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## COMMUNICATION

## Direct synthesis of ester-containing indium homoenolate and its application in palladium-catalyzed cross-coupling with aryl halide†

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**An efficient method for the synthesis of ester-containing indium homoenolate *via* a direct insertion of indium into  $\beta$ -halo ester in the presence of CuI/LiCl was described. The synthetic utility of the indium homoenolate was demonstrated by palladium-catalyzed cross-coupling with aryl halides in DMA with wide functional group compatibility.**

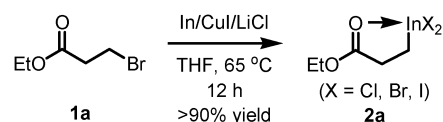
Homoenolate<sup>1</sup> is useful synthon for organic synthesis as it readily allows the nucleophilic functionalization of organic molecules with a carbonyl-containing three-carbon moiety. The first efficient method for the preparation of synthetically useful metal homoenolate was reported by Kuwajima and Nakamura *via* siloxycyclopropane ring-opening with various metal halides.<sup>2</sup> Later on, Yoshida *et al.* described an alternative method for the synthesis of zinc homoenolate *via* a direct insertion of zinc to  $\beta$ -iodo ester.<sup>3</sup> In addition, Knochel and others also have developed other typical methods for the preparation of metal homoenolates.<sup>4</sup> Recently, it was found that homoenolate intermediates also can be easily generated from enals in the presence of a nucleophilic heterocyclic carbene (NHC) catalysis.<sup>5</sup>

More recently, our group has described the synthesis of a ketone-type indium homoenolate *via* oxidative addition of indium(i) halide to enone in aqueous media, as well as its application in the synthesis of 1,4-dicarbonyl compounds *via* palladium-catalyzed cross-coupling with acid chloride.<sup>6</sup> However, by using this method, our attempt to synthesize the ester-containing indium homoenolate was unsuccessful because the  $\alpha,\beta$ -unsaturated ester remained intact under the aforementioned conditions. On the other hand, to the best of our knowledge, currently there is no report available associated with the preparation of the ester-containing indium homoenolate. Therefore, it is still desirable to develop an efficient method for the synthesis of the synthetically useful ester-containing indium homoenolate. Recent development in organoindium chemistry has indicated that organoindium reagents show great tolerance to important functional groups

such as formyl and hydroxyl groups.<sup>6–8</sup> We envisaged that if the ester-containing indium homoenolate can be successfully prepared, it will allow the transition metal-catalyzed cross-coupling with aryl halide to take place with wide functional group tolerance. In continuation of our efforts in exploring facile methods for the synthesis of indium homoenolate as well as its application in organic synthesis, herein we report an efficient method for the synthesis of ester-containing indium homoenolate *via* a direct insertion of indium into  $\beta$ -halo ester in the presence of CuI/LiCl. The synthetic utility of the ester-containing indium homoenolate was demonstrated through the synthesis of  $\beta$ -aryl ester<sup>9</sup> *via* a palladium-catalyzed cross-coupling<sup>10,11</sup> with aryl halide in DMA with wide functional group compatibility.

Initially, commercially available ethyl 3-bromopropionate (**1a**) was chosen as a substrate to optimize the reaction conditions for the synthesis of ester-containing indium homoenolate **2a** *via* a direct insertion of indium into  $\beta$ -halo ester. After many trials, it was found that the insertion proceeded efficiently in the presence of one equiv. of indium, one equiv. of CuI, and one equiv. of LiCl<sup>8a–c</sup> in refluxing THF, affording exclusively the ester-containing indium homoenolate **2a**<sup>12</sup> in excellent yield (>90%, Scheme 1). Both CuI and LiCl are indispensable for the efficient transformation of **1a** to **2a**: without the use of LiCl, the reaction proceeded sluggishly; without the use of CuI, mainly two types of organoindium reagents were generated (see ESI† for details of <sup>1</sup>H NMR comparison of the reaction products obtained under different conditions). As a result, both CuI and LiCl were employed as additives for the insertion reaction in order to exclusively generate a single type of ester-containing indium homoenolate.

Transition metal-catalyzed cross-coupling of organoindium reagents with various aryl halides has emerged as one of the most powerful platforms for carbon–carbon bond formation because of its mild reaction conditions and its compatibility with a wide variety of functional groups.<sup>6–8,10</sup>



**Scheme 1** Synthesis of ester-containing indium homoenolate **2a** from ethyl 3-bromopropionate (**1a**).

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**Table 1** Screening of various organic solvents<sup>a</sup>

Entry	Solvent	T/°C	Yield <sup>b</sup> (%)	
			4a	4a'
1	THF	65	< 10	— <sup>c</sup>
2	1,4-Dioxane	70	< 10	— <sup>c</sup>
3	Toluene	70	< 10	— <sup>c</sup>
4	<i>n</i> -PrOH	70	< 10	— <sup>c</sup>
5	CH <sub>3</sub> NO <sub>2</sub>	70	< 10	— <sup>c</sup>
6	NMP	50	30	0
7	NMP	70	72	12
8	DMSO	70	48	9
9	DMF	70	64	8
10	DMA	70	83	4

<sup>a</sup> Unless otherwise noted, the reactions were carried out at 50–70 °C for 24 h using indium homoenolate **2a** (~1.0 mmol, prepared from 1.0 mmol **1a**), ArI **3a** (0.7 mmol), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (0.05 mmol), LiCl (1.0 mmol), and solvent (3 mL). <sup>b</sup> A combined isolated yield of **4a** and **4a'**, based on ArI **3a** as limiting reagent, was obtained due to non-separation of the mixture. The exact yields of **4a** and **4a'** listed was determined by <sup>1</sup>H NMR analysis of the isolated mixture of **4a** and **4a'** after silica gel column chromatography purification. <sup>c</sup> Not determined.

Thus, the cross-coupling of the ester-containing indium homoenolate **2a** with aryl halide was subsequently investigated. Normally, the cross-coupling of organoindium reagent with aryl halide was carried out in the presence of a palladium catalyst in THF. However, our attempt to perform the reaction of indium homoenolate **2a** with 4-iodoacetophenone (**3a**) in the presence of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (5 mol%) in refluxing THF failed. Poor yield (<10%) was obtained under the above reaction conditions which might be due to the low reactivity of the indium homoenolate generated in our protocol. Thus, we embarked on the optimization of the cross-coupling reaction conditions by screening various organic solvents.

As shown in Table 1, the reactions proceeded sluggishly in some commonly used organic solvents such as THF, 1,4-dioxane, toluene, *n*-propanol and nitromethane (Table 1, entries 1–5). Interestingly, it was observed that the reactions proceeded well in relatively polar organic solvents such as DMF, DMSO, NMP and DMA (Table 1, entries 7–10). Among them, it was gratifying to find that the best yield of 83% was obtained when DMA was employed as reaction solvent (Table 1, entry 10). However, the formation of a by-product of **4a'** was also observed in the cross-coupling reaction which made the isolation of a pure product **4a** difficult, owing to a similar polarity of **4a** and **4a'** on silica gel column chromatography purification. Thus, in order to eliminate the formation of the undesired by-product **4a'**, we continued to optimize the reaction conditions by surveying various palladium catalysts.

As can be seen from Table 2, when the palladium-catalyzed cross-coupling reaction was performed at 70 °C in DMA, most of the palladium catalysts examined in the reaction produced the undesired by-product of **4a'** (Table 2, entries 1, 3–6). Only with the use of Pd(PPh<sub>3</sub>)<sub>4</sub> (5 mol%) as catalyst, formation of

**Table 2** Screening of various palladium catalysts<sup>a</sup>

Entry	Pd cat. (mol%)	T/°C	Yield <sup>b</sup> (%)	
			4a	4a'
1	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> (5)	70	83	4
2	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> (5)	100	60	13
3	Pd(OAc) <sub>2</sub> -MePhos (5/10)	70	27	27
4	Pd(dppf)Cl <sub>2</sub> (5)	70	18	8
5	Pd <sub>2</sub> (dba) <sub>3</sub> -PPh <sub>3</sub> (2.5/10)	70	80	3
6	Pd(PhCN) <sub>2</sub> Cl <sub>2</sub> -PPh <sub>3</sub> (5/10)	70	72	8
7	Pd(PPh <sub>3</sub> ) <sub>4</sub> (5)	70	45	0
8	Pd(PPh <sub>3</sub> ) <sub>4</sub> (5)	90	88	0

<sup>a</sup> Unless otherwise noted, the reactions were carried out at 70–100 °C for 24 h using indium homoenolate **2a** (~1.0 mmol, prepared from 1.0 mmol **1a**), ArI **3a** (0.7 mmol), Pd catalyst (0.05 mmol), phosphine ligand (0.1 mmol), LiCl (1.0 mmol), and DMA (3 mL). <sup>b</sup> See footnote b in Table 1.

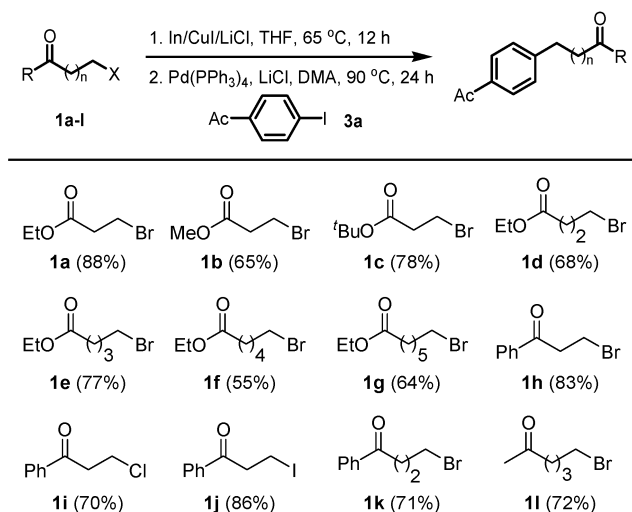
**Table 3** Substrate scope study<sup>a,b</sup>

<b>3a</b> (88%)	<b>3b</b> (79%)	<b>3c</b> (71%)	<b>3d</b> (80%)	
<b>3e</b> (57%)	<b>3f</b> (75%)	<b>3g</b> (53%)	<b>3h</b> (60%)	
<b>3i</b> (81%)	<b>3j</b> (86%)	<b>3k</b> (53%)	<b>3l</b> (46%)	

<sup>a</sup> See ESI† for detailed reaction conditions. <sup>b</sup> Isolated yield based on ArX **3** as limiting reagent.

the by-product **4a'** can be completely suppressed, though only a moderate yield (45%) of the desired product **4a** was obtained (Table 2, entry 7). Encouragingly, a good isolated yield of **4a** (88%) was obtained when the reaction was carried out at an elevated temperature of 90 °C (Table 2, entry 8), along with complete suppression of the by-product **4a'**. The direct comparison of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (entry 1) with Pd(PPh<sub>3</sub>)<sub>4</sub> (entries 7–8) shows that an excess of PPh<sub>3</sub> is necessary to stabilize the *in situ* generated Pd(0) catalysis in the reaction and thus suppress β-hydride elimination as an unwanted side-reaction.

With the success of the above reactions, we continued to explore the substrate scope of the reaction by using various aryl halides with embedded functional groups. As shown in Table 3, the palladium-catalyzed cross-coupling of the indium

**Table 4** Substrate scope study using various carbonyl-containing organohalides<sup>a,b</sup>

<sup>a</sup> See ESI† for detailed reaction conditions. <sup>b</sup> Isolated yield based on ArI **3a** as limiting reagent.

homoenolate **2a** with a broad range of aryl halides proceeded smoothly under the optimized conditions, leading to the target products of β-aryl esters in moderate to good yields. Various important functional groups, including ketone, nitro group, nitrile, ester and formyl group can be well tolerated in the protocol. In addition, heterocyclic halides containing pyridine and furan moieties also can be well employed as coupling partners (substrates **3f**, **3g** and **3k**). Moreover, the aryl chloride 4-chlorobenzaldehyde **3l** also underwent the coupling reaction, albeit in a moderate yield of 46%.

In addition, a range of carbonyl-containing organohalides were employed as substrates in the synthesis of various indium homoenolates (and their higher homologues) followed by palladium-mediated cross-coupling with 4-iodoacetophenone (**3a**). As shown in Table 4, the cross-coupling of various β-, γ-, δ-, ε- and ζ-indium esters with **3a** occurred efficiently under optimal conditions to give the cross-coupled products in moderate to good yields. In addition, various β-, γ-, δ-halo ketones (**1h**, **1i**, **1j**, **1k** and **1l**) can be well converted into their corresponding organoindium reagents as well, and effectively underwent the subsequent cross-coupling reactions.

In summary, a facile method for the synthesis of ester-containing indium homoenolate *via* a direct insertion of indium into β-halo ester in the presence of CuI/LiCl was described. The synthetic utility of the indium homoenolate was demonstrated by palladium-catalyzed coupling with aryl halides in DMA. The cross-coupling reaction proceeded efficiently with a great tolerance to functional groups such as formyl and hydroxyl groups which renders the method more synthetically useful, and will serve as a complement to their organomagnesium and organozinc counterparts.

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- Currently, we propose the structure of the ester-containing indium homoenolate **2a** as shown in Scheme 1. In addition, chelation of the carbonyl group to indium was observed (in <sup>13</sup>C NMR, the chemical shift of the carbonyl group moved downfield from 170.5 to 180.4 ppm). Moreover, the coordination of THF to the indium center was also observed and it might help to stabilize the generated indium homoenolate by forming a five-coordinated indium center.