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# Palladium(II) Catalyst Systems for the Addition of Boronic Acids to Bicyclic Alkenes: New Scope and Reactivity

**Mark Lautens* and Chris Dockendorff**

*Davenport Laboratories, Department of Chemistry, University of Toronto, Toronto, Ontario, Canada M5H 3H6*

*mlautens@chem.utoronto.ca*

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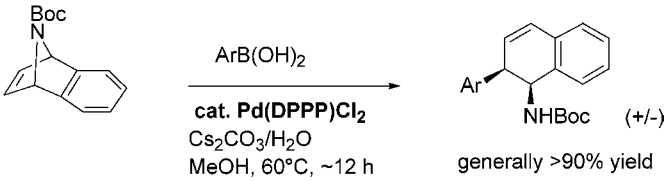
## ABSTRACT

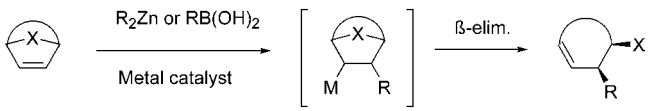



**The palladium-catalyzed ring-opening addition of arylboronic acids to heterobicyclic alkenes is reported. Excellent yields are obtained for the addition of a wide variety of arylboronic acids to aza- and oxabicyclic alkenes. This methodology is especially useful in the synthesis of 1-amino-2-aryldihydronaphthalene scaffolds, for which rhodium catalysts are currently unreactive or give complex mixtures. Asymmetric versions of these reactions are under development, and preliminary results are reported.**

The transition metal-catalyzed addition of various nucleophiles to activated alkenes has proven to be a method of great utility in synthetic chemistry. The formation of carbon−carbon bonds in this manner has undergone significant development in recent years. Useful asymmetric methods in this area now include the copper-catalyzed conjugate addition of dialkylzincs,[1] the rhodium-catalyzed conjugate addition of aryl- and alkenylboronic acids,[2] and various metal-catalyzed allylic alkylations.[3] One of our interests in this area has been in the generation of multiple stereocenters and new carbon−carbon bonds through the addition of carbon-based nucleophiles to heterobicyclic alkenes, with concomitant ring opening (Scheme 1).[4] Herein we report the use of easily handled Pd(II) catalysts for the ring-opening addition of arylboronic acids to heterobicyclic alkenes, which has proven to be especially useful for the addition of a wide variety of aryl (and heteroaryl) groups to less reactive azabicyclic substrates.

Recently, we reported the asymmetric rhodium-catalyzed ring-opening of oxabicyclic alkenes with boronic acids.[5] During subsequent studies to expand the scope of this reaction, we found that the addition of heteroarylboronic acids (in particular) was often problematic, giving unopened addition products as well as oligomeric products. For example, ring-opening of oxabenzonorbornadiene **1a** with furan-3-boronic acid gave the desired product **2af** in only 16% isolated yield (Scheme 2). Additionally, ring-opening

**Scheme 1.** Carbometalation/Ring-Opening




(1) For a recent review, see: Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem* **2002**, *19*, 3221.

(2) For a recent review, see: Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829.

(3) See for example: (a) Trost, B. M.; Lee, C. In *Catalytic Asymmetric Synthesis*, 4th ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 593−649. (b) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E., Ed.; Springer: Heidelberg, 1999; pp 833−866. (c) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395.

(4) Our progress in this area has been reviewed recently: Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48.

(5) (a) Lautens, M.; Dockendorff, C.; Fagnou, K.; Malicki, A. *Org. Lett.* **2002**, *4*, 1311. A racemic version was also reported: (b) Murakami, M.; Igawa, H. *Chem. Commun.*. **2002**, 390.

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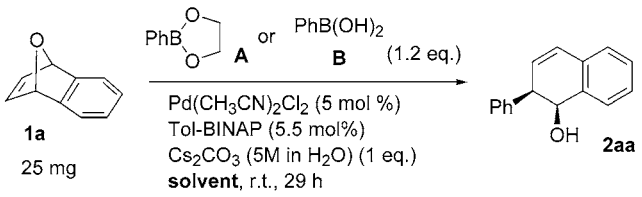
of azabenzonorbornadiene **3a** with arylboronic acids was inconsistent, giving quantitative reaction with phenylboronic acid but a complex mixture of products with 4-chlorophenylboronic acid. Attempts to improve the yield of these reactions were not fruitful: changes in ligand, solvent, and protocol for addition of reagents led to no significant improvement in yield.[6]

Few examples of the addition of heteroaryl species to activated alkenes have been reported,[7] and the development of such reactions would be especially interesting and valuable for medicinal chemistry purposes. For this reason we broadened our studies by investigating the boronic acid addition reaction with different metals. Palladium was an obvious choice, because we have previously reported asymmetric ring-opening reactions with dialkylzinc nucleophiles and Pd(II) catalysts[8] and because Pd(II) species are known intermediates in the Suzuki cross-coupling reaction and undergo transmetalation with organoborons.[9]

Satisfyingly, we immediately observed the desired reaction[10] of **1a** with phenylboronic acid and Pd[(*R*)-Tol-BINAP]$Cl_2$ catalyst, using our standard conditions previously used with rhodium catalysts.[5a] Complete conversion was observed, and the product **2aa**[11] was obtained with 67% ee, as a single diastereomer (cis) as observed previously with rhodium.[12] No reaction was observed with either nickel or platinum catalysts.[13] Among the wide variety of ligands screened in this model reaction, Tol-BINAP showed the best combination of reactivity and enantioselectivity.[14] Surprisingly, poor enantioselectivities are observed with the ferrocene-based ligands, which give excellent enantioselectivities in the analogous rhodium-catalyzed reaction.[5a] With THF as a solvent, the reaction requires an inorganic base and water for good activity.[15]

Using Tol-BINAP as our standard ligand, we next investigated the effects of different solvents on reactivity and enantioselectivity (Table 1). No obvious trend was observed;

**Table 1.** Solvent Studies[a]




| entry | nucleophile | solvent | ee (%)[b] | conversion (%)[b] |
|---|---|---|---|---|
| 1 | A | toluene | 80 | 77 |
| 2 | A | DCE[c] | 68 | 100 |
| 3 | B | THF | 67 | 95 |
| 4 | B | $CH_3CN$ | 72 | 38 |
| 5 | B | EtOAc | 75 | 87 |
| 6 | B | acetone | 83 | 32 |
| 7 | B | DMF | | 0 |
| 8 | B | *i*-PrOH | 65 | 50 |
| 9 | B | MeOH | 70 | 100 (after 1 h) |
| 10 | B | MeOH (−20°C) | 86 | 100 |
| 11 | B | 8:2 MeOH/$H_2O$ | 65 | 100 |

[a] Protocol: Pd$(CH_3CN)_2Cl_2$ (2.2 mg, 0.05 equiv) and ligand (0.055 equiv) were added to a 1 dram vial containing a stir bar. The vial was sealed with a 14 mm septum and flushed with $N_2$ before solvent (0.5 mL) was added. The resulting solution/suspension was stirred for ~40 min before a solution of oxabicycle **1** (25 mg, 1 equiv) and $PhB(OH)_2$ (26 mg, 1.2 equiv) was added by syringe from a sealed vial with solvent (0.5 mL total). Finally, an aqueous solution of $Cs_2CO_3$ (5 M in $H_2O$, 35 $\mu$L, 1 equiv) was added. [b] As measured by chiral HPLC (see Supporting Information for details). [c] 1,2-Dichloroethane.

however, reaction in methanol was found to be much faster than any of the other solvents, giving complete reaction in less than 1 h (entry 9).[16] The high reactivity in methanol allowed us to bring the temperature down to −20 °C, which gave improved ee (86%) and complete conversion using 5 mol % catalyst (entry 10).[17]

Since our objective with the switch in metal from rhodium to palladium was to increase the scope of the ring-opening reactions (nucleophiles and alkene substrates), we also examined the ring-opening of the less-reactive azabicyclic alkene **3a** with furan-3-boronic acid. An initial screening of achiral ligands[18] indicated drastic differences in reactivity. Among the ligands studied, only DPPP (1,3-bisdiphenylphosphinopropane) gave excellent results.[19] Monophosphines

(6) Deuterium labeling studies and characterizations of the oligomeric products demonstrate that rhodium catalysts can promote C−H activation reactions from carbometalated intermediates, leading to undesired products. These results will be presented in a forthcoming full paper.

(7) An April 2003 SciFinder (http://www.cas.org/SCIFINDER/) search of reactions with furan- and thiophene-3-boron species yielded one example from the literature: the rhodium-catalyzed conjugate addition of thiophene-3-tetrafluoroborate to cyclohexenone: Batey, R. A.; Thadani, A. N.; Smil, D. V. *Org. Lett.* **1999**, *1*, 1683.

(8) (a) Lautens, M.; Hiebert, S.; Renaud, J.-L. *J. Am. Chem. Soc.* **2000**, *122*, 1804. (b) Lautens, M.; Hiebert, S.; Renaud, J.-L. *Org Lett.* **2000**, *2*, 1971. (c) Lautens, M.; Hiebert, S.; Renaud, J.-L. *J. Am. Chem. Soc.* **2001**, *123*, 6834.

(9) For reviews of the Suzuki reaction, see: (a) Suzuki, A.; Miyaura, N. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (c) Danishefsky, S. J.; Chemler, S. R.; Trauner, D. *Angew. Chem., Int. Ed. Eng.* **2001**, *40*, 4544. (d) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633.

(10) It should be noted that during the preparation of this manuscript, the Pd(II)-catalyzed conjugate addition of organoboronic acids was reported by Miyaura and co-workers: Miyaura, N.; Nishikata, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 2768.

(11) For other ring-opening syntheses of compound **2aa**, see refs 5 and 21 and also: (a) Fiaud, J.-C.; Moinet, C. *Tetrahedron Lett.* **1995**, *36*, 2051. (b) Kosugi, M.; Fugami, K.; Hagiwara, S.; Oda, H. *Synlett* **1998**, 477. (c) Nakamura, M.; Nakamura, E.; Matsuo, K.; Inoue, T. *Org. Lett.* **2003**, *5*, 1373.

(12) Generally, addition of carbon-centered nucleophiles gives cis ring-opened products; however, Cu(I)-catalyzed ring-openings of **1a** have recently been reported giving predominantly trans products: (a) Feringa, B. L.; Pineschi, M.; Bertozzi, F.; Macchia, F.; Arnold, L. A.; Minnaard, A. J. *Org. Lett.* **2002**, *4*, 2703. (b) Carretero, J. C.; Arrayás, R. G.; Cabrera, S. *Org. Lett.* **2003**, *5*, 1333.

(13) Ni(DPPP)$Cl_2$ and Pt[(*R*)-BINAP]$Cl_2$ both failed to catalyze any reaction of **1a** under the optimized conditions given in Table 2 (5 mol % catalyst).

(14) See Supporting Information for complete details.

(15) $Cs_2CO_3$ and CsF gave enantioselectivity and reactivity superior to that of NaOAc, $NEt_3$, and KOH.

(16) Use of methanol with Rh(I) catalysts leads to exclusive ring-opening with methanol as a nucleophile; no such products are observed with Pd(II) catalysts.

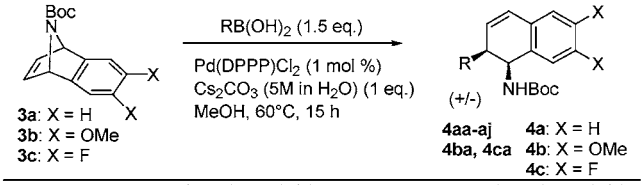
(17) This optimized result is slightly lower than that observed with the Rh(I)/PPF−P(*t*-Bu)$_2$ system (ref 5a).

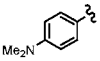
(18) Low enantioselectivites (<30%) have been observed in a preliminary screening of chiral ligands in the ring opening of **3a** with phenylboronic acid.

(19) See Supporting Information for full details.

(including $PPh_3$) gave sluggish reaction only at elevated temperatures. Pd(DPPP)$Cl_2$ was thus prepared[20] and tested in the ring-opening of **3a**[21] with a variety of arylboronic acids of interest (Table 2). We were pleased to observe the desired

**Table 2.** Scope of Azabicycle Ring-Opening[a]

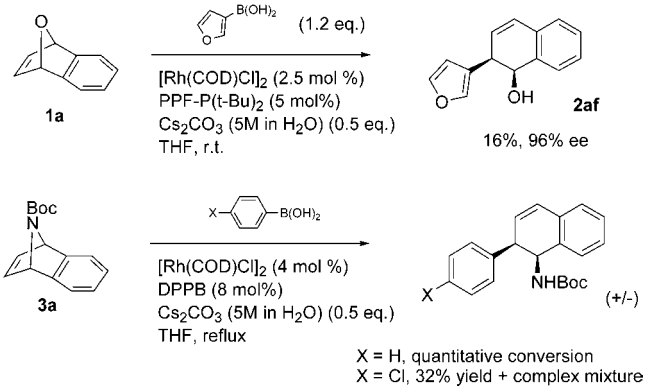



| R | prod. | iso. yield (%) | R | prod. | iso. yield (%) |
|---|---|---|---|---|---|
|  | **4aa** | 98[b] |  | **4ae** | 93 |
|  | **4ba** | 79 |  | **4af** | 92[c] |
|  | **4ca** | 91[c] |  | **4ag** | 71[c] |
|  | **4ab** | 92 |  | **4ah** | 94 |
|  | **4ac** | 84 |  | **4ai** | 99[b] |
|  | **4ad** | 93 |  | **4aj** | 99[c] |

[a] Protocol: Pd(DPPP)$Cl_2$ (2.4 mg, 0.01 equiv), azabicycle (0.411 mmol, 1 equiv), and boronic acid (1.2 equiv) were added to a 10 mL flask containing a stir bar. The flask was sealed with a 14 mm septum and flushed with $N_2$ before MeOH (2 mL) and $Cs_2CO_3$ (~5M in $H_2O$, 82 $\mu$L, 1 equiv) were added. The resulting solution/suspension was stirred for ~15 h in an oil bath at 60 °C. [b] This reaction was performed with 5 g of substrate. [c] Reaction performed with no added base/water.

reaction with phenylboronic acid proceeding at room temperature, which was not observed with analogous rhodium systems. To decrease the catalyst loading to 1 mol %, subsequent reactions were run at higher temperature (60 °C) to allow reactions to proceed to completion in <15 h for all boronic acids tested. Excellent yields were obtained with a variety of heterocyclic and electron-deficient arylboronic acids, some of which give poor yields with rhodium catalysts in oxabicycle ring openings. Good reactivity was observed with 2-methylphenylboronic acid, which gave no reaction with Rh(I)/PPF−P(*t*-Bu)$_2$.[22] Some deboronation of the boronic acid was observed with, e.g., thiophene-3-boronic acid, but reactions generally proceeded to completion with 1.5 equiv. Good reactivity was also observed with azabicycles substituted with electron-withdrawing and -donating

**Scheme 2.** Limitations of Rh-Catalyzed Ring-Opening

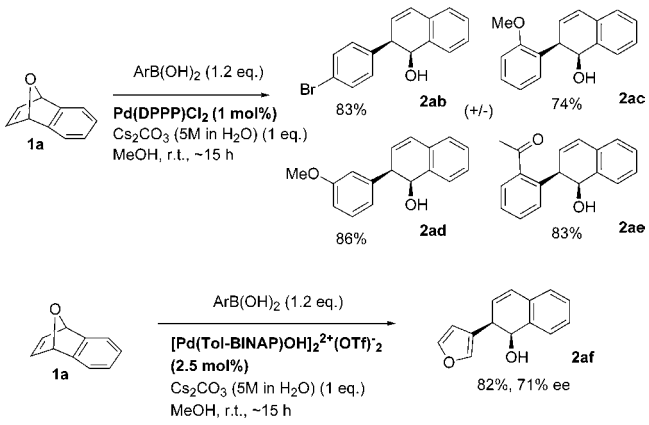



groups (products **4ba**, **4ca**). Under the conditions of Table 2, complete reaction with phenylboronic acid is observed with 0.1 mol % catalyst within 24 h.

In the Suzuki reaction, transmetalation of boronic acids to palladium normally requires the addition of base to activate the boron species and/or to generate the active catalyst.[9] Interestingly, it was found that the palladium-catalyzed ring-opening reactions can proceed to completion with 1 mol % catalyst and *no added base* (see Table 2). However, the reaction is faster in the presence of base: ring-opening of **3a** with phenylboronic acid and Pd(DPPP)$Cl_2$ (0.5 mol %) in methanol proceeded to completion *at room temperature* with $Cs_2CO_3$ (1 equiv) within 30 min, but conversion was just 38%[23] in the same time without added base.

To further investigate the scope of this new catalyst system, Pd(DPPP)$Cl_2$ was used for the ring opening of oxabicycle **1a** (Scheme 3). Good results[24] were obtained at

**Scheme 3.** Palladium-Catalyzed Ring-Openings of Oxabicycles




room temperature with a variety of arylboronic acids. Ortho-substituted products **2ac** and **2ae** were not accessible via our previously reported Rh catalyst system. 4-Bromophenylboronic acid reacts cleanly without side products arising from any insertion of Pd into the C−Br bond, giving product **2ab**.

(20) (a) Synthesis: Strukul, G.; Gavagnin, R.; Cataldo, M.; Pinna, F. *Organometallics* **1998**, *17*, 661. (b) Characterization: Housecroft, C. E.; Rheingold, A. L.; Shaykh, B. A. M.; Haggerty, B. S. *Inorg. Chem.* **1991**, *30*, 125.

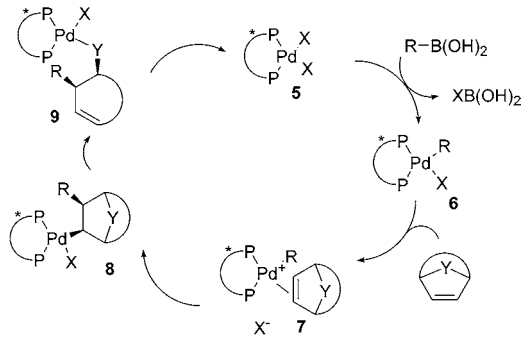
(21) Ni- and Pd-catalyzed reductive ring-opening of azabicyclic alkenes with aryl halides has been reported by Cheng and co-workers: (a) Cheng, C.-H.; Feng, C.-C.; Nandi, M.; Sambaiah, T. *J. Org. Chem.* **1999**, *64*, 3538. (b) Cheng, C.-H.; Duan, J.-P. *Organometallics* **1995**, *14*, 1608. (c) Cheng, C.-H.; Duan, J.-P. *Tetrahedron Lett.* **1993**, *34*, 4019.

(22) It should be noted that ring opening of **1** with 2-methylphenylboronic acid has been reported with a Rh(I)/P(OEt)$_3$ catalyst system: see ref 5b.

The ring opening of **1a** with furan-3-boronic acid was sluggish with Pd(DPPP)$Cl_2$. Better results were observed with the cationic catalyst $[Pd(Tol\text{-}BINAP)OH]_2^{2+}(OTf)^{2-}$,[25] which gave good yield and moderate enantioselectivity of product **2af** (Scheme 3).

The proposed mechanism for the Pd(II)-catalyzed reaction is given in Scheme 4. Transmetalation of the aryl group from

**Scheme 4.** Proposed Mechanism




boron to palladium occurs to give intermediate **6**. The precise nature of the palladium species (**5**) which reacts with the incoming organoboronic acid is not known, but in methanol we expect that the reacting species is Pd(ligand)$(OMe)_2$. Dissociation of an X ligand followed by complexation of the heterobicyclic alkene substrate (Y = oxygen or protected nitrogen) gives cationic complex **7**. Carbopalladation followed by $\beta$-heteroatom elimination leads to ring-opened product.[26] It should be noted that in this proposed mechanism, palladium remains in the +2 oxidation state throughout the catalytic cycle.

In conclusion, we have developed a new palladium-catalyzed ring opening of heterobicyclic alkenes with organoboronic acids. The addition of a variety of aryl groups proceeds in excellent yield, including heteroaryl groups which can be problematic with other catalyst systems. These reactions utilize easy to handle and relatively nontoxic boronic acids, and the Pd(II) catalysts are very convenient because they are air-insensitive[27] and are compatible with undistilled solvents. The reaction is especially useful for the ring-opening of azabicyclic alkenes, for which Pd(II) catalysts are currently more reactive than Rh(I) catalysts. The resulting 1-amino-2-aryldihydronaphthalenes, conveniently synthesized on a multigram scale, are useful scaffolds for the synthesis of potentially bioactive compounds, as we have demonstrated previously with hydride[28] and amine-addition[29]/ring-opening methodologies. Experiments are currently underway to improve enantioselectivities and to expand the scope of the reaction, in addition to more detailed mechanistic studies.

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**Supporting Information Available:** Experimental details, additional data tables, and characterization data (including $^1H$ and $^{13}C$ 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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(23) As measured by HPLC.
(24) Isolated yields in oxabicycle ring-opening reactions are generally lower than the analogous azabicycle reactions due to their decreased stability (elimination of water) relative to the Boc-protected amino products.
(25) Synthesis: Sodeoka, M.; Fujii, A.; Hagiwara, E. *J. Am. Chem. Soc.* **1999**, *121*, 5450.
(26) For more detailed discussions of this mechanism, see ref 8c.
(27) Complete conversion of **3a** to **4aa** was observed when the reaction was performed under air with Pd(DPPP)$Cl_2$ (1 mol %).
(28) Lautens, M.; Rovis. T. *Tetrahedron* **1999**, *55*, 8967.
(29) Lautens, M.; Fagnou, K.; Zunic, V. *Org. Lett.* **2002**, *4*, 3465.