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Diastereoselective Formation of Indanes from Arylboronate Esters Catalyzed by Rhodium(I) in Aqueous Media

Mark Lautens* and John Mancuso

Davenport Chemical Laboratories, Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario M5S 3H6, Canada

mlautens@chem.utoronto.ca

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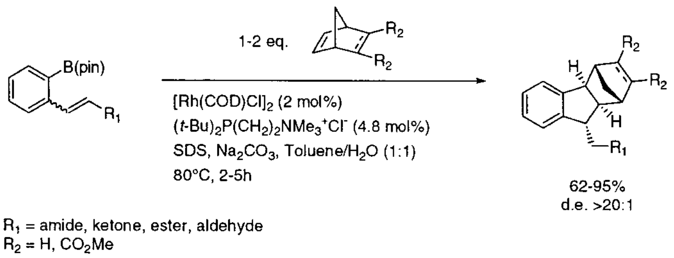
ABSTRACT



Arylboronate esters bearing a pendant Michael-acceptor alkene can add to norbornene and cyclize to give indane systems in yields ranging from 62% to 95% with high diastereomeric excess (>20:1). The reaction is performed in an organic/aqueous emulsion and catalyzed using $[Rh(COD)Cl]_2$ with *t*-Bu-amphos chloride, a sterically bulky, electron-rich, water-soluble phosphine ligand.

Aqueous transition metal catalysis is gaining in popularity as a method for generating complex organic molecules with reduced environmental impact.[1] Water exhibits a combination of properties difficult to emulate with organic solvents (i.e., polarity, H-bonding, basicity) and can provide a means for catalyst recovery, reducing overall cost.

One of the goals of our investigation is to generate arylrhodium species and react them with unactivated olefins in aqueous media. Studies by several groups have shown that arylrhodium species can be generated from arylmetal precursors where the metal is boron,[2] silicon,[3] tin,[4] bismuth,[4a] or mercury.[5] Typically, saturated products are obtained, but in certain cases formation of the Heck product is a competing process.[3b,6]

Methodologies to date focus on intermolecular processes with the rhodium mediating the formation of one carbon−carbon bond. Palladium chemistry is well-known for tandem or “cascade” processes,[7] whereby a single mole of catalyst can effect the formation of several bonds within a single substrate molecule, resulting in a complex and functionally diverse product.

In an attempt to create a rhodium-based tandem reaction process, we envisaged the trapping of an intermediate

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(1) (a) Cornils, B.; Herrmann, W. A. *Aqueous-Phase Organometallic Catalysis*; Wiley-VCH: Weinheim, Germany, 1998. (b) Horváth, I. T.; Joó, F. *Aqueous Organometallic Chemistry and Catalysis*; Kluwer Academic: Dordrecht, The Netherlands, 1995. (c) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; Wiley-Interscience: New York, 1997.

(2) Selected recent references: (a) Murakami, M.; Igawa, H. *Chem. Commun.* **2002**, *4*, 390. (b) Lautens, M.; Yoshida, M. *Org. Lett.* **2002**, *4*, 123. (c) Frost, C. G.; Wadsworth, K. J. *Chem. Commun.* **2001**, *22*, 2316. Asymmetric additions: (d) Hayashi, T. *Synlett* **2001**, *Spec. Iss.*, 879. (e) Sakuma, S.; Miyaura, N. *J. Org. Chem.* **2001**, *66*, 8944. (f) Itooka, R.; Iguchi, Y.; Miyaura, N. *Chem. Lett.* **2001**, *7*, 722.

(3) (a) Oi, S.; Honma, Y.; Inoue, Y. *Org. Lett.* **2002**, *4*, 667. (b) Mori, A.; Danda, Y.; Fujii, T.; Hirabayashi, K.; Osakada, K. *J. Am. Chem. Soc.* **2001**, *123*, 10774. (c) Huang, T. S.; Li, C.-J. *Chem. Commun.* **2001**, *22*, 2348.

(4) (a) Huang, T.; Meng, Y.; Venkatraman, S.; Wang, D.; Li, C.-J. *J. Am. Chem. Soc.* **2001**, *123*, 7451. (b) Oi, S.; Moro, M.; Ito, H.; Honma, Y.; Miyano, S.; Inoue, Y. *Tetrahedron* **2002**, *58*, 91.

(5) (a) Larock, R. C.; Bernhardt, J. C. *J. Org. Chem.* **1977**, *42*, 180. (b) Larock, R. C.; Hershberger, S. S. *J. Org. Chem.* **1980**, *45*, 3840.

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

(7) For selected reviews on Pd cascade reactions, see: (a) Heumann, A.; Réglier, M. *Tetrahedron* **1996**, *52*, 9289. (b) Grigg, R.; Sridharan, V. *J. Organomet. Chem.* **1999**, *576*, 65.

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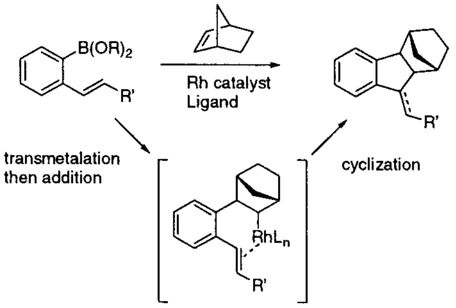
arylrhodium species with a strained olefin, such as norbornene,[8] to generate an alkylrhodium species that cannot β-hydride eliminate (Scheme 1). The presence of a pendant olefin would allow intramolecular cyclization and eject the product either via protodemetalation or β-hydride elimination of the rhodium intermediate. In either case, in order for this process to be an efficient methodology, the problem of competitive hydrolytic deboronation of arylboronic acids by rhodium in water would have to be minimized.

Scheme 1. Proposal for Tandem Reaction



We have previously shown that arylboronic acids add to substituted styrenes in water in the presence of a rhodium catalyst, a water-soluble ligand (Figure 1, TPPDS, **1**), and a phase transfer agent (sodium dodecyl sulfate, SDS), to generate stilbene derivatives resulting from a Heck-type process.[6] We now introduce *t*-Bu-amphos chloride (**2**)[9] as a superior ligand for the transmetalation of arylboron substrates to arylrhodium intermediates in water. Ligand **2** effects transmetalation at room temperature and greatly reduces the problem of hydrolytic deboronation, presumably as a result of its steric bulk and basic properties.

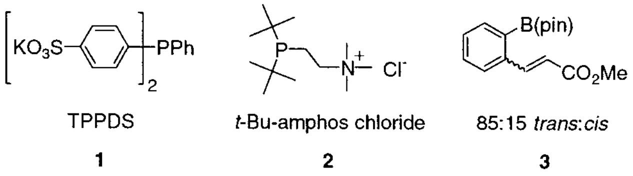
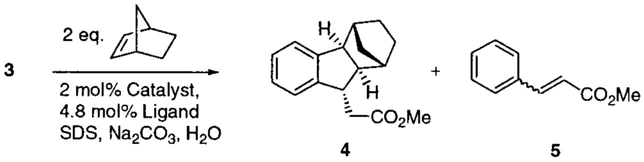


Figure 1. Water-soluble ligands and model substrate.

The pinacol (pin) boronate ester **3** was selected as a model substrate and tested with a catalytic amount of $[Rh(cod)Cl]_2$ in water with SDS and norbornene. Poor conversion was seen (Table 1, entry 1), and a mixture of deboronated product **5** and the desired indane **4** was obtained.

Table 1. Optimization Study for the Formation of Indane **4**[a]



entry	catalyst/ligand	conversion, %[b]	**4**:**5**[c]
1	$[Rh(cod)Cl]_2$	13	69:31
2	$[Rh(cod)Cl]_2$/**1**[d]	>99	27:73
3	$[Rh(cod)Cl]_2$/**2**	>99	*e*
4[f]	$[Rh(cod)Cl]_2$/**2**	>99 (95)	>99:<1
5[f,g]	$[Rh(cod)Cl]_2$/**2**	>99	96:4
6[f,h]	$[Rh(cod)Cl]_2$/**2**	>99	>99:<1
7[f]	$[Rh(cod)OH]_2$/**2**	>99	>99:<1

[a] cod = 1,5-cyclooctadiene. Reactions run in 0.2 M degassed water under nitrogen with 0.6 equiv of SDS and 1 equiv of Na_2CO_3 at 80 °C for 2 h. [b] Determined by ^1H NMR. Isolated yield of **4** in parentheses. [c] Determined by ^1H NMR. [d] 8 mol % ligand used. [e] Variable (see text). [f] 1:1 water/toluene (degassed) was used as the solvent. [g] 1 equiv of norbornene used. [h] Reaction run at rt for 14 h.

Adding a water-soluble ligand such as TPPDS (**1**) resulted in a significant increase in the rate of consumption of the boronate ester, although the ratio of products changed to favor **5** (entry 2). Switching to a more electron-rich and bulky water-soluble phosphine such as **2** showed similar conversion rates; however, yields of **4** were irreproducible, ranging from 30% to 95% (entry 3).

This problem was resolved through the addition of an organic cosolvent. With **2** as the ligand in a 1:1 mixture of water and toluene (entry 4), excellent selectivity for the cyclized product was observed. To prove that the improved results were due to the amphos ligand, we repeated the TPPDS experiment (entry 2, Table 1) in a 1:1 mixture of toluene/water and obtained very little change in product ratios. Thus we believe that ligand **2** is responsible for the high activity/selectivity seen. SDS was added to ensure proper mixing of both phases, resulting in an organic/aqueous emulsion. Product **4** could be isolated in 95% yield in diastereomeric excess of >20:1, and the stereochemical configuration was assigned by 2D-NMR and NOE experiments.

The use of only 1 equiv of norbornene still gave the desired adduct with >95% selectivity (entry 5), indicating that this reaction is attractive from an atom economy point of view.[10] It was also possible to run the reaction at room temperature (entry 6) rather than at 80 °C, albeit with a longer reaction time (14 h). The use of $[Rh(cod)OH]_2$[11] exhibited activity similar to that of the chloride dimer (entry 7), emphasizing the likelihood that a hydroxorhodium(I) species is part of the catalytic cycle.

The scope of the reaction was investigated using other norbornene and norbornadiene derivatives. Unstrained alkenes such as styrene and 3-sulfolene were also tested and

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(8) Oguma, K.; Miura, M.; Satoh, T.; Nomura, M. *J. Organomet. Chem.* **2002**, *648*, 297.

(9) (a) For preparation of *t*-Bu-amphos Cl (**2**) and account of its efficiency for Pd-catalyzed Suzuki couplings in aqueous media, see: Shaughnessy, K. H.; Booth, R. S. *Org. Lett.* **2001**, *3*, 2757. (b) Original amphos ligand: Smith, R. T.; Baird, M. C. *Inorg. Chim. Acta* **1982**, *62*, 135.

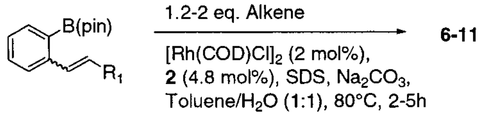
(10) Trost, B. M. *Science* **1991**, *254*, 1471.

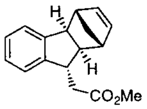
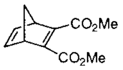
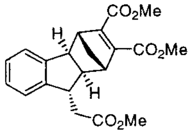
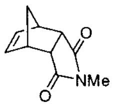
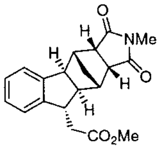
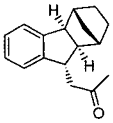
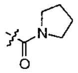
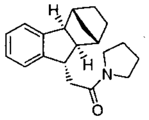
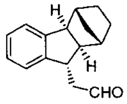
(11) Uson, R.; Oro, L. A.; Cabeza, J. A. *Inorg. Synth.* **1985**, *23*, 126.

exhibited no reactivity. The ratio of boronate ester to alkene was kept at 1:2, except in cases where the presence of excess alkene could interfere with purification.

The results in Table 2 showed that the reaction gave high diastereoselectivity with various substrates of >20:1. The relative stereochemical configurations of products **6**−**11** were assigned on the basis of the spectroscopic data of **4**. Norbornadiene (entry 1) gave the *exo*-adduct **6** in excellent yield.[12] A substituted norbornadiene only reacted at the unsubstituted olefin (entry 2) to give product **7**, and a functionalized norbornene gave pentacycle **8** in high yield (entry 3).

Table 2. Tandem Reactions with a Variety of Boronate Esters and Alkenes

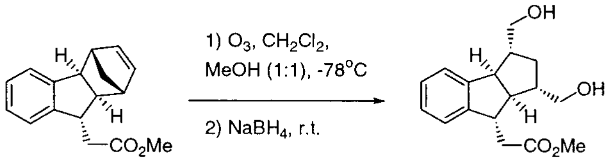


entry[a]	R_1	alkene	product, isolated yield (%)[b]	
1	CO_2Me			**6**, 94
2	CO_2Me			**7**, 82
3[c]	CO_2Me			**8**, 90
4	COMe			**9**, 88
5				**10**, 87
6[d]	CHO			**11**, 62

[a] Ratio of boronate ester to alkene is 1:2. [b] Isolated by column chromatography. Diastereomeric excess is >20:1 for all entries. [c] Ratio of boronate ester to alkene is 1:1.2. [d] Slow addition of boronate ester to reaction mixture over 12 h at rt.

The use of boronate esters with pendant enone and acrylamide moieties were also tolerated giving *exo*-adducts **9** (entry 4) and **10** (entry 5), respectively. A boronate ester containing an α,*β*-unsaturated aldehyde moiety (entry 6) showed extensive intermolecular coupling under the standard reaction conditions. In this case, a good yield of the product **11** could be achieved if the reaction was conducted at room temperature with slow addition of the substrate to the reaction mixture.

An example of a postsynthetic modification to yield functionalized tricyclic systems is shown in Figure 2. Ozonolysis of **6** followed by reductive workup with $NaBH_4$ gave the diquinane **12** in quantitative yield. Compound **12** bears five stereocenters, three of which are created in the coupling step.



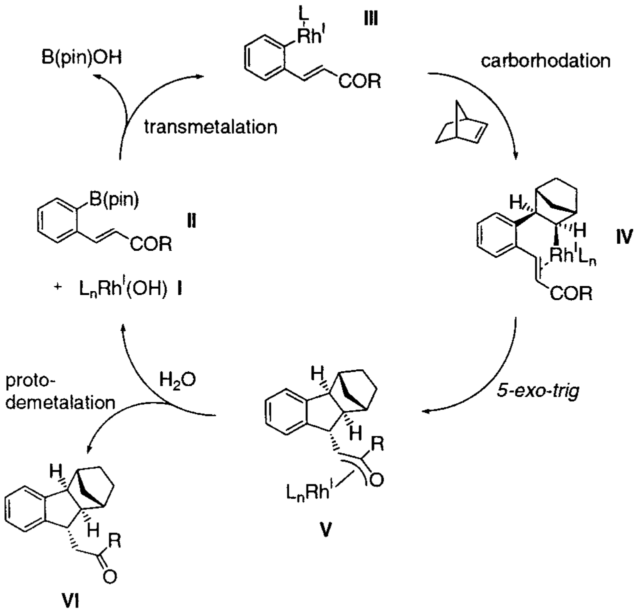
6

12, quantitative

Figure 2. Oxidative cleavage of **6** to yield diquinane **12**.

The catalytic cycle is believed to follow the path shown in Scheme 2, whereby the active catalyst is $L_nRh(OH)$ (**I**), which transmetalates with **II** to give the arylrhodium(I) species **III**. Carborhodation of the alkene ensues to give **IV** in which the rhodium is presumably coordinated to the

Scheme 2. Proposed Catalytic Cycle



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[12] Stereochemistry of **6** proved by hydrogenation, which gives only product **4**.

internal pendant olefin. Carbocyclization then occurs via a 5-*exo*-trig process to generate the rhodium(I) enolate **V**. Protodemetalation of **V** by water generates the product **VI** and regenerates **I**, which can re-enter the catalytic cycle.

To the best of our knowledge, this is the first example of tandem carbocyclization process utilizing a water-soluble rhodium catalyst system. Utilizing water as cosolvent poses an obvious advantage due to its environmental and economic benefits. In addition, the use of the *t*-Bu-amphos chloride ligand prevents hydrolytic deboronation; therefore yields can be based on the boronate ester, improving atom economy and reducing cost, as the boronate ester is typically the more expensive coupling partner.

We are currently investigating the use of heterocyclic arylboronate esters, as well as evaluating alternative alkene coupling partners to replace norbornyl olefins.

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Supporting Information Available: General procedures and spectroscopic data for compounds **4** and **6**−**12** and ^{1}H NMR, COSY, and ROESY spectra for compound **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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