Reductive Coupling of Aryl Bromides Using Cat. Pd/TDAE System in Ionic Liquids

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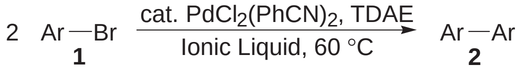
Pd/TDAE-promoted reductive coupling of aryl bromides (Ar–Br) proceeded in ionic liquids, e.g., $BdmimBF_4$ and $BdmimTf_2N$, to afford the corresponding symmetric biaryls (Ar–Ar) in good yields. Proper choice of ionic liquids and Pd catalysts is indispensable. Recycle use of $BdmimTf_2N$ and Pd catalyst was performed successfully.

Development of environmentally benign organic synthesis has been a keen project, and environmentally friendly solvents such as water,[1] supercritical CO_2,[2] and ionic liquids (ILs)[3] have been intensively investigated. Recently, we reported that Pd/tetrakis(dimethylamino)ethylene (TDAE) promoted reductive coupling of Ar–Br in DMF to give a symmetrical biaryl Ar–Ar.[4] Herein, we describe that the Pd/TDAE-promoted reductive coupling of Ar–Br in ILs proceeded smoothly by the proper choice of the Pd catalyst and the ILs (Eq 1).[5] The recycle use of the Pd catalyst and the ILs is also discussed.



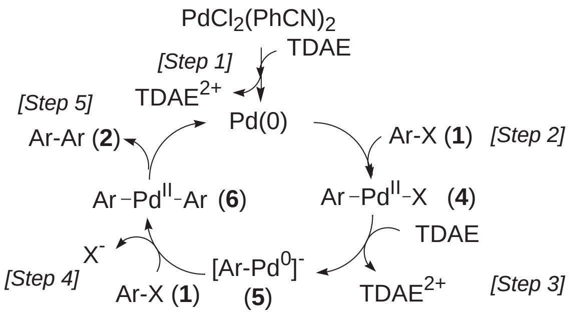
$$2\ \underset{\mathbf{1}}{\text{Ar—Br}} \xrightarrow[\text{Ionic Liquid, 60 °C}]{\text{cat. PdCl}_2\text{(PhCN)}_2\text{, TDAE}} \underset{\mathbf{2}}{\text{Ar—Ar}} \qquad (1)$$

A typical procedure is as follows: To a solution of methyl *p*-bromobenzoate (**1a**, 1 mmol) in 1-butyl-2,3-dimethylimidazolium tetrafluoroborate ($BdmimBF_4$, 2 mL) containing a catalytic amount of $PdCl_2(PhCN)_2$ (0.05 mmol) was added TDAE (2 mmol). After being stirred under argon atmosphere at 60 °C, the mixture was extracted with Et_2O. Evaporation of the solvent of the Et_2O extracts followed by column chromatography (SiO_2, Hexane/EtOAc = 5/1) afforded 4,4′-bis(methoxycarbonyl)-biphenyl (**2a**) in 72% yield.

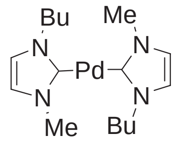
The reductive coupling of *p*-bromoanisole (**1b**) proceeded similarly to give 4,4′-dimethoxybiphenyl (**2b**) in 68% yield. Biaryls **2a** and **2b** were obtained in 87 and 69% yields, respectively, in 1-butyl-2,3-dimethylimidazolium bis(trifluoromethanesulf)imide ($BdminTf_2N$). In contrast, the coupling did not occur in 1-butyl-3-methylimidazolium tetrafluoroborate ($BmimBF_4$) and 1-butyl-3-methylimidazolium hexafluorophosphate ($BmimPF_6$).

Proper choice of Pd catalysts is also indispensable.[6] *p*-Bromoanisole (**1b**) afforded biphenyl **2b** in 68, 46, and 39% yields with $PdCl_2(PhCN)_2$, $PdCl_2$, and $Pd(OAc)_2$, respectively. 4-Cyanobromobenzene (**1c**) gave 4,4′-dicyanobiphenyl (**2c**) in 83 and 73% yield with $PdCl_2(PhCN)_2$ and $Pd(OAc)_2$, respectively. From these results, $PdCl_2(PhCN)_2$ gave the best results. Nickel catalyst, e.g., $NiBr_2(bpy)$, was not effective for this reaction.

A plausible mechanism of the reductive coupling reaction is shown in Scheme 1. Pd(II) would be reduced with TDAE to generate Pd(0) species (Step 1). Oxidative addition of Ar–X (**1**) to the Pd(0) would form $Ar–Pd^{II}–X$ **4** (Step 2), which would be, in turn, reduced with TDAE to give $[Ar–Pd^0]^-$ **5** (Step 3). Subsequent reaction of **5** with **1** would afford $Ar–Pd^{II}–Ar$ **6** (Step 4). Finally, reductive elimination of **6** would produce biaryl Ar–Ar **2** and Pd(0) species to complete the catalytic cycle (Step 5). $BmimBF_4$ and $BmimPF_6$ would form Pd-carbene complex **3**[7] to retard the desired catalytic cycle. Methyl group at the 2-position of $Bdmim^+$ ion would prevent the formation of the carbene complex.



Scheme 1. A plausible mechanism.



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In a similar manner to that described above, the Pd/TDAE-promoted reductive coupling of various Ar–Br in $BdmimBF_4$ was examined (Table 1). Ar–Br having an electron-donating group (EDG), such as MeO (**1b**), Me_2N (**1d**), Me (**1e**), and EtCH(OH) (**1f**) groups, at *p*-position gave the corresponding biaryls **2b**, **2d**, **2e**, and **2f** in 53–80% yields, respectively (Entries 1–4). The coupling of 2-bromotoluene (**1g**) did not proceed probably owing to steric hindrance of methyl group (Entry 5).

The reductive coupling of Ar–Br having an electron-withdrawing group (EWG) proceeded more efficiently than that having an EDG;[8] indeed, the coupling reaction of Ar–Br having EWG, such as MeOCO (**1a**), BuOCO (**1h**), EtCO (**1i**), and CN (**1c**, **1j**) groups, at *p*- or *m*-position completed within 2–3 h to give the corresponding biaryls **2a**, **2h**, **2i**, **2c**, and **2j** in 68–83% yields (Entries 6–10). *o*-Cyanobromobenzene (**1k**) gave **2k** in 80% yield after 6 h (Entry 11). To be compared with **1g**, **1k** would be activated by EWG, e.g., CN group, and steric hindrance of CN group would much smaller than that of Me group. Therefore, the coupling of **1k** proceeded but completed after rather long reaction time.

In the coupling of the substrate having an easily reducible functional groups, such as HCO and NO_2 groups, over-reduction of these functional groups would take place. Indeed, the coupling of 4-bromobenzaldehyde (**1l**) gave the corresponding biaryl **2l** in only 19% yield, though the substrate **1l** was consumed

Table 1. Reductive coupling of aryl halides

$$\underset{\mathbf{1}\ \text{(1 mmol)}}{2\ \text{Ar—Br}}\ \xrightarrow[\text{[Bdmim][BF}_4\text{] (2 ml), 60 °C}]{\text{PdCl}_2\text{(PhCN)}_2\text{ (0.05 mmol)}\quad\text{TDAE (2 mmol)}}\ \underset{\mathbf{2}}{\text{Ar—Ar}}$$

Entry	Aryl Bromide **1**		Time /h	Yield **2** /%[a]
1	4-$MeOC_6H_4$	**1b**	5	68 (45)
2	4-$Me_2NC_6H_4$	**1d**	10	58 (50)
3	4-MeC_6H_4	**1e**	8	80 (50)
4	4-$EtCH(OH)C_6H_4$	**1f**	7	53 (54)
5	2-MeC_6H_4	**1g**	24	—[b]
6	4-$MeOC(O)C_6H_4$	**1a**	2	72 (70)
7	4-$BuOC(O)C_6H_4$	**1h**	3	68 (75)
8	4-$EtC(O)C_6H_4$	**1i**	3	72 (75)
9	4-NCC_6H_4	**1c**	3	83 (83)
10	3-NCC_6H_4	**1j**	3	82
11	2-NCC_6H_4	**1k**	6	80
12	4-$HC(O)C_6H_4$	**1l**	3	19 (43)
13	4-$O_2NC_6H_4$	**1m**	3	—[c] (80[d])

[a] Isolated yield. Yield in the parentheses were the values using of 0.6 mmol (60 mol %) of TDAE. [b] Ar–Br **1g** was recovered. [c] 4-Amino-4′-nitrobiphenyl (**7**) was obtained in 28% yield. [d] No **7** was detected.

within 3 h. When the coupling of *p*-nitrobromobenzene (**1m**) was carried out in $BdmimBF_4$ at 60 °C for 3 h, the reduction of the nitro group occurred with TDAE and 4-amino-4′-nitrobiphenyl was formed in 28% yield, and no **2m** was obtained. According to the plausible mechanism, 50 mol % of TDAE is enough to complete the reaction. When a small excess (60 mol %) of TDAE was used, the desired 4,4′-diformylbiphenyl (**2k**) and 4,4′-dinitrobiphenyl (**2m**) were obtained in 43 and 80% yield, respectively (Entries 12, 13).

The recycle use of ionic liquid containing the Pd catalysts was studied using 4-cyanobromobenzene (**1c**) (Table 2).

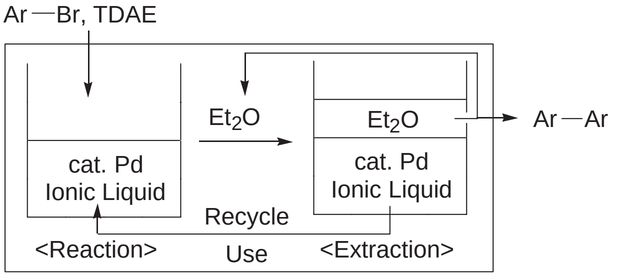
Table 2. Recycle use of ionic liquids and Pd catalyst

Cycle[a]	Ionic liquid	Yield **2c**/%[b]	Recov. **1c**/%[b]
1st	$BdminTf_2N$	93	—
2nd	$BdminTf_2N$	93	4
3rd	$BdminTf_2N$	86	7
1st	$BdmimBF_4$	83	—
2nd	$BdmimBF_4$	4	71
3rd	$BdmimBF_4$	3	79

[a] **1c** (1 mmol), TDAE (2 mmol), ionic liquid (2 mL), 60 °C, 3 h. Pd catalyst (0.05 mmol) was added for the 1st cycle. No Pd catalyst was added in the 2nd and 3rd cycles. [b] Isolated yield.

Biaryl **2c** was obtained in more than 80% yield even in the third cycle when $BdminTf_2N$ was used.[9] On the other hand, when the recovered $BdmimBF_4$ was reused at the second cycle, the biaryl **2c** was obtained in only 4% yield. It is not clear yet, but a small amount of acid, which was generated from decomposition of BF_4^- during the reaction and/or work-up, would prevent the reductive coupling reaction.

In conclusion, Pd/TDAE-promoted reductive coupling of Ar–Br can be performed in ionic liquids such as $BdmimBF_4$ and $BdminTf_2N$. The reaction proceeded effectively with Ar–Br having both EDG and EWG. The reductive coupling of Ar–Br having easily reduced functional groups, such as nitro and formyl groups, can be performed successfully by using a small excess amount of TDAE. Recycle-use of ionic liquid and Pd catalyst was performed successfully when $BdminTf_2N$ was used as a reaction solvent, which offers a totally closed system (Scheme 2).



Scheme 2. A totally closed system.

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5 Recently, Alper reported a similar Pd/TDAE-promoted coupling of aryl iodides in an IL (S. B. Park and H. Alper, *Tetrahedron Lett.*, **45**, 5515 (2004).) The scope of the reaction was, however, strictly limited; thus, only aryl iodides could undergo the reductive coupling.

6 In a previous reports, we found that Pd catalysts having phosphine ligands, such as $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, and $PdCl_2(dppb)$ did not promote this Pd/TDAE-promoted homo-coupling, and $Pd_2(dba)_3$ was less effective. See, Refs. 4a and 4b.

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8 In a previous reports, we also found that reactivity of Ar–Br having EWG is higher than that of Ar–Br having EDG in DMF. It is likely that EWG accelerates both Step 2 and Step 3 by reducing the electron density (redox potential) of Ar–Br (**1**) and Ar–Pd–X (**4**).

9 After extractive work-up with Et_2O, no significant increase of the volume of the reaction medium (ionic liquid) was observed, suggesting that by-products derived from TDAE would be extracted with Et_2O.

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