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FULL PAPER

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Cesium carbonate-catalyzed indium insertion into alkyl iodides and their synthetic utilities in cross-coupling reactions

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A catalytic amount of cesium carbonate (10 mol%) was found to be capable of effectively catalyzing the insertion of indium powder into alkyl iodides. The thus-generated alkyl indium reagents could readily undergo palladium-catalyzed cross-coupling reactions with a wide variety of aryl halides, showing compatibility to a range of important functional groups.

KEYWORDS

alkyl indium reagent, cesium carbonate, cross-coupling reaction, indium, palladium

1 | INTRODUCTION

In recent decades, organoindium reagents[1] have found broad utilities in synthetic organic chemistry because of their unique properties (e.g. mild reactivities, good functional group tolerance, and good chemo- and stereoselectivities) as compared with other more reactive organometallic compounds,[2] and their capabilities to participate in a wide variety of organic transformations.[1,3] Generally, organoindium reagents could be synthesized by means of the transmetallation of more reactive organometallic reagents with indium (III) salt[4] or via the direct indium insertion into organohalides.[5–9] However, the direct insertion of indium into some unactivated organohalides normally could not take place with the sole use of indium metal in the absence of any additive or catalyst. With regard to relatively less reactive organic halides, such as aryl halides,[5] alkenyl halides,[6] benzyl halides[7] and alkyl halides,[8] the insertion reactions usually should be conducted in the co-existence of stoichiometric amounts of additives (such as LiX[5,6,7a,8c,d,10] or CuX[8a–c]). Recent advancements from our lab have shown that a catalytic amount of indium (III) chloride or iodine was also able to catalyze the direct insertion of metallic indium into alkyl halides.[11] In continuation of our efforts to develop efficient methods for the generation of organoindium reagents, herein we describe an efficient methodology for the synthesis of alkyl indium compounds through a Cs_2CO_3-catalyzed[12] direct oxidative addition of indium powder into alkyl iodides, as well as their ensuing cross-coupling reactions with a variety of aryl halides. Both the insertion and the subsequent

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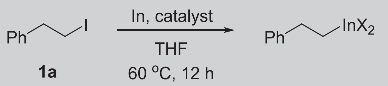
cross-coupling reaction worked with good efficiency, showing good tolerance to various functional groups.

2 | RESULTS AND DISCUSSION

Initially, a myriad of bases were tested to see their performance in catalyzing the direct indium insertion into typical alkyl iodide of (2-iodoethyl)benzene (**1a**) in THF at 60°C for 12 hr. As outlined in Table 1, it was good to find that various bases were capable of catalyzing the insertion reaction with differing catalytic activities. Of the different metallic carbonates screened (entries 1–6), cesium carbonate exhibited the best catalytic activity, leading to the desired alkyl indium reagent in 80% NMR yield (entry 4). In contrast to inorganic base, the use of organic base as reaction catalyst led to either poor product yield (entry 7) or no visible formation of product (entries 8 and 9). In addition, we also examined the use of some other cesium salts as reaction catalyst (entries 10–12); however, only reduced performances were observed when they were used in place of cesium carbonate. The results indicated that both cesium cation and carbonate ion were effective for the smooth progress of the transformation, though the reasons behind the catalytic effect are not clear thus far. It is interesting to know that base could also be used to catalyze the present indium insertion reaction. Moreover, it should be mentioned that the reaction either could not work in the absence of any catalyst (entry 13) or proceeded sluggishly when relatively less reactive (2-bromoethyl)benzene or (2-chloroethyl)benzene was used in place of (2-iodoethyl)benzene (< 5% yield).

TABLE 1 Optimization of reaction conditions[a]



Entry	Catalyst	Yield (%)[b]
1	Li_2CO_3	54
2	Na_2CO_3	30
3	K_2CO_3	25
4	$\mathbf{Cs_2CO_3}$	**80 (53)**[c]
5	Ag_2CO_3	45
6	$NaHCO_3$	0
7	DMAP	34
8	DBU	0
9	DBACO	0
10	CsCl	52
11	CsBr	76
12	CsOAc	27
13	–	0

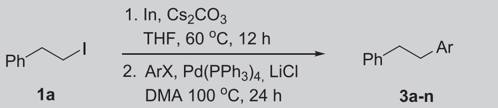
[a] The insertion step was performed at 60°C for 12 hr by using (2-iodoethyl) benzene (**1a**, 1 mmol), indium (1.5 mmol), catalyst (0.1 mmol) in THF (2 ml).

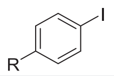
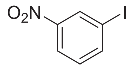
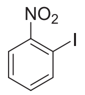
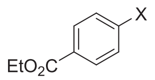
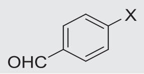
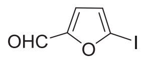
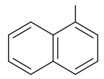
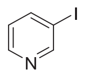
[b] The yield was determined by ^{1}H-NMR spectroscopy by using 1,4-dimethoxybenzene as an internal standard.

[c] Using 1 equiv. of indium powder.

With cesium carbonate being recognized as the most efficient base catalyst for the insertion reaction, subsequently we investigated the substrate scope of the reaction by applying the formed alkyl indium reagent to

TABLE 2 Substrate scope study by using various aryl halides[a,b]



Entry	Substrate	Product	Yield (%)[b]
	 R I		
1	**2a** (R = Ac)	**3a**	81
2	**2b** (R = CN)	**3b**	71
3	**2c** (R = NO_2)	**3c**	89
	 O_2N I		
4	**2d**	**3d**	87
	 NO_2 I		
5	**2e**	**3e**	98
	 EtO_2C X		
6	**2f** (X = I)	**3f**	52
7	**2g** (X = Br)	**3g**	63
	 OHC X		
8	**2h** (X = I)	**3h**	84
9	**2i** (X = Br)	**3i**	44
	 OHC O I		
10	**2j**	**3j**	58
			
11	**2k**	**3k**	85
	 N I		
12	**2l**	**3l**	70

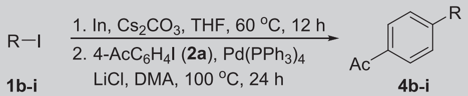
[a] See the Supporting Information for detailed reaction conditions.

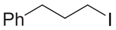
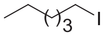
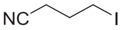
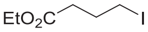
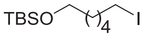
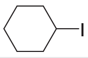
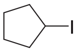
[b] Yield of isolated product based on aryl halides **2a–l** as limiting reagent.

palladium-catalyzed cross-coupling reactions with various aryl halides. As shown in Table 2, the thus-generated alkyl indium compound efficiently underwent Pd-catalyzed reactions with a wide variety of aryl halides, producing the corresponding cross-coupled products in moderate to good yields. Aryl iodides containing nitro group at the *para*, *meta* and *ortho* positions of the phenyl ring all reacted well with alkyl metallic reagent to deliver the expected products **3c–e** with equal ease (entries 3–5). Besides normal aryl halides, heteroaryl iodides (e.g. **2j** and **2l**) were also proven to be suitable substrates for the coupling reactions, affording the desired products **3j** and **3l** in reasonable yields (entries 10 and 12). A range of functional groups, including acetyl (**2a**), cyano (**2b**), nitro (**2c–e**), ester (**2f–g**) and formyl (**2h–j**), were found to be compatible with the mild reaction conditions, which could potentially be derivatized at a stage where they are required.

Next, a spectrum of structurally varied alkyl iodides was surveyed as reaction substrates. As shown in Table 3, alkyl iodides **1b–d** with varying carbon chain length were amenable to the insertion reaction as well as the ensuing palladium-catalyzed cross-coupling reactions with aryl iodide **2a**, giving rise to the anticipated products **4b–d** in good yields (entries 1–3). In the same manner, alkyl iodides containing cyano (**1e**), ester (**1f**) and OTBS (**1g**) group also participated well in the organic transformations, providing the corresponding products **4e–g** in moderate to good yields (entries 4–6). Aside from linear alkyl iodides, branched alkyl iodides **1h–i** were also able to effectively undergo the reactions with moderate performance, leading to the cross-coupled products **4h–i** in acceptable yields (entries 7 and 8). However, no desired product was obtained when sterically hindered *tert*-BuI was used as substrate, which might be due to the steric hindrance of the *t*-Bu group.

TABLE 3 Substrate scope study by using various alkyl iodides[a]



Entry	Substrate	Product	Yield (%)[b]
1	 **1b**	**4b**	73
2	 **1c**	**4c**	84
3	 **1d**	**4d**	94
4	 **1e**	**4e**	86
5	 **1f**	**4f**	44
6	 **1g**	**4g**	45
7	 **1h**	**4h**	53
8	 **1i**	**4i**	64

[a]See the Supporting Information for detailed reaction conditions.

[b]Yield of isolated product based on aryl iodide **2a** as limiting reagent.

3 | CONCLUSIONS

In summary, a catalytic amount of cesium carbonate (10 mol%) was found to be capable of effectively catalyzing the insertion of indium powder into alkyl iodides. The generated alkyl indium reagents could be easily transformed into cross-coupled products after undergoing palladium-catalyzed cross-coupling reactions with a wide variety of aryl halides. A range of important functional groups were tolerated, due to the mild reaction conditions and the mildness of the formed alkyl indium compounds.

4 | EXPERIMENTAL

4.1 | The insertion step 1

Alkyl iodide (1 mmol), indium (172.2 mg, 1.5 mmol), cesium carbonate (32.6 mg, 0.1 mmol) and analytical grade THF (2 ml) were added in a flask equipped with a septum and a magnetic stir bar. The reaction mixture was vigorously stirred at 60°C for 12 hr. Then, the upper clear solution was carefully separated from the bottom black precipitate by centrifuge. The remaining black precipitate was additionally stirred with THF (3 ml), and the THF layer was carefully separated from the bottom precipitate by pipette. The combined organic layers were concentrated under vacuum. The crude mixture was directly used in the next step without further purification.

4.2 | The cross-coupling step 2

To the above residue was added aryl halide (0.7 mmol), LiCl (84.8 mg, 2 mmol), Pd $(PPh_3)_4$ (57.8 mg, 0.05 mmol) and DMA (2 ml), and the reaction mixture was stirred at 100°C for 24 hr. Upon completion of the reaction, the reaction mixture was directly purified by flash silica gel column chromatography using petroleum ether/ethyl acetate as eluent to afford the pure products.

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