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# Palladium-Catalyzed Cross-Coupling Reactions of Triorganoindium Compounds with Vinyl and Aryl Triflates or Iodides

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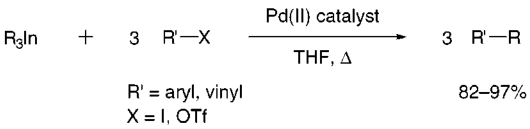
## ABSTRACT



$$R_3In + 3\ R'{-}X \xrightarrow[\text{THF, }\Delta]{\text{Pd(II) catalyst}} 3\ R'{-}R$$

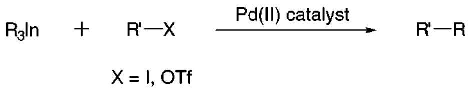
R' = aryl, vinyl
X = I, OTf

82–97%

**A novel palladium-catalyzed cross-coupling reaction of organoindium compounds with vinyl and aryl triflates or iodides is described. The reaction proceeds for alkyl-, vinyl-, alkynyl-, and arylindium compounds in excellent yields and high chemoselectivity without any excess of the organometallic. Remarkably, indium organometallics transfer efficiently the three organic groups attached to the metal.**

The chemistry of indium has recently gained great interest in organic synthesis because of the chemical properties of this metal with regard to its reactivity, selectivity, and low toxicity.[1] However, the synthetic applications of indium have been limited to the use of the metal for allylation and related reactions in aqueous media[2] or organic solvents[3] under Barbier conditions. The use of classic organometallic species of indium is practically unknown and limited to additions to chloroalkenes[4] and to our recently reported nickel-catalyzed 1,4-conjugate addition to electron deficient olefins.[5] Our belief that indium can achieve the importance of other main group metals such as boron or tin led us to further investigate the participation of indium organometallics in metal-catalyzed reactions. In this Letter, we report the palladium-catalyzed cross-coupling reaction of triorganoindium compounds with vinyl and aryl triflates or iodides (Scheme 1).

**Scheme 1**



$$R_3In + R'{-}X \xrightarrow{\text{Pd(II) catalyst}} R'{-}R$$

X = I, OTf

The metal-catalyzed cross-coupling reaction of aryl and vinyl halides (or pseudohalides) with organometallics is one of the most straightforward methods currently available for carbon−carbon bond formation.[6] Hitherto, a variety of metals (Zn, Mg, B, Al, Sn, Cu, Zr) have been used in palladium or

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[1] (a) Cintas, P. *Synlett* **1995**, 1087. (b) Marshall, J. A. *Chemtracts: Org. Chem.* **1997**, *10*, 481.

[2] (a) Allylation of carbonyls: Chan, T. H.; Yang, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3228. (b) Allenylations of carbonyls: Yi, X.-H.; Meng, Y.; Hua, X.-G.; Li, C.-J. *J. Org. Chem.* **1998**, *63*, 7472. (c) Reductive dimerization of aldimines: Kalyanam, N.; Rao, G. V. *Tetrahedron Lett.* **1993**, *34*, 1647.

[3] (a) Allylation of carbonyls: Lloyd-Jones, G. C.; Russell, T. *Synlett* **1998**, 903. (b) Allylation of imines: Choudhury, P. K.; Foubelo, F.; Yus, M. *J. Org. Chem.* **1999**, *64*, 3376. (c) Allylation of enamines: Bossard, F.; Dambrin, V.; Lintanf, V.; Beuchet, P.; Mosset, P. *Tetrahedron Lett.* **1995**, *36*, 6055. (d) Allylation of triple bonds: Fujiwara, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 2318. (e) Reformatsky-type reactions: Schick, H.; Ludwig, R.; Schwarz, K.-H.; Kleiner, K.; Kunath, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1191. (f) Allylation of cyclopropenes: Araki, S.; Nakano, H.; Subburaj, K.; Hirashita, T.; Shibutani, K.; Yamamura, H.; Kawaki, M.; Butsugan, Y. *Tetrahedron Lett.* **1998**, *39*, 6327.

[4] Nomura, R.; Miyazaki, S.-I.; Matsuda, H. *J. Am. Chem. Soc.* **1992**, *114*, 2378.

[5] Pérez, I.; Pérez Sestelo, J.; Maestro, M. A.; Mouriño, A.; Sarandeses, L. A. *J. Org. Chem.* **1998**, *63*, 10074.

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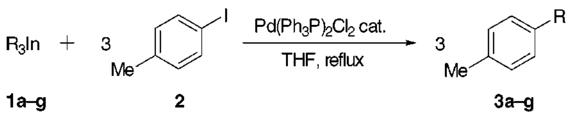
nickel cross-coupling reactions, with the Sn-organometallics (Stille reaction),[7] organoboron compounds (Suzuki reaction),[8] and Zn-organometallics[9] being the most common and useful in organic synthesis. Ideally, this reaction must show high conversion of the organometallic, high chemoselectivity, minimization of the side products, and the capacity to form C−C bonds between the different carbon types ($sp^3$, $sp^2$, and sp). In this sense, the main synthetic limitations have been found in the preparation of the organometallics, in the use of alkyl ($sp^3$) derivatives as coupling partners, and with the associated toxicity (especially of tin compounds) or side reactions observed. Additionally, the transfer of only one of the substituents attached to the metal has been an important handicap for copper, zinc, and aluminum compounds. The development of mixed organometallics has overcome this difficulty in the case of tin and boron.[7,8]

The cross-coupling reaction of indium organometallics was envisaged from easily available triorganoindium compounds (**1a**−**g**, Table 1)[10] and standard electrophiles as the aryl halide 4-iodotoluene (**2**) under palladium catalysis (Scheme 2).

**Scheme 2**



The reaction of 4-iodotoluene with triphenylindium (100 mol %) in the presence of a catalytic amount of Pd($Ph_3P$)$_2$Cl$_2$ (3 mol %) afforded, after just half-hour of refluxing, the cross-coupling product 4-phenyltoluene (**3a**) in quantitative yield. Exploring this new reaction, we observed that other organoindium compounds showed the same quantitative yields, even when other palladium complexes were used. This total conversion led us to think that more of one group could be transferred to the electrophile, a fact that was previously observed with arylic boron derivatives[11] and for the addition of triorganoindium compounds to chloroalkenes.[4] When the cross-coupling reaction of **2** was carried out with just 34 mol % of triphenylindium and 3 mol % of Pd($Ph_3P$)$_2$Cl$_2$, the coupled product **3a** was obtained in 96% yield (Table 1, entry 1), showing that the three phenyl groups attached to indium are transferred to **2**. The reaction with other palladium complexes such as Pd($PPh_3$)$_4$ or Pd($CH_3CN$)$_2$Cl$_2$ led to lower yields, and in the absence of a palladium catalyst the coupling product was not observed.

**Table 1.** Results of the Palladium-Catalyzed Cross-Coupling Reaction of Triorganoindium Compounds **1a**−**g** with Electrophiles **2**, **4**, and **6**[a]

| entry no. | R | electrophile | $t$ (h) | product | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | Ph (**1a**) | **2** | 1 | **3a** | 96 |
| 2 | $CH_2{=}CH$ (**1b**) | | 0.5 | **3b** | 89 |
| 3 | PhC≡C (**1c**) | | 0.5 | **3c** | 90 |
| 4 | TMSC≡C (**1d**) | | 1 | **3d** | 93 |
| 5 | *n*-Bu (**1e**) | | 4 | **3e** | 82 |
| 6 | Me (**1f**) | | 1 | **3f** | 85 |
| 7 | c-$C_3H_5$ (**1g**) | | 3 | **3g** | 92 |
| 8 | Ph (**1a**) | **4** | 6 | **5a** | 95 |
| 9[c] | $CH_2{=}CH$ (**1b**) | | 3 | **5b** | 89 |
| 10[c] | PhC≡C (**1c**) | | 1 | **5c** | 94 |
| 11[c] | TMSC≡C (**1d**) | | 1 | **5d** | 93 |
| 12 | *n*-Bu (**1e**) | | 1.5 | **5e** | 91 |
| 13 | Me (**1f**) | | 4.5 | **5f** | 91 |
| 14 | c-$C_3H_5$ (**1g**) | | 3 | **5g** | 89 |
| 15 | Ph (**1a**) | **6** | 1 | **7a** | 93 |
| 16 | $CH_2{=}CH$ (**1b**) | | 0.5 | **7b** | 97 |
| 17 | PhC≡C (**1c**) | | 0.5 | **7c** | 95 |
| 18 | TMSC≡C (**1d**) | | 0.5 | **7d** | 93 |
| 19 | *n*-Bu (**1e**) | | 1 | **7e** | 90 |
| 20 | Me (**1f**) | | 7 | **7f** | 92 |
| 21 | c-$C_3H_5$ (**1g**) | | 4 | **7g** | 90 |

[a] Reactions were conducted in THF at reflux using 34 mol % of $R_3In$ and 3 mol % of Pd($Ph_3P$)$_2$Cl$_2$, except for entries 9−11. [b] Isolated yield based on the electrophile added. [c] Pd(dppf)$Cl_2$ (3 mol %) as catalyst.

The reaction of alkyl-, vinyl-, and alkynylindium compounds (**1b**−**g**) with **2**, under the same reaction conditions (3:1 ratio of electrophile/$R_3In$), afforded the cross-coupling products **3b**−**g** in good yields (82−93%) and short reaction times (0.5−4 h, Table 1, entries 2−7).[12] Therefore, indium organometallics proved to be efficient at transferring different organic groups ($sp^3$, $sp^2$, and sp), with a remarkable aspect being the coupling of alkylindium derivatives without observation of $\beta$-elimination products.[6,13]

These results show that indium organometallics transfer all of the groups attached to the metal in the palladium-catalyzed cross-coupling reaction.

Expanding this reaction with other types of electrophiles, we studied the palladium-catalyzed cross-coupling reaction

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(6) (a) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: Chichester, U.K., 1995; Chapter 4. (b) Geissler, H. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 2.10.

(7) (a) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771. (b) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (c) Mitchell, T. N. *Synthesis* **1992**, 803. (d) Farina, V.; Krishnamurty, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1. (e) Mitchell, T. N. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 4.

(8) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 2.

(9) Negishi, E. In *Organozinc Reagents*; Knochel, P., Jones, P., Eds.; Oxford University Press: Oxford, U.K., 1999; Chapter 11.

(10) Prepared from organolithium or Grignard reagents by addition to a THF solution of $InCl_3$. See Supporting Information or ref 5.

(11) (a) Bumagin, N. A.; Bykov, V. V. *Tetrahedron* **1997**, *53*, 14437. (b) Bumagin, N. A.; Tsarev, D. A. *Tetrahedron Lett.* **1998**, *39*, 8155.

(12) **Representative General Experimental Procedure:** A solution of freshly prepared $R_3In$ (0.34 mmol, ca. 0.1 M in dry THF) was added over a refluxing mixture of the olefinic electrophile (1 mmol) and Pd($Ph_3P$)$_2$Cl$_2$ (0.03 mmol) in dry THF (4 mL). The resulting mixture was refluxed under an argon atmosphere until consumption of the starting material (0.5−7 h); then the reaction was quenched by addition of a few drops of MeOH. Usual workup and flash chromatography affords the cross-coupling product.

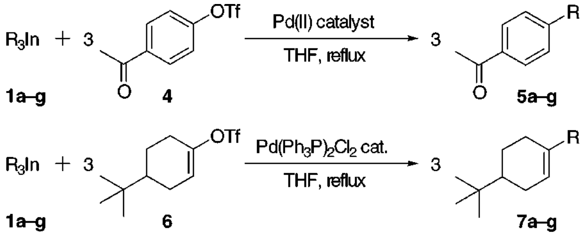
(13) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158.

(14) Ritter, K. *Synthesis* **1993**, 735.

(15) Other palladium catalysts such as Pd($Ph_3P$)$_4$, Pd($CH_3CN$)$_2$Cl$_2$, and Pd(dppe)$Cl_2$ gave lower yields.

of organoindium compounds with aryl and vinyl triflates.[14] Thus, the reaction of the aryl triflate **4** (Scheme 3) with 34 mol % of triphenylindium or the alkylindium derivatives **1e**, **1f**, and **1g** also gave the cross-coupling products in a chemoselective manner and in excellent yield (91−95%, Table 1, entries 8, 12, 13, and 14). The reaction with the alkenyl- and alkynylindium compounds **1b**, **1c**, and **1d** afforded lower yields of coupling products (25−40%), with the remainder being recovered as unreacted triflate. In these cases, the use of Pd(dppf)$Cl_2$ improved the yields significantly (89−94%, Table 1, entries 9, 10, and 11).[15]

**Scheme 3**



When the reaction was tested with the vinyl triflate **6** (Scheme 3), we observed, as expected, a higher reactivity than for the aryl triflate **4**. The coupling products were obtained, under the same conditions, in shorter reaction times (0.5−7 h) and with almost quantitative yields (90−97%, Table 1, entries 15−21).

The different behavior observed for indium organometallics in the palladium cross-coupling reaction with regard to the other metals used suggests that the reaction mechanism pathways could be other than that proposed for the Stille reaction.[16] Nomura and co-workers invoked the large difference of the bond strength between organoindium compounds and indium halides to explain related results in coupling with chloroalkenes.[17] On the other hand, the formation of a transient Pd−In complex as intermediate could be an alternative way to explain our results.[18]

In conclusion, we describe a novel palladium-catalyzed cross-coupling reaction of indium organometallics with aryl halides and aryl and vinyl triflates. In this reaction we show that, unlike with other metals used in this reaction type, all the groups attached to the metal are efficiently transferred (high conversion). Triorganoindium compounds can transfer different groups in excellent yields and high chemoselectivity. These features make triorganoindium compounds useful alternatives to other organometallics used in organic synthesis.

Further applications of indium organometallics in synthesis and studies about the mechanism of this reaction are in progress.

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**Supporting Information Available:** Experimental procedures and relevant spectral data for compounds **3**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[16] (a) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033. (b) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585. (c) Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434. (d) Farina, V. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, U.K., 1995; Vol. 12, Chapter 3.4. (e) Casado, A. L.; Espinet, P. *J. Am. Chem. Soc.* **1998**, *120*, 8978.

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[18] (a) Carmalt, C. J.; Norman, N. C.; Clarkson, L. M. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, U.K., 1995; Vol. 1, Chapter 12, p 566. (b) Marshall, J. A.; Grant, C. M. *J. Org. Chem.* **1999**, *64*, 696 and references therein.