Chiral P-Containing Palladacycle-Catalyzed Asymmetric Ring-Opening Reactions of Oxabicyclic Alkenes with Alkenyl Boronic Acids

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Dedicated to Professors Xi-Yan Lu and Li-Xin Dai

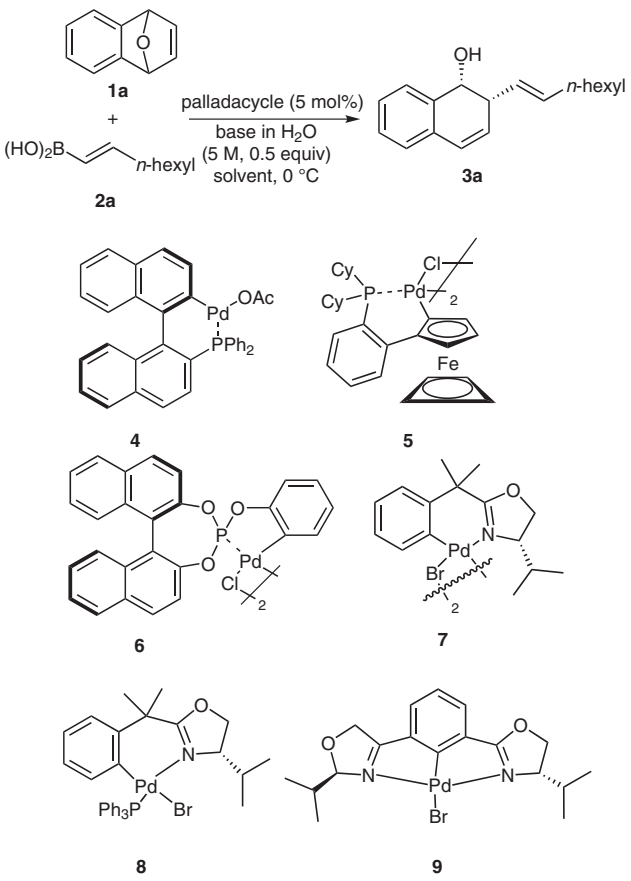
Abstract: An efficient palladacycle-catalyzed asymmetric ring-opening reaction of oxabicyclic alkenes with alkenyl boronic acids was developed to afford the corresponding products in good to excellent yields and enantioselectivity.

Key words: palladacycle, asymmetric catalysis, ring-opening reaction, oxabicyclic alkenes, alkenyl boronic acids.

The past two decades have witnessed significant development in palladacycle chemistry.[1] The palladacycles have found their wide applications in a variety of fields such as biological chemistry,[2] material science,[3] organic synthesis,[4] and ligand resolution.[5,7a] Palladacycles have also been used as catalyst in asymmetric catalysis,[6,7b–d,8] however, in most of these cases, palladacycles serve as Lewis acids. In addition, racemic products were obtained in some cases,[7e,f,9] despite chiral palladacycles were used.

On the other hand, transition-metal-catalyzed ring-opening reactions of oxabicyclic alkenes have become a useful tool for the synthesis of biologically active molecules[10] and polymer components.[11] Many efficient enantioselective transformations involving the oxabicyclic alkenes were reported to afford hydroxy-dihydronapthalene cores.[12] We recently found that palladacycle should be the real catalyst in the ring-opening reactions of oxabicyclic alkenes with organozinc halides,[9] and realized an asymmetric ring-opening reaction of oxabicyclic alkenes with aryl boronic acids using chiral phosphorus-containing palladacycle as catalyst.[7b] As our continuing efforts to explore the asymmetric catalysis by means of chiral palladacycles, we describe herein chiral P-containing palladacycle-catalyzed ring-opening reactions of oxabicyclic alkenes with alkenyl boronic acids. The newly incorporated C–C double bond from alkenyl boronic acids enables the resulted products flexible for further elaboration.

We commenced our study by treatment of 7-oxabicycle alkene **1a** with (*E*)-oct-1-enylboronic acid (**2a**) in dichloromethane at 0 °C in the presence of palladacycle **4** and Cs_2CO_3 according to our previous work.[7b] To our delight, the reaction proceeded smoothly, and the desired ring-opening product **3a** was obtained in 75% yield with 76% ee. Encouraged by this result, a series of P-containing and N-containing palladacycles were examined under the conditions shown in Scheme 1. It can be found from Table 1 that P-containing palladacycle **5** led to the product in high yield,[13] while the enantioselectivity dropped to 8% ee (entry 2, Table 1). Chiral phosphapalladacycle **6** was also tested, but it could not catalyze the reaction effectively (entry 3, Table 1). Meanwhile, all N-containing palladacycles screened afforded the corresponding product in trace amounts (entries 4–6, Table 1), which suggested that the presence of a P atom coordinated to a Pd atom should be important on the catalytic activity of palladacycles in the present reaction. With palladacycle **4**, the solvent effect on the reaction was also evaluated. We can see that the reaction proceeded smoothly to give the product in



Scheme 1

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moderate to good yields and enantioselectivities in various nonprotic solvents (entries 7–13, Table 1). The best solvent was still dichloromethane in terms of both yield and enantioselectivity (entry 1, Table 1). The protic solvent has detrimental effect to the reaction. When MeOH was used only 24% yield of **3a** was obtained accompanying 57% yield of the side product resulted from dehydration of ring-opening product **3a** (entry 14, Table 1).

Table 1 Optimization of Reaction Conditions for the Reaction Shown in Scheme 1[a]

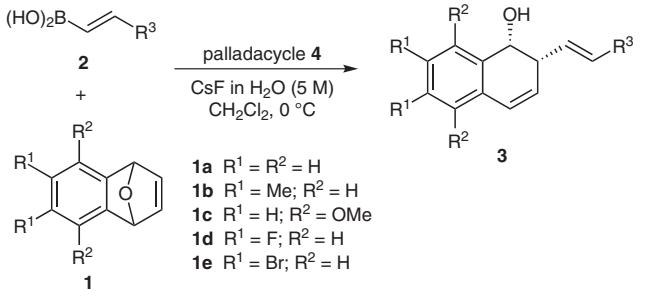
Entry	Palladacycle	Solvent	Base	Yield (%)[b]	ee (%)[c]
1	**4**	CH_2Cl_2	Cs_2CO_3	75	76
2	**5**	CH_2Cl_2	Cs_2CO_3	66	8
3	**6**	CH_2Cl_2	Cs_2CO_3	trace	–[d]
4	**7**	CH_2Cl_2	Cs_2CO_3	trace	–[d]
5	**8**	CH_2Cl_2	Cs_2CO_3	trace	–[d]
6	**9**	CH_2Cl_2	Cs_2CO_3	trace	–[d]
7	**4**	DME	Cs_2CO_3	52	70
8	**4**	Et_2O	Cs_2CO_3	77	72
9	**4**	MeCN	Cs_2CO_3	56	66
10	**4**	DCE	Cs_2CO_3	62	75
11	**4**	THF	Cs_2CO_3	62	70
12	**4**	toluene	Cs_2CO_3	65	71
13	**4**	$CHCl_3$	Cs_2CO_3	63	74
14	**4**	MeOH	Cs_2CO_3	24	76
15	**4**	CH_2Cl_2	CsF	93	81
16	**4**	CH_2Cl_2	K_3PO_4	86	80
17	**4**	CH_2Cl_2	KF	94	74
18	**4**	CH_2Cl_2	K_2CO_3	trace	–[d]
19	**4**	CH_2Cl_2	Na_2CO_3	trace	–[d]

[a] Molar ratio of **1a**/**2a**/palladacycle/base = 1:1.5:0.05:0.5.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] Starting material was recovered in >90%.

Next, the impact of bases was investigated to improve the efficiency of the reaction (entries 15–19, Table 1) as the base usually plays an important role in the reaction involving boronic reagent.[14] CsF was proved to be a better base than Cs_2CO_3, K_3PO_4, and KF, providing the product **3a** in 93% yield and 81% ee (entry 15 vs. entries 1, 16, and 17, Table 1). The reaction proceeded barely when the weak bases such as K_2CO_3 and Na_2CO_3 were used (entries 18 and 19, Table 1).

The scope of the reaction was examined under optimized reaction conditions, and the results are compiled in Table 2. It can be seen that a wide range of oxabicyclic alkenes **1** and alkenyl boronic acids **2** are suitable substrates for the reaction, affording ring-opening products **3** in good to excellent yields with 53–97% ee. The length of the chain has a slight effect on the enantioselectivity when substituents of alkenyl were linear alkyl groups (entries 1–4, Table 2). The incorporation of bulkier group into alkenyl boronic acid led to the significant effect on stereochemistry of the reaction. The enantioselectivity decreased to 66% ee for boronic acid **2e** with cyclohexyl group, although the yield was as high as 93% (entry 5, Table 2). It is noteworthy that the excellent enantioselectivity (over 89%) was obtained in case of alkenyl boronic acid with *tert*-butyl substituent (entries 6, 9, and 12, Table 2), especially, 97% ee was achieved when it was treated with substrate **1e** (entry 12, Table 2). The same trend was observed for oxabicyclic alkene **1b** (entries 7–9, Table 2). Substituent on the oxabicyclic alkene has a negative effect on the reaction. Neither the presence of electron-donating groups nor electron-withdrawing groups could increase the enantioselectivity (entries 7, 10, and 11, Table 2).

Table 2 Substrate Scope[a]



Entry	**1**	**2** R^3	Yield of **3** (%)[b]	ee (%)[c]
1	**1a**	**2a** *n*-hexyl	**3a** 93	81
2	**1a**	**2b** *n*-pentyl	**3b** 94	76
3[16]	**1a**	**2c** *n*-Bu	**3c** 92	75
4	**1a**	**2d** *n*-Pr	**3d** 95	78
5	**1a**	**2e** Cy	**3e** 93	66
6	**1a**	**2f** *t*-Bu	**3f** 80	91
7	**1b**	**2a** *n*-hexyl	**3g** 82	79
8	**1b**	**2e** Cy	**3h** 87	68
9	**1b**	**2f** *t*-Bu	**3i** 72	89
10	**1c**	**2a** *n*-hexyl	**3j** 78	53
11	**1d**	**2a** *n*-hexyl	**3k** 85	70
12	**1e**	**2f** *t*-Bu	**3l** 70	97

[a] Molar ratio of **1**/**2**/**4**/CsF = 1:1.5:0.05:0.5.
[b] Isolated yields.
[c] Determined by chiral HPLC.

The absolute configuration of product **3c** was assigned as 1*R*,2*R* by comparison its optical rotation with that reported in literature.[15]

In summary, we have developed an efficient palladacycle-catalyzed asymmetric ring-opening reaction of oxabicycle alkenes with alkenyl boronic acids to afford the corresponding products in good to excellent yields and enantioselectivities. Further investigations on the applications of this method in organic synthesis as well as on the understanding of the reaction mechanism are in progress.

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References and Notes

(1) Some reviews: (a) Herrmann, W. A.; Böhm, V. P. W.; Reisinger, C. P. *J. Organomet. Chem.* **1999**, *576*, 23. (b) Bedford, R. B. *Chem. Commun.* **2003**, 1787. (c) van der Boom, M. E.; Milstein, D. *Chem. Rev.* **2003**, *103*, 1759. (d) Beletskaya, I. P.; Cheprakov, A. V. *J. Organomet. Chem.* **2004**, *689*, 4055. (e) Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527. (f) Phan, N. T. S.; van der Sluys, M.; Jones, C. W. *Adv. Synth. Catal.* **2006**, *348*, 609. (g) Djukic, J. P.; Hijazi, A.; Flack, H. D.; Bernardinelli, G. *Chem. Soc. Rev.* **2008**, *37*, 406.

(2) (a) Navarro-Ranninger, C.; Lopez-Solera, I.; Perez, J. M.; Masaguer, J. R.; Alonso, C. *Appl. Organomet. Chem.* **1993**, *7*, 57. (b) Bincoletto, C.; Tersariol, I. L. S.; Oliveira, C. R.; Dreher, S.; Fausto, D. M.; Soufen, M. A.; Nascimento, F. D.; Caires, A. C. F. *Bioorg. Med. Chem.* **2005**, *13*, 3047.

(3) (a) Espinet, P.; Esteruelas, M. A.; Oro, L. A.; Serrano, J. L.; Sola, E. *Coord. Chem. Rev.* **1992**, *117*, 215. (b) Beley, M.; Chodorowski-Kimmes, S.; Collin, J. P.; Sauvage, J. P. *Tetrahedron Lett.* **1993**, *34*, 2933. (c) El-Ghayourry, A.; Douce, L.; Skoulios, A.; Ziessel, R. *Angew. Chem. Int. Ed.* **1998**, *37*, 1255.

(4) (a) Ryabov, A. D. *Synthesis* **1985**, 233. (b) Pfeffer, M. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 567. (c) Pfeffer, M. *Pure Appl. Chem.* **1992**, *64*, 335.

(5) (a) Kerr, P. G.; Leung, P.-H.; Wild, S. B. *J. Am. Chem. Soc.* **1987**, *109*, 4321. (b) Chen, Y.; Smith, M. D.; Shimizu, K. D. *Tetrahedron Lett.* **2001**, *42*, 7185.

(6) (a) Hollis, T. K.; Overman, L. E. *Tetrahedron Lett.* **1997**, *38*, 8837. (b) Longmire, J. M.; Zhang, X.; Shang, M. *Organometallics* **1998**, *17*, 4374. (c) Albrecht, M.; Kocks, B. M.; Spek, A. L.; van Koten, G. *J. Organomet. Chem.* **2000**, *19*, 1282. (d) Overman, L. E.; Remarchuk, T. P. *J. Am. Chem. Soc.* **2002**, *124*, 12. (e) Takenaka, K.; Uozumi, Y. *Org. Lett.* **2004**, *6*, 1833. (f) Kirsch, S. F.; Overman, L. E.; Watson, M. P. *J. Org. Chem.* **2004**, *69*, 8101. (g) Kirsch, S. F.; Overman, L. E. *J. Am. Chem. Soc.* **2005**, *127*, 2866. (h) Kirsch, S. F.; Overman, L. E.; White, N. S. *Org. Lett.* **2007**, *9*, 911.

(7) (a) Zhang, T.-Z.; Dai, L.-X.; Hou, X.-L. *Tetrahedron: Asymmetry* **2007**, *18*, 251. (b) Zhang, T.-K.; Mo, D.-L.; Dai, L.-X.; Hou, X.-L. *Org. Lett.* **2008**, *10*, 3689. (c) Zhang, T.-K.; Mo, D.-L.; Dai, L.-X.; Hou, X.-L. *Org. Lett.* **2008**, *10*, 5337. (d) Ding, C.-H.; Hou, X.-L. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 992. (e) Yuan, K.; Zhang, T.-K.; Hou, X.-L. *J. Org. Chem.* **2005**, *70*, 6085. (f) Zhang, T.-K.; Yuan, K.; Hou, X.-L. *J. Organomet. Chem.* **2007**, *692*, 1912.

(8) (a) Navarro, R.; Urriolabeitia, E. P.; Cativiela, C.; Diaz-de-Villegas, M. D.; Lopez, M. P.; Alonso, E. *J. Mol. Catal. A: Chem.* **1996**, *105*, 111. (b) Leung, P. H.; Ng, K.-H.; Li, Y. X.; White, A. J. P.; Williams, D. J. *Chem. Commun.* **1999**, 2435. (c) Donde, Y.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 2933. (d) Anderson, C. E.; Overman, L. E. *J. Am. Chem. Soc.* **2003**, *125*, 12412. (e) Moyano, A.; Rosol, M.; Moreno, R. M.; López, C.; Maestro, M. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 1865. (f) Anderson, C. E.; Donde, Y.; Douglas, C. J.; Overman, L. E. *J. Org. Chem.* **2005**, *70*, 648. (g) Kirsch, S. F.; Overman, L. E. *J. Am. Chem. Soc.* **2005**, *127*, 2866. (h) Weiss, M. E.; Fischer, D. F.; Xin, Z.-q.; Jautze, S.; Schweizer, W. B.; Peters, R. *Angew. Chem. Int. Ed.* **2006**, *45*, 5694. (i) Jautze, S.; Seiler, P.; Peters, R. *Angew. Chem. Int. Ed.* **2007**, *46*, 1260. (j) Fischer, D. F.; Xin, Z.-q.; Peters, R. *Angew. Chem. Int. Ed.* **2007**, *46*, 7704. (k) Nomura, H.; Richards, C. J. *Chem. Eur. J.* **2007**, *13*, 10216. (l) Suzuma, Y.; Yamamoto, T.; Ohta, Y. *Chem. Lett.* **2007**, *36*, 470. (m) Feng, J.-J.; Chen, X.-F.; Shi, M.; Duan, W.-L. *J. Am. Chem. Soc.* **2010**, *132*, 5562. (n) Weber, M.; Jautze, S.; Frey, W.; Peters, R. *J. Am. Chem. Soc.* **2010**, *132*, 12222.

(9) Bravo, J.; Cativiela, C.; Navarro, R.; Urriolabeitia, E. P. *J. Organomet. Chem.* **2002**, *650*, 157.

(10) (a) Lautens, M. *Synlett* **1993**, 177. (b) Lautens, M.; Rovis, T. *Tetrahedron* **1999**, *55*, 8967. (c) Lautens, M.; Fagnou, K.; Zunic, V. *Org. Lett.* **2002**, *4*, 3465. (d) Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48. (e) Madan, S.; Cheng, C. *J. Org. Chem.* **2006**, *71*, 8312. (f) Fan, E.; Shi, W.; Lowary, T. *J. Org. Chem.* **2007**, *72*, 2917.

(11) (a) Rehahn, M.; Roth, M.; Seggern, H.; Scmechel, R.; Ahles, M. DE 102005029574, **2006**. (b) Wegner, S.; Muellen, K. *Macromolecules* **1993**, *26*, 3037.

(12) (a) Warrener, R. *1,4-Dihydro-1,4-epoxynapthalene,* In *Encyclopedia of Reagents for Organic Synthesis (e-EROS)*; Wiley-VCH: Weinheim, **2001**. (b) Bertozzi, F.; Pineschi, M.; Macchia, F.; Arnold, L.; Minnaard, A.; Feringa, B. *Org. Lett.* **2002**, *4*, 2703. (c) Cabrera, S.; Arrayas, R.; Alonso, I.; Carretero, J. *J. Am. Chem. Soc.* **2005**, *127*, 17938. (d) Cho, Y.; Zunic, V.; Senboku, H.; Olsen, M.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 6837. (e) Nishimura, T.; Kawamoto, T.; Sasaki, K.; Tsurumaki, E.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 1492. (f) Webster, R.; Böing, C.; Lautens, M. *J. Am. Chem. Soc.* **2009**, *131*, 444.

(13) P-containing palladacycle **5** was provided by Professor Christopher J. Richards.

(14) (a) Sakuma, S.; Miyaura, N. *J. Org. Chem.* **2001**, *66*, 8944. (b) Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* **1998**, *39*, 8497. (c) Liu, G.-X.; Lu, X.-Y. *J. Am. Chem. Soc.* **2006**, *128*, 16504.

(15) Lautens, M.; Dockendorff, C.; Fagnou, K.; Malicki, A. *Org. Lett.* **2002**, *4*, 1311.

(16) **A Representative Procedure for Palladacycle 4 Catalyzed Asymmetric Ring-Opening Reactions of Oxabicyclic Alkenes with Alkenyl Boronic Acids (Table 2, Entry 3)**
To a mixture of 7-oxabicycle alkene **1a** (28.8 mg, 0.2 mmol), (*E*)-hex-1-enylboronic acid (**2c**, 38.4 mg, 0.3 mmol), and palladacycle **4** (6.0 mg, 5 mol%) in CH_2Cl_2 (3 mL) was added a solution of CsF in H_2O (5 M, 0.1 mmol, 20 μL) at 0 °C with stirring. The reaction was monitored by TLC until completion. The solvent was removed under reduced pressure. The residue was purified by column chromatography (PE–CH_2Cl_2 = 2:1, v/v) to afford 42 mg of oil product

3c, 92% yield, ee: 75%. $[\alpha]_D^{25}$ –193 (*c* 1.06, $CHCl_3$). HPLC: Chiralcel OD (250 mm × 4.6 mm), *n*-hexane–*i*-PrOH = 98:2, 1.0 mL/min, 254 nm, t_R = 8.7 min, 10.6 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.8 Hz, 3 H), 1.26–1.37 (m, 4 H), 1.85 (d, *J* = 8.0 Hz, 1 H), 2.02 (dd, *J* = 6.8, 14.0 Hz, 2 H), 3.08–3.13 (m, 1 H), 4.79 (t, *J* = 6.8 Hz, 1 H), 5.33 (dd, *J* = 8.8, 15.2 Hz, 1 H), 5.69–5.76 (m, 1 H), 5.93 (dd, *J* = 4.8, 9.6 Hz, 1 H), 6.48 (d, *J* = 9.6 Hz, 1 H), 7.06 (t, *J* = 3.6 Hz, 1 H), 7.22–7.25 (m, 2 H), 7.43 (t, *J* = 4.0 Hz, 1 H). MS (EI): *m/z* (rel.) = 228 (45) [M^+], 167 (67), 165 (30), 146 (100), 131 (53), 128 (42), 118 (69), 115 (46).