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Rhodium-Catalyzed Asymmetric Ring Opening of Oxabicyclic Alkenes with Organoboronic Acids

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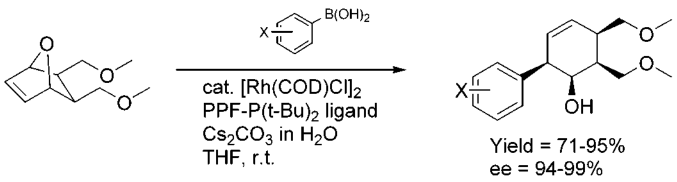
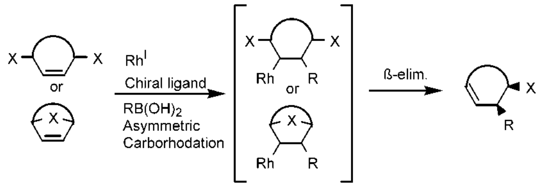
ABSTRACT



The first rhodium(I)-catalyzed asymmetric addition of organoboronic acids to oxabicyclic alkenes is reported. This asymmetric ring-opening (ARO) reaction can proceed in high yield under very mild conditions with electronically diverse organoboronic acids, in a highly diastereoselective and enantioselective manner.

Significant advances have been made in the area of rhodium-catalyzed additions of aryl-[1] and alkenylboronic acids to activated olefins since the first report by Miyaura.[2] Highly enantioselective conjugate additions of boronic acids to olefins have been reported by Hayashi.[3] A common step in these reactions is the carborhodation of the carbon−carbon double bond followed by hydrolysis of the organorhodium intermediate. We imagined a system whereby after carborhodation, a β-elimination instead of hydrolysis would occur (Scheme 1). Where two enantiotopic leaving groups are available, an asymmetric carborhodation/β-elimination pathway would result in the enantioselective formation of a new carbon−carbon bond and regeneration of the olefin.

Scheme 1



Herein, we present the realization of this concept by the development of a rhodium-catalyzed asymmetric ring opening (ARO)[4] reaction of oxabicyclic alkenes with organoboronic acids. The reaction proceeds under very mild conditions and generates multiple stereocenters in high yield with excellent diastereoselectivity[5] and enantioselectivity.

Our early efforts focused on the enantioselective addition of arylboronate esters to activated oxabicyclic alkenes. It was found that oxabenzonorbornadiene **1** undergoes rapid ring-opening addition of various phenylboron species to give **2**, using catalytic $[Rh(COD)Cl]_2$ and various phosphine ligands. PPF-P^tBu_2 **3** was identified as the ligand giving the best reactivity and enantioselectivity for the addition of phenylboronate (activated by MeLi)[6] to **1** (Scheme 2).[7]

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[1] Review of asymmetric arylations: Bolm, C.; Hildebrand, J. P.; Muñiz, K.; Hermanns, N. *Ang. Chem., Int. Ed.* **2001**, *40*, 3284.

[2] Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229.

[3] (a) Hayashi, T. *Synlett* **2001**, 879. (b) Senda, T.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **2001**, *66*, 6852 and references therein.

[4] For other examples of ARO reactions, see, for example: (a) Lautens, M.; Hiebert, S.; Renaud, J.-L. *J. Am. Chem. Soc.* **2001**, *123*, 6834. (b) Lautens, M.; Fagnou, K.; Taylor, M.; Rovis, T. *J. Organomet. Chem.* **2001**, *624*, 259. (c) Lautens, M.; Rovis, T. *J. Am. Chem. Soc.* **1997**, *119*, 11090.

[5] Only a single diastereomer has ever been detected for any of the ring-opened products in this Letter.

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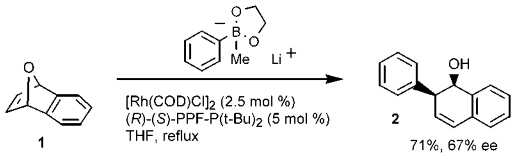
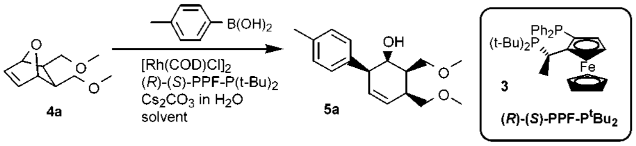
Scheme 2



Shortly after these early experiments, it was found that the ARO of other oxabicyclic substrates with a [Rh(COD)-Cl]$_2$/PPF-P^{t}Bu$_2$ catalyst system can occur in high yield with excellent enantioselectivity using arylboronic acids as the nucleophillic partner, plus added water and base. The ARO of [2.2.1] oxabicycle **4a** with 4-methylphenylboronic acid was adopted as the prototype reaction. Initial optimization studies examined the effect of temperature on enantioselectivity (Table 1).

Table 1. Enantioselectivity vs Temperature Studies[a]



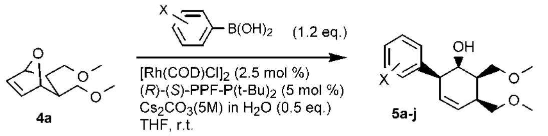
entry[b]	solvent	temp (°C)	ee (%)[c]
1	THF	65	88
2	THF	55	90
3	THF	40	94
4	THF	25	95
5	1,4-dioxane	25	93
6[d]	THF/H$_2$O[e]	−20	99

[a] Conditions (unoptimized): oxabicycle **4a** (50 mg, 1 equiv) and Cs$_2$CO$_3$ (2 M in H$_2$O, 50 mL, 0.4 equiv) is added to a stirred solution of [Rh(COD)Cl]$_2$ (3.3 mg, 0.025 equiv), (*R*)-(*S*)-PPF-P(^{t}Bu)$_2$ (7.4 mg, 0.05 equiv), and 4-methylphenylboronic acid (0.111 g, 3 equiv) in the solvent of choice (3 mL), at the stated reaction temperature, under a nitrogen atmosphere. [b] All reactions gave complete conversion of starting material to product as observed by TLC. Isolated yield for entry 4 = 92%. [c] As determined by chiral HPLC (Chiracel OD column). [d] With 0.1 equiv of [Rh(COD)Cl]$_2$, 0.2 equiv of PPF-P(t-Bu)$_2$, and 20 equiv of Cs$_2$CO$_3$ (2 M in H$_2$O) solution. [e] Reaction was biphasic.

The enantioselectivity of the ARO reaction increases with decreasing temperature, within the studied range. This result is in contrast to other known Rh(I)-catalyzed conjugate additions, where enantioselectivities are improved at elevated temperatures.[3,4b] The reaction is very sluggish at −20 °C, though it was discovered that it is much faster at this temperature when an excess of base solution is used (entry 6).[8] The reaction requires a minimum amount of water for catalytic turnover,[9] and at room temperature it appears to work best with 5−10 equiv relative to the oxabicycle. We also found that complete reaction occurs with only 1.2 equiv of ArB(OH)$_2$ in THF at both room temperature and reflux, indicating that catalytic deboronation of the arylboronic acid does not occur to any appreciable extent, as has been observed with Rh(I)-catalyzed reactions at higher temperatures.[10]

On the basis of these findings, we used as our standard conditions 5 mol % of catalyst, 1.2 equiv of organoboronic acid, and 0.5 equiv of Cs$_2$CO$_3$[11] (5 M in H$_2$O) in THF at room temperature and stirring for ~15 h. The ARO reaction of oxabicycle **4a** works equally well with both electron-rich and electron-poor arylboronic acids (Table 2). However, it appears to be intolerant of substituents on the phenyl ring ortho to boron (entries 3 and 6). Even under harsher conditions (refluxing 1,4-dioxane with 10 mol % of Rh catalyst), no measurable amount of ring-opened product was observed. 3-Iodophenylboronic acid is compatible with the catalyst, indicating that insertion into the Ar−I bond is not competitive with insertion of the alkene (although higher catalyst loadings were necessary for the reaction to proceed to completion), permitting subsequent functionalization of the product (entry 7).

Table 2. ARO of Oxabicycle **4a** with Arylboronic Acids[a]



entry	phenyl substituent	product[b]	yield (%)[c]	ee (%)[d]
1	4-Me	**5a**	88	95
2	none	**5b**	91	95
3	2-Me	**5c**	n.r.	
4	4-Cl	**5d**	95	95
5	3-Cl	**5e**	73	99
6	2-Cl	**5f**	n.r.	
7[e]	3-I	**5g**	85	95
8	4-Ac	**5h**	71	94
9	4-OMe	**5i**	87	96
10	3-OMe	**5j**	91	95

[a] Reactions performed with 50 mg (0.271 mmol) of **4a**. [b] Products are diastereomerically pure. [c] Isolated yield after column chromatography. [d] As determined by chiral HPLC (Chiracel OD or AD columns). [e] Required 5 mol % of [Rh(COD)Cl]$_2$ to proceed to completion.

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(6) Our initial efforts were inspired by a report by Kobayashi where boronates were found to show enhanced reactivity relative to the analagous boronic esters and acids: Kobayashi, Y.; Mizojiri, E.; Ikeda, E. *J. Org. Chem.* **1996**, *61*, 5391.

(7) Other ligands giving worse reactivity and/or enantioselectivity were BINAP, tol-BINAP, and i-Pr-POX. See the Supporting Information for more details.

(8) It is hypothesized that the use of base accelerates the transmetalation of the boronic acid to rhodium. This has been proposed in the Pd-catalyzed Suzuki reaction. See, for example: (a) Suzuki, A.; Miyaura, N. *Chem. Rev.* **1995**, *95*, 2457. (b) Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095.

(9) No reaction was observed in the presence of 4 Å molecular sieves and no added water.

(10) Lautens, M.; Roy, A.; Fukuoka, K.; Fagnou, K.; Martín-Matute, B. *J. Am. Chem. Soc.* **2001**, *123*, 5358.

(11) ARO of **4** with 4-methylphenylboronic acid works equally well (same yield and enantioselectivity) with CsF instead of Cs$_2$CO$_3$.

Alkenylboronic acids are also compatible in the reaction. ARO of **1** and **4b** with *trans*-1-hexen-1-ylboronic acid using the standard conditions occurs in high yield with good enantioselectivity (Scheme 3). Application of these conditions to the ARO of **1** with PhB(OH)$_2$ gave a complex mixture of products (Table 3, entry 1).[12] At first it was hypothesized that the product **2** may not be stable under the reaction conditions, but this was disproven by resubmitting pure **2** to the reaction conditions. While the slow addition of **1** resulted in a cleaner reaction, the yield was still low (entry 2). Surprisingly, much better results were obtained with the ethylene glycol ester of PhB(OH)$_2$ using the standard reaction conditions (entry 3). The absolute configuration of **2** was determined by an X-ray crystal structure of the hydrogenated (tetrahydronaphthalene) 4-bromobenzoate derivative.[13] The reasons for the difference in reactivity between the two phenylboron species are under investigation. The boronic ester method was applied to oxabicycles **9a** and **9b** to investigate the electronic effects of the substrate (Scheme 4). Preliminary results indicate a comparable yield and enantioselectivity with the difluoro compound **9a**, but reaction with **9b** led to a complex mixture of products.[14]

Scheme 3

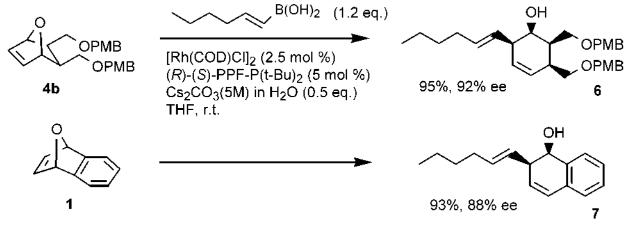
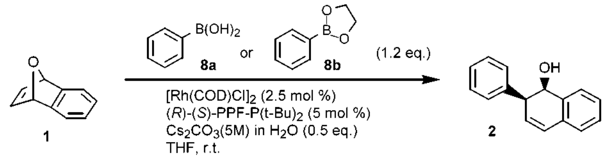


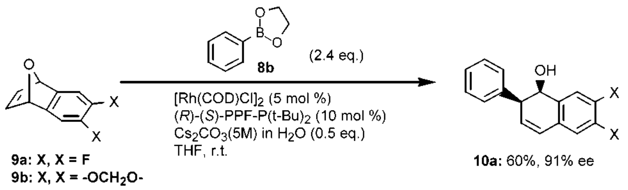
Table 3. ARO of Oxabicycle **1** with Ph Nucleophile **8a** or **8b**[a]



entry	Ph source	yield (%)[b]	ee (%)[c]	method[d]
1	**8a**	20	93	A
2	**8a**	28	92	B
3	**8b**	78	92	C

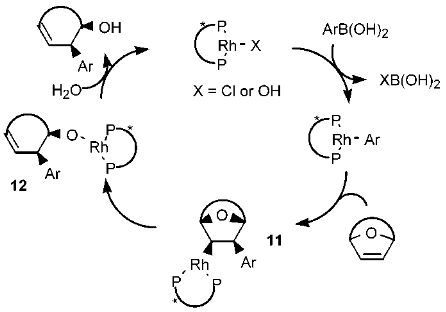
[a] All reactions performed with 50 mg (0.347 mmol) of **1**. Reactions were stirred for ~15 h. [b] Isolated yield after column chromatography. [c] As determined by chiral HPLC (Chiracel OD column). [d] Method A: Rh, ligand, **1**, and **8a** were added to a flask and placed under nitrogen. THF (1 mL) and Cs$_2$CO$_3$ solution were then added. Method B: Rh, ligand, and **8a** were added to a flask and placed under nitrogen. THF (1.5 mL) and Cs$_2$CO$_3$ solution were then added. **1** (0.35 M THF solution) was added by syringe pump to the reaction over 3.5 h. Method C: Rh, ligand, and **1** were added to a flask and placed under nitrogen. **8b** was added with THF (3 mL), followed by Cs$_2$CO$_3$ solution.

Scheme 4



The proposed mechanism for the ARO of oxabicyclic alkenes is given in Scheme 5.[15] The first step involves a transmetalation of the arylboronic acid to a rhodium(I) chloride or hydroxide. This species will then undergo an *exo*-selective asymmetric carborhodation at the oxabicycle olefin to generate intermediate **11**. Chelation of the olefin and the oxygen atom of the oxabicycle may help to contribute to the high *exo* selectivity with **1**. β-Elimination of oxygen[16] to give ring-opened intermediate **12** occurs, followed by hydrolysis to liberate the ring-opened product and rhodium(I) hydroxide.

Scheme 5



In conclusion, we have developed a novel asymmetric ring-opening reaction of oxabicyclic alkenes with addition of alkenyl or aryl groups. The reactions can proceed in high yield under very mild conditions with a variety of boronic acids, with excellent enantio- and diastereoselectivities using the [Rh(COD)Cl]$_2$/PPF-P^{t}Bu$_2$ catalyst system.

Acknowledgment. We thank AstraZeneca (Montreal), NSERC, the ORDCF, and the University of Toronto for the

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(12) (a) A racemic version of this reaction using Rh(I)/P(OEt)$_3$ was recently reported: Murakami, M.; Igawa, H. *Chem. Commun.* **2002**, 390. (b) Pd-catalyzed asymmetric arylation reactions of **1** have been reported: Fiaud, J.-C.; Moinet, C. *Tetrahedron Lett.* **1995**, *36*, 2051.

(13) See the Supporting Information for details. Absolute configurations of the other compounds in this Letter have been tentatively assigned by analogy.

(14) Additional catalyst and phenylboronic ester were added to both reactions (performed with 50 mg of oxabicycle) to push reactions to completion.

(15) Studies to support this mechanism are underway.

(16) See ref 4a for a discussion of this step in a Pd-catalyzed ARO.

funding of this research. We also thank Solvias for providing the PPF-P^{t}Bu$_2$ ligand used in these studies and Dr. Alan Lough for X-ray structure determination. K.F. thanks NSERC for a postgraduate scholarship (Ph.D.). K.F. and C.D. thank AstraZeneca and NSERC for industrial postgraduate scholarships. A.M. thanks NSERC for a summer scholarship.

Supporting Information Available: Experimental details and characterization data including ^{1}H and ^{13}C NMR, X-ray crystal data, IR, HR-MS, and HPLC conditions. This material is available free of charge via the Internet at http://pubs.acs.org.

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