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Asymmetric Intermolecular Boron Heck-Type Reactions via Oxidative Palladium(II) Catalysis with Chiral Tridentate NHC-Amidate-Alkoxide Ligands

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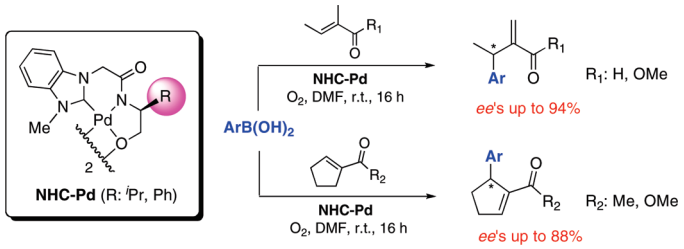
Received September 15, 2009



Chiral dimeric tridentate NHC-amidate-alkoxide palladium(II) complexes, **3a** and **3b**, effected oxidative boron Heck-type reactions of aryl boronic acids with both acyclic and cyclic alkenes at room temperature to afford the corresponding coupling products with high enantioselectivities. The high degree of enantioselection, far superior to existing methods, stems from differences in the nonbonding interactions in the proposed transition states, due to the influence from bulky substituents of the alkene substrates and the "counter axial groups" of the palladium(II) catalysts.

Introduction

Asymmetric palladium catalyzed carbon−carbon bond formation is one of the most useful protocols in organic synthesis and medicinal chemistry.[1] In particular, asymmetric Heck-type variants are important in providing an alternative to the traditional asymmetric Mizoroki−Heck reaction,[2] as well as extending the synthetic scope of the asymmetric Fujiwara−Moritani reaction,[3] which is initiated through C−H activation by chiral palladium(II) species. One of the most attractive palladium(II)-catalyzed reactions is the organoboron-mediated Heck-type reaction, which proceeds through transmetalation of a palladium(II) species with an organoboronic acid as the initial step, rather than oxidative addition of an organohalide to a palladium(0) species.[4] Due to the commercial availability of organoboronic acids as nucleophilic substrates and the ability to introduce boronic acids and esters late in complex syntheses, Heck-type reactions are very attractive in synthetic organic chemistry. In addition, these boron Heck-type reactions which do not often require high temperatures or the use of bases are made

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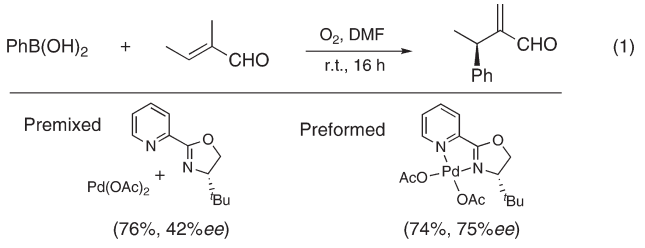
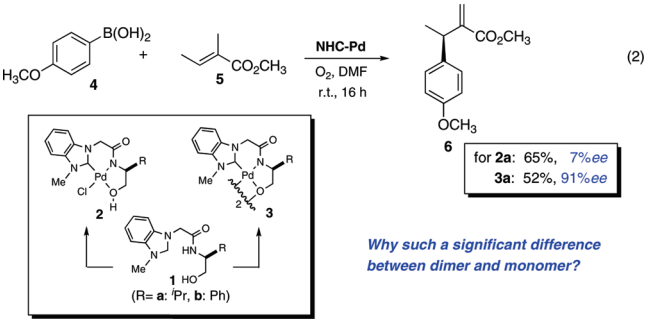
DOI: 10.1021/jo901977n Published on Web 12/02/2009

possible by avoiding the oxidative addition of organohalides to palladium(0) species. Due to these advantages, the palladium(II) catalyzed organoboron-mediated Heck-type reactions with $Cu(OAc)_2$[1a,5] and molecular oxygen[6] as oxidants have recently been reported. However, the challenges of the asymmetric oxidative palladium catalyzed Heck-type reactions of organoborons have not been well studied.[7]

Several approaches to asymmetric oxidative Heck reactions that are initiated by transmetalation of organoborons have been reported in the past several years. Mikami et al. have employed a palladium(II)-chiraphos ligand system that is catalytically active in inter- and intramolecular oxidative boron Heck-type coupling reactions,[7a,d] and Gelman et al. demonstrated a protocol for the enantioselective palladium-(II)-catalyzed Heck-type reaction between arylboronic acids and 2,3-dihydrofuran in the presence of an (*R*)-BINAP ligand.[7b] In addition, we have succeeded in developing intermolecular asymmetric oxidative boron Heck-type reactions between arylboronic acids and acyclic trisubstituted alkenes assisted by a chiral PyOX ligand-palladium(II) complex under an oxygen atmosphere.[7c] In this study, we observed that nonchelated free palladium catalysts played a critical role in racemic couplings that resulted in low enantioselectivities under commonly used premixed conditions, demonstrating the significance of utilizing a preformed tight well-bound palladium(II)-ligand complex.



To develop a tighter chiral palladium(II)-ligand complex, we considered the use of an N-heterocyclic carbene (NHC) as a ligand due to its ability to strongly coordinate to transition metals.[8] We also envisioned that tridentate ligands including an NHC, amidate, and alkoxide would constitute stronger metal−ligand complexes than common bidentate ligands. Therefore, newly designed tridentate ligands would afford higher enantioselectivities by keeping stereocontrol elements locked in place during the entire catalytic processes. On the basis of these criteria, we designed and synthesized the NHC ligand **1**, which is composed of benzimidazole and a chiral amino alcohol. We then produced their corresponding chiral silver complexes, which underwent transpalladation to give monomeric NHC-Pd complexes **2** and dimeric catalysts **3**.[9] Surprisingly, we found that the cross-coupling reaction of 4-methoxy phenylboronic acid and methyl tiglate by tridentate Pd complex **2** and **3** gave drastically different enantioselectivities as depicted in eq 2.[9] While the dimeric chiral NHC-Pd complex **3** gave excellent enantioselective rearrangement product, the monomeric NHC-Pd complex **2** gave poor selectivity. Herein, we wish to discuss our rationale and transition states to account for the observed high enantioselection using dimeric tridentate chiral NHC-Pd complexes. In addition, we would like to disclose various cases of asymmetric oxidative Heck-type reactions, as our previous publication focused mainly on these catalysts and reported only a few examples of successful coupling reactions. In particular, arylboronic acids coupled easily with both acyclic and cyclic alkenes.



Results and Discussion

According to recent reports, highly enantioselective asymmetric Heck reactions have been observed in a number of intramolecular Heck-type cyclizations; however, intermolecular reactions have thus far given poor enantioselectivities except when using cyclic olefins such as dihydrofuran and dihydropyrrole.[10] While extensively investigating carbon−carbon bond formation with oxidative Pd(II) catalysis of organoborons, we found that the cross-coupling reaction of 4-methoxyphenyl boronic acid (**4**) and methyl tiglate (**5**) in the presence of the novel chiral NHC-Pd(II) complex **3a** produced the rearrangement compound **6** exclusively, generating a new stereogenic center. Under an O_2 atmosphere (1 atm), this reaction gave methyl 2-methylene-3-(4-methoxyphenyl)butanoate (**6**) in 52% yield (*cross-coupling compound*) with 4-methoxyphenol (43%, *deboronylation*) and a small amount of the corresponding biaryl compound (2%, *homocoupled compound*) (Table 1, entry 1). More importantly, it was

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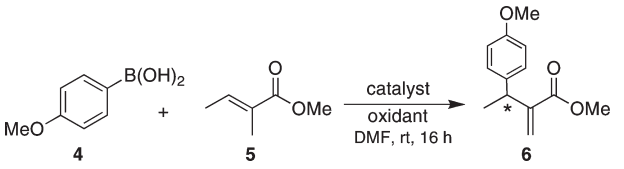
TABLE 1. Effect of Oxidants on Asymmetric Oxidative Coupling Reactions of 4-Methoxyphenylboronic Acid (4) with Methyl Tiglate (5)



entry[a]	catalyst	oxidant	yield (%)[b]	ee (%)[c]
1	**3a**	O_2	52	91
2	**3a**	Air	11	
3[d]	**3a**	$CuCl_2$	>1	
4[d]	**3a**	$Cu(OAc)_2$	>1	
5[d]	**3a**	BQ	0	
6	**3a**	O_2 (6 atm)	50	
7	**2a**	O_2	65	7

[a] **4** (0.5 mmol) was reacted with **5** (1.5 mmol) in the presence of a catalyst (0.02 mmol) in DMF (1.25 mL) at room temperature in the presence of an oxidant for 16 h. [b] Yields based on boronic acid (**4**) used. [c] For the determination of enantiomeric excess, see the Supporting Information. [d] 1 mmol of $CuCl_2$, $Cu(OAc)_2$, and BQ (benzoquinone) added to entries 3, 4, and 5.

found that **6** was formed in 91% enantiomeric excess. As shown in Table 1, we screened representative oxidants for the asymmetric Heck-type reactions in the presence of **3a**. However, under an air atmosphere the reaction resulted in a low yield of **6** (11%) (entry 2), and almost no reaction occurred by employing $CuCl_2$, $Cu(OAc)_2$, or benzoquinone as oxidants (entries 3−5).[1a,11] Formation of the cross-coupled product was not improved under high pressure of O_2 (entry 6). We also examined the coupling reaction with the monomeric complex **2a** (entry 7). Although the reaction conversion was enhanced, enantioselectivity was much lower (7% ee) than that observed in the reaction with dimeric complex **3a**.

From these results, we suspected that higher enantioselectivities via dimer catalyst **3a** as compared to the monomeric catalyst **2a** were due to the steric effect of the borate group transferred to the alkoxide of the catalyst **3a**, which was not the case with **2a**. To account for this difference, we studied the transmetalation step by identifying potential borate intermediates such as **7** by the coupling of **3a** and phenylboronic acid (eq 3). The intended transmetalation of phenylboronic acid was very slow in a DMF solution without generating isolable products. However, phenyl-palladium complex **7** comprising the borate moiety was detected by ^{1}H NMR spectra analysis.[12] In particular, the chemical shifts of the methylene protons (CH_2O) in **7** were further downfield than the corresponding ones in **2a** and **3a**, implying the formation of a boric ester. On the other hand, transmetalation of monomeric catalyst **2a** and phenylboronic acid did not follow suit, presumably furnishing the simple transmetalated intermediate **8** (eq 4). Consequently, these observed intermediate structures could provide a reasonable mechanistic rationale in asymmetric intermolecular

(11) (a) Bäckvall, J.-E.; Gogoll, A. *J. Chem. Soc., Chem. Commun.* **1987**, 1237. (b) Sigman, M. S.; Schultz, M. J. *Org. Biomol. Chem.* **2004**, *2*, 2551. (c) Eastgate, M. D.; Buono, F. G. *Angew. Chem., Int. Ed.* **2009**, *48*, 5958. (d) Chen, X.; Li, J.-J.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 78. (e) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 9651.

(12) The details are described in the Supporting Information.

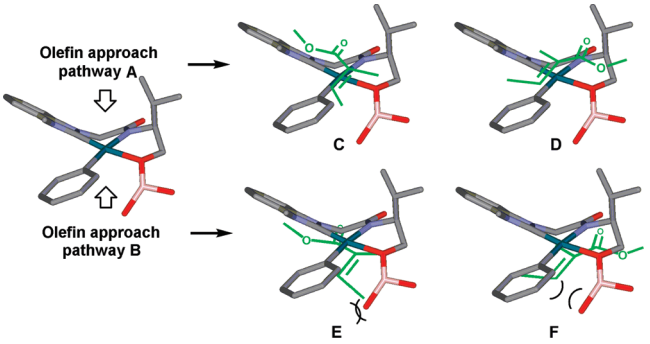


FIGURE 1. Possible transition state for orientation of olefin to the Pd complex **7**.

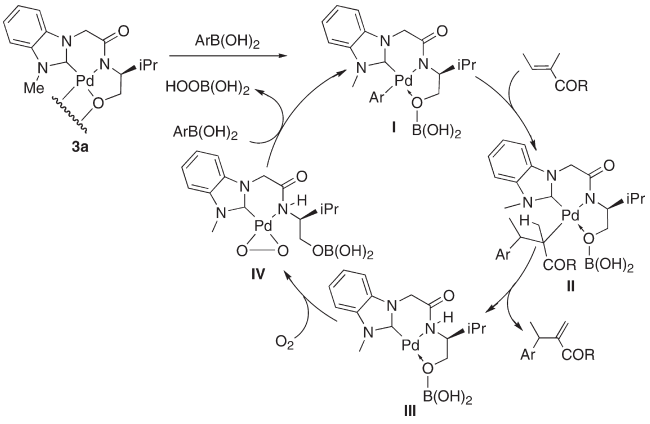
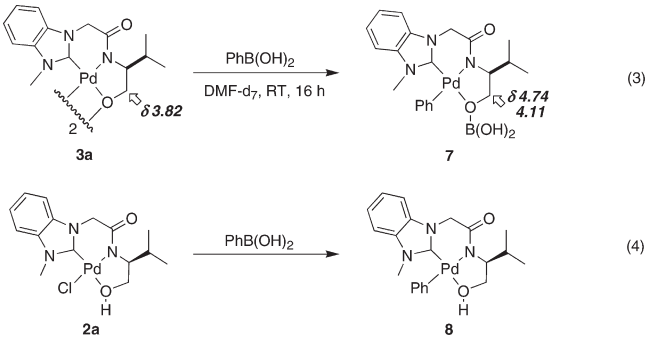


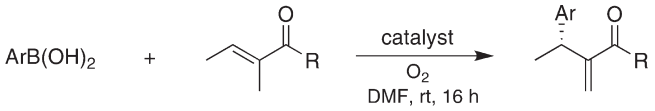
FIGURE 2. Plausible catalytic mechanism.

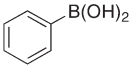
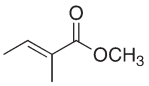
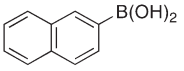
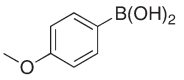
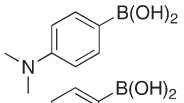
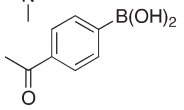
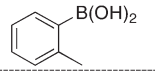
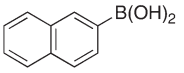
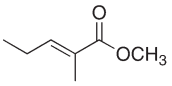
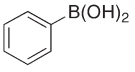
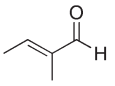
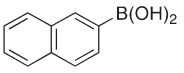
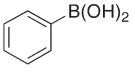
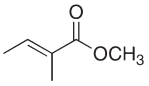
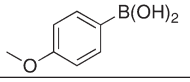
boron-Heck-type reactions via oxidative palladium(II) catalysis.



On the basis of the X-ray crystallographic data for structure **3a**, we have suggested the proper spatial positions of the NHC, isopropyl, phenyl, and borate groups in complex **7**. As shown in Figure 1, the phenyl group would be coordinated at the open site to form the palladium(II) complex, and the borate group would occupy the position remote to the axially positioned isopropyl group based upon the calculated steric energy value. It was also noted that the transmetalated complex **7** would possess a *concave* shape, formed by the benzimidazole and lactam rings. After the transmetalation process, the olefin is envisioned to coordinate by either pathway A (upward) or B (downward) to subsequently undergo migratory insertion into the Pd−Ph bond, where

TABLE 2. Asymmetric Oxidative Heck Reaction with Pd-Ligand Complexes 3a and 3b



Entry[a]	$ArB(OH)_2$	Alkene	Cat.	Product[b]	Conf. [c]
1			**3a**	**9** (49%, 91% ee)	R
2			**3a**	**10** (61%, 92% ee)[d]	-
3			**3a**	**6** (51%, 91% ee)	R
4			**3a**	**11** (52%, 91% ee)	R
5			**3a**	**12** (42%, 89% ee)	R
6			**3a**	**13** (29%, 82% ee)	-
7			**3a**	**14** (41%, 88% ee)	-
8			**3a**	**15** (45%, 87% ee)	R
9			**3a**	**16** (41%, 88% ee)	-
10			**3b**	**9** (33%, 90% ee)	R
11			**3b**	**6** (29%, 94% ee)	R

[a]The reaction was carried out with arylboronic acid (0.5 mmol) and alkene (1.5 mmol) in the presence of catalyst **3a** (0.02 mmol). [b]Yields based on arylboronic acids. For determination of enantiomeric excess, see the Supporting Information. [c]Absolute configuration. [d]Enantioselectivity was determined by NMR analysis with a chiral Eu reagent.

pathway A would be disfavored by the steric hindrance due to concave repulsion (coordination models C and D). Therefore, pathway B would offer two possible transition states (E and F) for the C−C bond formation, which would determine enantioselection modes. In structural model E, there would be significant steric repulsion between the methyl substituent of the olefin and the borate group of the ligand structure, whereas such an interaction would not persist in the coordination model F. Consequently, the reaction would be expected to proceed through the transition state model F, which would lead to the observed excellent enantioselectivity as well as the observed stereochemical (*R*)-configuration. In summary, the concave conformation of these catalysts would augment the steric effect of both the upward axial isopropyl group and the downward axial borate group. We would like to call this opposite alignment of two groups including isopropyl and borate "counter axial groups", which could be a decisive factor in determining enantioselectivity.[13] In the transition states, the facial selectivity of the incoming alkene substrates can be governed by the axial borate group in **3a**, which would not be present in the monomer **2a**. As a result, the "counter axial groups" and the transition state models are an important feature of the design for asymmetric catalysis.

On the basis of these results, we propose a plausible catalytic mechanism as follows (Figure 2): (i) Initial transmetalation between the palladium(II) complex and an arylboronic

(13) Bis-oxazoline type counter axial arrangement in metal catalyzed reaction: (a) Cornejo, A.; Fraile, J. M.; Gracía, J. I.; Gracía-Verdugo, E.; Gil, M. J.; Legarreta, G.; Luis, S. V.; Martínez-Merino, V.; Mayoral, J. A. *Org. Lett.* **2002**, *4*, 3927. (b) Benaglia, M.; Benincori, T.; Mussini, P.; Pilati, T.; Rizzo, S.; Sannicolo, F. *J. Org. Chem.* **2005**, *70*, 7488. (c) Zhang, W.; Xie, F.; Matsuo, S.; Imahori, Y.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron: Asymmetry* **2006**, *17*, 767. (d) Albano, V. G.; Bandini, M.; Monari, M.; Marcucci, E.; Piccinelli, F.; Umani-Ronchi, A. *J. Org. Chem.* **2006**, *71*, 6451.

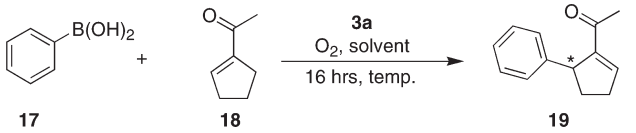
acid would form the intermediate **I**, which was detected by ^{1}H NMR when transmetalation was conducted in the absence of alkenes. (ii) Incorporation of an alkene can be carried out via migratory insertion to afford intermediate **II**, which would be followed by β-hydride elimination to produce the migrated cross-coupling product. Simultaneously, the amidate group is likely to be protonated to generate palladium(0) species **III**. (iii) Molecular oxygen would then oxidize the resulting palladium(0) to a peroxo-palladium complex **IV**,[14] which can react with another arylboronic acid to regenerate complex **I**.[15] As confirmed in our previous work,[16] oxygen was crucial for the catalytic cycle, acting as an efficient palladium(0) reoxidant.

Having established optimized conditions, the representative asymmetric coupling reactions of arylboronic acids and trisubstituted olefins were examined to evaluate the scope of this methodology as shown in Table 2. The cross-coupling reactions of phenylboronic acid and 2-naphthylboronic acid with methyl tiglate took place smoothly to provide the desired rearrangement products, **9** and **10** in 49% and 61% yields, respectively, with excellent enantioselectivities (entries 1 and 2). Electron-donating groups on the arylboronic acids offered comparable yields and enantioselectivities (entries 3 and 4), whereas an electron-withdrawing group gave a slightly lower yield with high enantioselectivity (entry 5). As expected, a more sterically hindered *o*-tolylboronic acid reacted sluggishly to give 29% yield of the desired product **13** (entry 6). The absolute configurations of **6**, **9**, **11**, and **12** were confirmed as (*R*)-enriched by transforming[7c,9] the products to the corresponding phenyl propionic esters and comparing them with authentic samples.[17] This observed stereochemistry matched the explanation using the preferred transition state F (Figure 1).

With use of phenyl- and 2-naphthylboronic acids, we varied alkene substrates including 2-methyl-2-pentenoic methyl ester and *trans*-2-methyl-2-butenal, which exhibited slightly lower yields and ee values (entries 7−9). The absolute configuration of **15** was also determined as the (*R*)-enriched form. Under similar conditions, NHC-Pd(II) complex **3b** provided the desired rearrangement products **9** and **6** in moderate yields; however, this catalyst afforded higher enantioselectivities compared to **3a** (entries 10 and 11). To our knowledge, existing methods for the enantioselective intermolecular arylation of acyclic alkenes have provided only up to 17% ee,[18] whereas our chiral tridentate NHC-amidate-Pd(II) complexes induced excellent enantioselectivities (generally higher than 90% ee) despite moderate yields in some cases due to the deboronylation side reaction.

Independently from acyclic alkenes, we also examined the use of cyclic olefins for these asymmetric oxidative boron-Heck reactions by screening various solvents, temperatures, and catalyst loadings (Table 3). Optimal yields were obtained

TABLE 3. Asymmetric Oxidative Heck Reaction of 1-Acetylcyclopetene and Phenylboronic Acid

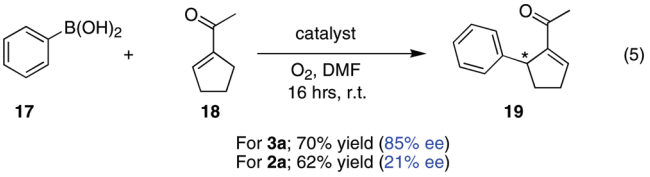


entry[a]	solvent	temp (°C)	Pd (mol %)	yield[b] (%)
1	DMF	rt	5	70 (85% ee)
2	DMF	50	5	67
3	DMF	50	10	71
4	acetonitrile	rt	5	61
5	THF	rt	5	28
6	methanol	rt	5	29
7	toluene	rt	5	24
8	DMA	rt	5	21

[a]The reaction was carried out with olefin (1.5 mmol) and phenylboronic acid (1.0 mmol) in DMF (1.5 mL) at room temperature for 16 h. [b]Yields based on phenylboronic acid.

similarly to acyclic cases with DMF at room temperature (entry 1). In comparison, higher temperatures such as 50 °C were not suitable because the desired cross-coupling diminished slightly due to the increase of homocoupling and deboronylation (entries 2 and 3). Acetonitrile was comparable to DMF; however, other solvents including THF, MeOH, toluene, and DMA provided only poor yields (entries 4−8).

Interestingly, dimeric and monomeric catalysts exhibited distinguished patterns similar to the those of acyclic system as shown in the eq 5. The monomeric complex **2a** afforded poor enantioselectivity (21% ee); however, complex **3a** induced an asymmetric sense to a great extent (85% ee). The dimeric complex also offered higher yield than the monomer. Once again, the aforementioned transition state model accounts for this difference and is thus general for these reactions.



(5)

Under optimized conditions, the substrate scope of the reaction was examined as represented in Table 4. The use of sterically hindered *o*-tolylphenylboronic acid resulted in a lower yield than phenylboronic acid. However, unlike the acyclic alkene (cf. Table 2, entry 6), the use of the cyclic alkene 1-acetyl-1-cyclopentene furnished a moderate yield and high enantioselectivity (entry 1). Electron donating and withdrawing groups had little effect on the course of the reaction, resulting in comparable yields and high enantioselectivities (entries 2−4). A slightly modified alkene, methyl 1-cyclopentene-1-carboxylate, was used for the same transformation, which offered similar yields and enantioselectivities (entries 5−7). In addition, we confirmed that the other palladium(II) complex **3b** generated similar results to **3a** (entry 8). Overall, this asymmetric oxidative palladium(II) catalysis offered an efficient enantioselective protocol for intermolecular cross-coupling reactions between arylboronic acids and cyclic olefins under mild conditions.

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(15) Adamo, C.; Amatore, C.; Ciofini, I.; Jutand, A.; Lakmini, H. *J. Am. Chem. Soc.* **2006**, *128*, 6829.

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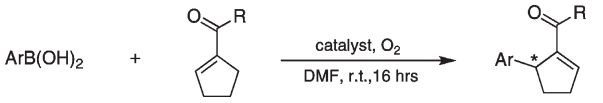
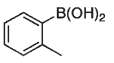
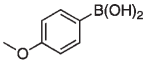
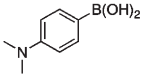
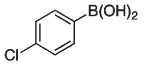
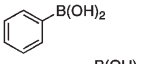
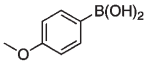
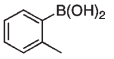
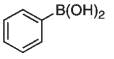
(17) (a) Nishimura, K.; Ono, M.; Nagaoka, Y.; Tomioka, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 440. (b) Miyamoto, K.; Ohta, H. *J. Am. Chem. Soc.* **1990**, *112*, 4077. (c) Miyamoto, K.; Tsuchiya, S.; Ohta, H. *J. Fluorine Chem.* **1992**, *59*, 225.

(18) Yonehara, K.; Mori, K.; Hashizume, T.; Chung, K.-G.; Ohe, K.; Uemura, S. *J. Organomet. Chem.* **2000**, *603*, 40.

TABLE 4. Asymmetric Oxidative Heck Reaction with Pd-Ligand Complexes 3a and 3b



Entry[a]	$ArB(OH)_2$	Alkene	Catalyst	Product (yield) [b]
1			**3a**	**20** (44%, 87% ee[c])
2			**3a**	**21** (54%, 81% ee[c])
3			**3a**	**22** (51%, 82% ee[c])
4			**3a**	**23** (57%, 88% ee[c])
5			**3a**	**24** (62%, 83% ee)
6			**3a**	**26** (56%, 85% ee)
7			**3a**	**26** (48%, 82% ee)
8			**3b**	**19** (52%, 84% ee[c])

[a]The reaction was carried out with arylboronic acid (0.5 mmol) and alkene (1.5 mmol) in the presence of catalyst **3** (0.02 mmol). [b]On the basis of arylboronic acids. For determination of enantiomeric excess, see the Supporting Information. [c]Enantioselectivity was determined by NMR analysis with a chiral Eu reagent.

Conclusion

In conclusion, chiral tridentate amidate/alkoxy/carbene palladium(II) complexes **3a** and **3b** successfully catalyzed oxidative Heck-type reactions of arylboronic acids with both acyclic and cyclic alkenes to offer high enantioselectivities unprecedented in intermolecular Heck-type couplings. The high degree of asymmetric catalysis was presumably due to the biased facial selection of the alkenes, which was caused by counter axial groups (isopropyl and borate groups) embedded in the possible transition states. These ligand architectures can be readily altered by using different chiral components for general use. Thus, we hope that these types of catalysts and the transition state concepts will be utilized for a wide array of asymmetric cross-coupling reactions.

Experimental Section

Typical Catalytic Asymmetric Boron-Heck Coupling Reaction. To a solution of the Pd-ligand complex **3a** or **3b** (10 mg) in DMF (2.5 mL) was added olefin (1.5 mmol) and arylboronic acid (0.5 mmol). The reaction flask was fitted with an oxygen balloon, and the reaction mixture was stirred at room temperature for 16 h, then diluted with EtOAc (10 mL), and washed with water (2 × 10 mL). The separated organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated in vacuo, and the residue was chromatographed on silica gel (hexanes/EtOAc = 40/1) to give a cross-coupled product. To determine enantiomeric excess of the products, HPLC analysis and ^{1}H NMR analysis were performed with chiral Daicel (eluent: *n*-hexane/isopropyl alcohol = 95/5 or 99/1; flow: 1.00 mL/min; DAD: 230.4−450.80 nm) and europium tris[3-(heptafluoropropylhydroxylmethylene)-(+)-camphorate] as a shift reagent, respectively. Compounds **6**, **9**, **10**, **15**, and **16** were identified through comparing their spectral data of the products with those of the previously reported ones,[7c] and other acyclic coupling products were described below. The data analysis on cross-coupling compounds with cyclic olefins and arylboronic acids is included in the Supporting Information.

Methyl 3-(4-(dimethylamino)phenyl)-2-methylenebutanoate (11): ^{1}H NMR ($CDCl_3$) δ 7.08 (d, J = 8.8 Hz, 2H), 6.68 (d, J = 8.8 Hz, 2H), 6.21 (s, 1H), 5.56 (s, 1H), 3.94 (q, J = 6.8 Hz, 1H), 3.67 (s, 3H), 2.01 (s, 6H), 1.38 (d, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 167.9, 158.8, 145.4, 132.3, 128.1, 123.2, 112.9, 51.8, 40.9, 39.5, 20.8. Anal. Calcd for $C_{14}H_{19}NO_2$: C 72.07, H 8.21, N 6.00. Found: C 72.25, H 8.14, N 5.81. HRMS-ESI (m/z) [M + H$^+$] calcd for $C_{14}H_{19}NO_2$ 234.1489, found 234.1493; $[\alpha]^{20}_D$ −48.9 (c 1.01, $CHCl_3$). HPLC (Daicel CHIRALCEL OD-H; 99:1 hexanes/isopropanol, detection wavelength = 254 nm, flow rate = 1.0 mL/min) t_r = 6.8 (minor) and 7.5 min (major).

Methyl 3-(4-acetylphenyl)-2-methylenebutanoate (12): ^{1}H NMR ($CDCl_3$) δ 7.88 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.8 Hz, 2H), 6.35 (s, 1H), 5.68 (s, 1H), 4.07 (q, J = 6.8 Hz, 1H), 3.66 (s, 3H), 2.57 (s, 3H), 1.42 (d, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 197.9, 167.0, 150.1, 143.8, 135.4, 128.5, 127.5, 124.4, 51.8, 40.5, 26.4, 20.4. Anal. Calcd for $C_{14}H_{16}O_3$: C 72.39, H 6.94. Found: C 72.07, H 7.03. HRMS-ESI (m/z) [M + H$^+$] calcd for $C_{14}H_{16}O_3$ 233.1172, found 233.1176. $[\alpha]^{20}_D$ −68.1 (c 0.10, $CHCl_3$). HPLC (Daicel CHIRALCEL OD-H; 99:1 hexanes/isopropanol, detection wavelength = 254 nm, flow rate = 1.0 mL/min) t_r = 21.9 (minor) and 22.5 min (major).

Methyl 2-methylene-3-*o*-tolylbutanoate (13): ^{1}H NMR ($CDCl_3$) δ 7.07−7.15 (m, 4H), 6.27 (s, 1H), 5.52 (s, 1H), 4.22

(q, J = 6.8 Hz, 1H), 3.68 (s, 3H), 2.36 (s, 3H), 1.36 (d, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 167.4, 144.8, 142.4, 138.6, 135.9, 130.4, 126.1, 125.9, 123.8, 51.8, 36.1, 19.9, 19.3. Anal. Calcd for $C_{13}H_{16}O_2$: C 76.44, H 7.90. Found: C 76.19, H 8.02. HRMS-ESI (m/z) [M + H$^+$] calcd for $C_{13}H_{16}O_2$ 205.1223, found 205.1229. $[\alpha]^{20}_D$ −56.7 (c 0.65, $CHCl_3$). HPLC (Daicel CHIRALCEL OD-H; 99:1 hexanes/isopropanol, detection wavelength = 254 nm, flow rate = 1.0 mL/min) t_r = 21.3 (minor) and 22.2 min (major).

Methyl 2-methylene-3-(2-naphthalenyl)pentanoate (14): ^{1}H NMR ($CDCl_3$) δ 7.81−7.74 (m, 3H), 7.65 (m, 1H), 7.46−7.33 (m, 3H), 6.34 (s, 1H), 5.72 (s, 1H), 3.91 (m, 1H), 3.65 (s, 3H), 1.94 (m, 2H), 0.89 (t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 167.5, 143.7, 140.1, 133.4, 132.3, 127.8, 127.7, 127.5, 126.9, 126.6, 125.8, 125.3 129.3, 51.8, 48.0, 27.4, 12.4. Anal. Calcd for $C_{17}H_{18}O_2$: C 80.28, H 7.13. Found: C 80.25, H 7.14. HRMS-ESI (m/z) [M + H$^+$] calcd for $C_{17}H_{19}O_2$ 255.1340, found 255.1342; $[\alpha]^{20}_D$ −71.8 (c 0.75, $CHCl_3$). HPLC (Daicel CHIRALCEL OD-H; 95:5 hexanes/isopropanol, detection wavelength = 270 nm, flow rate = 1.0 mL/min) t_r = 4.5 (minor) and 5.4 min (major).

Acknowledgment. The authors acknowledge generous financial support from the National Institute of General Medical Sciences of the National Institutes of Health (RO1 GM 71495).

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all compounds in addition to experimental data for compounds **11**−**14** and **19**−**26**. This material is available free of charge via the Internet at http://pubs.acs.org.