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# Tetraorganoindates as Nucleophilic Coupling Partners in Pd-Catalyzed Cross-Coupling Reactions

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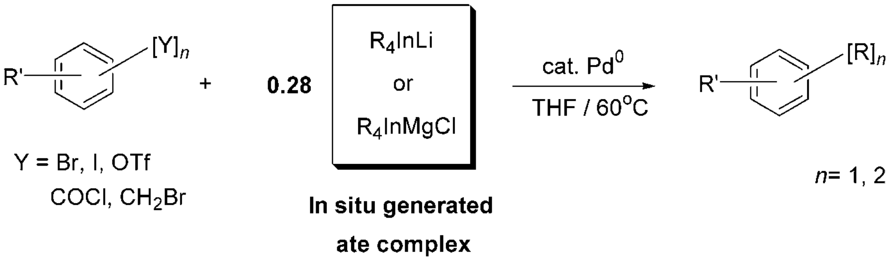
## ABSTRACT



**In situ-generated tetraorganoindate complexes from the reaction of 1 equiv of indium trichloride with 4 equiv of appropriate organometallics are efficient nucleophiles in Pd-catalyzed cross-coupling reactions. In this novel reaction tetraorganoindates containing methyl, 1°- and 2°-alkyl, vinyl, alkynyl, and aryl groups transfer the four organic groups to a variety of electrophiles with high atom efficiency.**

Synthetic applications of metallic indium have attracted much attention during the past decade due to this metal's chemical properties in terms of reactivity, selectivity, and low toxicity.[1] Among many indium-mediated reactions, the Barbier-type allylation reaction using allylic indium sesquihalides is most widely applied in organic synthesis.[2] Recently, we reported Pd-catalyzed cross-coupling reactions of in situ-generated allylindium[3] or allenylindium[4] reagents and carbonylative cross-coupling reactions of in situ-generated triorganoindium[5] with a variety of electrophiles. Also, it was found that a variety of organoindium reagents could be used in Pd-catalyzed cross-coupling reactions as nucleophilic coupling partners.[6] During the course of this study,[7] we considered the possibility of extending the metal-catalyzed crosscoupling reaction by using indate complexes. While tetramethylindate was pre-

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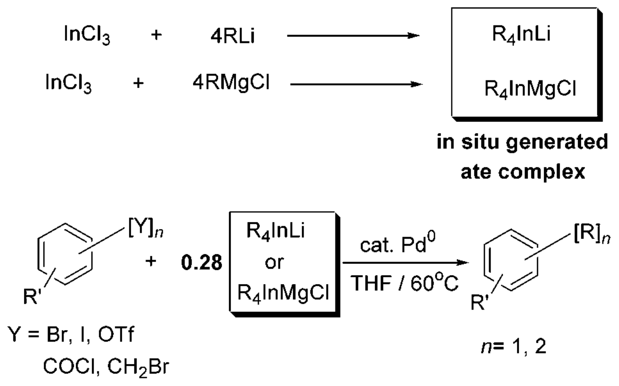
10.1021/ol035883o CCC: $25.00

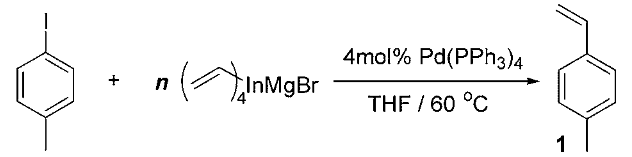
**Scheme 1**



pared and structurally elucidated as the first indate complex,[8] its application to organic synthesis was not reported except for selective conjugate addition to α,β-enones and substitution with allylic halides.[9] In addition, trivalent organoindiums are among the indium reagents that were most generally investigated in many organic reactions.[1] Although metal ate complexes have attracted a great deal of interest in organic reactions, as far as we are aware, *no successful report has appeared for applications of indate to cross-coupling reactions by transition-metal catalysis*.[10] The absence of systematic investigations of cross-coupling reactions using these metal ate complexes as nucleophilic coupling partners prompted a detailed study of the cross-coupling reactions of organic compounds with in situ-generated indate complexes.[11] In continuation with our studies directed toward the development of efficient metal-catalyzed reactions, we describe herein a realization of this goal with an indate complex (Scheme 1).

We first studied the stoichiometry of indate complexes and the catalytic activity of several palladium catalysts in the reaction of 1-iodotoluene with a tetravinylindate, which was generated in situ from the reaction of 1 equiv of indium trichloride with 4 equiv of vinylmagnesium bromide. The results are summarized in Table 1. Of the conditions screened, the best results were obtained with *0.28 equiv of tetravinylindate and 4 mol % Pd(PPh*$_3$*)*$_4$ *in THF at 60 °C*, which led to the formation of 4-methylstyrene (**1**) in quantitative yield (entry 4). Also, the desired product was obtained in 29, 54, and 78% yields by using 0.07, 0.14, and 0.21 equiv of tetravinylindate, respectively (entries 1−3). *This result means that all of the vinyl groups attached to the indium were involved in product formation.* The fact that there is no cross-coupling product formed without Pd(0) catalyst suggests that the desired product is produced via a cross-coupling reaction (entry 6). Evidence for the synthesis of an indate complex was provided by the Michael addition reaction[9] of a tetraorganoindate to an α,β-enone. In contrast, the corresponding triorganoindium was found not to react with α,β-enone.[12] 4-Chlorotoluene did not react with tetravinylindate despite the presence of Pd(0) catalyst (entry 5).

**Table 1.** Stoichiometry Optimization of Pd-Catalyzed Cross-Coupling Reactions of Tetravinylindate with 4-Iodotoluene[a]

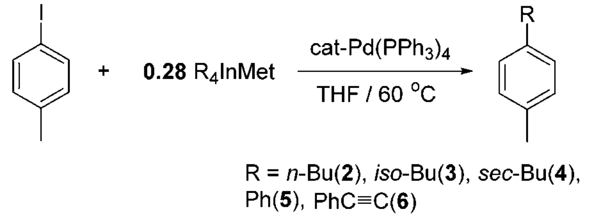


| | | | GC ratio[b] | |
|---|---|---|---|---|
| entry | *n* | theoretical yield | product | starting material |
| 1 | 0.07 | 28 | 29 | 71 |
| 2 | 0.14 | 56 | 54 | 46 |
| 3 | 0.21 | 83 | 78 | 22 |
| 4 | 0.28 | 100 | 100 | 0 |
| 5[c] | 0.28 | 100 | 0 | 100 |
| 6[d] | 0.28 | 100 | 0 | 100 |

[a] Reaction performed in the presence of 4 mol % Pd(PPh$_3$)$_4$ and *n* equiv of R$_4$InMgBr in THF at 60 °C. [b] Ratios were determined by GC integration of the crude reaction mixture before column chomatography. [c] 4-Chlorotoluene was used. [d] Reaction performed without Pd(0) catalyst.

Using the conditions stated above, Pd-catalyzed cross-coupling reactions of various indates with 4-iodotoluene were studied to determine the reactivity and efficiency of a variety of indate complexes as nucleophilic coupling partners (Table 2). In the case of tetra-*n*-butylindate, the desired compound was obtained in 91% yield (entry 1). Although tetra-*tert*-butylindate did not produce the cross-coupling product due to steric considerations and its basicity (entry 4), tetraisobutylindate and tetra-*sec*-butylindate participated as nucleo-

**Table 2.** Pd-Catalyzed Cross-Coupling Reactions of Various Indate with 4-Iodotoluene[a]



| entry | R$_4$InMet | isolated yield(%) |
|---|---|---|
| 1 | *n*-Bu$_4$InLi | 91(9)[b] |
| 2 | *iso*-Bu$_4$InMgBr | 68 |
| 3 | *sec*-Bu$_4$InMgCl | 47(12)[b] |
| 4 | *tert*-Bu$_4$InMgBr | 0 |
| 5 | Ph$_4$InMgCl | 79(19)[c] |
| 6 | $(\mathrm{Ph}{-}{\equiv}{-})_4\mathrm{InLi}$ | 98 |

[a] Reaction performed in the presence of 4 mol % Pd(PPh$_3$)$_4$ and 0.28 equiv of R$_4$InMet in THF at 60 °C. [b] 4,4′-Dimethylbiphenyl. [c] Biphenyl.

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(8) (a) Hoffmann, K.; Weiss, E. *J. Organomet. Chem.* **1972**, *37*, 1. (b) Hoffmann, K.; Weiss, E. *J. Organomet. Chem.* **1973**, *50*, 25. (c) Hoffmann, K.; Weiss, E. *J. Organomet. Chem.* **1973**, *50*, 17.

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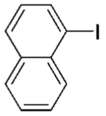
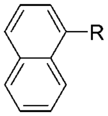
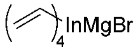
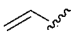
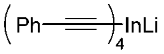
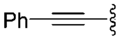
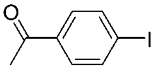
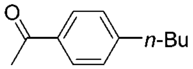
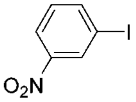
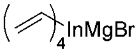
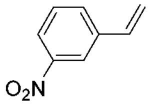
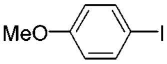
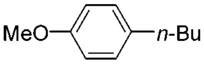
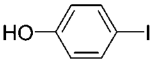
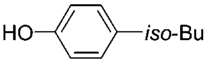
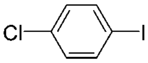
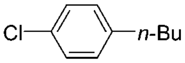
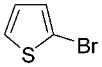
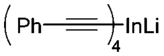
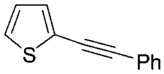
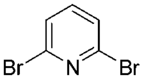
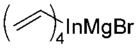
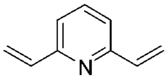
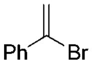
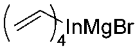
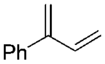
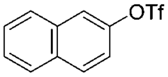
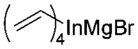
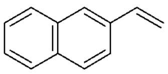
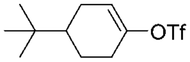
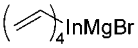
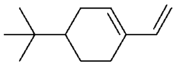
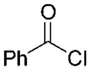
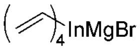
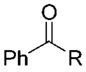
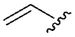
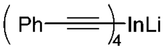
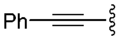
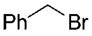
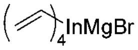
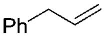
**Table 3.** Pd-Catalyzed Cross-Coupling Reactions of Indate with Organic Electrophiles[a]

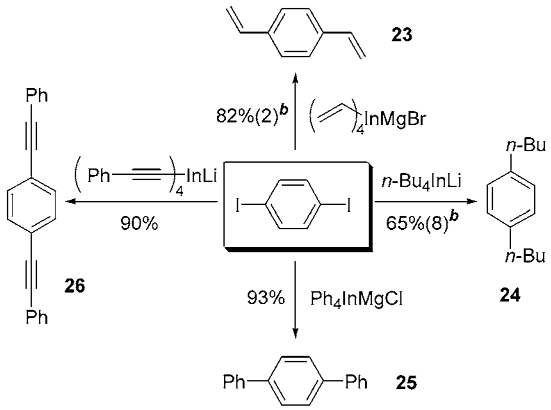
| entry | organic electrophile | $R_4InMet$ | product | | isolated yield(%) |
|---|---|---|---|---|---|
| 1 |  | $Me_4InLi$ |  Me | **7** | 94[b] |
| 2 | |  |  | **8** | 96[c] |
| 3 | |  |  | **9** | 96 |
| 4 |  | $n$-$Bu_4InLi$ |  | **10** | 80 |
| 5 |  |  |  | **11** | 96 |
| 6 |  | $n$-$Bu_4InLi$ |  | **12** | 81 |
| 7 |  | $iso$-$Bu_4InMgBr$ |  | **13** | 63 |
| 8 |  | $n$-$Bu_4InLi$ |  | **14** | 77 |
| 9 |  |  |  | **15** | 89[d] |
| 10 |  |  |  | **16** | 87[e] |
| 11 |  |  |  | **17** | 80 |
| 12 |  |  |  | **18** | 88[b] |
| 13 |  |  |  | **19** | 90 |
| 14 |  |  |   | **20** | 86[f] |
| 15 | |  |  | **21** | 88[f] |
| 16 |  |  |  | **22** | 82 |

[a] Reaction performed in the presence of 4 mol % $Pd(PPh_3)_4$ and 0.28 equiv of $R_4InLi$ or $R_4InMgBr$ in THF at 60 °C. [b] Performed with 0.55 equiv of indate. [c] Performed with 0.32 equiv of indate. [d] Diphenylbutadiyne was obtained in 6% yield. [e] Performed with 0.83 equiv of indate. [f] Reaction was carried out at 25 °C for 1 h.

philes in Pd-catalyzed cross-coupling reactions (entries 2 and 3). Reaction of tetraphenylindate with 4-iodotoluene gave 4-methyl-biphenyl (**5**) in 79% yield (entry 5). Subjecting tetraphenylethynylindate to 4-iodotoluene resulted in all of the phenylethynyl groups attached to indium being converted into product **6** (entry 6).

To demonstrate the efficiency and scope of the present method, we applied this catalytic system to a variety of organic electrophiles and indates (Table 3). For a large number of aryl iodides, the presence of various substituents on the aromatic ring showed little effect on the efficiency of the reactions. It should be mentioned that 4-iodoacetophenone, having a reactive keto group toward the indate, provided the desired products in good yields (entry 4). Notably, 4-iodoanisole, possessing a methoxy group as a strong electron-donating group, underwent cross-coupling reactions to produce 4-*n*-butyl anisole in 81% yield (entry 6). The reaction of 4-iodophenol with 0.28 equiv of tetraisobutylindate produced the desired product **13** in 63% yield (entry 7). This result means that tetraisobutylindate acts as a nucleophilic coupling partner before playing a role as a base. 4-Chloroiodobenzene was subjected to the coupling reaction to produce selectively 4-*n*-butylchlorobenzene (**14**) in 77% yield (entry 8). Heteroatoms (nitrogen and sulfur) turned out

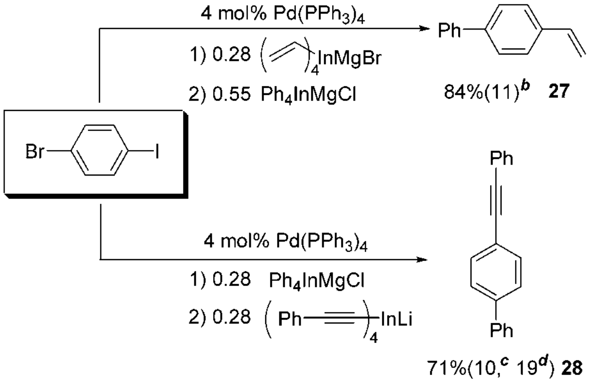
**Scheme 2** [a]



[a] Reaction conditions: 4 mol % Pd(PPh$_3$)$_4$/0.83 equiv of indate/THF/60 °C. [b]Isolated yield of mono-cross-coupling product.

to be compatible with the employed reaction conditions (entries 9 and 10). The reaction of 2,6-dibromopyridine with tetravinylindate afforded the 2-fold cross-coupling product **16** in 87% yield. Treatment of α-bromostyrene with 0.28 equiv of tetravinylindate afforded α-vinylstyrene (**17**) in 80% yield (entry 11). To enlarge the scope of indate complexes in Pd-catalyzed cross-coupling reactions, we studied the reactivity toward other electrophiles such as aryl triflates, vinyl triflates, acid chlorides, and benzyl bromide. Aryl triflates and vinyl triflates exhibit a similar reactivity to aryl iodides. Reaction of vinyl triflates with tetravinylindate, catalyzed by 4 mol % Pd(PPh$_3$)$_4$, produced the corresponding product **19** in 90% yield (entry 13). The low nucleophilicity of indate compounds led us to investigate their reactivity with benzoyl chloride under catalysis. Pd-catalyzed cross-coupling of benzoyl chloride with tetravinylindate or tetraphenylethynylindate worked equally well at room temperature (entries 14 and 15). The cross-coupling reactions of organometallics with benzyl bromide usually take place without catalysis due to the high reactivity of the halides. Nevertheless, poorly nucleophilic indates require a Pd catalyst. Accordingly, the reaction of 0.28 equiv of tetravinylindate with benzyl bromide in the presence of Pd-(0) led to the formation of allyl benzene (**22**) in 82% yield (entry 16).

**Scheme 3** [a]



[a] Reaction conditions: THF/60 °C. [b]Isolated yield of 4-bromostyrene. [c]Isolated yield of diphenylbutadiyne. [d]Isolated yield of 1,4-diphenylbenzene.

Encouraged by this result, we applied the present method to dihalogenated aromatic compounds to obtain disubstituted benzenes to provide products that can be used effectively in materials and dendrimer sciences. Reaction of 1,4-diiodobenzene with 0.83 equiv of tetravinylindate and tetraphenylethynylindate produced 1,4-divinylbenzene (**23**) and 1,4-diphenylethynylbenzene (**26**) in 82 and 90% yields, respectively. We were pleased to observe that treatment of 1,4-diiodobenzene with tetraphenyindate gave the desired 1,4-diphenylbenzene (**25**) in 93% yield (Scheme 2).

Reaction of 4-bromoiodobenzene with 0.28 equiv of tetravinylindate followed by 0.55 equiv of tetraphenylindate afforded 4-vinylbiphenyl (**27**) in 84% yield. The consecutive 2-fold Pd-catalyzed cross-coupling reaction by using structurally different indate complexes occurred to produce 4-phenyl-1,2-diphenylacetylene (**28**) chemoselectively and regioselectively in 71% yield (Scheme 3).

In conclusion, we have developed a new and atom-efficient Pd-catalyzed cross-coupling reaction involving in situ-generated tetraorganoindate complexes from the reaction of 1 equiv of indium trichloride with 4 equiv of organolithium and Grignard reagents. In this reaction, tetraorganoindates containing methyl, 1°- and 2°-alkyl, vinyl, alkynyl, and aryl groups transferred the four organic groups to a variety of electrophiles. Because indate complexes were not previously applied to metal-catalyzed cross-coupling reactions, these results should provide more opportunities for the discovery of efficient and selective C−C bond-forming reactions.

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**Supporting Information Available:** Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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