Highly efficient Suzuki–Miyaura coupling reactions catalyzed by bis(oxazolinyl)phenyl–Pd(II) complex

Toshihide Takemoto,[a] Seiji Iwasa,[a,*] Hiroshi Hamada,[a] Kazutaka Shibatomi,[a] Masayuki Kameyama,[b] Yukihiro Motoyama[c] and Hisao Nishiyama[d]

[a]*Department of Materials Science, Toyohashi University of Technology, Tempaku-cho, Toyohashi 441-8580, Japan*
[b]*Department of Materials Chemistry and Bioengineering, Oyama National College of Technology, Nakakuki, Oyama, Tochigi 323-0806, Japan*
[c]*Institute of Materials Chemistry and Engineering, Division of Applied Chemistry Research Section of Cluster Chemistry, Kyushu University, Kasuga, Fukuoka 816-8580, Japan*
[d]*Graduate School of Engineering, Department of Applied Chemistry, Nagoya University, Chikusa, Nagoya 464-860, Japan*
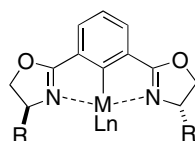
Abstract—Bis(oxazolinyl)phenyl–palladium(II)(Phebox–Pd) complexes were found to be efficient catalysts for Suzuki–Miyaura coupling reactions of aryl boronic acids and their derivatives with aryl halides to give the corresponding biaryl products in high yield along with moderate enantioslectivities in the case of axially chiral induction. The catalytic activity was attained more than 900,000 of TON and 45,000 of TOF. The catalyst can be recovered quantitatively and could be reused for Suzuki–Miyaura reactions. © 2007 Elsevier Ltd. All rights reserved.

We recently reported enantioselective carbon–carbon bond forming reactions such as allylation, alkylations, aldol type reactions, hetero Diels–Alder reactions, and Michael reactions using tridentate chiral Lewis acid catalysts, which were a series of 2,6-bis(oxazolinyl)-phenyl(phebox)/transition metal complexes (**1**) involving a carbon–transition metal bond in C_2-symmetry chiral environment as shown below (Fig. 1).[1]

During the course of our continuous studies on the development of phebox ligands,[2] we became interested in phebox–Pd complexes for the carbon–carbon bond forming reaction including oxidative addition and reductive elimination process in mechanistic point of


1: phebox-MLn

Figure 1.

view, since pincer type ligands and their transition metal complexes have been proven to be highly active catalysts in organic synthesis.[3] Our initial research in this area is described herein. A series of phebox ligands were synthesized from 2-chloro-xylene in five steps in 50–60% isolated yields. Previous studies have shown that phebox–transition metal complexes can be prepared by transmetalation of the low valent transition metals to 2-stannyl-1,3-bis(oxazolinyl)benzene derivatives.[2] We elected to pursue a different approach to the synthesis of phebox–Pd complexes that did not depend on the use of organo tin compound **2a** (Scheme 1).

Denmark et al. had previously shown that oxidative addition of palladium(0) could be used for the conversion of 1-bromo-2,6-bis(oxazolinyl)benzene derivatives to phebox–Pd(II).[4] The desire phebox–Pd complexes were obtained in high yields by using slightly modified method of Denmark, Richards, and van Kotene's research group. 1-Chloro-2,6-bis(oxazolinyl)benzene was treated with Pd(0) in toluene at 80 °C for 5 h under N$_2$ atmosphere to give the corresponding phebox–Pd complex via oxidative addition in high yield. Specifically, we investigated the reaction of a phenylboronic acid with an aryl halide, namely Suzuki–Miyaura coupling reaction,[5] using catalysis by a chiral phebox–Pd(II)

* Corresponding author. Tel.: +81 532 44 6817; fax: +81 532 48 5833; e-mail: iwasa@tutms.tut.ac.jp
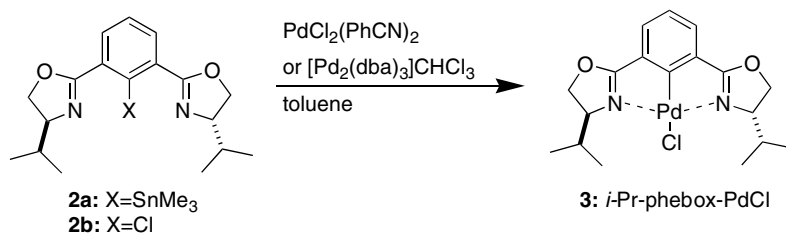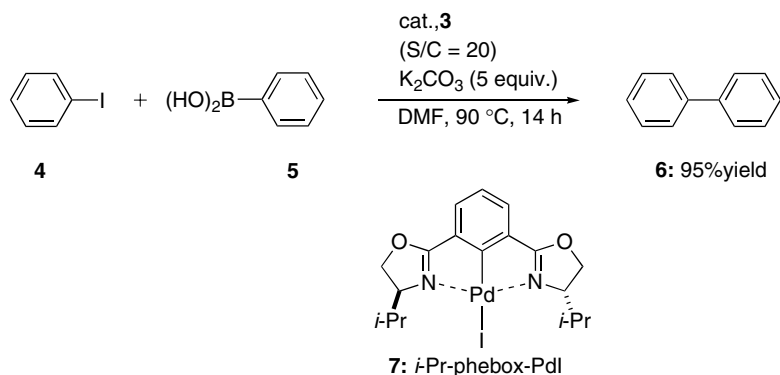
Scheme 1.

Scheme 2.

complex since palladium catalyst has been proven to be a wide variety for catalytic chemical process. The reaction of phenyl boronic acid and iodobenzene proceeded smoothly in the presence of 5 mol % of phebox–Pd(II) without any palladium black or metal aggregations to give the corresponding biphenyl in quantitative yield (Scheme 2). Surprisingly, the catalyst was completely recovered after simple column chromatography on silica gel and the structure was determined as phebox–PdI by elemental analysis and NMR, which could be reused for Suzuki–Miyaura coupling reaction and gave same level of catalytic activity.

We screened several solvents and catalytic activity for the reaction of aryl boronic acid with iodobenzene (Table 1). Phebox–Pd(II) complexes as catalysts for the Suzuki–Miyaura coupling reaction worked well in many different type of organic solvents. Interestingly, even in water phase, biphasic and no solvent reaction condition, the reaction was efficiently proceeded (entries 3, 6, and 8). Furthermore, the catalyst can be recovered in high yields for every cases (entries 1–10). As these results, we choose *i*-PrOH as a solvent for further optimization because of its cost merit, easy handling, and low toxicity. Catalytic activity in *i*-PrOH was briefly examined and attained more than 900,000 of TON and 45,000 of TOF (entries 11–15).

Standard reaction condition was as follows: a mixture of aryl boronic acid **5** (0.22 mmol), aryl halide (0.23 mmol) and catalytic amount of *i*-Pr–phebox–Pd(II) (**3**) (0.011 mmol, S/C = 20) in *i*-PrOH (1.0 mL) was heated to 90 °C under N_2 atmosphere for 14 h. Restricted N_2 atmosphere was unnecessary during the reaction. At the end of this period, the reaction mixture was cooled

to room temperature followed by removal of the solvent and the residue was purified by flash column chromatography on silica gel to give the corresponding biaryl coupling product in high yield along with recovery of the catalyst in quantitative yield.

Various aryl boronic acids were screened using phebox–Pd(II) catalyst (Scheme 3). Phebox–Pd(II) catalyst worked well in the various substrates for Suzuki–Miyaura coupling reactions. Boronic acids involving both electron withdrawing groups and electron donating groups such as nitro, carbonyl and methoxy functional groups also gave high yields (**10a**–**i**) and high recovery of the catalyst. In the case of chloro- and bromo-aryl compounds, the catalytic activity was decreased and further high temperature and long reaction time seem to be necessary (**10d**–**f** and **10i**). Boronic esters also screened and found to react well with aryl halides in the presence of phebox–Pd catalyst resulting in high yields (Scheme 4). Aryl boronic esters **11** were reacted with aryl iodides in the presence of catalyst **3** (S/C = 10,000) to give the corresponding aryl coupling products in high yields. With ester group substituted aryl boronic ester in methanol or ethanol, methyl or ethyl ester was observed as a side product (entry 4) (Table 2).

On the other hand, Jones, et al., and Eberhard, et al., reported independently that the true catalyst related pincer transition metal complexes were metallic form derived from the decomposition of the complex based on their observations.[6] The pincer catalysts such as PCP, SCS or SCN–Pd(II) complexes merely act as only precatalysts. In order to find out mechanistic information on phebox–Pd(II) catalyzed reaction, this coupling reaction was monitored by ^{1}H NMR resulting in no

Table 1. Solvent effect and catalytic activities for phebox–Pd(II) catalyzed Suzuki–Miyaura coupling reactions of iodobenzene **4** and phenyl boronic acid **5**
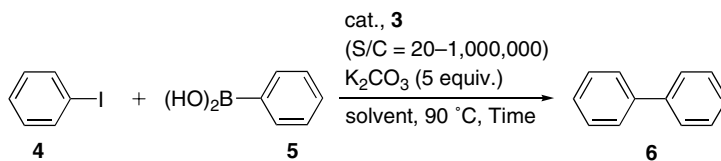
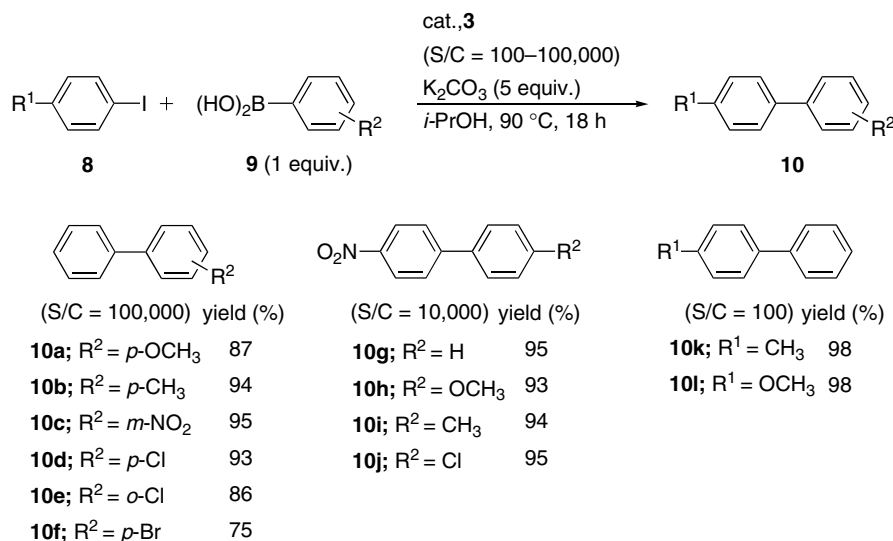| Entry	Solvent	S/C^a	T (h)	6 Yield[b] (%)	Recovery of catalyst[c] (%)	TON[d]	TOF[e]
1	DMF	20	14	95	>99		
2	DMA	20	14	97	>99		
3	H_2O	20	14	94	>99		
4	Toluene	20	14	74	>99		
5	i-PrOH	20	14	97	>99		
6	DMF/H_2O (1/4 = v/v)	20	14	95	86		
7	CH_3CN	20	14	90	>99		
8	Neat	20	14	86	>99		
9	1,4-Dioxane	20	14	69	>99		
10	DMSO	20	14	75	95		
11	i-PrOH	100	16	94	—	94	6
12	i-PrOH	1000	20	99	—	990	50
13	i-PrOH	10,000	19	97	—	9700	511
14	i-PrOH	100,000	19	91	—	91,000	4790
15	i-PrOH	1,000,000	20	90	—	900,000	45,000

[a] S/C = substrate (mol)/catalyst (mol).
[b] Isolated yield.
[c] i-Pr–phebox–Pd(I) (**7**).
[d] TON (turnover number) = product (mol)/catalyst (mol).
[e] TOF (turnover frequency) = TON/reaction time (h).

(S/C = 100,000) yield (%)
10a; R^2 = p-OCH_3 87
10b; R^2 = p-CH_3 94
10c; R^2 = m-NO_2 95
10d; R^2 = p-Cl   93
10e; R^2 = o-Cl   86
10f; R^2 = p-Br   75

(S/C = 10,000) yield (%)
10g; R^2 = H   95
10h; R^2 = OCH_3 93
10i; R^2 = CH_3 94
10j; R^2 = Cl   95

(S/C = 100) yield (%)
10k; R^1 = CH_3 98
10l; R^1 = OCH_3 98

Scheme 3. Phebox–Pd(II) catalyzed Suzuki–Miyaura coupling reactions of various arylhalides **8** and boronic acids **9**.
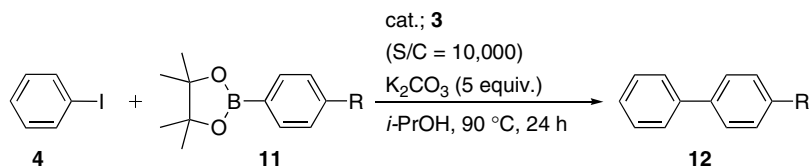
Scheme 4. Phebox–Pd(II) catalyzed Suzuki–Miyaura coupling reactions with various boronic esters **11**.

Table 2.

Entry	11 (R)	12 Yield[a] (%)	TON[b]	TOF[c]
1	11a (H)	12a (66)	6600	275
2	11a (CH₃)	12b (66)	6600	275
3	11a (CI)	12c (84)	8400	350
4[d]	11a (CO₂Me)	12d (84)	8400	350
5	11a (NO₂)	12e (87)	8700	363

[a] Isolated yield.
[b] TON (turnover number) = product (mol)/catalyst (mol).
[c] TOF (turnover frequency) = TON/reaction time (h).
[d] *i*-Pr ester was obtained.

Table 3.

Entry	15	R¹	R²	Temperature (°C)	Yield[a] (%)	ee[b] (%)
1	15a	H	CH₃	80	34	45 (*S*)
2	15b	CH₃	H	80	78	46 (*S*)
3	15b	CH₃	H	50	61	49 (*S*)
4	15c	OCH₃	H	50	71	40 (*R*)
5	15d	O*i*-Pr	H	50	55	39 (*R*)
6	15e	OBn	H	50	62	43 (*R*)

[a] Isolated yields.
[b] Determined by chiral HPLC.

induction period. Furthermore, chiral inductions using phebox–Pd(II) catalyst in asymmetric Suzuki–Miyaura aryl coupling reactions were briefly examined and moderate chiral induction was observed in the case of 1-naphto boronic acid and 2-alkyl or methoxy-1-iodo-napthalene using chiral phebox–Pd(II) catalyst **16** (Table 3). The absolute configuration of this product was determined as *R* by comparison with the known levorotatory *R*-enantiomer.[7] Although there were not very high enantioselectivities for this reaction, phebox–Pd(II) catalyzed Suzuki–Miyaura coupling reaction may not include Pd(0)–Pd(II) catalytic cycle compare to the recent reports (Scheme 5).

In conclusion, phebox–Pd(II) complexes were found to be efficient catalysts for the synthesis of biaryl compounds without induction periods and palladium metal aggregations along with complete recovery of the catalyst. In addition, our results suggest that the mechanism of aryl coupling reaction include Pd(II)–Pd(IV) catalytic cycle, which is different from another pincer type precatalysts such as PCP, SCS and SCN systems. In axial chiral induction reactions of the aryl halides and aryl boronic acids or their derivatives, chiral phebox ligands can serve as effective controllers of enantioselectivity for axis symmetry. Further research is underway to demonstrate Heck–Mizoroki reaction and Sonogashira coupling reaction.

Acknowledgement

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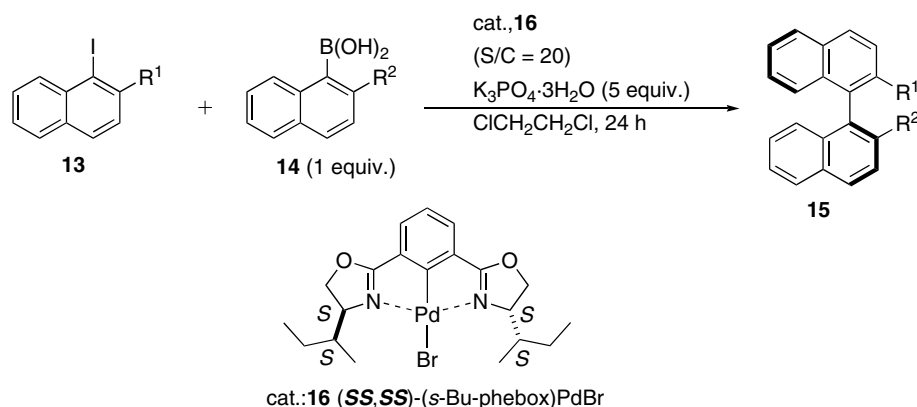
Scheme 5. Phebox–PdCl catalyzed asymmetric Suzuki–Miyaura coupling reactions.

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