), a benzyl group (entry 9), various oxygenated alkyl groups (entries 2, 3, 7–9, and 11), and a cyclopropane (entry 10). The process is tolerant of lower loadings of copper and ligand. For example, reduction of **1g** on a 1.0 mmol scale using 2 mol % each of $Cu(OAc)_2 \cdot H_2O$ and **L5** provided **2g** in 92% yield and 96% ee (entry 7, values in parentheses).

Experiments to explore the origins of reactivity were then

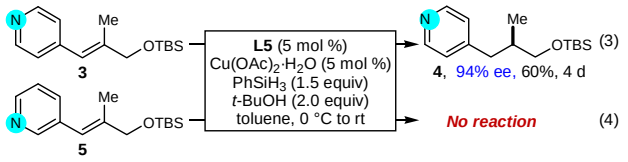
Table 2. Scope of Cu-Catalyzed Asymmetric Conjugate Reduction[a]



entry	product		yield (%)[b]	ee (%)[c]
1		**2a**	90	93
2		**2b**	67	94
3		**2c**	88	95
4[d]		**2d**	95	87
5		**2e**	93	90
6		**2f**	86	95
7		**2g**	90 (92)[e]	>99 (96)[e]
8[f]		**2h**	81	98
9		**2i**	90	97
10		**2j**	90	96
11		**2k**	89	96

[a] Reactions were conducted using 0.20 mmol of **1a**–**1k** unless otherwise stated. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Using 0.155 mmol of **1d**. [e] Values in parentheses refers to reaction conducted using 1.0 mmol of **1g**, 2 mol % Cu, and 2 mol % **L5**. [f] Using 0.10 mmol of **1h** and 2.0 equiv of $PhSiH_3$.

conducted. Reduction of 4-alkenylpyridine **3** provided **4** in 60% yield and 94% ee, albeit in a slower reaction that was incomplete even after 4 days (eq 3). This result suggests that alkene reduction by copper hydride can occur without assistance of a directing effect from the nitrogen atom. In contrast, 3-alkenylpyridine **5** was unreactive (eq 4), demonstrating the importance of conjugation of the alkene to a C=N moiety for reactivity.



In summary, copper-catalyzed asymmetric conjugate reductions of β,β'-disubstituted 2-alkenylheteroarenes are reported. In addition to serving as a further demonstration of the power of chiral copper hydride catalysis,[6] this work has shown nitrogen-containing aromatic heterocycles can provide effective activation of an adjacent alkene for highly enantioselective catalytic conjugate addition reactions. Extension of the general concept to other classes of asymmetric reactions should provide a range of useful tools for chemists working with heteroarenes. Future studies from our laboratory will be directed towards this goal.

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Supporting Information Available: Experimental procedures, full spectroscopic data for new compounds, and crystallographic data in cif format. This material is available free of charge via the Internet at http://pubs.acs.org.

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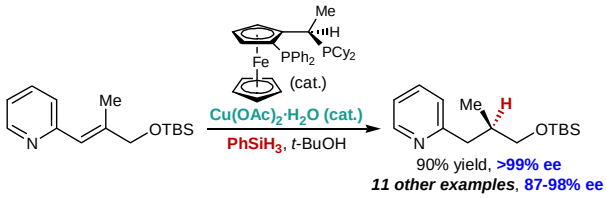
(11) The stereochemistries of the products obtained herein were assigned tentatively by analogy with that of **2c**, which was secured through X-ray crystallography of a derivative. See Supporting Information for details.



The versatility of chiral copper hydride catalysis has been demonstrated through development of highly enantioselective 1,4-reductions of 2-alkenylheteroarenes, substrates that have been rarely considered for asymmetric conjugate addition reactions. Both azoles and azines serve as efficient activating groups for this process.