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C–C Coupling

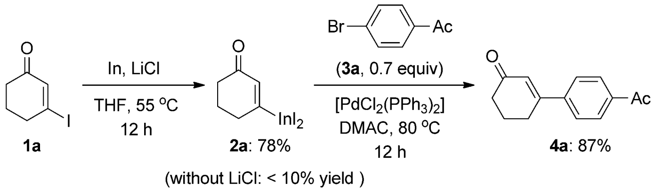
Stereoselective Preparation of Polyfunctional Alkenylindium(III) Halides and Their Cross-Coupling with Unsaturated Halides

Zhi-Liang Shen and Paul Knochel*[a]

Abstract: The direct insertion of indium powder to cycloalkenyl iodides in the presence of LiCl in THF allows the preparation of new highly functionalized cycloalkenylindium(III) derivatives. In addition, we discovered that, in contrast to many metal insertions to alkenyl iodides which proceed with a loss of stereochemistry, the insertion of In/LiCl to stereodefined (*Z*)- and (*E*)-styryl iodides in THF proceeded with high retention of stereochemistry. After a palladium-catalyzed cross-coupling, various polyfunctionalized (*Z*)- and (*E*)-stilbenes were obtained with high stereoselectivity.

Organometallics that are compatible with many functionalities are important nucleophilic intermediates in organic synthesis.[1–3] The tolerance of functional groups is essential to shorten long natural product syntheses since such reagents avoid the need for protecting and deprotecting steps.[4] Recently, we and others reported that the insertion of indium into aryl and heteroaryl iodides[5] or benzylic chlorides[6] is dramatically accelerated by the presence of lithium chloride,[7–10] allowing the preparation of functionalized organoindium species. The high functional group tolerance of indium(III) organometallics[11–12] led us to examine the preparation of polyfunctional alkenylindium(III) reagents for organic synthesis. In fact, organoindium(III) derivatives have been shown to be compatible with various functional groups.[13] The insertion rate of a metal into a carbon–halide bond highly depends on the activation of its surface, and lithium chloride has been found to be an excellent activator for many metals, such as magnesium,[7] zinc,[8] aluminum,[9] and manganese.[10] Although such activation leads to a fast insertion, the stereoselectivity of the metal insertion into *E*- and *Z*-alkenyl halides usually cannot be controlled.[14] Metal insertions are dominated by electron-transfer reaction steps,[15] which implies the formation of free radical intermediates, and therefore lead to a loss of stereoselectivity. The use of zinc activated by lithium chloride has allowed a stereoselective insertion to some electron-poor alkenyl bromides.[16] Herein, we report a mild preparation of highly functionalized alkenylindium(III) reagents[17] and the stereoselective insertion of indium powder into functionalized *E*- and *Z*-styryl iodides as well as their subsequent Pd-catalyzed stereoselective cross-coupling with unsaturated iodides.

Thus, we have treated 3-iodocyclohex-2-enone (**1a**) with indium powder (2 equiv) and lithium chloride (2 equiv) in THF at 55 °C for 12 h leading to a full conversion and affording the indium(III) species **2a** in 78 % yield, as determined by GC analysis of reaction aliquots quenched with a THF solution of iodine (Scheme 1). In the absence of lithium chloride, less than 10 % insertion was observed. The organoindium reagent **2a** readily underwent a palladium-catalyzed cross-coupling with 4-bromoacetophenone (**3a**) in *N*,*N*-dimethylacetamide (DMAC)[11e] at 80 °C for 12 h leading to the expected 3-arylated cyclohexenone **4a** in 87 % yield. This reaction sequence has some generality and the organoindium reagent **2a** underwent couplings with aryl bromide **3b** and iodide **3c** affording the corresponding cyclohexenones **4b** and **4c** in high yields (Table 1, entries 1 and 2). Similarly, we have prepared the 2-methyl-3-indium cyclohexenone derivative **2b** (55 °C, 16 h, 90 % yield) and the 3-indium cyclopentenone reagent **2c** (55 °C, 20 h, 66 % yield) under similar reaction conditions. These indium species underwent smooth cross-couplings with electron-poor and electron-rich aryl halides leading to the 3-arylated enones **4d**–**4h** in 53–94 % yields (entries 3–7). In addition, we noted that the indium insertion to α-iodostyrene (**1d**) proceeded also smoothly to generate the corresponding organoindium **2d** in 68 % yield (55 °C, 12 h), which cross-coupled with aryl iodide **3c** to produce the expected product **4i** in 91 % yield (entry 8). This led us to examine the stereochemistry of indium insertion into the carbon–iodine bond of stereodefined styryl iodides.[18]



Scheme 1. Preparation of organoindium reagent **2a** by In/LiCl insertion and its subsequent palladium-catalyzed cross-coupling with aryl bromide **3a**.

Thus, we treated *Z*- and *E*-(2-iodovinyl)benzonitrile (**1e**)[19] with indium powder and lithium chloride (55 °C, 18–24 h) leading to the styrylindium reagents *Z*-**2e** and *E*-**2e** in 85 % yield (Scheme 2). Remarkably, the *Z*-styrylindium *Z*-**2e** retained its stereochemistry almost completely and an iodolysis showed

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[a] Z.-L. Shen, Prof. Dr. P. Knochel
Department Chemie, Ludwig-Maximilians-Universität München
Butenandtstrasse 5–13, Haus F, 81377 München (Germany)
E-mail: paul.knochel@cup.uni-muenchen.de

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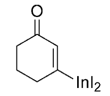
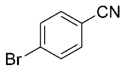
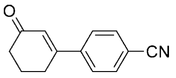
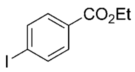
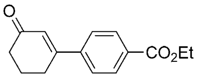
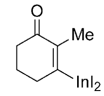
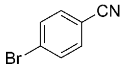
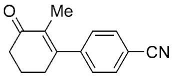
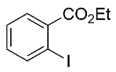
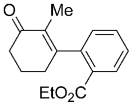
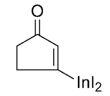
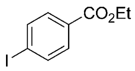
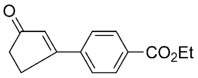
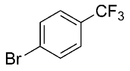
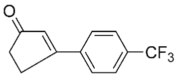
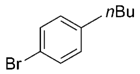
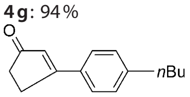
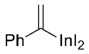
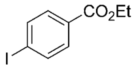
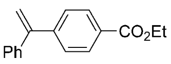
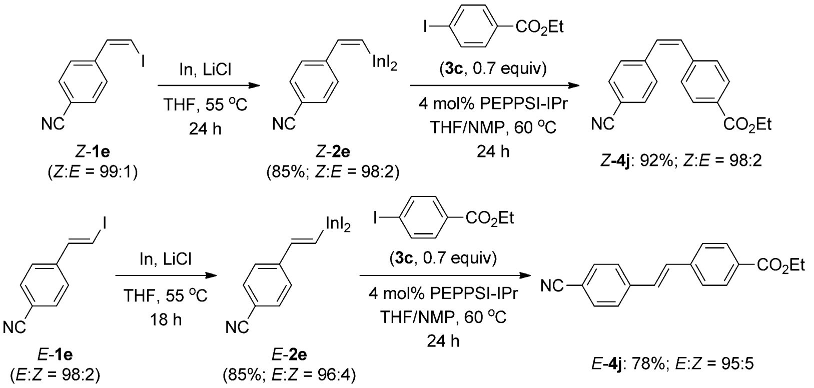
Table 1. Preparation of alkenylindium(III) reagents **2a**–**2d** and subsequent palladium-catalyzed cross-coupling with aryl halides **3b**–**3f**.

Entry	Indium reagent	Electrophile[a]	Product[b]/Yield[c]
1	 **2a** (12 h, 78%)	 **3b**	 **4b**: 98%
2	**2a**	 **3c**	 **4c**: 96%
3	 **2b** (16 h, 90%)	 **3b**	 **4d**: 91% (< 10%)[d]
4	**2b**	 **3d**	 **4e**: 88%
5	 **2c** (20 h, 66%)	 **3c**	 **4f**: 79%
6	**2c**	 **3e**	 **4g**: 94%
7	**2c**	 **3f**	 **4h**: 53%
8	 **2d** (12 h, 68%)	 **3c**	 **4i**: 91%

[a] 0.7 equivalents of electrophile was used. [b] The cross-coupling reactions were performed in DMAC at 80 °C for 12 h using 5 mol% [$PdCl_2(PPh_3)_2$]. [c] Yield of isolated, analytically pure product. [d] The same reaction using 4-chlorobenzonitrile as an electrophile led to < 10% yield of the product **4d**.



Scheme 2. Preparation of stereodefined cyano-containing *Z*- and *E*-styrylindium reagents **2e** and their palladium-catalyzed cross-coupling with ethyl 4-iodobenzoate (**3c**).

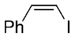
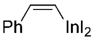
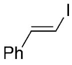
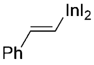
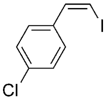
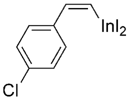
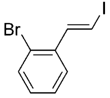
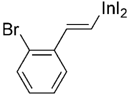
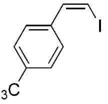
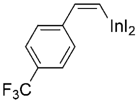
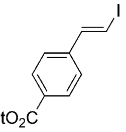
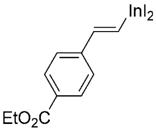
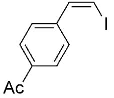
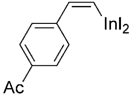
a *Z*:*E* ratio of 98:2.[20] It should be noted that THF is the solvent of choice for the insertion reaction since the performance of the same reaction in other ethereal solvents led to either low yield or relatively low stereochemistry (DME: 82% yield, *Z*:*E* = 90:10; *t*BuOMe: 22% yield, *Z*:*E* = 99:1; tetrahydropyran: 80% yield, *Z*:*E* = 81:19; 1,4-dioxane: 68% yield, *Z*:*E* = 98:2). Subsequently, Pd-catalyzed cross-coupling of *Z*-**2e** with ethyl 4-iodobenzoate (**3c**) using 4 mol% PEPPSI-IPr[21,22] led to the unsymmetrical *Z*-stilbene *Z*-**4j** in 92% yield and a *Z*:*E* ratio of 98:2. Also, the styrylindium reagent *E*-**2e** showed by iodolysis a *E*:*Z* purity of 96:4. Pd-catalyzed cross-coupling of *E*-**2e** with the aryl iodide **3c** produced the *E*-stilbene *E*-**4j** in 78% yield and an *E*:*Z* ratio of 95:5.

Subsequently, the method was extended to the preparation of a variety of styrylindium(III) reagents using various styryl iodides. As shown in Table 2, unsubstituted *Z*-**1f** and *E*-**1f** were converted to the corresponding indium reagents *Z*-**2f** and *E*-**2f** in 51–72% yields with high stereoselectivities (entries 1 and 2). Styryl iodides **1g**–**1i** bearing a halogen substituent either in the *ortho* or *para* position readily underwent the insertion reactions without touching the halogen substituent, leading to the desired styrylindium(III) reagents **2g**–**2i** in 70–83% yields and excellent stereoretention (> 95:5 d.r., entries 3–5). The presence of an ester or acetyl substituent in the starting styryl iodides **1j**–**1k** was well tolerated and the resulting indium reagents *E*-**2j** and *Z*-**2k** were obtained under the standard conditions in 73–86% yields and 98:2 d.r. (entries 6 and 7).

In the same manner, the palladium-catalyzed cross-coupling of *Z*–**2e** and *E*-**2e** with aryl iodides **3g** and **3h** proceeded well, leading to the corresponding stilbenes **4k** and **4l** in 69–80% yields and high stereoselectivities (Table 3, entries 1–4). Unsubstituted styrylindium(III) reagents *Z*-**2f** and *E*-**2f** also underwent efficient cross-coupling with iodoarenes **3c** and **3i** with good yields and high level of stereoselectivities (entries 5 and 6). The palladium-catalyzed cross-coupling reactions of indium reagents *Z*-**2g**, *E*-**2h**, and *Z*-**2i** with electrophiles **3j** and **3k** proceeded smoothly to furnish the corresponding products **4o**–**4q** in 65–94% yields and high stereoretention (entries 7–9). This behavior of cross-coupling was further extended to the use of organoindium reagents *E*-**2j** and *Z*-**2k** (bearing an ester or acetyl substituent) with aryl iodides **3g**–**3m**, providing the expected stilbenes *E*-**4r**, *Z*-**4s**, and *Z*-**4t** in 72–84% yields (up to 98:2 d.r., entries 10–12). In addition, it is noteworthy that important functional groups embedded in the coupling partners, including nitrile, ester, ketone, and even aldehyde, were compatible with the styrylindium(III) reagents.

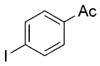
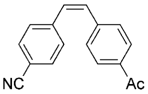
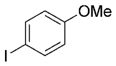
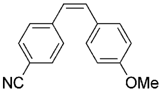
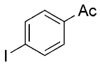
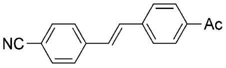
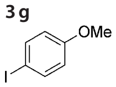
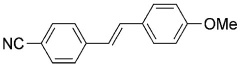
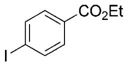
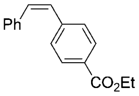
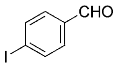
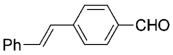
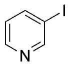
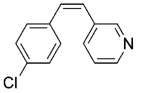
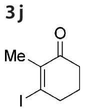
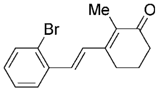
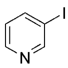
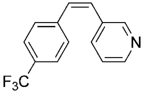
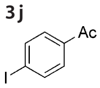
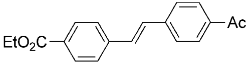
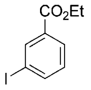
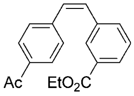
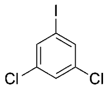
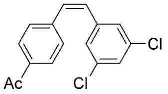
In summary, we have reported that the direct insertion of indium powder into cycloalkenyl iodides in the presence of LiCl in THF allows the preparation of new highly functionalized cycloalkenylindium(III) derivatives, such as 1-oxo-cyclohexen-3-yl

Table 2. Stereoselective preparation of styrylindium(III) reagents **2 f**–**2 k**.

Entry	Styryl iodide (*E*:*Z*)	Time	Styrylindium reagent [Yield[a] (*E*:*Z*)[b]]
1	 *Z*-**1 f** (3:97)	48 h	 *Z*-**2 f** [51 % (5:95)]
2	 *E*-**1 f** (99:1)	5 d	 *E*-**2 f** [72 % (98:2)]
3	 *Z*-**1 g** (1:99)	12 h	 *Z*-**2 g** [83 % (2:98)]
4	 *E*-**1 h** (99:1)	6 d	 *E*-**2 h** [70 % (99:1)]
5	 *Z*-**1 i** (3:97)	70 h	 *Z*-**2 i** [72 % (5:95)]
6	 *E*-**1 j** (98:2)	20 h	 *E*-**2 j** [73 % (98:2)]
7	 *Z*-**1 k** (1:99)	18 h	 *Z*-**2 k** [86 % (2:98)]

[a] The yield was determined by GC analysis of reaction aliquots quenched with a THF solution of iodine against internal standard. [b] The *E*:*Z* ratio was determined by GC analysis.

Table 3. Pd-catalyzed cross-coupling of styrylindium(III) reagents **2 e**–**2 k** with electrophiles **3 c**–**3 m** using 4 mol % PEPPSI-IPr as catalyst.

Entry	Styrylindium (*E*:*Z*)	Electrophile[a]	Product[b] [Yield[c] (*E*:*Z*)[d]]
1	*Z*-**2 e** (2:98)	 **3 g**	 *Z*-**4 k** [80 % (3:97)]
2	*Z*-**2 e** (2:98)	 **3 h**	 *Z*-**4 l** [74 % (6:94)]
3	*E*-**2 e** (96:4)	 **3 g**	 *E*-**4 k** [71 % (96:4)]
4	*E*-**2 e** (96:4)	 **3 h**	 *E*-**4 l** [69 % (96:4)]
5	*Z*-**2 f** (5:95)	 **3 c**[e]	 *Z*-**4 m** [82 % (6:94)]
6	*E*-**2 f** (98:2)	 **3 i**	 *E*-**4 n** [89 % (97:3)]
7	*Z*-**2 g** (2:98)	 **3 j**	 *Z*-**4 o** [65 % (2:98)]
8	*E*-**2 h** (99:1)	 **3 k**	 *E*-**4 p** [94 % (98:2)]
9	*Z*-**2 i** (5:95)	 **3 j**	 *Z*-**4 q** [77 % (6:94)]
10	*E*-**2 j** (98:2)	 **3 g**	 *E*-**4 r** [74 % (98:2)]
11	*Z*-**2 k** (2:98)	 **3 l**	 *Z*-**4 s** [72 % (5:95)]
12	*Z*-**2 k** (2:98)	 **3 m**	 *Z*-**4 t** [84 % (4:96)]

[a] Unless otherwise indicated, 0.7 equivalents of electrophile was used for the cross-coupling reaction. [b] The cross-coupling reactions were performed in THF/NMP (2:1) at 60 °C for 24 h using 4 mol % PEPPSI-IPr. [c] Yield of isolated, analytically pure product. [d] The *E*:*Z* ratio was determined by GC analysis. [e] 0.5 equivalents of electrophile **3 c** was used.

indium. In addition, we discovered that, in contrast to many metal insertions to alkenyl iodides which proceed with a loss of stereochemistry,[23] the insertion of In/LiCl to stereodefined (*Z*)- and (*E*)-styryl iodides in THF led to the corresponding indium reagents with high retention of stereochemistry. After palladium-catalyzed cross-coupling, various polyfunctionalized diastereomerically enriched (*Z*)- and (*E*)-stilbenes were obtained.

Experimental Section

Typical procedure for the indium insertion: To a 20 mL Schlenk flask equipped with a magnetic stirrer and a rubber septum was added LiCl (0.17 g, 4 mmol, 2 equiv) and the flask was dried at 380 °C by heat gun for 5 min under high vacuum. After cooling, the flask was flushed with nitrogen gas, and then anhydrous THF (6 mL), indium powder (0.46 g, 4 mmol, 2 equiv), an internal standard ($C_{10}H_{22}$, 0.2 mL), and alkenyl iodides (2 mmol) were sequentially added. The reaction mixture was stirred vigorously at 55 °C for the time indicated in Table 1 and Table 2. The reaction progress was monitored by GC analysis of reaction aliquots quenched by saturated NH_4Cl solution until it showed >95 % conversion of the starting material. The yield of the insertion reaction was determined by GC analysis of reaction aliquots quenched with a THF solution of iodine.

Typical procedure for palladium-catalyzed cross-coupling reactions using alkenylindium(III) reagents 2 a–d: The supernatant solution of the prepared alkenylindium(III) reagents **2a**–**d** in THF was carefully transferred into another pre-dried and nitrogen-flushed flask (without the remaining indium powder; otherwise relatively low yield of the cross-coupling product was obtained) with a syringe. Then THF was carefully removed under vacuum and the flask was flushed with nitrogen gas. DMAC (6 mL), aryl halide (0.7 equiv), and $[PdCl_2(PPh_3)_2]$ (70 mg, 0.10 mmol, 5 mol%) were sequentially added and the reaction mixture was stirred at 80°C for 12 h. Then, the reaction mixture was quenched with saturated NH_4Cl solution (20 mL) followed by extraction with ethyl acetate (3×20 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude residue obtained was purified by silica gel column chromatography using ethyl acetate and isohexane as eluant to give the analytically pure product.

Typical procedure for palladium-catalyzed cross-coupling reactions using styrylindium(III) reagents 2e–k: The supernatant solution of the prepared styrylindium(III) reagents **2e**–**k** in THF was carefully transferred into another pre-dried and nitrogen-flushed flask (without the remaining indium powder) with a syringe. *N*-Methyl-2-pyrrolidone (NMP, 3 mL), aryl iodide (0.5–0.7 equiv), and PEPPSI-IPr (54 mg, 0.08 mmol, 4 mol%) were sequentially added and the reaction mixture was stirred at 60°C for 24 h. Then the reaction mixture was quenched with saturated NH_4Cl solution (20 mL) followed by extraction with ethyl acetate (3×20 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude residue obtained was purified by silica gel column chromatography using ethyl acetate and isohexane as eluant to give the analytically pure product.

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Keywords: alkenylindium · C–C coupling · indium · palladium · stereoselectivity

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[20] See Supporting Information for the GC method for the determination of the yield and *Z*:*E* ratio of the formed alkenylindium(III) reagent by

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[23] Indium is up to now the only metal that undergoes insertion to alkenyl iodides with retention of the configuration. The use of zinc dust is not general and limited to some isolated examples (see ref. [16a]).

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