



Pd(0)/C-catalyzed cross-couplings of acyl chlorides with triarylbismuths as atom-efficient sub-stoichiometric multi-coupling reagents

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ABSTRACT

Aromatic and hetero-aromatic acyl chlorides were efficiently cross-coupled with triarylbismuths as atom-efficient nucleophilic organometallic coupling reagents in sub-stoichiometric amounts using catalytic Pd(0)/C. Thus, the coupling reactions of various triarylbismuths with a variety of acyl chlorides furnished a plethora of both symmetrical/unsymmetrical aromatic and hetero-aromatic ketones in high yields.

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Organometallic coupling reactions such as the Suzuki, Negishi, and Stille have enriched the art of organic synthesis in recent times.¹ This has attracted the attention to develop various palladium-catalyzed protocols using organo-boron, -zinc, -tin, and other organometallic reagents.^{1,2} In general, palladium catalytic protocols often utilize palladium pre-catalysts in combination with a variety of phosphine ligands.² While the use of Pd(0)/C as catalyst with or without phosphines is still limited for coupling reactions,³ utility of Pd(0)/C in catalytic hydrogenations is well known in organic synthesis. Thus, there is a wide scope for the development of new protocols using Pd(0)/C.^{3–6} The importance of Pd(0)/C stems from the fact that this catalytic system is heterogeneous in nature, can be easily separated from product, which is cheap and easily available.³

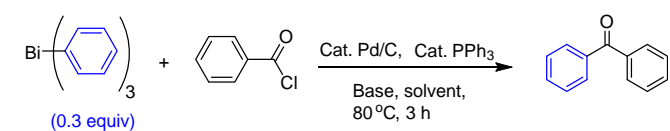
Synthesis of aromatic ketones using cross-coupling methodology outweighs the traditional Friedel–Crafts acylation,⁷ as this approach facilitates the synthesis of isomeric ketones in a facile manner. Further, use of higher amounts of Lewis acid is another inevitable draw back associated with Friedel–Crafts method. On the other hand, coupling reactions of acyl chlorides with 1 equiv of aryl-boron, -zinc, or -tin are useful for the synthesis of ketones under metal-catalyzed conditions.^{8,9} Notably in this context, triarylbismuths as atom-efficient, sub-stoichiometric, and multi-coupling reagents provides an additional coupling opportunity with its three aryl groups under metal-catalyzed conditions.^{10a} Thus, if all the three aryl groups react, sub-stoichiometric amount

(~0.33 equiv) of triarylbismuth is enough to cross-couple with 1 equiv of acyl chloride to obtain 1 equiv of the corresponding ketone stoichiometrically. This advantage of triarylbismuths will have direct bearing in large-scale preparations involving such coupling reactions. As known, triarylbismuths are non-toxic, stable, and can be easily prepared using standard methods.^{11a} Our recent interest to develop triarylbismuths as an atom-efficient, sub-stoichiometric, and multi-coupling organometallic reagents unraveled new efficient cross-coupling reactivity of these reagents under palladium catalysis in short reaction times.¹⁰ In continuation, we report herein, the Pd(0)/C-catalyzed coupling reaction of acyl chlorides with sub-stoichiometric amounts of triarylbismuths for atom-efficient synthesis of ketones.

The catalytic activity of Pd(0)/C was studied with triphenylbismuth and benzoyl chloride as a model coupling reaction (Table 1). The coupling was carried out with Pd(0)/C (0.003 equiv) and PPh₃ (0.075 equiv) in the presence of triethylamine (0.3 equiv) at 80 °C for 3 h in tetrahydrofuran solvent. Significantly, the reaction furnished 69% cross-coupling conversion and 51% isolated yield of cross-coupled product, benzophenone (entry 1). Encouraged by this, the reactivity of Pd(0)/C was further studied with different catalytic loadings. These combinations provided good to moderate conversions (entries 2–4). Importantly, the coupling reaction carried out without triphenylphosphine provided very poor conversion (entry 5). With the additional screening carried out in different solvents, it was found that 1,4-dioxane, toluene, 1,2-dimethoxyethane, and acetonitrile are not suitable for this reaction (entries 6–9).

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Table 1
Screening conditions^{a–c}

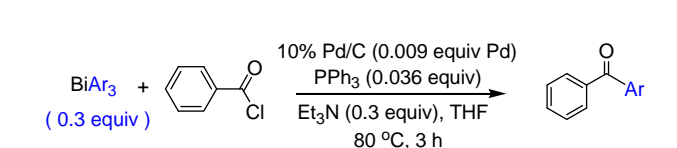
Entry	Catalyst (equiv)	Ligand (equiv)	NEt ₃ (equiv)	Solvent	Conv (%)
1	0.003	0.075	0.3	THF	69 (51)
2	0.003	0.012	None	THF	73
3	0.015	0.06	None	THF	66
4	0.003	0.006	None	THF	44
5	0.003	None	0.3	THF	04
6	0.003	0.012	None	Dioxane	25
7	0.003	0.012	None	Toluene	6
8	0.003	0.012	None	DME	5
9	0.003	0.012	None	MeCN	1
10	0.006	0.024	None	THF	88 (82)
11	0.009	0.036	None	THF	89 (86)
12	0.009	0.036	None	THF	42 (41) ^d
13	None	0.036	None	THF	6
14	0.009	0.036	0.3	THF	91 (90)

^a Conditions: PhCOCl (1 equiv), BiPh₃ (0.303 equiv), solvent (3 mL).^b Conversions are based on GC analysis of the crude reaction mixture. Isolated yield based on benzoyl chloride given in parentheses.^c Homo-coupling biphenyl from triaryl bismuths formed as side product.^d Reaction carried out at 60 °C.

Further, catalyst Pd(0)/C loading up to 0.009 equiv provided increased conversion along with 86% of isolated ketone (entries 10 and 11). Lowering the temperature to 60 °C produced inferior conversion to ketone (entry 12). A control carried out without Pd(0)/C did not produce appreciable amount of ketone (entry 13). Importantly, we have also observed some inconsistency in yields when reactions were carried out without triethylamine. So, we further studied the reaction in presence of triethylamine and obtained ketone upto 90% isolated yield (entry 14). Hence, we decided to utilize acyl chloride (1 equiv), BiAr₃ (0.303 equiv), Pd/C (0.009 equiv), PPh₃ (0.036 equiv), and NEt₃ (0.30 equiv) in THF at 80 °C for our further studies with different triaryl bismuths and acyl chlorides.

The new efficient protocol thus obtained above with Pd(0)/C was studied further for elaboration with different triaryl bismuths and acyl chlorides.¹² Firstly, efforts were made to establish cross-coupling ability of various electronically diverse triaryl bismuths and heteroaryl bismuths with benzoyl chloride. The various functionalized triaryl bismuths with both electron-rich and -deficient aryl groups substituted with -methyl, -methoxy, -fluoro, -chloro, -formyl, and -acetyl groups were studied with benzoyl chloride as given in Table 2. This study revealed an efficient cross-coupling reactivity of various triaryl bismuths to give high yield of ketones with benzoyl chloride. (entries 1–9). The coupling reactivity of tri-thiophen-2-ylbismuth was efficient with benzoyl chloride and furnished the corresponding mixed ketone in good yield (entry 10). Further, it also clearly establishes the atom-efficient and multi-coupling reactivity of triaryl bismuths, as we have used only 0.3 equiv of triaryl bismuth for cross-coupling reaction with 1 equiv of acyl chloride in all these reactions.

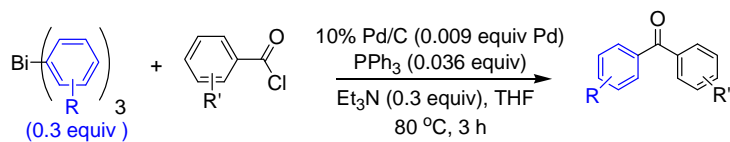
The striking atom-efficient and multi-coupling reactivity observed with different triaryl bismuths under Pd(0)/C catalysis prompted our further study with a variety of divergent aryl and heteroaryl acyl chlorides (Table 3). From this, the Pd(0)/C-based protocol proved to be efficient to couple a variety of functionalized electron-rich and-deficient acyl chlorides with different triaryl bismuths. Thus, benzoyl chlorides with 4-methyl and 4-methoxy groups reacted efficiently furnishing high yields of the ketones with different triaryl bismuths (compounds **11–16**). Additionally,

Table 2
Cross-coupling of different triaryl bismuths with benzoyl chloride^{13,14}

Entry	Ar (BiAr ₃)	Ketone	Yield ^{a–c} (%)
1			(1) 90
2			(2) 89
3			(3) 85
4			(4) 95
5			(5) 85
6			(6) 71
7			(7) 75
8			(8) 87
9			(9) 81
10			(10) 76

^a Conditions: PhCOCl (0.825 mmol, 1.0 equiv), BiPh₃ (0.25 mmol, 0.303 equiv), NEt₃ (0.25 mmol, 0.30 equiv), 10% Pd/C (0.0075 mmol, 0.009 equiv Pd), PPh₃ (0.03 mmol, 0.036 equiv), THF (3 mL), 80 °C, 3 h.^b Isolated yields are reported based on acyl chlorides used. All products were characterized by ¹H NMR, ¹³C NMR, IR, and in comparison with literature data.^c 5–10% Homo-coupling bi aryls from triaryl bismuths formed.

benzoyl chlorides substituted with 3-methyl and 3-methoxy groups also produced corresponding isomeric ketones in good yields (compounds **17–22**). The 4-nitrobenzoyl chloride rendered moderate coupling reactivity due to strong electron-withdrawing nature of the nitro group (compounds **23–25**). The cross-coupling reactivity of both 1- and 2-naphthoyl chlorides was found to be

Table 3Cross-coupling of triarylbi-muths with aromatic acyl chlorides^{13,14}

	90%		66%		88%
	87%		58%		86%
	86%		52%		92%
	73%		50%		94%
	74%		74%		83%
	76%		83%		84%
	83%		71%		86%
	80%		90%		83%
	80%		83%		80%
	63%		85%		72%
	60%		87%		79%

Note: (a) Conditions: ArCOCl (0.825 mmol, 1.0 equiv), BiAr₃ (0.25 mmol, 0.303 equiv), NEt₃ (0.25 mmol, 0.30 equiv), 10% Pd/C (0.0075 mmol, 0.009 equiv Pd), PPh₃ (0.03 mmol, 0.036 equiv), THF (3 mL), 80 °C, 3 h. (b) Isolated yields are reported based on acyl chlorides used. (c) All products were characterized by ¹H NMR, ¹³C NMR, IR, and in comparison with literature data. (d) In general, ~5–10% of homo-coupling bi aryls formed from triarylbi-muths. (e) In reactions yielding moderate cross-coupled ketones, homo-coupling bi aryls from triarylbi-muths invariably formed in appreciable amounts.

excellent, furnishing high yields of ketones with triarylbismuths (compounds **26–31**). The coupling reactions with 4-bromo and 4-chloro benzoyl chlorides were found to be efficient with chemo-selective coupling furnishing the corresponding halo-benzophenones in high yields (compounds **32–37**). The couplings of furan-2-carbonyl chloride and thiophene-2-carbonyl chloride were efficient with triarylbismuths and produced mixed ketones in good yields (compounds **38–43**).

As described above, the Pd(0)/C-catalyzed coupling of a variety of acyl chlorides with triarylbismuths provided novel atom-efficient synthesis of functionalized symmetrical/unsymmetrical aromatic and hetero-aromatic ketones. This method also proved to be facile for chemo-selective synthesis of functionalized bromo- and chloro benzophenones. The regio-selective synthesis of certain isomeric ketones (Tables 2 and 3) through cross-coupling demonstrated the ease associated with this method when compared to Friedel–Crafts acylation reaction. In addition, the facile reactivity of various aryl chlorides as atom-efficient acyl donors is superior to anhydrides for such couplings. The coupling reactions involving anhydride as acyl donor produce invariably an equivalent amount of corresponding acid as a by-product.¹⁵

Thus, we have disclosed Pd(0)/C-catalyzed coupling reaction of acyl chlorides with triarylbismuths as atom-efficient, sub-stoichiometric, and multi-coupling reagents for the synthesis of aromatic and hetero-aromatic ketones. The coupling reactions involving triarylbismuths proved to be very efficient and notably involves conversion of three Bi–C bonds to three C–C bonds in one-pot operation under Pd(0)/C catalysis.

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References and notes

- Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442–4489.
- (a) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651–2710; (b) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469.
- Pd/C microreview: Felpin, F.-X.; Ayad, T.; Mitra, S. *Eur. J. Org. Chem.* **2006**, 2679–2690.
- (a) Heidenreich, R. G.; Kohler, K.; Krauter, J. G. E.; Pietsch, J. *Synlett* **2002**, 1118–1122; (b) Marck, G.; Villiger, A.; Buchecker, R. *Tetrahedron Lett.* **1994**, *35*, 3277–3280; (c) Taylor, R. H.; Felpin, F.-X. *Org. Lett.* **2007**, *9*, 2911–2914; (d) Sakurai, H.; Tsukuda, T.; Hirao, T. *J. Org. Chem.* **2002**, *67*, 2721–2722; (e) Hallberg, A.; Westfelt, L. *J. Chem. Soc., Perkin Trans. 1* **1984**, 933–935; (f) Novak, Z.; Szabo, A.; Repasi, J.; Kotschy, A. *J. Org. Chem.* **2003**, *68*, 3327–3329; (g) Caspi, D. D.; Garg, N. K.; Stoltz, B. M. *Org. Lett.* **2005**, *7*, 2513–2516; (h) Cossy, J.; Belotti, D. *Org. Lett.* **2002**, *4*, 2557–2559; (i) Sajiki, H.; Aoki, F.; Esaki, H.; Maegawa, T.; Hirota, K. *Org. Lett.* **2004**, *6*, 1485–1487; (j) Mandal, P. K.; McMurray, J. S. *J. Org. Chem.* **2007**, *72*, 6599–6601.
- (a) Subramanian, V.; Batchu, V. R.; Barange, D.; Pal, M. *J. Org. Chem.* **2005**, *70*, 4778–4783; (b) Felpin, F.-X. *J. Org. Chem.* **2005**, *70*, 8575–8578; (c) Kabalka, G. W.; Nambodiri, V.; Wang, L. *Chem. Commun.* **2001**, 775; (d) Tagata, T.; Nishida, M. *J. Org. Chem.* **2003**, *68*, 9412–9415.
- (a) Felpin, F.-X.; Landais, Y. *J. Org. Chem.* **2005**, *70*, 6441–6446; (b) Shimizu, T.; Seki, M. *Tetrahedron Lett.* **2001**, *42*, 429–432; (c) Lai, C. W.; Kwong, F. Y.; Wang, Y.; Chan, K. S. *Tetrahedron Lett.* **2001**, *42*, 4883–4885.
- (a) Hwang, J. P.; Prakash, G. K. S.; Olah, G. A. *Tetrahedron* **2000**, *56*, 7199–7203; (b) Nara, S. J.; Harjani, J. R.; Salunkhe, M. M. *J. Org. Chem.* **2001**, *66*, 8616–8620; (c) Ross, J.; Xiao, J. *Green Chem.* **2002**, *4*, 129–133; (d) Furstner, A.; Voigtlander, D.; Schrader, W.; Giebel, D.; Reetz, M. T. *Org. Lett.* **2001**, *3*, 417–420; (e) Larock, R. C. *Comprehensive Organic Transformations*; Wiley-VCH: New York, 1989; (f) Chiche, B.; Finiels, A.; Gauthier, C.; Geneste, P.; Graille, J.; Pioch, D. *J. Org. Chem.* **1986**, *51*, 2128–2130.
- (a) Bandgar, B. P.; Patil, A. V. *Tetrahedron Lett.* **2005**, *46*, 7627–7630; (b) Xin, B.; Zhang, Y.; Cheng, K. J. *Org. Chem.* **2006**, *71*, 5725–5731; (c) Bumagin, N. A.; Korolev, D. N. *Tetrahedron Lett.* **1999**, *40*, 3057–3060; (d) Urawa, Y.; Ogura, K. *Tetrahedron Lett.* **2003**, *44*, 271–273; (e) Haddach, M.; McCarthy, J. R. *Tetrahedron Lett.* **1999**, *40*, 3109–3112; (f) Kabalka, G. W.; Malladi, R. R.; Tejedor, D.; Kelley, S. *Tetrahedron Lett.* **2000**, *41*, 999–1001; (g) Polackova, V.; Toma, S.; Augustinova, I. *Tetrahedron* **2006**, *62*, 11675–11678.
- (a) Dieter, R. K. *Tetrahedron* **1999**, *55*, 4177–4236; (b) Wang, X.-J.; Zhang, L.; Sun, X.; Xu, Y.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2005**, *7*, 5593–5595; (c) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636–3638; (d) Lerebours, R.; Camacho-Soto, A.; Wolf, C. J. *Org. Chem.* **2005**, *70*, 8601–8604; (e) Silbestri, G. F.; Masson, R. B.; Lockhart, M. T.; Chopra, A. B. *J. Organomet. Chem.* **2006**, *691*, 1520–1524; (f) Grey, R. A. *J. Org. Chem.* **1984**, *49*, 2288–2289.
- (a) Rao, M. L. N.; Venkatesh, V.; Banerjee, D. *Synfacts* **2008**, *4*, 406; (b) Rao, M. L. N.; Jadhav, D. N.; Banerjee, D. *Tetrahedron* **2008**, *64*, 5762–5772; (c) Rao, M. L. N.; Venkatesh, V.; Jadhav, D. N. *J. Organomet. Chem.* **2008**, *693*, 2494–2498; (d) Rao, M. L. N.; Venkatesh, V.; Banerjee, D. *Tetrahedron* **2007**, *63*, 12917–12926; (e) Rao, M. L. N.; Banerjee, D.; Jadhav, D. N. *Tetrahedron Lett.* **2007**, *48*, 6644–6647; (f) Rao, M. L. N.; Banerjee, D.; Jadhav, D. N. *Tetrahedron Lett.* **2007**, *48*, 2707–2711; (g) Rao, M. L. N.; Venkatesh, V.; Jadhav, D. N. *Tetrahedron Lett.* **2006**, *47*, 6975–6978.
- (a) *Organobismuth Chemistry*; Suzuki, H., Matano, Y., Eds.; Elsevier, 2001; (b) Rao, M. L. N.; Yamazaki, O.; Shimada, S.; Tanaka, T.; Suzuki, Y.; Tanaka, M. *Org. Lett.* **2001**, *3*, 4103–4105.
- Aromatic acyl chlorides were prepared using the literature procedures: (a) Chaudhari, S. S.; Akamanchi, K. G. *Synlett* **1999**, 1763–1765; (b) Bessard, Y.; Crettaz, R. *Heterocycles* **1999**, *51*, 2589–2602.
- Representative coupling procedure*: An oven-dried Schlenk tube was charged with PhCOCl (0.825 mmol, 0.116 g), BiPh₃ (0.25 mmol, 0.11 g), 10% Pd(0)/C (0.0075 mmol of Pd, 0.024 g), PPh₃ (0.03 mmol, 0.0078 g), and Et₃N (0.25 mmol, 0.025 g) followed by anhydrous THF (3 mL) under nitrogen atmosphere. The reaction mixture in Schlenk tube was stirred in an oil bath at 80 °C for 3 h. In the end, the reaction mixture was cooled to room temperature, quenched with water, and extracted with ethyl acetate (2 × 15 mL). The combined ethyl acetate extract was washed with dilute hydrochloric acid (5 mL), saturated sodium bicarbonate solution (5 mL), brine (2 × 5 mL), and dried over anhydrous magnesium sulfate and was concentrated under vacuo to obtain the crude product. The crude product was further purified on silica gel by column chromatography to afford benzophenone (**1**) (0.123 g) in 90% yield based on the amount of based on acyl chlorides used.
- In all the reactions, 1 equiv of BiPh₃ was used with 3.3 equiv of acyl chloride.
- (a) Gooßen, L. J.; Ghosh, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 3458–3460; (b) Kakino, R.; Yasumi, S.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 137–148; (c) Wang, D.; Zhang, Z. *Org. Lett.* **2003**, *5*, 4645–4648; (d) Kakino, R.; Narahashi, H.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1333–1345.