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Palladium-Catalyzed Cross-Coupling Reaction of Triorganoindium Reagents with Propargylic Esters

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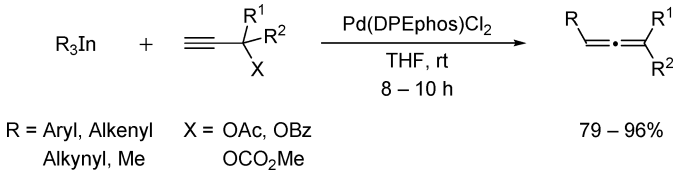
ABSTRACT



Triorganoindium reagents (R_3In) react with propargylic esters under palladium catalysis via an S_N2' rearrangement to afford allenes in good yields and with high regioselectivity. The reaction proceeds smoothly at room temperature with a variety of R_3In (aryl, alkenyl, alkynyl, and methyl). When chiral, nonracemic propargylic esters are employed, the reaction takes place with high anti-stereoselectivity providing allenes with high enantiomeric excess.

Since our discovery in 1999,[1] the palladium-catalyzed cross-coupling reaction of indium(III) organometallics with organic halides has been shown to be a useful reaction in organic synthesis.[2,3] In this reaction, triorganoindium reagents (R_3In) can efficiently couple with aryl, alkenyl, benzyl, and acyl halides and triflates under palladium catalysis with high atom economy. The reaction was later extended to other indium organometallics such as tetraorganoindates or allylindium species.[4]

Recently, we have shown that R_3In can be regioselectively coupled with allyl halides and esters under palladium catalysis affording the S_N2 product or, under copper catalysis, affording the S_N2' product.[5] In this communication, we report the S_N2' palladium-catalyzed cross-coupling reaction of triorganoindium compounds with propargylic esters and the utility of this reaction in the synthesis of allenes.

The allene functionality is present in natural products[6] and is a versatile group in organic synthesis. It can react as either a nucleophile or an electrophile[7] and also participate in cycloaddition reactions.[8] In addition to these abilities, allenes

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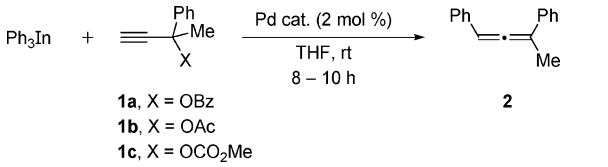
are chiral compounds, so they are useful intermediates in asymmetric synthesis.[9]

One of the most important ways to synthesize allenes is by nucleophilic S_N2' displacement of the leaving group from propargylic halides, esters, or sulfonates. Nevertheless, this reaction has been much less extensively investigated than the corresponding allylic substitution reaction.[10] In the propargylic reaction, various types of nucleophiles such as hydrides, halides, and organometals can be employed. Organocopper reagents react stereoselectively with propargylic derivatives via S_N2' in good yields.[11] Other organometals such as Grignard[12] or organozinc reagents[13] can also be employed for the S_N2' propargylic substitution under transition-metal catalysis.[14]

To explore the reactivity of triorganoindium reagents toward propargylic substrates, we selected as coupling partners triphenylindium and propargylic esters (acetates, benzoates, and carbonates), easily prepared from the corresponding alcohols. In our first experiment, we tested the reaction conditions developed for the S_N2' copper-catalyzed reaction of R_3In with allylic halides and esters.[5a] In this way, the reaction of Ph_3In with the benzoate **1a**, using $Cu(OTf)_2$ (15 mol %) and $P(OEt)_3$ (30 mol %) as the catalytic system, failed to produce the allene **2** and most of the starting benzoate was recovered. Alternatively, the use of $CuBr{\cdot}SMe_2$ as catalyst provided the desired allene in low yield (26%).

Under these circumstances, we turned our attention toward palladium catalysis. In this case, we observed that the reaction of Ph_3In (1.2 equiv) with the propargylic benzoate **1a** using $Pd_2(dba)_3$ (1 mol %) and PPh_3 (4 mol %) as the catalytic system afforded, after 24 h in refluxing THF, the allene **2** in 70% yield with high regioselectivity (only the S_N2' product was detected by NMR, Table 1, entry 1). In the reaction, besides the allene, the formation of biphenyl by reductive homodimerization occurred and some of the starting benzoate **1a** was recovered. The nucleophilic addition of Ph_3In to the ester group was not observed. This encouraging result prompted us to examine new reaction conditions using other

Table 1. Reactions of Ph_3In with Propargylic Esters[a]



1a, X = OBz
1b, X = OAc
1c, X = OCO_2Me

2

entry	X	catalyst	yield (%)[b]
1	OBz (**1a**)	Pd_2dba_3, PPh_3	70[c] (54)[d]
2	OBz (**1a**)	Pd_2dba_3, P(2-fur)$_3$	78
3	OBz (**1a**)	$Pd(PPh_3)_4$	71
4	OBz (**1a**)	Pd(DPEphos)Cl_2	79 (56)[d]
5	OAc (**1b**)	Pd(DPEphos)Cl_2	96
6	OCO_2Me (**1c**)	Pd(DPEphos)Cl_2	90

[a] Reactions performed using 1.2 equiv of Ph_3In. [b] Isolated yield. [c] Reaction performed at reflux for 24 h. [d] In parentheses, yield using 0.5 equiv of Ph_3In.

catalytic systems and propargylic esters. In subsequent experiments, we observed that the palladium complexes $Pd_2(dba)_3{\cdot}P(2\text{-Furyl})_3$, $Pd(PPh_3)_4$, or Pd(DPEphos)Cl_2[15] allowed the reaction at room temperature, in shorter reaction times and with total consumption of the starting benzoate (entries 2−4). In this study, we also found that other propargylic esters such as acetate **1b** or carbonate **1c** gave the allene **2** in good yield under the same reaction conditions (entries 5 and 6). In these experiments, we also realized that stoichiometric amounts of Ph_3In are necessary to consume totally the propargylic ester. Although the results obtained showed the transfer of more than one phenyl group attached to indium, using lower amounts of Ph_3In, the reaction is not complete and afforded higher quantities of biphenyl after 10 h (entries 1 and 4, yields in parentheses).

After studying the S_N2' reaction of Ph_3In with various propargylic esters, we explored the reaction of other triorganoindium reagents (aryl, alkenyl, alkynyl, and alkyl) with the propargylic benzoate **1a** and the propargylic acetate **3b**.[16] The results of this study are shown in Table 2. We found that substituted arylindium reagents such as tri(*o*-methoxyphenyl)indium reacted efficiently with benzoate **1a** affording aryl allene **4** in good yield (Table 2, entry 2). The reaction of alkenylindium reagents, such as trivinylindium, with benzoate **1a** also afforded the corresponding alkenyl allene **5** in high yield (Table 2, entry 3). The alkynyl group can be efficiently transferred from indium reagents; tri(phenylethynyl)indium or tris[(trimethylsilyl)ethynyl]indium reacted with benzoate **1a** affording the corresponding allenynes **6** and **7**, as a nice complement to the copper chemistry developed for the propargylic substitution reaction (Table 2, entries 4 and 5). Unfortunately, the reaction of *n*-Bu_3In with benzoate **1a**

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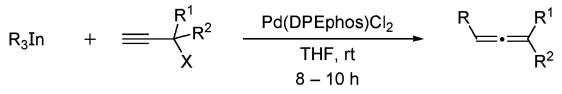
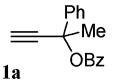
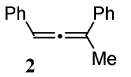
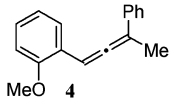
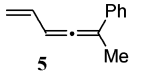
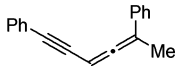
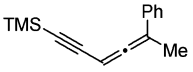
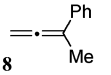
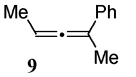
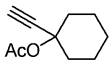
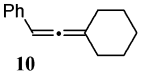
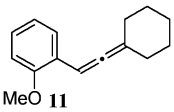
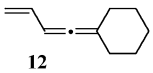
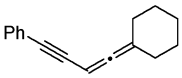
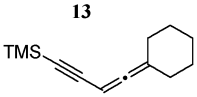
(15) DPEphos = bis(*o*-(diphenylphosphino)phenyl) ether. (a) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J. *Organometallics* **1995**, *14*, 3081−3089. (b) Huang, Z.; Qian, M.; Babinski, D. J.; Negishi, E. *Organometallics* **2005**, *24*, 475−478.

(16) For a general experimental procedure for the preparation of triorganoindium reagents as well the experimental conditions for the S_N2' propargylic reaction, see Supporting Information.

Table 2. Reactions of Triorganoindium Reagents with **1a** and **3b**



1a, **3b** **2–14**

entry	R	electrophile	allene	yield (%)[a]
1	Ph	 **1a**	 **2**	79
2	*o*-MeOC$_6$H$_4$	**1a**	 **4**	81[b]
3	CH$_2$=CH	**1a**	 **5**	85
4	PhC≡C	**1a**	 **6**	85[c]
5	TMSC≡C	**1a**	 **7**	83
6	*n*-Bu	**1a**	 **8**	—[d]
7	Me	**1a**	 **9**	25
8	Ph	 **3b**	 **10**	96
9	*o*-MeOC$_6$H$_4$	**3b**	 **11**	94[b,c]
10	CH$_2$=CH	**3b**	 **12**	45[c]
11	PhC≡C	**3b**	 **13**	92
12	TMSC≡C	**3b**	 **14**	88

[a] Isolated yield. [b] Reaction performed at reflux. [c] Pd_2dba_3·P(2-furyl)$_3$ (1:4, 2 mol %) as catalyst. [d] Compound **8** was obtained in 70% yield.

afforded only allene **8**, the product of a β-hydride elimination reaction prior to the formation of the carbon−carbon bond by reductive elimination, in 70% yield (Table 2, entry 6). Only the reaction of alkylindium reagents without β-hydrogens such as trimethylindium afforded the desired allene **9** in modest yield (Table 2, entry 7).[17]

In an analogous way, when the reactions were performed using the propargylic acetate **3b**, derived from the propargylic alcohol of cyclohexanone, the corresponding allenes **10**−**14** were obtained in good yields (Table 2, entries 8−12).

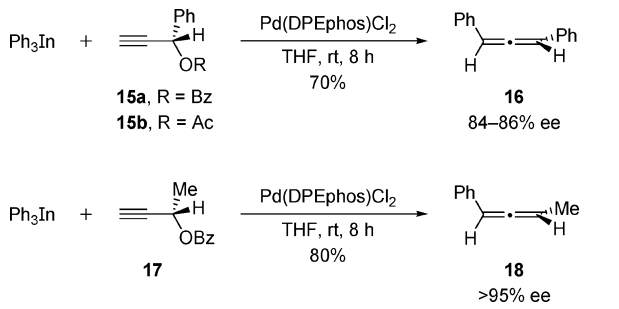
Finally, we also studied the asymmetric synthesis of allenes by reaction of R_3In with chiral, nonracemic propargylic esters. As mentioned before, the axial chirality of allenes makes them particularly amenable to organic synthesis.[9a] Additionally, these reactions can be used to test the general mechanism proposed in the palladium-catalyzed propargylic reaction with organometallic nucleophiles.[18]

(17) In the reaction, compound **8** (Table 2, entry 6) was also obtained as a major byproduct.

Hitherto, the synthesis of chiral, nonracemic allenes by palladium propargylation has been limited to few examples using organozinc and organoboron reagents as nucleophiles and is shown to proceed with anti-stereoselectivity.[13,18] To investigate the behavior of R_3In, and with the aim of comparing results, we carried out the reaction of Ph_3In with the enantiopure propargylic benzoate **15a** (Scheme 1).[19] In this reaction, we observed the formation of (*R*)-1,3-diphenylallene (**16**) in 70% yield and 86% ee. The enantiomeric excess was determined by ^1H NMR using as chiral shift reagents the complexes (+)-Yb(hfbc)$_3$ and Ag(fod).[20] This result shows that the propargylic reaction using Ph_3In is enantioselective and proceeds with anti-stereoselectivity. To measure the influence of the leaving group, we also carried out the reaction of Ph_3In with the enantiopure acetate **15b**. As in the case of benzoate **15a**, the (*R*)-1,3-diphenylallene (**16**) was obtained with high anti-stereoselectivity, good yield, and similar enantioselectivity (84% ee). Under the same reaction conditions, the reaction of Ph_3In with the enantiopure benzoate **17** afforded the (*R*)-1-phenyl-3-methylallene (**18**) in good yield as the only enantiomer detected by ^1H NMR. The anti-stereoselectivity observed in these reactions can be explained by assuming that the formation of a σ-allenylpalladium species takes place with inversion of configuration, whereas the transmetalation and the ensuing reductive elimination proceed with retention of configuration.

In summary, triorganoindium reagents react with propargyl esters under palladium catalysis to afford allenes in good yields and in high regioselectivity. The reaction can take place among various propargylic esters and triaryl-, trialkenyl-, trialkynyl-, and trimethylindium reagents. The reaction proceeds smoothly at room temperature, and the scope of the propargylic substitution is comparable with that of organozinc and organocopper reagents. The reaction with chiral, nonracemic propargylic esters proceeds with anti-stereoselectivity, providing chiral allenes with high enantiomeric excess. Further studies and applications of this reaction in the asymmetric synthesis of allenes are in progress.

Scheme 1. Reactions of Ph_3In with Enantiopure Propargylic Esters



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Supporting Information Available: A general experimental procedure and relevant spectral data for compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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