JOC *Note*

Palladium-Catalyzed Cross-Coupling Reactions of Allylic Halides and Acetates 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

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Abstract: The palladium(0)-catalyzed cross-coupling reaction of allylic halides and acetates with indium organometallics is reported. In this synthetic transformation, triorganoindium compounds and tetraorganoindates (aryl, alkenyl, and methyl) react with cinnamyl and geranyl halides and acetates to afford the S_N2 product regioselectively and in good yield. The reaction proceeds with net inversion of the stereochemical configuration.

The metal-catalyzed cross-coupling reaction of organometallic reagents with organic halides and related electrophiles is one of the most convenient methodologies for carbon−carbon bond formation.[1] A variety of organometallic reagents (Mg, Zn, Cu, B, Sn, Si, In) and unsaturated electrophiles (vinyl or aryl halides or pseudohalides) can be used in conjunction with palladium or nickel catalysis, and only alkyl and allyl electrophiles suffer from limitations.[2] Allylic substrates represent a particular class of organic compounds due to their high reactivity and bidentate electrophilicity. The control of both the regio- and stereochemistry in allylic substitution reactions are fundamental aspects of the reactivity of such systems.[3] Reactions involving allylic electrophiles have been traditionally performed using organocopper species[4] (or copper-catalyzed reactions using other organometallics)[5] and, more recently, using soft nucleophiles under palladium catalysis (Tsuji−Trost reaction).[6] Transition-metal-catalyzed cross-coupling reactions of allylic substrates involving the oxidative addition/transmetalation/reductive elimination sequence have been performed using several organometals.[7] However, the reaction has limited synthetic scope, probably due to the slow rate of the reductive elimination step.[8]

In the past decade, indium and organoindium reagents have proven to be useful in organic synthesis due to their high chemoselectivity, low toxicity, and tolerance to aqueous media.[9] In 1999, we discovered the metal-catalyzed cross-coupling reaction using indium organometallics.[10] In this reaction, triorganoindium compounds (R_3In) react efficiently under palladium catalysis with alkenyl or aryl halides and triflates. The whole process has a high atom economy, with all three groups attached to indium being efficiently transferred to the electrophile (eq 1). Since then, we have been interested in extending the synthetic scope of this reaction to encompass new scenarios.[11]

$$R_3In + 3\ R'{-}X \xrightarrow[\text{THF}]{\text{Pd or Ni catalyst}} 3\ R'{-}R \qquad (1)$$

Recently, we discovered that triorganoindium compounds react regioselectively with allylic halides and acetates under copper catalysis to afford the S_N2' product in good yield.[12] We report here our results on the palladium-catalyzed reaction of indium organometallics with allylic electrophiles.[13]

As a starting point for our investigation, and in accordance with literature precedents,[14] we initially studied the reactivity of Ph_3In with cinnamyl chloride under palladium(0) catalysis [$Pd_2(dba)_3$] without ligands. Under these conditions, we observed that Ph_3In (40 mol %) reacted with cinnamyl chloride (**1a**, 100 mol %) in the presence of $Pd_2(dba)_3$ (5 mol %) under reflux in THF to afford the S_N2 product (**2a**) regioselectively in 53% yield (Table 1, entry 1). In the reaction, isomerization of the alkene was not observed, but starting cinnamyl chloride

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[†] Dedicated *in memoriam* to Dr. Juan Carlos del Amo (Universidad Complutense de Madrid, Spain), victim of the terrorism in Madrid on March 11, 2004.

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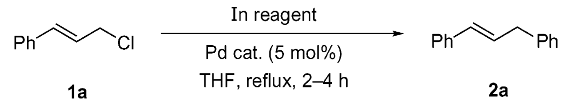
10.1021/jo0491511 CCC: $27.50

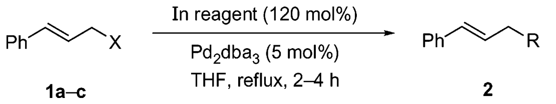
TABLE 1. Reaction of Indium Reagents with Cinnamyl Chloride (1a) under Palladium Catalysis[a]



entry	In reagent (mol %)	catalyst	yield (%)[b]
1	Ph_3In (40)	Pd_2dba_3	53 (85)[c]
2		Pd_2dba_3, PPh_3 (1:2)	50
3		$Pd(PPh_3)_4$	56[d,e]
4		$Pd(PCy)_2$	53
5		$Pd(Pt\text{-}Bu_3)_2$	56
6	Ph_2InCl (120)[f]	Pd_2dba_3	60
7	$PhInCl_2$ (120)[f]	Pd_2dba_3	27
8	Ph_4InLi (40)	Pd_2dba_3	69 (80)[c]

[a] Reaction conditions: 40−120 mol % In reagent, 100 mol % **1a**, 5 mol % palladium catalyst, THF, reflux, 2−4 h. [b] Isolated yield. [c] Values in parentheses correspond to yields obtained on using 120 mol % indium reagent. [d] Reaction performed in DMF at 100 °C. [e] Mixture (1:1) of S_N2 and S_N2' products. [f] Ph_2InCl and $PhInCl_2$ were prepared by addition of PhLi (2 or 1 equiv, respectively) to $InCl_3$ and stirring the mixture at room temperature.

TABLE 2. Results of the Palladium-Catalyzed Reaction of Indium Organometallics with Cinnamyl Derivatives (1a−c)



entry	X	In reagent (R)	yield (%)[a]
1	Cl (**1a**)	Ph_3In	85
2		$(p\text{-}MeOC_6H_4)_3In$	80
3		$(CH_2{=}CH)_3In$	55
4		Me_3In	63
5		Ph_4InLi	80
6		Me_4InLi	67
7		$(CH_2{=}CH)_4InLi$	57
8	Br (**1b**)	Ph_3In	60
9		$(CH_2{=}CH)_3In$	62
10		Me_3In	45
11	OAc (**1c**)	Ph_3In	70
12		$(CH_2{=}CH)_3In$	48
13		Me_3In	61

[a] Isolated yield.

was recovered (20%), and biphenyl was also formed. On the basis of this result, we reasoned that the triorganoindium reagent transfers more than one group during the palladium-catalyzed allylic substitution reaction but that the transfer of all three groups is not complete. In an effort to improve this result, we tried different catalysts and reaction conditions (Table 1). The use of $Pd(PPh_3)_4$ in a polar solvent such as DMF at 100 °C gave a similar yield, although in this case a mixture of regioisomers was detected (Table 1, entry 3). With the aim of facilitating the reductive elimination step, we tested the highly reactive $14e^-$ palladium complexes $Pd(PCy_3)_2$ and $Pd(Pt\text{-}Bu_3)_2$.[15] Unfortunately, neither of these systems gave better results (Table 1, entries 4 and 5). The addition of phosphine ligands such as PPh_3 or the use of additives such as LiCl or CsF did not increase the yields either. The yield of the reaction was only increased significantly by using stoichiometric amounts of Ph_3In. Under these conditions, the S_N2 product (**2a**) was obtained exclusively in 85% yield along with 5% of the starting cinnamyl chloride (**1a**, Table 1, entry 1).

The results of this study are in contrast to our previous experience in the palladium cross-coupling reaction of R_3In with alkenyl and aryl halides.[10] Here, it seems that the transfer of the three organic groups is not particularly efficient. This result can be explained by the slow rate of the reductive elimination step, a situation that favors the consumption of the organometallic reagent by dimerization of the R_3In species.[16] To further explore the reactivity of indium organometallics in palladium-catalyzed allylic substitutions, we proceeded to study the reactivity of different organoindium species prepared by varying the ratio RLi:$InCl_3$. In all cases, except using $PhInCl_2$ (Table 1, entry 7), the cross-coupling product was formed in good yields (Table 1, entries 6 and 8) and the utility of tetraorganoindates, a less explored type of indium organometallic, in allylic substitution was also proved.[17] For example, the reaction of lithium tetraphenylindate (40 mol %) with cinnamyl chloride under palladium(0) catalysis afforded the S_N2 product in 69% yield, which demonstrates the efficient transfer of more than one phenyl group (Table 1, entry 8).

The synthetic scope of the reaction was subsequently explored with various organoindium species (alkyl, alkenyl, aryl, and alkynyl) and allylic electrophiles such as cinnamyl and geranyl derivatives. In the reactions of triorganoindium reagents with cinnamyl chloride, we observed that, besides triphenylindium, phenyl derivatives such as *p*-methoxyphenyl can be also used (Table 2, entry 2). The reaction with alkenylindium species such as trivinylindium can also be performed using $Pd_2(dba)_3$ to give the cross-coupled product in moderate yield (55% yield, Table 2, entry 3). Unfortunately, the reaction with alkylindium reagents such as tributylindium did not afford the cross-coupled product. In this case, only the reduction product from the β-hydride elimination reaction in the σ-butyl-π-allyl-palladium(II) intermediate was formed. Nevertheless, the reaction with trimethylindium proceeded in good yield (63% yield, Table 2, entry 4) and represents a good alternative to other organometallics such as organotins. The use of trialkynylindium reagents only gave the product from the reductive dimerization of the organometallic.[18] Tetraorganoindates also showed high reactivity on using 120 mol % reagent. The transfer of aryl (phenyl), alkyl (methyl), and vinyl groups was efficient, and the S_N2 products were obtained regioselectively in yields ranging from 55 to 80% (Table 2, entries 5−7).

The reaction of R_3In with other cinnamyl derivatives such as cinnamyl bromide (**1b**) and acetate (**1c**) also proceeded in moderate to good yields (45−70%, Table 2, entries 8−13) with similar reaction times.

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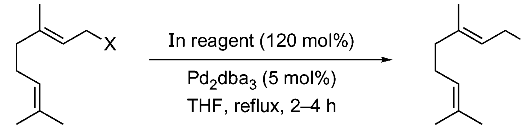
[17] (a) Araki, S.; Shimizu, T.; Jin, S.-J.; Butsugan, Y. *J. Chem. Soc., Chem. Commun.* **1991**, 824−825. (b) Lee, P. H.; Lee, S. W.; Seomoon, D. *Org. Lett.* **2003**, *5*, 4963−4966.

[18] Same result has been reported recently; see ref 13.

TABLE 3. Results of the Palladium-Catalyzed Reaction of Indium Organometallics with Geranyl Derivatives (3a−c)



3a–c **4**

entry	X	In reagent (R)	yield (%)[a]
1	Cl (**3a**)	Ph_3In	70
2		Me_3In	66
3		Ph_4InLi	90
4		Me_4InLi	69
5	Br (**3b**)	Ph_3In	87
6		Me_3In	60
7	OAc (**3c**)	Ph_3In	84
8		Me_3In	40
9		Ph_4InLi	80
10		Me_4InLi	38

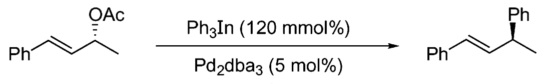
[a] Isolated yield.

Of particular relevance in the use of indium organometallics in palladium-catalyzed allylic reactions is the high regioselectivity observed (only the S_N2 product was detected by NMR) and the full retention of stereochemistry in the alkene (NMR spectroscopy or GC analysis). These findings are of particular interest when compared with other organometallics used in this allylic cross-coupling reaction.[7]

The same reaction patterns were observed on using other allylic electrophiles such as geranyl chloride (**3a**), bromide (**3b**), and acetate (**3c**). These compounds react efficiently with triphenyl- and trimethylindium to afford regioselectively the S_N2 product in moderate to good yields (40−90%). The reaction with trivinylindium afforded complex mixtures of products that proved to be difficult to separate, and the yields were below 30%. In addition, the reactions of these electrophiles with tetraorganoindates afforded the S_N2 products in similar yields. The results are summarized in Table 3.

Having established the reaction conditions, we turned our attention to some aspects concerning the mechanism of these reactions. In palladium-catalyzed allylic substitution reactions, one important aspect is the different stereochemical outcome depending on the nature of the nucleophile (soft or hard). The use of carbon-stabilized (soft) nucleophiles is associated with a net retention of configuration, which is a consequence of a double inversion produced by the oxidative addition of the palladium(0) to the allylic substrate followed by an anti addition of the nucleophile to the ligand in the intermediate π-allylpalladium complex. On the other hand, the palladium-catalyzed allylic substitution with organometallics (hard nucleophiles) led to net inversion of configuration through a sequence of oxidative addition, transmetalation, and reductive elimination.[3,7,8a] To investigate the stereochemical outcome of the allylic substitution with indium organometallics, and to shed some light on the mechanism of this process, we performed the reaction of Ph_3In with the enantiopure (>98% ee) acetate (*R*)-(*E*)-**5**.[19,20] The reaction of Ph_3In with (*R*)-(*E*)-**5** using Pd_2dba_3 (5 mol %) in refluxing THF for 4 h afforded the S_N2 product (*S*)-(*E*)-**6** (96% ee) in 73% yield.[21] The value of the optical rotation observed is consistent with a net inversion of configuration.[22] In addition, this result demonstrates the efficiency of the reaction with secondary allylic acetals.

SCHEME 1. Reaction of Ph_3In with Enantiopure Acetate (*R*)-(*E*)-5



(*R*)-(*E*)-**5**

(*S*)-(*E*)-**6**
73%

In summary, we have shown that indium organometallics (triorganoindium and tetraorganoindium compounds) react under palladium(0) catalysis with cinnamyl and geranyl halides and acetates to afford S_N2 products with high regioselectivity and in good yields. Despite the fact that indium organometallics can efficiently transfer all three organic groups attached to indium in cross-coupling reactions, the highest yields obtained in the reactions reported here were obtained in the coupling with acyclic allyl halides using a stoichiometric amount of R_3In. Preliminary mechanistic studies show that the stereochemistry of these reactions proceeds with net inversion of configuration, which is consistent with the mechanistic pathway of oxidative addition, transmetalation, and reductive elimination. Finally, these novel reaction conditions complement the previous study on copper-catalyzed allylic substitution with indium organometallics[12] and allow indium organometallics to be used for regiocontrolled allylic substitutions. In comparison with the recent paper by Baker and Minehan,[13] we report the use of acyclic allylic electrophiles such as cinnamyl and geranyl halides and acetates, and tetraorganoindates as nucleophiles.

Experimental Section[23]

Triorganoindium Reagents. Triorganoindium compounds were prepared according to previously published methods[10] 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 to room temperature. In this procedure triphenyl-, trimethyl, and tributylindium were prepared from the corresponding organolithium reagents, and trivinylindium and tri(*p*-methoxyphenyl)indium were prepared from vinylmagnesium bromide and *p*-methoxyphenylmagnesium bromide, respectively.

General Procedure for the Palladium-Catalyzed Allylic Substitution Reaction. To a solution of $Pd_2dba_3 \cdot CHCl_3$ (52 mg, 0.05 mmol) and the allylic substrate (1.00 mmol) in dry THF (3 mL) was slowly added a solution of R_3In (1.20 mmol, ~0.24 M in dry THF), and the resulting solution was heated under reflux for 2−4 h. The reaction was quenched by the addition of a few drops of MeOH; the mixture was concentrated in vacuo, and Et_2O (20 mL) was added. The organic phase was washed with aqueous HCl (5%, 10 mL), saturated aqueous $NaHCO_3$ (15 mL),

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(19) Allylic alcohol derived from (*R*)-(*E*)-**5** was prepared by a Sharpless kinetic resolution: (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780. (b) Carlier, P. R.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 2978−2979.

(20) *R*)-(*E*)-**5**: $[\alpha]^{21}_{D}$ +146.7 (*c* 1.3, $CHCl_3$); lit. $[\alpha]^{20}_{D}$ +142.2 (*c* 1, $CHCl_3$): Kazmaier, U.; Zumpe, F. L. *Eur. J. Org. Chem.* **2001**, 4067−4076.

(21) *S*)-(*E*)-**6**: $[\alpha]^{22}_{D}$ −37.7 (*c* 2.25, $CHCl_3$); lit. $[\alpha]^{20}_{D}$ −39.3 (*c* 2.51, $CHCl_3$): Schwink, L.; Knochel, P. *Chem.*−*Eur. J.* **1998**, *4*, 950−968.

(22) Baker and Minehan have also reported that the palladium-catalyzed allylic substitution reaction using triorganoindium reagents proceeds with inversion of configuration; see ref 13.

(23) For general experimental methods, see ref 12.

and saturated aqueous NaCl (15 mL), dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes) to afford, after concentration and high-vacuum drying, the allylic substitution products. All compounds obtained were fully characterized by NMR spectroscopy and mass spectrometry and exhibit physical data identical to those reported in the literature (see Supporting Information).

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Supporting Information Available: Relevant spectral data and copies of NMR spectra for compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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