JOC Note

Copper-Catalyzed Regioselective Allylic Substitution Reactions with Indium Organometallics

David Rodríguez, José Pérez Sestelo,* and
Luis A. Sarandeses*

Departamento de Química Fundamental, Universidade da Coruña, E-15071 A Coruña, Spain

qfsarand@udc.es

Abstract: The first nucleophilic allylic substitution reactions of triorganoindium compounds with allylic halides and phosphates are reported. The reactions of trialkyl- and triarylindium reagents with cinnamyl and geranyl halides and phosphates, with the aid of copper catalysis [$Cu(OTf)_2$/$P(OEt)_3$], are described. In general, the reaction proceeds efficiently to give good yields and regioselectively to afford the S_N2' product.

Over the past decade, indium has received a great deal of attention from organic chemists due to its interesting chemical properties, which include a low first oxidation potential, stability under aqueous conditions, and low toxicity.[1] As a consequence, indium metal has been widely used in the addition reactions of allylic systems to carbonyls and related derivatives under aqueous or anhydrous conditions.[2] More recently, indium organometallics have emerged as useful reagents for fundamental reactions in organic synthesis, such as conjugate additions,[3] cross-coupling reactions,[4,5] or additions to triple bonds.[6] Despite the increasing synthetic utility of indium reagents in organic synthesis, a number of important reactions remain unexplored.

Nucleophilic allylic substitution constitutes a powerful reaction in synthesis and the ability to control the regio- and stereoselectivity to as well as the application of different types of nucleophiles is a desirable goal.[7] This reaction can be performed using soft nucleophiles and organometallic reagents under transition metal catalysis (generally palladium or nickel)[8] or, alternatively, by the stoichiometric use of organocopper species[9] and copper-catalyzed reactions of several organometallics.[10] From the standpoint of organic synthesis, palladium and copper are the most important metals for selective metal-catalyzed nucleophilic allylic substitution.

As part of a project aimed at finding new applications for indium organometallics in organic synthesis, we explored the synthetic utility of triorganoindium reagents in the nucleophilic allylic substitution reaction. The only examples of the use of group 13 organometallics in allylic substitution involved a few examples of the palladium-catalyzed reactions of boron reagents[11] and the copper-catalyzed reactions of aluminum alkyls.[12] Hitherto, the use of indium organometallics has been limited to tetraorganoindates[13] and to the recently published palladium-catalyzed allylic substitution using allylindium reagents generated in situ.[14] In this paper, we wish to report the first use of triorganoindium reagents (R_3In) in nucleophilic allylic substitution under copper catalysis (eq 1).

$$R' \diagdown X \ + \ R_3In \ \xrightarrow{\text{Cu catalyst}} \ R' \diagdown^{R} \qquad (1)$$
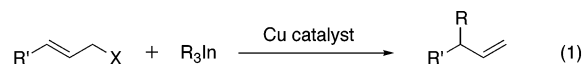
Our investigation started with a study of the reactions of tri-n-butylindium (n-Bu$_3$In) and triphenylindium (Ph$_3$In) with cinnamyl bromide (**1a**, Table 1). In the absence of catalyst the reaction failed, but the addition of a catalytic amount of a copper salt promoted a rapid reaction that gave the nucleophilic allylic substitution products in moderate yields. These products were ob-

(1) (a) Cintas, P. *Synlett* **1995**, 1087−1096. (b) Marshall, J. A. *Chemtracts: Org. Chem.* **1997**, *10*, 481−496. (c) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; Wiley: New York, 1997; Chapter 4, pp 64−114. (d) Paquette, L. A. In *Green Chemistry: Frontiers in Benign Chemical Synthesis and Processing*; Anastas, P. T., Williamson, T. C., Eds.; Oxford University Press: Oxford, U.K., 1998; Chapter 15, pp 250−264.

(2) (a) Li, C.-J.; Chan, T.-H. *Tetrahedron* **1999**, *55*, 11149−11176. (b) Ranu, B. C. *Eur. J. Org. Chem.* **2000**, 2347−2356. (c) Pae, A. N.; Cho, Y. S. *Curr. Org. Chem.* **2002**, *6*, 715−737.

(3) (a) Araki, S.; Shimizu, K.; Jin, S.-J.; Butsugan, Y. *J. Chem. Soc., Chem. Commun.* **1991**, 824−825. (b) Pérez, I.; Pérez Sestelo, J.; Maestro, M. A.; Mouriño, A.; Sarandeses, L. A. *J. Org. Chem.* **1998**, *63*, 10074−10076.

(4) For contributions from this group, see: (a) Pérez, I.; Pérez Sestelo, J.; Sarandeses, L. A. *Org. Lett.* **1999**, *1*, 1267−1269. (b) Pérez, I.; Pérez Sestelo, J.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155−4160. (c) Pena, M. A.; Pérez, I.; Pérez Sestelo, J.; Sarandeses, L. A. *Chem. Commun.* **2002**, 2246−2247.

(5) (a) Nomura, R.; Miyazaki, S.-I.; Matsuda, H. *J. Am. Chem. Soc.* **1992**, *114*, 2738−2740. (b) Takami, K.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Org. Lett.* **2001**, *3*, 1997−1999. (c) Lee, P. H.; Sung, S.; Lee, K. *Org. Lett.* **2001**, *3*, 3201−3204.

(6) (a) Araki, S.; Imai, A.; Shimizu, K.; Yamada, M.; Mori, A.; Butsugan, Y. *J. Org. Chem.* **1995**, *60*, 1841−1847. (b) Ranu, B. C.; Majee, A. *Chem. Commun.* **1997**, 1225−1226. (c) Fujiwara, N.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 4095−4101. (d) Klaps, E.; Schmid, W. *J. Org. Chem.* **1999**, *64*, 7537−7546. (e) Takami, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 2993−2995.

(7) For a general overview, see: Tsuji, T. *Transition Metal Reagents and Catalysts*; Wiley: New York, 2000; Chapter 4, pp 109−168.

(8) (a) Godleski, S. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 4, Chapter 3.3, pp 585−661. (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395−422. (c) Heumann, A. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 2.15, pp 251−264.

(9) Lipshutz, B. H. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, U.K., 1995; Vol. 12, Chapter 3.2, pp 59−130.

(10) (a) Yanagisawa, A.; Yamamoto, H. In *Transition Metal Catalysed Reactions*; Murahashi, S.-I., Davies, S. G., Eds.; Blackwell Science: Oxford, U.K., 1999; Chapter 11, pp 225−240. (b) Sofia, A.; Karlström, E.; Bäckvall, J.-E. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim: 2002; Chapter 8, pp 259−288. For recent examples, see: (c) Dübner, F.; Knochel, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 379−381. (d) Meuzelaar, G. J.; Karlström, A. S. E.; van Klaveren, M.; Persson, E. S. M.; del Villar, A.; van Koten, G.; Bäckvall, J.-E. *Tetrahedron* **2000**, *56*, 2895−2903. (e) Luchaco-Cullis, C.; Mizutani, H.; Murphy, K. E.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1456−1460. (f) Malda, H.; van Zijl, A. W.; Arnold, L. A.; Feringa, B. L. *Org. Lett.* **2001**, *3*, 1169−1171.

(11) (a) Moreno-Mañas, M.; Pajuelo, F.; Pleixats, R. *J. Org. Chem.* **1995**, *60*, 2396−2397. (b) Cortés, J.; Moreno-Mañas, M.; Pleixats, R. *Eur. J. Org. Chem.* **2000**, 239−243.

(12) Flemming, S.; Kabbara, J.; Nickisch, K.; Westermann, J.; Mohr, J. *Synlett* **1995**, 183−185.

(13) Araki, S.; Jin, S.-J.; Butsugan, Y. *J. Chem. Soc., Perkin Trans. 1* **1995**, 549−552.

(14) Lee, P. H.; Sung, S.-Y.; Lee, K.; Chang, S. *Synlett* **2002**, 146−148.

TABLE 1. Effect of Catalyst on the Reaction of Triorganoindium Compounds with Cinnamyl Bromide (1a)[a]

entry no.	R	Cu catalyst	ligand	yield[b] (%)	ratio 2/3[c]
1	n-Bu	Cu(OTf)$_2$		40	72:28
2		CuCN		65	80:20
3		CuBr·SMe$_2$	P(OEt)$_3$	33	68:32
4		CuCN	P(OEt)$_3$	50	88:12
5		Cu(OTf)$_2$	P(OEt)$_3$	85	82:18
6	Ph	CuBr·SMe$_2$		19	76:24
7		CuBr·SMe$_2$	P(OEt)$_3$	32	67:33
8		CuI	P(OEt)$_3$	13	67:33
9		Cu(OTf)$_2$	P(OEt)$_3$	80	76:24

[a] Reaction conditions: 120 mol % of R$_3$In, 100 mol % of **1a**, 15 mol % of copper catalyst, 30 mol % of P(OEt)$_3$, −30 °C to rt, 3 h. [b] Isolated yield of **2** + **3**. [c] Determined by GC.

TABLE 2. Results of the Copper-Catalyzed Reaction of Triorganoindium Compounds with Cinnamyl Derivatives (1a−e)

entry no.	X	R	yield[a] (%)	ratio 2/3[b]
1	Br (**1a**)	n-Bu	85	82:18
2		Me	73	92:8
3		Ph	80	76:24
4		Me$_3$SiCH$_2$	93	86:14
5	Cl (**1b**)	n-Bu	70	96:4
6		Me	38	91:9
7		Ph	30	66:34
8	OAc (**1c**)	n-Bu	−	−
9	OBoc (**1d**)	n-Bu	−	−
10	OP(O)(OEt)$_2$ (**1e**)	n-Bu	70	99:1
11		Me	79	92:8
12		Ph	83	50:50

[a] Isolated yield of **2** + **3**. [b] Determined by GC.

tained as mixtures of S$_N$2′ and S$_N$2 products (**2** and **3**, respectively) where the major regioisomer was the S$_N$2′ product. Table 1 lists the results obtained in the reactions of n-Bu$_3$In and Ph$_3$In with **1a** using copper catalysis under a variety of reaction conditions.

The reaction of triorganoindium compounds (120 mol %) with cinnamyl bromide in the presence of 15 mol % of various copper salts [e.g., CuBr·SMe$_2$, Cu(OTf)$_2$, or CuCN] afforded the S$_N$2′ product (**2**) in low-to-moderate yields but with good regioselectivity (Table 1, entries 1, 2, and 6). Interestingly, in this series of reactions we found that the addition of a copper ligand such as triethyl phosphite (30 mol %), in combination with Cu(OTf)$_2$ as a catalyst, increased the yields markedly (up to 85%) while maintaining the regioselectivity (Table 1, entries 5 and 9).[15] Curiously, the combination of P(OEt)$_3$ with Cu(I) salts gave rise to lower yields (Table 1, entries 3, 4, 7, and 8). In these studies, we also found that the temperature had an influence on the regioselectivity, with the best results obtained when the reaction was performed at −30 °C. The use of lower amounts of R$_3$In decreased the yields which suggest that, under these conditions, indium organometallics are able to transfer only one of the groups attached to the metal.[16]

The mechanism for this process is unclear, but according to the proposal for the copper-catalyzed allylic substitution with Grignard or organozinc reagents, copper species of the type (RCuOTf)InR$_2$, derived from a transmetalation of the organic group from indium to copper, could be involved in the reaction. The reactivity of this species is dependent on the nature of the initial metal, which in many cases is still intimately associated with the resulting copper reagent.[17,18]

After the most appropriate reaction conditions had been established, we explored the scope of the reaction using other indium organometallics and different allylic substrates. In the reaction of cinnamyl halides, we observed that alkyl and aryl groups can be efficiently transferred using Cu(OTf)$_2$/P(OEt)$_3$ as a catalytic system. The best results were obtained in the reaction of triorganoindium reagents with cinnamyl bromide (**1a**) (73−93%, Table 2, entries 1−4). Under the same reaction conditions, cinnamyl chloride (**1b**) showed a lower reactivity, although high regioselectivities were obtained for tri-n-butyl- and trimethylindium compounds (Table 2, entries 5 and 6).

At this point, we were also interested in extending the reaction to other electrophiles such as allylic alcohol derivatives. With this aim in mind, we first studied the behavior of oxygenated cinammyl derivatives. Acetate **1c** and carbonate **1d** were both found to be unreactive, but the cinammyl phosphate **1e** reacted efficiently, under copper catalysis conditions, with triorganoindium reagents to give high yields of products (Table 2, entries 10−12). The regioselectivity obtained in the reactions was excellent for trialkylindium reagents (up to 99:1, Table 2, entries 10 and 11), but triphenylindium gave only a 1:1 mixture of regioisomers. This result can be explained according to the reaction pathways proposed for allylic substitution using organocopper reagents:[18] the presence of aryl or sterically hindered ligands could slow the rate of the reductive elimination in the initial σ-Cu complex leading the S$_N$2′ product (**2**) and thus favoring the formation of a π-allyl-Cu complex, which increases the ratio of the S$_N$2 product (**3**). Interestingly, indium organometallics are useful alternatives to diorganozinc reagents, which in some cases have proven to be unreactive toward allylic phosphates.[10f] In this sense, the reactivity

(15) Phosphorus ligands have been successfully used in enantioselective copper-catalyzed allylic substitution reactions with diorganozinc reagents; see ref 10f.

(16) This result is coincident with the observed in the nickel-catalyzed 1,4-conjugate addition of R$_3$In to electron deficient olefins (ref 3b), but contrary to the palladium-catalyzed cross-coupling reaction with R$_3$In to organic halides and pseudohalides where all three groups attached to indium are transferred (ref 4).

(17) (a) Wipf, P. *Synthesis* **1993**, 537−557. (b) Knochel, P.; Betzemeier, B. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim: 2002; Chapter 2, pp 45−78.

(18) For a mechanistic proposal for the reaction, see ref 10b and: (a) Bäckvall, J.-E.; Sellén, M.; Grant, B. *J. Am. Chem. Soc.* **1990**, *112*, 6615−6621. (b) Nakamura, E.; Mori, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3750−3771. (c) Mori, S.; Nakamura, E.; Morokuma, K. *J. Am. Chem. Soc.* **2000**, *122*, 7294−7307. (d) Bertozzi, F.; Crotti, P.; Macchia, F.; Pineschi, M.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 930−932.

TABLE 3. Results of the Copper-Catalyzed Reaction of Triorganoindium Compounds with Geranyl Derivatives (4a−c)

entry no.	X	R	yield^a (%)	ratio **5/6**^{b}
1	Br (**4a**)	*n*-Bu	74	96:4
2		Me	75	92:8
3		Ph	84	79:21
4		Me$_3$SiCH$_2$	96	60:40
5	Cl (**4b**)	*n*-Bu	50	76:24
6	OP(O)(OEt)$_2$ (**4c**)	*n*-Bu	83	90:10
7		Me	60	98:2
8		Ph	80	50:50

^{a} Isolated yield of **5** + **6**. ^{b} Determined by GC.

of R$_3$In with oxygenated allylic substrates is more similar to that observed with trialkylaluminum reagents,[12] presumably because the copper species generated by the transmetalation from indium or aluminum to copper are close in reactivity.

Prompted by the results obtained in the copper-catalyzed allylic substitution of cinnamyl derivatives with triorganoindium, we explored the reactivity of geranyl derivatives. These substrates serve as interesting models to explore the formation of quaternary centers by an S$_N$2′ reaction.

The reaction of R$_3$In with geranyl derivatives followed the same reaction patterns as cinnamyl derivatives. The reaction of geranyl bromide (**4a**) with trialkyl- and triarylindium reagents afforded the corresponding S$_N$2′ products regioselectively (up to 92:8 of ratio **5:6**) and with high yields (74−84%, Table 3, entries 1−3). The use of bulkier reagents, such as tris(trimethylsilylmethyl)indium, also afforded the nucleophilic substitution product in excellent yield but without the same level of regioselectivity (Table 3, entry 4). As observed previously, the reactivity of geranyl chloride with triorganoindium compounds was low (Table 3, entry 5). As for cinnamyl derivatives, the reaction of geranyl phosphate **4c** with trialkylindium reagents proceeded with good yields and high S$_N$2′ regioselectivity but the addition of triphenylindium, despite giving a good yield, was not regioselective (Table 3, entries 6−8). These results show indium organometallics to be useful reagents for the preparation of quaternary centers by regioselective S$_N$2′ nucleophilic allylic substitution reactions, a central feature of copper reagents.[19]

In conclusion, we have discovered that triorganoindium reagents react with allylic halides and phosphates under copper catalysis conditions. In the reaction, alkyl and aryl organic groups are efficiently transferred in good yields

and with high S$_N$2′ regioselectivities. A plausible mechanism for this reaction involves the formation of organocopper species by indium transmetalation.[17,18] Although the transmetalation from indium to nickel and palladium has been reported in conjugate additions and in cross-coupling reactions, this is the first example of a transmetalation from indium to copper to be applied in organic synthesis. Additionally, the use of phosphorus compounds as copper ligands opens up the possibility of performing the reaction enantioselectively.[10f] Further investigations in this direction are currently underway.

Experimental Section

General Methods. All reactions were conducted in flame-dried glassware under a positive pressure of argon. Reaction temperatures refer to external bath temperatures. All dry solvents were distilled under argon immediately prior to use. Tetrahydrofuran (THF) was dried by distillation from the sodium ketyl of benzophenone. Liquid reagents or reagent solutions were added by syringe or cannula. The total volume of solvent is given for these additions. Usually the compound was dissolved in 80% of the stated volume and the flask was then rinsed with the remaining 20% of fresh solvent. Organic extracts were dried over anhydrous MgSO$_4$, filtered, and concentrated using a rotary evaporator at aspirator pressure (20−30 mmHg). Thin-layer chromatography was effected on silica gel 60 F$_{254}$ (layer thickness 0.2 mm), and components were located by observation under UV light and/or by treating the plates with a phosphomolybdic acid or *p*-anisaldehyde reagent followed by heating. Flash chromatography was performed on silica gel 60 (230−400 mesh) by Still's method.[20]

Triorganoindium compounds were prepared according to previously published methods[4] by treatment of the corresponding organolithium or Grignard reagents (3 equiv) with InCl$_3$ (1.1 equiv) in dry THF at −78 °C and warming up to room temperature. All other reagents were commercial products and used as received.

General Procedure for the Allylic Substitution Reaction. To a cooled (−30 °C) solution of Cu(OTf)$_2$ (54 mg, 0.15 mmol) and P(OEt)$_3$ (50 μL, 0.30 mmol) in dry THF (2 mL) was slowly added a solution of R$_3$In (1.20 mmol, ∼0.05 M in dry THF). The reaction mixture was stirred for 10 min, and a solution of the allylic substrate (1.00 mmol) in dry THF (4 mL) was added. The resulting mixture was stirred at −30 °C for 2 h and allowed to warm to room temperature for 1 h. The reaction was quenched by the addition of few drops of MeOH, the mixture was concentrated in vacuo, and Et$_2$O (30 mL) was added. The organic phase was washed with aqueous HCl (5%, 10 mL), saturated aqueous NaHCO$_3$ (15 mL), and saturated aqueous NaCl (15 mL), dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography to afford, after concentration and high-vacuum-drying, the allylic substitution products. All compounds obtained were fully characterized by NMR and mass spectrometry and exhibit identical physical data to those reported in the literature (see the Supporting Information).

Supporting Information Available: Relevant spectral and analytical (GC) data for compounds **1e**, **2**, **4c**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0265939

(19) For some other methods for the preparation of quaternary carbon centers by copper-catalyzed allylic substitution of organometallics, see refs 12, 18a, and: (a) Yanagisawa, A.; Nomura, N.; Yamamoto, H. *Synlett* **1993**, 689−690. (b) Yanagisawa, A.; Nomura, N.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 6017−6028. (c) Reddy, C. K.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1700−1701.

(20) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.