Tetrahedron Letters 53 (2012) 2388–2391

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Highly effective activation of aryl chlorides for Suzuki coupling in aqueous media using a ferrocene-based Pd(II)–diimine catalyst

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ARTICLE INFO

Article history:
Received 1 December 2011
Revised 13 February 2012
Accepted 23 February 2012
Available online 3 March 2012

Keywords:
Suzuki coupling
Green chemistry
Pd(II) complexes
Microwave irradiation
Aryl chlorides

ABSTRACT

The Suzuki coupling of aryl chlorides with boronic acids using a ferrocene-containing Pd(II)–diimine complex as catalyst, in aqueous media, under microwave heating is reported. A small amount of the catalyst (0.1%) was found to be highly effective for coupling unactivated aryl chlorides with boronic acids to form sterically hindered *ortho*-substituted biaryls. The same catalyst also enabled the coupling of aryl bromides and iodides with various boronic acids in very high yields. The catalyst is air stable and the catalytic reaction can be completed in 15 min.

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Among palladium-catalyzed cross-coupling processes, the Suzuki reaction of aryl and vinyl halides/triflates with boronic acids has gained significant attention and is a very powerful method for the formation of biaryls.[1,2] This popularity of the Suzuki reaction is attributable to a variety of factors including the large number of boronic acid derivatives that are commercially available, their good stability and nontoxic nature and tolerance to a large number of functional groups. However, Suzuki coupling reactions still show some limitations, especially in relation to the use of certain reagents. In particular, for many years, a major restriction of palladium-catalyzed coupling processes has been the poor reactivity of aryl chlorides. Moreover, in many cases, the use of aryl chlorides is more desirable when compared with the corresponding bromides, iodides, and triflates, mainly due to their low cost and ready availability.[3] Until 1998, there were no examples of effective palladium-catalyzed Suzuki reactions using electron-neutral or electron-rich aryl chlorides.

In attempts to utilize aryl chlorides as substrates in Suzuki coupling reactions several catalysts have been developed. For example, Fu and Buchwald independently discovered that certain phosphine-based catalysts were very effective for the coupling of aryl chlorides with various aryl boronic acids. The key property of their catalysts was to have ligands that were both electron-rich and sterically bulky. By using these catalysts the authors were able to activate both electron-rich and electron-poor aryl chlorides for Suzuki coupling reactions at room temperature.[4,5] Since these seminal works, some additional studies have been reported. Najera and co-workers prepared oxime-derived palladacycles for the Suzuki coupling of aryl chlorides in aqueous media which were not very effective for the coupling of unactivated aryl chlorides.[6] Buchwald and co-workers reported that the use of water soluble sulfonated salts in Suzuki coupling reactions of aryl chlorides, gave excellent yields of products. This procedure however, required high temperatures, long reaction times, and high catalyst loadings.[7] Hanhan and Zhou independently studied sulfonated Pd-diimine catalysts for the coupling of several aryl halides with aryl boronic acids showing negligible activity for the coupling of aryl chlorides.[8,9] Ferrocene derivatives have attracted significant attention as ligands because of their large size and electron-rich nature. In fact, several examples using ferrocene-like derivatives have been described as very effective in activating aryl chlorides.[10–15] In these examples, ferrocene-containing phosphine ligands were used, however the use of other ligands such as diimines has received limited study.[16,17] The use of diimine or pyridylimine ligands instead of phosphine ligands has major advantages such as easy synthetic procedures, simple handling, and easy tuning of the steric and electronic properties of the final catalysts. We report herein a new ferrocene-containing Pd(II)–diimine complex catalyst as a highly effective system for the Suzuki cross-coupling of aryl chlorides (including unactivated and sterically hindered substrates) in aqueous media under microwave irradiation.

The ferrocene based diimine ligand (**L**) was synthesized via a simple condensation procedure involving the reaction of

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doi:10.1016/j.tetlet.2012.02.102

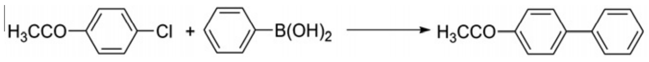
ferrocenecarboxaldehyde with the sodium salt of 5,6-diamino-1-naphthalenesulfonic acid in toluene under reflux. The precipitated derivative was then dissolved in *iso*-propanol in the presence of excess tetrabutylammonium chloride to give the ammonium salt **L**. Complex **1** was obtained via reaction of the ferrocene-containing diimine ligand **L** and $PdCl_2(CH_3CN)_2$ in acetonitrile under reflux (Scheme 1).[18]

As has been reported previously, one disadvantage of the use of ionic diimine ligands is their potential hydrolysis in water even when they are forming complexes with metal cations.[19,20] Therefore, prior to the testing of **1** as a catalyst, studies of the stability of **1** in water were carried out using ^1H NMR spectroscopy. The extent of hydrolysis of ligand was followed by the signal due to the aldehyde proton. These studies demonstrated that the catalyst was fairly stable in water and only after a period of 4 h was evidence of decomposition observed. Nevertheless catalyst **1** was found to be stable within the range of time of the tested Suzuki coupling reactions which typically required periods of 15 min (vide infra).

Next, simple preliminary tests demonstrated that the ferrocene–diimine Pd(II) complex was active in catalyzing Suzuki coupling reactions between aryl chlorides and boronic acids. In order to select the best reaction conditions, different heating regimes were studied in water using the coupling of *p*-chloroacetophenone and phenylboronic acid in the presence of K_2CO_3 as a model system. The Suzuki coupling reaction did not proceed at room temperature or at 50 °C when using catalyst **1** (Table 1, entries 1 and 2). When the temperature was increased to 100 °C, yields >89% were obtained (Table 1, entries 3 and 4). When 800 W microwave irradiation was used instead of conventional heating, the yield increased to 99% in 20 min without any appreciable decomposition of the catalyst (Table 1, entry 7). To assess the effect of M.W. irradiation, lower power output irradiation (180 and 360 W) was studied. The yields did not pass 54% yield (Table 1, entries 5 and 6).

Additional studies were carried out in order to test the effect of different bases. K_2CO_3, Na_2CO_3, Cs_2CO_3, K_3PO_4, and NaOMe were investigated as bases for the coupling of *p*-chloroacetophenone and phenylboronic acid in the presence of catalyst **1** in water using 800 W microwave irradiation for 5, 10 and 15 min (Table 2, entries 1–9). In general it was found that yields of almost 99% were reached after 15 min when using K_2CO_3 or Cs_2CO_3. Despite the fact that slightly better yields were obtained when using Cs_2CO_3, further studies were carried out with K_2CO_3 due to its ready availability and low cost. In addition a reaction time of 15 min was selected.

Table 1
Effect of conventional heating versus microwave irradiation[a]

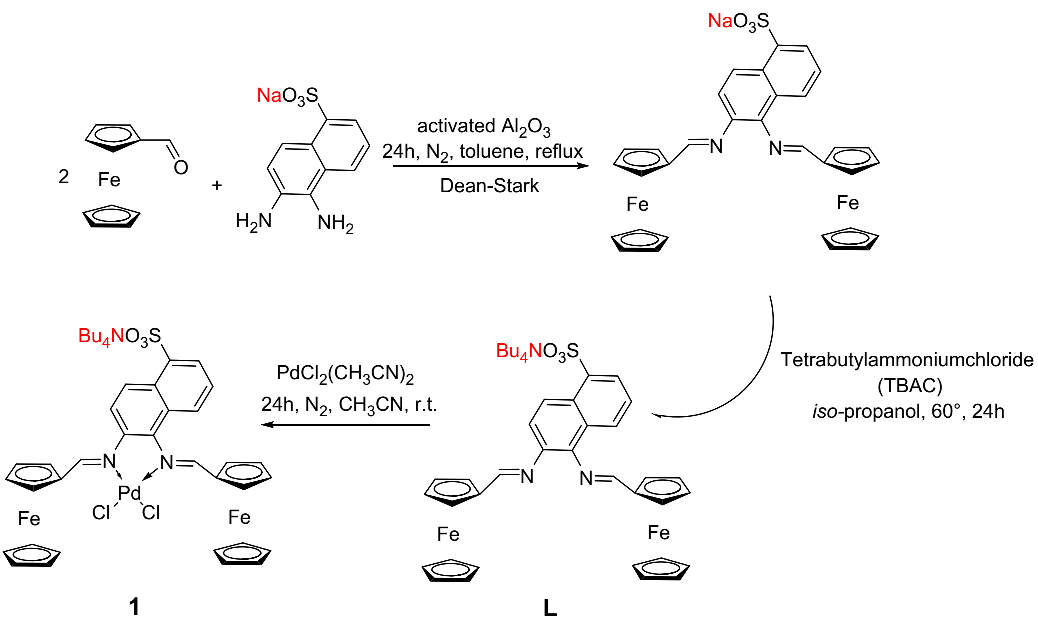


Entry	Heating type[b]	Temperature (°C)	Time (min)	Yield[c] (%)
1	C.H.	rt	300	N/A
2	C.H.	50	300	N/A
3	C.H.	100	300	89
4	C.H.	100	360	92
5	M.W.[d]	–	20	N/A
6	M.W.[e]	–	20	54
7	M.W.[f]	–	20	99

[a] Conditions: *p*-chloroacetophenone (1.0 equiv), phenyl boronic acid (1.0 equiv), K_2CO_3 (1.5 equiv), **1** (0.1 mol%), H_2O (5 mL).
[b] C.H. = conventional heating, M.W. = microwave irradiation (Industrial Bosch-Mars Microwave System with reflux glassware).
[c] Yields estimated by GC.
[d] 180 W M.W. irradiation.
[e] 360 W M.W. irradiation.
[f] 800 W M.W. irradiation.

After the reaction conditions had been optimized, the effect of the amount of catalyst was examined. A 0.1% catalyst loading was found to be very effective for coupling unactivated aryl chlorides. On the other hand, amounts as low as 0.0001% of the catalyst was sufficient to couple aryl bromides and iodides with boronic acids in yields that ranged from 97% to 99% (Table 3, entries 13 and 14).

Finally, the effect of the catalyst on the Suzuki reaction using various aryl chlorides and boronic acid substrates was studied. Table 3 summarizes the results. Significantly catalyst **1** was able to couple unactivated electron-rich aryl chlorides with various boronic acids in yields >91% (Table 3, entries 3–5). The Suzuki reaction using catalyst **1** was also tested using sterically hindered substrates. It is well-known that Suzuki coupling reactions using sterically demanding substrates are difficult and generally occur



Scheme 1. Synthetic route to catalyst **1**.

Table 2
Base and time optimization results[a]

Entry	Base	Time (min)	Yield[b] (%)
1	K_2CO_3	5	61
2	K_2CO_3	10	89
3	K_2CO_3	15	99
4	Cs_2CO_3	5	69
5	Cs_2CO_3	10	91
6	Cs_2CO_3	15	99
7	Na_2CO_3	15	86
8	K_3PO_4	15	79
9	NaOMe	15	86

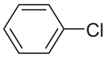
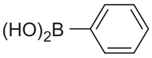
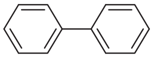
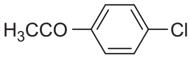
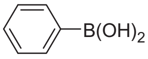
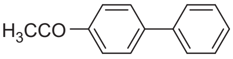
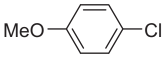
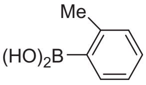
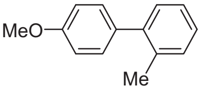
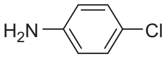
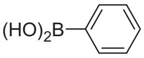
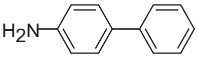
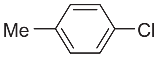
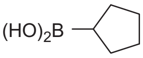
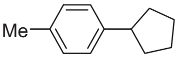
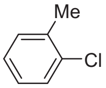
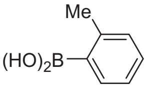
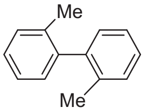
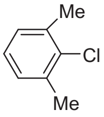
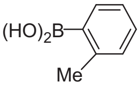
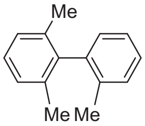
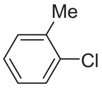
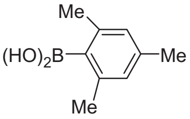
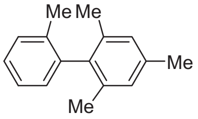
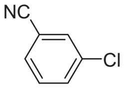
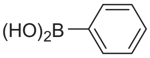
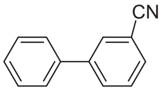
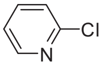
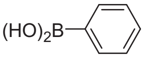
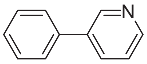
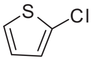
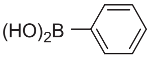
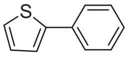
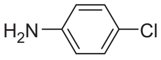
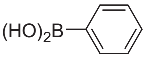
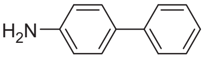
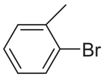
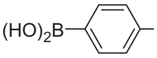
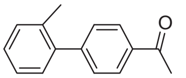
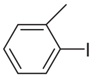
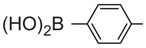
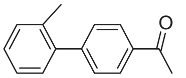
[a] Conditions: *p*-chloroacetophenone (1.0 equiv), phenylboronic acid (1.0 equiv), base (1.5 equiv), **1** (0.1%), 800 W M.W. irradiation, H_2O (5 mL).

[b] Yields estimated by GC.

with the formation of unwanted homocoupling products.[4] As shown in Table 3 (entries 6–8) sterically hindered biaryls could be obtained in remarkably high yields (>94%). Aryl chlorides with different functional groups also underwent the coupling reaction efficiently (Table 3, entries 9–12).

In summary, we have reported the Suzuki coupling of aryl chlorides with boronic acids using a ferrocene-containing Pd(II)–diimine complex as catalyst, in aqueous media, under microwave heating. The use of the diimine ligand containing two ferrocene units was found to be very effective for Suzuki coupling reactions due to the sterically demanding nature of the ligand and the electron-rich properties of the ferrocene moiety.[21] These properties of the catalyst allow stabilization of the active Pd(0) species in the catalytic cycle to sustain the reaction. A series of aryl boronic acids and aryl halides were tested in the Suzuki coupling reaction using **1** as the catalyst. Small amounts of **1** (0.1%) were found to be very effective for the coupling of unactivated aryl chlorides with boronic acids to form sterically hindered *ortho*-substituted biaryls under aqueous conditions. On the other hand, the use of very low

Table 3
Suzuki cross-couplings between aryl halides and boronic acids using **1** as the catalyst[a]

Entry	Aryl halide	Boronic acid	Product	Yield[d] (%)
1				93
2				97
3				91
4				90
5				93
6				97
7				94
8				96
9				99
10				96
11				77
12				92
13				97[b]
14				99[b,c]

[a] Conditions: aryl chloride (1.0 equiv), boronic acid (1.0 equiv), K_2CO_3 (1.5 equiv), **1** (0.1%), 800 W M.W. irradiation, 15 min, H_2O (5 mL).

[b] Compound **1** (0.0001%).

[c] $AgBF_4$ (1.1 equiv) was added.

[d] Isolated yield after column chromatography.

amounts of catalyst (0.0001%) permitted the coupling of aryl bromides and iodides with boronic acids in very high yields. When **1** was compared with other reported catalysts for Suzuki couplings, catalyst **1** did not need any additional solvent other than H_2O or additives such as TBAB.[22–25] Furthermore, **1** is air-stable and the reactions were complete in 15 min. The effects of catalyst **1** on other cross-coupling reactions are currently under investigation.

Acknowledgments

The authors thank the Research Board of Zonguldak Karaelmas University (BAP-2010-13-02-02, BAP-2011-10-03-11 and BAP-2011-10-03-012), the Spanish Government (projects MAT2009-14564-C01) and the Generalitat Valenciana (project PROMETEO/2009/016) for support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.102. These data include MOL files and InChiKeys of the most important compounds described in this article.

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18. Characterization data for selected compounds; **L**: (ATR, ν, cm^{-1}) 1632 (C═N), 1181 (S═O); ^1H NMR (DMSO-d_6, δ, ppm) 8.21 (2H, s, CH═N), 7.54–7.43 (3H, m, Ar-H), 7.03 (2H, Ar-H, m), 4.91 (4H, t, *J* 1.7 Hz, C_5H_4), 4.73 (4H, t, *J* 1.6 Hz, C_5H_4), 4.38 (10H, s, C_5H_5), 3.17 (8H, m, $N(CH_2–CH_2–CH_2–CH_3)_4$), 1.72 (8H, m, $N(CH_2–CH_2–CH_2–CH_3)_4$), 1.29 (8H, m, $N(CH_2–CH_2–CH_2–CH_3)_4$), 0.96 (12H, m, $N(CH_2–CH_2–CH_2–CH_3)_4$); ^{13}C NMR (DMSO-d_6, δ, ppm) 159.3 (N═CH), 142.4 (Ar-C), 133.6 (Ar-C), 130.2 (Ar-C), 127.6 (Ar-C), 122.1 (Ar-C), 121.9 (Ar-C), 121.6 (Ar-C), 121.1 (Ar-C), 119.6 (Ar-C), 117.3 (Ar-C), 80.9 (C_5H_5), 72.4 (C_5H_5), 71.3 (C_5H_5), 70.4 (C_5H_5), 61.3 ($N(CH_2–CH_2–CH_2–CH_3)_4$), 30.7 ($N(CH_2–CH_2–CH_2–CH_3)_4$), 18.2 ($N(CH_2–CH_2–CH_2–CH_3)_4$), 15.4 ($N(CH_2–CH_2–CH_2–CH_3)_4$); LC–MS (API-ES) *m/z* 631 (M^++1-NBu_4, 14%), 630 (M^+-NBu_4, 36%), 415(28), 260 (100), 242 (NBu_4^+, 48%), 205(14). Anal. Calcd for $C_{48}H_{61}Fe_2N_3O_3S$: C, 66.13; H, 7.05; N, 4.82. Found: C, 66.21; H, 6.97; N, 4.61. Compound **1**: FT-IR (ATR, ν, cm^{-1}) 1562 (C═N), 1183 (S═O); ^1H NMR (DMSO-d_6, δ, ppm) 9.04 (2H, s, CH═N), 7.61–7.58 (3H, m, Ar-H), 7.14 (2H, Ar-H, m), 4.96 (4H, t, *J* 1.9 Hz, C_5H_4), 4.77 (4H, t, *J* 2.0 Hz, C_5H_4), 4.46 (10H, s, C_5H_5), 3.36 (8H, m, $N(CH_2–CH_2–CH_2–CH_3)_4$), 1.87 (8H, m, $N(CH_2–CH_2–CH_2–CH_3)_4$), 1.41 (8H, m, $N(CH_2-CH_2-CH_2-CH_3)_4$), 1.14 (12H, m, $N(CH_2–CH_2–CH_2–CH_3)_4$); ^{13}C NMR (DMSO-d_6, δ, ppm) 168.6 (N═CH), 145.7 (Ar-C), 134.1 (Ar-C), 133.7 (Ar-C), 131.6 (Ar-C), 126.3 (Ar-C), 125.3 (Ar-C), 125.1 (Ar-C), 124.9 (Ar-C), 123.1 (Ar-C), 121.7 (Ar-C), 84.1 (C_5H_5), 75.9 (C_5H_5), 75.1 (C_5H_5), 73.6 (C_5H_5), 66.9 ($N(CH_2–CH_2–CH_2–CH_3)_4$), 37.2 ($N(CH_2–CH_2–CH_2–CH_3)_4$), 23.8 ($N(CH_2–CH_2–CH_2–CH_3)_4$), 17.6 ($N(CH_2–CH_2–CH_2–CH_3)_4$); LC-MS (API-ES) *m/z* 807 (M^++1-NBu_4, 21%), 606 (M^+-NBu_4, 77%), 421(39), 272 (14), 242 (NBu_4^+, 21%), 106(100). Anal. Calcd for $C_{48}H_{61}Cl_2Fe_2N_3O_3PdS$; C, 54.95; H, 5.86; N, 4.01; Cl, 6.76. Found: C, 54.59; H, 6.07; N, 4.42; Cl, 7.11.
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