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A highly efficient asymmetric Suzuki–Miyaura coupling reaction catalyzed by cationic chiral palladium(II) complexes

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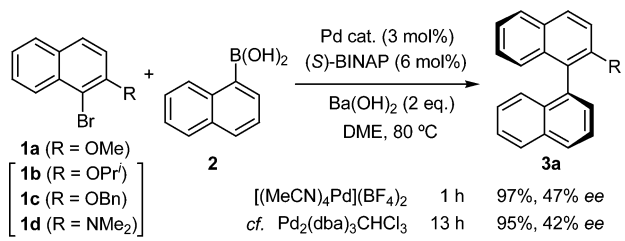
Cationic chiral palladium(II) complexes are shown to catalyze the asymmetric coupling reaction of aryl boronates and aryl halides within a short period of time in good yield and enantioselectivity.

The practice of organic synthesis is primarily based on the construction of carbon–carbon bonds and the introduction of chirality therein mediated by chiral metal complexes (nickel and palladium, *etc.*).[1] However, the applicability of coupling reactions of reactive aryl metals (*via* the aryl palladium intermediate) with aryl halides have been limited in terms of functional group tolerance. Palladium catalyzed Suzuki–Miyaura coupling reaction[2] of aryl boronates with aryl halides is one of the most useful coupling reactions in terms of a wide range of functional group applicability[3,4] but has one serious drawback of the low reactivity, namely the long period of reaction time (low catalyst turnover efficiency).[5] We have been involving, in the context of chiral biphenyl liquid crystalline molecule,[6] an investigation on the asymmetric Suzuki–Miyaura coupling reaction under cationic chiral palladium conditions,[7] to afford the binaphthyl coupling products within shorter reaction times than that with the generally employed neutral palladium(0) catalysts.[8] We describe here the successful results of the reaction catalyzed by cationic chiral palladium complexes, which afford the coupling products in good yield and enantioselectivity.

Typical experimental is as follows: the reaction of aryl halides **1a** (1 mmol) and aryl boronate **2** (1.5 mmol) with Pd catalyst (3 mol%) and (*S*)-BINAP (6 mol%) in the presence of $Ba(OH)_2{\cdot}8H_2O$ (2 mmol) in 1 mL of dimethoxyethane (DME) afforded the coupling product **3a** after column chromatographic separation (Scheme 1).[9] A typical Pd(0) species $Pd_2(dba)_3{\cdot}CHCl_3$ showed low catalytic activity (13 h for full conversion). When the reaction was allowed to proceed for longer time, we sometimes observed the decomposition of boronic acids or racemization of the Suzuki–Miyaura products. During our ongoing project on cationic chiral palladium catalysis, we have proven that dicationic chiral Pd(II) species derived from $[(MeCN)_4Pd](BF_4)_2$ in the presence of P,P- or P,N-ligands is a powerful catalyst in intra-molecular ene-type cyclizations.[7] Indeed, the use of this cationic catalyst system facilitates the asymmetric Suzuki–Miyaura coupling reaction. Cationic species, $[(MeCN)_4Pd](BF_4)_2$, showed significantly high activity to give **3a** (47% ee) within 1 h in an excellent yield (Scheme 1).

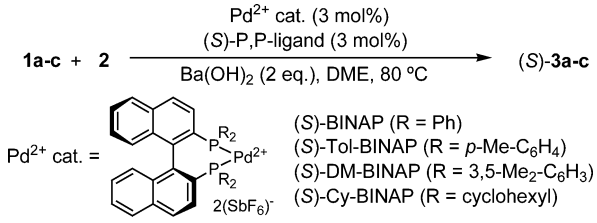
Moreover, the combined use of [(*S*)-P,P-ligand]Pd^{2+} (3 mol%) and the corresponding (*S*)-P,P-ligand (3 mol%) was effective to increase the enantioselectivity up to 56% ee from 47% ee just by simply mixing $[(MeCN)_4Pd](BF_4)_2$ (3 mol%) and P,P-ligand (6 mol%) (Table 1, entry 1 *vs.* Scheme 1). Unexpectedly, sterically demanding Pd^{2+} complexes, such as Pd^{2+}/(*S*)-Tol-BINAP or Pd^{2+}/(*S*)-DM-BINAP, didn't give good selectivities (entries 2 and 3). To our surprise, further increase in enantioselectivity (70% ee) was observed with the use of (*S*)-cyclohexyl-BINAP (Cy-BINAP) instead of (*S*)-BINAP (entry 4). Finally, the enantioselectivity increased up to 84% ee when the reaction was executed at room temperature though the yield was low (entry 5). The high catalytic activity and enantioselectivity stem from the highly sterically demanding nature of this complex. X-ray analysis of a single crystal of [(*S*)-Cy-BINAP]$PdCl_2$ complex **4**† was thus performed to show the novel C_1 symmetric field (Fig. 1).[10,11] This is in sharp contrast to the C_2 symmetric field as usually seen in other $PdCl_2$ complexes with BINAP analogues.[12] Cationic Pd^{2+}/BINAP or Pd^{2+}/Cy-BINAP catalysts were effective for other substrates to afford the products quantitatively although the selectivities were moderate (entries 6–11).

Indeed, this cationic Pd^{2+}/BINAP catalyst is highly active in the Suzuki–Miyaura coupling reaction even with *ortho*-substituted aryl chloride (Table 2). Aryl chloride Cl-**5** reacted with **6** to afford the *ortho*-substituted biphenyl product **7** in 87% yield within 2 h (entry 3). Aryl bromide or iodide reacted more rapidly within 10 min in excellent yields (entries 1 and 2).



Scheme 1

Table 1 Cationic Pd^{2+} catalyzed asymmetric Suzuki–Miyaura coupling[a]



Entry	Substrate	P,P-ligand	Reaction time/h	% Yield[b] (% ee[c])
1	**1a**	(*S*)-BINAP	0.5	91 (56)
2	**1a**	(*S*)-Tol-BINAP	1	97 (40)
3	**1a**	(*S*)-DM-BINAP	4	0 (—)
4	**1a**	(*S*)-Cy-BINAP	1	92 (70)
5[d]	**1a**	(*S*)-Cy-BINAP	6	17 (84)
6	**1b**	(*S*)-BINAP	0.5	99 (50)
7	**1b**	(*S*)-Tol-BINAP	1.5	86 (37)
8	**1c**	(*S*)-BINAP	2	99 (49)
9	**1c**	(*S*)-Cy-BINAP	4	99 (54)
10	**1d**	(*S*)-BINAP	0.5	61 (58)
11	**1d**	(*S*)-Cy-BINAP	24	11 (54)

[a] All reactions were carried out on a 1 mmol scale. [b] Isolated yield. [c] ee values were determined by chiral HPLC analysis (Ref. 9). [d] At r.t.

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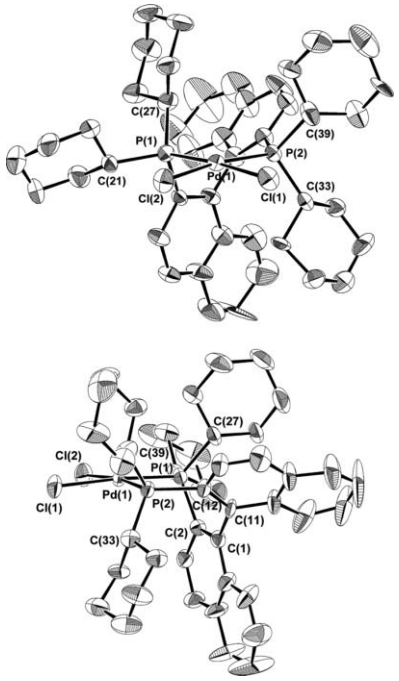
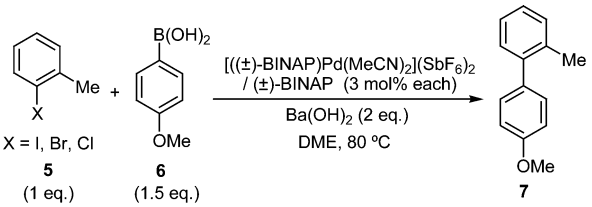


Fig. 1 The ORTEP drawing (front view (up) and side view (down)) of [(*S*)-Cy-BINAP]$PdCl_2$ complex **4** (H atoms are omitted for clarity). Selected bond lengths (Å) and angles (°): Pd(1)–P(1) 2.259(2), Pd(1)–P(2) 2.310(2), Pd(1)–Cl(1) 2.376(2), Pd(1)–Cl(2) 2.343(2), Cl(1)–Pd–Cl(2) 87.56(10), P(1)–Pd–P(2) 94.19(8), P(1)–Pd–P(2)–C(33) 61.6(4), P(1)–Pd–P(2)–C(39) 128.7(5), P(2)–Pd–P(1)–C(21) 173.1(4), P(2)–Pd–P(1)–C(27) 119.7(4), C(2)–C(1)–C(11)–C(12) 69.2(14).

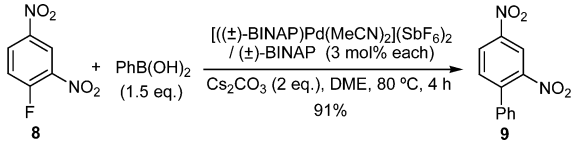
Table 2 Cationic Pd^2 catalyzed Suzuki–Miyaura coupling[a]



Entry	X in **5**	Reaction time	Isolated yield (%)
1	I	10 min	88
2	Br	10 min	90
3[b]	Cl	2 h	87

[a] All reactions were carried out on a 1 mmol scale. [b] 3 equiv. of boronic acid **6** were used.

We next turn our attention to the challenging coupling with aryl-fluoride.[13] Although the C–F bond is much less reactive than C–Cl or C–Br bond, for nitrophenyl fluoride **8**, Pd^{2+}/BINAP catalyst could facilitate the coupling reaction with $PhB(OH)_2$ to give **9** in an excellent (91%) yield within 4 h (eqn. (1)).



(1)

In conclusion, we have uncovered the successful example of the efficient catalytic asymmetric Suzuki–Miyaura coupling by cationic chiral palladium complexes to induce high enantioselectivity and yield. Detailed mechanistic studies on cationic Pd^{2+} catalysis are now under investigation.

Notes and references

† Crystal data of **4**: formula $C_{44}H_{56}Cl_2P_2Pd$, orthorhombic, space group $P2_12_12$(#18), a = 27.4346(9) Å, b = 12.8063(9) Å, c = 14.2675(9) Å, V = 5012.7(5) $Å^3$, Z = 4, and D = 1.092 g cm^{-3}. X-ray diffraction data were collected on a Rigaku R-AXIS CS diffractometer with graphite-monochromated Mo-Kα (λ = 0.71069 Å) at −50 °C and the structure was solved by direct methods (SIR97, SHELXL-97). The final cycle of full-matrix least-squares refinement was based on 5819 observed reflections ($I > 3\sigma(I)$) and 442 variable parameters and converged to R = 0.0916 and Rw = 0.2671. Flack parameter = 0.3387. CCDC 211532. See http://www.rsc.org/suppdata/cc/b4/b407250b/ for crystallographic data in .cif or other electronic format.

1 (*a*) J. Tsuji, *Palladium Reagents and Catalysts: New Perspective for the 21st Century*, New York, Wiley, 2004; (*b*) E. Negishi, *Handbook of Organopalladium Chemistry for Organic Synthesis*, New York, Wiley, 2002; (*c*) T. Naota, H. Takaya and S.-I. Murahashi, *Chem. Rev.*, 1998, **98**, 2599–2660.

2 For reviews: (*a*) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457–2483; (*b*) N. Miyaura, *Top. Curr. Chem.*, 2002, **219**, 11–59.

3 S. R. Chemler, D. Trauner and S. J. Danishefsky, *Angew. Chem. Int. Ed.*, 2001, **40**, 4544–4568.

4 (*a*) A. F. Littke, C. Dai and G. C. Fu, *J. Am. Chem. Soc.*, 2000, **122**, 4020–4028; (*b*) N. Kataoka, Q. Shelby, J. P. Stambuli and J. F. Hartwig, *J. Org. Chem.*, 2002, **67**, 5553–5566.

5 Recently, neutral palladium catalyses have been reported: (*a*) A. Zapf, A. Ehrentraut and M. Beller, *Angew. Chem. Int. Ed.*, 2000, **39**, 4153–4155; (*b*) M. G. Andreu, A. Zapf and M. Beller, *Chem. Commun.*, 2000, 2475–2476; (*c*) G. Y. Li, *Angew. Chem. Int. Ed.*, 2001, **40**, 1513–1516; (*d*) R. B. Bedford, C. S. J. Cazin and S. L. Hazelwood, *Angew. Chem. Int. Ed.*, 2002, **41**, 4120–4122; (*e*) L. Botella and C. Nájera, *Angew. Chem. Int. Ed.*, 2002, **41**, 179–181; (*f*) G. Altenhoff, R. Goddard, C. W. Lehmann and F. Glorius, *Angew. Chem. Int. Ed.*, 2003, **42**, 3690–3693; (*g*) G. Adjabeng, T. Brenstrum, J. Wilson, C. Frampton, A. Robertson, J. Hillhouse, J. McNulty and A. Capretta, *Org. Lett.*, 2003, **5**, 953–955.

6 Consult: (*a*) Y. Takanishi, H. Takezoe, Y. Suzuki, I. Kobayashi, T. Yajima, M. Terada and K. Mikami, *Angew. Chem. Int. Ed.*, 1999, **38**, 2353–2356; (*b*) K. Mikami, T. Yajima, M. Terada, Y. Suzuki and I. Kobayashi, *Chem. Commun.*, 1997, 57–58; (*c*) K. Mikami, T. Yajima, N. Siree, M. Terada, Y. Suzuki and I. Kobayashi, *Synlett*, 1996, 837–838.

7 (*a*) M. Hatano, M. Terada and K. Mikami, *Angew. Chem. Int. Ed.*, 2001, **40**, 249–253; (*b*) M. Hatano and K. Mikami, *J. Mol. Cat. A: Chemical*, 2003, **196**, 165–169; (*c*) M. Hatano and K. Mikami, *Org. Biomol. Chem.*, 2003, **1**, 3871–3873; (*d*) M. Hatano, M. Yamanaka and K. Mikami, *Eur. J. Org. Chem.*, 2003, 2552–2555; (*e*) M. Hatano and K. Mikami, *J. Am. Chem. Soc.*, 2003, **125**, 4704–4705; (*f*) K. Mikami and M. Hatano, *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 5767–5769.

8 Precedent examples of asymmetric catalysis: (*a*) A. N. Cammidge and K. V. L. Crépy, *Chem. Commun.*, 2000, 1723–1724; (*b*) J. Yin and S. L. Buchwald, *J. Am. Chem. Soc.*, 2000, **122**, 12051–12052; (*c*) A.-S. Castanet, F. Colobert, P.-E. Broutin and M. Orbringer, *Tetrahedron: Asymmetry*, 2002, **13**, 659–665; (*d*) J. F. Jensen and M. Johannsen, *Org. Lett.*, 2003, **5**, 3025–3028; (*e*) A. N. Cammidge and K. V. L. Crépy, *Tetrahedron*, 2004, **60**, 4377–4386.

9 Chiral HPLC analysis: OJ–H, hexane: 2-propanol = 4:1, 1.0 mL min^{-1}, 15 °C. t_R is 11.2 min ((*S*)-**3a**) and 23.0 ((*R*)-**3a**). ^1H NMR ($CDCl_3$, 300 MHz) δ 3.78 (s, 3H), 7.18–7.38 (5H), 7.47–8.01 (8H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 56.7, 113.8, 123.2, 123.5, 125.5, 125.6, 125.7, 125.8, 126.1, 126.4, 127.7, 127.8, 128.2, 128.4, 129.0, 129.4, 132.9, 133.7, 134.2, 134.5, 154.6.

10 Pd-complex **4** suitable for X-ray analysis was obtained by recrystallization in CH_2Cl_2/hexane: ^1H NMR (300 MHz, $CDCl_3$) δ 0.40–2.0 (40H), 2.28 (br, 2H), 3.57 (br, 2H), 6.95 (d, J = 8.4 Hz, 2H), 7.15 (t, J = 7.5 Hz, 2H), 7.47 (d, J = 7.2 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2H), 7.91 (d, J = 7.5 Hz, 2H), 8.01 (d, J = 8.1 Hz, 2H). ^{31}P NMR (109 MHz, $CDCl_3$) δ 38.57 (br, 2P).

11 X-ray analysis of [Rh{(*S*)-Cy-BINAP}(cod)]ClO_4: X. Zhang, K. Mashima, K. Koyano, N. Sayo, H. Kumobayashi, S. Akutagawa and H. Takaya, *J. Chem. Soc. Perkin Trans 1*, 1994, 2309–2322.

12 F. Ozawa, A. Kubo, Y. Matsumoto, T. Hayashi, E. Nishida, K. Yanagi and K. Moriguchi, *Organometallics*, 1993, **12**, 4188–4196.

13 (*a*) Y. M. Kim and S. Yu, *J. Am. Chem. Soc.*, 2003, **125**, 1696–1697; (*b*) D. A. Widdowson and R. Wilhelm, *Chem. Commun.*, 2003, 578–579.