

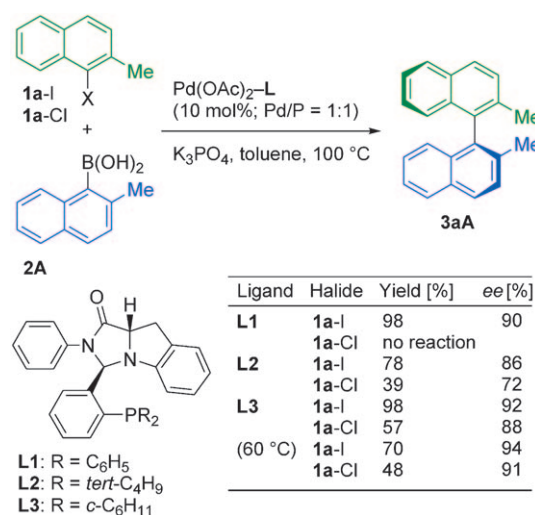
Asymmetric Suzuki–Miyaura Coupling in Water with a Chiral Palladium Catalyst Supported on an Amphiphilic Resin**

Yasuhiro Uozumi,* Yutaka Matsuura, Takayasu Arakawa, and Yoichi M. A. Yamada

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*,9*aS*)-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 K₃PO₄ (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 configu-



Scheme 1. Asymmetric Suzuki–Miyaura binaphthyl coupling.

ration 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 %).

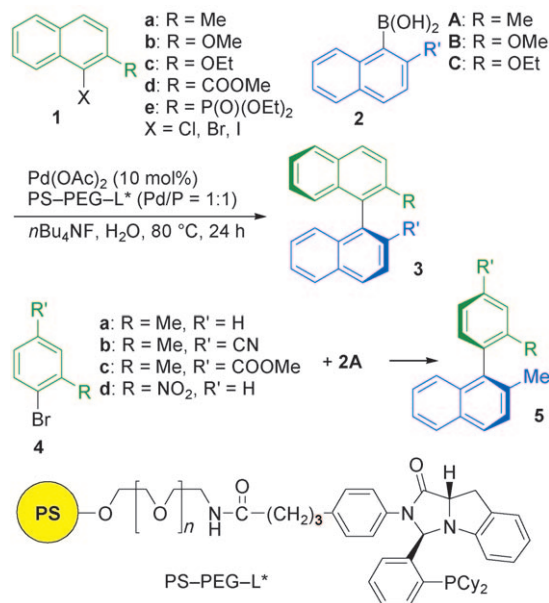
We next attempted aqueous and heterogeneous switching of this asymmetric biaryl-coupling catalysis. Asymmetric catalysis in water with a recyclable heterogeneous catalyst would approach what may be considered an ideal organic chemical process. Over the past ten years, we have demonstrated that a wide 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

[*] Prof. Dr. Y. Uozumi, Dr. Y. Matsuura, Dr. T. Arakawa
 Institute for Molecular Science and
 The Graduate School for Advanced Studies
 Myodaiji, Okazaki, Aichi 444-8787 (Japan)
 Fax: (+81) 564-59-5574
 E-mail: uo@ims.ac.jp
 Homepage: http://groups.ims.ac.jp/organization/uoazumi_g/
 Prof. Dr. Y. Uozumi, Dr. Y. M. A. Yamada
 RIKEN
 Hirosawa, Wako, Saitama 351-0198 (Japan)

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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 H₂O. 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)/H₂O (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 CO₂ 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, NO₂) 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 Na₂SO₄ 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*,9*aS*)-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). ¹H NMR (500 MHz, CDCl₃, 25 °C): δ = 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); ¹³C NMR (126 MHz, CDCl₃, 25 °C): δ = 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; ³¹P{¹H} NMR (202 MHz, CDCl₃, 25 °C): δ = –21.1 ppm (s); [α]_D²⁵ = +43.2 deg cm³ g^{–1} dm^{–1} (*c* = 9.2 × 10^{–3} g cm^{–3}, CHCl₃); elemental analysis: calcd (%) for C₃₈H₄₅N₂O₃P: 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-NH₂ (1.50 g, 0.39 mmol (total loading of amino residue)), (3*R*,9*aS*)-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}); ³¹P{¹H} NMR (swollen-resin magic-angle spinning (SR MAS), 162 MHz): δ = –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 H₂O (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 CO₂ 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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