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Palladium(II)-Catalyzed Coupling of Electron-Deficient Arenes via C−H Activation

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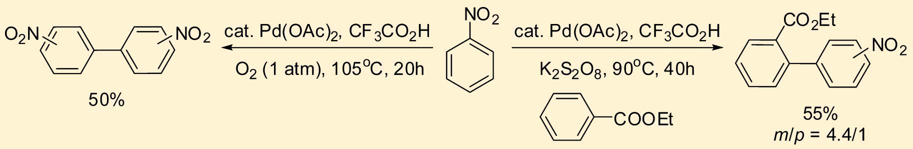
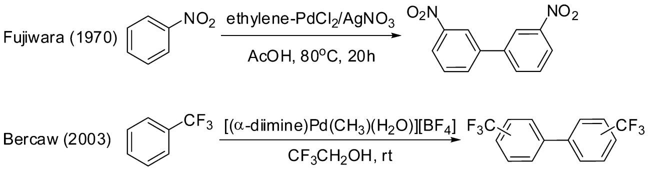
Supporting Information



ABSTRACT: Homocoupling and cross-coupling of electron-deficient arenes, including nitrobenzene, (trifluoromethyl)benzene, ethyl benzoate, etc., have been developed to afford biaryls using a catalytic system of $Pd(OAc)_2$/trifluoroacetic acid (TFA)/O_2 or $K_2S_2O_8$. The crucial step is to tune the concentrations of arenes and the loading of TFA carefully to enhance the reaction rates and the selectivity of these couplings involving dual C−H activation.

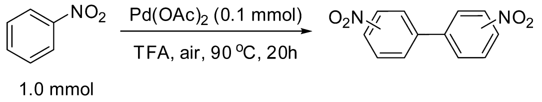
In the past 5 years, catalytic cross-coupling of arenes to form unsymmetrical biaryls through double aryl C−H bond cleavages has been focused largely on the field of organic synthesis.[1] Heteroarenes[2] and special arenes[3] such as ortho-group-directing arenes and polyfluoroarenes were mostly studied in this area. However, the coupling reactions between simple arenes such as benzene, alkylbenzene, halobenzene, nitrobenzene, etc. through aryl C−H activation have been rarely reported because either their reactivity or selectivity of their aryl C−H bonds is still a challenge to researchers.[4] A major pathway of aryl C−H bond cleavage is the electrophilic attack on electron-rich aromatic rings by various nonmetal cations and metal ions, which is the S_EAr process. Obviously, normal electron-deficient arenes called deactivated arenes, such as nitrobenzene, (trifluoromethyl)benzene, and carbonyl-substituted arene, are more difficult to functionalize through electrophilic aromatic substitution, especially to form the C−C bonds directly. It is noted that Fujiwara and Bercaw disclosed that a stoichiometric amount of ethylene−Pd(II) or a special cationic Pd(II) complex was very effective in homocoupling reactions of nitrobenzene or (trifluoromethyl)benzene under mild conditions, respectively (Scheme 1).[5] Here we describe that the catalytic coupling of electron-deficient arenes, including nitrobenzene, (trifluoromethyl)benzene, and ethyl benzoate, can proceed successfully just by controlling the amount of trifluoroacetic acid (TFA) in a simple system of $Pd(OAc)_2$/TFA/oxidant without any other additives and special ligands.

Scheme 1. Coupling of Nitrobenzene or (Trifluoromethyl)benzene



In our previous work on intermolecular cross-coupling of simple arenes, including naphthalene, anisole, mesitylene, *p*-xylene, benzene, and chlorobenzene, we found that Pd(II) species were more powerful in attacking the aryl C−H bond at a high concentration of TFA and at elevated temperature.[6] However, for nitrobenzene, the yield of coupling products was very poor without TFA or with addition of 9.9 mmol of TFA to 1.0 mmol of nitrobenzene at 90 °C (Table 1, entries 1 and 2).

Table 1. Catalytic Coupling of Nitrobenzene in TFA



entry	amt of TFA (mmol)	yield[a] (%)
1	none	trace
2	9.9	trace
3	4.9	32
4	1.0	34
5	0.5	31
6[b]	0.9	21
7[c]	1.0	43
8[d]	3.0	50 (43)

[a] Yield based on nitrobenzene and detected by ^1H NMR; isolated yield in parentheses. [b] Under N_2 (1 atm). [c] Under O_2 (1 atm). [d] Conditions: $Pd(OAc)_2$ (0.15 mmol, 15 mol %), O_2 (1 atm), 105 °C.

Interestingly, after just tuning the amount of TFA to 0.5−5.0 mmol, a catalytic coupling reaction of nitrobenzene occurred and the yield could be enhanced to around 34% in the presence of 10 mol % $Pd(OAc)_2$ just in air (Table 1, entries 3−5). It seems that the high concentration of nitrobenzene with TFA in

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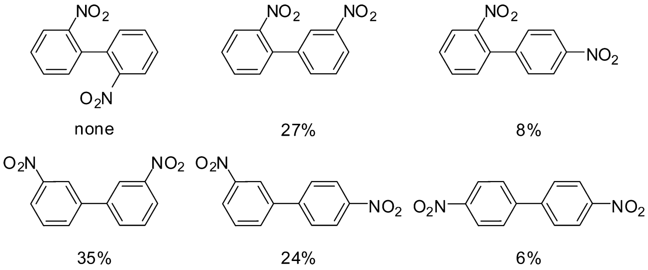
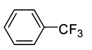
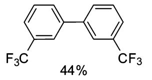
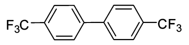
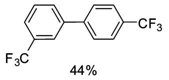
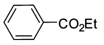
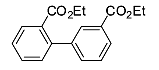
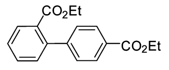
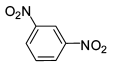
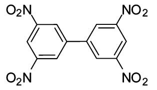
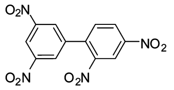
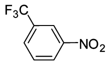
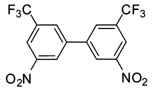
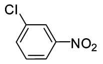
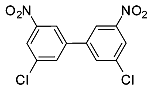
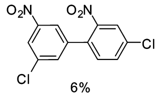
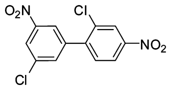
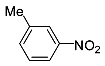
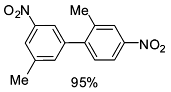
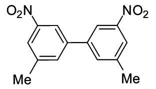
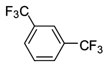
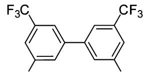
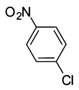
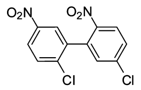
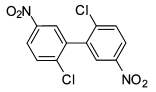
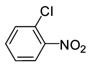
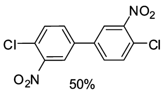
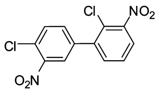
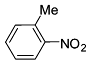
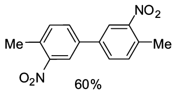
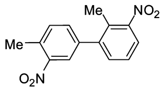
the reaction mixture is the key factor for catalytic coupling reactions through double aryl C−H bond cleavages. Oxygen from air acting as the oxidant during the reactions was proved from the following two control tests. Under an atmosphere of nitrogen, quantitative coupling products were generated based on $Pd(OAc)_2$ (Table 1, entry 6). In contrast, when the reaction was carried out in oxygen (1 atm), a catalytic process was established and the yield was up to 50% in the presence of 15 mol % catalyst at 105 °C (Table 1, entries 7 and 8). However, further improvement of the yield was unsuccessful because polymerization apparently happened when the dimeric products accumulated in the reaction phase. In comparison with Fujiwara's Pd(II) system,[5a] $Pd(OAc)_2$/TFA is a more reactive electrophile, which could attack all aryl C−H bonds of nitrobenzene to form five biaryl isomers, detected by ^1H NMR. Steric hindrance might retard the formation of 2,2′-biaryl, and the ratio of *o*/*m*/*p* positions of nitrobenzene activated by Pd(II) catalyst was 1/3.5/1.3, which was in accordance with an S_EAr process (Scheme 2). These results indicate that catalytic couplings of strongly electron-deficient arenes are feasible in the presence of $Pd(OAc)_2$ by only tuning the amount of TFA with an efficient oxidant.

Scheme 2. Selectivity of Catalytic Coupling of Nitrobenzene in TFA Determined by ^1H NMR[a]



[a]Conditions: nitrobenzene (1.0 mmol), $Pd(OAc)_2$ (0.15 mmol, 15 mol %), O_2 (1.0 atm), TFA (3.0 mmol), 105 °C, 20 h. Isolated yield: 43% based on nitrobenzene. For details, see the Supporting Information.

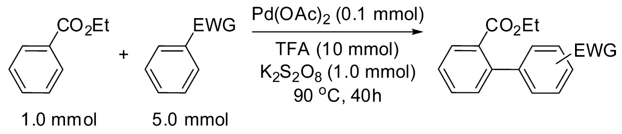
Table 2. Catalytic Homocoupling of Electron-Deficient Arenes in TFA

substrate	coupling products (selectivity)		yield[a] (%)
	 44%  12% CF_3: *o*/*m*/*p* = 0/2/1	 44%	60[b]
	 80% CO_2Et: *o*/*m*/*p* = 4.9/3.9/1	 20%	40
	 70% NO_2: *o*,*p*/*m* = 1/5.7	 30%	52
	 >99% NO_2: *o*/*m*/*p* = 0/1/0 CF_3: *o*/*m*/*p* =0/1/0		40
	 72%  6% NO_2: *o*/*m*/*p* = 1/28.7/3.7 Cl: *o*/*m*/*p* =3.7/28.7/1	 22%	35
	 95% NO_2: *o*/*m*/*p* = 0/1.1/1 Me: *o*/*m*/*p* =1/1.1/0	 5%	68(51)
	 100% CF_3: *o*/*m*/*p* = 0/1/0		33
	 67% NO_2: *o*/*m* = 1/2 Cl: *o*/*m* = 2/1	 33%	36
	 50% NO_2: *o*/*m*/*p* = 0/1/0 Cl: *o*/*m*/*p* =1/0/3	 50%	30[c]
	 60% NO_2: *o*/*m*/*p* = 0/1/0 Me: *o*/*m*/*p* =1/0/4	 40%	31[c](25)

[a]Conditions: substrate (0.5−5.0 mmol), $Pd(OAc)_2$ (10 mol %), TFA (1.0−10 mmol), O_2 (1 atm), 90−150 °C, 20 h. Yield and product isomers determined by ^1H NMR; isolated yield in parentheses. [b]$Pd(OAc)_2$ (2 mol %), $K_2S_2O_8$ (0.6 equiv). [c]$Pd(OAc)_2$ (15 mol %).

In further investigations into the homocoupling of electron-deficient arenes, it was found that not only nitrobenzene but also (trifluoromethyl)benzene, ethyl benzoate, and their substituted derivatives could be coupled as well (Table 2). For (trifluoromethyl)benzene, $K_2S_2O_8$ was a more effective oxidant than oxygen and other oxidants. The product yield increased from 30% with 10 mol % $Pd(OAc)_2$ in air to 60% with 2 mol % $Pd(OAc)_2$ using $K_2S_2O_8$ as the oxidant, and the turnover number (TON) could be up to 70 in the presence of 0.25 mol % $Pd(OAc)_2$ under the same reaction conditions. Similarly, the coupling of ethyl benzoate also required $K_2S_2O_8$ to complete the catalytic cycle. However, in comparison with nitrobenzene and (trifluoromethyl)benzene to generate 3,3′- and 3,4′-biaryl products, ethyl benzoate showed a strong ortho-directing effect and mainly gave the 2,3′-biaryl species as the major product (Schemes 2 and 3). 2,2′-Biaryls were not formed in the coupling reaction due to steric effects, and the meta positions were still favorable to form aryl C−C bonds in the cases of (trifluoromethyl)benzene and ethyl benzoate. Oxygen (1 atm) as an available oxidant was employed successfully in most of the coupling reactions of those substituted nitrobenzenes, and the product yields ranged from 35% to 68%, except for ortho-substituted nitrobenzenes. In the coupling reactions of meta-substituted nitrobenzenes and (trifluoromethyl)benzenes, 5,5′-biaryls were the major products. Both electronic effects for the S_EAr pathway and steric hindrance determined the ratios of product isomers. For the ortho-substituted nitrobenzenes, 2-methyl-1-nitrobenzene gave fewer arylation products at the

Scheme 3. Catalytic Cross-Coupling of Ethyl Benzoate with Nitrobenzene or (Trifluoromethyl)benzene[a]



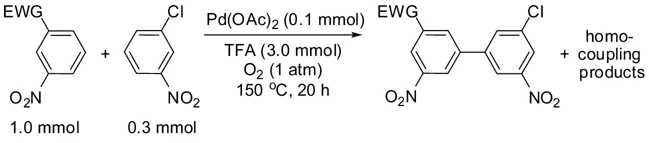
EWG	coupling products (selectivity)	yield (%)
NO_2	*m*/*p* = 4.4/1	55
CF_3	*m*/*p* = 3.5/1	56

[a]Yield and selectivity determined by ^{1}H NMR.

6-position of the aromatic ring than did 2-chloro-1-nitrobenzene. Although the current Pd(II) system is effective in the activation of aryl C−H bonds on strongly electron-deficient arenes without a CN, COR, or COOH group by controlling the loading of TFA, the reasons for some low yields of couplings of these substrates, especially ortho-substituted nitrobenzenes, are still unclear.

The cross-coupling reactions between these electron-deficient arenes were also studied. Since ethyl benzoate showed a very effective ortho-directing effect in the homocoupling reactions, nitrobenzene and (trifluoromethyl)benzene were selected as the partners, respectively, to couple with it, and nearly all cross-coupling products in moderate yields were obtained successfully. The major products were 2,3′-biaryls, which means that the S_EAr process was still involved (Scheme 3). The more challenging work was the cross-coupling of two different electron-deficient arenes without ortho-directing groups. As mentioned before, in the catalytic system of $Pd(OAc)_2$/TFA for cross-coupling of two different simple arenes, tuning the molar ratio of two arenes and the loading of TFA can diminish or eliminate the homocoupling products and thus increase the selectivity of cross-coupling reactions.[6] After a large number of tests, it was found that the reaction between 1,3-dinitrobenzene or 3-(trifluoromethyl)-1-nitrobenzene and 3-chloro-1-nitrobenzene could give the cross-coupling biaryls as the major products, respectively, showing a moderate selectivity in cross-couplings (Scheme 4). Homocoupling products could not be avoided completely in these cross-coupling reactions, because the reactivity and selectivity conflicted with each other sharply in the activation of aryl C−H bonds on electron-deficient arenes by an electrophilic metalation pathway with TFA at elevated temperature.

Scheme 4. Cross-Coupling of 1,3-Dinitrobenzene or 3-(Trifluoromethyl)-1-nitrobenzene with 3-Chloro-1-nitrobenzene[a]



EWG	cross-coupling products	homocoupling products	selectivity (%)
NO_2	0.10 mmol	(0.01 + 0.06) mmol	59
CF_3	0.10 mmol	(0.01 + 0.05) mmol	62

[a]Selectivity: cross-coupling product/all coupling products. Coupling products and selectivity determined by ^{1}H NMR.

In summary, a simple Pd(II) catalytic system has been established for the coupling of electron-deficient arenes to prepare biaryls, including nitrobenzene, (trifluoromethyl)-benzene, and ethyl benzoate, which are among the most inert arenes to C−H bond cleavage through the S_EAr process. Tuning the concentration of arene and TFA precisely can make either homocoupling or cross-coupling reactions proceed smoothly under the normal reaction conditions. Oxygen can also play the role of an effective oxidant in most of these catalytic reactions. Further research on the scope, mechanism, and application of these coupling reactions is ongoing.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text, figures, and tables giving experimental details and characterization data for biaryl compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507. (b) Bergman, R. G. *Nature* **2007**, *446*, 391. (c) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (d) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (e) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (f) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215.

(2) (a) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (b) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137. (c) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072. (d) Potavathri, S.; Dumas, A. S.; Dwight, T. A.; Naumiec, G. R.; Hammann, J. M.; DeBoef, B. *Tetrahedron Lett.* **2008**, *49*, 4050. (e) Kita, Y.; Morimoto, K.; Ito, M.; Ogawa, C.; Goto, A.; Dohi, T. *J. Am. Chem. Soc.* **2009**, *131*, 1668. (f) Xi, P.; Yang, F.; Qin, S.; Zhao, D.; Lan, J.; Gao, G.; Hu, C.; You, J. *J. Am. Chem. Soc.* **2010**, *132*, 1822. (g) Potavathri, S.; Pereira, K. C.; Gorelsky, S. I.; Pike, A.; LeBris, A. P.; DeBoef, B. *J. Am. Chem. Soc.* **2010**, *132*, 14676. (h) Do, H,-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2011**, *133*, 13577.

(3) (a) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (b) Xia, J.-B.; You, S.-L. *Organometallics* **2007**, *26*, 4869. (c) Brasche, G.; García-Fortanet, J.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2207. (d) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (e) Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115. (f) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 9651. (g) Zhao, X.; Yeung, C. S.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 5837. (h) Yeung, C. S.; Zhao, X.; Borduas, N.; Dong, V. M. *Chem. Sci.* **2010**, *1*, 331. (i) Wei, Y.; Su, W. *J. Am. Chem. Soc.* **2010**, *132*, 16377. (j) Wang, X.; Leow, D.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 13864.

(4) (a) Caron, L.; Campeau, L.; Fagnou, K. *Org. Lett.* **2008**, *10*, 4533. (b) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072. (c) Emmert, M. H.; Cook, A. K.; Xie, Y. J.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 9409. (d) Dohi, T.; Ito, M.; Morimoto, K.; Iwata, M.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 1301. (e) Dohi, T.; Ito, M.; Itani, I.; Yamaoka, N.; Morimoto, K.; Fujioka, H.; Kita, Y. *Org. Lett.* **2011**, *13*, 6208.

(5) (a) Fujiwara, Y.; Moritani, I.; Ikegami, K.; Tanaka, R.; Teranishi, S. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 863. (b) Ackerman, L. J.; Sadighi, J. P.; Kurtz, D. M.; Labinger, J. A.; Bercaw, J. E. *Organometallics* **2003**, *22*, 3884.

(6) (a) Li, R.; Jiang, L.; Lu, W. *Organometallics* **2006**, *25*, 5973. (b) Rong, Y.; Li, R.; Lu, W. *Organometallics* **2007**, *26*, 4376.