

Ferrocene-based phosphine–triazine ligands for highly efficient Suzuki–Miyaura cross-coupling reaction of aryl chlorides

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Abstract

A series of ferrocene-based phosphine–triazine ligands were successfully employed in the Pd-catalyzed Suzuki–Miyaura cross-coupling reaction of aryl chlorides with arylboronic acids, with ligand **1b** was demonstrated to be the most effective one. Under optimized reaction conditions, the catalytic system displayed a remarkable tolerance towards electron-donating substituents and electron-withdrawing substituents.

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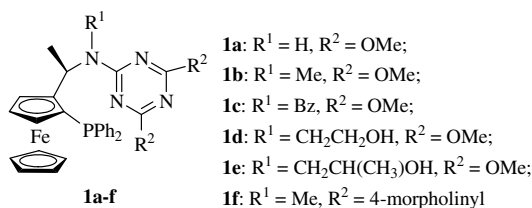
C–C coupling reactions play a key role in the synthesis of the complex bio-active molecules that can be utilized as pharmaceuticals and agrochemicals.¹ Among the existing C–C coupling reactions, the Suzuki–Miyaura cross-coupling reaction is a powerful and versatile protocol, owing to the advantages of tolerance to a broad range of functional groups, ease of accessibility with materials, minimal toxicity and mild reaction conditions.² Although aryl iodides and bromides as substrates can quicken the reactions, aryl chlorides are cheaper and more readily available. As a result, great efforts have been devoted to the preparation and the use of catalysts capable of activating aryl chloride substrates for the Suzuki–Miyaura cross-coupling, and some promising outcomes have been obtained.³ However, comparable to the great success in the cross-coupling of aryl bromides, the corresponding coupling of aryl chlorides is still less explored. The development of new catalytic system for highly efficient Suzuki–Miyaura coupling of aryl chlorides remains an interesting challenge.

In past decades, a great number of ligands bearing bulky phosphines,⁴ N-heterocyclic carbenes⁵ or palladacyclic complexes⁶ have been found to effectively activate the Suzuki–Miyaura coupling reaction of halides. To our knowledge, however, there are few examples of P,N-ligands that were reported to be highly effective in the Suzuki–Miyaura coupling reaction of aryl halides, especially aryl chlorides,⁷ although this kind of ligands have been extensively applied in many other palladium-promoted catalytic reactions.⁸ In our previous research, we have found that the optically pure ferrocene-based phosphine–triazine ligands (*R_c,S_p*)-**1** exhibited excellent selectivity and activity in the Pd-catalyzed asymmetric allylic substitution.⁹ These ligands are highly modular, readily available and stable towards oxygen and moisture. As we have reported, the introduction of the additional heterocyclic N-donor atoms into P,N-ligands is highly advantageous to improve the selectivity and activity of the catalytic reaction.^{9,10} We then surmised that these ligands may be also effective for the Pd-catalyzed Suzuki–Miyaura coupling reaction of aryl halides, especially aryl chlorides. As a result, here we wish to report this preliminary result.

These ferrocenylphosphine–triazine ligands were easily prepared according to our recently reported method,⁹

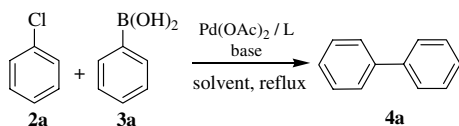
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Fig. 1. Ferrocenylphosphine–triazine ligands (*R_c,S_p*)-**1a–f**.

and some representative structures are summarized in Figure 1. In a model reaction of Pd-catalyzed Suzuki–Miyaura coupling reaction of chlorobenzene with phenylboronic acid, the efficiency of these ligands was screened, and the results are summarized in Table 1. The reactions were performed with 0.5 mol % catalyst formed in situ from Pd(OAc)₂·3H₂O and 2 equiv of P,N-ligand in dioxane at refluxing temperature for 2 h. The results indicated that the substituent in the amino moiety and triazine-heterocycle of ligands had a profound effect in the catalytic activity. Thus, ligand **1a** with an H-proton in the amino moiety showed very low catalytic activity (entry 1), while ligand **1b** bearing a methyl group in the amino moiety surprisingly gave the coupling product in 90% yields (entry

Table 1
Ligand and condition screening experiments in the palladium-catalyzed cross-coupling reaction of chlorobenzene with phenylboronic acid^a



Entry	Ligand	Solvent	Base (equiv)	Conv. ^b (%)
1	1a	Dioxane	Cs ₂ CO ₃ (2.0)	<5
2	1b	Dioxane	Cs ₂ CO ₃ (2.0)	90 ^c
3	1c	Dioxane	Cs ₂ CO ₃ (2.0)	85 ^c
4	1d	Dioxane	Cs ₂ CO ₃ (2.0)	87 ^c
5	1e	Dioxane	Cs ₂ CO ₃ (2.0)	19 ^c
6	1f	Dioxane	Cs ₂ CO ₃ (2.0)	65 ^c
7	1b	Dioxane	Cs ₂ CO ₃ (2.0)	94
8	1b	Dioxane	Na ₂ CO ₃ (2.0)	50
9	1b	Dioxane	KF (2.0)	73
10	1b	Dioxane	KOBu- <i>t</i> (2.0)	7
11	1b	Dioxane	K ₃ PO ₄ ·3H ₂ O (2.0)	95
12	1b	Dioxane	K ₃ PO ₄ ·3H ₂ O (3.0)	96
13	1b	Dioxane	K ₃ PO ₄ (3.0)	98
14	1b	Toluene	K ₃ PO ₄ (3.0)	69
15	1b	THF	K ₃ PO ₄ (3.0)	73
16	1b	DMF	K ₃ PO ₄ (3.0)	<5
17	1b	Dioxane	K ₃ PO ₄ (3.0)	45 ^d
18	1b	Dioxane	K ₃ PO ₄ (3.0)	95 ^e
19	1b	Dioxane	K ₃ PO ₄ (3.0)	57 ^f

^a Reaction conditions (unless otherwise specified): 1.0 mmol of PhCl, 1.2 mmol of PhB(OH)₂, 5.0 ml of solvent, 0.5 mol % of Pd(OAc)₂·3H₂O; the catalyst was prepared in situ from Pd(OAc)₂·3H₂O and 2 equiv of ligand; the reactions were performed at refluxing temperature for 12 h.

^b Conversions estimated by GC.

^c Reaction time: 2 h.

^d Pre-catalyst: PdCl₂.

^e Pre-catalyst: Pd₂(dba)₃CHCl₃.

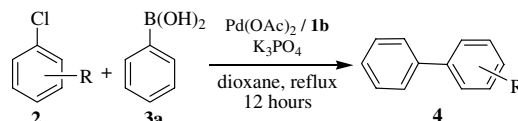
^f Pre-catalyst: [Pd(η³-C₃H₅)Cl]₂.

2). The introduction of other groups into the amino moiety or replacing two methoxy groups in the triazine ring with two morpholinyl groups did not improve the coupling results in comparison with that obtained with ligand **1b** (entries 3–6).

The above-experiments disclosed that ligand **1b** showed the best catalytic activity, and we then selected it to optimize the reaction conditions. The extension of the reaction time to 12 h gave an increased conversion, however, further extending the reaction time could not improve the coupling results (entry 7). The effect of the base additives in the catalytic activity was next investigated. As shown in Table 1, the base additives strongly affected the coupling reaction. Using Na₂CO₃, KF and *t*-BuOK instead of Cs₂CO₃ resulted in the decreased conversions (entries 8–10), while the use of K₃PO₄·3H₂O could slightly improve the conversion (entry 11). Further investigations found that the use of 3 equiv of anhydrous K₃PO₄ tended to give better results (entries 11–13). The effect of solvents on the coupling reaction was also examined, and a significant variation in the catalytic activity was observed. Thus, the reaction performed in toluene and THF gave the moderate conversions (entries 14 and 15). However, when DMF was selected as the reaction solvent, little coupling product was detected (entry 16). A variety of catalyst precursors were finally tested. However, no results surpassed that obtained with Pd(OAc)₂·3H₂O (entries 13, 17–19).

From the above condition screening experiments, we then selected Pd(OAc)₂·3H₂O as pre-catalyst, **1b** as ligand, anhydrous K₃PO₄ as the base additive, and the reaction was performed in dioxane at refluxing temperature for 12 h.¹¹ The cross-coupling reaction of various substituted aryl chlorides with phenylboronic acid was then carried out to determine the generality of our standard protocol. As shown in Table 2, the cross-coupling reaction displayed

Table 2
Suzuki–Miyaura cross-coupling of phenylboronic acid with aryl chlorides^a



Entry	Aryl chloride	Product	Yield ^b (%)
1	2b: R = 2-Me	4b: R = 2-Me	96
2	2c: R = 3-Me	4c: R = 3-Me	98
3	2d: R = 4-Me	4d: R = 4-Me	99
4	2e: R = 3-CF ₃	4e: R = 3-CF ₃	99
5	2f: R = 4-CN	4f: R = 4-CN	96
6	2g: R = 3-COMe	4g: R = 3-COMe	99
7	2h: R = 4-COEt	4h: R = 4-COEt	98
8	2i: R = 2-NO ₂	4i: R = 2-NO ₂	97
9	2j: R = 2,6-dimethyl	4j: R = 2,6-dimethyl	95

^a The reactions were carried out in the presence of 1.0 mmol of aryl chlorides, 1.2 mmol of phenylboronic acid, 0.5 mol % of catalyst prepared in situ from Pd(OAc)₂·3H₂O and ligand **1b**, and 3.0 equiv of K₃PO₄ in 5 mL of dioxane at refluxing temperature for 12 h.

^b Isolated yields, purity >95% was confirmed by ¹H NMR.

remarkable tolerance towards the substitution pattern and electronic properties of the substrates. Both electron-donating substituents and sterically encumbering *o*-substituents in the aryl ring gave good results. For examples, various chlorotoluenes could smoothly couple with phenylboronic acids, and the yields exceeded 96% (entries 1–3). For the chlorides bearing electron-withdrawing groups, excellent yields were obtained (entries 4–8). In particular, the chlorides with sterically encumbering substituent such as *o*-NO₂, 2,6-dimethyl also coupled with phenylboronic acid in good yields (entries 8 and 9). However, when sterically encumbering phenylboronic acids were coupled with 2,6-dimethylchlorobenzene, the results were less satisfactory. Thus, the reaction of 2-methylphenylboronic acid and 2,6-dimethylchlorobenzene gave the coupling product in 66% yield.

To further demonstrate the scope and flexibility of the present catalytic system, the cross-coupling of sterically demanding *o*-chlorotoluene with various arylboronic acids was also studied under the optimized conditions. The results are summarized in Table 3. The arylboronic acids with electron-donating and electron-withdrawing substituents were coupled smoothly with *o*-chlorotoluene. For the arylboronic acids with a methyl group in the 2, 3 and 4-position of the phenyl ring, the coupling yields exceeded 95% (entries 2–4). The yields for the coupling of substrates with a methoxy group in the 3- or 4-position were also excellent (entries 6 and 7). However, when 2-methoxyphenylboronic acid was used as a substrate, the yield was decreased to 86% (entry 5). For the coupling of 4-CF₃ and 4-F substituted substrates, 97% and 96% yields were obtained (entries 8 and 9), respectively. These results indicated that there is no major effect on the electronic proper-

ties of the substituent in the phenyl ring. However, the position of the methoxy group in the phenyl ring had some effect in this catalytic reaction. Thus, 2-OMe substituted substrate was coupled in 86% yield, while the corresponding ones with 3- or 4-OMe group resulted in over 95% yield of the coupling product (entries 5–7).

In conclusion, we have found that ferrocenylphosphine–triazine ligands were highly effective for the Pd-catalyzed Suzuki–Miyaura cross-coupling of aryl chlorides with arylboronic acids. Under the optimized conditions, the reaction proceeded in excellent yields, and displayed remarkable tolerance towards the electronic properties of the substrates. Further application of the present catalytic system in the coupling reaction is still in progress.

Acknowledgement

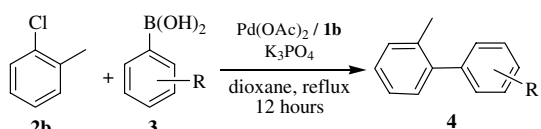
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Table 3

Suzuki–Miyaura cross-coupling of 2-chlorotoluene with arylboronic acids^a



Entry	Arylboronic acid	Product	Yield ^b (%)
1	3a : R = H	4b : R = H	96
2	3b : R = 2-Me	4k : R = 2-Me	95
3	3c : R = 3-Me	4l : R = 3-Me	95
4	3d : R = 4-Me	4m : R = 4-Me	96
5	3e : R = 2-OMe	4n : R = 2-OMe	86
6	3f : R = 3-OMe	4o : R = 3-OMe	98
7	3g : R = 4-OMe	4p : R = 4-OMe	96
8	3h : R = 4-CF ₃	4q : R = 4-CF ₃	97
9	3i : R = 4-F	4r : R = 4-F	96
10	3j : R = 3,5-difluoro	4s : R = 2,6-difluoro	95

^a The reactions were carried out in the presence of 1.0 mmol of *o*-chlorotoluene, 1.2 mmol of arylboronic acid, 0.5 mol % of catalyst prepared in situ from Pd(OAc)₂·3H₂O and ligand **1b**, and 3.0 equiv of K₃PO₄ in 5 mL of dioxane at refluxing temperature for 12 h.

^b Isolated yields, purity >95% was confirmed by ¹H NMR.

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11. Typical procedure for cross-coupling: Arylboronic acid (1.2 mmol), K_3PO_4 (3.0 mmol), $Pd(OAc)_2 \cdot 3H_2O$ (0.5 mol % to aryl chloride) and ligand **1b** (1.0 mmol % to aryl chloride) were placed in a 10 mL schlenk tube, which was evacuated and backfilled with argon (three cycles). To the tube 5 mL of dried 1,4-dioxane was added and then stirred at room temperature for 5 minutes. A 1.0 mmol of aryl chloride was added, and then the reaction mixture was stirred at refluxing temperature for 12 h. After that, the mixture was cooled to room temperature and diluted with 5 ml of ethyl acetate and 5 ml of H_2O . The aqueous phase was extracted three times with ethyl acetate, dried over $MgSO_4$ and evaporated to dryness. The crude product was purified via column chromatography over silica gel (petroleum ether) to give the coupling product, its purity was determined by 1H NMR.