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Pd(II)-CATALYZED ENANTIOSELECTIVE INTRAMOLECULAR HECK-TYPE REACTION TO CONSTRUCT CHIRAL SULFONAMIDE RINGS

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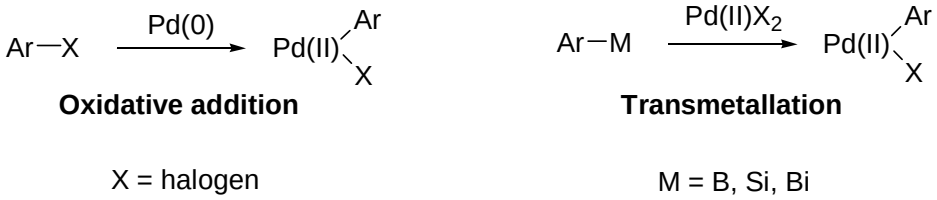
Abstract – The first example of enantioselective intramolecular Heck-type reaction to construct chiral quaternary carbon centers of sulfonamide rings is reported. The reaction provides the expected Heck products along with the unexpected olefin reduction products. We discovered the catalyst prepared from (*S*,*S*)-chiraphos and Pd_2dba_3 to afford the products in high yields and enantioselectivities up to 86% *ee* at room temperature. Deuterated solvent and base are also examined to elucidate the mechanism of reduction of olefin. Pd hydride species produced from β–elimination are responsible for olefin reduction.

INTRODUCTION

Organoboron-mediated Heck-type reactions is one of the most attractive Pd(II)-catalyzed reactions as an alternative to Mizoroki-Heck reactions.[1,2] Initial step of these reactions are transmetallation of Pd(II) species instead of oxidative addition from Pd(0) species (Scheme 1).[3] Therefore the advantages of these reactions are as follows; 1) The organoboronic acids are employed as nucleophilic substrates in Heck-type reactions. 2) Pd(II) species do not oxidatively add to organohalides. Halide functional groups in substrates would thus be preserved. From this concept, successful examples of the Pd(II)-catalyzed organoboron-mediated Heck-type reactions have recently been established using $Cu(OAc)_2$[4] and molecular oxygen as oxidants.[5,6] However asymmetric catalysis of Heck-type reactions had not been well studied.[7]

This paper is dedicated to Professor Dr. Ekkehard Winterfeldt on the occasion of his 75th birthday.



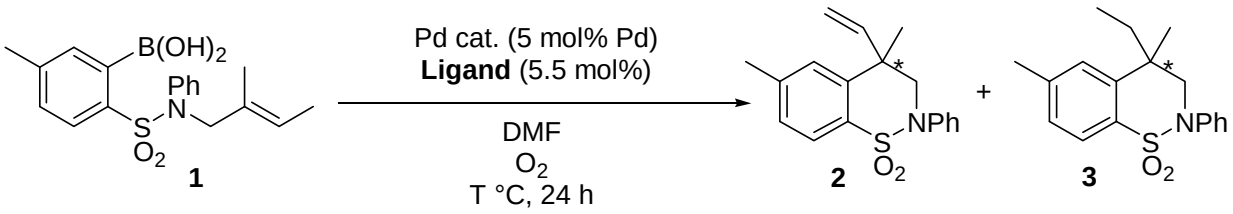
Scheme 1

Asymmetric Heck-type reactions are important not only to provide an alternative to the asymmetric Mizoroki-Heck reaction[8] but also to extend the synthetic scope of the asymmetric Fujiwara-Moritani reaction[9] initiated from the C-H activation by chiral Pd(II) species. Herein we report the first example of highly enantioselective intramolecular Heck-type reaction to construct sulfonamide rings with quaternary carbon center.[10]

RESULTS AND DISCUSSION

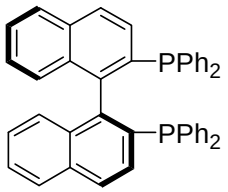
The construction of chiral quaternary carbon center with sulfonylamide moiety was examined (Table 1). The substrate **1** was treated with 2.5 mol% of $Pd_2(dba)_3$ and 5.5 mol% of ligands in DMF at 50 ℃. Several achiral ligands were firstly examined; dppe, dppp, and dppb (entries 1, 2, and 3). Dppb gave the desired product **2** in low yield (37%). Interestingly smaller ring chelate ligands; dppp and dppe afforded **2** and an unexpected olefin reduced product **3** in 81:19 and 59:41 ratios, respectively. The ratio of product **3** was increased with smaller ligand bite angle. Chiral phosphorus ligands; (*S*,*S*)-chiraphos, (*S*,*S*)-skewphos, and (*S*)-BINAP ligand were then examined. (*S*)-BINAP and (*S*,*S*)-skewphos provided only product **2** selectively, although the enantioselectivity and yield were low (entries 4 and 5). In contrast, (*S*,*S*)-chiraphos gave **2** and **3** (56:44) with highest yield and enantioselectivity (79%, 82% *ee*) (entry 6).[11] Several Pd precatalysts; $Pd(CH_3CN)_4(BF_4)_2$, $Pd(OCOCF_3)_2$, $Pd(OAc)_2$, and $Pd_2(dba)_3$ were examined under the same conditions. $Pd(OAc)_2$ provided almost the same result as $Pd_2(dba)_3$ did (72%, 81% *ee*) (entry 7). Cationic Pd complexes were not effective in the reaction. $Pd(OCOCF_3)_2$, gave products **2** and **3** in low yield (10%) (entry 8). $Pd(CH_3CN)_4(BF_4)_2$ did not give the desired product (entry 9). The highest yield and enantioselectivity was achieved at 25 ℃ (91%, 86% *ee*) (entry 10).[12] To clarify the active species in this reaction, oxygen effect on this reaction was also investigated (entry 11); the reaction did not proceed under an argon atmosphere. This result suggests that oxygen is essential and active catalyst species should be a Pd(II) peroxo species.

Table 1 Pd(II) catalyzed enantioselective intramolecular Heck-type reaction

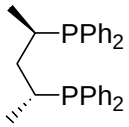


Entry	Pd cat.	Ligand	T[°C]	Yield [%][a] **2**+**3** (**2**/**3**)[b]	ee [%][c]
1	Pd_2dba_3	dppb	50	37 (>98/<2)	-
2		dppp		63 (81/19)	-
3		dppe		62 (59/41)	-
4		(*S*)-BINAP		16(>98/<2)	23 (-)
5		(*S,S*)-skewphos		30 (>98/<2)	35 (+)
6		**(*S,S*)-chiraphos**		79 (57/43)	82 (+)
7	$Pd(OAc)_2$	(*S,S*)-chiraphos	50	72 (55/45)	81 (+)
8	$Pd(OCOCF)_2$			10 (69/31)	71 (+)
9	$[Pd(CH_3CN)_4](BF_4)_2$			n.r.	-
10d)	Pd_2dba_3		25	91(56/44)	86 (+)
11e)	Pd_2dba_3	(*S,S*)-chiraphos	50	trace	-

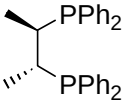
a) Isolated yield, b) Ratio of (1/2) were determined by ^{1}H NMR, c) The *ee* were determined after Pd/C hydrogenation of mixture **2** and **3**. d) Reaction time was 48 hours e) Under Ar atmosphere



(*S*)-BINAP



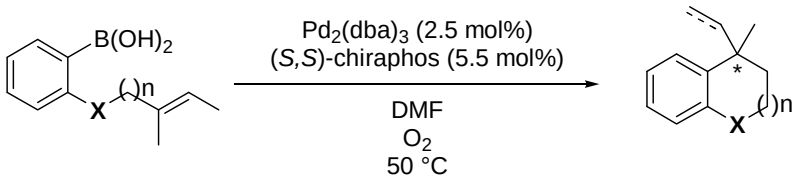
(*S,S*)-skewphos

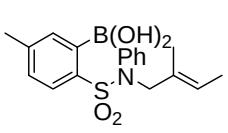
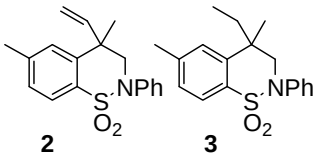
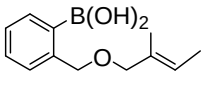
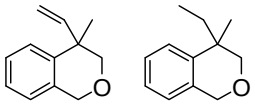
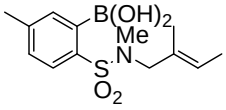
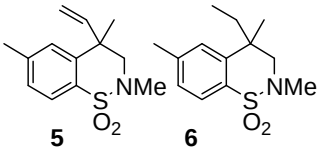
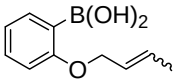
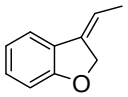
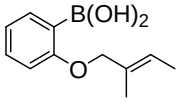
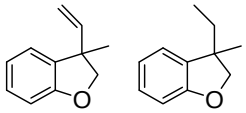
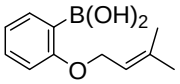
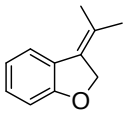


(*S,S*)-chiraphos

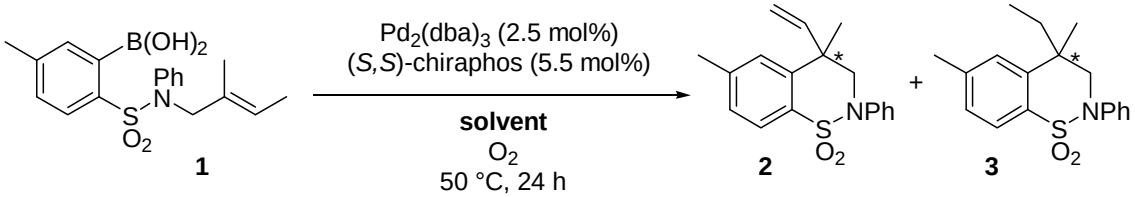
Several substrates were examined under the same conditions (Table 2). The N-methyl substrate **4** provided **5** and **6** (87/13) in 63% yield and 69% ee. Ether substrate **7** gave five-membered ring product **8** and **9** (56/44) in good yield but lower enantioselectivity. Moderate yield and enantioselectivity were obtained with substrate **10**. Substrates **13** and **15** gave the exo olefin products **14** and **16** in 39% and 58% respectively.

Table 2 Substrate examination of Pd(II) catalyzed enantioselective intramolecular Heck-type reaction.



Substrate	Product	Substrate	Product
 **1**	 **2** **3** **79% (57/43)** **82% *ee***	 **10**	 **11** **12** **45% (83/17)** **45% *ee***
 **4**	 **5** **6** **63% (87/13)** **69% *ee***	 **13**	 **14** **39%**
 **7**	 **8** **9** **80% (56/44)** **25% *ee*, 19% *ee***	 **15**	 **16** **58%**

To elucidate the origin of hydrogen in **3,** deuterated solvent were examined (Scheme 2). If the hydrogen atoms were derived from boronic acid in substrates, deuterated products **3** should be obtained in the deuterated protic solvent. Deuterium oxide (5 equiv) in DMF and deuterated methanol were examined. However, no duterated products **3** were observed and the same ratio of products **2**/**3** were obtained compared in the non deuterated solvents.



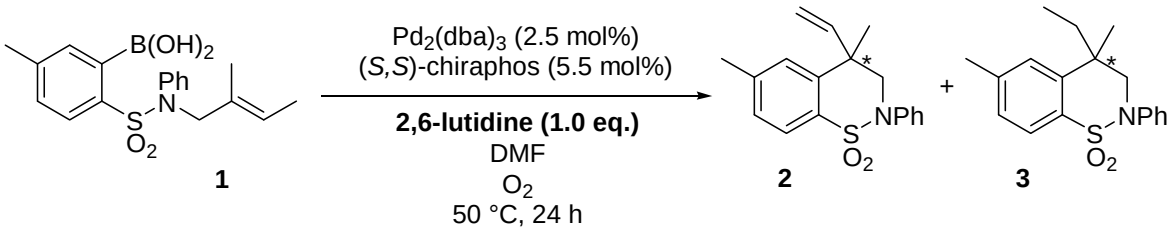
DMF+ **D_2O** (5.0 eq) 70% (55/45), 81% *ee*

CD_3OD 30% (57/43), 85% *ee*

No deuterium incorporation was observed

Scheme 2

The effect of base was also examined (Scheme 3). The addition of 1 equiv of 2,6-lutidine changed the ratios of products **2** and **3** (73:27). This base effect suggests a relation between Pd hydride species and products **3**.



Scheme 3

From these results, the hypothesis of reaction mechanism is exemplified in Figure 1; Pd(0) phosphine complexes **17** are oxidized with O_2 to produce Pd (II) peroxo species **18**.[13] The peroxo complexes react with substrates to provide the products **2** and Pd hydride species **19**. Instead of the reduction of the Pd hydride species, they react with substrates again to produce the intermediates **20**. The reductive elimination of intermediates **20** and reoxidation provide products **3** and regenerate Pd(II) peroxo complexes.

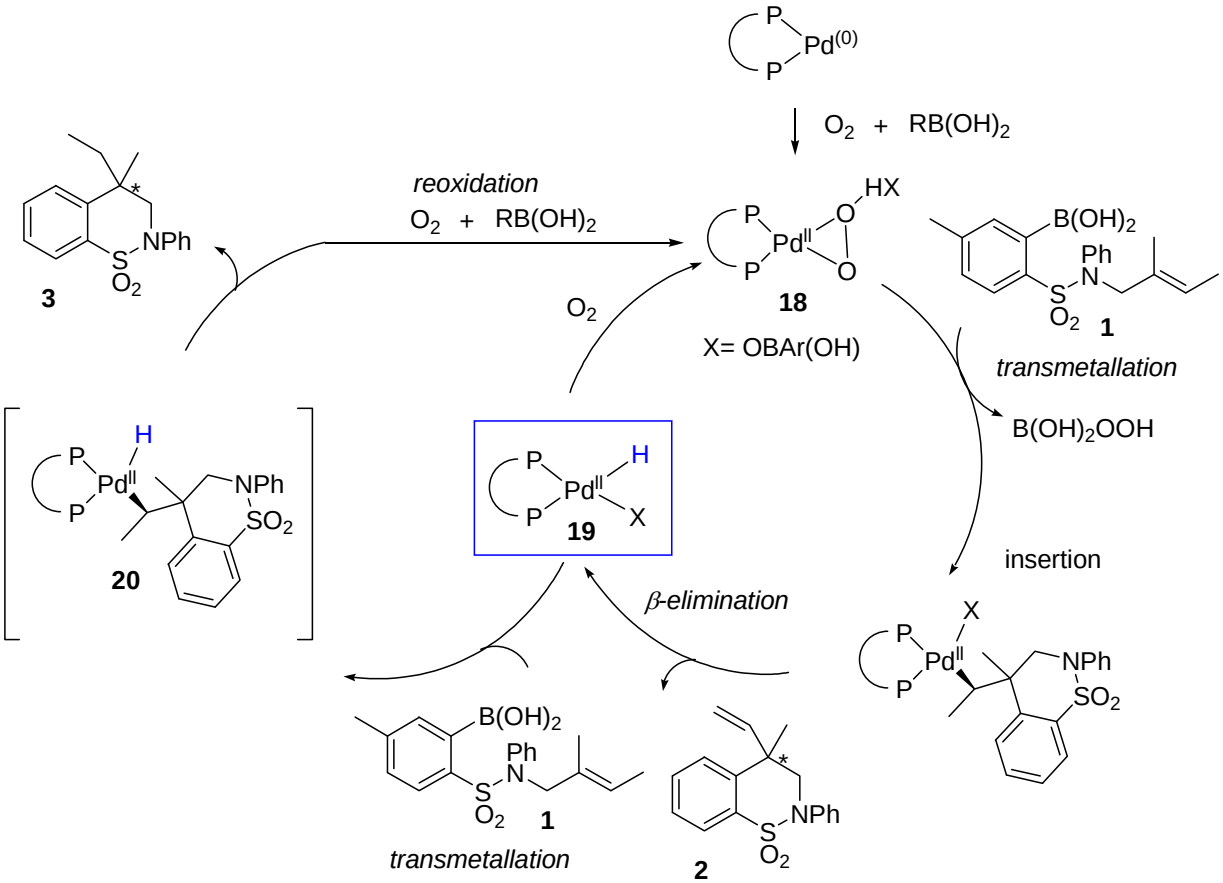


Figure 1

In conclusion, we have reported the first example of enantioselective intramolecular Heck-type reaction. The sulfonyl amide rings with quaternary carbon center were successively constructed with high yields and enantioselectivities. The reaction provide the expected products **2** and the unexpected saturated products **3**. (*S*,*S*)-Chiraphos gave high yield and enantioselectivity up to 86% *ee* at room temperature. The examination of deuterated solvent and base effect suggests that the Pd hydride species **19** is responsible for the satutated product **3**.

EXPERIMENTAL

General procedure for enantioselective intramolecular Heck-type reaction

To a test tube charged with Pd_2dba_3 (4.6 mg, 0.005 mmol), and (*S*,*S*)-chiraphos (4.7mg, 0.011) under argon was added DMF (2.0 mL). After an hour stirring, to another test tube charged with arylboronic acid substrate (53.9 mg, 0.15 mmol) equipped with oxygen balloon was added 1.5 mL of Pd catalyst DMF solution (Pd_2dba_3 3.4 mg, 0.00375 mmol, (*S*,*S*)-chiraphos 3.5 mg, 0.00825 mmol, DMF 1.5 mL). The reaction mixture was stirred at rt. After stirring for 48 hours, the mixture was diluted with Et_2O, filtered through a pad of Celite, washed with water and brine, and dried over with anhydrous magnesium sulfate. After evaporation under reduced pressure, the residue was purified by column chromatography to give the title product. The ratio of product **1** and **2** was determined by ^{1}H NMR analysis. After the hydration by palladium-carbon, the enantiomer excess was determined by HPLC analysis.

4,6-Dimethyl-2-phenyl-4-vinyl-3,4-dihydro-2*H*-benzo[*e*][1,2]thiazine 1,1-dioxide (2)

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54 (s, 3H), 2.39 (s, 3H), 3.75 (d, *J* = 13.8 Hz, 1H), 4.10 (d, *J* = 13.8 Hz, 1H), 5.20 (dd, *J* = 17.4, 0.6 Hz, 1H), 5.28 (d, *J* = 13.2 Hz, 1H), 6.02 (dd, *J* = 17.4, 10.8 Hz, 1H), 7.07(brs, 1H), 7.23 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.32-7.45 (m, 5H), 7.82 (d, *J* = 8.4 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6 (CH_3), 24.8 (CH_3), 43.3 (4°), 60.7 (CH_2), 115.7 (CH_2), 123.9 (CH), 127.5 (CH), 127.7 (CH), 128.5 (CH), 129.0 (CH), 129.3 (CH), 134.7 (4°), 139.7 (4°), 141.2 (4°), 142.5 (CH), 142.8 (4°).

HPLC analysis (DAICEL CHIRALCEL AD-H, eluent, Hexane/2-Propanol= 95/5, flow rate 0.6 ml/min, 25 °C detection 210 nm light)

t_R of minor isomer 64.6 min, major isomer 84.0 min. ((*S*,*S*)- skewphos ligand)

$[\alpha]_D^{22}$ + 10.3 (*c* 0.103, $CHCl_3$); 38% *ee* product from (*S*,*S*)- skewphos ligand.

MS (ESI-TOF) m/z= 336 $[M+Na]^+$

4-Ethyl-4,6-dimethyl-2-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,2]thiazine 1,1-dioxide (3)

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, *J* = 7.5 Hz, 3H), 1.36 (s, 3H), 1.70 (sext, *J* = 7.3 Hz, 1H), 1.97

(sext, *J* = 7.4 Hz, 1H), 2.42 (s, 3H), 3.79 (d, *J* = 13.2 Hz, 1H), 3.98 (d, *J* = 13.2 Hz, 1H), 7.14 (s, 1H), 7.21 (d, *J* = 8.7 Hz, 1H), 7.30-7.47 (m, 5H), 7.81 (d, *J* = 8.4 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 8.8 (CH_3), 21.7 (CH_3), 26.1 (CH_3), 33.3 (CH_2), 39.8 (4°), 59.1 (CH_2), 124.0 (CH), 127.5 (CH), 127.6 (CH), 127.7 (CH), 128.0 (CH), 129.3 (CH), 134.8 (4°), 139.7 (4°), 142.7 (4°), 143.0 (4°).

IR (KBr) 2966, 1957, 1887, 1806, 1734, 1603, 1570, 1493, 1381, 1307, 1145, 1120, 1067, 1006, 946, 874, 814, 772, 725, 698, 681, 611, 578, 545, 491, 476. cm^{-1}.

HPLC analysis (DAICEL CHIRALCEL OD-H, eluent, Hexane/2-Propanol = 97/3, flow rate 0.6 ml/min, 25 °C detection 210 nm light)

t_R of minor isomer 46.9 min, major isomer 54.9 min. ((*S*,*S*)- chiraphos ligand)

$[\alpha]_D^{22}$ +2.8 (*c* 0.10, $CHCl_3$); 86% *ee* product from (*S*,*S*)-chiraphos ligand.

MS (ESI-TOF) m/z= 338 $[M+Na]^+$

REFERENCES AND NOTES

1. The author differentiates the Mizoroki-Heck reaction from the Heck-type reaction. The Mizoroki-Heck reaction involves aryl or vinyl halide. The Heck-type reaction employs organoboron compound. This reaction is first reported by Heck. H. A. Dieck and R. F. Heck, *J. Org. Chem*., 1975, **40**, 1083.
2. The first achiral example; C. S. Cho and S. Uemura, *J. Organomet. Chem.,* 1994, **465**, 85.
3. Recent examples of enantioselective Pd(II) catalyzed C-C bond forming reaction via transmetallation of aryl metal compound. B; (a) M. Lautens and C. Dockendorff, *Org. Lett.,* 2003, **5**, 3695. (b) F. Gini, B. Hessen, and A. J. Minnaard, *Org. Lett.,* 2005, **7**, 5309.
   Bi; (a) T. Nishikata, Y. Yamamoto, and N. Miyaura, *Chem. Commun.*, 2004, 1822. Si and B; (d) T. Nishikata, Y. Yamamoto, I. D. Gridnev, and N. Miyaura, *Organometallics*, 2005, **24**, 5025.
4. X. Du, M. Suguro, K. Hirabayashi, and A. Mori, *Org. Lett.,* 2001, **3**, 3313.
5. (a) Y. C. Jung, R. K. Mishra, C. H. Yoon, and K. W. Jung, *Org. Lett.,* 2003, **5**, 2231.(b) C. H. Yoon, K. S. Yoo, S. W. Yi, R. K. Mishra, and K. W. Jung, *Org. Lett.,* 2004, **6**, 4037. (c) K. S. Yoo, C. H. Yoon, and K. W. Jung, *J. Am. Chem. Soc.,* 2006, **128**, 16384.
6. M. M. S. Andappan, P. Nilsson, and M. Larhed, *Chem. Commun*., 2004, 218.
7. Recent studies of asymmetric Heck-type reaction; (a) K. Akiyama, K. Wakabayashi, and K. Mikami, *Adv. Synth. Catal.*, 2005, **347**, 1569. (b) L. Penn, A. Shpruhman, and D. Gelman, *J. Org. Chem.*, 2007, **72**, 3875. (c) K. S. Yoo, C. P. Park, C. H. Yoon, S. Sakaguchi, J. O'Neill, and K. W. Jung, *Org. Lett.*, 2007, **9**, 3933.
8. Review on enantioselective Mizoroki-Heck reaction; (a) A. B. Dounay and L. E. Overman, *Chem.*

Rev., 2003, **103**, 2945. (b) M. Shibasaki, E. M. Vogl, and T. Ohshima, *Adv. Synth. Catal.*, 2004, **346**, 1533.

9. The example of asymmetric Fujiwara-Moritani reaction; K. Mikami, M. Hatano, and M. Terada, *Chem. Lett.*, 1999, 55.
10. (a) S. F. Martin, *Tetrahedron*, 1980, **36**, 419. (b) K. Fuji, *Chem. Rev.*, 1993, **93**, 2037. (c) E. J. Corey and A. Guzman-Perez, *Angew. Chem., Int. Ed.*, 1998, **37**, 388. (d) J. Christoffers and A. Mann, *Angew. Chem., Int. Ed.*, 2001, **40**, 4591. (e) I. Denissova and L. Barriault, *Tetrahedron*, 2003, **59**, 10105. (f) C. J. Douglas and L. E. Overman, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5363. (g) B. M. Trost and C. Jiang, *Synthesis*, **2006**, 369.
11. We have determined the enantioselectivity of products **12a** and **12b**. Almost the same enantioselectivity of product 12a and 12b was confirmed.
12. Time dependence of enantioselectivity was examined under the conditions. The same enantioselectivity were confirmed in 6, 12, 24, and 48 h.
13. The mechanism of Pd(II) catalyzed homocoupling of arylboronic acid has been reported; C. Adamo, C. Amatore, I. Ciofini, A. Jutand, and H. Lakmini *J. Am. Chem. Soc.*, 2006, 128, 6829.