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Pd-catalyzed synthesis of α-aryl ketones through couplings of α-arylacetyl chlorides with triarylbismuths as multi-coupling nucleophiles

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ABSTRACT

The cross-coupling reaction of α-arylacetyl chlorides with triarylbismuths was studied under Pd-catalyzed conditions. The reaction was found to be facile under the established protocol and furnished high yields of α-aryl ketones in short reaction times. This work also demonstrated a facile synthesis of various regio-isomeric mono-, di- and tri-substituted α-aryl ketones in high yields. Triarylbismuths were employed as sub-stoichiometric multi-coupling organometallic nucleophiles in this coupling protocol.

With the advent of new organometallic nucleophiles and organic electrophiles, the versatility of cross-coupling methodology is further expanding in organic synthesis.[1,2] Some of these reactions are currently being used in industry for the synthesis of active pharmaceutical ingredients (APIs).[3] Direct α-arylations of ketones have been the subject of several recent studies for the synthesis of α-aryl ketones.[4,5] Some of the methods reported for the purpose include (i) nucleophilic acylation of *o*-quinone methides using umpolung,[4a] (ii) hydration of alkynes,[4b,5c] (iii) α-arylation of ketones using organometallic reagents,[4c] or aryl halides,[4d,5a,b,e] (iv) coupling of aryl bromides with an acyl anion equivalent,[4e] (v) addition reaction of arylboronic acid to nitriles[4f] (vi) Heck arylation of 2-substituted enol ethers,[4g] (vii) homologation of aldehydes[5d], etc. Although Friedel–Crafts acylation reaction also provides another option, this method lacks the flexibility to synthesize regioisomeric compounds.[6]

α-Aryl ketones attracted attention due to their role as useful precursors for a variety of transformations including the synthesis of heterocyclic compounds in organic chemistry.[7] The cross-coupling of acyl chloride with organometallic nucleophile is a novel route for the synthesis of ketones.[8,1d] However, the reactivity of these acid chlorides varies under different cross-coupling reaction conditions.

Although many coupling methods have been reported using aryl and aliphatic acid chlorides,[8,9] reactivity studies involving α-arylacetyl chlorides are scarce.[10,12h] Thus, coupling reactions of α-arylacetyl chlorides with organometallic nucleophiles under catalytic conditions were limited to a few substrates. We envisioned that the development of an efficient protocol using α-arylacetyl chlorides would make the process more versatile for the synthesis of α-aryl ketones. Given the known complexity of general methods as cited before, we intended to develop a facile metal-catalyzed method using α-arylacetyl chlorides and triarylbismuth[11] nucleophiles for α-aryl ketones synthesis. Triarylbismuth compounds[1d,12] have been demonstrated to possess additional multi-coupling ability unlike some of the well-known organometallic nucleophiles.[2] In continuation of our interest in organobismuth chemistry, we report here an efficient palladium protocol for the coupling of α-arylacetyl chloride with triarylbismuth nucleophiles.

The reaction of α-phenylacetyl chloride with triphenylbismuth was initially studied by Barton et al. with Pd catalyst in hexamethylphosphoramide (HMPA) as a solvent.[12h] This methodology however suffers from drawbacks such as the use of a highly toxic and polluting solvent. So, in the search for a novel protocol, we have carried out a systematic investigation using α-phenylacetyl chloride and triphenylbismuth under different catalytic conditions. As illustrated in Table 1, reaction with $Pd(OAc)_2$ as a catalyst precursor in THF provided 57% conversion to cross-coupling product α-phenylaceto phenone in 51% isolated yield (Table 1, entry 1) along with homo-coupling biphenyl as a minor side product. Homo-coupling of triarylbismuths usually gives bi-aryls under Pd-catalyzed conditions.[12h,11b] Hence, to drive the reaction toward cross-coupling further screening was carried out using different catalysts, solvents, and reaction conditions.

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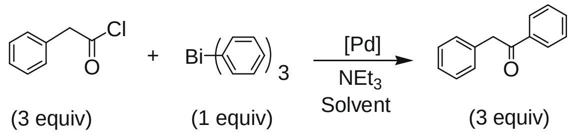
Table 1
Screening conditions[a,b,c,d]

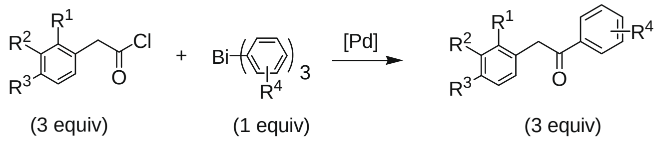


Entry	Catalyst	Solvent	Temp (°C), time (h)	Conv (%)
1	$Pd(OAc)_2/2PPh_3$	THF	80, 3 h	57 (51)
2	$PdCl_2(PPh_3)_2$	Dioxane	80, 3 h	56
3	$PdCl_2(PPh_3)_2$	DME	80, 3 h	50
4	$PdCl_2(PPh_3)_2$	MeCN	80, 3 h	35
5	$Pd(PPh_3)_4$	Dioxane	80, 3 h	32
6	$PdCl_2(MeCN)_2$	THF	80, 3 h	15
7	$PdCl_2(PhCN)_2$	THF	80, 3 h	27
8	$PdCl_2(PPh_3)_2$	THF	80, 3 h	74 (72)
9	$PdCl_2/2PPh_3$	THF	80, 3 h	76 (69)
10	$PdCl_2(PPh_3)_2$	THF	80, 2 h	65 (63)
11	$PdCl_2(PPh_3)_2$	THF	80, 1 h	57 (50)
12	$PdCl_2(PPh_3)_2$	THF	60, 3 h	70 (61)
13	$PdCl_2(PPh_3)_2$	THF	40, 3 h	54 (47)
14	$PdCl_2(PPh_3)_2$	THF	80, 3 h	55 (50)[e]
15	$PdCl_2(PPh_3)_2$	THF	80, 3 h	85 (83)[f]
16	$PdCl_2(PPh_3)_2$	THF	80, 3 h	52 (44)[g]
17	—	THF	80, 3 h	20

[a] Reaction conditions: $BiPh_3$ (0.25 mmol, 1 equiv), α-phenylacetyl chloride (0.825 mmol, 3.3 equiv), Pd (0.0225 mmol, 0.09 equiv), Et_3N (0.25 mmol, 1 equiv), solvent (3 mL), 80 °C.
[b] Conversions are based on GC analysis with reference to $BiPh_3$.
[c] Isolated yields are given in parentheses.
[d] Homo-coupling biphenyl formed as a minor side product.
[e] Without triethylamine.
[f] With 4 equiv of α-phenylacetyl chloride.
[g] With Pd (0.0025 mmol, 0.01 equiv).

The reaction was studied employing $PdCl_2(PPh_3)_2$ catalyst in different solvents such as 1,4-dioxane, 1,2-dimethoxyethane (DME), and acetonitrile. These combinations yielded mixed conversion to the desired product (Table 1, entries 2–4). The catalytic efficiency of other Pd sources was checked using $Pd(PPh_3)_4$, $PdCl_2(MeCN)_2$, and $PdCl_2(PhCN)_2$, and these catalytic systems showed poor reactivity (Table 1, entries 5–7). Encouragingly, the efficiency of $PdCl_2(PPh_3)_2$ or $PdCl_2/2PPh_3$ catalysts was found to be promising to accomplish high product conversion in THF solvent (Table 1, entries 8 and 9). Under similar conditions, the reactions which have been carried out for 2 h and 1 h afforded moderate yield of product (Table 1, entries 10 and 11). This also indicated that 3 h time is essential for the reaction to reach completion (Table 1, entries 9–11). Additional study by varying temperature did not improve the product yield (Table 1, entries 12 and 13). Notably, the absence of Et_3N has lowered the product conversion and the respective isolated yield (Table 1, entry 14). Importantly, in these screening studies, we have used 3.3 equiv of α-phenylacetyl chloride with 1 equiv of triphenylbismuth and this resulted in 72% yield of the product (Table 1, entry 8). Gratifyingly, the reaction with 4 equiv of acid chloride furnished increased isolated product yield up to 83% (Table 1, entry 15). Although 3 equiv of acid chloride is enough to cross-couple 1 equiv of triphenylbismuth, additional 1 equiv acid chloride has been employed to further drive the reaction toward cross-coupling and to suppress the competitive homo-coupling from triphenylbismuth. Further, the reaction with low Pd catalyst (0.01 equiv) loading afforded 44% yield of product (Table 1, entry 16). It is noteworthy that $PdCl_2(PPh_3)_2$ has served as an efficient catalyst to furnish high yield of α-phenylacetophenone product in short reaction time as its absence afforded only poor conversion in a control experiment that has been carried out without Pd catalyst (Table 1, entry 17). From

Table 2
Coupling of α-arylacetyl chlorides with triarylbismuths[a,b,c,d]



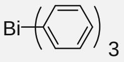
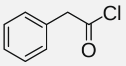
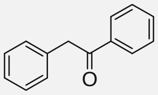
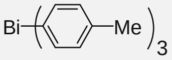
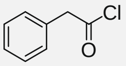
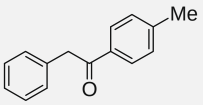
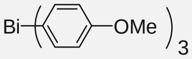
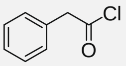
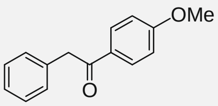
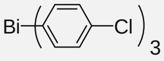
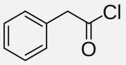
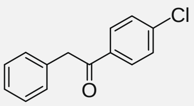
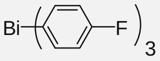
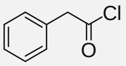
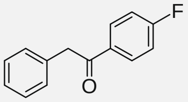
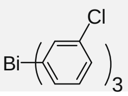
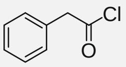
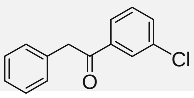
Entry	$BiAr_3$	α-Arylacetyl chloride	Ketone	Yield[b] (%)
1				83
2				84
3				64
4				71
5				81
6				65

Table 2 (*continued*)

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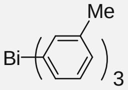
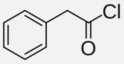
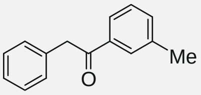
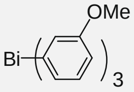
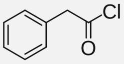
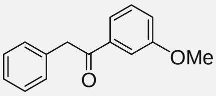
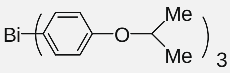
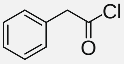
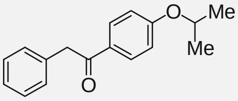
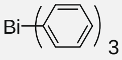
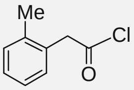
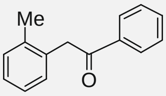
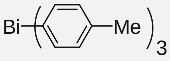
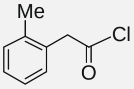
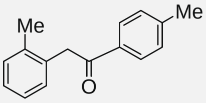
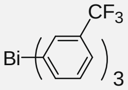
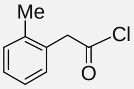
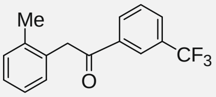
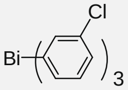
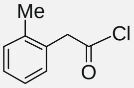
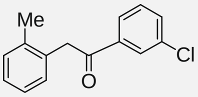
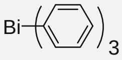
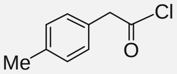
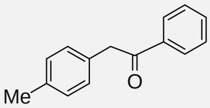
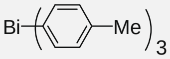
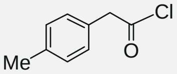
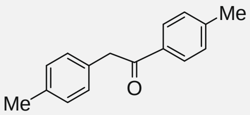
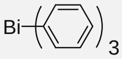
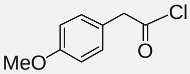
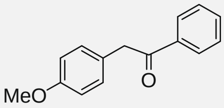
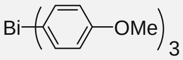
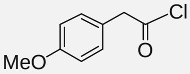
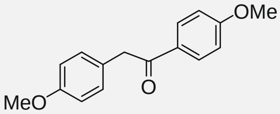
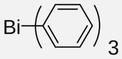
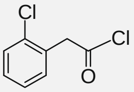
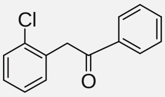
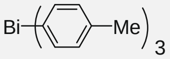
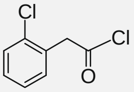
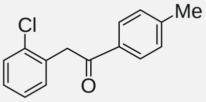
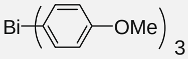
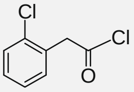
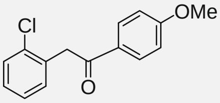
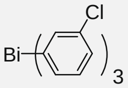
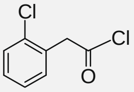
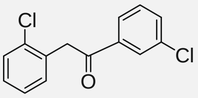
7				66
8				72
9				91
10				75
11				86
12				50
13				65
14				74
15				75
16				70
17				66
18				74
19				71
20				72
21				65

(*continued on next page*)

Table 2 (*continued*)

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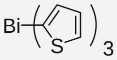
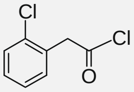
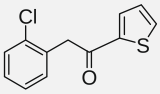
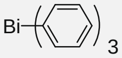
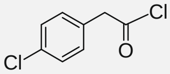
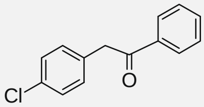
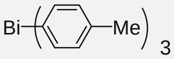
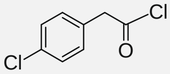
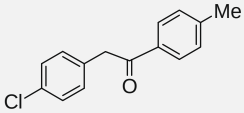
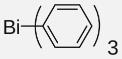
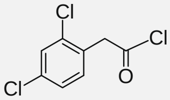
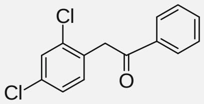
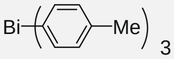
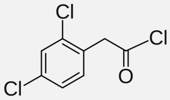
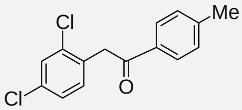
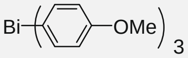
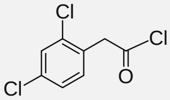
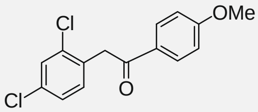
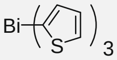
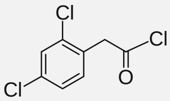
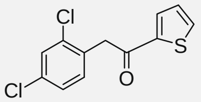
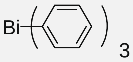
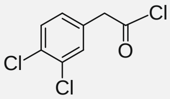
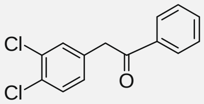
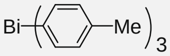
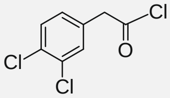
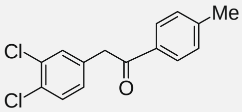
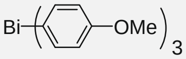
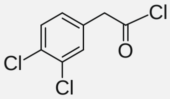
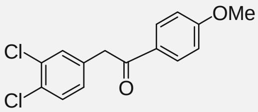
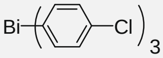
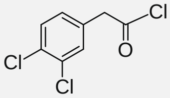
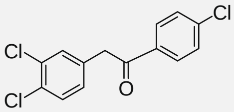
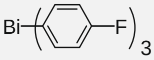
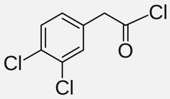
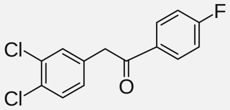
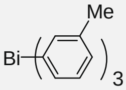
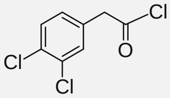
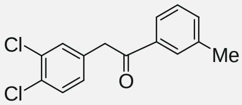
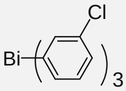
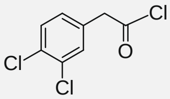
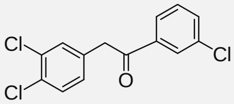
22				76
23				76
24				65
25				71
26				71
27				63
28				75
29				71
30				61
31				74
32				60
33				73
34				75
35				68

[a] Conditions: $BiAr_3$ (1 equiv, 0.25 mmol), α-arylacetyl chloride (4 equiv, 1 mmol), $PdCl_2(PPh_3)_2$ (0.09 equiv, 0.0225 mmol), NEt_3 (1 equiv, 0.25 mmol), THF (3 mL), 80 °C, 3 h.

[b] Isolated yields were reported. Product yields were calculated considering all the three aryl groups for coupling from triarylbismuth. Thus, 3 equiv of cross-coupling product (0.75 mmol) corresponds to 100% yield.

[c] All the products were characterized by ^1H NMR, ^{13}C NMR, IR, and ESI-MS spectroscopic studies and in comparison with known literature data.

[d] In general, varied minor amounts of homo-coupling bi-aryls from triarylbismuths were formed as side products.

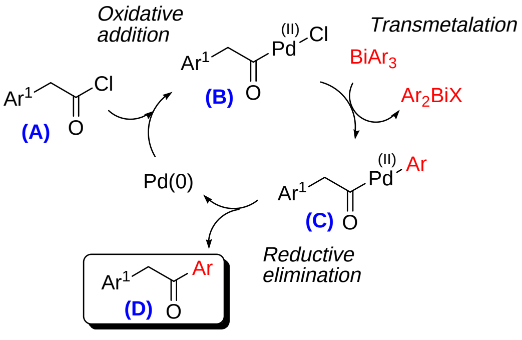
this study, the coupling reaction was demonstrated to be facile using catalytic Pd with Et_3N (1 equiv) in THF to furnish the high yield of product at 80 °C in short reaction time (Table 1, entry 15).

Hence, it was decided to study the scope of cross-coupling of α-arylacetyl chlorides with triarylbismuths to generalize the reaction. Firstly, the reactivity of α-phenylacetyl chloride with a variety of triarylbismuths was checked using the optimized protocol (Table 2).[13,14]

As illustrated, both *electron-deficient* and *electron-rich* triarylbismuths have fared well in furnishing the corresponding α-arylacetophenones in good to high yields (Table 2, entries 1–9). The overall reactivity of α-phenylacetyl chloride with electronically divergent triarylbismuths was facile under the present protocol. Further, various functionalized α-arylacetyl chlorides were studied with different triarylbismuth nucleophiles (Table 2, entries 10–35). These reactions furnished moderate to high yields of corresponding α-arylacetophenones. The mono- and di-substituted α-arylacetyl chlorides with *ortho*, *meta*, and *para* substitutions reacted efficiently giving high yields of regio-isomeric α-arylacetophenones. The reactions carried out with trithiophen-2-ylbismuth also afforded high yields of corresponding coupling products (Table 2, entries 22 and 28). At large, the coupling ability of various triarylbismuths was found to be efficient with electronically divergent α-arylacetyl chlorides. Notably, *ortho* substitution in α-arylacetyl chloride also afforded high yields of products. Notably, in all reactions homo-coupling bi-aryl products from triarylbismuths[12h,11b] were formed in minor amounts. However, higher amounts of bi-aryls were formed in reactions with moderate cross-coupling yields. In addition, the moderate cross-coupling yields in some cases may also be due to electronics of the triarylbismuth nucleophiles to some extent. This study has also demonstrated to be a viable route for the synthesis of various regio-isomeric mono-, di- and tri-substituted α-arylketones in high yields. It is noteworthy that synthesis of some of these compounds through traditional Friedel–Crafts condition would be difficult.

The probable Pd-catalyzed mechanism given in Scheme 1 was similar to the one proposed by Barton et al. for acid chloride couplings.[12h] The initial oxidative addition of arylacetyl chloride **A** to in situ generated-Pd(0) provides Pd(II) species **B**. This intermediate upon transmetalation with triarylbismuth reagent further provides **C** which undergoes reductive elimination to give the product **D**. Participation of other species such as $Ar_2BiX/ArBiX_2$ or Ar_3Bi (formed through disproportionative regeneration of Ar_2BiX or Ar_2BiX)[12h] is also possible during transmetalation. This way, triarylbismuths would function as multi-coupling organometallic nucleophile with the transfer of three aryl groups for coupling reaction. However, homo-coupling of triarylbismuths in the presence of Pd catalyst is a competitive pathway with the generation of bi-aryls as side products.[12h,11b]

In summary, we have disclosed an efficient cross-coupling of α-arylacetyl chlorides with triarylbismuth nucleophiles as stoichiometric multi-coupling reagents. This study demonstrated the efficient synthesis of various regio-isomeric mono-, di- and tri-substituted α-arylketones under the Pd-catalytic protocol. The coupling reaction has been found to be facile for the synthesis of a variety of α-aryl mixed ketones with both electronically divergent α-arylacetyl chlorides as electrophiles and triarylbismuths as nucleophiles. The coupling ability of triarylbismuths with 3 equiv of α-arylacetyl chloride is an added advantage associated with this class of compounds in comparison with some of the known organometallic nucleophiles used for such coupling reactions.



Scheme 1. Proposed catalytic cycle.

Acknowledgments

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References and notes

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13. *General procedure*: In a hot oven-dried Schlenk tube under nitrogen atmosphere were taken α-aryl acetyl chloride (1 mmol, 4 equiv), Ar_3Bi (0.25 mmol, 1 equiv), $PdCl_2(PPh_3)_2$ (0.0225 mmol, 0.09 equiv), and Et_3N (0.25 mmol, 1 equiv) followed by 3 mL of dry THF solvent. The contents were stirred at 80 °C in an oil bath for 3 h. After the reaction time, the contents were cooled to room temperature, quenched with dil HCl (10 mL), and extracted using ethyl acetate (20 mL × 3). The combined organic extract was treated with saturated $NaHCO_3$ solution (20 mL × 2) and brine (20 mL × 3), and dried over anhydrous $MgSO_4$. The solvent was removed on rotator evaporator under reduced pressure. The crude product was subjected to column chromatography on silica gel (100–200 mesh) using ethyl acetate:petroleum ether (3:97) as eluent to obtain α-aryl ketone as a pure product. The product was characterized by ^1H NMR, ^{13}C NMR, IR, and ESI-MS spectroscopic studies.
14. For all reactions, yields were calculated considering three aryl groups from triarylbismuth for coupling. Thus, 1 equiv of $BiAr_3$ is equal to 3 equiv of Bi–Ar. So, 3 equiv of cross-coupling product (0.75 mmol) corresponds to 100% yield.