Asymmetric Catalysis

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Asymmetric Suzuki–Miyaura Coupling Reactions Catalyzed by Chiral Palladium Nanoparticles at Room Temperature**

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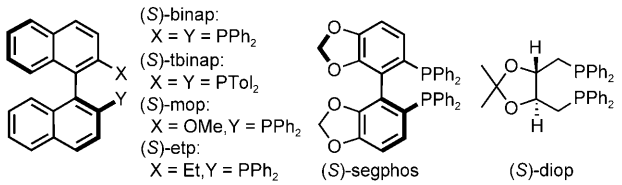
Recently, there has been great interest on the use of metal nanoparticles (NPs) for nanocatalysis.[1,2] The catalytic properties of metal NPs depend on the particle size, which is controlled by the nature of the protective ligands (stabilizers; for example, thiol and phosphine). Although a number of thiol-stabilized metal NPs have been reported, metal NPs stabilized by bisphosphine ligands have received much less attention.[3,4] Palladium NPs have become of increasing scientific interest as catalysts for carbon–carbon bond-forming reactions, such as Suzuki–Miyaura cross-coupling reactions, which are among the most powerful methods in organic synthesis. These reactions are typically performed under heating or at reflux.[1,2,5,6] Much less is known about the room-temperature Suzuki–Miyaura cross-coupling reaction catalyzed by phosphine-stabilized Pd NPs.

The Suzuki–Miyaura cross-coupling reaction of naphthyl halides and naphthylboronic acids catalyzed by a chiral palladium–phosphine complex led to axially chiral binaphthalenes. These coupling products constitute an important class of atropisomeric compounds.[7] Such chiral 1,1′-binaphthyl derivatives have found extensive use in chiral auxiliaries for a variety of synthetic asymmetric reactions, including catalytic ones. A small number of asymmetric biaryl syntheses involving Suzuki–Miyaura cross-coupling reactions catalyzed by chiral palladium–phosphine complexes have been reported.[8] Despite the growing success of Suzuki–Miyaura coupling reactions for the construction of biaryl derivatives, its asymmetric variant still remains a challenge, probably because of the inherent difficulty in coupling two sterically hindered arenes in a transition-metal-mediated process. There have so far been no reports of the asymmetric Suzuki–Miyaura coupling of a naphthyl halide and naphthylboronic acid by using Pd NPs stabilized by chiral phosphines as catalysts.

We have succeeded in the preparation of small Pd NPs stabilized by the optically active mono- and bisphosphines (*S*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthene ((*S*)-binap), (*S*)-2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthene ((*S*)-tbinap), (4,4′-bi-1,3-benzodioxole)-5,5′-diylbis(diphenylphosphine) ((*S*)-segphos), (4*S*,5*S*)-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane ((*S*)-diop), (*S*)-2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl ((*S*)-mop), and (*S*)-2-(diphenylphosphino)-2′-ethyl-1,1′-binaphthene ((*S*)-etp; Scheme 1). The chiral Pd NPs with these ligands have similar diameters of 1.2–1.7 nm, but give very different catalytic activities and enantioselectivities in the room-temperature asymmetric Suzuki–Miyaura cross-coupling reactions of aryl halides with aryl boronic acids. Specifically, the chiral binap-stabilized Pd NPs (diameter: 1.6 nm) can efficiently catalyze asymmetric Suzuki–Miyaura cross-coupling reactions of naphthyl halides with naphthylboronic acid at room temperature with short reaction times. Herein we report the asymmetric Suzuki–Miyaura cross-coupling reactions of aryl halides and aryl boronic acids catalyzed by chiral Pd NPs at room temperature, with a focus on the effect of the protective ligand on the catalysis. Although there are a few reports on asymmetric reactions catalyzed by chiral metal NPs,[1,3a,9] to our knowledge, this is the first such an example of the asymmetric Suzuki–Miyaura reaction.



Scheme 1. Protective ligands of the chiral Pd NPs. Tol = tolyl.

The chiral Pd NPs with the stabilizing ligands (*S*)-binap, (*S*)-tbinap, (*S*)-segphos, (*S*)-diop, (*S*)-mop, and (*S*)-etp were prepared by the reduction of K_2PdCl_4 with $NaBH_4$ in the presence of the chiral phosphine. Notably, the (*S*)-binap-Pd NPs were stable for several months. The size of the Pd NPs was determined by transmission electron microscopy (TEM)[10] as: (1.6 ± 0.2) nm for (*S*)-binap-Pd NPs, (1.2 ± 0.2) nm for (*S*)-tbinap-Pd NPs, (1.2 ± 0.2) nm for (*S*)-segphos-Pd NPs, (1.2 ± 0.2) nm for (*S*)-diop-Pd NPs, (1.5 ± 0.2) nm for (*S*)-mop-Pd NPs, and (1.7 ± 0.3) nm for (*S*)-etp-Pd NPs. These values indicate a small core size and a narrow size distribution. The X-ray photoelectron spectroscopy spectra (XPS) of these Pd NPs showed the Pd 3d binding energies at 336.0 and 341.3 eV, which correspond to the Pd^0 state. The circular dichroism (CD) spectra of the chiral Pd NPs showed negative Cotton effects.

It is noteworthy that high temperatures and prolonged reaction times are usually needed to obtain acceptable yields of sterically hindered biaryl derivatives.[8] The asymmetric

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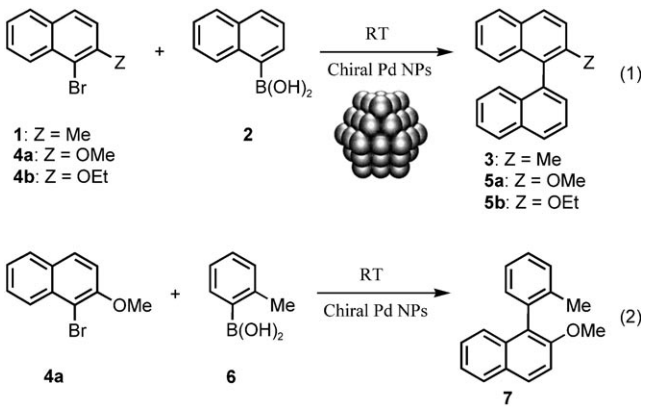
synthesis of binaphthalenes catalyzed by a chiral palladium–bisphosphine complex has been reported; for example, the reaction of 1-iodonaphthalene with 2-methyl-naphthylboronic acid in the presence of 3 mol% $PdCl_2$/3 mol% chiral binap and CsF or $Ba(OH)_2$ as a base in dimethoxyethane (DME) or DME/H_2O at reflux for 19 h gave the cross-coupling product **3** in yields of 43–55% and 8–25% enantiomeric excess.[8a] Thus, the use of sterically congested coupling partners generally leads to poor yields in Suzuki–Miyaura reactions under reflux,[5,6,8] and the enantioselectivity is low. In contrast, we found that the reaction of 1-bromo-2-methylnaphthalene (**1**, 1 mmol) with 1-naphthylboronic acid (**2**, 1.5 mmol) in the presence of a small amount of (*S*)-binap-Pd NPs (0.01 mol% at 25 °C for 44 h or 0.1 mol% at 0 °C for 75 h) and KF (3 mmol) in THF (1.5 mL) afforded the cross-coupling product **3** (72% yield, 24% *ee* at 25 °C, and 44% yield, 60% *ee* at 0 °C)[11] after preparative liquid chromatographic separation [Scheme 2, Eq. (1)].

We then extended our investigations to the asymmetric Suzuki–Miyaura coupling of 2-substituted naphthyl bromides **4** with **2** using several bases and chiral Pd NPs under our best conditions [Scheme 2, Eq. (1)]. A variety of bases were screened (Table 1). The reaction of **4a** with **2** in the presence of a small amount of (*S*)-binap-Pd NPs (0.1 mol%) as a catalyst and K_2CO_3 as a base at 25 °C for 24 h afforded the coupling product **5a** (83% yield, 50% *ee*; Table 1, entry 3).



Scheme 2. Suzuki–Miyaura coupling reactions catalyzed by the chiral Pd NPs.

Table 1: Suzuki–Miyaura reactions catalyzed by (*S*)-binap-Pd NPs.[a]

Entry	Halide	Boronic acid	Base	*T* [°C]	*t* [h]	Product	Yield [%][b] (*ee* [%])[c]
1	**4a**	**2**	KF	25	24	**5a**	47 (18)
2	**4a**	**2**	CsF	25	12	**5a**	52 (54)
3	**4a**	**2**	K_2CO_3	25	24	**5a**	83 (50)
4	**4a**	**2**	K_3PO_4	25	24	**5a**	84 (48)
5	**4a**	**2**	$Ba(OH)_2$	25	3	**5a**	96 (69)
6	**4a**	**2**	$Ba(OH)_2$	-7	72	**5a**	42 (74)
7	**4b**	**2**	$Ba(OH)_2$	25	3	**5b**	90 (70)
8	**4a**	**6**	$Ba(OH)_2$	25	24	**7**	89 (55)

[a] Conditions: 1 mmol halide, 1.5 mmol **2**, 3 mmol base, 0.1 mol% (*S*)-binap-Pd NPs [1.6 nm], DME/H_2O (DME/H_2O 9/1) as solvent. [b] Ref. [12]. [c] Ref. [13]. The absolute configuration of **5a** is *R*.[14]

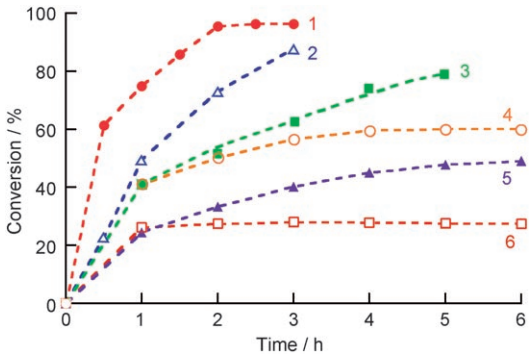


Figure 1. Comparison of the catalytic activity of the chiral Pd NPs for the reaction of **4a** with **2** at room temperature. 1: (*S*)-binap-Pd NPs, 2: (*S*)-tbinap-Pd NPs, 3: (*S*)-segphos-Pd NPs, 4: (*S*)-etp-Pd NPs, 5: (*S*)-mop-Pd NPs, and 6: (*S*)-diop-Pd NPs.

Significantly, a dramatic improvement in the rate and enantioselectivity of the coupling reaction of **4a** with **2** was obtained by using $Ba(OH)_2$ instead of K_2CO_3 at 25 °C: the binaphthalene **5a** (96% yield, 69% *ee*) was obtained after a shorter reaction time of 3 h (Table 1, entry 5; Figure 1). Thus, the reaction of **4a** with **2** was affected by the strength of the bases $Ba(OH)_2$, K_3PO_4, K_2CO_3, CsF, and KF (Table 1, entries 1–5). The enantioselectivity increased up to 74% *ee* when the reaction was carried out at −7 °C, although the yield was low (Table 1, entry 6). A similar result was obtained in the reaction of **4b** with **2** at 25 °C for 3 h (Table 1, entry 7). In contrast to (*S*)-binap-Pd NPs, it was reported that the reaction of **4a** with **2** in the presence of 3 mol% of the Pd^0 species $[Pd_2(dba)_3CHCl_3]$/(*S*)-binap (dba = *trans*,*trans*-benzylideneacetone) and $Ba(OH)_2$ in DME at 80 °C for 13 h gave **5a** (95% yield, 42% *ee*).[8g] Moreover, the use of (*S*)-binap-Pd NPs in the reaction of **4a** with 2-methylphenylboronic acid (**6**) increased the enantioselectivity of the coupling product **7** from 12% *ee*[8h] and 76% yield with the chiral palladium–phosphine/$Pd(OAc)_2$ (5 mol%) catalyst and CsF in DME at 70 °C for 16 h up to 55% *ee* and 89% yield in the presence of (*S*)-binap-Pd NPs (0.1 mol%) and $Ba(OH)_2$ in DME/H_2O at 25 °C for 24 h [Scheme 2, Eq. (2); Table 1, entry 8].[13]

The reaction of **4a** with **2** catalyzed by chiral Pd NPs was chosen for screening experiments with the protective ligands (Table 2 and Figure 1). The enantioselectivity decreased to 58% *ee* when (*S*)-tbinap-Pd NPs were used (Table 2, entry 1). It is known that a change in the dihedral angle of the backbone axes of aryl bisphosphine ligands can have a significant impact on the enantioselectivity in some reactions catalyzed by a chiral Pd complex in the presence of phosphine;[15] the enantioselectivity of the coupling product **5a** (69% *ee*) with the (*S*)-binap-Pd NP catalyst was higher than that obtained with (*S*)-segphos-Pd NPs (32% *ee*; Table 2, entry 2). Palladium NPs stabilized with the bisphosphine (*S*)-diop or monophosphines (*S*)-mop and (*S*)-etp were found to be inefficient for the reaction of **4a** with **2** (Table 2, entries 3–5). Most notably, the yields and enantioselectivities in the reaction of **4a** with **2** were influenced remarkably by the protective ligand on the chiral Pd NPs, even though the chiral Pd NPs have similar diameters (1.2–1.7 nm). The chiral (*S*)-binap-Pd NPs behave as a highly effective catalyst for

Table 2: Suzuki–Miyaura reactions of **4a** with **2** catalyzed by Pd NPs.[a]

Entry	Ligand (mol%) [diameter, nm]	*t* [h]	**5a**: Yield [%][b] (*ee* [%])[c]
1	(*S*)-tbinap (0.2) [1.2]	3	88 (58)
2	(*S*)-segphos (0.3) [1.2]	5	89 (32)
3	(*S*)-diop (0.2) [1.2]	6	25 (10)
4	(*S*)-mop (0.2) [1.5]	6	50 (12)
5	(*S*)-etp (0.2) [1.7]	6	60 (12)

[a] Conditions: 1 mmol **4a**, 1.5 mmol **2**, 3 mmol $Ba(OH)_2$, 25 °C, DME/H_2O (9/1) as solvent. [b] Ref. [12]. [c] Ref. [13]. The absolute configuration of **5a** is *R*.[14]

the asymmetric Suzuki–Miyaura coupling at room-temperature and a short reaction time.

In summary, we have developed a room-temperature asymmetric Suzuki–Miyaura coupling reaction by using chiral-phosphine-stabilized Pd NPs with small core sizes as catalysts. Although the chiral Pd NPs have similar diameters of 1.2–1.7 nm, they showed very different catalytic activities and enantioselectivities for the reactions. We believe that this study provides a new dimension to the asymmetric Suzuki–Miyaura coupling by using chiral Pd NPs as a chiral nanocatalyst. Our current efforts are focused on developing asymmetric cross-coupling reactions for naphthyl compounds, as well as on gaining a better understanding of the reaction mechanism.

Experimental Section

Protective chiral phosphine ligands (*S*)-binap, (*S*)-tbinap, (*S*)-segphos, and (*S*)-diop were purchased from Aldrich and Strem Chemicals, Inc. Chiral phosphines (*S*)-mop and (*S*)-etp were prepared according to a literature method.[16]

Synthesis of chiral Pd NPs: The synthesis of the mono- and bisphosphine-stabilized palladium nanoparticles was carried out by using a modification of a procedure previously reported.[3a] Typical procedure for the preparation of (*S*)-binap-Pd NPs is as follows. A solution of (*S*)-binap (968 mg, 1.6 mmol) in CH_2Cl_2 (80 mL) was added to a vigorously stirred solution of K_2PdCl_4 (200 mg, 0.6 mmol) in deionized water (28 mL) and tetra-*n*-octylammonium bromide (436 mg, 0.8 mmol) in CH_2Cl_2 (20 mL). A solution of $NaBH_4$ (72 mg, 1.9 mmol) in deionized water (10 mL) was then added and the mixture stirred for 1 h at room temperature under Ar. The filtrate was evaporated in vacuo to yield (*S*)-binap-Pd NPs. Purification (dichloromethane/*n*-hexane) of the NPs was repeated until no free phosphine remained, as evident by TLC as well as by ^1H and ^{13}C NMR spectroscopy. Other chiral Pd NPs were prepared by the same procedure. The chiral Pd NPs were characterized by TEM, XPS, CD, and UV/Vis spectroscopy.

Typical procedure for Suzuki–Miyaura coupling (Table 1, entry 5): 2-Methoxynaphthyl bromide (**4a**; 237 mg, 1 mmol), 1-naphthylboronic acid (**2**; 258 mg, 1.5 mmol), (*S*)-binap-Pd NPs (60 mg, 0.1 mol%), and $Ba(OH)_2$ (514 mg, 3 mmol) were dissolved in DME/H_2O (3 mL, DME/H_2O 9/1), and the solution was stirred at 25 °C for 3 h under argon. The conversion was monitored by HPLC. After work-up, the crude product was purified by column chromatography on silica gel (hexane/benzene 3/1) and further purified by preparative liquid chromatography to give binaphthalene **5a** (96% yield, 69% *ee*). The *ee* value of **5a** was determined by HPLC on a Chiralpak AD-H column.

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[1] D. Astruc, *Nanoparticles and Catalysis*, Wiley-VCH, Weinheim, **2008**.
[2] a) A. Roucoux, J. Schulz, H. Patin, *Chem. Rev.* **2002**, *102*, 3757; b) J. A. Widegren, R. G. Finke, *J. Mol. Catal. A* **2003**, *198*, 317; c) M. M. Manas, R. Pleixats, *Acc. Chem. Res.* **2003**, *36*, 638; d) D. Astruc, F. Lu, J. R. Aranzaes, *Angew. Chem.* **2005**, *117*, 8062; *Angew. Chem. Int. Ed.* **2005**, *44*, 7852; e) D. Astruc, *Inorg. Chem.* **2007**, *46*, 1884.
[3] a) M. Tamura, H. Fujihara, *J. Am. Chem. Soc.* **2003**, *125*, 15742; b) Y. Yanagimoto, Y. Negishi, H. Fujihara, T. Tsukuda, *J. Phys. Chem. B* **2006**, *110*, 11611.
[4] S. U. Son, Y. Jang, K. Y. Yoon, E. Kang, T. Hyeon, *Nano Lett.* **2004**, *4*, 1147.
[5] J. Tsuji, *Palladium Reagents and Catalysts*, Wiley, New York, **2004**.
[6] a) *Metal-catalyzed Cross-coupling Reactions* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1998**; b) A. Suzuki, *Suzuki Coupling*, *Organic Syntheses via Boranes*, *Vol. 3*, Aldrich, Milwaukee, **2003**.
[7] L. Pu, *Chem. Rev.* **1998**, *98*, 2405.
[8] a) A. N. Cammidge, K. V. L. Crepy, *Chem. Commun.* **2000**, 1723; b) J. Yin, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 12051; c) A.-S. Castanet, F. Colobert, P.-E. Broutin, M. Obringer, *Tetrahedron: Asymmetry* **2002**, *13*, 659; d) J. F. Jensen, M. Johannsen, *Org. Lett.* **2003**, *5*, 3025; e) A. Herrbach, A. Marinetti, O. Baudoin, D. Guenard, F. Gueritte, *J. Org. Chem.* **2003**, *68*, 4897; f) A. N. Cammidge, K. V. L. Crepy, *Tetrahedron* **2004**, *60*, 4377; g) K. Mikami, T. Miyamoto, M. Hatano, *Chem. Commun.* **2004**, 2082; h) P. Kasak, K. Mereiter, M. Widhalm, *Tetrahedron: Asymmetry* **2005**, *16*, 3416; i) O. Baudoin, *Eur. J. Org. Chem.* **2005**, 4223; j) M. Ciclosi, J. Lloret, F. Estevan, P. Lahuerta, M. Sanau, J.-P. Prieto, *Angew. Chem.* **2006**, *118*, 6893; *Angew. Chem. Int. Ed.* **2006**, *45*, 6741; k) M. Genov, A. Almorin, P. Espinet, *Chem. Eur. J.* **2006**, *12*, 9346; l) T. Takemoto, S. Iwasa, H. Hamada, K. Shibatomi, M. Kameyama, Y. Motoyama, H. Nishiyama, *Tetrahedron Lett.* **2007**, *48*, 3397; m) M. Genov, A. Almorin, P. Espinet, *Tetrahedron: Asymmetry* **2007**, *18*, 625.
[9] a) S. Jansat, M. Gomez, K. Philippot, G. Muller, E. Guiu, C. Claver, S. Castillon, B. Chaudret, *J. Am. Chem. Soc.* **2004**, *126*, 1592; b) G. Szollosi, A. Mastalir, Z. Kiraly, I. Dekany, *J. Mater. Chem.* **2005**, *15*, 2464; c) S. Jansat, D. Picurelli, K. Pelzer, K. Philippot, M. Gomez, G. Muller, P. Lecante, B. Chaudret, *New J. Chem.* **2006**, *30*, 115; d) I. Favier, M. Gomez, G. Muller, M. R. Axet, S. Castillon, C. Claver, S. Jansat, B. Chaudret, K. Philippot, *Adv. Synth. Catal.* **2007**, *349*, 2459; e) D. Han, X. Li, H. Zhang, Z. Liu, G. Hu, C. Li, *J. Mol. Catal. A* **2008**, *283*, 15.
[10] TEM images of the chiral Pd NPs are given in the Supporting Information.
[11] The *ee* values of (*R*)-**3** were determined by optical rotation measurements: T. Hayashi, K. Hayashizaki, T. Kiyoi, Y. Ito, *J. Am. Chem. Soc.* **1988**, *110*, 8153.
[12] The products were isolated and purified by column chromatography and then by preparative liquid chromatography.
[13] The *ee* values of **5a**,**b** were determined by HPLC on a Chiralpak AD-H column and for **7** on a Chiralcel OJ-H column. The HPLC data are given in the Supporting Information.
[14] The absolute configuration of **5a** was determined on the basis of the sign of the optical rotation: J. M. Wilson, D. J. Cram, *J. Org. Chem.* **1984**, *49*, 4930.
[15] A. Hu, M. Ogasawara, T. Sakamoto, A. Okada, K. Nakajima, T. Takahashi, W. Lin, *Adv. Synth. Catal.* **2006**, *348*, 2051.
[16] Y. Uozumi, A. Tanahashi, S.-Y. Lee, T. Hayashi, *J. Org. Chem.* **1993**, *58*, 1945.

