Facile Preparation of Aryl Sulfides Using Palladium Catalysis under Mild Conditions

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Abstract: A convenient method for C–S cross-coupling of aryl bromides with various thiols has been developed that involves the use of a 1,1′-bis(diphenylphosphino)ferrocene (DPPF)-ligated palladium complex with *N*,*N*-diisopropylethylamine (DIPEA) as the base. This coupling is tolerant of a wide range of functional groups, including hydroxy, amino, cyano, nitro, formyl, and carboxyl groups.

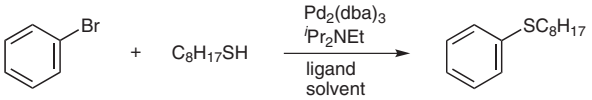
Key words: palladium, thiols, cross-coupling, C–S bond formation, sulfide

Palladium-catalyzed cross-coupling reactions of aryl halides with heteroatoms such as nitrogen, oxygen, and sulfur are powerful tools for the formation of carbon–heteroatom bonds. Aryl sulfides have been widely used as intermediates in synthetic chemistry and as products in the pharmaceutical industry.[1,2]

Among the various cross-coupling reactions, S-arylation has been less studied than the corresponding N- and O-arylations due to deactivation of the metal catalyst by the strong coordinating properties of sulfur compounds.[3] In 1980, Migita and co-workers first reported the cross coupling of thiols and aryl halides in the presence of $Pd(PPh_3)_4$ as catalyst and *t*-BuONa as base.[4] A wide range of transition-metals have been used to catalyze this coupling, including palladium,[5] nickel,[6] copper,[7] cobalt,[8] iron,[9] and indium.[10] Recently, a highly general palladium catalyst for S-arylation was reported by Hartwig and coworkers.[11] However, this process requires strongly basic reaction conditions and a well-defined, expensive ligand. Thus, we wanted to develop a new protocol for palladium-catalyzed S-arylation using *N*,*N*-diisopropylethylamine (DIPEA) as a base to avoid the need for strongly basic conditions.

Initially, the activity of several palladium catalysts was examined in the coupling of bromobenzene and 1-octanethiol. The results were summarized in Table 1. The reaction did not proceed smoothly with Pd-monophosphine ligand complexes (Table 1, entries 1–4), due to strong coordinating properties of thiols.[3] Thus, the more stable Pd–bidentate phosphine ligand complexes were used (Table 1, entries 5–8). Such ligands were more effective than the monophosphine ligands. Among them, 1,1′-bis(diphenylphosphino)ferrocene (DPPF)-ligated palladium showed the highest catalytic activity. We then examined the effect of solvents on this coupling. As shown in Table 1 (entries 9–17), DMF, DMSO and toluene were found to be efficient. Although the cross-coupling in toluene proceeded slower than that in DMF and DMSO (entries 9, 11, and 13), toluene was chosen as the solvent for further study because of its convenient boiling point.

Table 1 Optimization of Ligand and Solvent in C–S Cross-Coupling[a]



Entry	Ligand (mol%)	Solvent	Time (h)	Temp (°C)	Yield (%)[b]
1	Ph_3P(4.0)	DMF	3	110	3
2	P(*o*-Tol)$_3$ (4.0)	DMF	3	110	trace
3	P(2-Furyl)$_3$ (4.0)	DMF	3	110	trace
4	*t*-Bu_3P (4.0)	DMF	3	110	trace
5	$Ph_2P(CH_2)_2PPh_2$ (2.0)	DMF	3	110	5
6	$Ph_2P(CH_2)_3PPh_2$ (2.0)	DMF	3	110	15
7	$Ph_2P(CH_2)_4PPh_2$ (2.0)	DMF	3	110	57
8	DPPF (2.0)	DMF	3	110	99
9	DPPF (2.0)	DMF	1	110	95
10	DPPF (2.0)	DMSO	3	110	99
11	DPPF (2.0)	DMSO	1	110	84
12	DPPF (2.0)	toluene	3	reflux	99
13	DPPF (2.0)	toluene	1	reflux	72
14	DPPF (2.0)	THF	3	reflux	14
15	DPPF (2.0)	*t*-BuOH	3	reflux	20
16	DPPF (2.0)	dioxane	3	reflux	trace
17	DPPF (2.0)	DME	3	reflux	7

[a] Reaction conditions: $C_8H_{17}SH$ (1.0 equiv), [$Pd_2(dba)_3$] (1 mol%), DIPEA (1.1 equiv).
[b] Isolated yield.

The coupling of 1-octanethiol with aryl halides and their analogues was then studied (Table 2). It was found that

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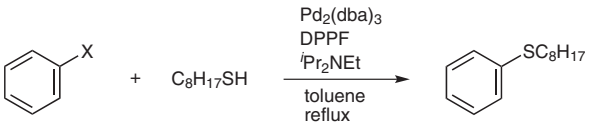
the use of bromide, iodide, or triflate substituents did not result in any significant change in the yields. Chlorobenzene and phenyl tosylate did not react under the same reaction conditions.

Table 2 Cross-Coupling of Aryl Halides and Their Analogues[a]



Entry	X	Time (h)	Yield (%)[b]
1	Cl	15	0
2	Br	1	99
3	I	1	99
4	OTs	15	0
5	OTf	1	99

[a] Reaction conditions: $C_8H_{17}SH$ (1.0 equiv), [$Pd_2(dba)_3$] (1 mol%), DPPF (2 mol%), DIPEA (1.1 equiv).
[b] Isolated yield.

Table 3 Cross-Coupling of Aryl Bromide with Thiols[a]

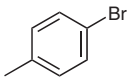
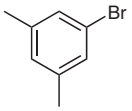
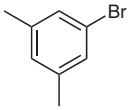
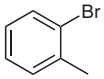
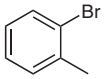
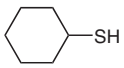
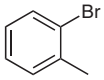
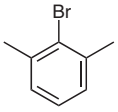
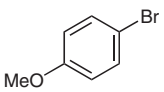
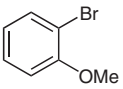
Entry	Aryl Bromide	Thiol	Yield (%)[b]
1		$C_8H_{17}SH$	99
2		$C_8H_{17}SH$	99
3[c]		PhSH	99
4		$C_8H_{17}SH$	99
5[d]			99
6[c]		PhSH	83
7		$C_8H_{17}SH$	–
8		$C_8H_{17}SH$	99
9		$C_8H_{17}SH$	99

Table 3 Cross-Coupling of Aryl Bromide with Thiols[a] (continued)

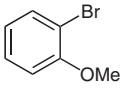
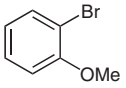
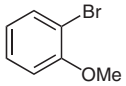
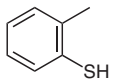
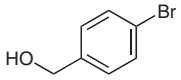
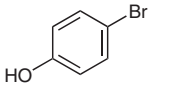
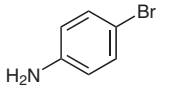
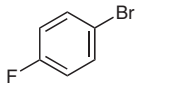
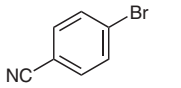
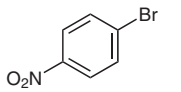
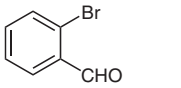
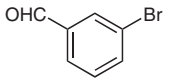
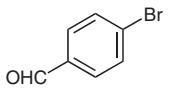
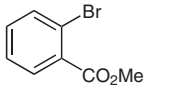
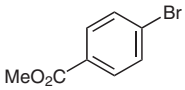
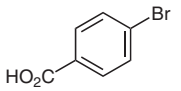
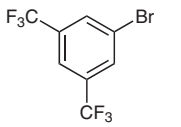
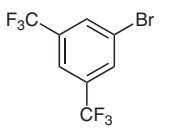
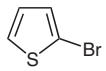
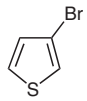
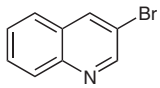
Entry	Aryl Bromide	Thiol	Yield (%)[b]
10[d]		*t*-BuSH	75
11[c]		PhSH	97
12[c]			99
13		$C_8H_{17}SH$	99
14[e]		$C_8H_{17}SH$	75
15[e,f]		$C_8H_{17}SH$	60
16		$C_8H_{17}SH$	99
17		$C_8H_{17}SH$	98
18		$C_8H_{17}SH$	99
19		$C_8H_{17}SH$	99
20		$C_8H_{17}SH$	99
21		PhSH	99
22		$C_8H_{17}SH$	99
23		PhSH	99
24[g]		$C_8H_{17}SH$	98
25		$C_8H_{17}SH$	99
26		PhSH	99

Table 3 Cross-Coupling of Aryl Bromide with Thiols[a] (continued)

Entry	Aryl Bromide	Thiol	Yield (%)[b]
27		$C_8H_{17}SH$	99
28		$C_8H_{17}SH$	95
29		$C_8H_{17}SH$	99

[a] Unless otherwise stated, reaction conditions: thiol (1.0 equiv), [$Pd_2(dba)_3$] (1 mol%), DPPF (2 mol%), DIPEA (1.1 equiv), reflux, 3 h, under N_2.
[b] Isolated yield.
[c] [$Pd_2(dba)_3$] (2 mol%), DPPF (4 mol%), DIPEA (1.1 equiv) were used.
[d] Heated at reflux for 6 h.
[e] [$Pd_2(dba)_3$] (2 mol%), DPPF (4 mol%), DIPEA (2.4 equiv) were used.
[f] Heated at reflux for 15 h.
[g] DIPEA (2.4 equiv) was used.

To study the scope of this procedure, the cross-coupling of various aryl bromides with alkyl and aromatic thiols was then studied (Table 3). In general, aryl bromides bearing either an electron-donating group or an electron-withdrawing group were successfully coupled with aromatic and alkyl thiols in good yields. This coupling is tolerant of a wide range of functional groups, including hydroxy, amino, cyano, nitro, formyl, and carboxyl groups. The coupling of aromatic thiols with aryl bromides bearing an electron-donating group required high catalyst loading (entries 3, 6, 11, and 12). Sterically demanding *ortho*-substituted aryl bromides reacted with secondary and tertiary thiols in the presence of the same catalyst loading, although longer reaction times were required (entries 5 and 10). The coupling of a more hindered di-*ortho*-substituted aryl bromide did not occur (entry 7). Aryl bromides with *para*-hydroxy or *para*-amino groups required high catalyst loading; in these cases the presence of the strong electron-donating group slowed down the oxidative addition of Pd(0) to the aryl bromide (entries 14 and 15).[12] The transesterification of a methoxy carbonyl group was not observed (entries 22 and 23). Heterocyclic aryl bromides coupled to form the corresponding sulfide in good yield (entries 27–29).

In conclusion, we have developed a convenient catalyst system for C–S cross-coupling.[13] The approach does not require a strong base and tolerates various functional groups.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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References and Notes

(1) Metzner, P.; Thuillier, A. *Sulfur Reagents in Organic Synthesis*; Katritzky, A. R.; Meth-Cohn, O.; Rees, C. W., Eds.; Academic Press: London, **1994**.
(2) (a) De Martino, G.; Edler, M. C.; La Regina, G.; Coluccia, A.; Barbera, M. C.; Barrow, D.; Nicholson, R. I.; Chiosis, G.; Brancale, A.; Hamel, E.; Artico, M.; Silvestri, R. *J. Med. Chem.* **2006**, *49*, 947. (b) Alcaraz, M. L.; Atkinson, S.; Cornwall, P.; Foster, A. C.; Gill, D. M.; Humphries, L. A.; Keegan, P. S.; Kemp, R.; Merifield, E.; Nixon, R. A.; Noble, A. J.; O'Beirne, D.; Patel, Z. M.; Perkins, J.; Rowan, P.; Sadler, P.; Singleton, J. T.; Tornos, J.; Watts, A. J.; Woodland, I. A. *Org. Process Res. Dev.* **2005**, *9*, 555. (c) Liu, L. P.; Stelmach, J. E.; Natarajan, S. R.; Chen, M. H.; Singh, S. B.; Schwartz, C. D.; Fitzgerald, C. E.; O'Keefe, S. J.; Zaller, D. M.; Schmatz, D. M.; Doherty, J. B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3979.
(3) Kondo, T.; Mitsudo, T. *Chem. Rev.* **2000**, *100*, 3205.
(4) (a) Migita, T.; Shimizu, T.; Asami, Y.; Shiobara, J.; Kato, Y.; Kosugi, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1385. (b) Kosugi, M.; Shimizu, T.; Migita, T. *Chem. Lett.* **1978**, 13.
(5) (a) Eichman, C. C.; Stambuli, J. P. *J. Org. Chem.* **2009**, *74*, 4005. (b) Dahl, T.; Tornoe, C. W.; Bang-Andersen, B.; Nielsen, P.; Jorgensen, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 1726. (c) Norris, T.; Leeman, K. *Org. Process Res. Dev.* **2008**, *12*, 869. (d) Lee, J. Y.; Lee, P. H. *J. Org. Chem.* **2008**, *73*, 7413. (e) Mispelaere-Canivet, C.; Spindler, J. F.; Perrio, S.; Beslin, P. *Tetrahedron* **2005**, *61*, 5253. (f) Itoh, T.; Mase, T. *Org. Lett.* **2004**, *6*, 4587.
(6) (a) Jammi, S.; Barua, P.; Rout, L.; Saha, P.; Punnlyamurthy, T. *Tetrahedron Lett.* **2008**, *49*, 1484. (b) Cao, Y.-Q.; Zhang, Z.; Guo, Y.-X.; Wu, G.-Q. *Synth. Commun.* **2008**, *38*, 1325. (c) Zhang, Y. G.; Ngeow, K. C.; Ying, J. Y. *Org. Lett.* **2007**, *9*, 3495. (d) Millois, C.; Diaz, P. *Org. Lett.* **2000**, *2*, 1705.
(7) (a) Bagley, M. C.; Dix, M. C.; Fusillo, V. *Tetrahedron Lett.* **2009**, *50*, 3661. (b) Haldón, E.; Álvarez, E.; Nicasio, M. C.; Pérez, P. J. *Organometallics* **2009**, *28*, 3815. (c) Herrero, M. T.; SanMartin, R.; Domínguez, E. *Tetrahedron* **2009**, *65*, 1500. (d) Jammi, S.; Sakthivel, S.; Rout, L.; Mukherjee, T.; Mandal, S.; Mitra, R.; Saha, P.; Punniyamurthy, T. *J. Org. Chem.* **2009**, *74*, 1971. (e) Larsson, P. F.; Correa, A.; Carril, M.; Norrby, P. O.; Bolm, C. *Angew. Chem. Int. Ed.* **2009**, *48*, 5691. (f) Prasad, D. J. C.; Naidu, A. B.; Sekar, G. *Tetrahedron Lett.* **2009**, *50*, 1411. (g) Rout, L.; Saha, P.; Jammi, S.; Punniyamurthy, T. *Eur. J. Org. Chem.* **2008**, 640. (h) She, J.; Jiang, Z.; Wang, Y. G. *Tetrahedron Lett.* **2009**, *50*, 593. (i) Xu, H. J.; Zhao, X. Y.; Deng, J.; Fu, Y.; Feng, Y. S. *Tetrahedron Lett.* **2009**, *50*, 434. (j) Xu, H. J.; Zhao, X. Y.; Fu, Y.; Feng, Y. S. *Synlett* **2008**, 3063. (k) Goyot, O.; Gingras, M. *Tetrahedron Lett.* **2009**, *50*, 1977. (l) Prasad, D. J. C.; Seker, G. *Synthesis* **2010**, 79.
(8) Wong, Y.-C.; Jayanth, T. T.; Cheng, C.-H. *Org. Lett.* **2006**, *8*, 5613.
(9) (a) Correa, A.; Carril, M.; Bolm, C. *Angew. Chem. Int. Ed.* **2008**, *47*, 2880. (b) Wu, J.-R.; Lin, C.-H.; Lee, C.-F. *Chem. Commun.* **2009**, 4450.
(10) Reddy, V. P.; Kumar, A. V.; Swapna, K.; Rao, K. R. *Org. Lett.* **2009**, *11*, 1697.

(11) (a) Alvaro, E.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 7858. (b) Fernández-Rodríguez, M. A.; Hartwig, J. F. *J. Org. Chem.* **2009**, *74*, 1663. (c) Fernandez-Rodriguez, M. A.; Shen, Q. L.; Hartwig, J. F. *Chem. Eur. J.* **2006**, *12*, 7782. (d) Fernandez-Rodriguez, M. A.; Shen, Q. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 2180.

(12) Amatore, C.; Pflüger, F. *Organometallics* **1990**, *9*, 2276.

(13) **Typical Experimental Procedure**: To a solution of $[Pd_2(dba)_3]$ (9.2 mg, 0.010 mmol) and DPPF (11.1 mg, 0.020 mmol) in toluene (1.0 mL) were added bromobenzene (0.11 mL, 1.0 mmol), DIPEA (0.19 mL, 1.1 mmol) and octanethiol (0.17 mL, 1.0 mmol) at r.t. The solution was stirred under reflux for 3 h then cooled to r.t. The reaction was quenched by addition of H_2O and extracted with EtOAc (3×10 mL), and the combined organic layers were washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel to afford octyl phenyl sulfide (222.3 mg, quantitative).