Available online at www.sciencedirect.com

ScienceDirect

Tetrahedron Letters

Tetrahedron Letters 48 (2007) 2707–2711

Palladium catalyzed atom-efficient cross-coupling reactions of triarylbismuths with aryl bromides

Maddali L. N. Rao,* Debasis Banerjee and Deepak N. Jadhav

Department of Chemistry, Indian Institute of Technology, Kanpur 208 016, India

Received 8 December 2006; revised 4 February 2007; accepted 14 February 2007
Available online 17 February 2007

Abstract—Aryl bromides (3 equiv) were coupled efficiently with triarylbismuths (1 equiv) in an atom-efficient way using the $Pd(OAc)_2/PPh_3$ catalytic system in the presence of K_3PO_4 as base in DMF at 90 °C, providing excellent yields of the cross-coupled biaryls in short reaction times.

The exciting potential of metal-catalyzed cross-coupling reactions for C–C bond formation has been amply demonstrated in organic synthesis.[1] The well-known Suzuki, Stille, Negishi and Hiyama cross-coupling reactions involving organoboron, organotin, organozinc and organosilicon reagents amongst others are popular methods in this category.[2–5] Besides, there is a growing importance of these reactions in industry[6] for the synthesis of pharmaceutically active ingredients, agrochemicals and fine chemicals. Importantly, some of these methods suffer from drawbacks such as atom efficiency and stoichiometric loading of organometallic reagents. Thus, the development of atom-efficient organometallic reagents to react with more than 1 equiv of the electrophilic coupling reagents reduces the stoichiometric loading of the organometallic reagents. In this context, triarylbismuths offer the required potential as atom-efficient organometallic reagents for C–C bond formation. Triarylbismuths can be readily prepared by known procedures, they are nontoxic and are stable to air and some are commercially available.[7]

The unique advantage associated with triarylbismuths, unlike with organoboron, organotin, organosilicon and other reagents is that they can react with 3 equiv of electrophilic reagents. Despite this obvious advantage, only a few reactions involving triarylbismuths for C–C bond formation have been reported.[1b,7–9] The known cross-coupling reactivity of triarylbismuths with aryl bromides involves long reaction times and with varied reactivity profiles of the aryl bromides.[8a] Hence, to expand the scope and reactivity of triarylbismuths, development of new and efficient catalytic protocols is in demand. Herein, we report a highly efficient palladium catalyzed protocol for an atom-efficient coupling of triarylbismuths with aryl bromides.

Recently, DABCO has served as an efficient ligand in palladium catalyzed cross-coupling reactions.[10] Hence, in our initial efforts, we screened the cross-coupling reactivity of *p*-bromoacetophenone (3.3 equiv) as a representative example with $BiPh_3$ (1 equiv) using $Pd(OAc)_2$ (0.05 equiv with respect to $BiPh_3$) in the presence of DABCO as ligand using different bases and solvents (Table 1, entries 1–4). Unfortunately, DABCO failed to promote formation of the corresponding cross-coupling products. Further screening with triphenylphosphine as ligand was found to be beneficial. As shown in Table 1, the reactions carried out in different solvents in the presence of triphenylphosphine and K_3PO_4 as base revealed DMF as a suitable solvent giving 56% cross-coupling conversion (entry 7). Other solvents such as toluene, 1,4-dioxane, 1,2-dimethoxyethane (DME), acetone, tetrahydrofuran, acetonitrile and *N*-methyl-2-pyrrolidone (NMP) provided very poor conversions (entries 5, 6 and 8–13). In addition, the reactions carried out at lower temperatures did not produce good conversions (entries 14 and 15). Additional experiments proved that $Pd(OAc)_2$ (0.1 equiv)/PPh_3 (0.4 equiv) along with K_3PO_4 (6 equiv) in DMF at 90 °C were the ideal reagent combination affording high conversions of the

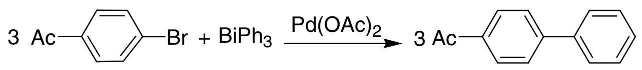
---

Keywords: Cross-coupling; Triarylbismuth; Aryl bromides; Atom-efficient; Palladium catalyzed.

* Corresponding author. Tel./fax: +91 512 2597532; e-mail: maddali@iitk.ac.in

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.02.068

Table 1. Catalyst screening[a]

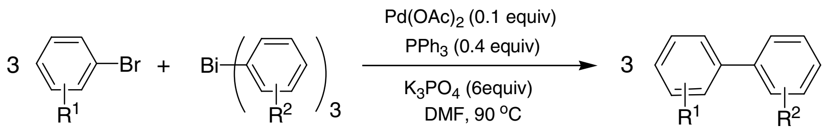


Entry	Base	$Pd(OAc)_2$ (equiv)	Ligand (equiv)	Solvent	Temp (°C)	Time (h)	Conv[b] (%)
1	K_2CO_3	0.05	DABCO (0.2)	Acetone	90	12	<1
2	K_2CO_3	0.05	DABCO (0.2)	DME	90	12	<1
3	K_3PO_4	0.05	DABCO (0.2)	Dioxane	90	12	<1
4	Cs_2CO_3	0.05	DABCO (0.2)	Dioxane	90	12	<1
5	K_3PO_4	0.05	PPh_3 (0.1)	DME	90	12	10
6	K_3PO_4	0.05	PPh_3 (0.1)	NMP	90	12	12
7	K_3PO_4	0.05	PPh_3 (0.1)	DMF	90	12	56
8	K_3PO_4	0.05	PPh_3 (0.2)	Acetone	90	1	2
9	K_3PO_4	0.05	PPh_3 (0.2)	THF	90	1	4
10	K_3PO_4	0.05	PPh_3 (0.2)	CH_3CN	90	1	14
11	K_3PO_4	0.05	PPh_3 (0.2)	Toluene	90	1	17
12	K_3PO_4	0.05	PPh_3 (0.2)	Dioxane	90	1	18
13	K_3PO_4	0.05	PPh_3 (0.2)	DME	90	1	4
14	K_3PO_4	0.05	PPh_3 (0.2)	DMF	60	1	32
15	K_3PO_4	0.05	PPh_3 (0.2)	DMF	30	1	31
16	K_3PO_4	0.1	PPh_3 (0.4)	DMF	90	2	92
17	K_3PO_4	0.1	PPh_3 (0.4)	DMF	90	1	92
18	None	0.1	PPh_3 (0.4)	DMF	90	1	18
19	K_3PO_4	0.1	None	DMF	90	1	<1
20	K_3PO_4	None	PPh_3 (0.4)	DMF	90	1	<1

[a] Conditions: equiv ratios are based on $BiPh_3$ (1 equiv), aryl bromide (3.3 equiv), base (6 equiv) and solvent (3 mL).

[b] Based on GC analysis.

Table 2. Cross-coupling reaction of triarylbismuths with aryl bromides[12]



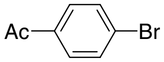
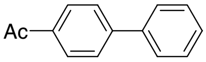
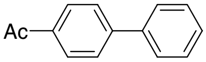
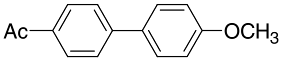
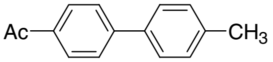
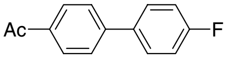
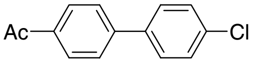
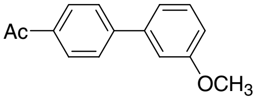
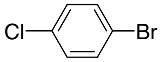
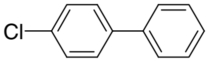
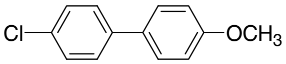
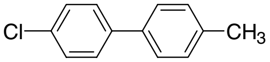
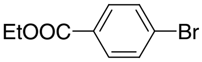
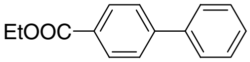
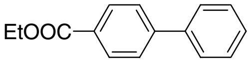
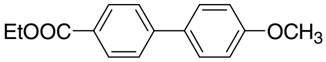
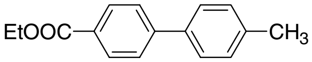
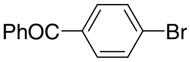
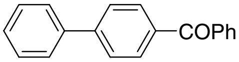
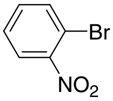
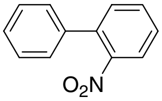
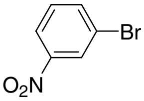
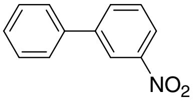
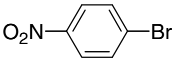
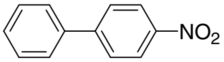
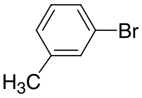
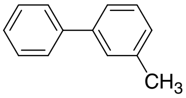
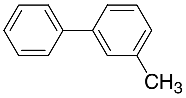
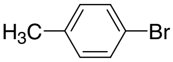
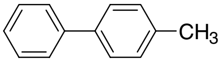
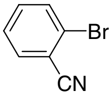
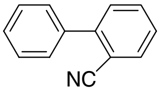
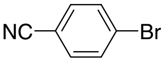
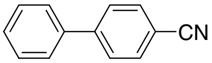
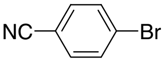
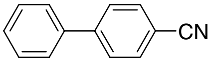
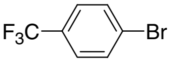
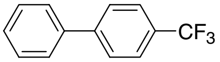
Entry	Ar–Br	$BiAr_3$	Time (h)	Product	Yield[a,b,c] (%)
1		4-H	2		92
2		4-H	1		85
3		$4-OCH_3$	1		86
4		$4-CH_3$	1		89
5		4-F	1		73
6		4-Cl	1		65
7		$3-OCH_3$	1		74
8		4-H	1		62
9		$4-OCH_3$	1		76

Table 2 (*continued*)

Entry	Ar–Br	$BiAr_3$	Time (h)	Product	Yield[a,b,c] (%)
10		4-CH_3	1		72
11		4-H	1		83
12		4-H	2		88
13		4-OCH_3	1		94
14		4-CH_3	1		94
15		4-H	1		85
16		4-H	1		95
17		4-H	1		91
18		4-H	1		92
19		4-H	1		60
20		4-H	2		72
21		4-H	1		49
22		4-H	1		72
23		4-H	1		75
24		4-H	2		85
25		4-H	1		76

[a] Conditions: equiv ratios are based on $BiAr_3$: $BiAr_3$ (1 equiv), aryl bromide (3.5 equiv), $Pd(OAc)_2$ (0.1 equiv)/PPh_3 (0.4 equiv), K_3PO_4 (6 equiv), DMF (3 mL), 90 °C.

[b] In the cases of observed poor cross-coupling reactivity, homo coupled biphenyls resulting from the triarylbismuths were also formed as side products.

[c] Isolated yields after purification by column chromatography. All the products were characterized by ^1H, ^{13}C NMR and IR spectral data and by comparison with the literature reported values.

cross-coupled products (entries 16 and 17). Control reactions carried out without base (entry 18), phosphine ligand (entry 19) and palladium catalyst (entry 20), revealed that catalyst, ligand and base were necessary to achieve efficient cross-coupling reactivity. In addition, it was also found that 6 equiv of base were essential for the cross-coupling of 3 equiv of aryl bromide with the three aryl groups from 1 equiv of triphenylbismuth.

Thus, we investigated the cross-coupling reaction of various triarylbismuths with a variety of electronically diverse aryl bromides (Table 2). The reactivity and substrate scope provided by the aryl bromides under the present conditions are excellent giving good to high yields of the cross-coupled products. As shown in Table 2, the cross-coupling reaction of various functionalized aryl bromides occurred efficiently with different triarylbismuths. For example, the reaction of 4-bromoacetophenone with a range of electronically diverse $BiAr_3$ reagents produced good to high yields of the corresponding cross-coupled products (entries 1–7). Further, a variety of functionalized electron-rich and electron-poor aryl bromides reacted very well with triarylbismuths leading to good to high yields of the cross-coupled biaryls (entries 8–25). Evidently, the coupling reaction of triarylbismuths with electron-poor aryl bromides resulted in high yields, while the corresponding reaction with electron-rich aryl bromides produced moderate yields. It is noteworthy that bromobenzene substituted with 2-nitro, 3-nitro and 4-nitro groups reacted efficiently giving high yields of the corresponding cross-coupled products (entries 16–18). 1-Bromo-2-nitrobenzene reacted without any discernible steric encumbrance to afford the corresponding 2-nitrobiphenyl product in 95% yield (entry 16).[11] It also emerged that the reactivity of a range of triarylbismuths in the cross-coupling reaction was unaffected by a change in the electronics of the aryl rings in the triarylbismuths.

In conclusion, we have disclosed a palladium catalyzed protocol for the cross-coupling reaction of triarylbismuths with aryl bromides. The catalytic system employs readily available $Pd(OAc)_2$ and PPh_3 as ligand along with K_3PO_4 as base. The excellent cross-coupling reactivity of aryl bromides observed with various triarylbismuths clearly underscores the efficiency of the present protocol in addition to the wide scope of triarylbismuths as atom-efficient reagents for carbon–carbon bond formation in organic synthesis.

Acknowledgements

We thank DST, India and IIT-Kanpur for supporting this work. D.B. and D.N.J. thank IIT-Kanpur and CSIR, New Delhi, respectively, for research fellowships.

References and notes

1. Selected reviews and books on metal catalyzed coupling reactions, see: (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442; (b) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359; (c) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633; (d) *Cross-Coupling Reactions: A Practical Guide*; Miyaura, N., Ed.; Topics in Current Chemistry, Series 219; Springer: New York, 2002; (e) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; (f) Christmann, U.; Vilar, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 366.
2. (a) Kudo, N.; Perseghini, M.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1282; (b) Gonzalez-Bobes, F.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 5360; (c) Powell, D. A.; Maki, T.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 510; (d) Billingsley, K. L.; Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3484; (e) Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6173; (f) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685; (g) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871; (h) Molander, G. A.; Yokoyama, Y. *J. Org. Chem.* **2006**, *71*, 2493; (i) Molander, G. A.; Felix, L. A. *J. Org. Chem.* **2005**, *70*, 3950; (j) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302.
3. (a) Miura, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2201; (b) Singh, R.; Viciu, M. S.; Kramareva, N.; Navarro, O.; Nolan, S. P. *Org. Lett.* **2005**, *7*, 1829; (c) Kells, K. W.; Chong, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 15666; (d) Wiskur, S. L.; Korte, A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 82; (e) Denmark, S. E.; Baird, J. D. *Org. Lett.* **2004**, *6*, 3649; (f) Denmark, S. E.; Ober, M. H. *Org. Lett.* **2003**, *5*, 1357; (g) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527; (h) Molander, G. A.; Yun, C.-S.; Ribagorda, M.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 5534.
4. (a) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818; (b) Netherton, M. R.; Dai, C.; Neuschutz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099; (c) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028; (d) Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2001**, *123*, 6439; (e) Molander, G. A.; Rivero, M. R. *Org. Lett.* **2002**, *4*, 107; (f) Molander, G. A.; Biolatto, B. *Org. Lett.* **2002**, *4*, 1867.
5. (a) Denmark, S. E.; Baird, J. D. *Org. Lett.* **2006**, *8*, 793; (b) Dubbaka, S. R.; Vogel, P. *J. Am. Chem. Soc.* **2003**, *125*, 15292; (c) Dubbaka, S. R.; Vogel, P. *Org. Lett.* **2004**, *6*, 95; (d) Perez, I.; Sestelo, J. P.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155; (e) Su, W.; Urgaonkar, S.; McLaughlin, P. A.; Verkade, J. G. *J. Am. Chem. Soc.* **2004**, *126*, 16433; (f) Zhang, Y.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 15964.
6. Rouhi, A. M. *Chem. Eng. News* **2004**, *82*, 49.
7. *Organobismuth Chemistry*; Suzuki, H., Matano, Y., Eds.; Elsevier: Amsterdam, 2001.
8. (a) Rao, M. L. N.; Yamazaki, O.; Shimada, S.; Tanaka, T.; Suzuki, Y.; Tanaka, M. *Org. Lett.* **2001**, *3*, 4103; (b) Venkatraman, S.; Li, C.-J. *Tetrahedron Lett.* **2001**, *42*, 781; (c) Rao, M. L. N.; Venkatesh, V.; Jadhav, D. N. *Tetrahedron Lett.* **2006**, *47*, 6975; (d) Barton, D. H. R.; Ozbalik, N.; Ramesh, M. *Tetrahedron* **1988**, *44*, 5661; (e) Wada, M.; Ohki, H. *J. Synth. Org. Chem. Jpn.* **1989**, *47*, 425; (f) Suzuki, H.; Murafuji, T.; Azuma, N. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1593; (g) Asano, R.; Moritani, I.; Fujiwara, Y.; Teranishi, S. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2910; (h) Kawamura, T.; Kikukawa, K.; Takagi, M.; Matsuda, T. *Bull Chem. Soc. Jpn.* **1977**, *50*, 2021.
9. Recently, organobismuth compounds such as azabismocines and organobismuth dialkoxides were used in cross-coupling reactions with 1 equiv of electrophilic reagents,

see: (a) Rao, M. L. N.; Shimada, S.; Tanaka, M. *Org. Lett.* **1999**, *1*, 1271; (b) Rao, M. L. N.; Shimada, S.; Yamazaki, O.; Tanaka, M. *J. Organomet. Chem.* **2002**, *659*, 117; (c) Shimada, S.; Yamazaki, O.; Tanaka, T.; Rao, M. L. N.; Suzuki, Y.; Tanaka, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1845; (d) Yamazaki, O.; Tanaka, T.; Shimada, S.; Suzuki, Y.; Tanaka, M. *Synlett* **2004**, *11*, 1921.

10. (a) Li, J.-H.; Liu, W.-J. *Org. Lett.* **2004**, *6*, 2809; (b) Li, J.-H.; Liang, Y.; Wang, D.-P.; Liu, W.-J.; Xie, Y.-X.; Yin, D.-L. *J. Org. Chem.* **2005**, *70*, 2832; (c) Li, J.-H.; Liu, W.-J.; Xie, Y.-X. *J. Org. Chem.* **2005**, *70*, 5409.
11. Gonzalez, R. R.; Liguori, L.; Carrillo, A. M.; Bjorsvik, H.-R. *J. Org. Chem.* **2005**, *70*, 9591.
12. *Representative procedure for the cross-coupling reaction of aryl bromides* (Table 2): A hot oven-dried Schlenk tube was charged with 4-bromoacetophenone (0.173 g, 0.87 mmol) followed by triphenylbismuth (0.110 g, 0.25 mmol), K_3PO_4 (0.318 g, 1.5 mmol), PPh_3 (0.026 g, 0.1 mmol), $Pd(OAc)_2$ (0.0056 g, 0.025 mmol) and solvent DMF (3 mL) under a nitrogen atmosphere. The mixture was stirred at an oil bath temperature of 90 °C for 1 h. Then the reaction mixture was cooled to room temperature, quenched with dil HCl (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic extract was washed with water (2 × 10 mL) and brine (10 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was further purified by column chromatography on silica gel (100–200 mesh) using hexane–ethyl acetate (8:2) as eluent to afford pure 4-acetylbiphenyl (0.125 g) in 85% yield. The product was characterized by comparing ^1H, ^{13}C NMR and IR data with the reported data.