JOC*Note*

Phosphine-Free Palladium(II)-Catalyzed Arylation of Naphthalene and Benzene with Aryl Iodides

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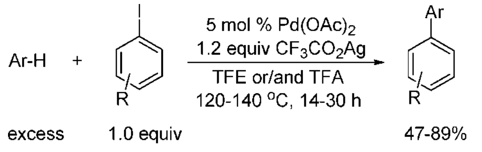

Ar-H: naphthalene, benzene, anisole, *tert*-butyl benzene, *p*-xylene
R: H, *p*-OMe, *m*-OMe, *p*-Me, *p*-COMe, *p*-NO$_2$, *m*-NO$_2$

A phosphine-free arylation of naphthalene and benzene with aryl iodides to give biaryls in moderate to good yields is carried out in the presence of catalytic Pd(OAc)$_2$ and stoichiometric CF$_3$CO$_2$ Ag in TFE or/and TFA.

Formation of aryl−aryl bonds has been one of the most important methods in organic synthesis since the Ullmann reaction, a homocoupling of aryl halides with a stoichiometric amount of copper, was discovered one century ago.[1] A promising protocol of this chemistry, especially for yielding unsymmetric biaryls, is the direct arylation of aromatic C−H bonds with aryl halides in the presence of catalytic transition metals. Although significant progress was achieved most recently in arylations of heteroaromatics,[2] fluoroarenes,[3] and directing-group containing arenes,[4] the intermolecular coupling of aryl halides with simple arenes such as benzene[5] in the absence of directing groups still has been rarely reported. Herein, we describe a Pd(OAc)$_2$-catalyzed arylation of naphthalene or benzene with various aryl iodides in the presence of CF$_3$CO$_2$Ag in trifluoroethanol (TFE) or/and trifluoroacetic acid (TFA).

According to the previous reports on palladium-catalyzed couplings of heteroaromatics with aryl halides, the arylations involve a Pd$^{0/II}$ cycle, as shown in Scheme 1, and additional reductants are necessary if the initial catalyst is a Pd(II) complex.[2] In this Pd$^{0/II}$ cycle, the first arylpalladium(II) intermediate **I** is formed through an oxidative addition of a Pd(0) complex with an aryl halide. However, since only the aryl C−H bond of heteroaromatics and directing-group assisted arenes could be cleaved successfully by the intermediate **I** to give a diarylpalladium(II) complex **II** under the reaction conditions, the scope of this arylation is severely limited. To overcome this barrier, we propose a Pd$^{II/IV}$ cycle for our intermolecular arylation of simple arenes with aryl iodides as first suggested in the *ortho*-alkylation of acetanilides with excess alkyl iodides,[7a] then applied in other arylations. [4b,7b,c] In the Pd$^{II/IV}$ cycle, as shown in Scheme 1, the first step is the attack of a highly electrophilic Pd(II) complex on a simple aryl C−H bond to generate an arylpalladium(II) intermediate **III** under similar reaction conditions in the cross-coupling of simple arenes via double C−H bond activations we reported recently,[6] followed by an oxidative addition with an aryl halide to afford a diarylpalladium(IV) complex **IV**.

In our initial investigation of the coupling of naphthalene (**1a**) with *p*-iodonitrobenzene (**2a**), as shown in Table 1, the above hypothesis on Pd$^{II/IV}$ cycle is partly supported. In the cases of Pd/C and Pd(PPh$_3$)$_4$, no biaryl was found (Table 1, entries 5 and 6). In contrast, when Pd(OAc)$_2$ was employed, trace coupling products were detected by GC analysis (Table 1,entry 1). Notably, by loading Pd(II) or Pd(0) as the catalyst (5 mol %), the yields of arylation products could be up to 88% and 61% (Table 1, entries 4 and 7), respectively, after 1.2 equiv of CF$_3$CO$_2$Ag was added into the reactions. This indicates that not only Pd(II) can make the arylation occur but also a Pd$^{II/IV}$ cycle may be involved in the process. Moreover, CF$_3$CO$_2$Ag should be necessary to keep the Pd(II) catalyst more active by either Ag$^+$ eliminating I$^-$ to prevent forming an inactive PdI$_2$

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(1) Reviews: (a) Bellina, F.; Cauteruccio, S.; Rossi, R. *Curr. Org. Chem.* **2008**, *12*, 774. (b) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (c) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichim. Acta* **2007**, *40*, 35. (d) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (e) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (f) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (g) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253. (h) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (i) Hassan, J.; Sevignon, M.; Gozzi, C.; Shulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.

(2) For recent arylation of heteroaromatics see: (a) Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926. (b) Fleageau, E. F.; Popkin, M. E.; Greaney, M. F. *Org. Lett.* **2008**, *10*, 2717. (c) Martin, T.; Verrier, C.; Hoarau, C.; Marsais, F. *Org. Lett.* **2008**, *10*, 2909. (d) Bellina, F.; Cauteruccio, S.; DiFiore, A.; Marchetti, C.; Rossi, R. *Tetrahedron* **2008**, *64*, 6060. (e) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404. (f) Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, *9*, 1449. (g) Wang, X.; Gribkov, D. V.; Sames, D. *J. Org. Chem.* **2007**, *72*, 1476. (h) Battace, A.; Lemhadri, M.; Zair, T.; Doucet, H.; Santelli, M. *Organometallics* **2007**, *26*, 472. (i) Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *J. Am. Chem. Soc.* **2006**, *128*, 11748.

(3) For arylation of fluoroarenes see: (a) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128. (b) Ozdemir, I.; Demir, S.; Cetinkaya, B.; Gourlaouen, C.; Maseras, F.; Bruneau, C.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 1156. (c) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299. (d) Shabashov, D.; Daugulis, O. *J. Org. Chem.* **2007**, *72*, 7720. (e) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. (f) Lafrance, M.; Shore, D.; Fagnou, K. *Org. Lett.* **2006**, *8*, 5097.

(4) For recent *ortho*-arylation of various arenes see: (a) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266. (b) Larivee, A.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 52. (c) Ackermann, L.; Vicente, R.; Althammer, A. *Org. Lett.* **2008**, *10*, 2299. (d) Ozdemir, I.; Demir, S. *J. Am. Chem. Soc.* **2008**, *130*, 1156. (e) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879. (f) Shabashov, D.; Daugulis, O. *J. Org. Chem.* **2007**, *72*, 7720. (g) Lazareva, A.; Daugulis, O. *Org. Lett.* **2006**, *8*, 5211. (h) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510.

(5) For arylation of benzene see: (a) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496. (b) Fujita, K.-I.; Nonogawa, M.; Yamaguchi, R. *Chem. Commun.* **2004**, 1926. For arylation of azulene see: (c) Dyker, G.; Borowski, S.; Heiermann, J.; Kö rning, J.; Opwis, K.; Henkel, G.; Kö ckerling, M. *J. Organomet. Chem.* **2000**, *606*, 108.

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

(7) (a) Tremont, S. J.; Rahman, H. *J. Am. Chem. Soc.* **1984**, *106*, 5759. (b) Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 15142. (c) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330.

10.1021/jo801345b CCC: $40.75

SCHEME 1. Hypothesis for Pd-Catalyzed Arylation of Various Arenes with Aryl Iodides

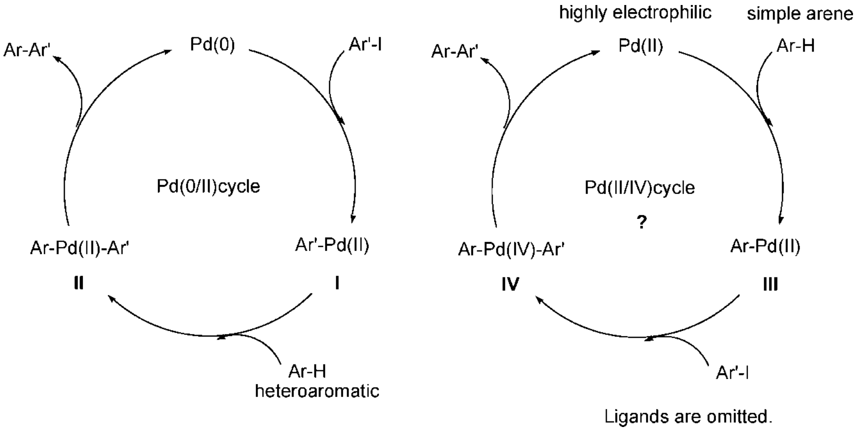
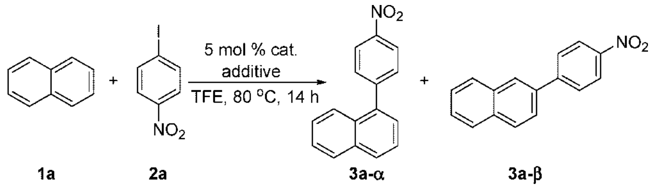


TABLE 1. Optimization of the Coupling of Naphthalene (1a) with *p*-Iodonitrobenzene (2a)[a]



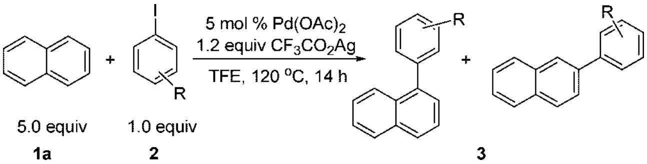
entry	catalyst	additive	yield[b] (%)
1	$Pd(OAc)_2$	none	trace
2	$Pd(OAc)_2$	AgOAc	trace
3	$Pd(OAc)_2$	CF_3SO_3Ag	trace
4	$Pd(OAc)_2$	CF_3CO_2Ag	88
5	Pd/C	none	
6	$Pd(PPh_3)_4$	none	
7	$Pd(PPh_3)_4$	CF_3CO_2Ag	61
8	$Pd(CF_3CO_2)_2$	none	trace
9	none	CF_3CO_2Ag	

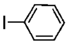
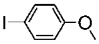
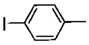
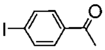
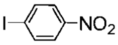
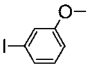
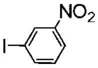
[a] Conditions: **1a** (1.0 mmol), **2a** (0.2 mmol), catalyst (0.01 mmol, 5 mol %), additive (0.24 mmol), TFE (7.0 mmol), 80 °C, 14 h. [b] Yield based on **2a**, **3a**-α/**3a**-β = 3.3/1 detected by ^{1}H NMR.

complex[7a] or $CF_3CO_2^-$ enhancing the electrophilic reactivity of Pd(II) species for aryl C−H bond activations[8] (Table 1, entries 1−4 and 8). In addition, for Pd(0) complex (Table 1, entry 7), CF_3CO_2Ag as an oxidant might also convert Pd(0) to Pd(II) initially,[9] followed by a $Pd^{II/IV}$ catalytic cycle. However, aryl bromides and chlorides were not found to be available in this intermolecular arylation under the same conditions. One possible reason is the arylpalladium(II) intermediate **III** could not react with aryl bromides and chlorides through an oxidative addition under these reaction conditions as the Pd(0) complex did in inter-[2−4] or intramolecular couplings.[10]

We next examined the Pd(II)-catalyzed arylation of **1a** with other aryl iodides in the presence of CF_3CO_2Ag in TFE. As shown in Table 2, the ratio of **1a**/**2b** apparently could affect this coupling and excess **1a** was employed to afford the biaryls in a good yield (Table 2, entry 1). Moreover, the cross-coupling product isomers as the major products were obtained in all cases. On the other hand, electron-releasing groups on the phenyl rings

TABLE 2. Pd(II)-Catalyzed Arylation of 1a in TFE[a]



entry	2		3, yield(%)[b]	α/β[c]
1	**2b**		**3b**, 73[d] 72 29[e]	3.0/1
2	**2c**		**3c**, 62	4.8/1
3	**2d**		**3d**, 63	3.6/1
4	**2e**		**3e**, 76	3.0/1
5	**2a**		**3a**, 89	3.3/1
6	**2f**		**3f**, 60	3.6/1
7	**2g**		**3g**, 73	3.0/1

[a] Conditions: **1a** (1.0 mmol), **2** (0.2 mmol), $Pd(OAc)_2$ (0.01 mmol, 5 mol %), CF_3CO_2Ag (0.24 mmol), TFE (7.0 mmol), 120 °C, 14 h. [b] Yield based on **2**. [c] The ratio of α/β was detected by ^{1}H NMR. [d] **1a** (2.0 mmol). [e] **1a** (0.2 mmol).

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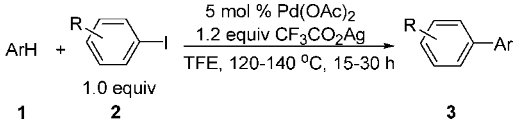
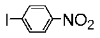
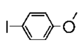
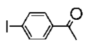
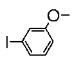
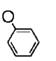
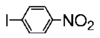
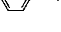
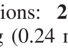
(8) (a) Jia, C.; Lu, W.; Oyamada, J.; Kitamura, T.; Matsuda, K.; Irie, M.; Fujiwara, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7252. (b) Lu, W.; Yamaoka, Y.; Taniguchi, Y.; Kitamura, T.; Takaki, K.; Fujiwara, Y. *J. Organomet. Chem.* **1999**, *580*, 290.

(9) (a) Potavathri, S.; Dumas, A. S.; Dwight, T. A.; Naumiec, G. R.; Hammann, J. M.; DeBoef, B. *Tetrahedron Lett.* **2008**, *49*, 4050. (b) Fujiwara, Y.; Moritani, I.; Danno, S.; Teranishi, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166.

(10) (a) Parisien, M.; Valette, D.; Fagnou, K. *J. Org. Chem.* **2005**, *70*, 7578. (b) Echavarren, A. M.; Gomez-Lor, B.; Gonzalez, J. J. *Synlett* **2003**, 585.

TABLE 3. Pd(II)-Catalyzed Arylation of Benzene (1b) and Its Derivates[a]



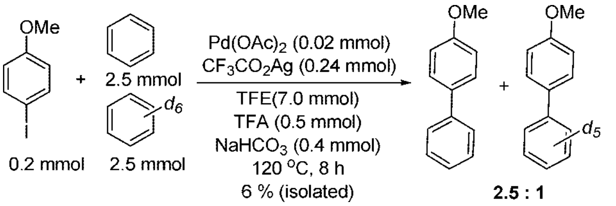
entry	1, ArH(mmol)		2		TFE(mmol)	TFA(mmol)	3, yield(%)[b]
1	**1b** 	5.0	**2a**		7.0	-	**3h**, 18
		5.0	**2a**		7.0	0.5	**3h**, 59(64)
		5.0	**2c**		7.0	0.5	**3i**, 60(71)
		6.0	**2e**		7.0	0.5	**3j**, 54(56)
		10.0	**2f**		7.0	1.0	**3k**, 56(64)
2	**1c** 	1.0	**2a**		1.0	-	**3l**, 48(56) ***o*/*m*/*p*** = 1/0/1.1
3	**1d** 	5.0	**2a**		4.0	-	**3m**, 50(56) ***o*/*m*/*p*** = 0/1/1.2
4	**1e** 	1.0	**2a**		10.0	-	**3n**, 58

[a] Conditions: **2** (0.2 mmol), $Pd(OAc)_2$ (0.01 mmol, 5 mol %), CF_3CO_2Ag (0.24 mmol), 120−140 °C, 15−30 h. Entry 1, for **2c** and **2f**, $NaHCO_3$ (0.4 mmol); entry 2, ClC_2H_4Cl (0.5 mL); entry 4, $NaHCO_3$ (0.4 mmol). See the Supporting Information for experimental details. [b] Yield (GC yield in parentheses) based on **2**. The ratio of ortho/meta/para was detected by ^{1}H NMR.

of aryl iodides cannot influence the coupling enormously though a Pd(II) species generally prefers to react with an aryl iodide bearing an electron-withdrawing group to form a Pd(IV) complex (Table 2, entries 2−5). Both *m*-iodoanisole and *m*-iodonitrobenzene underwent this arylation very well (Table 2, entries 6 and 7), but *o*-iodonitrobenzene just gave its own homocoupling product under the same reaction conditions.

Benzene (**1b**) and its derivatives were tested in this arylation further. However, **1b** cannot undergo the coupling reaction via aryl C−H activation very effectively only in TFE since it is not an active arene like **1a**. Thus, TFA was introduced into this reaction system to enhance the reactivity of Pd(II) catalyst considerably for phenyl C−H bond activation.[6,8] In some cases, $NaHCO_3$ was added to decrease the acidity of reaction solutions for enhancing the yields of coupling products. The crucial procedure here is to control the amount of TFA and the ratio of **1**/**2** in the reaction to obtain the desired biaryls and to prevent the generation of homocoupling products from arenes or aryl iodides. As shown in Table 3, by tuning the concentrations of arenes, TFE/TFA, and other reaction conditions, not only benzene but also anisole, *tert*-butylbenzene, and *p*-xylene can be arylated with aryl iodides to give the corresponding biaryls in moderate yields. Some cross-coupling isomers were also generated in the cases of anisole and *tert*-butylbenzene (Table 3, entries 2 and 3) through an electrophilic pathway without the assistance from these directing groups on phenyl rings.[4] For those arenes with larger steric hindrance such as mesitylene and iodomesitylene or electron-deficient arenes such as nitrobenzene and chlorobenzene, little or no arylation products were found.

To elucidate further the proposed mechanism of this arylation shown in Scheme 1, a competition coupling between benzene and benzene-d_6 with **2c** was studied (eq 1). After 8 h, the ratio of the coupling products (H/D biaryls) was 2.5/1 detected by ^{1}H NMR, which means the activation of aryl C−H bonds on benzene has a significant effect on the entire reaction rate. However, since H/D exchange was observed in the case of naphthalene-d_8 in TFE under the reaction conditions, the measurment of kinetic isotope effect for the coupling of naphthalene with aryl iodide was thwarted. Although no direct evidence was found for a $Pd^{II/IV}$ cycle in this intermolecular arylation and those normal $Pd^{0/II}$ cycle, proton abstraction,[5a] phenyl radical,[5b] or other mechanisms could not be ruled out completely, we still prefered that the formation of Pd(IV) species might be involved in these coupling reactions based on the coupling of naphthalene (**1a**) with iodobenzene (**2b**) could proceed in the presence of Pd(II) catalyst in TFA instead of TFE without any potential reducing agents, but not in the presence of Pd(0) catalyst without additional oxidents. Furthermore, since two isomers of coupling products were obtained from Pd(II)-catalyzed arylations of excess naphthalene (**1a**) with various aryl iodides in the presence of CF_3CO_2Ag listed in Table 2, compared to only one cross-coupling product generated in the Pd(II)-catalyzed arylation of **1a** with excess benzene in TFA,[6b] it is reasonable to suggest that two kinds of aryl C−H bonds of **1a** were activated by the more reactive Pd(II) catalyst to form the intermediate **III** before the cleavage of aryl C−I bonds of iodides (as shown in Scheme 1) and $CF_3CO_2^-$ could mainly enhance the electrophilic reactivity of the initial Pd(II) catalyst, not other intermediate Pd species for aryl C−H activations during the couplings.[6b,8]



(1)

In conclusion, a novel method for direct formation of aryl−aryl bonds has been established, which is a phosphine-free intermolecular arylation of simple arenes such as naphthalene and benzene with aryl iodides to afford biaryls in moderate to good yields through a postulated $Pd^{II/IV}$ cycle in the presence of catalytic $Pd(OAc)_2$ and stoichiometric CF_3CO_2Ag in TFE or/and TFA. The scope and mechanistic studies of this arylation are ongoing.

Experimental Section

Typical Arylation of Naphthalene (1a) with Aryl Iodides: Preparation of 1-(4-Nitrophenyl)naphthalene (3a). 2a (49.8 mg, 0.2 mmol), **1a** (128.2 mg, 1.0 mmol), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol), CF_3COOAg (53.0 mg, 0.24 mmol), TFE (7.0 mmol), and a magnetic stir bar were placed in a flame dried glass tube (10 mL) with a screw cap. The mixture was stirred at 80 °C for 14 h until complete consumption of the aryl iodide, as monitored by TLC analysis. Then the reaction mixture was diluted by CH_2Cl_2 and filtered. The organic layer was successively washed with water (3 × 10 mL), dried over anhydrous $MgSO_4$, and then evaporated under reduced pressure. The crude products were isolated by flash column chromatography over silica (petroleum ether/ethyl benzoate 50/1) to produce 46.8 mg (88%) of **3a**. The products were characterized by their physical constants and spectral analysis: **3a**-α/**3a**-β = 3.3/1.0.

1-(4-Nitrophenyl)naphthalene (**3a**-α): pale yellow solid (mp 132−133 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J = 9.2 Hz, 2H), 7.95−7.93 (dd, J = 7.6 Hz, 2H), 7.80 (d, J = 7.6 Hz, 1H), 7.68 (d, J = 8.4 Hz, 2H), 7.58−7.42 (m, 4H).

2-(4-Nitrophenyl)naphthalene (**3a**-β): pale yellow solid (mp 183−184 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, J = 8.4 Hz, 2H), 8.10 (s, 1H), 7.98−7.85 (m, 5H), 7.75−7.73 (dd, *J* = 8.4 Hz, 1H), 7.56 −7.54 (m, 2H).

Typical Arylation of Benzene (1b) with Aryl Iodides: Preparation of 4-Methoxybiphenyl (3i). 2c (46.8 mg, 0.2 mmol), **1b** (390.5 mg, 5.0 mmol), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol), CF_3COOAg (53.0 mg, 0.24 mmol), TFE (7.0 mmol), TFA (0.5 mmol), and a magnetic stir bar were placed in an autoclave (10 mL). The mixture was stirred at 120 °C. After 2 h, $NaHCO_3$ (0.4 mmol, 33.6 mg) was added. The reaction propagation was monitored by TLC and GC analysis. After 30 h, the aryl iodide was completely consumed. Then the reaction mixture was diluted by CH_2Cl_2 and filtered. The organic layer was successively washed with water (3 × 10 mL), dried over anhydrous $MgSO_4$, and then evaporated under reduced pressure. The crude products were isolated by flash column chromatography over silica to (petroleum ether) produce 22.3 mg (60%) of **3i** as a white solid (mp 88−89 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.53 (m, 4H), 7.45−7.41 (t, *J* = 8.0 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H).

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Supporting Information Available: Experimental procedures and characterization of coupling compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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