

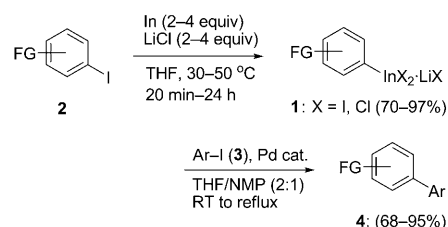
Preparation of Aryl and Heteroaryl Indium(III) Reagents by the Direct Insertion of Indium in the Presence of LiCl**

Yi-Hung Chen and Paul Knochel*

Dedicated to Professor Rolf Huisgen

Functionalized organometallic compounds are key intermediates in organic synthesis.^[1] In particular, organozinc reagents are compatible with a wide range of functional groups and have broad application in synthesis.^[2] However, sensitive functional groups, such as aldehyde or ketone functionalities with α acidic hydrogen atoms, are only tolerated in special cases.^[3] Furthermore, the reactivity of unsaturated zinc reagents toward acidic hydrogen atoms of alcohols and phenols precludes the performance of Negishi cross-coupling reactions^[4] of aromatic iodides containing these functionalities. In contrast to organozinc reagents, organoindium reagents have been shown to be compatible with water and several important functionalities.^[5] However, in classical syntheses of these organoindium compounds through Li/In or Mg/In transmetalation, the corresponding organometallic precursors require protecting groups. Recently, we reported that LiCl accelerates dramatically the insertion of zinc^[6] or magnesium^[7] into organic halides. Herein, we report a preparation of polyfunctional aryl and heteroaryl indium(III) reagents **1** through the direct insertion of indium metal in the presence of LiCl into iodides **2**. To the best of our knowledge, only allyl, propargyl,^[5] pentafluorophenyl,^[8] and benzyl indium(III) reagents^[9] have been prepared by the direct treatment of the corresponding halides with indium metal. Commercially available indium does not react with aryl iodides. However, when LiCl (2–4 equiv)^[10] was added to indium powder (2–4 equiv) that had been activated with 1,2-dibromoethane and TMSCl^[11] in THF, an efficient insertion occurred within 20 min to 24 h at 30–50 °C to provide polyfunctional aryl and heteroaryl indium(III) species **1** in 70–97 % yield (Scheme 1).

Thus, the treatment of 4-iodoacetophenone (**2a**) with activated indium powder (4 equiv) in the presence of LiCl (4 equiv) in THF at 50 °C for 24 h provided the desired aryl indium(III) reagent **1a** in 96 % yield, as indicated by iodolysis (Table 1).^[12] No insertion occurred in the absence of LiCl.



Scheme 1. Preparation of organoindium reagents **1** through direct indium insertion in the presence of LiCl, followed by palladium-catalyzed cross-coupling. FG = functional group.

Similarly, the iodoketones **2b** and **2c** were converted into the corresponding keto-substituted indium derivatives **1b** (50 °C, 24 h) and **1c** (35 °C, 2 h) in 93 and 90 % yield, respectively. The functionalized aryl iodides **2d–g** with an ester or aldehyde functionality also reacted smoothly with indium metal in the presence of LiCl to give the organoindium(III) reagents **1d–g** in 70–86 % yield. The presence of an electron-withdrawing group or metalation-directing group increased the insertion rate considerably.

This method was extended to the preparation of heteroaryl indium(III) reagents. Heterocyclic iodides (and a heterocyclic bromide), some of which contained a ketone, aldehyde, or ester functionality, reacted smoothly with indium powder in the presence of LiCl to furnish the heteroaryl indium(III) compounds **1h–m** in 78–97 % yield (Table 1, entries 8–13). This method provides access to organoindium reagents containing a range of important and sensitive functional groups that are not compatible with organozinc reagents.

Organoindium species are useful reagents in organic synthesis.^[5] Palladium-catalyzed cross-coupling reactions with triorganoindium compounds^[13] were pioneered by Sarandeses and co-workers.^[13a] Typically, the cross-coupling reactions are conducted in THF at reflux. Under these conditions, the cross-coupling of the less reactive functionalized aryl indium(III) reagents **1a–m** was inefficient. However, upon the addition of *N*-methylpyrrolidinone (NMP) as a cosolvent (NMP/THF 1:2),^[14] the cross-coupling reactions proceeded smoothly in the presence of [Pd(dppf)Cl₂]^[15] at 25–66 °C (dppf = 1,1'-bis(diphenylphosphanyl)ferrocene).

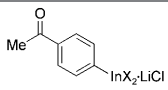
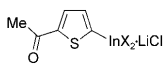
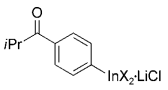
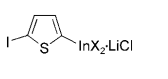
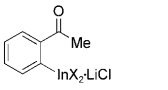
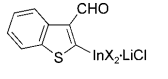
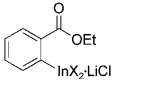
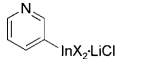
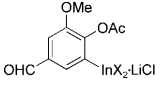
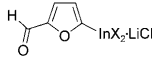
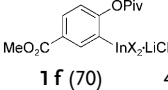
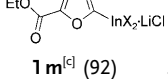
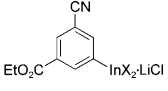
This Pd-catalyzed cross-coupling procedure proved to be quite general: A range of aryl iodides **3** reacted with the functionalized organoindium compounds **1** to afford products of type **4** (Table 2). [Pd(dppf)Cl₂], a catalyst developed by Hayashi et al.,^[15] catalyzed these cross-coupling reactions effectively (Table 2, entries 1, 2, 6, 7, and 9–11). In the case of

[*] Dr. Y.-H. Chen, Prof. Dr. P. Knochel
Ludwig-Maximilians-Universität München
Department Chemie
Butenandtstrasse 5–13, Haus F, 81377 München (Germany)
Fax: (+49) 892-1807-7680
E-mail: paul.knochel@cup.uni-muenchen.de

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Table 1: LiCl-mediated indium insertion of aryl and heteroaryl compounds **1**.^[a]

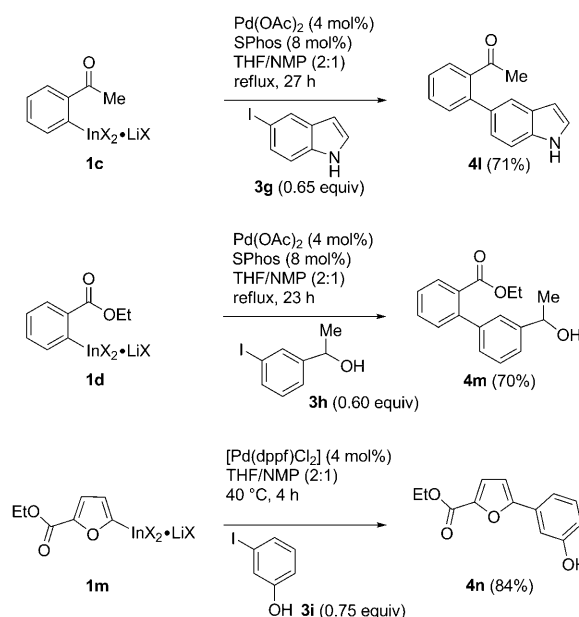
Entry	Indium reagent (yield [%]) ^[b]	T [°C], t [h]	Entry	Indium reagent (yield [%]) ^[b]	T [°C], t [h]
1	 1 a (96)	50, 24	8	 1 h (91)	30, 0.33
2	 1 b (93)	50, 24	9	 1 i (97)	30, 0.33
3	 1 c (90)	35, 2	10	 1 j (78)	30, 0.33
4	 1 d (86)	35, 8	11	 1 k (88)	50, 4
5	 1 e (70)	35, 4	12	 1 l (83)	30, 0.33
6	 1 f (70)	40, 13	13	 1 m ^[c] (92)	50, 16
7	 1 g (78)	50, 6			

[a] Indium powder and LiCl were used in equimolar amounts: 2–4 equivalents with respect to the aryl or heteroaryl iodide. [b] The yield was determined by GC analysis of a sample that had been quenched with a solution of iodine in anhydrous THF. [c] Ethyl 5-bromo-2-furoate (**2m**) was used as the starting material. Piv = pivaloyl.

particularly unreactive organoindium reagents, such as **1e**, **1f**, and **1j** with a chelating group in the *ortho* position, a more powerful catalytic system introduced by Buchwald and co-workers^[16] and formed from Pd(OAc)₂ and SPhos (2-dicyclohexylphosphanyl-2',6'-dimethoxybiphenyl) was required. In these cases, a longer reaction time (15–27 h) and a higher temperature (reflux in THF) were necessary; the desired coupling products were obtained in 68–90% yield (Table 2, entries 3–5 and 8).

The exceptional functional-group compatibility of these organoindium reagents is emphasized further by cross-coupling reactions with electrophiles containing acidic hydro-

gen atoms.^[13e] Thus, reactions with the iodoindole **3g**, the iodoalcohol **3h**, and the iodophenol **3i** led to the expected products **4l–n** in 70–84% yield (Scheme 2).



Scheme 2. Palladium-catalyzed cross-coupling of functionalized organoindium reagents with aryl iodides containing unprotected acidic functional groups.

In summary, we have developed a convenient method for the preparation of functionalized organoindium reagents by the direct insertion of indium in the presence of LiCl. Ketone, ester, and aldehyde groups may be present in the reagents. Moreover, the organoindium reagents undergo cross-coupling reactions under mild conditions with a variety of aryl iodides, including those containing NH or OH groups with acidic hydrogen atoms, in good to excellent yields. We are currently investigating further applications of these organoindium reagents.

Experimental Section

1a: LiCl (340 mg, 8 mmol) was placed in an argon-flushed flask and dried for 5–10 min at 380°C under high vacuum (1 mbar). Indium powder (918 mg, 8 mmol) was added under argon, the flask was evacuated and refilled with argon three times, and THF (1 mL) was added. 1,2-Dibromoethane (5 mol%) was then added, followed by chlorotrimethylsilane (2 mol%), and the resulting mixture was heated with a heat gun to activate the indium powder. A solution of 4-iodoacetophenone (**2a**; 492 mg, 2 mmol) and an internal standard (C₁₄H₃₀) in THF (1 mL) was added at 25°C, and the resulting mixture was stirred at 50°C for 24 h. The insertion reaction was monitored by GC analysis of reaction-mixture aliquots quenched with a saturated aqueous solution of NH₄Cl. Upon completion of the reaction, the yield of **1a** (96%) was determined by GC analysis of an aliquot quenched with a solution of iodine in anhydrous THF.

4a: Ethyl 4-iodobenzoate (414 mg, 1.50 mmol) and [Pd(dppf)Cl₂] (44 mg, 0.06 mmol) were placed in an argon-flushed flask. NMP (2 mL) was added, and the solution of **1a** in THF (prepared as

Table 2: Palladium-catalyzed cross-coupling of functionalized aryl and heteroaryl organoindium reagents.

Entry	Indium reagent	Electrophile	Product 4 (yield [%]) ^[c]	Entry	Indium reagent	Electrophile	Product 4 (yield [%]) ^[c]
1	1a ^[a]		 4a (95 %)	7	1i ^[a]		 4g (73 %)
2	1b ^[a]		 4b (70 %)	8	1j ^[b]		 4h (90 %)
3	1e ^[b]		 4c (84 %)	9	1k ^[a]		 4i (92 %)
4	1f ^[b]		 4d (68 %)	10	1l ^[a]		 4j (78 %)
5	1g ^[b]		 4e (85 %)	11	1l ^[a]		 4k (73 %)
6	1h ^[a]		 4f (95 %)				

[a] The cross-coupling reaction was conducted with [Pd(dppf)Cl₂] (4 mol %). [b] The cross-coupling reaction was conducted with Pd(OAc)₂ (4 mol %) and SPhos (8 mol %). [c] Yield of the pure isolated material.

described above) was transferred carefully (without the remaining indium powder) to the resulting mixture (with a syringe. The reaction mixture was stirred at 40 °C for 4 h (by which time TLC and GC analysis of aliquots quenched with a saturated aqueous solution of NH₄Cl showed complete conversion). The reaction was then quenched with acetic acid (0.5 mL) and water (2 mL), and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were dried with Na₂SO₄ and concentrated in vacuo. Purification of the crude residue by flash chromatography on silica gel (ether/pentane 1:4) yielded **4a** (380 mg, 95 %).

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[1] P. Knochel, *Handbook of Functionalized Organometallics*, Wiley-VCH, Weinheim, 2005.

[2] P. Knochel, N. Millot, A. L. Rodriguez, C. E. Tucker, *Org. React.* **2001**, 58, 417.

[3] A. Metzger, M. A. Schade, P. Knochel, *Org. Lett.* **2008**, 10, 1107.

[4] a) E.-i. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, 102, 3298; b) M. Kobayashi, E.-i. Negishi, *J. Org. Chem.* **1980**, 45, 5223; c) E.-i. Negishi, *Acc. Chem. Res.* **1982**, 15, 340; d) E.-i. Negishi, *Bull. Chem. Soc. Jpn.* **2007**, 80, 233.

[5] For recent reviews: a) S. Araki, T. Hirashita in *Comprehensive Organometallic Chemistry III*, Vol. 9 (Ed.: P. Knochel), Pergamon, Oxford, **2007**, p. 650; b) J. Augé, N. Lubin-Germain, J. Uziel, *Synthesis* **2007**, 1739.

[6] A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem.* **2006**, 118, 6186; *Angew. Chem. Int. Ed.* **2006**, 45, 6040.

[7] F. M. Piller, P. Appukkuttan, A. Gavryushin, M. Helm, P. Knochel, *Angew. Chem.* **2008**, 120, 6907; *Angew. Chem. Int. Ed.* **2008**, 47, 6802.

[8] W. E. Tyrre, *J. Fluorine Chem.* **2001**, 112, 149.

[9] N. Fujiwara, Y. Yamamoto, *J. Org. Chem.* **1999**, 64, 4095.

[10] 2-Iodothiophene was used to study the effect of the amount of LiCl on the rate of indium insertion (see the Supporting Information).

- [11] P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, 53, 2390.
- [12] The yield was determined by GC analysis (with an internal standard) of reaction aliquots quenched with a solution of iodine in anhydrous THF.
- [13] a) I. Pérez, J. P. Sestelo, L. A. Sarandeses, *Org. Lett.* **1999**, 1, 1267; b) I. Pérez, J. P. Sestelo, L. A. Sarandeses, *J. Am. Chem. Soc.* **2001**, 123, 4155; c) M. A. Pena, I. Pérez, J. P. Sestelo, L. A. Sarandeses, *Chem. Commun.* **2002**, 2246; d) R. Nomura, S.-I. Miyazaki, H. Matsuda, *J. Am. Chem. Soc.* **1992**, 114, 2738; e) K. Takami, H. Yorimitsu, H. Shinokubo, S. Matsubara, K. Oshima, *Org. Lett.* **2001**, 3, 1997; f) P. H. Lee, S. Sung, K. Lee, *Org. Lett.* **2001**, 3, 3201; g) M. A. Pena, J. P. Sestelo, L. A. Sarandeses, *Synthesis* **2003**, 780; h) B. Gotov, J. Kaufmann, H. Schumann, H.-G. Schmalz, *Synlett* **2002**, 361; i) N. Jaber, D. Gelman, H. Schumann, S. Dechert, J. Blum, *Eur. J. Org. Chem.* **2002**, 1628; j) K. Lee, J. Lee, P. H. Lee, *J. Org. Chem.* **2002**, 67, 8265; k) K. Lee, D. Seomoon, P. H. Lee, *Angew. Chem.* **2002**, 114, 4057; *Angew. Chem. Int. Ed.* **2002**, 41, 3901; l) K. Takami, H. Yorimitsu, K. Oshima, *Org. Lett.* **2002**, 4, 2993; m) P. H. Lee, S. W. Lee, K. Lee, *Org. Lett.* **2003**, 5, 1103; n) K. Takami, S. Mikami, H. Yorimitsu, H. Shinokubo, K. Oshima, *J. Org. Chem.* **2003**, 68, 6627; o) P. H. Lee, S. W. Lee, D. Seomoon, *Org. Lett.* **2003**, 5, 4963; p) for a review, see: M. A. Pena, J. P. Sestelo, L. A. Sarandeses, *Synthesis* **2005**, 485; q) M. A. Pena, J. P. Sestelo, L. A. Sarandeses, *J. Org. Chem.* **2007**, 72, 1271; r) E. Font-Sanchis, F. J. Céspedes-Guirao, Á. Sastre-Santos, F. Fernández-Lázaro, *J. Org. Chem.* **2007**, 72, 3589; s) R. Riveiros, L. Saya, J. P. Sestelo, L. A. Sarandeses, *Eur. J. Org. Chem.* **2008**, 1959; t) J. Caeiro, J. P. Sestelo, L. A. Sarandeses, *Chem. Eur. J.* **2008**, 14, 741.
- [14] a) A. Gavryushin, C. Kofink, G. Manolikakes, P. Knochel, *Org. Lett.* **2005**, 7, 4871; b) L. Melzig, A. Gavryushin, P. Knochel, *Org. Lett.* **2007**, 9, 5529.
- [15] T. Hayashi, M. Konishi, Y. Kobori, M. Kumada, T. Higuchi, K. Kirotzu, *J. Am. Chem. Soc.* **1984**, 106, 158.
- [16] a) S. D. Walker, T. E. Barder, J. R. Martinelli, S. L. Buchwald, *Angew. Chem.* **2004**, 116, 1907; *Angew. Chem. Int. Ed.* **2004**, 43, 1871; b) R. Martin, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, 129, 3844; c) T. E. Barder, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, 129, 5096; d) M. R. Biscoe, T. E. Barder, S. L. Buchwald, *Angew. Chem.* **2007**, 119, 7370; *Angew. Chem. Int. Ed.* **2007**, 46, 7232.