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

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

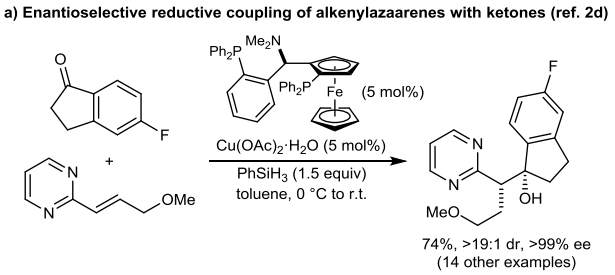
Key words: asymmetric catalysis, copper, enantioselectivity, imines, vinylazaarenes

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 Cu-catalyzed reductions of β,β-disubstituted alkenylazaarenes[2a] and Cu-catalyzed reductive couplings of alkenylazaarenes with ketones (Scheme 1a).[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.

Krische and co-workers have described the racemic Rh-catalyzed hydrogenative coupling of vinylazines with *N*-sulfonylaldimines (Scheme 1b),[3] and we envisaged that a related enantioselective variant employing chiral copper hydride chemistry[4] could be developed. Although the intermolecular reductive aldol reaction[5] of α,β-unsaturated carbonyl compounds, catalyzed by chiral copper–hydride complexes, has been successful,[6] the corresponding reductive Mannich reactions[7] have been less well studied.[8] To date, the only report of enantioselective copper-catalyzed 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]

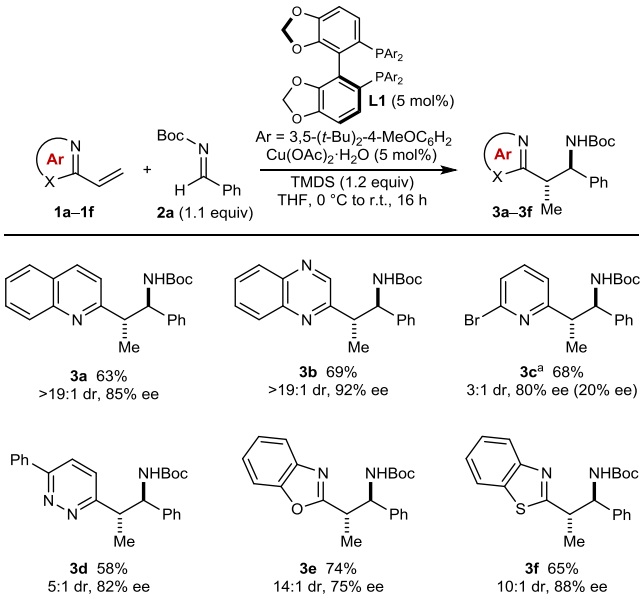
Herein, we describe the enantioselective Cu-catalyzed reductive coupling of vinylazaarenes with *N*-Boc aldimines. Both vinylazines and vinylazoles are effective substrates, and the Boc-protection in the products is advantageous for subsequent deprotection.

Our investigations began with an evaluation of chiral



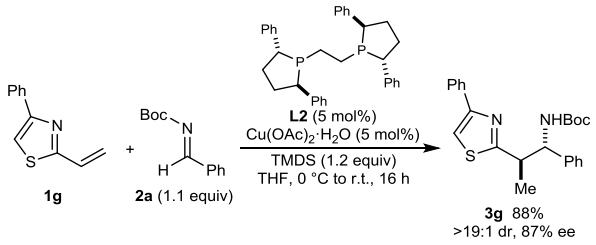
Scheme 1 Existing catalytic reductive coupling reactions of alkenylazaarenes.

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 $Cu(OAc)_2 \cdot H_2O$ (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 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**–**1f** were also effective in reactions with imine **2a**, which gave products **3b**–**3f** in 58–74% yield and 75–92% ee. Besides quinolone (**3a**), azaarenes that were tolerated included quinoxaline (**3b**), a bromopyridine (**3c**), a phenylpyridazine (**3d**), benzoxazole (**3e**), and benzothiazole (**3f**). High diastereoselectivities (≥10:1 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).



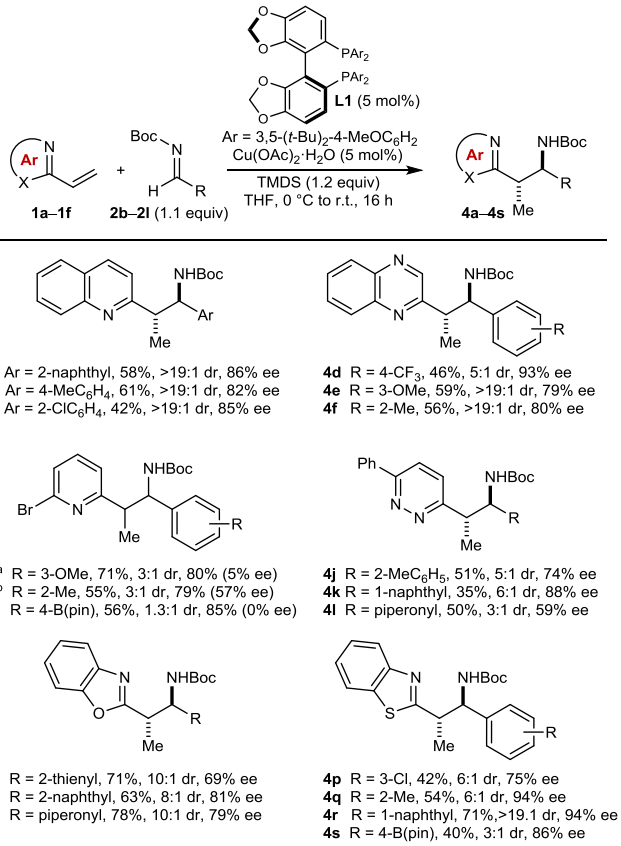
Scheme 2 Enantioselective reductive coupling of vinylazaarenes **1a**–**1f** with *N*-Boc imine **2a**. Reactions were conducted using 0.30 mmol of **1a**–**1f**. Unless stated otherwise, yields are of pure isolated major diastereomers. Diastereomeric ratios were determined by ^{1}H NMR analysis of the unpurified reaction mixtures. Enantiomeric excesses were determined by chiral HPLC analysis. [a] Yield of a 4.3:1 mixture of diastereomers. The enantiomeric excess of the minor diastereomer is indicated in parentheses.

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**.

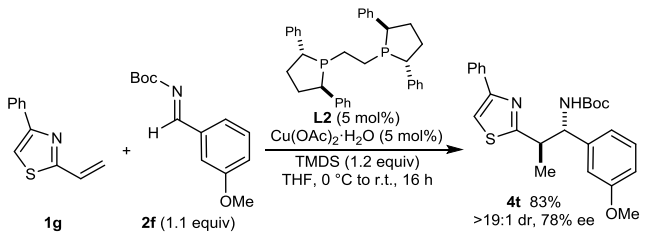
Various other (hetero)aromatic *N*-Boc aldimines **2b–2l** also underwent reductive coupling with vinylazaarenes **1a**–**1f**, giving products **4a**–**4s** in 59–94% ee for the major diastereomers (Scheme 4).[10] The diastereoselectivities of these reactions ranged from 1.3:1 dr (**4i**) to >19:1 dr (**4a**–**4c**, **4e**, **4f**, and **4r**). 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% ee or higher were observed in several cases (**4a**, **4c**, **4d**, **4i**, **4k**, and **4q**–**4s**). With respect to the imine, a range of substituents



Scheme 4 Enantioselective reductive coupling of vinylazaarenes **1a**–**1f** with various *N*-Boc imines. Reactions were conducted using 0.30 mmol of **1a**–**1f**. Unless stated otherwise, 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. 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.

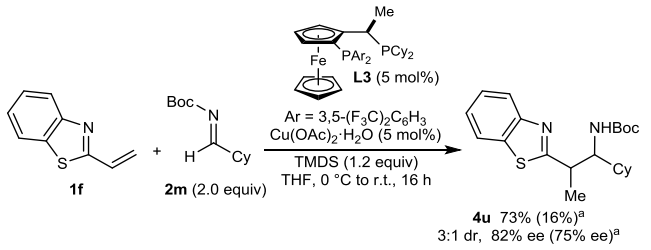
(methyl, trifluoromethyl, chloro-, methoxy, dioxolane, or boronate esters) at various positions on the phenyl ring were tolerated. Furthermore, reactions of imines containing 1-naphthyl, 2-naphthyl, or 2-thienyl groups were also successful. As observed previously (Scheme 1), the reactions of 2-bromo-6-vinylpyridine and 3-phenyl-6-vinylpyridazine generally gave lower diastereoselectivities (**4g**–**4l**) compared with the other vinylazaarenes. 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 non-existent enantiomeric excesses.

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



Scheme 5 Reductive coupling of **1g** with **2f** using ligand **L2**.

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 stereoselectivities 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% ee for the major and minor isomers, respectively.



Scheme 6 Reductive coupling of **1f** with an aliphatic *N*-Boc imine **2m** using ligand **L3**. [a] Values in parentheses refer to the yield and enantiomeric excess of the minor diastereomer.

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).

Scheme 7 Deprotection of **4a**.

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).

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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(9) **General Procedure for the Reductive Coupling of Vinylazaarenes with Imine 2a Using Ligand L1**
A solution of the appropriate vinylazaarene (0.30 mmol), $Cu(OAc)_2 \cdot H_2O$ (3.0 mg, 0.01 mmol), (*S*)-DTBM-SEGPHOS (**L1**) (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 μL, 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 SiO_2 and the resulting suspension was stirred for 15 min, before being filtered through a short plug of SiO_2 using EtOAc as eluent and concentrated *in vacuo*. Purification of the residue by flash column chromatography gave the reductive coupling product.
Data for 3a: R_f = (20% EtOAc/petroleum ether); mp 128-131 °C (EtOAc/petroleum ether); $[\alpha]_D^{24}$ +98.6 (*c* 1.10, $CHCl_3$); IR (film): 2970, 2934, 1709 (C=O), 1503, 1390, 1289, 827, 756, 700 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2CO$): δ = 8.14 (d, *J* = 8.4 Hz, 1 H), 8.05 (d, *J* = 8.3 Hz, 1 H), 7.88 (d, *J* = 8.0 Hz, 1 H), 7.75 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1 H), 7.57-7.51 (m, 1 H), 7.33 (d, *J* = 7.3 Hz, 2 H), 7.24 (t, *J* = 8.0 Hz, 3 H), 7.16 (t, *J* = 7.0 Hz, 2 H), 5.09 (t, *J* = 7.7 Hz, 1 H), 3.63-3.54 (m, 1 H), 1.35 (d, *J* = 6.9 Hz, 3 H), 1.27 (s, 9 H); ^{13}C NMR (125.8 MHz, $(CD_3)_2CO$): δ = 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; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{27}N_2O_2$ $[M+H]^+$: 363.2067, found: 363.2067; HPLC: Chiralcel OD-H column (90:10 *iso*-hexane:*i*-PrOH, 1.0 mL/min, 254 nm, 25 °C); t_R (major) = 4.6 min, t_R (minor) = 5.9 min; 85% ee.
Data for 3f: R_f = 0.32 (20% EtOAc/petroleum ether); mp 142-145 °C (EtOAc/petroleum ether); $[\alpha]_D^{24}$ +55.0 (*c* 1.00, $CHCl_3$); IR (film): 2979, 2928, 1713 (C=O), 1498, 1390, 1365, 1170, 1022, 759, 700 cm^{-1}; ^1H NMR (400 MHz, $(CD_3)_2CO$): 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); ^{13}C NMR (125.8 MHz, $(CD_3)_2CO$): 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; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{25}N_2O_2S$ $[M+H]^+$: 369.1631, found: 369.1634; HPLC: Chiralpak IC column (98:2 hexane:*i*-PrOH, 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**, **3g**, **4d**, **4k**, **4q**, and **4t**, 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 Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk