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Pd–EDTA as an efficient catalyst for Suzuki–Miyaura reactions in water

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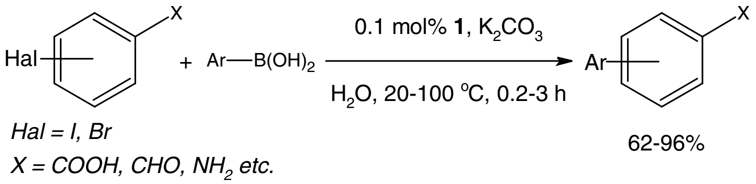
Abstract—$PdCl_2$–EDTA complex **1** is an efficient catalyst for the Suzuki–Miyaura reactions of aryl and heteroaryl halides with aryl(heteroaryl)boronic acids in water at 20–100 °C. Aryl iodides and bromides undergo the cross-coupling with turnover numbers (TON) up to 97,000 and turnover frequencies (TOF) up to 582,000 h^{-1}.

The palladium-catalyzed Suzuki–Miyaura reaction, which involves the cross-coupling of aryl halides with aryl boronic acids, has become one of the most powerful and convenient synthetic tools for preparation of biaryl compounds.[1] The widely employed reaction protocol utilizes aqueous organic solvents in the presence of an inorganic base (carbonate, bicarbonate, or hydroxide), a palladium catalyst precursor and a ligand that coordinates to the palladium center to stabilize the catalyst. The right choice of the ligand is a key factor determining the rate of the catalytic reaction. In addition to the traditional triphenylphosphine ligand,[2] electron-rich bulky phosphines,[3] phosphine oxides,[4] and phosphine-based palladacycles[5] have been suggested as efficient ligands or catalyst precursors.[5] Recently, a number of catalytic systems with phosphine-free ligands, such as C-based heterocyclic carbenes,[6] *C*,*N*-based 2-aryl-2-oxazolines,[7] aryl(heteroaryl)oximes,[8] arylimines,[9] and *N*,*N*-based diazabutadienes[10] have been reported.[11] However, most of these new ligands are not readily available and are very expensive. So simple, inexpensive, easily accessible, and stable catalysts are desired for these reactions.[12] Earlier, we and other authors showed that the Suzuki–Miyaura reaction proceeds most effectively in the presence of 'ligandless' palladium catalysts in basic aqueous media.[13] However, this catalytic system was not stable enough.

We report herein, a new $PdCl_2$–EDTA (ethylenediamine-*N*,*N*,*N*′,*N*′-tetraacetic acid)-based catalytic system for the Suzuki–Miyaura cross-coupling reaction (Scheme 1).

A solution of $PdCl_2$–EDTA complex **1** was prepared from $PdCl_2$, 1 equiv of EDTA (disodium salt dihydrate), and 2 equiv of Na_2CO_3 in water at room temperature. It is a yellow-red solution with pH ~ 8–9, which is stable at room temperature and can be stored in air. According to earlier data,[14] Pd(II) salts react with EDTA easily in water to form square complexes containing one ligand



Scheme 1. Cross-coupling reactions of aryl halides with arylboronic acids catalyzed by $PdCl_2$–EDTA.

Keywords: Suzuki–Miyaura reaction; Palladium; EDTA; Biaryls; Catalysis.

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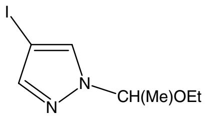
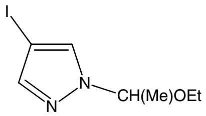
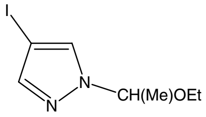
Table 1. Cross-coupling reactions of aryl iodides[a]

Entry	Ar-I	Ar′-B(OH)$_2$	T (°C)	Time (h)	Yield[b] (%)
1	4-$IC_6H_4CO_2H$	2-Furyl-B(OH)$_2$	20	10 min	83
2	3-$IC_6H_4CO_2H$	3-Thienyl-B(OH)$_2$	20	1	90
3	2-$IC_6H_4CO_2H$	2-$FC_6H_4B(OH)_2$	100	2	71
4	2-$IC_6H_4CO_2H$	2-$MeC_6H_4B(OH)_2$	100	3	91
5[c]	3-$IC_6H_4CO_2H$	2,4,6-$Me_3C_6H_2B(OH)_2$	20	15 min	76
6[d]		$PhB(OH)_2$	100	1	94[e]
7[d]		3-$HO_2CC_6H_4B(OH)_2$	100	15 min	76[e]
8[d,f]		3-$HO_2CC_6H_4B(OH)_2$	100	1	89[e]
9[d,g]	2-$IC_6H_4NH_2$	2-Furyl-B(OH)$_2$	20	2	88[h]
10[d,g]	4-$IC_6H_4NH_2$	2-Thienyl-B(OH)$_2$	20	2	83[h]

[a] 1 mmol of Ar-I, 2 mL of water, 2 mmol of K_2CO_3, 1.05 mmol of Ar′-B(OH)$_2$, 0.1 mol % of $PdCl_2$–EDTA, Ar.

[b] Isolated yield.

[c] 3 mmol of KOH as base.

[d] In the presence of 1 mol % of n-Bu_4NBr.

[e] After protecting group removal.

[f] 50 mmol scale, 0.001 mol % of **1**.

[g] MeOH–water (2:1).

[h] As hydrochloride.

residue per Pd atom. EDTA is used as bidentate ligand which coordinates with two nitrogen atoms.

To evaluate the scope and limitations of this protocol, we carried out a number of reactions of aryl- and heteroarylboronic acids with water-soluble and water-insoluble aryl iodides (Table 1).

For initial studies, we performed the Suzuki–Miyaura coupling of 4-iodobenzoic acid and 2-furylboronic acid (entry 1). In the presence of 0.1 mol % of complex **1**, the reaction proceeded in water without organic co-solvent at room temperature (2 equiv of K_2CO_3) in less than 10 min, clearly indicating the high activity of the new catalyst. The product was isolated in 83% yield.

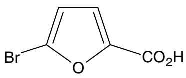
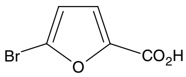
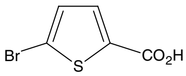
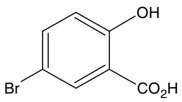
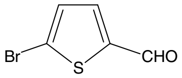
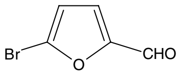
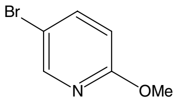
Even sterically hindered mesityleneboronic acid reacted with 3-iodobenzoic acid at room temperature in 15 min, yielding 76% of pure 3-mesitylbenzoic acid (entry 5). The reactions of electron-rich water-insoluble 2- and 4-iodoanilines also proceeded at room temperature in aqueous methanol, giving cross-coupling products with high yields in 2 h (entries 9 and 10).

While 3- and 4-iodobenzoic acid reacted with boronic acids in water at room temperature, 2-iodobenzoic acid required an elevated temperature. As shown in Table 1 (entries 3 and 4), the reactions of 2-iodobenzoic acid with 2-methylphenyl- and 2-fluorophenylboronic acids gave the coupling products in high yields at 90–100 °C in 2–3 h.

A high temperature was also required for the coupling reactions of some particular water-insoluble aryl iodides in water without an organic co-solvent. For example, the reactions of 1-(1-ethoxyethyl)-4-iodo-1H-pyrazole and arylboronic acids took place in water at 100 °C in the presence of 0.1 mol % of complex **1** and 1 mol % of Bu_4NBr in 0.4–1 h to give the cross-coupled products in good yields (entries 6 and 7). To provide a sense for the turnover numbers that are achievable with the new catalyst, we have examined the reactions of 1-(1-ethoxyethyl)-4-iodo-1H-pyrazole and 3-carboxyphenyl-boronic acid with low catalyst loadings (entry 8). The cross-coupling proceeded in 89% yield at 100 °C in 1 h with a 0.001% loading of palladium, corresponding to 89,000 turnover numbers (TON).

Then, we tested the catalytic activity of the new catalyst in cross-coupling reactions of aryl bromides (Table 2). While reactions of aryl iodides proceeded at room temperature in most cases, aryl bromides required an elevated temperature. In the presence of 0.1 mol % of complex **1**, water-soluble aryl bromides (3-bromobenzoic, 5-bromofuroic, 5-bromothiophene-2-carboxylic, and 5-bromosalicylic acids) afforded the coupled products in high yields at 100 °C in 0.5–2 h (entries 2–9). Even the electron-rich aryl bromide as 4-bromophenol reacted in 0.5 h (entry 10). Only 2-bromobenzoic acid was found to be inactive under the conditions tried (entry 1). Both aryl- and heteroarylboronic acids reacted smoothly to give cross-coupled products in high yields.

Table 2. Cross-coupling reactions of aryl bromides[a]

Entry	Ar-Br	Ar′-B(OH)$_2$	T (°C)	Time (h)	Yield[b] (%)
1	2-BrC$_6$H$_4$CO$_2$H	2-MeC$_6$H$_4$B(OH)$_2$	100	6	0
2	3-BrC$_6$H$_4$CO$_2$H	2-MeC$_6$H$_4$B(OH)$_2$	100	0.5	84
3	3-BrC$_6$H$_4$CO$_2$H	3-Thienyl-B(OH)$_2$	100	1	86
4[c]	4-BrC$_6$H$_4$CO$_2$H	4-ClC$_6$H$_4$B(OH)$_2$	100	10 min	97
5[c]	4-BrC$_6$H$_4$CO$_2$H	4-CF$_3$C$_6$H$_4$B(OH)$_2$	100	15 min	92
6		4-MeOC$_6$H$_4$B(OH)$_2$	100	1	96
7		3-Benzothienyl-B(OH)$_2$	100	0.5	81
8		2-MeOC$_6$H$_4$B(OH)$_2$	100	2	84
9		4-MeOC$_6$H$_4$B(OH)$_2$	100	0.5	78
10	4-BrC$_6$H$_4$OH	3-HO$_2$CC$_6$H$_4$B(OH)$_2$	100	0.5	66
11[d]	4-BrC$_6$H$_4$CHO	3-Thienyl-B(OH)$_2$	100	1	88
12[d,e]	3-BrC$_6$H$_4$CHO	3-MeOC$_6$H$_4$B(OH)$_2$	65	0.5	79
13[d,e]	3-BrC$_6$H$_4$COCH$_3$	2-ClC$_6$H$_4$B(OH)$_2$	65	2	74
14[d]		3-HO$_2$CC$_6$H$_4$B(OH)$_2$	50	10 min	86
15[d]		3-HO$_2$CC$_6$H$_4$B(OH)$_2$	50	10 min	92
16[d]		3-HO$_2$CC$_6$H$_4$B(OH)$_2$	100	8	82
17[d]	2-BrC$_6$H$_4$NH$_2$	3-HO$_2$CC$_6$H$_4$B(OH)$_2$	100	0.5	62
18[d]	3-BrC$_6$H$_4$NH$_2$	4-MeOC$_6$H$_4$B(OH)$_2$	100	1	95[f]
19[d,g]	4-BrC$_6$H$_4$NH$_2$	4-FC$_6$H$_4$B(OH)$_2$	100	0.5	91[f]
20[d,g]	4-BrC$_6$H$_4$NH$_2$	3-F,4-ClC$_6$H$_3$B(OH)$_2$	100	1	85

[a] 1 mmol of Ar-Br, 2 mL of water, 2 mmol of K$_2$CO$_3$, 1.05 mmol of Ar′-B(OH)$_2$, 0.1 mol % of PdCl$_2$–EDTA, Ar.

[b] Isolated yield.

[c] 50 mmol scale, 0.001 mol % of **1**.

[d] In the presence of 1 mol % of *n*-Bu$_4$NBr.

[e] In methanol–water (2:1) mixture.

[f] As hydrochloride.

[g] 0.01 mol % of **1**.

For preparative scale synthesis, the catalyst amount can be reduced to a 0.001 mol % level without a noticeable decrease in activity. For instance, 4-bromobenzoic acid reacted with 4-trifluoromethylphenyl- and 4-chlorophenylboronic acids (entries 4 and 5) in 10–15 min with turnover numbers (TON) up to 97,000 and turnover frequencies (TOF) up to 582,000 h^{-1}.

Reactions of water-insoluble aryl bromides also proceeded in water without an organic co-solvent in the presence of 0.1 mol % of complex **1** and 1 mol % of Bu$_4$NBr. Aryl bromides with electron-withdrawing groups gave the coupled products in high yields (entries 12–15) at 50–65 °C in 10–30 min. Reactions of arylboronic acids, which are unstable to protodeboration were carried out in aqueous methanol (entries 12 and 13).

Reactions of electron-rich bromoanilines proceeded at high temperature (entries 19 and 20). These reactions may also be carried out at lower catalyst loading. 4-Bromoaniline reacted at 100 °C in 85–91% yields in 0.5–1 h at a 0.01% loading of complex **1**, corresponding to 8500–9100 TON.

This catalytic system is highly tolerant to a broad range of functional groups. The cross-couplings proceeded smoothly to give the products in good yields even in the presence of very sensitive groups, such as CHO, MeCO, COOH, NH_2, and OH without any protection. In addition to substituted aryl iodides and bromides, the coupling reactions with heterocyclic halides also led to the formation of the desired products in high yields (Table 2, entries 6–8, 14–16). It is also noteworthy that these reactions can be performed in a short reaction time with low catalyst loadings. As a result, this new catalytic system provides an easy, quick, and convenient protocol for Suzuki–Miyaura reactions.

In summary, $PdCl_2$–EDTA was found to be an effective catalyst for the Suzuki–Miyaura cross-coupling. It is inexpensive, air-stable, and easy to prepare. A new catalytic system (K_2CO_3 or KOH in water or in H_2O–MeOH) provided good conditions for the coupling of aryl and heteroaryl halides in high yields, and demonstrated excellent tolerance to a wide range of sensitive functional groups on both substrates.

Procedure for catalyst preparation. To a 5 mL, 0.1 M solution of $PdCl_2$ (0.5 mmol) in distilled water, 0.186 g (0.5 mmol, 1 equiv) of EDTA (disodium salt dihydrate) and 0.106 g (1 mmol, 2 equiv) of Na_2CO_3 were added and the mixture stirred to give a yellow-red solution. The resulting solution can be kept in air for months without activity reduction.

Typical procedure for cross-coupling reactions. To a Schlenk vessel, 1 mmol of aryl halide, 2 mL of water, 2 mmol (0.276 g) of K_2CO_3, 1.05 mmol (5% excess) of arylboronic acid and 0.1 mL (0.01 M) solution of $PdCl_2$–EDTA (1×10^{-3} mmol, 0.1 mol %) were added, in that order, under argon. In the case of water-insoluble aryl halides, 0.0032 g (1×10^{-2} mmol, 1 mol %) of *n*-Bu_4NBr was also added to the reaction mixture. The mixture was stirred for the time and under conditions required (Tables 1 and 2). After the reaction was complete, the mixture was acidified. Analytically pure substances were isolated by filtration through a glass filter with drying for solids or by extraction with ether followed by solvent evaporation for liquids.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.06.085.

References and notes

1. For reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483; (b) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263–304; (c) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168; (d) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633–9695.
2. Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513–519.
3. (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387–3388; (b) Shae, B. L.; Perera, S. D. *Chem. Commun.* **1998**, 1863–1864; (c) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413–2416; (d) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028; (e) Feuerstein, M.; Laurenti, D.; Bougeant, C.; Doucet, H.; Santelli, M. *Chem. Commun.* **2001**, 325–326; (f) Shaughnessy, K. H.; Booth, R. S. *Org. Lett.* **2001**, *3*, 2757–2759; (g) Yin, J.; Rainka, M. P.; Zhang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162–1163; (h) Nishimura, M.; Ueda, M.; Miyaura, N. *Tetrahedron* **2002**, *58*, 5779–5787.
4. (a) Li, G. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513–1516; (b) Li, G. *J. Org. Chem.* **2002**, *67*, 3643–3650; (c) Bedford, R. B.; Hazelwood, S. L.; Limmert, M. E.; Albisson, D. A.; Draper, S. M.; Scully, P. N.; Coles, S. J.; Hursthouse, M. B. *Chem. Eur. J.* **2003**, *9*, 3216–3227.
5. Beller, M.; Fischer, H.; Herrmann, W. A.; Ofele, K.; Krobmer, C. *Angew. Chem., Int. Ed.* **1995**, *34*, 1848–1849.
6. (a) Weskamp, T.; Bohm, V. P. W.; Herrmann, W. *J. Organomet. Chem.* **1999**, *585*, 348–352; (b) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804–3805; (c) Bohm, V. P. W.; Gstottmayr, C. W. K.; Weskamp, T.; Herrmann, W. *J. Organomet. Chem.* **2000**, *595*, 186–190; (d) Zhang, C.; Trudell, M. L. *Tetrahedron Lett.* **2000**, *41*, 595–598; (e) Gstottmayr, C. W. K.; Bohm, V. P. W.; Herdtweck, E.; Grosche, M.; Herrmann, W. *Angew. Chem., Int. Ed.* **2002**, *41*, 1363–1365.
7. Tao, B.; Boykin, D. W. *Tetrahedron Lett.* **2002**, *43*, 4955–4957.
8. (a) Alonso, D. A.; Najera, C.; Pacheco, M. C. *Org. Lett.* **2000**, *2*, 1823–1826; (b) Botella, L.; Najera, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 179–181; (c) Solodenko, W.; Schön, U.; Messinger, J.; Glinschert, A.; Kirschning, A. *Synlett* **2004**, 1699–1702.
9. (a) Weissman, H.; Milstein, D. *Chem. Commun.* **1999**, 1901–1902; (b) Bedford, B.; Cazin, C. S. *Chem. Commun.* **2001**, 1540–1541.
10. Grasa, G. A.; Hillier, A. C.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 1077–1080.
11. Last review on catalyst systems for Suzuki–Miyaura reaction: Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419–2440.
12. The Pd complexes of simple amines have been reported as catalysts for Suzuki–Miyaura reactions: Tao, B.; Boykin, D. W. *J. Org. Chem.* **2004**, *69*, 4330–4335, and references cited therein.
13. (a) Bumagin, N. A.; Bykov, V. V.; Beletskaya, I. P. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1989**, *38*, 2206; (b) Wallow, T. I.; Novak, B. M. *J. Org. Chem.* **1994**, *59*, 5034–5037; (c) Campi, E. M.; Jackson, W. R.; Marcuccio, S. M.; Naesland, C. G. M. *Chem. Commun.* **1994**, 2395; (d) Moreno-Manas, M.; Pajuelo, F.; Pleixats, R. *J. Org. Chem.* **1995**, *60*, 6296–6297; (e) Bumagin, N. A.; Bykov, V. V. *Tetrahedron* **1997**, *53*, 14437–14450; (f) Badone, D.; Baroni, M.; Cardamone, R.; Ielmini, A.; Guzzi, U. *J. Org. Chem.* **1997**, *62*, 7170–7173; (g) Bumagin, N. A.; Korolev, D. N. *Tetrahedron Lett.* **1999**, *40*, 3057–3060, For recent applications of ligandless Pd catalysts see also Ref. 11.
14. Ezerskaya, N. A.; Filimonova, V. N.; Solovykh, T. P. *Zh. Neorgan. Khim.* **1965**, *10*, 2657–2663.