

# An atom-efficient palladium-catalyzed cross-coupling reaction of triarylbismuths with acid chlorides: synthesis of diaryl and alkyl aryl ketones

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**Abstract**—The cross-coupling reaction of triarylbismuths with acid chlorides using a catalytic amount of PdCl<sub>2</sub>/PPh<sub>3</sub> afforded the corresponding ketones in high yields. The reactions of aromatic and aliphatic acid chlorides occurred with atom efficiency, as 3 equiv of acid chlorides coupled effectively with 1 equiv of triarylbismuths to yield 3 equiv of the corresponding diaryl and alkyl aryl ketones.

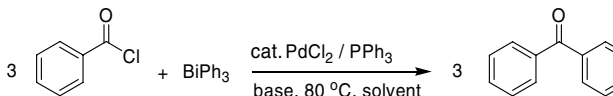
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Metal-catalyzed cross-coupling reactions of acid chlorides with organometallic reagents is an efficient methodology for the synthesis of ketones.<sup>1</sup> Ketones represent a distinct class of organic compounds, and are important building blocks in organic synthesis. The traditional method for the synthesis of aromatic ketones involves Friedel–Crafts acylation in the presence of Lewis acids,<sup>2</sup> which is limited by problems associated with regioselectivity. In this respect, the cross-coupling reactions of acyl chlorides with organometallic reagents provide flexibility for improving regioselectivity.<sup>1</sup> Thus, several metal-catalyzed cross-coupling reactions of acid chlorides with organoboron, organotin, organozinc reagents, etc. have been reported for the synthesis of ketones.<sup>3</sup> Although efficient, some of these methods suffer from disadvantages such as toxicity of the organometallic reagents and harsh reaction conditions.<sup>3</sup> Further, the low atom efficiency that necessarily results due to the use of stoichiometric amounts of the organometallic reagent is an added drawback.<sup>3</sup>

The utility of organobismuth compounds under transition metal-catalyzed conditions has not been explored in detail for C–C bond formation.<sup>4</sup> Organobismuth compounds are generally low or non-toxic, and hence

can be used effectively for C–C bond formation. Recent efforts in this direction have led to the development of new organobismuth compounds for C–C bond formation under palladium-catalyzed conditions.<sup>5</sup> In particular, the use of triarylbismuths for C–C bond formation would be atom efficient, as 3 equiv of electrophilic partners can be used for the cross-coupling reaction. Barton et al. reported the cross-coupling reaction of BiPh<sub>3</sub> with benzoyl chloride under palladium-catalyzed conditions.<sup>6</sup> Subsequently, no effort has been made in this direction to expand the scope of this reaction. In this letter, we

**Table 1.** Screening of the reaction of benzoyl chloride with BiPh<sub>3</sub><sup>a</sup>



Entry	Solvent	Base (equiv.)	Time (h)	Conv. <sup>b</sup> (%)
1	1,4-Dioxane	KOAc (4)	3	10
2	1,4-Dioxane	K <sub>2</sub> CO <sub>3</sub> (4)	3	61
3	THF	K <sub>2</sub> CO <sub>3</sub> (4)	3	67
4	CH <sub>3</sub> CN	K <sub>2</sub> CO <sub>3</sub> (4)	3	69
5	DMA	K <sub>2</sub> CO <sub>3</sub> (4)	3	5
6	1,4-Dioxane	NEt <sub>3</sub> (4)	3	90
7	1,4-Dioxane	NEt <sub>3</sub> (1)	3	88
8 <sup>c</sup>	1,4-Dioxane	NEt <sub>3</sub> (1)	4	95

<sup>a</sup> Equivalent ratios with respect to BiPh<sub>3</sub> (1 equiv): PdCl<sub>2</sub> (0.1 equiv)/PPh<sub>3</sub> (0.2 equiv), PhCOCl (5.0 equiv).

<sup>b</sup> Based on GC analysis.

<sup>c</sup> Equivalent ratios with respect to BiPh<sub>3</sub> (1 equiv): PdCl<sub>2</sub> (0.09 equiv)/PPh<sub>3</sub> (0.18 equiv), PhCOCl (3.3 equiv).

**Keywords:** Cross-coupling; Triarylbismuths; Acid chlorides; Diaryl ketones; Alkyl aryl ketones; Palladium catalyzed.

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**Table 2.** Cross-coupling reaction of triarylbismuths with acid chlorides<sup>a,b,c</sup>

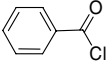
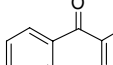
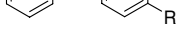
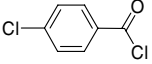
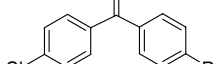
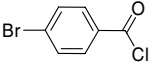
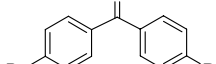
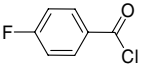
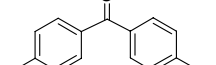
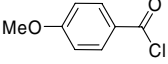
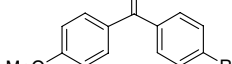
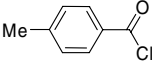
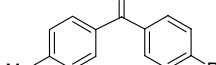
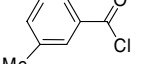
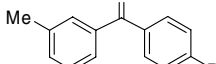
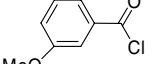
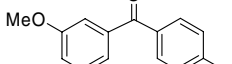
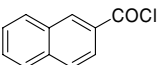
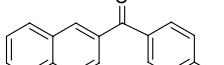
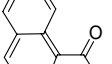
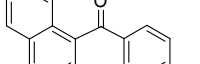
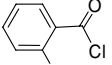
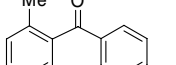
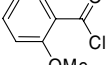
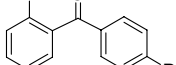
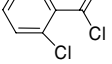
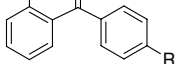
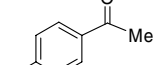
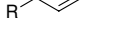
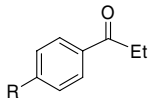
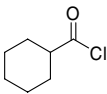
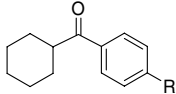
Entry	BiAr <sub>3</sub>	Acid chloride	Ketone		Yield (%)
1	BiPh <sub>3</sub>			R = -H	93
2	Bi( <i>p</i> -tolyl) <sub>3</sub>			R = -CH <sub>3</sub>	92
3	Bi( <i>p</i> -anisyl) <sub>3</sub>			R = -OCH <sub>3</sub>	76
4	BiPh <sub>3</sub>			R = -H	89
5	Bi( <i>p</i> -tolyl) <sub>3</sub>			R = -CH <sub>3</sub>	78
6	Bi( <i>p</i> -anisyl) <sub>3</sub>			R = -OCH <sub>3</sub>	66
7	BiPh <sub>3</sub>			R = -H	87
8	Bi( <i>p</i> -tolyl) <sub>3</sub>			R = -CH <sub>3</sub>	86
9	Bi( <i>p</i> -anisyl) <sub>3</sub>			R = -OCH <sub>3</sub>	63
10	BiPh <sub>3</sub>			R = -H	89
11	Bi( <i>p</i> -tolyl) <sub>3</sub>			R = -CH <sub>3</sub>	89
12	Bi( <i>p</i> -anisyl) <sub>3</sub>			R = -OCH <sub>3</sub>	61
13	BiPh <sub>3</sub>			R = -H	76
14	Bi( <i>p</i> -tolyl) <sub>3</sub>			R = -CH <sub>3</sub>	75
15	Bi( <i>p</i> -anisyl) <sub>3</sub>			R = -OCH <sub>3</sub>	48
16	BiPh <sub>3</sub>			R = -H	90
17	Bi( <i>p</i> -tolyl) <sub>3</sub>			R = -CH <sub>3</sub>	86
18	Bi( <i>p</i> -anisyl) <sub>3</sub>			R = -OCH <sub>3</sub>	66
19	BiPh <sub>3</sub>			R = -H	79
20	Bi( <i>p</i> -tolyl) <sub>3</sub>			R = -CH <sub>3</sub>	90
21	Bi( <i>p</i> -anisyl) <sub>3</sub>			R = -OCH <sub>3</sub>	68
22	BiPh <sub>3</sub>			R = -H	86
23	Bi( <i>p</i> -tolyl) <sub>3</sub>			R = -CH <sub>3</sub>	90
24	Bi( <i>p</i> -anisyl) <sub>3</sub>			R = -OCH <sub>3</sub>	71
25	BiPh <sub>3</sub>			R = -H	92
26	Bi( <i>p</i> -tolyl) <sub>3</sub>			R = -CH <sub>3</sub>	94
27	Bi( <i>p</i> -anisyl) <sub>3</sub>			R = -OCH <sub>3</sub>	81
28	BiPh <sub>3</sub>			R = -H	66
29	Bi( <i>p</i> -tolyl) <sub>3</sub>			R = -CH <sub>3</sub>	73
30	Bi( <i>p</i> -anisyl) <sub>3</sub>			R = -OCH <sub>3</sub>	66
31	BiPh <sub>3</sub>			R = -H	65
32	Bi( <i>p</i> -tolyl) <sub>3</sub>			R = -CH <sub>3</sub>	40
33	BiPh <sub>3</sub>			R = -H	27
34	BiPh <sub>3</sub>			R = -H	64
35	BiPh <sub>3</sub>	CH <sub>3</sub> COCl		R = -H	82
36	Bi( <i>p</i> -tolyl) <sub>3</sub>			R = -CH <sub>3</sub>	85
37	Bi( <i>p</i> -anisyl) <sub>3</sub>			R = -OCH <sub>3</sub>	61

Table 2 (continued)

Entry	BiAr <sub>3</sub>	Acid chloride	Ketone		Yield (%)
38	BiPh <sub>3</sub>	CH <sub>3</sub> CH <sub>2</sub> COCl		R = -H	78
39	Bi( <i>p</i> -tolyl) <sub>3</sub>			R = -CH <sub>3</sub>	88
40	Bi( <i>p</i> -anisyl) <sub>3</sub>			R = -OCH <sub>3</sub>	69
41	BiPh <sub>3</sub>			R = -H	95
42	Bi( <i>p</i> -tolyl) <sub>3</sub>			R = -CH <sub>3</sub>	90
43	Bi( <i>p</i> -anisyl) <sub>3</sub>			R = -OCH <sub>3</sub>	76

<sup>a</sup> Conditions for aromatic acid chlorides. Equivalent ratios with respect to BiAr<sub>3</sub>: acid chloride (3.3 equiv), BiAr<sub>3</sub> (1 equiv), PdCl<sub>2</sub> (0.09 equiv)/PPh<sub>3</sub> (0.18 equiv), Et<sub>3</sub>N (1 equiv), 1,4-dioxane (3 mL), 80 °C, 4 h.

<sup>b</sup> Conditions for aliphatic acid chlorides. Equivalent ratios with respect to BiAr<sub>3</sub>: acid chloride (5 equiv), BiAr<sub>3</sub> (1 equiv), PdCl<sub>2</sub> (0.15 equiv)/PPh<sub>3</sub> (0.30 equiv), Et<sub>3</sub>N (5 equiv), 1,4 dioxane (3 mL), 80 °C, 4 h.

<sup>c</sup> Isolated yields obtained after column chromatography. All the products were characterized by <sup>1</sup>H, <sup>13</sup>C NMR, IR and mass spectral analysis.

report a general and atom-efficient cross-coupling reaction of a variety of acid chlorides with triarylbi-muths using a catalytic amount of PdCl<sub>2</sub>/PPh<sub>3</sub> for the synthesis of a range of diaryl and alkyl aryl ketones.

Initial experiments using benzoyl chloride (5 equiv) with BiPh<sub>3</sub> (1 equiv) were carried out with various bases in acetone as the solvent at 65 °C for 3 h in the presence of PdCl<sub>2</sub> (0.1 equiv)/PPh<sub>3</sub> (0.2 equiv). It was found that bases such as Na<sub>2</sub>CO<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub>, KF and KOAc were ineffective in providing the corresponding cross-coupling product. To find suitable conditions for efficient cross-coupling of benzoyl chloride with BiPh<sub>3</sub>, a variety of other bases and solvents were screened (Table 1). As can be seen from Table 1, the cross-coupling reaction of benzoyl chloride with BiPh<sub>3</sub> was found to be inefficient with KOAc as base in 1,4-dioxane solvent (entry 1). However, an increase in the cross-coupling reactivity was observed with K<sub>2</sub>CO<sub>3</sub> under similar conditions (entry 2). Further screening with K<sub>2</sub>CO<sub>3</sub> in different solvents such as THF and CH<sub>3</sub>CN led to moderate conversions (entries 3 and 4), while DMA proved to be unsuitable as the solvent (entry 5). However, a dramatic increase in the conversion was observed in 1,4-dioxane in the presence of Et<sub>3</sub>N as base (entry 6). It was established from further experiments that 1 equiv of Et<sub>3</sub>N in the presence of PdCl<sub>2</sub> (0.09 equiv) and PPh<sub>3</sub> (0.18 equiv) in 1,4-dioxane at 80 °C led to 95% conversion in 4 h with 3.3 equiv of benzoyl chloride (entry 8).

At this stage, we chose BiPh<sub>3</sub>, Bi(*p*-tolyl)<sub>3</sub> and Bi(*p*-anisyl)<sub>3</sub> as representative triarylbi-muths to investigate the cross-coupling reactions further with a number of acid chlorides under the conditions established above. The results are summarized in Table 2. The cross-coupling of a variety of *para*-functionalized aromatic acid chlorides (*p*-fluoro, *p*-chloro, *p*-bromo, *p*-methyl and *p*-methoxy) proceeded efficiently with all the three triarylbi-muths to give excellent yields of the corresponding diaryl ketones (entries 1–18). Similarly, *m*-methyl and *m*-methoxy substituted aromatic acid chlorides also produced high yields of the diaryl ketones (entries 19–24). Thus, the results observed with various functionalized aromatic acid chlorides and triarylbi-muths show that the electronic factors intrinsic to the acid chlorides as well as the triarylbi-muths play little or no role in the outcome

of this cross-coupling reaction. In addition, the cross-coupling reaction of β-naphthoyl chloride with triarylbi-muths produced the corresponding naphthyl phenyl ketones in excellent yields (entries 25–27). In contrast, the reaction of α-naphthoyl chloride led to a moderate yield of the corresponding ketones (entries 28–30). In a similar manner, the cross-coupling reaction of sterically encumbered aromatic acid chlorides containing *o*-substituents (*o*-methyl, *o*-methoxy and *o*-chloro) led to low to moderate yields of the corresponding ketones (entries 31–34). This clearly shows that the cross-coupling reaction is influenced to some extent by steric factors.

Further, the cross-coupling of aliphatic acid chlorides with triarylbi-muths under the conditions employed above led to low yields of the corresponding ketones (30–40%). However, when the acid chloride and Et<sub>3</sub>N were employed in 5 M equiv with respect to BiAr<sub>3</sub> along with PdCl<sub>2</sub> (0.15 equiv)/PPh<sub>3</sub> (0.30 equiv), the corresponding ketones were formed in high yields (entries 35–43). As shown in Table 2, both acetyl chloride and propionoyl chloride yielded the corresponding acetophenone and propiophenone in high yields (entries 35–40). The cross-coupling reaction of cyclohexane carbonyl chloride was also found to be efficient with triarylbi-muths (entries 41–43).

In conclusion, we have disclosed a Pd-catalyzed cross-coupling reaction of acid chlorides with triarylbi-muths for the synthesis of a variety of diaryl and alkyl aryl ketones.<sup>7</sup> The use of 3 equiv of acid chlorides with 1 equiv of triarylbi-muth constitutes an atom-efficient process in addition to the fact that the catalytic system, that is, PdCl<sub>2</sub>/PPh<sub>3</sub> employed is inexpensive and readily accessible. The high cross-coupling reactivity of different triarylbi-muths with no perceptible differences in terms of the isolated yields of the corresponding ketones underscores the broad utility of this protocol for the syntheses of diaryl and alkyl aryl ketones.

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7. *Representative procedure*: In a typical experiment, an oven-dried round-bottom flask or a Schlenk tube was charged with PhCOCl (0.83 mmol, 0.117 g), BiPh<sub>3</sub> (0.25 mmol, 0.11 g), PdCl<sub>2</sub> (0.023 mmol, 0.004 g), PPh<sub>3</sub> (0.045 mmol, 0.012 g) and Et<sub>3</sub>N (0.25 mmol, 0.025 g) followed by the addition of anhydrous 1,4-dioxane (3 mL). The contents were heated under nitrogen at 80 °C for 4 h. Then, the reaction mixture was cooled to rt, quenched with water and extracted with ethyl acetate (2 × 15 mL). The combined ethyl acetate extract was washed with dilute HCl (5 mL), saturated sodium bicarbonate solution (5 mL), brine (2 × 5 mL) and dried over MgSO<sub>4</sub>. The crude product mixture thus obtained after removing the solvent was subjected to column chromatography and pure benzophenone was isolated in 93% yield. The product was characterized by <sup>1</sup>H, <sup>13</sup>C NMR, IR and mass spectral analysis. For aliphatic acid chlorides, the same procedure was followed, but with the following conditions: RCOCl (1.25 mmol, 5 equiv), BiPh<sub>3</sub> (0.25 mmol, 1 equiv), PdCl<sub>2</sub> (0.0375 mmol, 0.15 equiv), PPh<sub>3</sub> (0.075 mmol, 0.30 equiv), Et<sub>3</sub>N (1.25 mmol, 5 equiv), 1,4-dioxane (3 mL), 80 °C, 4 h.