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Cluster

NHBoc

69% Me

>19:1 dr, 92% ee

Enantioselective Copper-Catalyzed Reductive Coupling of Vinylazaarenes with *N*-Boc Aldimines

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Boo

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Abstract The diastereo- and enantioselective reductive coupling of vinylazaarenes with *N*-Boc aldimines is described. The reactions proceed using chiral copper–bisphosphine complexes in the presence of TMDS as a hydride source to give reductive coupling products in moderate to high enantioselectivities.

Key words asymmetric catalysis, copper, enantioselectivity, imines, vinylazaarenes

The broad significance of aromatic nitrogen heterocycles (azaarenes) in chiral biologically active compounds and other functional molecules has prompted our group to investigate the potential of C=N-containing azaarenes as activating groups in new catalytic enantioselective processes.^{1,2} During this program, we have reported enantioselective copper-catalyzed reductions of β , β -disubstituted alkenylazaarenes^{2a} and copper-catalyzed reductive couplings of alkenylazaarenes with ketones (Scheme 1, a).^{2d} This latter process enables the synthesis of products containing an azaarene and two stereogenic centers, including a tertiary alcohol. The ability to employ other types of electrophiles would be beneficial to expand the range of accessible products.

Cu (cat.) (S)-DTBM-SEGPHOS (cat.)

TMDS THE

27 examples

59-94% ee

Krische and co-workers have described the racemic rhodium-catalyzed hydrogenative coupling of vinylazines with *N*-sulfonylaldimines (Scheme 1, b),³ and we envisaged that a related enantioselective variant employing chiral copper hydride chemistry⁴ could be developed. Although the intermolecular reductive aldol reaction⁵ of α , β -unsaturated carbonyl compounds, catalyzed by chiral copper–hydride complexes, has been successful,⁶ the corresponding reductive Mannich reactions⁷ have been less well studied.⁸ To date, the only report of enantioselective copper-catalyzed



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reductive Mannich reactions is from Kanai, Shibasaki, and co-workers, who described the reductive coupling of α , β -unsaturated esters with *N*-phosphinoyl ketimines.^{7f}

Herein, we describe the enantioselective copper-catalyzed reductive coupling of vinylazaarenes with *N*-Boc aldimines. Both vinylazines and vinylazoles are effective substrates, and the Boc protection in the products is advantageous for subsequent deprotection.

Our investigations began with an evaluation of chiral bisphosphines, reductants, and reaction conditions for the copper-catalyzed reductive coupling of 2-vinylquinoline (**1a**) with *N*-Boc aldimine **2a** (1.1 equiv), which led to the identification of (*S*)-DTBM-SEGPHOS (**L1**) as an effective chiral ligand.

In the presence of Cu(OAc)₂·H₂O (5 mol%), L1 (5 mol%), and 1,1,3,3-tetramethyldisiloxane (TMDS, 1.2 equiv), the reaction proceeded smoothly in THF at room temperature to give the reductive coupling product **3a** as the *anti* diastereomer in 63% yield, >19:1 dr, and 85% ee (Scheme 2).^{9,10} Under these conditions, various other vinylazaarenes **1b**–**f** were also effective in reactions with imine **2a**, which gave products **3b**–**f** in 58–74% yield and 75–92% enantiomeric excess. Besides quinoline (**3a**), azaarenes that were tolerated included quinoxaline (**3b**), a bromopyridine (**3c**), a phenylpyridazine (**3d**), benzoxazole (**3e**), and benzothiazole (**3f**). High diastereoselectivities ($\geq 10:1 \text{ dr}$) were observed with vinylazaarenes containing benzannulation (**3a**, **3b**, **3e**, and **3f**), while 2-bromo-6-vinylpyridine and 3-phenyl-6-vinylpyridazine resulted in more modest diastereoselectivities (**3c** and **3d**). In the former case, the diastereomers were difficult to separate completely, and the minor isomer was formed in a much lower enantiomeric excess (20% ee) compared with the major isomer (80% ee).

The reductive coupling of 4-phenyl-2-vinylthiazole (**1g**) with imine **2a** proceeded with low enantioselectivity using ligand **L1**. Fortunately, (R,R)-Ph-BPE (**L2**) provided improved results and gave **3g** in 88% yield, >19:1 dr, and 87% ee (Scheme 3).¹⁰



Scheme 3 Reductive coupling of 1g with 2a using ligand L2



Scheme 2 Enantioselective reductive coupling of vinylazaarenes **1a–f** with *N*-Boc imine **2a**. Reactions were conducted using 0.30 mmol of **1a–f**. Unless stated otherwise, 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. ^a Yield of a 4.3:1 mixture of diastereomers. The enantiomeric excess of the minor diastereomer is indicated in parentheses.

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Various other (hetero)aromatic *N*-Boc aldimines **2b–l** also underwent reductive coupling with vinylazaarenes **1a– f**, giving products **4a–s** in 59–94% enantiomeric excess for the major diastereomers (Scheme 4).¹⁰ The diastereoselectivities of these reactions ranged from 1.3:1 (**4i**) to >19:1 (**4a–c,e,f,r**). Compared with the results shown in Scheme 2 and with similar reactions using ketones as electrophiles,^{2d} these reactions often provided lower yields of the reductive coupling products due to more prevalent side reactions, such as simple reduction of both reaction partners without C–C bond formation. Although no definitive trends could be deduced from the particular combinations of substrates that resulted in the highest enantioselectivities, values of 85% enantiomeric excess or higher were observed in several cases (**4a,c,d,i,k,q-s**). With respect to the imine, a range of substituents (methyl, trifluoromethyl, chloro-, methoxy, dioxolane, or boronate esters) at various positions on the phenyl ring were tolerated.

Furthermore, reactions of imines containing 1-naphthyl, 2-naphthyl, or 2-thienyl groups were also successful. As observed previously (Scheme 1), the reactions of 2-bromo-6-vinylpyridine and 3-phenyl-6-vinylpyridazine generally gave lower diastereoselectivities (**4g**–**l**) compared with the other vinylazarenes. Lower diastereoselectivities were also obtained with an imine containing a *p*-pinacol boronic ester (**4i** and **4s**). Interestingly, the minor diastereomers obtained for products **4g** and **4i** were obtained in low or nonexistent enantiomeric excesses.



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Scheme 4 Enantioselective reductive coupling of vinylazaarenes 1a-f with various *N*-Boc imines. Reactions were conducted using 0.30 mmol of 1a-f. Unless stated otherwise, 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. Where measured, the enantiomeric excess of the minor diastereomer is indicated in parentheses. ^a Yield of a 4.7:1 mixture of diastereomers. ^b Yield of a 3:1 mixture of diastereomers. ^c Yield of a 1.6:1 mixture of diastereomers.



Once again, (*R*,*R*)-Ph-BPE (**L2**) was a superior ligand compared with **L1** in a reductive coupling involving 4-phe-nyl-2-vinylthiazole (Scheme 5).¹⁰

The reaction of 2-vinylbenzothiazole (**1f**) with an imine **2m** (2.0 equiv) containing an aliphatic substituent (cyclohexyl) was also studied (Scheme 6). Although low stereose-lectivities were obtained using ligands **L1** or **L2**, the Josiphos ligand SL-J006-1 (**L3**) gave improved results and provided two diastereomers of **4u** in 73% and 16% yields, in 82% and 75% enantiomeric excess for the major and minor isomers, respectively.

Finally, removal of the Boc group from **4a** was achieved under acidic conditions (using HCl generated by the reaction of TMSCl with MeOH), which provided amine **5** in 90% yield with no loss of enantiopurity (Scheme 7).



In summary, the results presented herein demonstrate the ability of chiral copper–bisphosphine complexes to catalyze the enantioselective reductive coupling of vinylazaarenes with (hetero)aryl *N*-Boc imines. The reactions provide reductive coupling products with moderate to high enantioselectivities (up to 94% ee).

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379548.

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17.7 mg, 0.015 mmol), and imine **2a** (68 mg, 0.33 mmol) in THF (1.5 mL) was stirred at 0 °C for 15 min. TMDS (64 μ L, 0.36 mmol) was then added dropwise over 1 min. The mixture was stirred at 0 °C for 1 h, then at r.t. for 15 h. The reaction was quenched carefully with SiO₂, and the resulting suspension was stirred for 15 min before being filtered through a short plug of SiO₂ using EtOAc as eluent and concentrated in vacuo. Purification of the residue by flash column chromatography gave the reductive coupling product.

Data for 3a

$$\begin{split} R_f &= 0.31 \ (20\% \ \text{EtOAc-PE}); \ \text{mp} \ 128-131 \ ^\circ\text{C} \ (\text{EtOAc-PE}); \ [\alpha]_{\text{D}}^{24} \\ &+ 98.6 \ (c \ 1.10, \ \text{CHCl}_3). \ \text{IR} \ (\text{film}): \ 2970, \ 2934, \ 1709 \ (\text{C=O}), \ 1503, \\ 1390, \ 1289, \ 827, \ 756, \ 700 \ \text{cm}^{-1}. \ ^1\text{H} \ \text{NMR} \ [500 \ \text{MHz}, \ (\text{CD}_3)_2 \text{CO}]: \ \delta \\ &= 8.14 \ (d, \ J = 8.4 \ \text{Hz}, \ 1 \ \text{H}), \ 8.05 \ (d, \ J = 8.3 \ \text{Hz}, \ 1 \ \text{H}), \ 7.88 \ (d, \ J = 8.0 \\ \text{Hz}, \ 1 \ \text{H}), \ 7.75 \ (ddd, \ J = 8.4, \ 6.9, \ 1.4 \ \text{Hz}, \ 1 \ \text{H}), \ 7.57-7.51 \ (m, \ 1 \ \text{H}), \\ 7.33 \ (d, \ J = 7.3 \ \text{Hz}, \ 2 \ \text{H}), \ 7.24 \ (t, \ J = 8.0 \ \text{Hz}, \ 3 \ \text{H}), \ 7.16 \ (t, \ J = 7.0 \ \text{Hz}, \\ 2 \ \text{H}), \ 5.09 \ (t, \ J = 7.7 \ \text{Hz}, \ 1 \ \text{H}), \ 3.63-3.54 \ (m, \ 1 \ \text{H}), \ 1.35 \ (d, \ J = 6.9 \\ \text{Hz}, \ 3 \ \text{H}), \ 1.27 \ (s, \ 9 \ \text{H}). \ ^{13}\text{C} \ \text{NMR} \ [125.8 \ \text{MHz}, \ (\text{CD}_3)_2 \text{CO}]: \ \delta = \\ 165.1, \ 156.0, \ 148.5, \ 144.1, \ 137.0, \ 130.2, \ 129.7, \ 128.9, \ 128.6, \\ 128.0, \ 127.7, \ 127.5, \ 126.8, \ 122.8, \ 78.5, \ 60.2, \ 48.1, \ 28.5, \ 19.6. \ \text{ESI-HRMS}: \ m/z \ \text{calcd} \ \text{for} \ C_{23} \text{H}_{27} \text{N}_{2} \text{O}_2 \ \[\text{M} + \ \text{H}]^{+}: \ 363.2067; \ \text{found:} \\ 363.2067. \ \text{HPLC: \ Chiralcel \ OD-H \ column} \ (i-\text{hexane}-i-\text{PrOH}, \\ 90:10; \ 1.0 \ \text{mL/min}, \ 254 \ \text{nm}, \ 25 \ ^\circ\text{C}); \ t_{R} \ (\text{major}) = \ 4.6 \ \text{min}, \ t_{R} \ (\text{minor}) = 5.9 \ \text{min}; \ 85\% \ \text{ee}. \end{split}$$

Data for 3f

R_f = 0.32 (20% EtOAc–PE); mp 142–145 °C (EtOAc–PE); $[\alpha]_{D}^{24}$ +55.0 (*c* 1.00, CHCl₃). IR (film): 2979, 2928, 1713 (C=O), 1498, 1390, 1365, 1170, 1022, 759, 700 cm⁻¹. ¹H NMR [400 MHz, (CD₃)₂CO]: δ = 7.98 (t, *J* = 8.9 Hz, 2 H), 7.54–7.45 (m, 1 H), 7.45–7.35 (m, 3 H), 7.30 (t, *J* = 7.4 Hz, 2 H), 7.23 (t, *J* = 7.5 Hz, 1 H), 6.80 (d, *J* = 7.5 Hz, 1 H), 5.15–4.90 (m, 1 H), 3.88–3.65 (m, 1 H), 1.37 (d, *J* = 6.8 Hz, 3 H), 1.28 (s, 9 H). ¹³C NMR [125.8 MHz, (CD₃)₂CO]: δ = 174.7, 155.9, 154.1, 142.9, 135.6, 129.1, 128.0, 127.8, 126.8, 125.7, 123.4, 122.6, 78.9, 60.3, 45.1, 28.5, 19.5. ESI-HRMS: *m/z* calcd for C₂₁H₂₅N₂O₂S [M + H]*: 369.1631; found: 369.1634. HPLC: Chiralpak IC column (hexane–*i*-PrOH, 98:2; 0.8 mL/min, 280 nm, 25 °C); *t*_R (major) = 18.9 min, *t*_R (minor) = 27.9 min; 88% ee.

(10) Where indicated, the relative and absolute stereochemistries of the products were assigned by analogy with those of products **3f,g, 4d,k,q,t**, which were determined by X-ray crystallography (see Supporting Information for details). CCDC 1019731– 1019736 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif or by writing to the Cambridge CB2 1EZ, UK; fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk. Copyright of Synlett is the property of Georg Thieme Verlag Stuttgart and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.