Asymmetric Catalysis

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Asymmetric Suzuki–Miyaura Coupling in Water with a Chiral Palladium Catalyst Supported on an Amphiphilic Resin**

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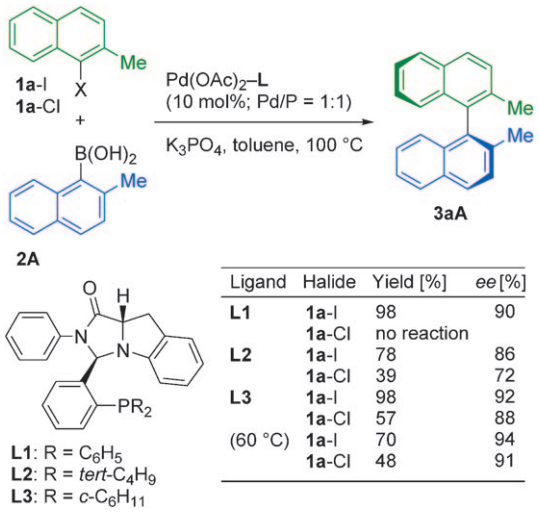
We report herein an asymmetric Suzuki–Miyaura coupling for the synthesis of a variety of axially chiral biaryl compounds with high stereoselectivity (up to 94% *ee*). The reaction is carried out in water with a novel recyclable palladium complex of a polymer-supported chiral imidazoindole phosphine ligand.

The cross-coupling of aryl halides and aryl boronic acids, known as the Suzuki–Miyaura coupling, is one of the most versatile and successful synthetic tools for carbon–carbon bond formation.[1] However, although axially chiral biaryl compounds are highly accessible by this reaction,[2] only scattered attention has been paid to the asymmetric Suzuki–Miyaura coupling.[3,4] Recently, Bermejo et al. reported a novel asymmetric catalytic system that promotes the Suzuki–Miyaura biaryl coupling with excellent enantioselectivity.[5] Although pioneering strides have been made, the development of highly enantioselective catalyst systems with wide substrate tolerance and acceptable catalytic activity still remains a major challenge. Furthermore, additional studies on aqueous switching and heterogeneous switching are clearly warranted.

Our continuing interest in the utility of chiral imidazoindole phosphines, that is, (3*R*,9a*S*)-2-aryl-(3-(2-dialkylphosphanyl)phenyl)tetrahydro-1*H*-imidazo[1,5-*a*]indol-1-one derivatives,[6] which we developed previously for the asymmetric catalysis of π-allylic substitution,[7] led us to examine their potential as catalyst ligands for stereoselective Suzuki–Miyaura coupling reactions to give biaryl compounds. Preliminary ligand screening was carried out under standard homogeneous conditions. Thus, 1-iodo-2-methylnaphthalene (**1a**-I) reacted with 2-methyl-1-naphthaleneboronic acid (**2A**; 5 equiv) in the presence of $Pd(OAc)_2$ (10 mol%), the imidazoindole diphenylphosphine ligand **L1** (Pd/P 1:1), and K_3PO_4 (10 equiv) in toluene at 100°C for 5 h to give 2,2′-dimethyl-1,1′-binaphthyl (**3aA**) in quantitative yield (Scheme 1). The enantiomeric purity and absolute configuration of **3aA** were found to be 90% *ee* and *S* by HPLC analysis on a chiral stationary phase and measurement of the specific rotation. The chemical yield and enantiomeric purity of **3aA** decreased to 78% yield and 86% *ee* with the imidazoindole di-*tert*-butylphosphine ligand **L2**. The imidazoindole dicyclohexylphosphine ligand **L3**, which afforded **3aA** in 98% yield with 92% *ee* under similar conditions, was identified as the best ligand. The palladium catalyst with **L3** was so catalytically active that the coupling took place at 60°C to give **3aA** with 94% *ee* (24 h, 70% yield). Interestingly, 1-chloro-2-methylnaphthalene (**1a**-Cl) also underwent coupling with **2A** in the presence of the palladium–**L3** catalyst at 60°C to afford **3aA** with 91% *ee*, although the chemical yield was modest (48%).



Ligand	Halide	Yield [%]	*ee* [%]
L1	**1a**-I	98	90
	1a-Cl	no reaction	
L2	**1a**-I	78	86
	1a-Cl	39	72
L3	**1a**-I	98	92
	1a-Cl	57	88
(60 °C)	**1a**-I	70	94
	1a-Cl	48	91

Scheme 1. Asymmetric Suzuki–Miyaura binaphthyl coupling.

We next attempted aqueous and heterogeneous switching of this asymmetric biaryl-coupling catalysis. Asymmetric catalysis in water with a recyclable heterogeneous catalyst would approach what may be considered an ideal organic chemical process. Over the past ten years, we have demonstrated that a wide variety of non-asymmetric and asymmetric catalytic organic transformations can be performed in water by the use of transition-metal complexes and nanoparticles supported on an amphiphilic polystyrene–poly(ethylene glycol) copolymer (PS–PEG) resin.[8] The chiral imidazoindole phosphines were developed as a novel series of chiral ligands with a view toward their use in water-based catalysis through immobilization on PS–PEG.[9] Upon thorough optimization of the reaction conditions, we found that the asymmetric Suzuki–Miyaura biaryl coupling took place smoothly in water with good to excellent stereoselectivity and broad substrate tolerance when a palladium complex of

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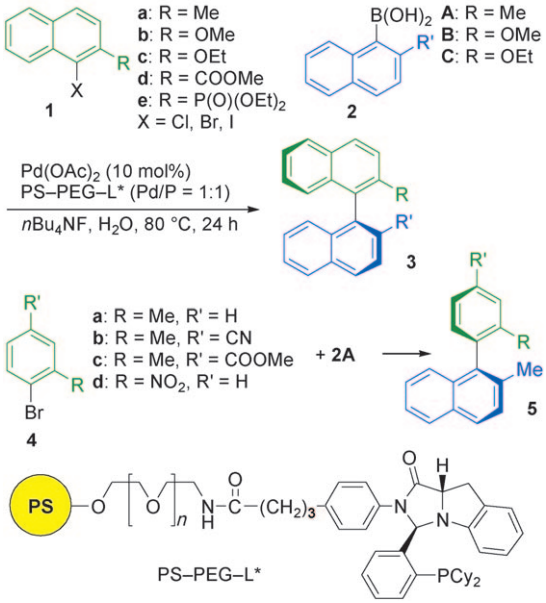
PS–PEG-supported imidazoindole dicyclohexylphosphine (PS–PEG–L*) was used in the presence of tetrabutylammonium fluoride (TBAF) at 80 °C (Scheme 2). Representative results are summarized in Table 1.



Scheme 2. Heterogeneous asymmetric biaryl coupling in H_2O. Cy = cyclohexyl.

Table 1: Asymmetric biaryl coupling in water with PS–PEG–L*.[a]

Entry	ArX	Ar′B(OH)$_2$	Ar–Ar′	Yield [%][b]	*ee* [%][c]
1	**1a**-I	**2A**	**3aA**	95	94 (*S*)
2	**1a**-Br	**2A**	**3aA**	90	88 (*S*)
3	Average of four recycling runs			86	88 (*S*)
4	**1a**-Cl	**2A**	**3aA**	53	89 (*S*)
5	**1b**-I	**2A**	**3bA**	85	92 (*R*)
6	**1b**-Cl	**2A**	**3bA**	86	88 (*R*)
7	**1a**-I	**2C**	**3aC**	93	92 (*R*)
8	**1c**-I	**2A**	**3cA**	90	92 (*R*)
9	**1b**-I	**2C**	**3bC**	90	92 (*S*)
10	**1d**-Br	**2A**	**3dA**	61	88 (*R*)
11	**1e**-Br	**2B**	**3eB**	70	99[d] (*S*)
12	**4a**	**2A**	**5aA**	96	92
13	**4b**	**2A**	**5bA**	89	92
14	**4c**	**2A**	**5cA**	93	94
15	**4d**	**2A**	**5dA**	96	92 (*R*)

[a] Reactions were carried out in water at 80 °C for 24 h with the reaction components in the following ratio: **1** (mol)/**2** (mol)/TBAF (mol)/Pd(OAc)$_2$ (mol)/PS–PEG–L* (mol of P)/H_2O (L) = 1.0:5.0:10:0.1:0.1:20. [b] Yield of the isolated product. [c] The *ee* value was determined by HPLC (chiralpak OD-H or AD-H). The absolute configuration is shown in parenthesis. [d] After crystallization.

Thus, the reaction of **1a**-I with **2A** was catalyzed by amphiphilic polymeric PS–PEG–L*–Pd to give **3aA** in 95% yield with 94% *ee* (*S*). The product was isolated by extraction with supercritical CO_2 from the catalyst resin beads, followed by chromatographic purification (Table 1, entry 1). Coupling of the bromide **1a**-Br under these conditions gave **3aA** in 90% yield with 88% *ee* (Table 1, entry 2). The catalyst PS–PEG–L*–Pd was recovered readily and reused four times to give **3aA** in 86% average yield with an average stereoselectivity of 88% *ee*; thus, no significant loss of catalytic activity or stereoselectivity was observed (Table 1, entry 3).[10]

Coupling of the naphthyl chloride **1a**-Cl took place under similar conditions to give **3aA** with 89% *ee* (Table 1, entry 4). Unsymmetrical 2-methoxy-2′-methyl-1,1′-binaphthyl (**3bA**) was obtained with 92 and 88% *ee* from **1b**-I and **1b**-Cl, respectively (Table 1, entries 5 and 6). The coupling reaction of **1a**-I and **2C**, and that of the reverse combination, **1c**-I and **3A**, gave essentially the same result, whereby **3aC** (=**3cA**) was obtained with 92% *ee* in both cases, in 93 and 90% yield (Table 1, entries 7 and 8). The asymmetric coupling of 1-iodo-2-methoxynaphthalene (**1b**-I) and 2-ethoxynaphthalene-1-boronic acid (**2C**) gave an unsymmetrical ether of binaphthol, 2-ethoxy-2′-methoxy-1,1′-binaphthyl (**3bC**), with 92% *ee* (Table 1, entry 9).

The broad functional-group tolerance of the Suzuki–Miyaura coupling enabled the asymmetric formation of biaryl compounds containing electrophilic functional groups. Thus, the reaction of 2-methoxycarbonyl-1-bromonaphthalene (**1d**-Br) with **2A** gave 2-methoxycarbonyl-2′-methyl-1,1′-binaphthyl (**3dA**) in 61% yield with 88% *ee* (Table 1, entry 10). The reaction of phosphonate **1e**-Br with **2B** afforded diethyl 2′-methoxy-1,1′-binaphth-2-yl phosphonate (**3eB**), a synthetic precursor of 2-diphenylphosphanyl-1,1′-binaphthyl (MOP) ligands,[11] in 70% yield as a white precipitate. The enantiomeric purity of **3eB** was increased through crystallization to 99% *ee* (Table 1, entry 11).

The axially chiral phenylnaphthalene derivatives **5** were prepared by the coupling of substituted bromobenzenes **4** with **2A**. Thus, 2-bromotoluene (**4a**), 4-bromo-3-methylbenzonitrile (**4b**), methyl 4-bromo-3-methylbenzoate (**4c**), and 2-bromonitrobenzene (**4d**) underwent asymmetric coupling with **2A** in water to afford the 1-(substituted aryl) 2-methylnaphthalenes **5aA**, **5bA**, **5cA**, and **5dA** in 89–96% yield with 92–94% *ee*, whereby the electrophilic substituents (CN, COOMe, NO_2) on the benzene ring of **4** were retained intact (Table 1, entries 12–15).

In summary, the highly enantioselective Suzuki–Miyaura biaryl coupling was carried out in water for the first time with a recyclable palladium complex of a chiral imidazoindole phosphine ligand supported on an amphiphilic PS–PEG resin.

Experimental Section

Synthesis of the ligand: (*S*)-2-((4-(methoxycarbonylpropyl)phenyl)-aminocarbonyl)indoline (676 mg, 2 mmol) and 2-(dicyclohexylphosphanyl)benzaldehyde (1.20 g, 3.8 mmol) were dissolved in methanol (5 mL). The reaction mixture was stirred at 80 °C in a sealed tube for 30 h, then cooled to room temperature and concentrated. The resulting residue was dissolved in 1,4-dioxane (20 mL). Aqueous NaOH (1N, 8 mL) was added to the solution at 0 °C, and the mixture was stirred at 25 °C for 10 h. The solvent was then removed, and the residual material was acidified with 5% HCl and extracted three times with methyl *tert*-butyl ether (MTBE). The combined extracts were dried over Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by chromatography on silica gel (eluent: acetone/hexane 1:10–1:2) to give (3*R*,9a*S*)-2-(4-(hydroxycarbonyl-

propyl)phenyl)-3-((2-bis(cyclohexyl)phosphanyl)phenyl)tetrahydro-1*H*-imidazo[1,5-*a*]indole-1-one (621 mg, 45% over two steps). ^{1}H NMR (500 MHz, $CDCl_3$, 25°C): $\delta = 7.97$ (d, $J = 7.3$ Hz, 1H), 7.65 (m, 1H), 7.54 (d, $J = 7.2$ Hz, 1H), 7.35–7.31 (m, 4H), 7.25–7.17 (m, 3H), 7.00–6.95 (m, 2H), 4.46 (d, $J = 10.0$ Hz, 1H), 3.58 (d, $J = 14.7$ Hz, 1H), 3.23 (dd, $J = 10.0, 14.7$ Hz, 1H), 2.52 (t, $J = 6.7$ Hz, 2H), 2.26 (t, $J = 7.4$ Hz, 2H), 2.16–2.01 (m, 4H), 1.83 (quin, $J = 7.4$ Hz, 2H), 1.73–1.39 (m, 8H), 1.34–1.10 ppm (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$, 25°C): $\delta = 178.8$, 174.6, 152.1, 144.4 (d, $J = 21.7$ Hz), 138.0, 135.2, 134.0, 129.5, 128.9, 128.7, 128.2, 127.7, 125.1, 125.0, 124.9, 122.3, 121.0, 114.3, 114.2, 81.6 (d, $J = 31.0$ Hz), 64.1, 35.8 (d, $J = 9.3$ Hz), 35.3 (d, $J = 9.3$ Hz), 34.3, 33.1, 31.5, 31.4, 30.9 (d, $J = 15.5$ Hz), 29.7 (d, $J = 9.3$ Hz), 29.6 (d, $J = 7.3$ Hz), 27.2, 27.1 (d, $J = 20.7$ Hz), 27.1 (d, $J = 18.3$ Hz), 26.9 (d, $J = 3.0$ Hz), 26.3, 26.1, 26.0, 22.6 ppm; ^{31}P{^{1}H} NMR (202 MHz, $CDCl_3$, 25°C): $\delta = -21.1$ ppm (s); $[\alpha]_D^{21} = +43.2$ deg cm^3 g^{-1} dm^{-1} ($c = 9.2 \times 10^{-3}$ g cm^{-3}, $CHCl_3$); elemental analysis: calcd (%) for $C_{38}H_{45}N_2O_3P$: C 74.97, H 7.45, N 4.60; found: C 75.12, H 7.40, N 4.58.

Preparation of PS–PEG–L*: A Merrifield vessel was charged with PS–PEG–NH_2 (1.50 g, 0.39 mmol (total loading of amino residue)), (3*R*,9a*S*)-2-(4-(hydroxycarbonylpropyl)phenyl)-3-((2-bis-(cyclohexyl)phosphanyl)phenyl)tetrahydro-1*H*-imidazo[1,5-*a*]indole-1-one (581 mg, 0.80 mmol), EDCI·HCl (319 mg, 1.67 mmol; EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide), 1-hydroxy-1*H*-benzotriazole (300 mg, 2.20 mmol), and *N*,*N*-dimethylformamide (DMF; 20.0 mL), and the reaction mixture was shaken on a wrist-action shaker at 25°C for 24 h (until the Kaiser test showed complete consumption of the primary amino residue). The reaction mixture was filtered, and the resin was washed with DMF (5 × 20 mL) and EtOAc (5 × 20 mL). The resin was dried under reduced pressure to give PS–PEG–L* (estimated loading potential for Pd: 0.25 mmol g^{-1}); ^{31}P{^{1}H} NMR (swollen-resin magic-angle spinning (SR MAS), 162 MHz): $\delta = -19.0$ ppm (s).

General cross-coupling procedure: The haloarene (1 mmol), aryl boronic acid (5 mmol), PS–PEG-supported Pd catalyst (10 mol% Pd), and TBAF (10 mmol) were dissolved in H_2O (20 mL), and the solution was stirred at 80°C for 24 h under nitrogen. The reaction mixture was then cooled to room temperature and filtered, and the resin beads were washed with water (3 × 20 mL). The resin beads were washed with supercritical CO_2 until the extraction of soluble organic materials was complete. The crude residue was purified by chromatography on silica gel to give the biaryl compound. The *ee* value of the product was determined by HPLC on a chiral stationary phase (chiralpak OD-H or AD-H).

The recovered catalyst beads were used for the next asymmetric coupling without further purification or additional charging with palladium salts.

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[1] For a recent review, see: G. Bringmann, A. J. P. Mortimer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, *Angew. Chem.* **2005**, *117*, 5518 – 5563; *Angew. Chem. Int. Ed.* **2005**, *44*, 5384 – 5427.

[2] For examples of asymmetric Grignard cross-coupling reactions to form axially chiral biaryl compounds, see: a) T. Hayashi, K. Hayashizaki, T. Kiyoi, Y. Ito, *J. Am. Chem. Soc.* **1988**, *110*, 8153 – 8156; b) T. Hayashi, S. Niizuma, T. Kamikawa, N. Suzuki, Y. Uozumi, *J. Am. Chem. Soc.* **1995**, *117*, 9101 – 9102, and references therein.

[3] For pioneering studies on the asymmetric Suzuki–Miyaura coupling, see: a) M. Uemura, H. Nishimura, T. Hayashi, *Tetrahedron Lett.* **1993**, *34*, 107 – 110; b) S. Y. Cho, M. Shibasaki, *Tetrahedron: Asymmetry* **1998**, *9*, 3751 – 3754; c) A. N. Cammidge, K. V. L. Crépy, *Chem. Commun.* **2000**, 1723 – 1724.

[4] Until the development of the chiral catalysts of Bermejo et al.,[5] to the best of our knowledge, only two reported ArX/Ar′B(OH)$_2$/ligand combinations led to product formation with greater than 90% *ee*: a) J. Yin, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 12051 – 12052; b) M. Genov, P. Almorin, P. Espinet, *Chem. Eur. J.* **2006**, *12*, 9346 – 9352.

[5] A. Bermejo, A. Ross, R. Fernández, J. M. Lassaletta, *J. Am. Chem. Soc.* **2008**, *130*, 15798 – 15799.

[6] K. Shibatomi, Y. Uozumi, *Tetrahedron: Asymmetry* **2002**, *13*, 1769 – 1772.

[7] a) Y. Uozumi, K. Shibatomi, *J. Am. Chem. Soc.* **2001**, *123*, 2919 – 2920 (alkylation); b) Y. Uozumi, H. Tanaka, K. Shibatomi, *Org. Lett.* **2004**, *6*, 281 – 283 (amination); c) Y. Nakai, Y. Uozumi, *Org. Lett.* **2005**, *7*, 291 – 293 (cyclization); d) Y. Uozumi, M. Kimura, *Tetrahedron: Asymmetry* **2006**, *17*, 161 – 166 (etherification); e) Y. Uozumi, T. Suzuka, *J. Org. Chem.* **2006**, *71*, 8644 – 8646 (nitromethylation); f) Y. Uozumi, H. Takenaka, T. Suzuka, *Synlett* **2008**, 1557 – 1561; g) Y. Uozumi, T. Suzuka, *Synthesis* **2008**, 1960 – 1964 (sulfonylation).

[8] For reviews, see: a) Y. Uozumi, *Top. Curr. Chem.* **2004**, *242*, 77 – 112; b) *Handbook of Asymmetric Heterogeneous Catalysis* (Eds.: K. Ding, Y. Uozumi), Wiley-VCH, Weinheim, **2008**.

[9] The parent chiral catalyst prepared from **L3** and Pd(OAc)$_2$ did not show any catalytic activity in water, presumably because it is less soluble (nearly insoluble) in an aqueous medium.

[10] After filtration and extraction of the catalyst beads, no palladium was detected in the combined filtrate by inductively coupled plasma–atomic emission spectrometry (ICP-AES) analysis.

[11] a) L. Kurz, G. Lee, D. Morgans, Jr., M. J. Waldyke, T. Wars, *Tetrahedron Lett.* **1990**, *31*, 6321 – 6324; b) Y. Uozumi, A. Tanahashi, S.-Y. Lee, T. Hayashi, *J. Org. Chem.* **1993**, *58*, 1945 – 1948.

