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Enantioselective Rhodium-Catalyzed Addition of Arylboronic Acids to Alkenylheteroarenes

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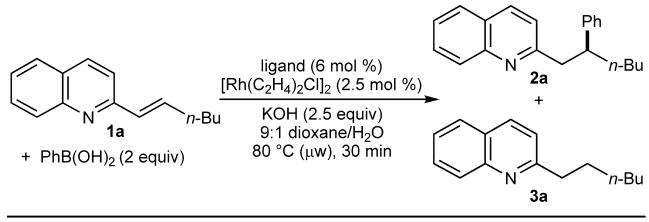
Abstract: In the presence of a rhodium complex containing a newly developed chiral diene ligand, alkenes activated by a range of π-deficient or π-excessive heteroarenes engage in highly enantioselective conjugate additions with various arylboronic acids.

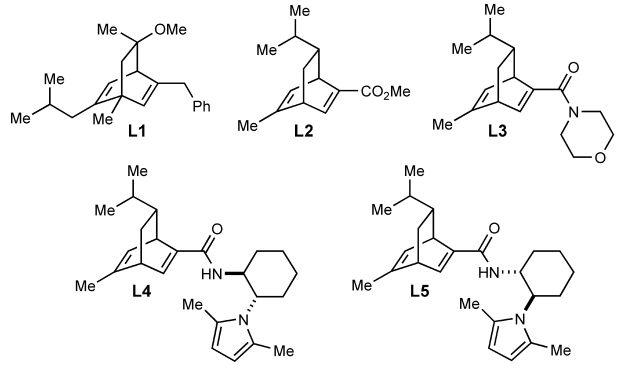
Heteroarenes are of widespread chemical significance, being present in numerous biologically active natural products, and serving as building blocks for the discovery of new medicines, agrochemicals, and functional molecules. Consequently, synthetic methods that enable functionalization of heteroarenes and their derivatives are of prime importance. Although metal-catalyzed cross-coupling reactions[1] and their modern equivalents involving C−H bond functionalization[2] have revolutionized this area, new methods that open up previously little explored pathways are of high value. In this regard, the addition of nucleophiles to β-substituted alkenylheteroarenes has captured our attention.[3] Despite the potential utility of catalytic asymmetric variants of these processes for generating chiral heteroarene-containing building blocks, such reactions have, until recently,[4,5] remained elusive.[6] We have demonstrated that alkenes conjugated to a C=N moiety in an adjacent heteroarene undergo highly enantioselective copper-catalyzed hydride additions.[4] Due to issues of convergency, analogous processes involving *C−C bond formation* are inherently of much greater value. Herein we report the catalytic enantioselective addition of arylboronic acids and an alkenyl MIDA boronate to alkenylheteroarenes.

Rhodium-catalyzed asymmetric 1,4-addition of arylboron compounds to alkenes activated by electron-withdrawing groups has emerged as a versatile method for the construction of chiral compounds.[7−9] However, examples where heteroarenes are employed in alkene activation are limited to β-*unsubstituted* vinylazines, which provide achiral products.[10−12] Although the possibility of future asymmetric variants was mentioned,[10a] such a report has not appeared, presumably due to the relatively poor reactivity of β-substituted alkenylheteroarenes.

Undeterred, we first studied the racemic addition of $PhB(OH)_2$ (2 equiv) to (*E*)-2-alkenylquinoline **1a** using $[Rh(cod)Cl]_2$ (2.5 mol %) and KOH in 9:1 dioxane/H_2O at 80 °C for 30 min under microwave (μw) irradiation. These experiments highlighted the importance of the amount of KOH in promoting the reaction; *rac*-**2a** was obtained in 43% and 14% NMR yield when 2.5 and 0.5 equiv of KOH were used, respectively. The remaining mass balance in these reactions was unreacted **1a**, along with traces (*ca.* 3−6%) of the reduction product **3a**.[13] Next, a variety of chiral diene ligands, which are known to exhibit high activities in related processes,[14,15] were evaluated (Table 1). Using $[Rh(C_2H_4)_2Cl]_2$ (2.5 mol %) in the presence of 2.5 equiv of KOH, the commercial ligand **L1**[16] provided **2a** in good conversion and a promising 79% ee (entry 1).[17] While (*R*)-α-phellandrene-derived diene **L2**[18,19] gave **2a** in similar enantioselectivity, the conversion was much lower (entry 2). New derivatives of **L2** were then prepared for evaluation. Although morpholine amide **L3** offered no improvement (entry 3), diene **L4**, constructed from (*S*,*S*)-2-(2,5-dimethyl)pyrrol-1-ylcyclohexylamine, provided **2a** in high enantioselectivity, though in incomplete conversion (entry 4). The chiralities of the diene and cyclohexyl fragments of **L4** appear to be a matched combination, as suggested by the inferior results obtained using diastereomeric ligand **L5** (entry 5). On the basis of the high enantioselectivity imparted by **L4**, this ligand was selected for further experimentation.

Table 1. Evaluation of Chiral Dienes for the Arylation of **1a**[a]



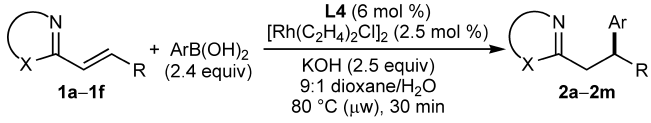


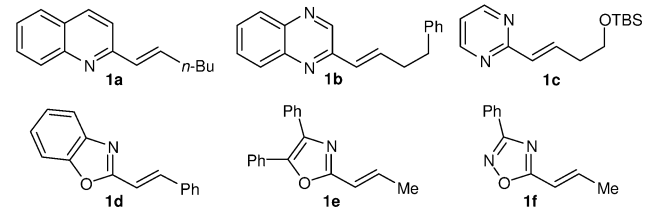
entry	ligand	**1a** (%)[b]	**2a** (%)[b,c]	**3a** (%)[b]
1	**L1**	0	89 (79% ee)	11
2	**L2**	60	33 (78% ee)	7
3	**L3**	75	19 (53% ee)	6
4	**L4**	26	68 (93% ee)	6
5	**L5**	65	31 (81% ee)	4

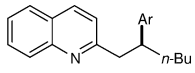
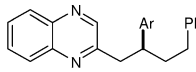
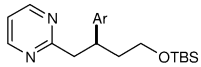
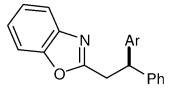
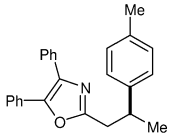
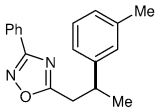
[a] Reactions were conducted using 0.10 mmol of **1a** (0.1 M). [b] Determined by ^{1}H NMR analysis. [c] Enantioselectivities of **2a** were determined by chiral HPLC analysis.

Table 2 presents the results of the investigation of the scope of the reaction using **L4**. Higher conversions into the products were realized by doubling the concentrations of the reactions to 0.2 M with respect to the alkenylheteroarene and by employing 2.4 equiv of the arylboronic acid.[20] Under these conditions, arylboronic acids containing various substituents (including methyl, chloro, fluoro, and alkoxy) underwent highly enantioselective addition to a range

Table 2. Asymmetric Rh-Catalyzed Arylation of Alkenylheteroarenes[a]





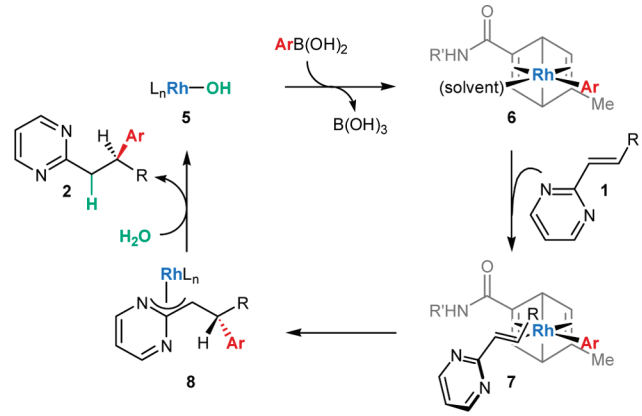
entry	product		yield (%)[b]	ee (%)[c]
1		Ar = Ph **2a**	56[d]	95
2		Ar = 4-MeC$_6$H$_4$ **2b**	67	92
3		Ar = 3-MeC$_6$H$_4$ **2c**	71	95
4[e]		Ar = Ph **2d**	80[f]	90
5		Ar = 2-MeC$_6$H$_4$ **2e**	72	97
6		Ar = 4-ClC$_6$H$_4$ **2f**	75	90
7[g]		Ar = 4-FC$_6$H$_4$ **2g**	91	91
8		Ar = 4-MeOC$_6$H$_4$ **2h**	90	93
9		Ar = Ph **2i**	72	98
10		Ar = 4-FC$_6$H$_4$ **2j**	65	97
11		Ar = 2-naphthyl **2k**	78	93
12		Ar = 3-Cl-4-*i*PrOC$_6$H$_3$ **2l**	69	93
13		**2m**	69	89
14		**2n**	64	94

[a] Unless otherwise stated, reactions were conducted using 0.50 mmol of **1a**−**1f** (0.2 M). [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Isolated as a 14:1 inseparable mixture of **2a** and **3a**. [e] Using 2.0 equiv of PhB(OH)$_2$. [f] Isolated as a 16:1 inseparable mixture of **2d** and the reduction product **3d** (see Supporting Information). [g] Reaction performed using 2.0 mmol of **1b** (0.2 M) at 80 °C under thermal heating for 1 h, using 3 mol % Rh and 3.6 mol % of **L4**.

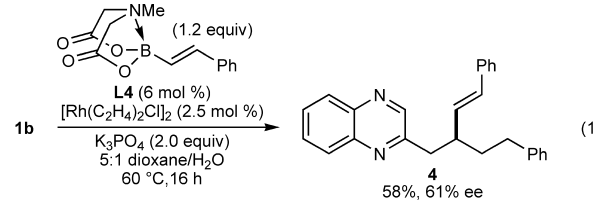
of (*E*)-alkenylheteroarenes.[17,21] In addition to 2-alkenylquinoline **1a** (entries 1−3), substrates that are effective include alkenes activated by π-deficient heteroarenes such as quinoxaline (entries 4−8) and pyrimidine (entries 9 and 10), as well as π-excessive heteroarenes such as benzoxazole (entries 11 and 12), 4,5-diphenyloxazole (entry 13), and 3-phenyl-1,2,4-oxadiazole (entry 14). Regarding the β-position of the alkene, both aliphatic (entries 1−10, 13, and 14) and aromatic (entries 11 and 12) substituents are tolerated. Microwave irradiation is not necessary for the reaction to proceed. For example, reaction of 2-alkenylquinoxaline **1b** with 4-fluorophenylboronic acid on a 2.0 mmol scale was readily accomplished under thermal heating using only 1.5 mol % of [Rh(C$_2$H$_4$)$_2$Cl]$_2$ and 3.6 mol % of **L4**, which provided **2g** in 91% yield and 91% ee (entry 7).

Attempts to expand the scope of the nucleophile to encompass alkenylboronic acids were largely unsuccessful. Under various

Scheme 1. Possible Catalytic Cycle



conditions, only small quantities of the desired 1,4-addition products were observed, with protodeboronation of the alkenylboronic acid being the dominant outcome. Recently, *N*-methyliminodiacetic acid (MIDA) boronates[22] have emerged as promising alternatives to boronic acids in transition-metal-catalyzed reactions[23−25] by virtue of their high benchtop stability and their capacity to gradually release unstable boronic acids in situ under carefully controlled aqueous basic conditions, thus minimizing decomposition pathways. These features are especially valuable for 2-heterocyclic[23] and alkenylboronic acids,[24] which generally exhibit lower stability than simple arylboronic acids.



Fortunately, in this study, alkenyl MIDA boronates also proved to be superior to their boronic acid counterparts in delivering the desired products.[24] For example, alkenylquinoxaline **1b** reacted with (*E*)-2-phenylvinyl MIDA boronate in 5:1 dioxane/H$_2$O in the presence of K$_3$PO$_4$ (2.0 equiv) at 60 °C for 16 h to provide **4** in 58% yield, though in a modest 61% ee (eq 1).

In accordance with the accepted catalytic cycle of conjugate addition of arylboronic acids to enones[26] and the stereochemical model proposed for arylation of acyclic substrates,[14a,18] a possible mechanism for the reactions described herein, using an alkenylpyrimidine for illustrative purposes, is presented in Scheme 1. Treatment of [Rh(C$_2$H$_4$)$_2$Cl]$_2$ and **L4** with KOH results in formation of chiral diene-ligated rhodium hydroxide **5**, which can undergo transmetalation with the arylboronic acid to form rhodium aryl species **6**, where the rhodium−aryl linkage is positioned *trans* to the more electron-deficient alkene. Coordination of the alkenylheteroarene **1** to the remaining binding site of **6** then occurs as depicted in **7** to minimize unfavorable nonbonding interactions between the heteroarene and the amide substituent of the ligand. Arylrhodation of the bound substrate results in the formation of aza-π-allylrhodium intermediate **8**, which then undergoes hydrolysis to regenerate the rhodium hydroxide **5** and liberate the product **2**.

The lower reactivity of alkenylheteroarenes compared with established substrates for Rh-catalyzed 1,4-arylation may be attributed, at least in part, to the loss of aromaticity that accompanies the formation of aza-π-allylrhodium species **8**. Therefore, structural features in the heteroarene that reduce this energetic penalty would

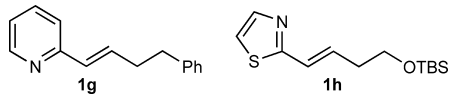


Figure 1. Poorly reactive substrates.

be expected to result in more reactive substrates.[27] Such features include benzannulation (Table 1, entries 1−8, 11, and 12), the presence of a second C═N moiety (entries 4−10 and 14), and conjugation with aryl substituents (entry 13). The importance of these features is underscored by attempted arylation of substrates that lack them. For example, under our standard conditions, 2-alkenylpyridine **1g** and 2-alkenylthiazole **1h** (Figure 1) remain largely unchanged, providing only small quantities (<30%) of arylation products and other unidentified side products. Work is underway to identify improved conditions to arylate these less reactive substrates.

In summary, by employing a new chiral diene ligand **L4**, highly enantioselective Rh-catalyzed additions of arylboronic acids to β-monosubstituted alkenylheteroarenes have been developed. This work further exemplifies the capacity of C═N-containing heteroarenes, chemotypes of relevance to chemists in the medicinal and agrochemical industries, to activate alkenes toward catalytic asymmetric conjugate addition reactions.[4,5] Further exploration of this reaction in more depth, along with the development of related processes, is ongoing in our laboratory.

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Supporting Information Available: Experimental procedures, full spectroscopic data for new compounds, and crystallographic data in cif format. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004.
(2) For recent, selected reviews, see: (a) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890–931. (b) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115. (c) Thansandote, P.; Lautens, M. *Chem.—Eur. J.* **2009**, *15*, 5874–5883. (d) Joucla, L.; Djakovitch, L. *Adv. Synth. Catal.* **2009**, *351*, 673–714. (e) Daugulis, O.; Do, H.-Q.; Shabashov, C. *Acc. Chem. Res.* **2009**, *42*, 1074–1086. (f) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238.
(3) (a) Hoffman, A.; Farlow, M. W.; Fuson, R. C. *J. Am. Chem. Soc.* **1933**, *55*, 2000–2004. (b) Gilman, H.; Gainer, G. C. *J. Am. Chem. Soc.* **1949**, *71*, 2327–2328. (c) Mathis, C.; Hogen-Esch, T. E. *J. Am. Chem. Soc.* **1982**, *104*, 634–635. (d) Dryanska, V.; Ivanov, C. *Synthesis* **1983**, 143–145. (e) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Tetrahedron* **1988**, *44*, 2021–2031. (f) Epifani, E.; Florio, S.; Troisi, L. *Tetrahedron* **1990**, *46*, 4031–4038. (g) Cliffe, I. A.; Ifill, A. D.; Mansell, H. L.; Todd, R. S.; White, A. C. *Tetrahedron Lett.* **1991**, *32*, 6789–6792.
(4) Rupnicki, L.; Saxena, A.; Lam, H. W. *J. Am. Chem. Soc.* **2009**, *131*, 10386–10387.
(5) For catalytic asymmetric conjugate additions of nitroalkanes to 4-nitro-5-styrylisoxazoles, see: Baschieri, A.; Bernardi, L.; Ricci, A.; Suresh, S.; Adamo, M. F. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9342–9345.
(6) For Ni-catalyzed addition of organometallics to 4-alkenylpyridines proceeding with low (≤15% ee) enantioselectivities, see: Houpis, I. N.; Lee, J.; Dorziotis, I.; Molina, A.; Reamer, B.; Volante, R. P.; Reider, P. J. *Tetrahedron* **1998**, *54*, 1185–1195.
(7) (a) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229–4231. (b) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579–5580.
(8) For reviews, see: (a) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829–2844. (b) Yoshida, K.; Hayashi, T. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; Chapter 3, pp 55−77. (c) Edwards, H. J.; Hargrave, J. D.; Penrose, S. D.; Frost, C. G. *Chem. Soc. Rev.* **2010**, *39*, 2093–2105.
(9) For a review of Rh-catalyzed carbon−carbon bond-forming reactions of organometallic compounds, see: Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169–196.
(10) (a) Lautens, M.; Roy, A.; Fukuoka, K.; Fagnou, K.; Martín-Matute, B. *J. Am. Chem. Soc.* **2001**, *123*, 5358–5359. (b) Amengual, R.; Michelet, V.; Genêt, J.-P. *Tetrahedron Lett.* **2002**, *43*, 5905–5908.
(11) During the preparation of this manuscript, a single example of a racemic cobalt-catalyzed addition of an alkenylboronic acid to 2-[(*E*)-prop-1-enyl]pyridine was reported: Kobayashi, T.; Yorimitsu, H.; Oshima, K. *Chem.—Asian J.* **2010**, DOI: 10.1002/asia.201000275.
(12) For examples of Rh-catalyzed addition of arylboronic acids to alkynylazines, see: (a) Lautens, M.; Yoshida, M. *Org. Lett.* **2002**, *4*, 123–125. (b) Lautens, M.; Yoshida, M. *J. Org. Chem.* **2003**, *68*, 762–769. (c) Genin, E.; Michelet, V.; Genêt, J.-P. *Tetrahedron Lett.* **2004**, *45*, 4157–4161. (d) Genin, E.; Michelet, V.; Genêt, J.-P. *J. Organomet. Chem.* **2004**, *23*, 3820–3830.
(13) For similar observations, see: (a) Walter, C.; Oestreich, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3818–3820. (b) Walter, C.; Frölich, R.; Oestreich, M. *Tetrahedron* **2009**, *65*, 5513–5520.
(14) For seminal references, see: (a) Hayashi, T.; Ueyama, N.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508–11509. (b) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628–1629.
(15) For reviews, see: (a) Shintani, R.; Hayashi, T. *Aldrichimica Acta* **2009**, *42*, 31–38. (b) Defieber, C.; Grützmacher, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4482–4502.
(16) Paquin, J.-F.; Defieber, C.; Stephenson, C. R. J.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 10850–10851.
(17) The absolute configurations of the products obtained herein were assigned by analogy with that of **2g**, which was determined by X-ray crystallography. See Supporting Information for details. The sense of enantioinduction obtained using **L4** is consistent with reported examples of 1,4-arylation of acyclic enones (ref 18).
(18) Okamoto, K.; Hayashi, T.; Rawal, V. H. *Org. Lett.* **2008**, *10*, 4387–4389.
(19) For the synthesis of a range of other (*R*)-α-phellandrene-derived chiral dienes using an improved route, see: Okamoto, K.; Hayashi, T.; Rawal, V. H. *Chem. Commun.* **2009**, 4815–4817.
(20) With these modestly reactive substrates, competing Rh-catalyzed protodeboronation is the likely side reaction, necessitating the use of an excess of arylboronic acid for acceptable yields.
(21) (*Z*)-Alkenylheteroarenes are also competent substrates in these reactions but provide the same major enantiomer of product as the corresponding (*E*)-isomers, using the same enantiomeric series of the chiral diene. For example, arylation of (*Z*)-**1a** with $PhB(OH)_2$ using ligand **L1** gave (*S*)-**2a** in 80% ee. We attribute this observation to isomerization of (*Z*)-substrates to the (*E*)-isomers under the reaction conditions, prior to arylation.
(22) (a) Mancilla, T.; Contreras, R.; Wrackmeyer, B. *J. Organomet. Chem.* **1986**, *307*, 1–6. (b) Mancilla, T.; Zamudio-Rivera, L. S.; Beltrán, H. I.; Santillan, R.; Farfán, N. *Arkivoc* **2005**, (vi), 366–376.
(23) For the use of MIDA boronates in Suzuki reactions through slow release of boronic acids, see: Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961–6963.
(24) For the use of MIDA boronates in rhodium-catalyzed alkenylation of *N-tert*-butylsulfinyl imines, see: (a) Brak, K.; Ellman, J. A. *J. Org. Chem.* **2010**, *75*, 3147–3150. (b) Brak, K.; Ellman, J. A. *Org. Lett.* **2010**, *12*, 2004–2007.
(25) For a review of the properties of MIDA boronates, including their use in iterative cross-couplings, see: Gillis, E. P.; Burke, M. D. *Aldrichimica Acta* **2009**, *42*, 17–27.
(26) Hayashi, T.; Takahishi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052–5058.
(27) For discussions of quantitative measures of aromaticity of heteroarenes, see: (a) Katritzky, A. R.; Jug, K.; Oniciu, D. C. *Chem. Rev.* **2001**, *101*, 1421–1449. (b) Simkin, B. Ya.; Minkin, V. I.; Glukhovtsev, M. N. *Adv. Heterocycl. Chem.* **1993**, *56*, 303–428. (c) Katritzky, A. R.; Karelson, M.; Malhotra, N. *Heterocycles* **1991**, *32*, 127–161. (d) Cook, M. J.; Katritzky, A. R.; Linda, P. *Adv. Heterocycl. Chem.* **1974**, *17*, 255–356.

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