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Copper-catalyzed borylative coupling of vinylazaarenes and *N*-Boc imines

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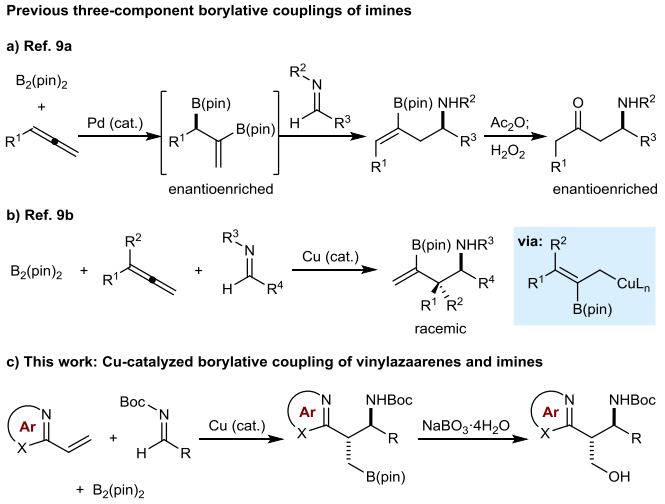
Cu-catalyzed three-component couplings of vinylazaarenes, $B_2(pin)_2$, and *N*-Boc imines are described. Oxidation of the initially formed boronate gives azaarene-containing, Boc-protected amino alcohols with reasonable to good diastereoselectivities.

Nitrogen-containing aromatic heterocycles (azaarenes) and α-branched amines are common structures in biologically active molecules. New catalytic reactions that can assemble compounds containing both of these motifs in a convergent and stereocontrolled manner are therefore highly valuable.[1] In this context, we have described enantioselective Pd-catalyzed additions of alkylazaarenes to *N*-Boc imines,[2] and enantioselective Cu-catalyzed reductive couplings of vinylazaarenes with *N*-Boc imines.[3] However, the integration of such coupling reactions with the simultaneous introduction of another, versatile functional group that can be exploited in subsequent manipulations would open up additional synthetic possibilities. Given the widely recognized utility of organoboron compounds,[4] and in connection with our interest in the use of azaarenes as activating groups in catalytic reactions,[5,6,7] we were prompted to examine the borylative coupling of vinylazaarenes with imines. Precedent for such a transformation is limited; although numerous borylative three-component coupling reactions have been described,[8,9] none employ alkenylazaarenes, and to our knowledge, only two examples employ imines (Scheme 1a and 1b).[9] The Morken group has reported enantioselective Pd-catalyzed diborations of allenes, followed by the addition of imines to the resulting bisboronates to give homoallylic amines (Scheme 1a).[9a] After acetylation of the amine and oxidation, β-acetamidoketones were isolated in good yields and high enantioselectivities.[9a] Recently, Procter and co-workers described Cu-catalyzed



Scheme 1 Catalytic borylative three-component couplings of imines.

borylative couplings of allenes with imines that give branched homoallylic amines containing an alkenylboronate (Scheme 1b).[9b] Extension of these processes to other substrate classes would lead to important increases in reaction scope. Herein, we report the first examples of Cu-catalyzed borylative couplings of vinylazaarenes with *N*-Boc imines to give highly functionalized heterocycle-containing building blocks (Scheme 1b).[10,11]

Our investigation began with a search for effective conditions for the three-component coupling of various vinylazaarenes and aldimines with bis(pinacolato)diboron. From these studies, we found that stirring a solution of the vinylazaarene (1.0 equiv), *N*-Boc aldimine (1.2 equiv), and $B_2(pin)_2$ (1.2 equiv) in TBME at 40 °C in the presence of $CuF(PPh)_3{\cdot}2MeOH$ (5.0 mol%) and dppf (5.0 mol%) successfully gave borylative coupling products with high conversions.[12,13,14] These products undergo decomposition on silica gel, and were therefore oxidized to the corresponding chromatographically stable primary alcohols with $NaBO_3{\cdot}4H_2O$.[15] Under these conditions, a range of vinylazaarenes **1a–1h** underwent smooth reaction with the *N*-Boc imine **2a** derived from

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† Electronic Supplementary Information (ESI) available: Experimental procedures, spectroscopic data for new compounds, and crystallographic data for **3b** and **3h**. CCDC 1431894 and 1431895. See DOI: 10.1039/x0xx00000x

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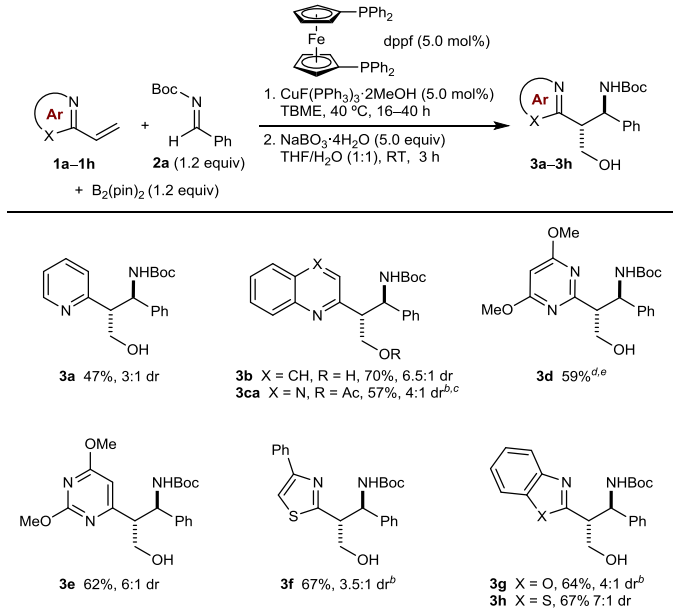
Table 1 Borylative coupling of vinylazaarenes with imine **2a**.[a]



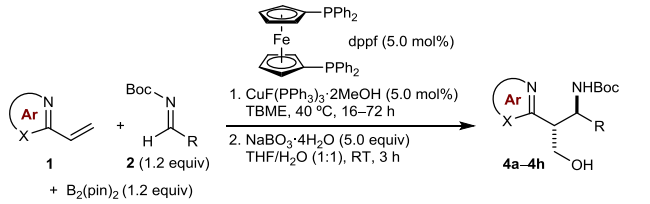
[a] Reactions were conducted using 0.50 mmol of vinylazaarene in TBME (1.25 mL). Yields are of isolated single diastereomers unless otherwise stated. Diastereomeric ratios were determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [b] Isolated as a mixture of diastereomers in the same ratio as in the unpurified reaction mixture. [c] Unpurified **3c** was treated with Ac_2O/pyridine to give **3ca** to facilitate purification. [d] Reaction performed at 60 °C. [e] Overlapping signals precluded accurate determination of dr by ^{1}H NMR analysis.

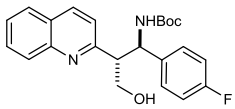
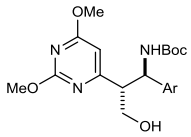
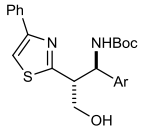
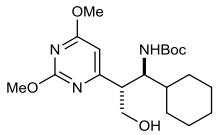
benzaldehyde to give azaarene-containing, Boc-protected amino alcohols **3a**, **3b**, and **3d–3h** (Table 1). Products containing pyridine (**3a**), quinoline (**3b**), one of two different dimethoxypyrimidines (**3d** and **3e**), 5-phenylthiazole (**3f**), benzoxazole (**3g**), or benzothiazole (**3h**) groups were prepared in reasonable to good yields and diastereoselectivities (up to 73% yield over two steps and up to 7:1 dr). The relative configurations of the products were assigned by analogy with those of **3b** and **3h**, which were determined by X-ray crystallography to be the *anti*-diastereomers.[16] In the case of **3d**, a higher temperature of 60 °C was required for good conversion. When 2-vinylquinoxaline was employed as the substrate, acetylation of the primary alcohol **3c** was performed to give **3ca** to facilitate separation from pinacol, a byproduct of the boronate oxidation.[15]

Table 2 presents the results of borylative coupling of various vinylazaarenes with a range of *N*-Boc aldimines, which gave products with diastereoselectivities ranging from 3:1 dr (entry 8) to 8.5:1 dr (entry 4). Imines derived from benzaldehydes containing methyl (entries 2, 7, and 9), fluoro (entries 1 and 11), chloro (entry 3), bromo (entry 5), or methoxy substituents (entries 4 and 8) at various positions of the aromatic ring are compatible with this process. The *N*-Boc imine derived from cyclohexane carboxaldehyde also successfully underwent borylative coupling, although with moderate conversion and diastereoselectivity (entry 12).

A tentative stereochemical model that could account for

Table 2 Borylative coupling of vinylazaarenes with various imines. [a]



Entry	Product		Yield (%)[b]	dr[c]
1		**4a**	73	6.5:1 (>19:1)
2		**4b** Ar = 3-MeC_6H_4	83	7.5:1
3		**4c** Ar = 3-ClC_6H_4	60	3:1 (5:1)
4		**4d** Ar = 4-$MeOC_6H_4$	58	8.5:1 (18:1)
5		**4e** Ar = 4-BrC_6H_4	60	3.5:1 (5:1)
6		**4f** Ar = 2-naphthyl	56	8:1 (11:1)
7		**4g** Ar = 2-MeC_6H_6	41[d]	7.5:1 (>19:1)
8		**4h** Ar = 3-$MeOC_6H_4$	58	3:1 (5:1)
9		**4i** Ar = 4-MeC_6H_4	69	3.5:1 (4:1)
10		**4j** Ar = 4-$MeOC_6H_4$	60	4:1
11		**4k** Ar = 4-FC_6H_4	64	3.5:1
12		**4l**	37	4:1 (>19:1)

[a] Reactions were conducted using 0.50 mmol of vinylazaarene in TBME (1.25 mL). [b] Yield of isolated products. [c] Diastereomeric ratios were determined by ^{1}H NMR analysis of the unpurified reaction mixtures. Ratios in parentheses are those of the isolated product. Where ratios in parentheses are absent, the products were isolated in the same ratio as in unpurified reaction mixture. [d] A second fraction consisting of a 2:1 mixture of diastereomers was also obtained in 17% yield.

the *anti*-selectivity of these reactions involves the addition of an *E*-azaallylcopper species to the imine in a chair-like transition state (Figure 1). However, we cannot exclude alternative models involving boat-like structures or open transition states.

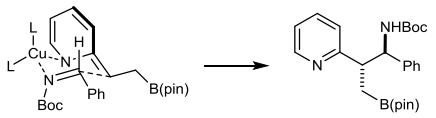


Figure 1 Possible stereochemical model.

To further demonstrate the synthetic utility of the borylative coupling products, the reaction of vinylpyrimidine **1e** and *N*-Boc imine **2a** was repeated to give alkylboronate **5**. Without isolation, **5** was reacted with bromobenzene under Suzuki-Miyaura cross-coupling conditions described previously[17] using RuPhos[18] as the ligand, to give the phenylated product **6** in 47% yield over two steps as a single diastereoisomer (crude dr 6:1) (Scheme 2).[19,20]

The Boc group of the products may be removed under acidic conditions, as demonstrated by the deprotection of **3b** using TMSCl in MeOH,[2,3] which provided the bishydrochloride

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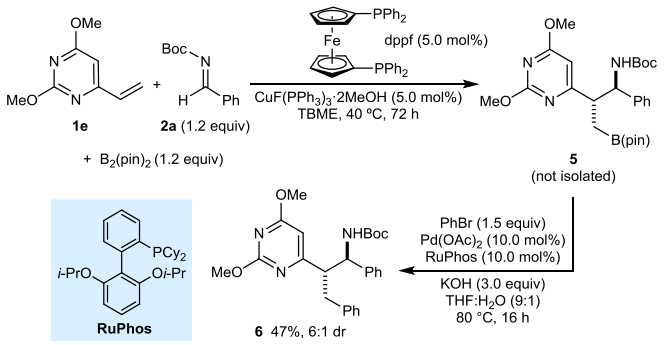
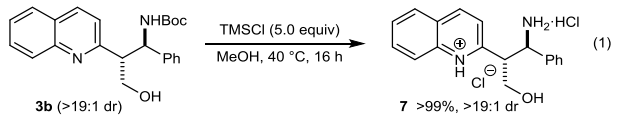


Scheme 2 Sequential borylative coupling and Suzuki reaction.



salt **7** in >99% yield (eq 1).

In conclusion, we have demonstrated the utility of vinylazaarenes as substrates for copper-catalyzed borylative couplings with *N*-Boc imines. The reactions provide, after oxidation of the initially formed alkylboronates, azaarene-containing, Boc-protected amino alcohols with moderate-to-good diastereoselectivities. Future work will be focused on the development of enantioselective variants of this process.[21]

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11 For examples of biologically active compounds containing a 2-(aminoalkyl)azaarene substructure, which are produced using the methodology described herein, see references cited within ref. 2.

12 In several cases, increasing the temperature significantly above 40 °C led to appreciable quantities of the products resulting from 1,4-boration of the vinylazaarene without coupling to the imine. Attempts to decrease the reaction times by increasing the concentration led to solubility problems.

13 Other bidentate ligands examined included DPEphos, dppe, dppbz, and bipy. No significant impact on the rate of the reaction was observed, but compared with dppf, these ligands gave products in poorer diastereomeric ratios. Using $CuF(PPh)_3{\cdot}2MeOH$ without an additional bidentate ligand gave low yields of borylative coupling products in poor diastereomeric ratios, along with significant quantities of products resulting from 1,4-boration of the vinylazaarene without coupling to the imine.

14 Control reactions conducted in the absence of the copper salt, but using PPh_3 (15.0 mol%) or dppf (5.0 mol%), with or without

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MeOH (10.0 mol% or 5.0 equiv), did not provide any products. For PPh_3- or dppf-catalyzed 1,4-boration of α,β-unsaturated ketones, see: A. Bonet, H. Gulyás and E. Fernández, *Angew. Chem., Int. Ed.*, 2010, **49**, 5130-5134.

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21 Thus far, our preliminary efforts at developing an enantioselective variant of these reactions have given only low enantiomeric excesses.

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