Indium Reagents

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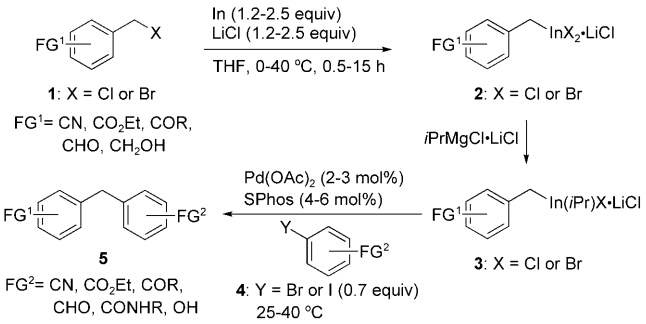
LiCl-Mediated Preparation of Functionalized Benzylic Indium(III) Halides and Highly Chemoselective Palladium-Catalyzed Cross-Coupling in a Protic Cosolvent**

*Yi-Hung Chen, Mai Sun, and Paul Knochel**

The development of palladium-catalyzed cross-coupling reactions has revolutionized the formation of carbon–carbon bonds.[1] These coupling reactions have found many applications in natural product synthesis,[2] material science,[3] and medicinal chemistry.[4] The Suzuki reaction, which involves organoboron compounds, has been widely used because of the ready availability of boronic esters and their excellent compatibility with many functional groups during the cross-coupling reaction.[5] Typically, functional groups bearing acidic protons, ketones, and aldehydes are compatible with these coupling reactions. However, the low reactivity of boronic acids may require harsh reaction conditions or sophisticated ligand systems. Furthermore, some classes of boronic acid derivatives such as functionalized benzylic boronic acids are more difficult to prepare.[6]

Indium organometallic reagents have attracted considerable attention because of their unique compatibility with aqueous media.[7] Palladium-catalyzed cross-coupling reactions of organoindium reagents with aryl halides and triflates were pioneered by Sarandeses and co-workers.[8] The standard method for the preparation of organoindium reagents involves a Li/In or Mg/In transmetalation. Recently, the preparation of arylindium(III) reagents by direct metal insertion in the presence of LiCl was reported by us and Papoian and Minehan.[9] Herein, we report a general way to prepare benzylic In^{III} reagents[10] by the direct insertion of In^0 into benzylic chlorides and bromides, as well as the use of these reagents in highly chemoselective cross-coupling reactions in protic cosolvents.

Various functionalized benzylic chlorides and bromides **1** were treated with In powder (1.2–2.5 equiv) in THF in the presence of LiCl (1.2–2.5 equiv), which allowed the smooth formation of the corresponding benzylic In^{III} reagents **2** (Scheme 1). The insertion reactions proceeded at 0 °C within 20–30 min for the benzylic bromides but required 40 °C and 6–15 h for benzylic chlorides. A broad range of sensitive functional groups such as CN, CO_2Et, COR, CHO, and CH_2OH were tolerated (see Table 1).



Scheme 1. Preparation of benzylic indium reagents **2** by the direct insertion of In^0 in the presence of LiCl followed by activation with *i*PrMgCl·LiCl and palladium-catalyzed cross-coupling. FG = functional group, SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl.

The palladium-catalyzed cross-coupling reactions of the In reagents **2** with aryl iodides were very sluggish and not preparatively useful. However, the addition of a protic solvent (such as ethanol) to these In reagents prior to the cross-coupling dramatically increased their reactivity. This compatibility of organoindium species with aqueous media has been reported previously.[7] Palladium-catalyzed cross-coupling reactions of indium organometallic reagents with aryl halides in aqueous media was first reported by Oshima and co-workers.[8k] The reaction in a protic cosolvent still required high temperature (reflux) to afford the cross-coupling product. However, we found that a transmetalation of **2** with *i*PrMgCl·LiCl[11] (1.1 equiv, −60 °C, 30 min) provided a more-reactive In^{III} reagent **3**. These mixed In^{III} reagents underwent smooth cross-coupling with various aryl iodides **4** at 25–30 °C and with aryl bromides at 40 °C to give products **5**, with selective transfer of the aryl group.

The treatment of ethyl (3-chloromethyl)benzoate (**1a**) with activated In powder (99.99 % from Chempur, 2.5 equiv) and LiCl (2.5 equiv) in THF at 40 °C for 12 h provided the corresponding In^{III} reagent **2a**. After the addition of *i*PrMgCl·LiCl (1.1 equiv, −60 °C, 30 min), ethanol or water was added to give a 6:1 (THF/cosolvent) ratio. Ethyl 4-bromobenzoate (**4a**; 0.7 equiv) was then added and the resulting reaction mixture was warmed to 25–30 °C. The cross-coupling was carried out in the presence of $Pd(OAc)_2$ (2 mol %) and SPhos[12,13] (4 mol %) at 40 °C for 4 h, which afforded the desired product **5a** (84 % yield with ethanol as

[*] Dr. Y.-H. Chen, M. Sun, Prof. Dr. P. Knochel
Department Chemie & Biochemie
Ludwig Maximilians-Universität München
Butenandtstrasse 5–13, Haus F, 81377 München (Germany)
Fax: (+49) 89-2180-77680
E-mail: paul.knochel@cup.uni-muenchen.de

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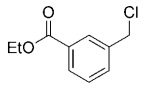
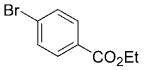
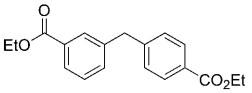
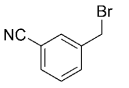
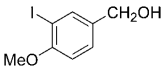
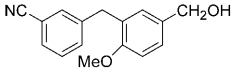
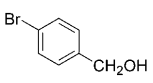
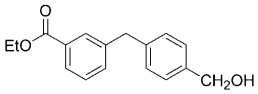
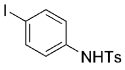
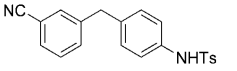
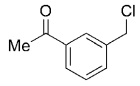
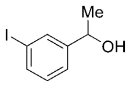
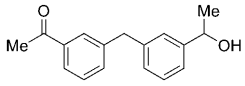
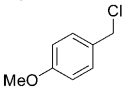
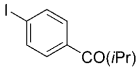
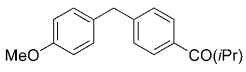
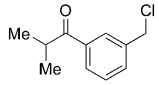
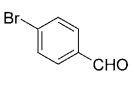
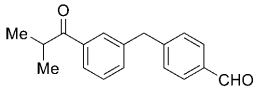
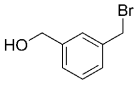
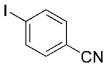
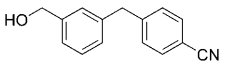
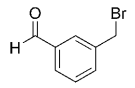
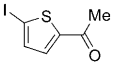
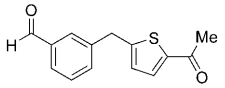
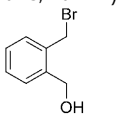
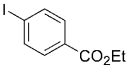
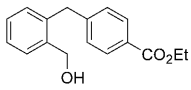
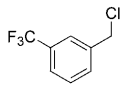
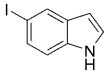
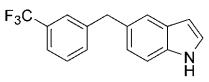
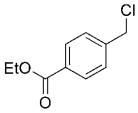
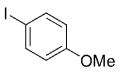
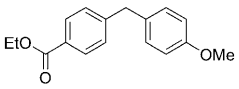
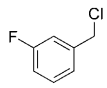
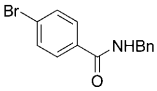
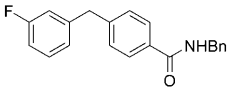
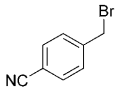
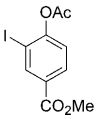
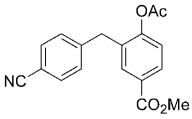
Table 1: Direct insertion of indium into benzylic halides **1** and cross-coupling with electrophiles **4** to give biphenylmethanes **5**.

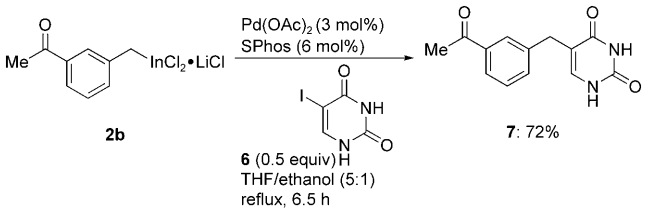
Entry	Benzyl halide[a]	Electrophile	Product yield [%][b]	Entry	Benzyl halide[a]	Electrophile	Product yield [%][b]
1				8			
	1a (2.5 equiv, 40 °C, 12 h)	**4a**	**5a**: 84 %[c] (86 %)[d]		**1g** (1.2 equiv, 0 °C, 20 min)	**4h**	**5h**: 75 %[c]
2				9			
	1a	**4b**	**5b**: 77 %[c]		**1g**	**4i**	**5i**: 75 %[c]
3				10			
	1b (2.5 equiv, 40 °C, 6 h)	**4c**	**5c**: 92 %[c]		**1h** (2.5 equiv, 40 °C, 15 h)	**4j**	**5j**: 82 %[c]
4				11			
	1c (2.5 equiv, 40 °C, 6 h)	**4d**	**5d**: 94 %[d]		**1i** (1.2 equiv, 0 °C, 20 min)[e]	**4k**	**5k**: 75 %[c]
5				12			
	1d (1.2 equiv, 0 °C, 20 min)[e]	**4e**	**5e**: 78 %[d]		**1j** (1.2 equiv, 0 °C, 20 min)[e]	**4l**	**5l**: 62 %[c]
6				13			
	1e (2.5 equiv, 40 °C, 8 h)	**4f**	**5f**: 72 %[c]		**1k** (2.5 equiv, 40 °C, 15 h)[e]	**4m**	**5m**: 37 %[f]
7				14			
	1f (2.5 equiv, 40 °C, 7 h)	**4g**	**5g**: 77 %[c]		**1l** (1.2 equiv, 0 °C, 20 min)[e]	**4n**	**5n**: 56 %[f]

[a] Reaction conditions for the formation of the benzylic indium reagents (equivalents of In powder and LiCl, reaction temperature, and reaction time). [b] Yields of pure and isolated material. Bn = benzyl, Ts = tosyl. [c] THF/EtOH (6:1). [d] THF/H_2O (6:1). [e] The indium reagent was used without activation with *i*PrMgCl·LiCl. [f] The cross-coupling reaction was performed in THF without any cosolvent.

cosolvent and 86 % yield with water as cosolvent; see Table 1, entry 1).[14] These cross-coupling reactions displayed a unique chemoselectivity and a range of functional groups were tolerated: the cross-coupling of **3a** with 4-bromobenzyl alcohol (**4b**; 0.7 equiv) bearing a free hydroxy group occurred smoothly without any protecting groups, and afforded the benzylic alcohol **5b** in 77 % yield (Table 1, entry 2). Similarly, benzylic organometallic compounds bearing a ketone or an aldehyde group were readily tolerated. Thus, the keto-substituted benzylic chlorides **1b**,**c** were cleanly converted into the corresponding benzylic In^{III} reagents **2b**,**c**. These reagents displayed a substantial thermostability and could be stirred at 40 °C for at least 15 h without appreciable decomposition. After their convertion into the isopropyl-indium-(III) intermediates **3b**,**c**, cross-coupling reactions with an aryl iodide **4c**, which bears a secondary alcohol, and 4-bromobenzaldehyde (**4d**[15]) provided the expected polyfunctionalized diarylmethanes **5c** and **5d** in 92 and 94 % yield, respectively (Table 1, entries 3 and 4). Similarly, (3-bromomethyl)benzaldehyde (**1d**) was smoothly converted into the corresponding In^{III} reagent **2d**. The activation of **2d** with *i*PrMgCl·LiCl was problematic in this case because of the presence of the formyl group. Nevertheless, its cross-coupling with iodothiophene **4e** in THF/water (5:1) at reflux was complete in 3.5 h, and afforded the desired product **5e** in 78 % yield (Table 1, entry 5). A range of electron-withdrawing substituents such as a trifluoromethyl group (**1e**), a fluorine atom (**1f**), or a cyanide group (**1g**) were tolerated during the formation of the corresponding benzylic In reagents. The subsequent cross-coupling reactions proceeded as expected

(after conversion into their isopropyl derivatives **3**) with a range of aryl halides bearing acidic hydrogen atoms, for example, with indole **4f**, amide **4g**, benzylic alcohol **4h**, and sulfonamide **4i**, with the cross-coupling products **5f–i** obtained in each case in 72–77% yield (Table 1, entries 6–9). Electron-donating substituents such as a methoxy group (**1h**) or even a hydroxymethyl group (**1i,j**) led in THF to the corresponding In reagents, despite the presence of the unprotected alcohol in **1i** and **1j**. Their cross-coupling reactions provided the diarylmethanes **5j–l** in 62–82% yield (Table 1, entries 10–12). Benzylic In reagents having an electron-withdrawing group in the *para* position (**2k,l**) showed moderate stability and were used directly for the cross-coupling step without activation with *i*PrMgCl·LiCl. These coupling reactions were performed in THF at reflux without any cosolvent and afforded the cross-coupling products **5m,n** in 37 and 56% yield, respectively (Table 1, entries 13 and 14).

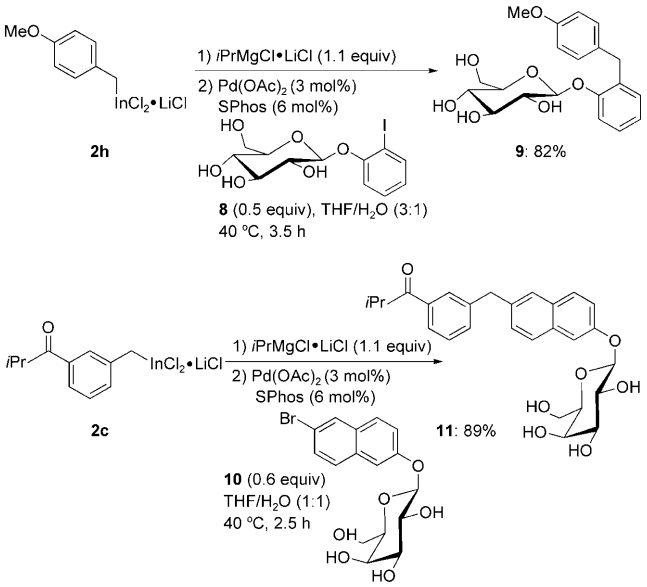
The exceptional chemoselectivity of these benzylic In^{III} reagents could be extended to 5-iodouracil (**6**, $pK_a = 14.1$ in DMSO; Scheme 2).[16] The reaction of the In^{III} derivative **2b** with unprotected 5-iodouracil (**6**; 0.5 equiv) in a 5:1 mixture of THF and EtOH at reflux provided the 5-substituted uracil **7** in 72% yield.



Scheme 2. Coupling of benzylic indium(III) **2b** with 5-iodouracil (**6**).

The preparation of aromatic carbohydrates is important due to their potential application as pharmaceuticals.[17] The reaction of sugar derivatives with organometallic reagents usually requires the extensive use of protecting groups; this could be completely avoided with benzylic organoindium reagents. Thus, biphenyl glucopyranoside **9**, which was identified as a lead compound for the treatment of type 2 diabetes,[18] could be prepared by the cross-coupling of organoindium reagent **2h** with the *O*-2-iodophenoxyglucoside (**8**; Scheme 3).[19] The glucopyranoside **9** was generated in 82% yield without the use of any protecting groups for the four hydroxy groups present in **8**. An aromatic bromide (such as **10**) also underwent a smooth palladium-catalyzed cross-coupling with the indium reagent **2c** to give the galactopyranoside **11** in 89% yield.

In summary, we have shown that a range of highly functionalized benzylic indium compounds can be readily prepared by the direct insertion of In powder in the presence of LiCl. A remarkable functional group compatibility, including the presence of a COR, CHO, or CH_2OH group in the starting benzylic halides, was observed. These benzylic reagents also display an exceptional chemoselectivity, undergoing palladium-catalyzed cross-coupling reactions with various electrophiles bearing acidic hydrogen atoms, such as an amide, an alcohol, a sulfonamide, an unprotected sugar, or a uracil derivative. Furthermore, the cross-coupling is accelerated by a protic cosolvent and may be well suited to combinatorial chemistry or drug screening. Further applications of these indium reagents for other transformations are currently underway.



Scheme 3. Coupling of benzylic indium(III) compounds **2h** and **2c** with unprotected carbohydrate derivatives.

Experimental Section

Typical procedure (indium insertion)—Preparation of In reagent **2b** (Table 1, entry 3): LiCl (212 mg, 5 mmol) was placed in an argon-flushed flask and dried with a heat gun under high vacuum (1 mbar). Indium powder (574 mg, 5 mmol) was added, followed by THF (2 mL). 1,2-Dibromoethane (5 mol%) was then added, followed by trimethylsilyl chloride (2 mol%), and the resulting mixture was heated with a heat gun to activate the indium powder. A solution of **1b** (338 mg, 2 mmol) in THF (2 mL) was added dropwise at 25 °C and the resulting mixture was stirred at 40 °C for 12 h. The completion of the reaction was checked by GC analysis.

Typical procedure (cross-coupling)—Preparation of **5c** (Table 1, entry 3): The solution of organoindium **2b** in THF was carefully transferred to an argon-flushed flask by syringe so as to separate it from any remaining In powder. The resulting solution was cooled to −60 °C and then *i*PrMgCl·LiCl (2.04 M solution in THF, 1.08 mL, 2.2 mmol) added. The reaction mixture was stirred at −60 to −50 °C for 30 min, then EtOH (1 mL) added, and the mixture warmed to 25–30 °C. **4c** (347 mg, 1.40 mmol) was then added, followed by a solution of $Pd(OAc)_2$ (10 mg, 0.042 mmol) and SPhos (35 mg, 0.084 mmol) in THF (1 mL). The reaction mixture was stirred at 40 °C for 8 h. After work-up, the residue was purified by flash chromatography on silica gel (diethyl ether/pentane 1:1) to afford compound **5c** (325 mg, 92%).

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[13] The cross-coupling reactions have been carried out with different catalytic systems (for example, $[Pd(dppf)Cl_2]$ and PEPPSI; dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, PEPPSI = pyridine-enhanced, precatalyst, preparation, stabilization, and initiation). However, higher catalytic loading and longer reaction times were required using those catalysts compared to SPhos and $Pd(OAc)_2$.

[14] The reactions provided almost the same yield when water or ethanol was used as the cosolvent, but we have found that more homodimer was generated in the reaction mixture when water was used as the cosolvent. As a consequence of the solubility of some aryl iodides in THF, a mixture of THF and EtOH (6:1) was the prefered reaction medium for cross-coupling at 25–30 °C.

[15] The reaction gave only 52 % yield when it was performed in 6:1 THF/EtOH.

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