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Efficient Palladium-Catalyzed Nucleophilic Addition of Triorganoindium Reagents to Carbocyclic Derivatives

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Received November 21, 2003

Abstract: Palladium (0)-catalyzed allylic substitution reactions employing triorganoindium reagents have been investigated. In situ generated vinyl- and arylindiums react with substituted and unsubstituted cyclohex-2-enyl esters in the presence of 1−3 mol % $Pd_2(dba)_3$ to produce vinyl- or arylcyclohexenes in moderate to excellent yields. The stereoselectivity of this process was also examined, and evidence is presented that the reaction proceeds with inversion of stereochemical configuration.

Transition-metal-promoted allylic substitution reactions have emerged as a powerful methodology in organic synthesis.[1] The palladium-catalyzed version of this reaction is an efficient and highly stereoselective method for the formation of carbon−carbon bonds.[2] Numerous studies have shown that allylations with stabilized ("soft") carbon nucleophiles proceed with retention of configuration, while reactions with unstabilized ("hard") nucleophiles proceed with inversion of configuration.[3]

Grignard reagents have traditionally been employed as unstabilized nucleophiles for allylic substitutions. However, the inability of organomagnesium (or organolithium and organoaluminum[4]) reagents to tolerate reactive functional groups on the allylic substrate limits the functionality that can be brought into the coupled product.[5] Reagents containing boron,[6] silicon,[7] zirconium, zinc,[8] and tin[9] avoid such reactivity and/or moisture-sensitivity issues; of these, perhaps the most commonly employed compounds for this purpose are the organostannanes. Although organotin species are stable, reliable nucleophilic reagents for allylic substitution, the high toxicity of these compounds as well as their atom inefficiency makes them less attractive for use in total synthesis. As another potential alternative, in situ prepared, nontoxic organoindium reagents are able to participate in highly atom-economical cross-coupling reactions with aryl and vinyl (pseudo)halides, even in the presence of protic solvents.[10]

Sarandeses has recently disclosed that acyclic allylic halides and phosphates undergo nucleophilic substitution reactions with triorganoindium compounds at low temperatures in the presence of a copper catalyst.[11] In this study, we report that substoichiometric amounts of trivinyl- and triarylindiums participate in palladium-catalyzed nucleophilic substitution reactions not only with acyclic allylic acetates but also with a variety of cyclohex-2-enyl esters in good yield.

To assess the reactivity of indium reagents with allylic esters, we undertook our investigations by treating commercially available *trans*-cinnamyl acetate **I** (Scheme 1) with 0.5 equiv of Ph_3In **2a** in THF (0.1 M) at 55 °C in the presence or absence of palladium catalyst. After 1.5 h, a 19% yield of the expected substitution product **II** was observed by GC−MS analysis of the uncatalyzed reaction mixture, with ∼80% of the starting material still present. In contrast, the catalyzed reaction (1 mol % Pd_2dba_3/4 mol % PPh_3) gave a 95% yield of **II** after the same amount of time at 55 °C. Gratifyingly, this reactivity extended to more difficult substitutions on cyclic templates: while stirring cyclohex-2-enyl acetate **1a**[12] with **2a** for 3 h at 55 °C in the absence of catalyst resulted in only an 11% conversion to the expected product 3-phenylcyclohexene **3aa** by GC−MS analysis,[13] the same reaction performed in the presence of 1 mol % Pd_2dba_3/4 mol % PPh_3 gave an 85% yield of **3aa**, with the only other compounds evident in the crude ^{1}HNMR being **1a** (∼10%) and biphenyl.[14] By comparison, the corresponding catalyzed and uncatalyzed substitution reactions of **1a** with PhMgBr at either room temperature or 55 °C led to low

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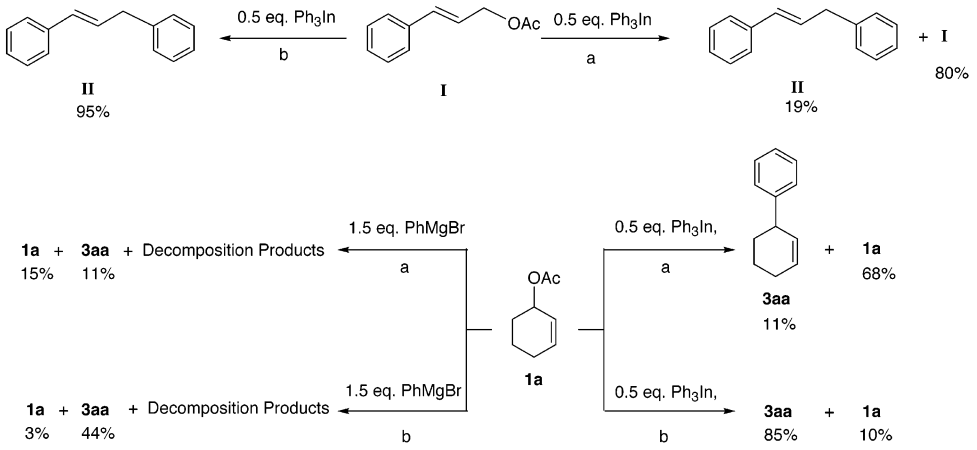
(12) Cylohexen-1-yl acetate was prepared from cyclohexen-2-one by DIBAH reduction (1 h, 0 °C, Et_2O) followed by acylation (Ac_2O/pyridine, rt, 14 h). See the Supporting Information for experimental details.

(13) Stirring the uncatalyzed reaction (**1a**, 0.5 equiv of **2a**, THF, 0.1 M, 55 °C) for 24 h in the presence of 1 equiv of $InCl_3$ as a Lewis acid promoter gave only unidentifiable decomposition products.

10.1021/jo0357162 CCC: $27.50
Published on Web 04/30/2004

SCHEME 1. Catalyzed and Uncatalyzed Allylic Substitution Reactions[a]



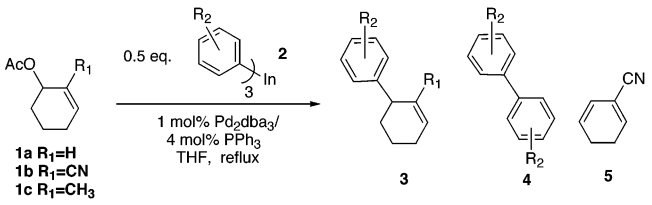
[a] Reaction conditions: (a) THF (0.1 M), 55 °C, 1−3 h; (b) THF (0.1 M), 1 mol % Pd_2dba_3/4 mol % PPh_3, rt or 55 °C, 1−3 h.

(<50%) yields of **3aa** along with several decomposition products arising from cleavage of the acetate group of **1a**.[15] The mildness and efficiency of the organoindium-mediated process prompted us to investigate its scope and generality.

As shown in Table 1, a wide variety of electron-rich and electron-poor arylindiums cross-couple efficiently with substituted (**1b**[16] and **1c**[17]) and unsubstituted (**1a**) cyclohex-2-enyl acetates. Optimal yields were obtained when the reactions were performed with 0.5 equiv of organoindium reagent **2** relative to **1** (0.5 equiv of Ar_3In can transfer 1.5 equiv of aryl group) in refluxing THF for 1−3 h. Diene **5** was also observed in reaction mixtures employing carbocyclic derivative **1b**; although it is probable that elimination products arising from **1a** and **1c** were also formed in small amounts in the corresponding reactions, these substances could not be detected by GC due to their high volatility.[18] Homocoupling product **4**[14a] was present in all reactions and in some cases complicated product purification because of its similar polarity to **3**. Interestingly, use of less nucleophilic electron-poor arylindiums (Table 1, entries 7−9, 14−16, and 19) resulted in the production of greater amounts of **4**. Sterically encumbered arylindium reagents (Table 1, entries 4, 9, and 13) also gave the expected substitution products in moderate to high yields, although reactions with trimesitylindium **2e** or tris(2,6-dimethoxyphenyl)-indium **2f** (Table 1, entries 5 and 6) gave <10% yield of the desired cross-coupled material.

Consistent with the original observations of Nomura[10c] and Sarandeses[10a] on the coupling reactions of triorganoindiums, these allylic substitution reactions display a level of atom-economy. Since 0.5 equiv of triarylindium reagent is employed in the optimized procedure, approximately one-half to two-thirds of the aryl groups on

TABLE 1. Pd(0)-Catalyzed Addition of Triarylindiums to Cyclohex-2-enyl Acetates



entry	1	2	R_2	3	3 (5) yield[a]/%	ratio 3/4[b]
1	**1a**	**2a**	H	**3aa**	85	3:1[c]
2	**1a**	**2b**	4-CH_3	**3ab**	77	6.1:1
3	**1a**	**2c**	4-OCH_3	**3ac**	50	10:1
4	**1a**	**2d**	2-CH_3	**3ad**	85	6.3:1
5	**1a**	**2e**	mesityl	**3ae**	<10	
6	**1a**	**2f**	2,6-di-OCH_3	**3af**	<10	
7	**1a**	**2g**	4-CF_3	**3ag**	75	2:1[c]
8	**1a**	**2h**	3-CF_3	**3ah**	80	2.4:1
9	**1a**	**2i**	2-CF_3	**3ai**	40	4:1
10	**1b**	**2a**	H	**3ba**	93(2)	8:1[c]
11	**1b**	**2b**	4-CH_3	**3bb**	62(33)	21:1
12	**1b**	**2c**	4-OCH_3	**3bc**	98(1)	33:1
13	**1b**	**2j**	2-OCH_3	**3bj**	49(3)	1.4:1
14	**1b**	**2k**	4-Cl	**3bk**	70(30)	3.5:1
15	**1b**	**2g**	4-CF_3	**3bg**	74(16)	2:1[c]
16	**1b**	**2h**	3-CF_3	**3bh**	70(30)	2.3:1
17	**1c**	**2b**	4-CH_3	**3cb**	85	5.5:1
18	**1c**	**2c**	4-OCH_3	**3cc**	95	7:1
19	**1c**	**2h**	3-CF_3	**3ch**	66	2.1:1

[a] Isolated yields after chromatographic purification are relative to **1** (e.g., [mol of **3**/initial mol of **1**] × 100). [b] Molar ratio obtained by GC−MS analysis; note that 0.5 equiv of **2** has 1.5 equiv of reactive aryl group: see ref 14a. [c] Ratios corrected for the amount of dimer present in the original Grignard or organolithium solutions.

(14) (a) Biaryls present in these reaction mixtures arise from palladium(II)-mediated dimerization of the indium reagent. Since in the optimized procedure 0.5 equiv of indium reagent **2** is employed, assuming all three ligands on indium can transfer, complete (100 mol %) conversion of **1** to **3** can be accompanied by the production of up to 25 mol % dimer **4** (giving a 4:1 ratio of **3**/**4**). Similarly, a 75% conversion of **1** to **3** can lead to a 2:1 ratio of **3**/**4** if all the remaining organoindium species undergo homocoupling rather than cross-coupling. (b) For two alternate environmentally friendly preparations of **3aa** via Pd-catalyzed cross-coupling, see: Uozumi, Y.; Danjo, H.; Hayashi, T. *J. Org. Chem.* **1999**, *64*, 3384−3388. Mowery, Molly E.; DeShong, Philip. *J. Org. Chem.* **1999**, *64*, 1684−1688.

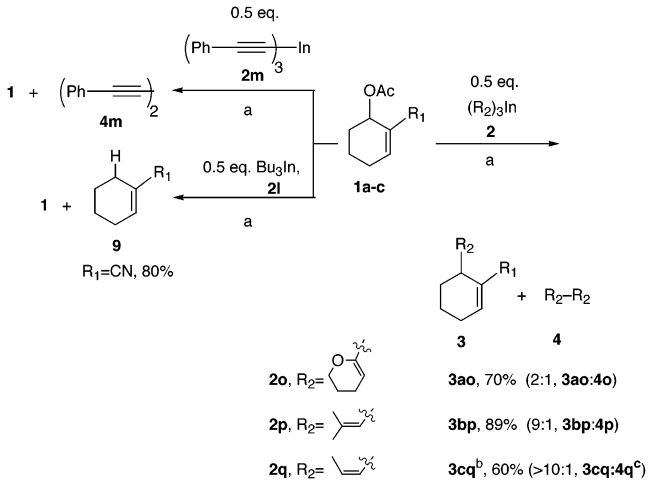
(15) Treatment of **1a** with PhLi at rt in the presence or absence of catalyst for 1 h gave only decomposition products.

(16) Acetoxy-1-cyclohexene-1-carbonitrile **1b** was prepared by acylation (Ac_2O/Pyridine, rt, 14 h) of 6-hydroxy-1-cyclohexene-1-carbonitrile. The latter compound was prepared according to the literature: Villieras, J.; Rambaud, M.; Graff, M. *Synth. Commun.* **1986**, *16*, 149−156. See also the Supporting Information.

(17) Acetoxy-1-methylcyclohexene **1c** was prepared from 2-methylcyclohexanone by a four-step route: Bromination (NBS, CCl_4, reflux, 4 h), elimination (Li_2CO_3, LiBr, DMF, 150 °C, 14 h), reduction (DIBAH, Et_2O, 0 °C, 1 h), and acylation (Ac_2O/Pyridine, rt, 14 h). See the Supporting Information for details.

(18) The 1,3-cyclohexadienes, likely formed via β-hydride elimination from a σ-allyl palladium intermediate, have been previously observed as byproducts in the addition of hindered aryl silicates to cyclohexenyl esters: see ref 7b.

SCHEME 2. Allylic Substitution Reactions of Alkyl-, Alkenyl-, and Alkynylindium Reagents[a]



[a] (a) Reaction conditions: (a) THF, 1 mol % Pd_2dba_3/4 mol % PPh_3, rt or 70 °C, 1−14 h. (b) Product volatility likely contributed to the moderate isolated yield. (c) The high volatility of dimer **4q** made it difficult to assess the amount present in the reaction mixture.

indium are being transferred to form **3** (the remainder contribute to form some level of **4**).[14a]

We next studied the cross-couplings of alkyl-, alkenyl-, and alkynylindium reagents with cyclohexenyl acetates (Scheme 2). Neither tributylindium **2l**[19] nor tris(phenylethynyl)indium **2m**[20] gave substitution products upon reaction with **1a**−**c** in the presence of Pd_2dba_3/PPh_3 at room temperature or reflux for 1−14 h. Reactions employing tributylindium showed significant conversion of **1** to reduced products **9**; in the alkynylindium case, large amounts of dimer **4m** were recovered from the mixture. The ease of β-hydride elimination for a butyl(π-allyl)-palladium(II) intermediate might explain the failure of the first reaction; the ease of palladium-catalyzed dimerization of the alkynylindium reagent (thus consuming this species prior to transmetalation) may explain the failure of the second reaction. However, palladium-catalyzed addition of trisdihydropyranylindium **2o**[21] to **1a** at room temperature for 14 h gave substituted dihydropyran **3ao** in 70% yield (2:1 ratio product to dimer, **3ao**/**4o**). Similar reactivity was observed for addition of trivinylindiums **2p** and **2q** to cyclohexenes **1b** and **1c**. Thus, vinyl- and arylindiums are the optimal nucleophiles for palladium-catalyzed allylic substitutions of carbocyclic derivatives.

Finally, we wished to investigate the stereoselectivity of the cross-coupling of organoindiums with diastereopure cyclohex-2-enyl esters.[22] *cis*- and *trans*-carvyl benzoates (+)-**6a** and (−)-**6b** were prepared according to literature procedures[23] starting from commercially available (*R*)-(−)-carvone. Treatment of *cis*-benzoate **6a** with Ph_3In in THF in the presence of 1 mol % Pd_2dba_3/4 mol % PPh_3 at either 55 °C or reflux for 3 h gave a 60% yield of (±)-**7a** (>15:1 diastereoselectivity), the product of inversion of configuration; biphenyl (4:1 product/biphenyl ratio) and unreacted starting material (35%) were also recovered.[24] Similarly, stirring (+)-**6a** with tris(4-methylphenyl)-indium at 55 °C under palladium catalysis for 2 h gave a 69% yield of sole inversion product (±)-**8a**. Interestingly, optimal yields and selectivities for the corresponding reactions of *trans*-benzoate (−)-**6b** with aryl indiums required careful control of the reaction conditions. Addition of 0.5 equiv of Ph_3In to a degassed DMF solution of (−)-**6b** and 3 mol % Pd_2dba_3 *in the absence of phosphine* gave, after 2.5 h at 55 °C, a 65% yield of (±)-**7b** (13:1 diastereoselectivity). Stirring the reaction either in the presence of excess phosphine or at elevated temperatures (70 °C) led to an erosion in diastereoselectivity (6:1−2:1 (±)-**7b**/(±)-**7a**). Repetition of the reaction of (−)-**6b** with tris(4-methylphenyl)indium at 55 °C under palladium catalysis (no phosphine) for 4 h gave a 70% yield of (±)-**8b** (16:1 diastereoselectivity). The stereochemistry of products (±)-**7a**,**b** and (±)-**8a**,**b** was established by comparing ^{1}H NMR chemical shifts and coupling constants with literature values.[25] The decrease in reaction diastereoselectivity observed at reflux or in the presence of phosphine clearly reflects the existence of competing reaction pathways. One possible mechanistic explanation for this outcome is based on the observation that the π-allyl complex derived from (−)-**6b** places the palladium atom syn to the C.3 propenyl group, and as a result of steric congestion (especially in the presence of phosphine ligands), the rate of transmetalation by the organoindium reagent is likely decreased (Scheme 3). Attack of a second Pd(0) anti to this complex gives a new unhindered palladium−π-allyl which can undergo standard transmetalation/reductive elimination to give (±)-**7a**.[26] Alternatively, the organoindium reagent itself may attack an

(19) Formed by addition of 1 equiv of *n*-BuLi (1.6 M in hexanes) to a THF solution of 0.33 equiv of $InCl_3$ at −78 °C, followed by warming to rt.

(20) Formed by addition of 1 equiv of phenylethynylmagnesium bromide (1.0 M solution in THF) to a THF solution of 0.33 equiv of $InCl_3$ at −78 °C, followed by warming to rt.

(21) For the preparation of **2o**, see: Lehmann, U.; Awasthi, S.; Minehan, T. G. *Org. Lett.* **2003**, *5*, 2703−2706.

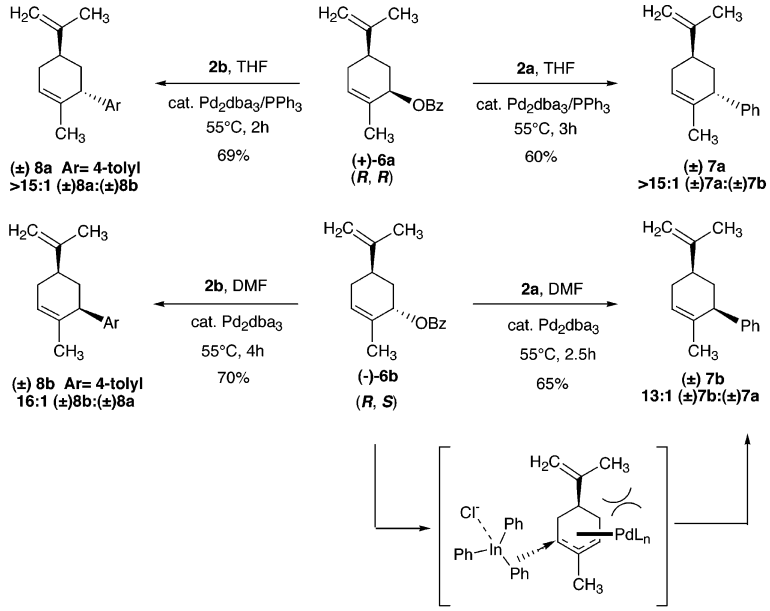
(22) Numerous previous studies address the factors controlling the regio- and stereoselectivity of Pd(0)-catalyzed alkylations of carbocyclic derivatives: (a) Brescia, M.-R.; Shimshock, Y. C.; DeShong, P. *J. Org. Chem.* **1997**, *62*, 1257−1263. (b) Class, Y. J.; DeShong, P. *Tetrahedron Lett.* **1995**, *36*, 7631−7634. (c) Curran, D. P.; Suh, Y.-G. *Carbohydr. Res.* **1987**, *171*, 161−191. (d) Dunkerton, L. V.; Serino, A. J. *J. Org. Chem.* **1982**, *47*, 2812−2814. (e) Baer, H. H.; Hanna, Z. S. *Can. J. Chem.* **1981**, *59*, 889−906. (f) Hoke, M. E.; Brescia, M.-R.; Bogaczyk, S.; DeShong, P. *J. Org. Chem.* **2002**, *67*, 327−335. (g) Hayashi, T.; Yamamoto, A.; Hagihara, T. *J. Org. Chem.* **1986**, *51*, 723−727.

(23) *cis*-Carvyl benzoate (+)-(*R*,*R*)-6**a** was prepared according to the procedure of DeShong and Mowery (ref 15b); the ^{1}H NMR and ^{13}C NMR data were consistent with those reported by these authors (see the Supporting Information). *trans*-Carvyl benzoate (−)-(*R*,*S*)-**6b** was prepared according to the procedure of Uesaka: Uesaka, N.; Saitoh, F.; Mori, M.; Shibasaki, M.; Okamura, K.; Date, T. *J. Org. Chem.* **1994**, *59*, 5633−5642. The ^{1}H NMR data are consistent with those reported by these authors and the ^{13}C NMR data are consistent with those reported by DeShong: Correia, R.; DeShong, P. *J. Org, Chem.* **2001**, *66*, 7159−7165.

(24) Yields in the substitution reactions of carvyl benzoates increased to 70−75% when the reactions were allowed to proceed at 55 °C overnight (8−14 h); however, the additional reaction time also leads to the production of greater amounts of homocoupling product **4** (~2:1 ratio product/dimer), which proved to be difficult to separate from the desired products. Also, small amounts (1−5%) of elimination product (5*R*)-2-methyl-5-(1-methylvinyl)cyclohexa-1,3-diene were observed by GC−MS analysis of all reaction mixtures employing **6a** and **6b**.

(25) Note that products (±)-**7a** and (±)-**8a** are racemic since a *meso*-π-allyl-Pd complex was an intermediate in each transformation. The spectroscopic data obtained for **7a** and **8a** are in accord with those reported previously. For (±)-**7a**, see: Brescia, M.-R.; DeShong, P. *J. Org. Chem.* **1998**, *63*, 3156−3157. For (±)-**8a**, see: DeShong: Correia, R.; DeShong, P. *J. Org, Chem.* **2001**, *66*, 7159−7165.

SCHEME 3. Reactions of Arylindiums with Carvyl Benzoates 6a and 6b



unhindered allylic carbon atom anti to the hindered π-allyl complex to produce (±)-**7a** directly, a process that may be favored more at elevated temperatures. The latter possibility is supported by experiments (vide supra) that demonstrate that nucleophilic triorganoindium reagents react with allylic esters to a significant extent *even in the absence of a transition-metal catalyst*.[27,28] Despite the moderate chemical yields obtained in this reaction at short (1−4 h) times,[24] the major products appear to result from a stereochemical inversion process, consistent with the previously proposed mechanism for palladium-catalyzed allylic substitutions with unstabilized nucleophiles.[3] Further studies on the uncatalyzed nucleophilic reactivity of organoindium reagents will be reported in due course.

In summary, the use of in situ generated organoindium reagents for palladium-catalyzed allylic substitution reactions provides a mild, practical, environmentally friendly, and atom-economical alternative to the use of Grignard and organotin reagents as unstabilized nucleophiles for such processes.

Experimental Section

Representative Procedure for the Preparation of Triarylindiums from Aryl Bromides and Indium Trichloride. To a stirred solution of aryl bromide (1.5 mmol) in dry THF (3 mL) at 0 °C under Ar^0 was added dropwise a solution of *tert*-butyllithium (approximately 1.9 mL, 3.2 mmol, 1.7 M in pentane) until the yellow color persisted. The solution was stirred at 0 °C for 1 h, cooled to −78 °C, and added to a stirred suspension of indium(III) chloride (0.11 g, 0.5 mmol) in dry THF (3 mL). The mixture was stirred at −78 °C for 5 min and then allowed to warm to rt, giving a clear solution of triarylindium. For trifluoromethyl- or chloro-substituted aromatics, the above procedure was modified as follows: to a stirred solution of aryl bromide (1.5 mmol) in dry THF (3 mL) at −78 °C under Ar^0 was added dropwise a solution of *tert*-butyllithium (approximately 1.9 mL, 3.2 mmol, 1.7 M in pentane) until the yellow color remained. The solution was immediately added to a stirred suspension of indium(III) chloride (0.111 g, 0.5 mmol) in dry THF (3 mL). The mixture was stirred at −78 °C for 5 min and then allowed to warm to rt, giving a clear solution of the triarylindium.

General Procedure for the Allylic Substitution Reaction. To a stirred solution of cyclohex-2-enyl acetate **1** (140 mg, 1 mmol), Pd_2dba_3 (9 mg, 1 mol %), and PPh_3 (11 mg, 4 mol %) in dry THF (3 mL) was added a THF solution of organoindium reagent **2** (0.5 mmol, ∼0.06 M) at rt. The mixture was either stirred at rt for 1−24 h or heated to reflux under Ar^0 for 1−3 h, and the progress of the reaction was monitored by GC−MS. The reaction was quenched by the addition of a few drops of MeOH, followed by dilution with Et_2O (50−100 mL) and filtration through Celite. Concentration in vacuo and purification of the residue by flash chromatography afforded the allylic substitution products. All compounds were fully characterized by NMR and mass spectrometry (see the Supporting Information).

Acknowledgment. We are grateful for the generous financial support of this work by the National Science Foundation (under Grant No. 0097262) and the ACS Petroleum Research Fund (PRF No. 38271-GB1). We also thank the UCLA and UC Riverside Mass spectrometry laboratories for high-resolution mass analyses.

Supporting Information Available: Characterization data for all compounds reported and experimental procedures for preparation of starting materials, including copies of ^1H NMR spectra of all reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0357162

(26) The corresponding reactions of $PhMe_3Sn$ with **6a** and **6b** (DMF, 3.0 equiv of LiCl, 3% Pd_2dba_3) at either 55 or 80 °C show very high (>15:1) selectivities for the expected inversion products, which indicates that stereoisomerization of the palladium π-allyl complex is likely not taking place during these reactions. Thus, such isomerization may not be the cause of the erosion in diastereoselectivity of the organoindium substitutions.

(27) We have recently discovered that triarylindiums react with carbohydrate allylic esters (such as tri-*O*-acetyl-D-glucal) *at room temperature* in ether to produce substitution products (2,3-unsaturated-*C*-aryl glycosides) in high yield in the absence of transition-metal catalysts: Price, S. A.; Edwards, S. T.; Wu, T.; Minehan, T. G. Unpublished results.

(28) Treatment of **6a** or **6b** with Ph_3In in THF or DMF at 55 °C for 3−24 h in the absence of palladium catalyst gave ∼30% (5*R*)-2-methyl-5-(1-methylvinyl)cyclohexa-1,3-diene and <1% substitution products **7a** and **7b**.