Enantioselective Copper-Catalyzed Reductive Coupling of Alkenylazaarenes with Ketones

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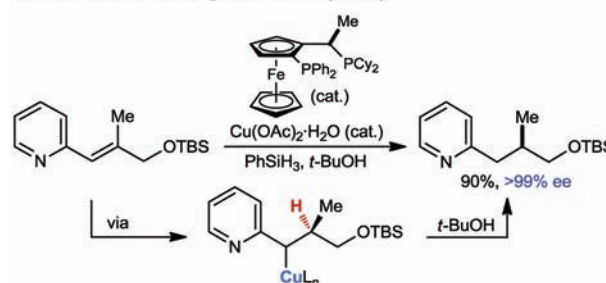
S *Supporting Information*

ABSTRACT: Catalytic enantioselective methods for the preparation of chiral azaarene-containing compounds are of high value. By combining the utility of copper hydride catalysis with the ability of C=N-containing azaarenes to activate adjacent alkenes toward nucleophilic additions, the enantioselective reductive coupling of alkenylazaarenes with ketones has been developed. The process is tolerant of a wide variety of azaarenes and ketones, and provides aromatic heterocycles bearing tertiary-alcohol-containing side chains with high levels of diastereo- and enantioselection.
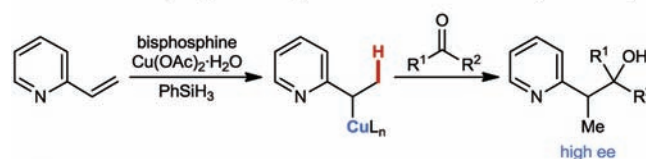
The development of new catalytic reactions for the functionalization of aromatic heterocycles and their derivatives continues to be a valuable endeavor due to the importance of these structures in natural products, pharmaceuticals, agrochemicals, and other molecules of interest. In this regard, recent efforts from our laboratory have targeted the development of processes that exploit the ability of a suitably positioned C=N moiety within azaarenes to activate adjacent alkenes toward catalytic enantioselective nucleophilic additions.[1−3] The first of these reports described copper-catalyzed reductions[4] of β,β-disubstituted 2-alkenylazaarenes, which result in alkylazaarenes with a new stereogenic center at the β-carbon (representative example in Figure 1A).[1] Since these reactions likely proceed via the intermediacy of organocopper species that undergo protonation with *t*-BuOH, we questioned whether these intermediates could be trapped in situ with an alternative electrophile such as a ketone (Figure 1B). Such a reductive coupling process would be synthetically more valuable, delivering more complex tertiary-alcohol-containing products with stereochemistry at both α- and β-carbons.

Although the proposed process is related to copper-catalyzed reductive aldol reactions described previously,[5−9] to our knowledge, there are no reports of alkenylazaarenes being employed as substrates in these reactions. To date, the only report of catalytic reductive coupling reactions of alkenylazaarenes is that from the Krische group, who described racemic rhodium-catalyzed hydrogenative coupling of vinylazines with N-sulfonylaldimines (Figure 1C).[10] The realization of *enantioselective* variants of this and related processes would therefore be of obvious value. Herein, we report highly enantioselective copper-catalyzed reductive coupling reactions of alkenylazaarenes with ketones.
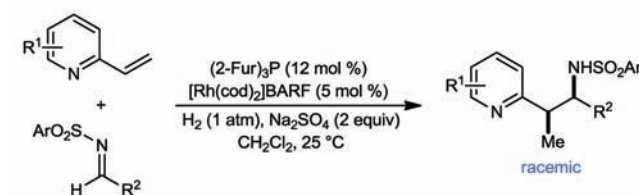

Figure 1. Catalytic transformations of alkenylazaarenes.

This study began with examination of the enantioselective reductive coupling of 2-vinylquinoline (**1a**) with acetophenone (1.1 equiv) using PhSiH₃ (1.2 equiv) as the hydride source, 5 mol % Cu(OAc)₂·H₂O, and 5 mol % of various chiral bisphosphines in toluene (Table 1).[4] Pleasingly, proof of concept was quickly established, and all ligands evaluated led to complete consumption of **1a** to provide the coupling product **2a** as a mixture of diastereomers, along with traces of the simple reduction product **3**.[11] Enantioselectivities were modest using ligands **L1**−**L3** (entries 1−3), but high using (*R,R*)-Quinox-P* (**L4**) (entry 4), the Josiphos ligand **L5** (entry 5), and the Taniaphos ligand **L6** (entry 6). However, no diastereoselectivity was observed in most cases, with the notable exception being the reaction using **L6** which provided **2a** in 5:1 dr and

Table 1. Evaluation of Chiral Bisphosphines[a]

entry	bisphosphine	2a:3[b]	dr[b]	ee (%)[c]
1	L1	11:1	1:1	43, 50
2	L2	13:1	1:1	67, 67
3	L3	24:1	1:1	27, 17
4	L4	17:1	1:1	−60, −92
5	L5	12:1	1:1	92, 93
6	L6	7:1	5:1	93, 60

[a]Reactions were conducted using 0.10 mmol of **1a**. [b]Determined by
¹H NMR analysis of the unpurified reaction mixtures. [c]Determined by
chiral HPLC analysis.

93% ee for the major isomer (entry 6). Accordingly, **L6** was
selected for further experimentation.

Chart 1 presents results of reductive coupling of various
vinylazaarenes **1a–1h**[12] with a range of ketones. Gratifyingly,
the scope of the process is broad, and the enantioselectivities of
the products were uniformly high (89–>99% ee).[11] Although
L6 provided the best results for products **2a–2i**, this ligand
resulted in a low yield in the attempted synthesis of **2j**, and
poor diastereo- and enantioselectivities in the attempted
syntheses of **2k** and **2l**. In these cases, (R,R)-Quinox-P* (**L4**)
was superior for **2j** and **2k**, and the Josiphos ligand **L5** was
optimal for **2l**. In addition to **1a**, effective substrates include
those containing azines such as pyridines (products **2c** and **2k**),
isoquinoline (products **2d–2g**), two different isomeric
dimethoxypyrimidines (products **2h** and **2i**), and quinoxaline
(product **2l**). A vinylthiazole also smoothly underwent the
reaction (product **2j**). With acyclic ketones, the diastereose-
lectivity of the reaction appears to be dependent on the steric
properties of the azaarene, with diastereoselectivity increasing
from pyridine to quinoline to isoquinoline (compare
diastereomeric ratios for products **2c**, **2a**, and **2d**). In the
coupling of 2-vinylpyridine with acetophenone, the two
diastereomeric products **2ca** and **2cb** were isolated with high
enantioselectivities (>99% and 92% ee, respectively). Regarding
the electrophile, the process is tolerant of acyclic ketones
containing various alkyl, aryl, or heteroaryl substituents
(products **2a–2g**). In addition, cyclic ketones are viable
substrates, as exemplified by the successful use of two
indanones (products **2h** and **2i**), 4-chromanone (product **2j**),
4-thiochromanone (product **2k**), and tetralone (product **2l**).

Chart 1. Reaction Scope with Vinylazaarenes[a]
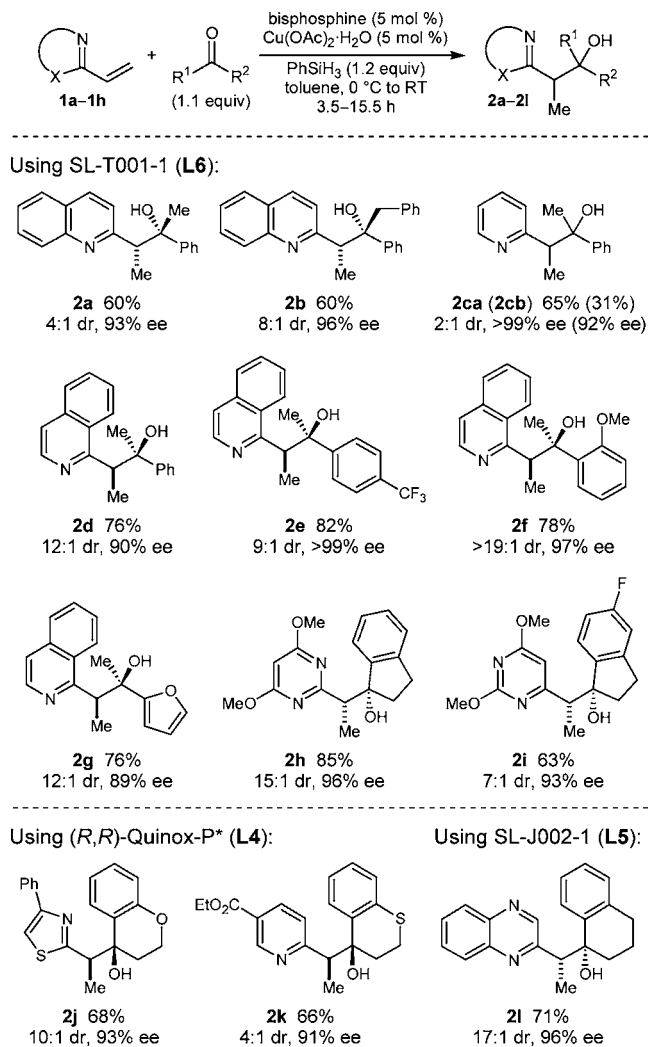
[a]Reactions were conducted using 0.30–0.40 mmol of **1a–1h**. Cited
yields are of pure isolated major diastereomers. Diastereomeric ratios
were determined by ¹H NMR analysis of the unpurified reaction
mixtures. Enantiomeric excesses were determined by chiral HPLC
analysis.

Interestingly, the absolute stereochemistries of isoquinoline-
containing products **2d–2g** are opposite to those of quinoline-
containing products **2a** and **2b**, even though the same
enantiomer of ligand **L6** was employed throughout.[11] In
addition, the diastereochemical outcomes of the reactions
producing **2h–2l** are different from those resulting in **2a**, **2b**,
and **2d–2g**.[11] Assuming that the reactions proceed via
Zimmerman–Traxler-type transition states where the larger
aryl group of the ketone occupies a pseudoequatorial
position,[13] Figure 2 depicts conformations that are consistent
with these observations. The stereochemical outcomes of the
reactions producing **2a**, **2b**, and **2d–2g** are consistent with the
participation of Z-azaallylcopper species[14] (**TS 1** and **TS 2**),
though the reasons for the opposite sense of enantioinduction
in **TS 2** compared with **TS 1** are not clear at this time.
Furthermore, while the preference for the Z-azaallylcopper
species in **TS 2** is readily explained by the severe $A_{1,3}$-strain[15]
that would disfavor the corresponding E-azaallylcopper species,
a similar argument cannot be used to explain the same
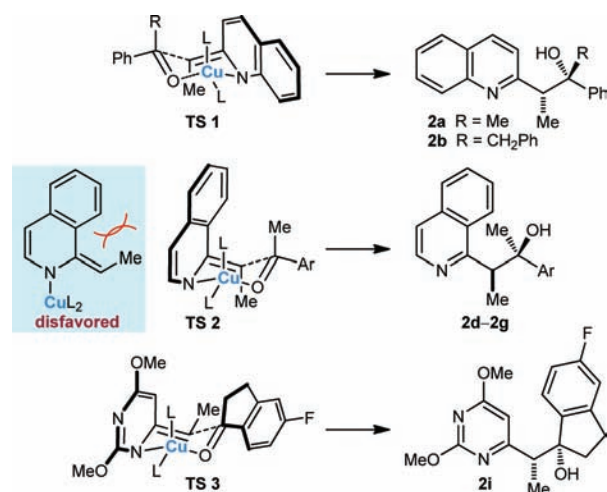preference in **TS 1**. For reactions producing **2h–2l**, reaction

Figure 2. Rationalization of stereochemical outcomes.

through the *E*-azaallylcopper species (or *Z*-azaallylcopper species in the case of **2j**) appears to be favored, as in **TS 3** for the formation of **2i**. The interplay between the steric and/or electronic properties of the alkenylazaarene and the ligand and the resulting effect on the stereochemical outcome are clearly complex. In addition, while the preceding discussion has been based upon the assumption that chairlike transition states are operative, reaction through boatlike structures cannot be excluded.

Notably, the process is not limited to vinylazaarenes; *β*-substituted alkenylazaarenes are also effective coupling partners (Chart 2). For example, alkenylazaarenes **4a–4c**[12] containing

Chart 2. Reductive Coupling of *β*-Substituted Alkenylazaarenes with Ketones[a]
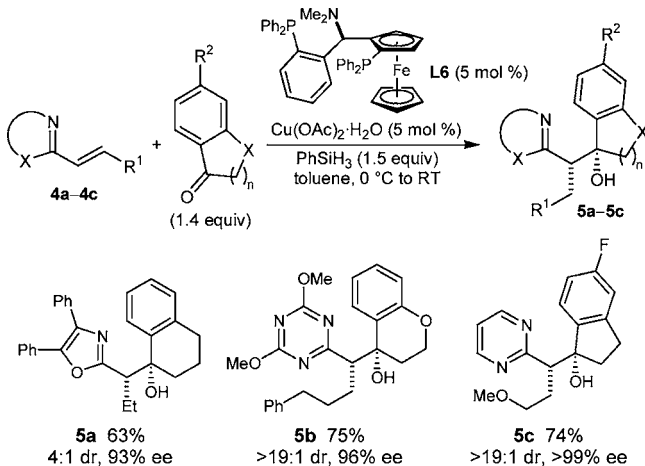
[a]Reactions were conducted using 0.30 mmol of **4a–4c**. Cited yields are of pure isolated major diastereomers. Diastereomeric ratios were determined by ^{1}H NMR analysis of the unpurified reaction mixtures. Enantiomeric excesses were determined by chiral HPLC analysis.

methyl, phenethyl, or allylic ether groups smoothly underwent reductive coupling to deliver products **5a–5c**, respectively, in high enantioselectivities.[11] Furthermore, these products contain additional examples of azaarenes not utilized in Chart 1, such as diphenyloxazole (product **5a**), a dimethoxytriazine (product **5b**), and 1,3-pyrimidine (product **5c**).

In summary, we have described the first examples of catalytic enantioselective reductive couplings of alkenylazaarenes. The scope of this process is broad, with 11 different types of azaarenes and a range of acyclic and cyclic ketones having been shown to be effective coupling partners. *β*-Substitution on the alkene is tolerated, and the reactions proceed under mild conditions to deliver products in good to high levels of diastereo- and enantioselection. These features should be advantageous for application of this process in the preparation of novel enantioenriched chiral azaarene-containing building blocks.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

Experimental procedures, full spectroscopic data for all 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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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(11) Where indicated, the relative and absolute stereochemistries of the products obtained herein were assigned by analogy with those of products **2a**, **2b**, **2d**, **2e**, **2j**, and **5c**, which were determined by X-ray crystallography using a copper radiation source (see Supporting Information for details). The stereochemistry of **2l** (obtained using ligand **L5**) was assigned by analogy with the product obtained using ligand **L6**, which was the same major enantiomer of **2l** but in 2:1 dr and 73% ee.

(12) See Supporting Information for the structures of **1b−1h** and **4a−4c**.

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