Enantioselective Copper-Catalyzed Reductive Coupling of Alkenylazaarenes with Ketones

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Supporting Information Placeholder

ABSTRACT: Catalytic enantioselective methods for the preparation of chiral azaaarene-containing compounds are of high value. By combining the utility of copper hydride catalysis with the ability of C=N-containing azaaarenes 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 azaaarenes and ketones, and provides aromatic heterocycles bearing tertiary-alcohol-containing sidechains 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 azaaarenes to activate adjacent alkenes toward catalytic enantioselective nucleophilic additions.1,2 The first of these reports described copper-catalyzed reductions4 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 intermediary 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,5,6,7,8,9 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.

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

Chart 1 presents results of reductive coupling of various vinylazines 1a–1h 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–2l, 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...
Table 1. Evaluation of Chiral Bisphosphines

<table>
<thead>
<tr>
<th>entry</th>
<th>bisphosphine</th>
<th>2a:3</th>
<th>dr</th>
<th>ee (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>L1</td>
<td>11:1</td>
<td>1:1</td>
<td>43,50</td>
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<td>L2</td>
<td>13:1</td>
<td>1:1</td>
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<td>L3</td>
<td>24:1</td>
<td>1:1</td>
<td>27,17</td>
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<tr>
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<td>L4</td>
<td>17:1</td>
<td>1:1</td>
<td>60,92</td>
</tr>
<tr>
<td>5</td>
<td>L5</td>
<td>12:1</td>
<td>1:1</td>
<td>92,93</td>
</tr>
<tr>
<td>6</td>
<td>L6</td>
<td>7:1</td>
<td>5:1</td>
<td>93,60</td>
</tr>
</tbody>
</table>

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

those containing azines such as pyridines (products 2c and 2k), isoquinoline (products 2d–2g), two different isomeric dimethoxyopyrimidines (products 2h and 2i), and quinoxaline (product 2l). A vinylthiazole also smoothly underwent the reaction (product 2j).

With acyclic ketones, the diastereoselectivity of the reaction appears to be dependent on the steric properties of theazaarene, 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).

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. In addition, the diastereomeric outcomes of the reactions producing 2h–2l are different from those resulting in 2a, 2b, and 2d–2g. Assuming that the reactions proceed via Zimmerman–Traxler-type transition states where the larger aryl group of the ketone occupies a pseudoequatorial position, 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\(^\text{14}\) (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\(^\text{15}\) 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 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 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 chair-like transition states are operative, reaction through boat-like structures cannot be excluded.

Notably, the process is not limited to vinylazaarenes; \(\beta\)-substituted alkenylazaarenes are also effective coupling partners (Chart 2). For example, alkenylazaarenes 4a–4c\(^\text{2}\) containing methyl, phenethyl, or allylic ether groups smoothly undergo reductive coupling to deliver products 5a–5c, respectively, in high enantioselectivities.\(^\text{11}\) 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 eleven different types of azaarenes and a range of acyclic and cyclic ketones having been shown to be effective coupling partners. \(\beta\)-Substitution on the alkene is tolerated, and the reactions proceed under mild conditions to deliver products in good to high levels of diastereo- and enantioselective. These features should be advantageous for application of this process in the preparation of novel enantioenriched chiral azaarene-containing building blocks.

**REFERENCES**


(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.


Cu(OAc)$_2$·H$_2$O (5 mol %) PhSiH$_3$ (1.5 equiv) toluene, 0 °C to RT

74% >19:1 dr, >99% ee

15 examples