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Rhodium-Catalyzed Asymmetric Allylic Substitution with Boronic Acid Nucleophiles

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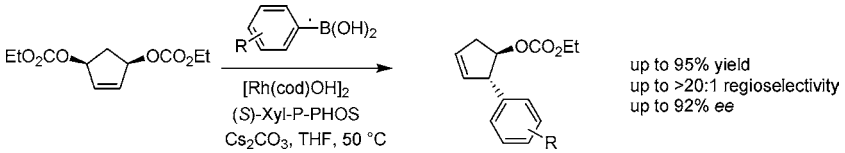
ABSTRACT



An enantio-, regio-, and diastereoselective rhodium(I)-catalyzed desymmetrization of a *meso*-cyclic allylic dicarbonate with organoboronic acid nucleophiles is described. The rhodium(I) catalyst formed in situ from $[Rh(cod)OH]_2$ and Xyl-P-PHOS allowed the S_N2' allylic substitution product to be obtained with a range of arylboronic acids in enantiomeric excesses of up to 92% with regioselectivities of up to >20:1.

The utility of the asymmetric allylic substitution reaction[1] has been the subject of intense study, as its application to the synthesis of a range of natural products demonstrates.[2] Usually, the enantiodetermining step is either the ionization of an enantiotopic leaving group or nucleophilic addition to a chiral π-allylmetal complex.[1b] Although asymmetric induction with palladium catalysts and soft nucleophiles, especially malonates, is well documented, there are very few examples of the use of unstabilized, hard carbon nucleophiles.[3]

Recent advances have been made in the asymmetric allylic substitution reaction for the introduction of hard nucleophiles through copper-catalyzed reactions with Grignard reagents or organozincs, with both acyclic[4] and cyclic[5] substrates. As these methods use mainly alkyl nucleophiles, we report herein complementary work that makes use of air and moisture tolerant organoboronic acids to achieve the regio- and enantioselective allylic substitution of *meso*-cyclic dicarbonates with a Rh(I)−biarylphospine catalytic system.

As an extension to our recently reported asymmetric rhodium-catalyzed ring-opening of oxabicyclic alkenes with boronic acids (eq 1),[6] we attempted to use similar conditions for the desymmetrization of *meso*-cyclic allylic diol derivatives (Scheme 1). The ready availability, low toxicity, and high functional group tolerance of boronic acids makes this reaction especially appealing.

Precedents by Evans in the case of *acyclic* chiral allylic alcohol derivatives have shown the stereospecific nature of the rhodium-catalyzed asymmetric allylic alkylation with both soft[7] and hard[8] nucleophiles. Also, Hayashi reported a

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(2) For reviews, see: (a) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (c) Graening, T.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2003**, *42*, 2580. (d) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1.

(3) (a) Indolese, A. F.; Consiglio, G. *Organometallics* **1994**, *13*, 2230. (b) Chung, K.-G.; Miyake, Y.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 15.

(4) (a) Tissot-Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 2426. (b) Hoveyda, A. H.; Kacprzynski, M. A. *J. Am. Chem. Soc.* **2004**, *126*, 10676. (c) Lopez, F.; van Zijl, A. W.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2006**, 409.

(5) (a) Piarulli, U.; Claverie, C.; Daubos, P.; Gennari, C.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 4493. (b) Piarulli, U.; Daubos, P.; Claverie, C.; Roux, M.; Gennari, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 234.

(6) (a) Lautens, M.; Dockendorff, C.; Fagnou, K.; Malicki, A. *Org. Lett.* **2002**, *4*, 1311. (b) For a review of selected ring-openings prior to 2003, see: Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48.

(7) (a) Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581. (a) Evans, P. A.; Lawler, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 8642. (b) Evans, P. A.; Leahy, D. K. *J. Am. Chem. Soc.* **2003**, *125*, 8974.

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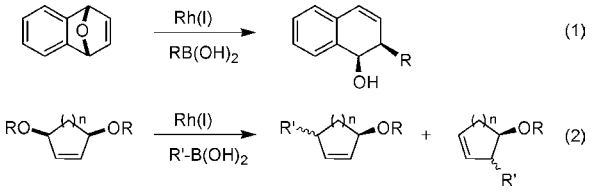
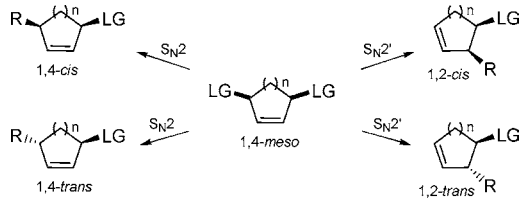
Scheme 1



highly enantioselective alkylation with malonate nucleophile using a chiral rhodium catalyst.[9] But there have been no reports of the use of chiral rhodium catalysts with nonstabilized carbon nucleophiles for the asymmetric allylic substitution reaction, despite its efficient use in conjugate addition reactions.[10]

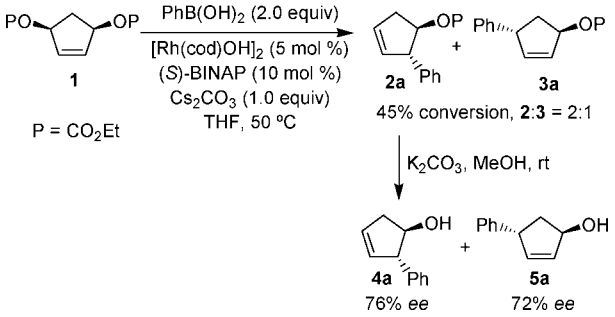
Meso-cyclic allylic diol derivatives are challenging substrates for this reaction due to the possibility of competing reaction pathways. Indeed, the allylic displacement reaction may take place via an S_N2- or S_N2'-type substitution, with overall inversion or retention of stereochemistry in both cases (Scheme 2).

Scheme 2



We found that *cis*-1,4-cyclopentene−diethyl carbonate **1**[11] could be desymmetrized in a highly diastereo- and enantioselective manner. Initial studies used a $[Rh(cod)OH]_2$ catalyst[12] and phenylboronic acid with (*S*)-BINAP as the ligand in the presence of Cs_2CO_3 in THF at 50 °C (Scheme 3). The 1,2-trans-substituted product **2** was obtained as the major product, in a 2:1 ratio over the 1,4-trans-substituted product **3**. Importantly, none of the diastereomeric cis isomers were observed. Although the conversion of starting material was low, the reaction profile was clean: only **2**, **3**, and unreacted starting material were present in the mixture. While the carbonate products could not be separated at this stage, they were readily hydrolyzed to yield the corresponding known alcohols **4**[5b] and **5**[13] by simple methanolysis at room

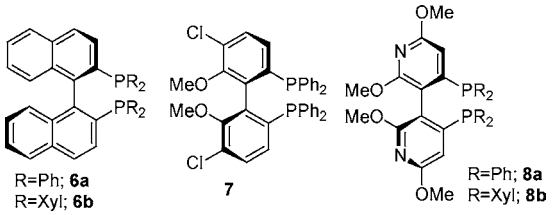
Scheme 3



temperature. The resulting regioisomeric alcohols were easily separated by chromatography and their enantiomeric excesses were determined by chiral HPLC (Chiralcel OD-H column, 76% ee for **4**, 72% ee for **5**).

Optimization of the reaction conditions was then undertaken in an effort to improve the conversion, regioselectivity, and enantioselectivity. Among the different parameters studied (leaving group,[14] base,[15] solvent,[16] temperature, concentration, and chiral ligand), variation of the ligand had the most significant effect. Biarylbisphosphine ligands proved to be the most effective class for this reaction (Table 1).[17]

Table 1. Desymmetrization with Selected Biaryl Ligands



entry	ligand	conversion[a] (%)	**2**/**3**[a]	% ee (**2**)[b]	% ee (**3**)[b]
1	**6a**[c]	45	2:1	76	72
2	**6b**[c]	59	2:1	82	60
3	**7**[c]	60	1:1	90	>98
4	**8a**[d]	74	>20:1	82	
5	**8b**[c]	65	13:1	88	>98
6	**8b**[d]	70	>20:1	90	

[a] Determined by ^1H NMR spectroscopy. [b] Determined by chiral HPLC (Daicel Chiralcel OD-H column) on the deprotected products. [c] Conditions: substrate (1.0 equiv), $PhB(OH)_2$ (2.0 equiv), Rh (5 mol %), ligand (10 mol %), Cs_2CO_3 (1.0 equiv), THF, 50 °C. [d] Conditions as for footnote c except ligand (12 mol %).

Xyl-BINAP **6b** gave an increased conversion versus BINAP **6a**, and it showed a small improvement in ee for **2**, but the

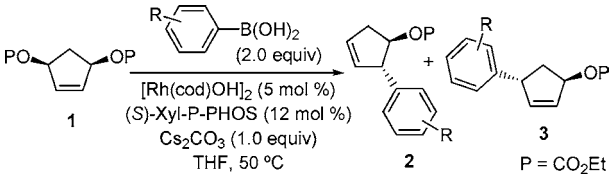
(8) Evans, P. A.; Uraguchi, D. *J. Am. Chem. Soc.* **2003**, *125*, 7158.
(9) Hayashi, T.; Okada, A.; Suzuka, T.; Kawatsura, M. *Org. Lett.* **2003**, *5*, 1713.
(10) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829.
(11) Arnau, N.; Cortés, J.; Moreno-Mañas, M.; Pleixats, R.; Villarroya, M. *J. Heterocycl. Chem.* **1997**, *34*, 233.
(12) The use of $[Rh(cod)OH]_2$ was vital to the success of the reaction; $[Rh(cod)Cl]_2$ with aqueous base gave no desired product. See the Supporting Information for catalyst screening details.
(13) (a) Kobayashi, Y.; Murugesh, M. G.; Nakano, M.; Takahisa, E.; Usmani, S. B.; Ainai, T. *J. Org. Chem.* **2002**, *67*, 7110. (b) Tueting, D. R.; Echavarren, A. M.; Stille, J. K. *Tetrahedron* **1989**, *45*, 979. (c) Marino, J. P.; Fernández de la Pradilla, R.; Laborde, E. *J. Org. Chem.* **1987**, *52*, 4898.
(14) Other leaving groups giving poorer conversion, regioselectivity, and/or enantioselectivity were $-OC(O)C_6H_5$, $-OC(O)C_6H_4NO_2$, $-OC(O)CH_3$, $-OC(O)OCH(CF_3)_2$, and $-OP(O)(OEt)_2$.
(15) Other bases giving poorer conversion, regioselectivity, and/or enantioselectivity were Na_2CO_3, KOH, Et_3N, DIPEA, and KF.
(16) Other solvents giving poorer conversion, regioselectivity, and/or enantioselectivity were toluene, dioxane, acetonitrile, DMF, methanol, and 2-propanol.
(17) See the Supporting Information for complete ligands screening.

regioselectivity remained poor (entry 2). Excellent enantioselectivity was obtained with Cl-OMe-BIPHEP **7** (entry 3), although no regioselectivity was achieved. Xyl-P-PHOS **8b**[18] gave good regioselectivity and high ee with acceptable conversion (entry 4). With a slight increase in ligand loading, the conversion was increased to 70%, the regioselectivity for **2**:**3** was >20:1, and an enantiomeric excess of 90% for **2** was achieved (entry 5). P-PHOS **8a** gave good conversion and regioselectivity but poorer enantioselectivity than Xyl-P-PHOS (entry 6).

The reaction is either complete or stops within the first hour. All attempts to lower the rhodium loading have so far led to significantly decreased yields. The relatively high catalyst loading arises from the rapid loss of activity, particularly with electron-rich arylboronic acids. Slow addition of $PhB(OH)_2$ actually led to a decrease in conversion. Also, premixing and heating of the rhodium catalyst and $PhB(OH)_2$ for 30 min at 50 °C before the substrate was added did not impede the reaction, but lower conversion was observed.

We next investigated the scope of the reaction with respect to the boronic acid (Table 2). Arylboronic acids substituted

Table 2. Scope of Desymmetrization with Arylboronic Acids



entry	product	R	yields[a] (%)	**2**/**3**[a]	% ee (**2**)[b,c]
1	**2a**	H	87	18:1	92
2	**2b**	4-CO_2Me	95	>20:1	90
3	**2c**	4-Ac	94	>20:1	88
4	**2d**	4-CF_3	86	13:1	88
5	**2e**	4-F	46	7:1	86
6	**2f**	4-Cl	53	13:1	90
7	**2g**	4-Br	35	10:1	86
8	**2h**	4-Me	70	20:1	84
9	**2i**	4-NHBoc	32	>20:1	84
10	**2j**	4-OMe	49	>20:1	89
11	**2k**	3-OMe	63	>20:1	92
12	**2l**	3-Cl	87	10:1	90
13	**2m**	3-Me	78	20:1	92
14	**2n**	2-naphthyl	78	>20:1	90
15	**2o**	1-naphthyl	50	1:1	70
16	**2p**	2-Me	25	6:1	92

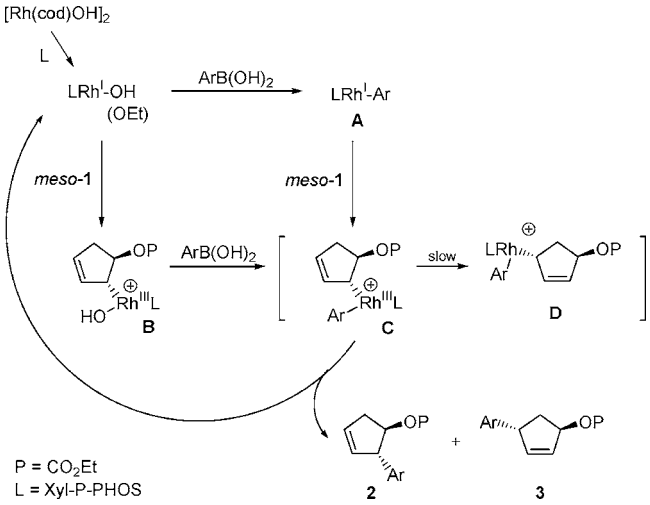
[a] Isolated yields of carbonates, average of at least two runs. [b] Determined by chiral HPLC (Chiralcell OD-H column) on the deprotected products. [c] Absolute stereochemistry of products was determined by the MTPA Mosher ester method.

with strongly electron-withdrawing groups in the 4-position gave excellent conversion and high regioselectivity and enantioselectivity (entries 2−4). 4-Halosubstituted boronic acids gave good regioselectivity and enantioselectivities (entries 5−7), albeit with lower conversions than for phenylboronic acid. *o*-Tolylboronic acid gave low conversion and decreased regioselectivity but high ee for the 1,2-product (entry 16). The *m*- and *p*-tolylboronic acids gave comparable results to phenyl (entries 8 and 13), but with lower ee.

Electron-rich arylboronic acids gave good regioselectivity and ee but poor conversion (entry 9−11), whereas 4-dimethylaminophenylboronic acid gave no reaction (not shown). The 3-substituted arylboronic acids all gave good conversion and ee (entries 11−13). The substrates that did not react (4-dimethylaminophenylboronic acid, 4-pyridylboronic acid) all contain a nitrogen atom that may interfere with the reaction by coordination to the rhodium complex, preventing catalyst turnover. 2-Naphthylboronic acid gave excellent results (entry 14), whereas 1-naphthylboronic acid suffered from a lack of regioselectivity and gave the 1,2- product in lower ee (entry 15).

The mechanism of the reaction is still unclear, as at least two major catalytic cycles can be considered. The first involves an enantioselective ionization of the leaving group by rhodium to generate a σ-enyl cation intermediate **C**, as suggested by Evans (Scheme 4).[7,8] The formation of the

Scheme 4. Proposed Catalytic Cycle Proceeding via a σ-Enyl Intermediate



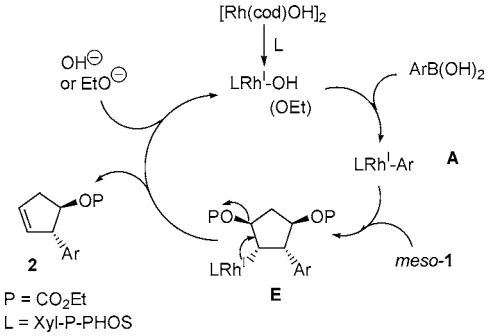
rhodium(III) complex **C** can arise from a transmetalation occurring first to generate the Rh(I)-Ar species **A**, followed by ionization to generate the σ-enyl intermediate **C**. On the other hand, the ionization by the presumed Rh-OH species could give the Rh(III)-OH intermediate **B**, followed by a transmetalation step with the boronic acid. Once the 1,2-σ-enyl complex **C** is formed, it could reductively eliminate to yield the 1,2-substituted product **2** or equilibrate to the isomeric 1,4-σ-enyl complex **D**, from which a reductive elimination would lead to the 1,4-substituted product **3**. Accordingly, the rate of isomerization versus the rate of reductive elimination would be pivotal in determining the

(18) Wu, J.; Kwok, W. H.; Lam, K. H.; Zhou, Z. Y.; Yeung, C. H.; Chan, A. S. C. *Tetrahedron Lett.* **2002**, *43*, 1539. Xyl-P-PHOS **8b** and P-PHOS **8a** are available from Strem Chemicals, Inc., in both (*R*)- and (*S*)-enantiomeric forms.

regioselectivity of the reaction. At this point, we cannot determine if both ionization mechanisms are operative.

A second option involves a carborhodation of the alkene as the key step (Scheme 5). Transmetalation of the aryl moiety from boron to rhodium would form **A**, followed by a stereo- and enantioselective carborhodation which would generate the key intermediate **E**. Subsequent β-alkoxy elimination would then yield the 1,2-product. This mechanism is based on our previous work for the Rh-catalyzed ring-opening reaction in more strained systems.[6] Interestingly, the desymmetrization of the *cis*-cyclopentene-1,4-diols yields exclusively the trans products, compared to the exclusive cis products observed with the ring-opening chemistry. To explain the stereochemistry, the carborhodation step would need to occur on the face of the olefin anti to the leaving groups. The leaving groups might prevent metalation from the syn face of the olefin and would not coordinate to the metal. However, this mechanism cannot explain the formation of the competing 1,4-adducts. If this mechanism is operational, the observed 1,4-product would imply that there is at least a partial contribution from the proposed σ-enyl-type mechanism.

Scheme 5. Proposed Catalytic Cycle Proceeding by a Carborhodation Mechanism



In summary, a highly enantio-, regio-, and diastereoselective *meso*-desymmetrization with a rhodium(I) catalyst and readily available organoboronic acid nucleophiles has been developed. The enantioselectivities in this reaction are consistently good to excellent. We are working to improve the problematic cases by examining alternative nucleophiles and catalysts. Mechanistic investigations, as well as the use of nonaromatic nucleophiles and the extension to acyclic alkenes substrates, are the focus of ongoing efforts.

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Supporting Information Available: Experimental details, additional data tables, and characterization data (including ^{1}H NMR, HR-MS, and HPLC conditions). This material is available free of charge via the Internet at http://pubs.acs.org.

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