JOC Note

Efficient Stille Cross-Coupling Reaction Catalyzed by the $Pd(OAc)_2$/Dabco Catalytic System

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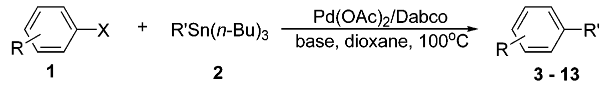
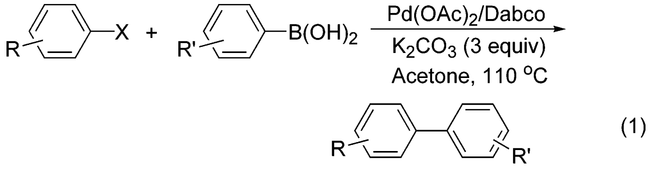


TONs: up to 980 000

An efficient $Pd(OAc)_2$/Dabco-catalyzed Stille cross-coupling reaction procedure has been developed. In the presence of $Pd(OAc)_2$ and Dabco (triethylenediamine), various aryl halides including aryl iodides, aryl bromides, and activated aryl chlorides were coupled efficiently with organotin compounds to afford the corresponding biaryls, alkene, and alkynes in good to excellent yields. Furthermore, high TONs [turnover numbers, up to 980 000 TONs for the coupling reaction of 1-bromo-4-nitrobenzene and furan-2-yltributyltin] for the Stille cross-coupling reaction were observed.

The palladium-catalyzed Stille cross-coupling reaction represents one of the most important transformations in constructing the carbon−carbon bonds in organic synthesis. For this reason, a number of effective palladium catalytic systems have been developed for the Stille cross-coupling reaction.[1−5] Generally, the combination of palladium catalysts with various phosphine ligands results in excellent yields and high efficiency.[1,2] However, most of the phosphine ligands are air-sensitive and expensive, which places significant limits on their synthetic applications.[6] On the other hand, it is desirable to be able to employ low catalyst loadings particularly for pharmaceutical and industrial application. Although many of the reported catalytic systems are effective, few reports employed the Stille reaction under <1 mol % loadings of palladium catalysts[2a,c,n−p,3a,e−g] (normal 1−5 mol % Pd).[1] Thus, the development of new and efficient phosphine-free palladium catalytic systems remains a potentially promising area for organic chemists.[3−5] Very recently, we found that Dabco was a highly efficient ligand for the palladium-catalyzed Suzuki−Miyaura cross-coupling reaction resulting in high TONs (up to 950 000 TONs for the reaction of PhI and *p*-chlorophenylboronic acid) (eq 1).[7,8] Thus, we expected to extend the use of this type of ligand to other palladium-catalyzed transformations. Here, we report a stable, inexpensive, and efficient $Pd(OAc)_2$/Dabco catalytic system for the Stille reactions of aryl halides with organotin compounds.



TONs: up to 950 000

To evaluate the efficiency of $Pd(OAc)_2$/Dabco in the Stille cross-coupling reaction, coupling of 4-bromoanisole (**1a**) with phenyltributyltin (**2a**) was first tested, and the

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(1) For reviews, see: (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Diederich, F.; Stang, P. J. *Metal-Catalyzed Cross-coupling Reactions*; Wiley−VCH: Weinheim, 1998. (c) Shirakawa, E.; Hiyama, T. *J. Organomet. Chem.* **1999**, *576*, 169. (d) Miyaura, N. *Cross-Coupling Reaction*; Springer: Berlin, 2002. (e) Hegedus, L. S. In *Oranometallics in Synthesis*; Schlosser, M., Ed.; J. Wiley & Sons: Chichester, 2002; p 1123. (f) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley−Interscience: New York, 2002. (g) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176. (h) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (i) Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704.

(2) For recent representative papers on phosphine-palladium catalysts, see: (a) Litter, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 2411. (b) Grasa, G. A.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 119. (c) Litter, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343 and references therein. (d) Kim, Y. M.; Yu, S. *J. Am. Chem. Soc.* **2003**, *125*, 1696. (e) Menzel, K.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 3718. (f) Kim, W.-S.; Kim, H.-J.; Cho, C.-G. *J. Am. Chem. Soc.* **2003**, *125*, 14288. (g) Dubbaka, S. R.; Vogel, P. *J. Am. Chem. Soc.* **2003**, *125*, 15292. (h) Tang, H.; Menzel, K.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5079. (i) Wolf, C.; Lerebours, R. *J. Org. Chem.* **2003**, *68*, 7077. (j) Wolf, C.; Lerebours, R. *J. Org. Chem.* **2003**, *68*, 7551. (k) Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 1132. (l) Su, W.; Urgaonkar, S.; Verkade, J. G. *Org. Lett.* **2004**, *6*, 1421. (m) Mazzola, R. D., Jr.; Giese, S.; Benson, C.; West, F. G. *J. Org. Chem.* **2004**, *69*, 220. (n) Högenauer, K. *Synlett* **2001**, 878. (o) Scrivanti, A.; Matteoli, U.; Beghetto, V.; Antonaroli, S.; Crociani, B. *Tetrahedron* **2002**, *58*, 6881. (p) Kim, N.; Kwon, M. S.; Park, C. M.; Park, J. *Tetrahedron Lett.* **2004**, *45*, 7057. (q) Crocian, B.; Antonaroli, S.; Canovese, L.; Uguagliat, P.; Visentin, F. *Eur. J. Inorg. Chem.* **2004**, 732. (r) Sünnemann, H. W.; de Meijere, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 895. (s) Ceccarelli, S.; Piarulli, U.; Gennari, C. *J. Org. Chem.* **2000**, *65*, 6254.

(3) For recent reviews and papers on N-heterocyclic carbene-palladium catalysts, see: (a) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290. (b) Yong, B. S.; Nolan, S. P. *Chemtracts: Org. Chem.* **2003**, 205. (c) Herrmann, W. A.; Öfele, K.; Preysing, D. v.; Schneider, S. K. *J. Organomet. Chem.* **2003**, *687*, 229. (d) Grasa, G. A.; Nolan, S. P. *Org. Lett.* **2001**, *3*, 119. (e) Hillier, A. C.; Grasa, G. A.; Viciu, M. S.; Lee, H. M.; Yang, C.; Nolan, S. P. *J. Organomet. Chem.* **2002**, *653*, 69.

(4) For recent representative papers on other phosphine-free ligand-palladium catalysts, see: (a) Albisson, D. A.; Bedford, R. B.; Lawrence, S. E.; Scully, P. N. *Chem. Commun.* **1998**, 2095. (b) Alonso, D. A.; Nájera, C.; Pacheco, M. C. *Org. Lett.* **2000**, *2*, 1823. (c) Chouday, B. M.; Madhi, S.; Chowdari, N. S.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2002**, *124*, 14127. (d) Davis, J. L.; Dhawan, R.; Arndtsen, B. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 590. (e) Amatore, C.; Bahsoun, A. A.; Jutand, A.; Meyer, G.; Ntepe, A. N.; Ricard, L. *J. Am. Chem. Soc.* **2003**, *125*, 4212. (f) Minière, S.; Cintrat, J.-C. *J. Org. Chem.* **2001**, *66*, 7385. (g) Serrano, J. L.; Fairlamb, I. J. S.; Sánchez, G.; García, L.; Pérez, J.; Vives, J.; López, G.; Crawforth, C. M.; Taylor, R. J. K. *Eur. J. Inorg. Chem.* **2004**, 2706.

(5) For a representative paper on diazabutadiene-palladium catalysts [Pd(Ar−BIAN)], see: van Asselt, R.; Elsevier, C. J. *Tetrahedron* **1994**, *50*, 323.

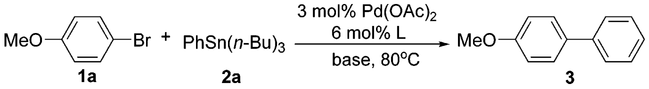
(6) (a) Pignolet, L. H., Ed. *Homogeneous Catalysis with Metal Phosphine Complexes*; Plenum: New York, 1983. (b) Parshall, G. W.; Ittel, S. *Homogeneous Catalysis*; J. Wiley and Sons: New York, 1992.

(7) Li, J.-H.; Liu, W.-J. *Org. Lett.* **2004**, *6*, 2809.

(8) For other papers on amine-palladium catalysts for the Suzuki cross-coupling reaction, see: (a) Tao, B.; Boykin, D. W. *Tetrahedron Lett.* **2003**, *44*, 7993. (b) Tao, B.; Boykin, D. W. *J. Org. Chem.* **2004**, *69*, 4330.

10.1021/jo048066q CCC: $30.25

TABLE 1. Palladium-Catalyzed Stille Coupling Reaction of 1a with 2a[a]



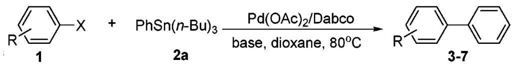
entry	ligand	base	solvent	yield (%)[b]
1	0	KF	dioxane	48
2	Dabco	KF	dioxane	84
3[c]	Dabco	KF	dioxane	82
4	$(i\text{-Pr})_2NEt$	KF	dioxane	26
5	$(c\text{-hexyl})_2NMe$	KF	dioxane	36
6	TMEDA	KF	dioxane	14
7	HMTA	KF	dioxane	72
8[d]	(−)-spartein e	KF	dioxane	10
9	Dabco	KF	DCE	15
10	Dabco	KF	DMF	27
11	Dabco	KF	acetone	57
12[e]	Dabco	Bu_4NF	dioxane	41
13	Dabco	Cs_2CO_3	dioxane	6
14	Dabco	K_2CO_3	dioxane	5
15	Dabco	Et_3N	dioxane	20

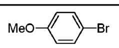
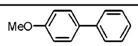
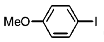
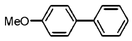
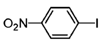
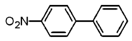
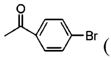
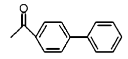
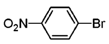
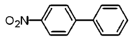
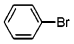
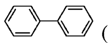
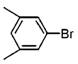
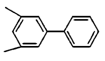
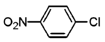
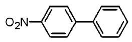
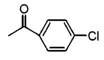
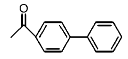
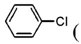
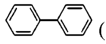
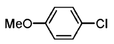
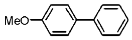
[a] Unless otherwise indicated, the reaction conditions were as follows: **1a** (0.5 mmol), **2a** (0.55 mmol), Pd(OAc)$_2$ (3 mol %), ligand (6 mol %), base (3 equiv), and solvent (5 mL) at 100 °C for 16 h. [b] Isolated yield. [c] Dabco (12 mol %). [d] 26 h. [e] The reaction was not clean, and some side products were observed.

results are summarized in Table 1. The results showed that Dabco was an effective ligand for the palladium-catalyzed Stille reaction. Without any ligands, only a 48% yield of the corresponding cross-coupled product **3** was isolated in the presence of 3 mol % of Pd(OAc)$_2$ and 3 equiv of KF (entry 1), whereas the yield of **3** was increased sharply to 84% when 6 mol % of Dabco was added (entry 2). An identical yield was obtained by even further increasing the loadings of Dabco to 12 mol % (entry 3). Other tertiary amines as the ligands were less effective than Dabco (entries 2 and 4−8). A series of solvents including dioxane, DCE (1,2-dichloroethane), DMF, and acetone were then examined; the highest yield was observed in dioxane (entries 2 and 9−11). Several bases were also investigated, and KF gave the best results (entries 2 and 12−15).

As demonstrated in Table 2, the Pd(OAc)$_2$/Dabco catalytic system is remarkably active and tolerant of a range of functionalities. The results showed that coupling of the organotin **2a** with a number of aryl halides, including aryl iodides (**1b** and **1c**), aryl bromides (**1d**−**g**), and activated aryl chlorides (**1h** and **1i**), was carried out smoothly and efficiently to afford good to excellent yields of the corresponding coupled products **3**−**7** with extremely high TONs in the presence of Pd(OAc)$_2$, Dabco, and base. By treatment of aryl iodides (**1b** and **1c**), activated aryl bromides (**1d** and **1e**), and activated aryl chlorides (**1h**) with **2a**, respectively, the loadings of the catalyst could be decreased to 0.0001 mol %, and desirable yields could still be obtained after prolonged heating (entries 5, 8, 11, 13, and 20, TONs up to 960 000), whereas for coupling of deactivated aryl bromides **1a** and **1g**, the results indicated that the catalytic efficiency decreased to some extent (entries 1, 2, and 15−17). For example, treatment of **1a** with **2a** afforded good yield of the corresponding product **3** for 24 h when the catalyst loadings were decreased to 0.001 mol % (75% yield, TONs = 75 000, entry 1). However, further decreasing the catalyst loadings to 0.0001 mol % led to a low yield (27% yield, TONs = 270 000, entry 2).

TABLE 2. Stille Coupling Reactions of Aryl Halides (1) with 2a Catalyzed by the Pd(OAc)$_2$/Dabco Catalytic System[a]

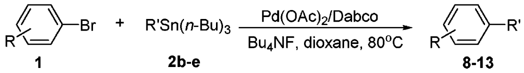


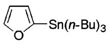
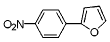
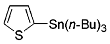
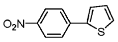
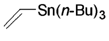
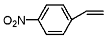
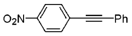
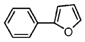
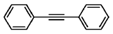
entry	ArX	Pd (mol%)	Additive	time (h)	product	yield (%)[b]
1	 (**1a**)	0.001	KF	24	 (**3**)	75
2	(**1a**)	0.0001	KF	24	(**3**)	27
3[c]	 (**1b**)	3	Bu_4NF	12	 (**3**)	90
4	(**1b**)	3	KF	12	(**3**)	95
5	(**1b**)	0.0001	KF	16	(**3**)	85
6	 (**1c**)	3	Bu_4NF	8	 (**4**)	100
7	(**1c**)	3	KF	12	(**4**)	96
8	(**1c**)	0.0001	Bu_4NF	16	(**4**)	96
9[c]	 (**1d**)	3	Bu_4NF	20	 (**5**)	33
10	(**1d**)	3	KF	12	(**5**)	90
11	(**1d**)	0.0001	Bu_4NF	24	(**5**)	78
12	 (**1e**)	3	Bu_4NF	10	 (**4**)	100
13	(**1e**)	0.0001	Bu_4NF	16	(**4**)	95
14	 (**1f**)	3	Bu_4NF	20	 (**6**)	93
15	 (**1g**)	3	Bu_4NF	20	 (**7**)	100
16	(**1g**)	3	KF	20	(**7**)	82
17	(**1g**)	0.001	Bu_4NF	24	(**7**)	77
18	 (**1h**)	3	Bu_4NF	12	 (**4**)	93
19	(**1h**)	0.001	Bu_4NF	16	(**4**)	82
20	(**1h**)	0.0001	Bu_4NF	16	(**4**)	62
21	 (**1i**)	3	Bu_4NF	12	 (**5**)	81
22	 (**1j**)	3	Bu_4NF	24	 (**6**)	9
23[d]	 (**1k**)	3	Bu_4NF	24	 (**3**)	–

[a] Unless otherwise indicated, the reaction conditions were as follows: **1** (0.5 mmol), **2a** (0.55 mmol), Pd(OAc)$_2$/Dabco (1:2), additive (3 equiv), and dioxane (5 mL) at 100 °C. [b] Isolated yield. [c] The reaction was not clean, and some side products were observed. [d] No reaction was observed.

The results also indicated that the additives affected the reaction (entries 3, 4, 6, 7, 9, 10, 15, and 16 in Table 2). Generally, Bu_4NF is more effective than KF.[1,2] For the present reaction, however, the efficacy of Bu_4NF and KF depended on aryl halides. By treatment of substrates **1c** and **1e**−**i** with **2a**, Pd(OAc)$_2$, and 6 mol % of Dabco (6 mol %), respectively, Bu_4NF as the additive provided higher yields of the desired cross-coupled products than did KF (entries 6, 7, and 12−22), whereas KF gave much higher yields for coupling of aryl halides bearing oxygen-contained groups **1a**, **1b**, and **1d**, respectively (entries 2 and 12 in Table 1; entries 3, 4, 9, and 10 in Table 2). It is noteworthy that all halides **1a**, **1b**, and **1d** were consumed completely, respectively, when Bu_4NF was

TABLE 3. Palladium-Catalyzed Stille Coupling Reactions of Aryl Bromides (1) with 2b−e Using Dabco as the Ligand[a]



entry	ArBr	R´Sn(n-Bu)$_3$	Pd (mol%)	time (h)	product	Yield (%)[b]
1	(**1e**)	 (**2b**)	3	16	 (**8**)	100
2	(**1e**)	(**2b**)	0.001	20	(**8**)	99
3	(**1e**)	(**2b**)	0.0001	40	(**8**)	98
4	(**1e**)	 (**2c**)	3	16	 (**9**)	100
5	(**1e**)	(**2c**)	0.0001	40	(**9**)	98
6	(**1e**)	 (**2d**)	3	16	 (**10**)	99
7	(**1e**)	(**2d**)	0.001	20	(**10**)	94
8	(**1e**)	(**2d**)	0.0001	40	(**10**)	64
9	(**1e**)	$Ph{-}{\equiv}{-}Sn(n\text{-}Bu)_3$ (**2e**)	3	16	 (**11**)	100
10	(**1f**)	(**2b**)	3	16	 (**12**)	98
11	(**1f**)	(**2e**)	3	16	 (**13**)	91

[a] Unless otherwise indicated, the reaction conditions were as follows: **1** (0.5 mmol), **2** (0.55 mmol), Pd(OAc)$_2$/Dabco (1:2), Bu$_4$NF (3 equiv), and dioxane (5 mL) at 100 °C. [b] Isolated yield.

used as the additive (entry 12 in Table 1; entries 3 and 9 in Table 2).[9] For the coupling reactions of another aryl halide bearing an oxygen-contained group **1i** with **2a**, however, good yield was observed in the presence of Bu$_4$NF (81%, entry 21). Unactivated aryl chlorides **1j** and **1k** were found to be unreactive under the present reaction conditions (entries 22 and 23).

The scope of the Pd(OAc)$_2$/Dabco catalytic system was further extended to the coupling reactions of aryl bromides **1e** and **1f** with other organotin reagents including furan-2-yltributyltin (**2b**), thiophen-2-yltributyltin (**2c**), vinyltributyltin (**2d**), and 2-phenylethynyltributyltin (**2e**), respectively, and the results are summarized in Table 3. In the presence of 3 mol % of Pd(OAc)$_2$, 6 mol % of Dabco, and 3 equiv of Bu$_4$NF, activated aryl bromide **1e** coupled efficiently with **2b**−**e**, respectively, to afford the corresponding desired products **8**−**11** in quantitative yields (entries 1, 4, 6, and 9). For coupling of aryl bromide **1f** with **2b** and **2e**, respectively, excellent yields were also obtained (entries 10 and 11). The results also demonstrated that aryl bromide **1e** was a suitable substrate at the loading of 0.0001 mol % of Pd (entries 3, 5, and 8). For example, 98% yield of **8** was still isolated after 40 h when coupling of **1e** with **2b** was carried out in the presence of 0.0001 mol % of Pd, 0.0002 mol % of Dabco, and 3 equiv of Bu$_4$NF (TONs = 980 000, entry 3).

In summary, we have developed an efficient Pd(OAc)$_2$/Dabco-ctalyzed Stille cross-coupling protocol for synthesizing various biaryls, alkene, and alkynes in good to excellent yields (maximum TONs up to 980 000 for the Stille cross-coupling reaction of 1-bromo-4-nitrobenzene and furan-2-yltributyltin). We also found that the efficacy of Bu$_4$NF and KF depended on aryl halides. Currently, further efforts to extend the application of these ligands and this protocol in organic synthesis are underway in our laboratory.

Experimental Section

(1) Typical Experimental Procedure for the Palladium-Catalyzed Stille Cross-Coupling Reaction. A mixture of aryl halide **1** (0.5 mmol), organotin **2** (0.55 mmol), Pd(OAc)$_2$ (3 mol %), Dabco (6 mol %), the indicated base (3 equiv), and dioxane (5 mL) was added to a sealed tube. The mixture was then stirred at 100 °C for the desired time until complete consumption of starting material as judged by TLC. After the mixture was filtered and evaporated, the residue was purified by flash column chromatography (hexane or hexane/ethyl acetate) to afford **3**−**13**.

(2) Typical Experimental Procedure for 0.0001 mol % of Pd and 0.0002 mol % of Dabco-Catalyzed Stille Cross-Coupling Reaction of 1-Bromo-4-nitrobenzene (1e) and Furan-2-yltributyltin (2b) (Entry 3 in Table 3). First, Pd(OAc)$_2$ (4.5 mg, 0.02 mmol) was dissolved in 200 mL of dioxane, and Dabco (4.5 mg, 0.04 mmol) was also dissolved in another 200 mL of dioxane. Next, 5 μL of Pd(OAc)$_2$ dioxane solution and 5 μL of Dabco dioxane solution were added to a mixture of 1-bromo-4-nitrobenzene (**1e**) (0.5 mmol), furan-2-yltributyltin (**2b**) (0.55 mmol), Bu$_4$NF (3 equiv), and dioxane (5 mL) in a sealed tube, respectively (by syringe). The mixture was stirred at 100 °C for 40 h as determined by TLC. After the mixture was filtered and evaporated, the residue was purified by flash column chromatography (hexane) to afford 98% yield of **8** (TONs: 980 000).

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Supporting Information Available: Analytical data and spectra (^{1}H and ^{13}C NMR) for all products **3**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[9] The reaction was not clean, and some side products were observed. Structures of the side products could not be determined by ^{1}H NMR and ^{13}C NMR spectra.