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Oxalyl chloride as carbonyl synthon in Pd-catalyzed carbonylations of triarylbismuth and triarylindium organometallic nucleophiles

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ABSTRACT

Oxalyl chloride has been demonstrated to function as C1 carbonyl synthon in the carbonylations of triarylbismuth and triarylindium nucleophiles under palladium-catalyzed conditions. All the three aryl groups from both bismuth and indium reagents participated in carbonylative couplings to afford the corresponding functionalized ketones in high yields. This study also disclosed a novel utilization of oxalyl chloride as facile alternative source of CO for carbonylations under palladium catalysis.

Development of new processes involving small molecules is a priority area of research in synthetic organic chemistry.[1,2] Carbonylation under metal-catalyzed conditions is a useful synthetic process widely used in industry as it provides an easy access to carbonyl compounds.[3] However, there are some inevitable problems associated in the utilization of CO gas for carbonylations from safety and other related issues.[3,4] This had led to the use of alternative carbonyl sources such as formates, formamides, chloroform, aldehydes, and metal carbonyls, as carbonyl synthons for various synthetic transformations in place of gaseous CO.[4]

In this context, oxalyl chloride needs a special mention. This has been known to be involved as C1 or C2 synthon in synthetic organic chemistry for ketone synthesis.[5,6] Notably, its use as C1 synthon under metal catalysis has not evolved so far for synthetic applications. For instance, oxalyl chloride as C1 synthon was reported in 1,1-cycloaddition reactions with dialkenyl metal compounds.[5] As C2 synthon[6] this has been utilized in combination with organometallic (Li, Mg, and Cu) reagents and in Friedel–Crafts reaction. Given the importance of carbonylations in pharmaceutical and industrial applications,[3] there is a genuine need for facile reactive alternate carbonyl synthons[7] for safer execution of these processes.[4]

In this direction, we describe here a novel carbonylations using oxalyl chloride as C1 carbonyl synthon under palladium-catalyzed conditions. These results are significant from the view point of its simplicity, facile reactivity, and associated convenience in the utilization of oxalyl chloride as carbonyl synthon under metal catalysis.

With the recent interest in the use of organobismuth[8] reagents for C–C bond formations,[8,9] we have elaborated the scope of acyl chloride reactions with triarylbismuths[10] involving non-decarbonylative couplings to give unsymmetrical ketones in the presence of palladium catalysts.[11] Driven by this, it was of interest to study these reactions with oxalyl chloride for new synthetic applications. To our astonishment, the reaction of oxalyl chloride with triphenylbismuth in the presence of palladium catalyst produced benzophenone (**1**) as a product (Table 1, entry 1). The formation of ketone and not a diketone[6a] as product indicated the participation of oxalyl chloride as C1 carbonyl synthon in this reaction. A brief literature survey revealed the Stille's observation in 1979 on the formation of acetone as product (10% yield) in the reaction of oxalyl chloride with tetramethyltin under palladium catalysis.[12] However, there are no reports afterwards on further utilization of oxalyl chloride in this direction. This made us to explore the potential use of oxalyl chloride as C1 carbonyl synthon in the carbonylative couplings with additional screening under various conditions (Table 1).

The coupling reactions carried out under different palladium conditions furnished the carbonylation product benzophenone (**1**) in lower amounts (entries 1–3). Further, it was revealed to us that the carbonylation process is more effective without NEt_3 (entries 4 and 5).[13] The reaction carried out with 1 equiv of oxalyl

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Table 1
Screening with $BiPh_3$[a–d]

$$BiPh_3 + (COCl)_2 \xrightarrow{[Pd]} \underset{(\mathbf{1})}{PhCOPh}$$

Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield (%)
1	$PdCl_2/2PPh_3$	1,4-Dioxane	80	4	38[e]
2	$Pd(PPh_3)_4$	1,4-Dioxane	rt	12	–(35)[e]
3	$PdCl_2/2PPh_3$	1,4-Dioxane	rt	12	–(32)[e]
4	$Pd(PPh_3)_4$	1,4-Dioxane	80	4	79[f]
5	$Pd(PPh_3)_4$	1,4-Dioxane	80	4	89[g]
6	$Pd(PPh_3)_4$	1,4-Dioxane	80	4	49[h]
7	$Pd(PPh_3)_4$	DME	80	4	78
8	$Pd(PPh_3)_4$	CH_3CN	80	4	80
9	$Pd(PPh_3)_4$	THF	80	4	47
10	$PdCl_2(PhCN)_2$	1,4-Dioxane	80	4	51
11	$Pd(PPh_3)_4$	1,4-Dioxane	rt	4	48
12	–	1,4-Dioxane	80	4	–(20)

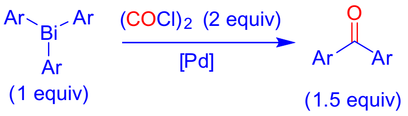
[a] Pd catalyst (0.09 equiv), $BiPh_3$ (1 equiv), $(COCl)_2$ (2 equiv), solvent (3 mL).
[b] Isolated yields are given.
[c] GC conversions are given in parenthesis.
[d] Biphenyl as minor side product formed in these reactions.
[e] Condition: Pd catalyst (0.15 equiv), PPh_3 (0.30 equiv), $BiPh_3$ (1 equiv), $COCl_2$ (2 equiv), Et_3N (5 equiv)
[f] With Et_3N (2 equiv).
[g] Without Et_3N.
[h] With $(COCl)_2$ (1 equiv).

chloride provided only moderate yield of ketone (entry 6). This may be due to insufficient amount of oxalyl chloride (1 equiv) used in the reaction to carbonylate 3 equiv of phenyl groups from triphenylbismuth reagent. So, further study was carried out with 2 equiv of oxalyl chloride. The screening carried out with different solvents, catalysts, and temperature conditions (entries 7–11) revealed that 2 equiv of oxalyl chloride at 80 °C in 1,4-dioxane is optimal to obtain high yield of ketone (entry 5). A control reaction without catalyst provided very poor yield of the carbonylation product (entry 12). Another reaction without oxalyl chloride under these conditions furnished homo-coupled biphenyl as a product from triphenylbismuth reagent.[10]

So, to expand the scope of this carbonylation, further studies have been carried out with divergently functionalized $BiAr_3$ reagents under the established coupling conditions[14] (Table 2). These reactions involving different triarylbismuth reagents reacted in a facile manner in the carbonylative couplings to furnish high yields of the corresponding functionalized ketones. It is noteworthy that both electron-rich and electron-deficient triarylbismuth compounds fared well to give various functionalized ketones under the established protocol.

Encouraged by these novel carbonylative couplings of triarylbismuths with oxalyl chloride, the corresponding carbonylation studies using arylindium reagents are of interest as these compounds showed facile reactivity under CO conditions.[15a,15b]

Table 2
Carbonylations of triarylbimuths[a–d]



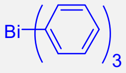
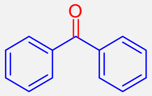
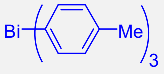
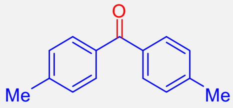
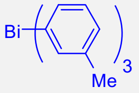
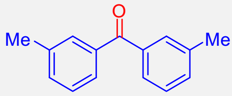
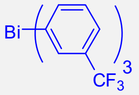
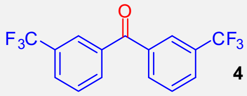
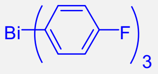
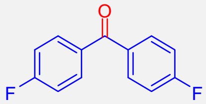
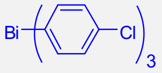
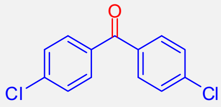
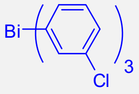
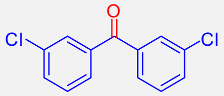
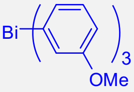
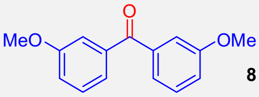
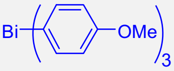
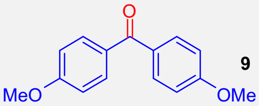
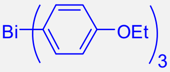
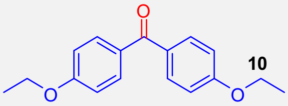
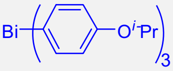
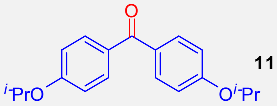
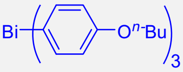
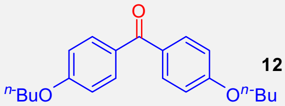
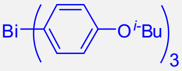
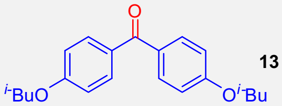
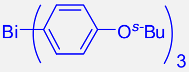
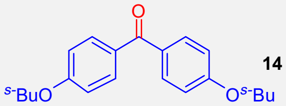
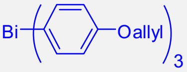
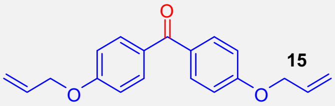
Entry	Triarylbismuth	Ketone	Yield (%)
1		 **1**	89
2		 **2**	80
3		 **3**	76
4		 **4**	70
5		 **5**	86
6		 **6**	82
7		 **7**	80

Table 2 (*continued*)

Entry	Triarylbismuth	Ketone	Yield (%)
8		 8	77
9		 9	84
10		 10	82
11		 11	76
12		 12	78
13		 13	75
14		 14	79
15		 15	72

[a] Conditions: $Pd(PPh_3)_4$ (0.09 equiv), $BiAr_3$ (1 equiv), $(COCl)_2$ (2 equiv), 1,4-dioxane (3 mL), 80 °C, 4 h.

[b] Isolated yields are given.

[c] Biaryls as minor side product formed in some reactions.

[d] All the ketone products were characterized by ^1H NMR, ^{13}C NMR, IR, and HRMS analyses.

Table 3

Screening with $InPh_3$[a–d]

$$InPh_3 + (COCl)_2 \xrightarrow{[Pd]} PhCOPh$$

(**1**)

Entry	Catalyst	Temp (°C)	Time (h)	Yield (%)
1	$Pd(PPh_3)_4$	rt	4	38
2	$Pd(PPh_3)_4$	40	4	54
3	$Pd(PPh_3)_4$	60	1	58
4	$Pd(PPh_3)_4$	60	3	76
5	$Pd(PPh_3)_4$	60	4	83
6	$PdCl_2(PhCN)_2$	60	4	–(16)
7	–	60	4	–(4)

[a] Conditions: Pd catalyst (0.09 equiv), $InPh_3$ (1 equiv), $(COCl)_2$ (2 equiv), THF (5 mL).

[b] Isolated yields are given.

[c] GC conversions are given in parenthesis.

[d] Biphenyl as minor side product formed in these reactions.

A brief screening of triphenylindium with oxalyl chloride was carried out as given in Table 3. The carbonylations using in situ-generated $InPh_3$[15c] offered moderate yield of benzophenone (**1**) at lower temperature conditions (entries 1 and 2). Further screening revealed $Pd(PPh_3)_4$ in THF solvent at 60 °C for 4 h (entry 5) as effective condition for carbonylation (entries 3–6). A control reaction without catalyst produced very poor amount of the carbonylation product (entry 7). Without oxalyl chloride under these conditions the reaction gave homo-coupled biphenyl as a product from triphenylindium reagent.

With the optimum condition in hand for the carbonylation of indium reagents, we elaborated the study with different triarylindium reagents[16,17] (Table 4). The reactions using different triarylindiums showed excellent reactivity in carbonylative couplings leading to the corresponding functionalized aromatic ketones in high yields. The coupling reactivity of both triarylbismuths and triarylindiums was found to be almost similar under the conditions studied. Thus the present process served as a novel carbonylation procedure using oxalyl chloride. This is a first successful demonstration of oxalyl chloride to serve as a C1 carbonyl synthon under palladium catalysis and is a long wait after Stille's initial observation.[12]

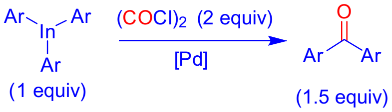
It is to be mentioned that carbonylative cross-coupling of organometallic reagents with organic electrophiles is a known route for the synthesis of ketones.[18] However, the corresponding carbonylative homo-coupling to give ketones is somewhat difficult in terms of reactivity and selectivity.[19]

For example, the rhodium- or palladium-catalyzed carbonylations of triarylbismuths led to the formation of either ketone or ester products depending on the conditions employed with atmospheric pressure of CO.[19a,19b] However, in this study it was also mentioned that the carbonylative couplings of triarylbismuths with CO were found to be ineffective with complexes such as

$Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, and $Pd(CO)(PPh_3)_3$ to give ketone products.[19b] Whereas the present method with $Pd(PPh_3)_4$ catalyst is effective for carbonylations of both triarylbismuths and triarylindiums using oxalyl chloride as carbonylating agent. Thus, the method described is uniquely advantageous as oxalyl chloride is serving as C1 synthon in a novel decarbonylative carbonylation process in the presence of palladium catalyst.

To understand the carbonylation process, we have carried out some cross-over experiments with the combination of two different triarylbismuths as given in Scheme 1. The product distribution

Table 4
Carbonylations of triaryindiums[a–d]



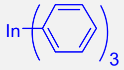
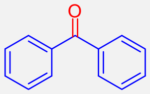
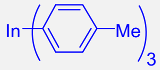
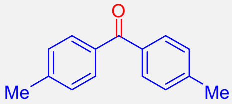
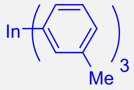
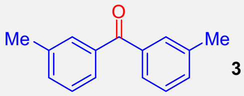
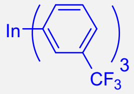
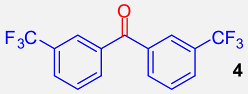
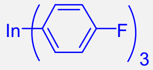
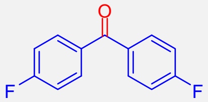
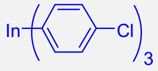
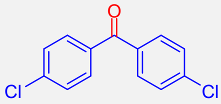
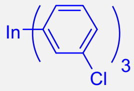
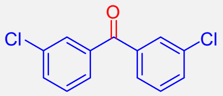
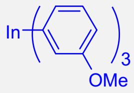
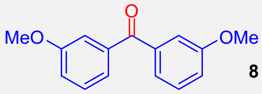
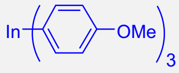
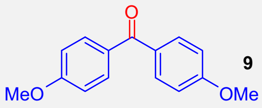
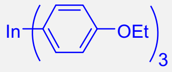
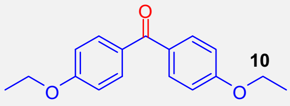
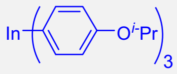
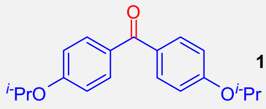
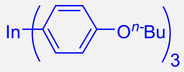
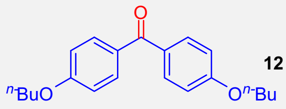
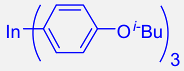
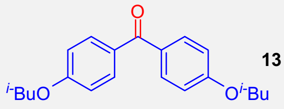
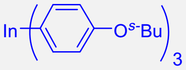
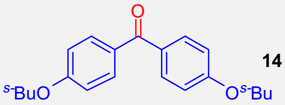
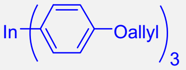
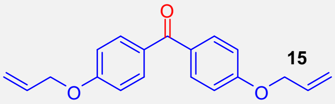
Entry	Triarylbismuth	Ketone	Yield (%)
1		 **1**	83
2		 **2**	71
3		 **3**	74
4		 **4**	69
5		 **5**	79
6		 **6**	71
7		 **7**	70
8		 **8**	76
9		 **9**	79
10		 **10**	70
11		 **11**	68
12		 **12**	67
13		 **13**	68

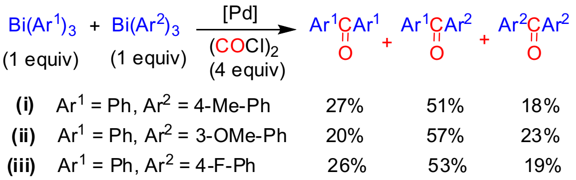
Table 4 (*continued*)

Entry	Triarylbismuth	Ketone	Yield (%)
14		 14	71
15		 15	70

[a] Condition for $InAr_3$: $Pd(PPh_3)_4$ (0.09 equiv), $InAr_3$ (1 equiv), $(COCl)_2$ (2 equiv), THF (5 mL), 60 °C, 4 h.
[b] Isolated yields are given.
[c] Biaryls as minor side product formed in some reactions.
[d] All the ketone products were characterized by ^{1}H NMR, ^{13}C NMR, IR, and HRMS analyses.

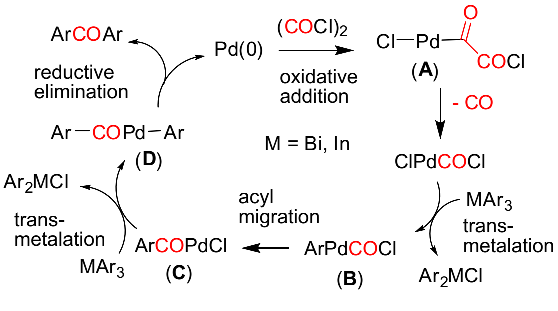
based on GC–MS analysis is given. In general, these experiments revealed the formation of unsymmetrical ketones derived from two different triarylbismuths along with symmetrical ketones directly from single triarylbismuth reagent. However, the formation of minor amounts (<2%) of homo-coupled biaryls was also observed in (**i**) and (**iii**) reactions (Scheme 1).[10] Hence, these cross-over experiments indicated: (i) the relative propensity of the aryl group transfer from different Ar-Bi species to give mixed ketones; (ii) the participation of three aryl groups from triarylbismuths in carbonylative couplings; (iii) the involvement of two different Ar-Bi species in the catalytic cycle to give mixed ketones. Importantly, similar trend of formation of mixed ketones was observed by Seyferth and Spohn in the carbonylations of organomercurials using metal carbonyls.[20]

Based on the above observations, the catalytic cycle proposed for carbonylative couplings is given in Scheme 2. The initial oxidative addition of oxalyl chloride to Pd(0) would give intermediate, **A**. This upon decarbonylation[21] followed by transmetalation with Ar-M (M = Bi, In) generates intermediate, **B**. This may undergo acyl migration and second transmetalation to give diorganylpalladium **D** via the intermediate **C**. Reductive elimination of intermediate **D** is expected to deliver the ketone product. The formation of mixed ketones in cross-over experiments supports two time involvement of Ar-Bi species during catalytic cycle. Alternate formation of **B** via transmetalation of **A** with Ar-M followed by decarbonylation cannot be ruled out at this stage.



(i)	Ar^1 = Ph, Ar^2 = 4-Me-Ph	27%	51%	18%
(ii)	Ar^1 = Ph, Ar^2 = 3-OMe-Ph	20%	57%	23%
(iii)	Ar^1 = Ph, Ar^2 = 4-F-Ph	26%	53%	19%

Scheme 1. Cross-over experiments. Reagents and conditions: (a) $Pd(PPh_3)_4$ (0.18 equiv), $BiAr_3^1$ (1 equiv) and $BiAr_3^2$ (1 equiv), $(COCl)_2$ (4 equiv), 1,4-dioxane (6 mL), 80 °C, 4 h; (b) GC–MS ratios are given.



Scheme 2. Proposed catalytic cycle.

In summary, we have demonstrated the use of oxalyl chloride as C1 carbonyl synthon in the carbonylation of triarylbismuth and triarylindium nucleophiles under palladium-catalyzed conditions. This is a novel protocol involving oxalyl chloride as facile alternative source of CO for carbonylations under palladium catalysis. In addition all the three aryl groups from both bismuth and indium reagents participated in carbonylative couplings to afford functionalized ketones in high yields. Given the need for the use of alternative carbonylating agents in metal-catalyzed carbonylations,[4] this study is expected to have immense synthetic potential in that direction. As the synthetic reactions using oxalyl chloride under metal catalysis are scarce, the present method would open up a plethora of opportunities in the use of oxalyl chloride as C1 carbonyl synthon for various synthetic applications.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.074.

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13. In our earlier couplings with acid chlorides, Et_3N was found to be beneficial as an additive (Ref. 11).
14. General procedure for the carbonylations of $BiAr_3$ with oxalyl chloride: A 50-mL oven-dried Schlenk tube was charged with $BiAr_3$ (0.5 mmol), $Pd(PPh_3)_4$ (0.045 mmol), and anhydrous 1,4-dioxane (3 mL) under nitrogen atmosphere. Then oxalyl chloride (1.0 mmol) was added and the contents were stirred at 80 °C for 4 h. After the reaction time, 1,4-dioxane was removed under vacuum. The residue was treated with water and extracted with ethyl acetate (25 mL × 1). The organic extract was washed with 10% HCl (5 mL × 1), brine (5 mL × 2), dried over anhydrous $MgSO_4$, and concentrated. The crude material was purified by column chromatography (SiO_2 60–120, ethyl acetate/petroleum ether as an eluent) to obtain the pure ketone product. All the ketone products were characterized by ^1H NMR, ^{13}C NMR, IR, and HRMS studies.
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16. The $InAr_3$ reagents used for carbonylation studies were prepared by following the reported procedure.[15c] Indium(III) chloride (0.5 mmol, 0.1105 g) was placed in a round-bottomed flask with a stirring bar and heated with a heat gun under high vacuum for 0.5 h. Once it was completely dried, the flask was filled with nitrogen and re-evacuated. Then THF (5 mL) was added through a syringe. To this, ArMgBr (1.62 mmol) was added dropwise via a pressure-equalizing funnel for about 1 h. The contents of the flask were allowed to stir for 0.5 h. The resultant triarylindium solution was directly used for carbonylation reactions using oxalyl chloride.
17. General procedure for the carbonylations of $InAr_3$ with oxalyl chloride: A 50-mL oven-dried Schlenk tube was charged with $InAr_3$ (0.5 mmol) in THF solvent. To this, $Pd(PPh_3)_4$ (0.045 mmol) catalyst was added followed by oxalyl chloride (1.0 mmol). The contents were stirred at 60 °C for 4 h. After the reaction, THF solvent was removed under vacuum. The residue was treated with water and extracted with ethyl acetate (25 mL × 1). The organic extract was washed with 10% HCl (5 mL × 1), brine (5 mL × 2), dried over anhydrous $MgSO_4$, and concentrated. The crude material was purified by column chromatography (SiO_2 60–120, ethyl acetate/petroleum ether as an eluent) to obtain the pure ketone product. All the ketone products were characterized by ^1H NMR, ^{13}C NMR, IR, and HRMS studies.
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