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Preparation of Unsymmetrical Biaryls by Pd(II)-Catalyzed Cross-Coupling of Aryl Iodides

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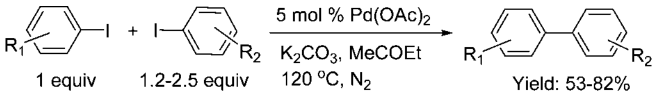
ABSTRACT



R_1, R_2: H, 4-OMe, 3-OMe, 2-OMe, 4-Me, 4-Cl, 4-Br, 3-NO_2, 3-CO_2Et;
and 1-iodonaphthalene

The Ullmann homo- and cross-couplings of aryl iodides are carried out to afford symmetrical and unsymmetrical biaryls in moderate to good yields in a catalytic system of $Pd(OAc)_2/K_2CO_3$/MeCOEt. The high selectivity of unsymmetrical biaryl products in cross-couplings mainly depends on the reactivity difference between two iodoarene substrates and their employed ratios.

Coupling of arenes to prepare symmetrical and unsymmetrical biaryls is one of the most useful methods in organic synthesis.[1] Since the Ullmann reaction, a reductive homocoupling of aryl halides mediated by excess copper as reductants was discovered one century ago,[2] a lot of advanced approaches especially on preparation of unsymmetrical biaryls have been developed including the cross-couplings of aryl halides with aryl organometallic reagents,[3] aryl halides with simple arenes,[4] and various arenes[5] in the presence of catalytic transition metals.

For the catalytic Ullmann-type cross-couplings of aryl halides, many attempts involving Pd,[6] Ni,[7] or Co[8] as catalysts with additional reductive agents such as Zn, Mn, amines, or alcohols have also been achieved successfully. Normally, we can find that the unsymmetrical biaryls could be prepared effectively from the cross-couplings between Ar−I and Ar−Br, Ar−I and Ar−Cl, or Ar−Br and Ar−Cl.[6−8] In contrast, the catalytic cross-couplings of only aryl iodides are rarely reported because of their poor selectivity on

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(6) For Pd-catalyzed Ullmann cross-couplings, see: (a) Amatore, C.; Carré, E.; Jutand, A.; Tanaka, H.; Ren, Q.; Torii, S. *Chem.−Eur. J.* **1996**, *2*, 957–966. (b) Hassan, J.; Hathroubi, C.; Gozzi, C.; Lemaire, M. *Tetrahedron* **2001**, *57*, 7845–7855. (c) Wang, L.; Zhang, Y.; Liu, L.; Wang, Y. *J. Org. Chem.* **2006**, *71*, 1284–1287.

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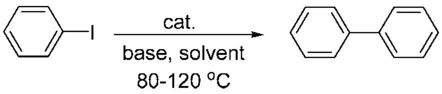
formation of unsymmetrical products.[6a] Herein, we describe a novel Pd(II)-catalyzed cross-coupling reaction of various aryl iodides in the absence of additional reductants.

Most recently, we found that benzene or naphthalene could be arylated with various aryl iodides in the presence of $Pd(OAc)_2$ through a possible Pd(II/IV) cycle.[4h] Then, we investigated the Pd(II)-catalyzed homocoupling of iodobenzene to produce biphenyl without additional reductants. Fortunately, biphenyl was produced from iodobenzene in 24% isolated yield, and the turnover number of Pd(II) catalyst was 24 when carried out neat with K_2CO_3 under nitrogen atmosphere after a long reaction time (Table 1, entry 1). After screening a few solvents and bases (Table 1, entries 2−14), we found that MeCOEt as the solvent with excess K_2CO_3 could enhance the yield of biaryl and reduce the reaction time effectively in this homocoupling of iodobenzene (Table 1, entries 5 and 6). Although both MeCOEt and K_2CO_3 were not used as the reducing agents under normal circumstances and no byproducts related to MeCOEt were detected by ^1H NMR analysis in the reaction mixtures, the isolated yield of biphenyl could be up to 82% especially under nitrogen atmosphere (Table 1, entry 5). However, in alcohol or nitrile (Table 1, entries 2 and 3), the potential reductants as solvents, the yields of biphenyl were not good. Notably, a few Pd(0) catalysts were also less active in this homocoupling under the same conditions (Table 1, entries 13 and 14). Meanwhile, both the amount of K_2CO_3 and the reaction temperature could affect the reaction rates and the product yields (Table 1, entries 7 and 8).

Table 1. Optimization of the Coupling of Iodobenzene[a]

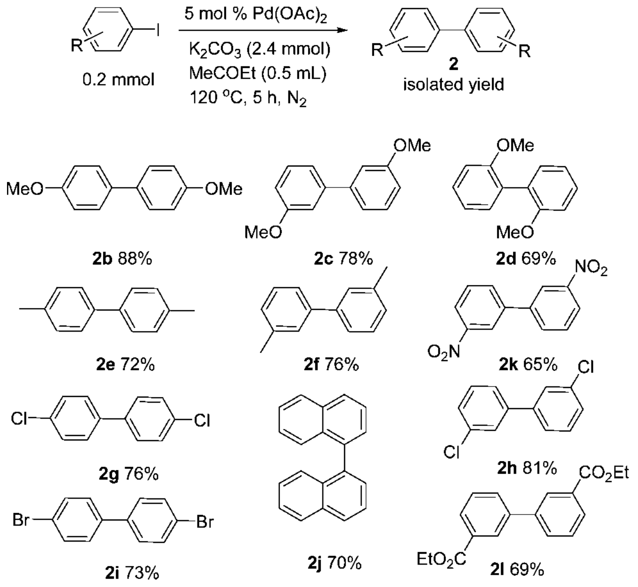


entry	catalyst	base	solvent	yield [b] [%]	convn [b][%]
1 [c]	$Pd(OAc)_2$	K_2CO_3	-	24	44
2	$Pd(OAc)_2$	K_2CO_3	EtOH	11	>99
3	$Pd(OAc)_2$	K_2CO_3	MeCN	54	62
4	$Pd(OAc)_2$	K_2CO_3	PhOEt	41	66
5	$Pd(OAc)_2$	K_2CO_3	MeCOEt	91(82)	94
6[d]	$Pd(OAc)_2$	K_2CO_3	MeCOEt	79(72)	>99
7[e]	$Pd(OAc)_2$	K_2CO_3	MeCOEt	70	84
8[f]	$Pd(OAc)_2$	K_2CO_3	MeCOEt	3	10
9[g]	$Pd(OAc)_2$	K_2CO_3	MeCOEt	64	71
10	$Pd(OAc)_2$	Na_2CO_3	MeCOEt	6	10
11	$Pd(OAc)_2$	Cs_2CO_3	MeCOEt	17	>90
12	$PdCl_2$	K_2CO_3	MeCOEt	17	62
13	Pd/C	K_2CO_3	MeCOEt	<1	<5
14	$Pd(PPh_3)_4$	K_2CO_3	MeCOEt	8	51

[a] Conditions: iodobenzene (0.2 mmol), catalyst (5 mol %, 0.01 mmol), base (2.4 mmol), solvent (0.5 mL), 120 °C, 5 h, under N_2. [b] Detected by GC, isolated yield in parentheses. [c] Iodobenzene (2 mmol), 6 days. [d] Under air. [e] K_2CO_3 (2.0 mmol). [f] 80 °C. [g] 1 mol % $Pd(OAc)_2$, 7 days.

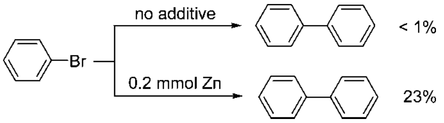
Subsequently, a variety of aryl iodides as substrates were examined in the Pd(II)-catalyzed homocouplings, and the results are shown in Scheme 1. Aryl iodides bearing not only electron-withdrawing groups but also electron-releasing groups underwent the homocouplings smoothly to afford the symmetrical biaryls in good yields, but more sterically hindered arenes such as 2-iodomesitylene did not generate the corresponding biaryls. On the other hand, the Pd(II)-catalyzed couplings of aryl C−Br or C−Cl bonds did not occur, which is in contrast to Pd(0)-catalyzed coupling reactions.[6] However, 4,4′-dibromo biphenyl was prepared in 73% yield with excellent selectivity from 1-bromo-4-iodobenzene, which provided the Br groups for further synthesis.

Scheme 1. Pd(II)-Catalyzed Coupling of Various Aryl Iodides



Interestingly, biphenyl was detected by GC analysis in 23% yield when Zn powder as the reductant was added into the coupling of bromobenzene, but only a trace amount of it was found without any additional reductants under the same conditions, as shown in Scheme 2. In the former reaction,

Scheme 2. Pd(II)-Catalyzed Coupling of Bromobenzenea



[a] Conditions: bromobenzene 0.2 mmol, $Pd(OAc)_2$ (5 mol %, 0.01 mmol), K_2CO_3 (2.4 mmol), MeCOEt (0.5 mL), 120 °C, 23 h, under N_2. GC yield based on bromobenzene.

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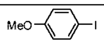
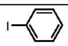
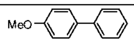
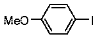
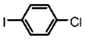
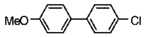
(7) For Ni-catalyzed Ullmann cross-couplings, see: (a) Meyer, G.; Rollin, Y.; Perichon, J. *J. Organomet. Chem.* **1987**, *333*, 263–267. (b) Gosmini, C.; Lasry, S.; Nédélec, J.-Y.; Périchon, J. *Tetrahedron* **1998**, *54*, 1289–1298. (c) Gosmini, C.; Nédélec, J.-Y.; Périchon, J. *Tetrahedron Lett.* **2000**, 201–203. (d) Gosmini, C.; Nédélec, J.-Y.; Périchon, J. *Tetrahedron Lett.* **2000**, *41*, 5039–5042.

Pd(0) was generated from the reduction of Pd(II) catalyst by Zn powder to activate aryl C−Br bonds the same as in the other Pd-catalyzed couplings of aryl halides with additional reductants.[6] However, in the latter one, Pd(0) was hardly formed. This might imply that this was a more sensitive catalytic system to different aryl halides, which would be suitable for the cross-coupling of aryl iodides.

Then, attempts were made to prepare unsymmetrical biaryls from aryl iodides using this catalytic system. To obtain high selectivity and good yields of unsymmetrical products in these preparations, we first studied the selection of substrate partners and the employed ratios of them. Herein, we observed that electron-rich aryl iodides were more reactive than electron-poor ones, although the latter ones should be attacked by Pd(II) catalysts in oxidative additions easily. Thus, if the reactivity difference between the two aryl iodides was not large due to them bearing different substituted groups, e.g., as in the case of 4-iodoanisole and iodobenzene, excess iodobenzene (2 equiv) was needed to avoid the formation of a homocoupling product from the more reactive 4-iodoansiole (1 equiv) according to the current study (Table 2, entry 2) and our previous reports.[4h,5b]

Table 2. Effects of Substrates and Ratios of Them on the Pd(II)-Catalyzed Cross-Coupling[a]

$$\text{Ar'-I} + \text{Ar-I} \xrightarrow[\text{120 °C, 12 h, N}_2]{\text{cat. Pd(OAc)}_2 \;/\; \text{K}_2\text{CO}_3\text{, MeCOEt}} \text{Ar'-Ar} + \text{Ar'}_2 + \text{Ar}_2$$

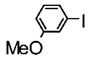
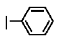
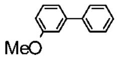
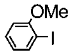
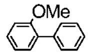
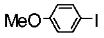
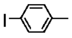
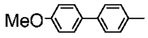
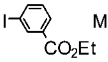
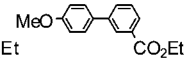
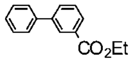
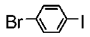
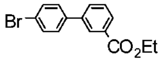
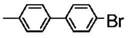
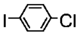
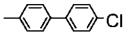
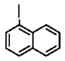
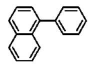
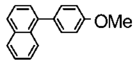
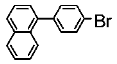
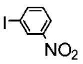
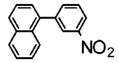
entry	Ar'-I [mmol]	Ar-I [mmol]	Ar'-Ar yield[b] [%]	Ar'$_2$ yield[b] [%]	Ar$_2$ Yield[c] [%]
	 **1b**	 **1a**	 **3ab**	**2b**	**2a**
1	0.2	0.6	81	<1	35
2	0.2	0.4	79	<1	20
3	0.2	0.2	35	37	25
4	0.4	0.2	12	59	11
	 **1b**	 **1g**	 **3bg**	**2b**	**2g**
5	0.2	0.4	65	<1	20
6	0.2	0.24	80	<1	14
7	0.2	0.2	61	11	19
8	0.2	0.16	55	32	20

[a] Conditions: Pd(OAc)$_2$ (5 mol %, 0.01 mmol), K$_2$CO$_3$ (2.4 mmol), MeCOEt (0.5 mL), 120 °C, 12 h, under N$_2$. [b] Isolated yield for Ar′−Ar and GC yield for Ar′$_2$ based on Ar′−I. [c] GC yield based on Ar−I.

Notably, if an electron-rich aryl iodide reacted with an electron-poor one, the major product was still the unsymmetrical biaryl when the ratio of them was reduced even to 1/1.2 (Table 2, entry 6).

Moreover, many pairs of aryl iodides were tested in the cross-coupling reactions, and the results are listed in Table 3. For the more electron-rich aryl iodides (Ar′−I) such as 4-iodoanisole or the more electron-poor ones (Ar−I) such as ethyl 3-iodobenzoate, the major products were the unsymmetrical biaryls (isolated yield 68−82%), and the symmetrical biaryls from the homocouplings of electron-rich aryl iodides (Ar′−I) were less than 1% by GC analysis when excess electron-poor aryl iodides were used (Table 3, entries 1−6). However, a small amount of homocoupling products from 1-iodonaphthalene were detected, although the

Table 3. Pd(II)-Catalyzed Cross-Coupling of Various Aryl Iodides[a]

entry	Ar'-I	Ar-I	Ar-Ar' yield[b] [%]	Ar'$_2$ yield[b] [%]	Ar$_2$ yield[c] [%]
1	 **1c**	 **1a**	 **3ac** 75	**2c** <1	**2a** 18
2[d]	**1c**	**1a**	**3ac** 63	**2c** <1	**2a** 3
3	 **1d**	**1a**	 **3ad** 78	**2d** <1	**2a** 24
4	 **1b**	 **1e**	 **3be** 68	**2b** <1	**2e** 19
5[e]	**1b**	 **1l**	 **3bl** 82	**2b** <1	**2l** 12
6	**1a**	**1l**	 **3al** 70	**2a** <1	**2l** 18
7	 **1i**	**1l**	 **3il** 70	**2i** <1	**2l** 14
8[f]	**1e**	**1i**	 **3ei** 54	**2e** <1	**2i** 17
9[f]	**1e**	 **1g**	 **3eg** 66	**2e** <1	**2g** 21
10	 **1j**	**1a**	 **3aj** 65	**2j** 10	**2a** 32
11	**1j**	**1b**	 **3bj** 53	**2j** 18	**2b** 40
12	**1j**	**1i**	 **3ij** 55	**2j** 11	**2i** 16
13	**1j**	 **1k**	 **3kj** 57	**2j** 32	**2k** 11

[a] Conditions: Ar′−I (0.2 mmol), Ar−I (0.4 mmol), Pd(OAc)$_2$ (5 mol %, 0.01 mmol), K$_2$CO$_3$ (2.4 mmol), MeCOEt (0.5 mL), 120 °C, 12 h, under N$_2$. [b] Isolated yield for Ar−Ar' and GC yield for Ar′$_2$ based on Ar′−I. [c] GC yield based on Ar−I. [d] 6 h. [e] Ar−I (0.24 mmol). [f] Ar−I (0.5 mmol).

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(8) For Co-catalyzed Ullmann cross-couplings, see: Amatore, M.; Gosmini, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 2089–2092.

cross-coupling products were the major ones (Table 3, entries 10−13). In the cases of 4-iodotoluene with 4-chloro- and with 4-bromo iodobenzene, respectively, the unsymmetrical biaryls were generated in moderate yields by decreasing the ratios of them to 1/2.5 (Table 3, entries 8 and 9). Although the homocoupling products from the excess electron-poor aryl iodides (Ar−I) were reduced by tuning the ratio of substrate partners (Table 2, entries 5 and 6) and reaction time (Table 3, entries 1 and 2) in some cases, they could not be avoided completely.

In conclusion, we established a convenient method for preparation of symmetrical and unsymmetrical biaryls by Pd(II)-catalyzed couplings of aryl iodides under mild conditions. The unsymmetrical biaryls as the major products could be obtained just by tuning the pairs of aryl iodide substrates and their ratios in this catalytic system. Further investigation on the reaction mechanism is ongoing.

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

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