

Synthesis of Alkyl Indium Reagents by Using Unactivated Alkyl Chlorides and Their Applications in Palladium-Catalyzed Cross-Coupling Reactions with Aryl Halides

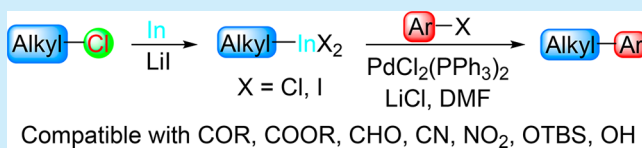
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S Supporting Information

ABSTRACT: An efficient method for the preparation of alkyl indium reagents by using unactivated and cheap alkyl chlorides as substrates in the presence of indium and LiI was developed. The thus-formed alkyl indium species effectively underwent palladium-catalyzed cross-coupling reactions with aryl halides with wide functional group tolerance.



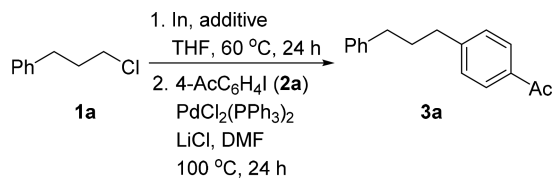
Organometallic reagents play a central role in organic synthesis.¹ In recent decades, apart from the extensive utilization of conventional organometallic reagents¹ (such as organolithium, organomagnesium, and organozinc) in synthetic organic chemistry, organoindium reagents have emerged as powerful and appealing reagents for various organic transformations as a result of their ready accessibility, mild reactivity, good chemoselectivity, and excellent compatibility with a broad range of important functional groups.² Since the first introduction of an organoindium reagent in organic synthesis by Nomura and co-workers in 1992,³ the synthetic versatility of organoindium reagents has been further demonstrated by Sarandeses, Perez Sestelo, Lee, Minenan, Lei, and others in transition metal-catalyzed cross-coupling reactions of triorganoindium reagents (R₃In; prepared by transmetalation of RMgCl or RLi with InCl₃) with organohalides.⁴ The findings thereafter have shown that organoindium reagents also can be conveniently prepared either by direct insertion of indium(0) into organohalides in the presence of an additive (e.g., LiCl, CuX) or by other miscellaneous methods (e.g., carboidation), as demonstrated by Knochel,⁵ Lee,⁶ Minehan,⁷ Yoshikai,⁸ Baba,⁹ our group,¹⁰ and others,¹¹ arousing further interest and applications of organoindium reagents in organic synthesis. Until now, the previously reported methods for the preparation of organoindium reagents via the direct insertion of indium into organohalides are largely limited to the use of relatively more reactive benzyl halides or aryl/alkyl iodides and bromides. In comparison, the synthesis of alkyl indium reagents commencing from cheap, stable, and unactivated alkyl chlorides remains unexplored. In continuation of our efforts to develop indium chemistry in our group,^{10,12} herein, we report an efficient method for the preparation of alkyl indium reagents by using unactivated alkyl chlorides as substrates in the presence of

indium and LiI. The thus-obtained alkyl indium species effectively underwent palladium-catalyzed cross-coupling reactions with aryl halides with wide functional group tolerance.

To begin with, 1-chloro-3-phenylpropane (**1a**) was employed as a model substrate in the presence of a variety of additives to study the feasibility of indium insertion (THF, 60 °C, 24 h) as well as a subsequent palladium-catalyzed cross-coupling reaction with 4-iodoacetophenone (**2a**) in the presence of PdCl₂(PPh₃)₂ (5 mol %) and LiCl (2 equiv) in DMF at 100 °C. As shown in Table 1, when LiCl⁵ or CuCl^{10a} was employed as additive, almost no insertion reaction of indium powder (2 equiv) was observed (entries 1 and 2). Attempts to improve the reaction efficiency by using either LiBr or CuBr also failed (entries 3 and 4). Gratifyingly, when LiI was introduced as reaction additive, both the insertion and the subsequent cross-coupling reaction proceeded efficiently to give the desired product **3a** in 95% yield (entry 5). However, when LiI was replaced by other metallic iodides (e.g., NaI, CuI, ZnI₂, AgI, InI₃), the reaction was found to proceed sluggishly (<5% yield; entries 6–10). It is evident that both Li⁺ and I⁻ play vital roles in promoting the reactions,¹³ and I⁻ might activate the alkyl chloride by converting it to more reactive alkyl iodide via Felkinstein-type reaction pathway. To test this hypothesis, we also performed the reaction of (2-chloroethyl)benzene (**1b**) with LiI under the optimized reaction conditions (THF, 60 °C, 24 h) in the absence of indium. As expected, it was found that 70% conversion of alkyl chloride **1b** to the corresponding alkyl iodide was achieved based on NMR analysis of reaction mixture after 24 h. Moreover, we also performed the insertion reaction of indium with (2-chloroethyl)benzene (**1b**) in the presence of

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Table 1. Optimization of Reaction Conditions^a

entry	additive	yield (%) ^b
1	LiCl	<5
2	CuCl	<5
3	LiBr	<5
4	CuBr	<5
5	LiI	95
6	NaI	<5
7	CuI	<5
8	ZnI ₂	<5
9	AgI	<5
10	InI ₃	<5

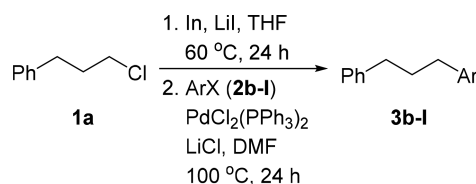
^aThe insertion step was performed at 60 °C for 24 h by using 1-chloro-3-phenylpropane (**1a**, 1 mmol), indium (2 mmol), additive (2 mmol) in THF (2 mL); the cross-coupling reaction was performed at 100 °C for 24 h by using 4-iodoacetophenone (**2a**, 0.7 mmol), PdCl₂(PPh₃)₂ (5 mol %), and LiCl (2 mmol) in DMF (2 mL).
^bIsolated yield.

LiI under the optimized reaction conditions. On the basis of the NMR analysis of the reaction mixture after 24 h, the formation of two different types of alkyl indium reagents (presumably as a mixture of R₂InX and RInX₂ or in the form of an aggregated indium sesquihalide R₃In₂X₃) with >80% conversion was observed, which is also in accordance with previously documented observations.^{8a,10a} After LiI was established as an efficient reaction additive, subsequently we explored the substrate scope of the reaction by using different alkyl chlorides as substrates and aryl halides as coupling partners.

As shown in Table 2, the alkyl indium reagents prepared by indium insertion in the presence of LiI effectively underwent PdCl₂(PPh₃)₂-catalyzed cross-coupling reactions with a variety of aryl halides to produce the cross-coupling products **3b–l** in moderate to good yields. In addition to aryl iodides, aryl bromide and chloride (**2g** and **2i**) were also proven to be suitable coupling partners for the reactions. Moreover, heteroaryl iodides containing furyl and pyridinyl substituents worked equally well under the optimized reaction conditions (**2k** and **2l**). Furthermore, a wide array of important functional groups (e.g., nitro, cyano, carbonyl, and formyl group) survived the present reaction conditions and were kept intact during the course of the reaction.

The substrate scope of the present protocol was further surveyed by utilizing a wide range of structurally varied alkyl chlorides as starting materials. As shown in Table 3, various alkyl chlorides were demonstrated to be appropriate substrates for the reaction, leading to the anticipated cross-coupling products in yields ranging between 52% and 94%. Most importantly, alkyl chlorides bearing cyano, carbonyl, hydroxyl, TBS, C=C, and other functionalities well tolerated the mild reaction conditions and, thus, could be kept for late-stage functional group manipulation.

To further demonstrate the effectiveness and mildness of the present method, an organoindium reagent synthesized by the insertion of indium into 4-chlorobutanenitrile (**1d**) was subjected to cross-coupling with (2-iodophenyl)methanol

Table 2. Substrate Scope Study by Using Various Aryl Halides^a

entry	additive	product	yield (%) ^b
1		3b	81
2		3c	71
3		3d	87
4		3e	94
5		3f	77
6		3g	62
7		3h	70
8		3i	49
9		3j	65
10		3k	70
11		3l	68

^aSee the Supporting Information for detailed reaction conditions.

^bYield of isolated product based on aryl halides **2** as limiting reagent.

Table 3. Substrate Scope Study by Using Various Alkyl Chlorides^a

entry	substrate	product	yield (%) ^b
1		4b	94 (71) ^c (79) ^d
2		4c	74
3		4d	86
4		4e	80
5		4f	76
6		4g	52
7		4h	71
8		4i	69
9		4j	62
10		4k	81

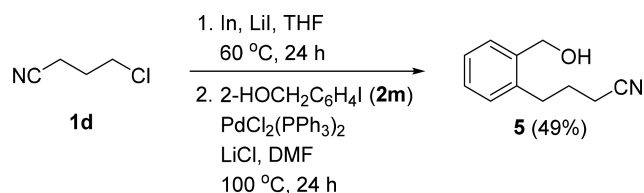
^aSee the Supporting Information for detailed reaction conditions.

^bYield of isolated product based on aryl iodide **2a** as limiting reagent.

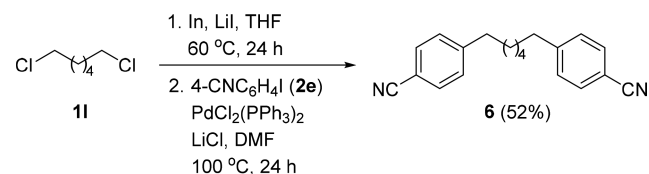
^cIndium (1 equiv) was used. ^d0.8 equiv **2a** was used as limiting reagent.

(**2m**) containing a labile hydroxyl group. As expected, the reaction proceeded with good compatibility with hydroxyl group to afford the corresponding product **5** in a moderate yield of 49% (Scheme 1).

In addition, dichloro-containing alkane **11** was also capable of undergoing indium insertion to give the desired alkyl indium species possessing two indium atoms. Upon Pd-catalyzed cross-coupling with 4-iodobenzonitrile (**2e**) under the optimum

Scheme 1. Substrate Scope Study by Using Hydroxyl-Containing Aryl Iodide (**2m**) as Coupling Partner

reaction conditions, product **6** was delivered in an acceptable yield (52%; Scheme 2).

Scheme 2. Substrate Scope Study by Using 1,6-Dichlorohexane (**11**) as Substrate

In summary, we have developed an efficient method for the synthesis of an alkyl indium reagent by indium insertion into unactivated alkyl chlorides. LiI was demonstrated to be an additive of choice for promoting the insertion reaction among all the additives screened. The thus-formed alkyl indium reagents participated in palladium-catalyzed cross-coupling reactions with various aryl halides to afford the desired products in moderate to good yields. The mild reaction conditions also allowed the presence of a spectrum of important functionalities, such as nitro, cyano, formyl, and hydroxyl groups, either in the alkyl chloride substrates or in the aryl halide coupling partners. Further applications of the method in organic synthesis are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00441.

Experimental procedures, characterization data, and NMR spectra of products (PDF)

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Notes

The authors declare no competing financial interest.

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they believed that LiCl might help to dissolve the formed organometallic reagent on the metal surface so that the metal is clean enough to allow further insertion reaction to proceed on its surface; see: Blümke, T. D.; Chen, Y. H.; Peng, Z.; Knochel, P. *Nat. Chem.* **2010**, 2, 313–318. We speculated that Li⁺ (or the in situ generated LiCl in our protocol after the reaction of alkyl chloride with LiI) should also play the same role.