Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 8905–8910

Palladium-catalyzed reactions of acetoxyenynes with triorganoindium reagents

John T. Metza, Jr., Raffi A. Terzian and Thomas Minehan*

Department of Chemistry and Biochemistry, California State University-Northridge, Northridge, CA 91330, USA

Received 23 August 2006; revised 6 October 2006; accepted 9 October 2006
Available online 30 October 2006

Dedicated with great respect to Professor Peter Dervan on the occasion of his 60th birthday and Professor Yoshito Kishi on the occasion of his 70th birthday

Abstract—The reaction of 1-acetoxy-2,7- and 2,8-enynes with triorganoindium reagents in the presence of 5 mol % palladium catalyst provides cyclic and/or acyclic substitution products depending upon substrate structure. Enynes bearing secondary acetates, quaternary centers, or heteroatoms furnish high yields of carbocyclic or heterocyclic substitution products. NMR studies show that a single trisubstituted alkene stereoisomer is formed in the reaction. A more atom-efficient procedure for the cyclization–substitution process utilizing heteroleptic indium reagents is presented.

Organoindium reagents have been the subject of increasing interest and attention because of their environmentally benign characteristics and their synthetic utility for carbon–carbon bond formation.[1] Triorganoindiums are easily prepared compounds capable of participating in atom-efficient, transition-metal catalyzed cross-coupling reactions[2] and allylic substitution reactions.[3] Recently, several indium-mediated intramolecular cyclization reactions have demonstrated the utility of indium reagents for forming five- and six-membered rings.[4] As part of our interest in applying organoindium chemistry to the preparation of the complex cyclic structures present in natural products,[2h,3b,5] we wish to report our findings on the palladium-catalyzed cyclization reactions of acetoxyenynes in the presence of triorganoindiums.

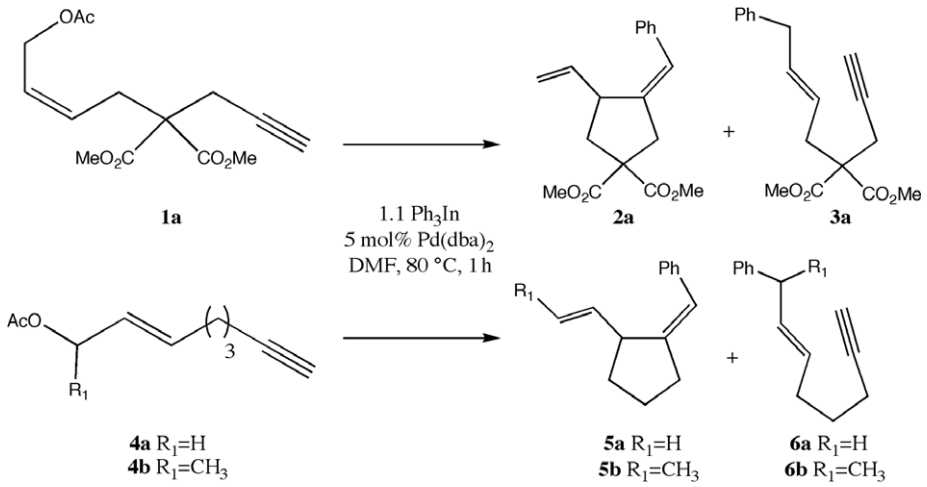
Acetoxy-2,7-enynes **1a**,[6] **4a**,[7] and **4b**[8] were prepared according to the literature protocols and treated with 1.1 equiv of triphenylindium in DMF at 80 °C in the presence of 5 mol % $Pd(dba)_2$. After 1 h, complete consumption of the starting material had taken place in each case. Enyne **1a** furnished cyclized product **2a** as a single alkene stereoisomer in a 90% isolated yield, with only trace amounts (<5%) of acyclic substitution product **3a** observed by ^1H NMR of the crude reaction mixture (Scheme 1). In contrast, enyne **4a** ($R_1 = H$) provided a 1:1 mixture of cyclic and acyclic substitution products **5a** and **6a** in an 85% combined yield. The differing conformer populations of **1a** and **4a** (*gauche* vs *anti*) are likely responsible for the product distributions obtained, a manifestation of the Thorpe–Ingold effect.[9] Interestingly, 2-acetoxy-3,8-enyne **4b** ($R_1 = CH_3$) produced a 10:1 mixture of **5b** and **6b** in 87% combined yield, suggesting that increased steric hindrance in the vicinity of the acetoxy leaving group also favors the formation of cyclic substitution products.

A variety of 2,7-enynes (**1a**–**f**) may be employed in palladium-catalyzed reactions with triorganoindium reagents (Table 1). Both electron-rich (entries 9 and 14) and electron-poor (entries 8, 10, and 15) arylindium reagents participate efficiently in the cyclization–substitution process. Only sterically encumbered arylindiums gave lower yields: the reaction of **1d**[10] with tri(2-tolyl)-indium (entry 13) in the presence of $Pd(dba)_2$ gave a 50% yield of tetrahydrofuran **2m**, with roughly 40% of the corresponding acyclic allylic substitution product **3m** also formed.

Of the alkylindium reagents, only trimethylindium (entry 2) furnished significant amounts of cyclized substitution product; reaction of **1a** with tributylindium (entry 3) gave a complex mixture of reduced products, likely resulting from β-hydride elimination of a butyl

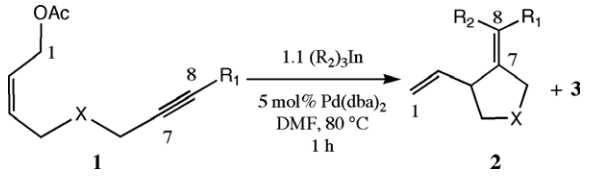
* Corresponding author. Tel.: +1 818 677 3315; fax: +1 818 677 4068; e-mail: thomas.minehan@csun.edu

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.10.043



Scheme 1. Palladium-catalyzed reactions of acetoxyenynes with triphenylindium.

Table 1. Scope of palladium-catalyzed organoindium-mediated cyclizations of acetoxyenynes



Entry	1	2	R_1	X	R_2	Yield (%) 2(3)[a]
1	**a**	**a**	H	$C(CO_2Me)_2$	Ph	90(4)
2	**a**	**b**	H	$C(CO_2Me)_2$	CH_3	89
3	**a**	**c**	H	$C(CO_2Me)_2$	Bu	—
4	**b**	**d**	Et	$C(CO_2Me)_2$	Ph	68(20)[c]
5	**c**	**e**	H	NTs	4-Tolyl	88
6	**c**	**f**	H	NTs	$CH_3(CH_2)C$	90
7	**c**	**g**	H	NTs	PhCC	—
8	**c**	**h**	H	NTs	4-F–Ph	68[b]
9	**c**	**i**	H	NTs	4-Anisyl	70
10	**c**	**j**	H	NTs	4-Cl–Ph	67[b]
11	**d**	**k**	H	O	Ph	78
12	**d**	**l**	H	O	4-Tolyl	73
13	**d**	**m**	H	O	2-Tolyl	50(40)
14	**d**	**n**	H	O	4-Anisyl	61[b]
15	**d**	**o**	H	O	4-Cl–Ph	82
16	**e**	**p**	4-Me–Ph	O	Ph	88
17	**f**	**q**	Me_3Si	O	Ph	43(25)[c]

[a] Yields shown are of purified products. The numbers in parenthesis represent the yield of acyclic allylic substitution products **3** (obtained as a mixture of *E*/*Z* olefin isomers) estimated from the ^{1}H NMR analysis of crude reaction mixtures.

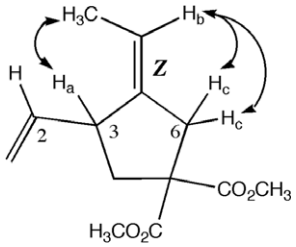
[b] Lower isolated yields due to difficulties in separating **2** from homodimer byproduct.

[c] Products **2** and **3** coelute by silica gel chromatography.

palladium(II) intermediate.[11] Moreover, the combination of tris(phenylethynyl)indium with **1c**[12] (entry 7) in the presence of 5 mol % $Pd(dba)_2$ led only to the formation of large amounts of homodimer 1,4-diphenyl-1,3-diyne, possibly due to the ease of palladium-catalyzed dimerization of the alkynylindium reagent (thus consuming this species prior to transmetalation).[13] However, tris(isopropenyl)indium reacted efficiently with **1c** (entry 6) to form conjugated diene **2f** in a 90% yield. Terminal substitution on the alkyne is also well tolerated, with substrates **1b**,[14] **1e**,[15] and **1f**[16] (R_1 = Et, 4-Me-Ph, and $SiMe_3$, entries 4, 16, and 17) undergoing reaction with triphenylindium to provide **2d**, **2p**, and **2q** in 68%, 88%, and 43% yields, respectively; in the case of **2d** and **2q**, significant amounts (20–25%) of acyclic allylic substitution product were also formed as a result of the increased steric bulk of the terminal ethyl and trimethylsilyl groups, which hinder access to the C.8 alkyne carbon of the substrate. Lowering the amount of palladium catalyst to 3 mol % in the reactions led to a slight (~10%) diminution in yields; employing less than 3 mol % $Pd(dba)_2$ required extended reaction times and resulted in significantly lower conversions overall. No reaction was observed in the absence of palladium catalyst except for substrate **1e**, which furnished cyclized product **2p** in a 15% yield upon combination with excess triphenylindium.[17]

The alkene stereochemistry of the products was investigated in a two-dimensional NMR (NOESY) experiment performed on product **2b** (Scheme 2). The cross-peaks observed between the alkene methyl group and the C.3 allylic proton H_a, as well as between the alkene proton H_b and the C.6 allylic methylene protons H_c confirm the *Z* configuration of the trisubstituted alkene.

Under the standard reaction conditions in which 1.1 equiv of triorganoindium reagent are employed, significant amounts of byproduct arising from palladium(II)-mediated dimerization of the indium reagent (vide supra) were often obtained; in several instances (Table 1, entries 8, 10, and 14) purification of the desired products away from the dimer was difficult due to their similar polarities, resulting in lower isolated yields. At least an equivalent of homodimer is produced in the reaction, indicating that the two unutilized ligands on indium are quantitatively dimerized. Nomura et al.[2d] and Sarandeses and co-workers[2a,b] have shown that triorganoindiums are capable of transferring all three of their organic ligands in coupling reactions; we thus decided to probe the atom-efficiency of the cyclization/



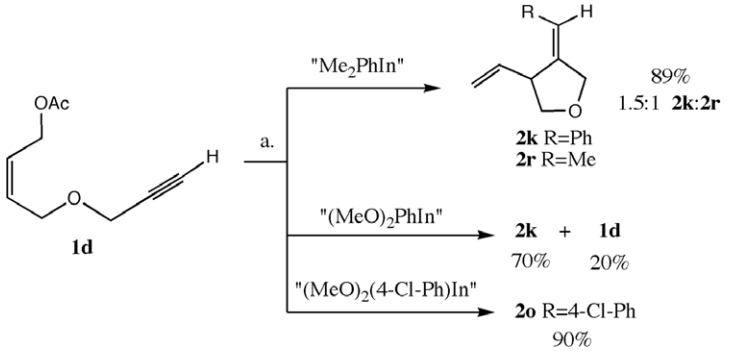
Scheme 2. NOEs observed for product **2b**.

substitution process. It was found that the reaction of **1a** with 0.5 equiv of Ph_3In and 5 mol % $Pd(dba)_2$ in DMF at 80 °C for 40 min furnished a ~1:1 mixture of **2a**:**1a**; no further reaction was observed upon continued heating. Replacement of the acetoxy group of **1a** with a better leaving group such as bromide gave significantly lower yields of product (~50%) for the reactions performed with 1.0 or 0.5 equiv of Ph_3In. Treatment of **1a** with 1.1 equiv of Ph_2InCl in the presence of 5 mol % $Pd(dba)_2$ gave **2a** in a 45% yield; a similar reaction of **1a** with 1.1 equiv of $PhInCl_2$ gave even lower percent conversions.[2b] From this data, we concluded that a stoichiometric amount of the triorganoindium reagent was indeed required for optimal conversions to be realized in this manifold.[18]

In order to improve the atom-efficiency of the reaction, we attempted preparation of the heteroleptic indium reagents[19] phenyldimethylindium and phenyldimethoxyindium by the addition of 1 equiv of phenylmagnesium chloride to indium trichloride at −78 °C in THF, followed by the addition of 2 equiv of either methyllithium or sodium methoxide and warming to room temperature. Each of the reagent solutions were added to ether **1d** and 5 mol % $Pd(dba)_2$ in DMF and stirred at 80 °C for 1 h (Scheme 3). When the phenyldimethylindium solution was employed, a 1.5:1 mixture of **2k** and **2r** was obtained in an 89% isolated yield, indicating similar propensities for methyl and phenyl transfer from indium. Employing the phenyldimethoxyindium solution gave instead a 70% yield of **2k**, along with approximately 20% unreacted starting material; GC–MS analysis of the crude reaction mixture indicated that greatly reduced amounts of homodimer byproduct were formed. The reaction of a similarly prepared (4-chlorophenyl)dimethoxyindium solution with **1d** gave **2o** in a 90% isolated yield with only trace amounts of dimer detected. Notably, the presence of excess methanol in the reaction mixture[20] led to no diminution in product yields, in line with the reported hydrolytic stability of organoindium reagents.[2e] Although the heteroleptic indium reagents appear to offer an improved atom efficiency and ease of product purification over the triarylindium case, we are still investigating the scope of this transformation and the precise structure of the organoindium species generated in our reagent solution.[21]

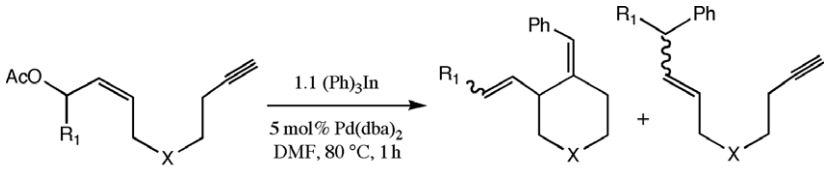
Encouraged by these findings, we next attempted the construction of six-membered rings by applying our cyclization–substitution protocol to acetoxy-2,8-enynes **7a**[22] and **7b**.[23] Complete starting material consumption was achieved for both substrates in 1 h at 80 °C in DMF in the presence of 1.1 equiv of Ph_3In and 5 mol % $Pd(dba)_2$. Whereas **7a** gave a 1:10 mixture of cyclic: acyclic substitution products **8a** and **9a** in a 75% yield, **7b** furnished a 1:1 mixture of **8b** and **9b** in a 90% combined yield (Table 2, entries 1 and 2). Similarly, subjecting ether **7d**[24] to the reaction conditions furnished a 1:1.25 ratio of cyclic:acyclic substitution products **8d** and **9d** (Table 2, entry 4). The increased amounts of acyclic substitution products obtained for the reactions employing the homologous 2,8-enynes may be attributed to both the greater alkene–alkyne distance and an increased entropic penalty of cyclization. In light of our successful cyclizations with substrate **4b**, we subjected 2-acetoxy-3,9-enyne **7c**[25] ($R_1 = CH_3$) to our standard reaction conditions employing 1.1 equiv of triphenylindium. Gratifyingly, a 2.2:1 ratio of **8c**:**9c** was obtained in a 55% combined yield. In a similar fashion, the subjection of **7e**[26] and **7f**[27] to the reaction conditions furnished heterocycles **8e** and **8f** as major products, each as a 5:1 mixture of *E*:*Z* disubstituted alkene isomers. Again, the additional methyl substitution appears to hinder reductive elimination from an acyclic allylpalladium intermediate, thus allowing carbon–carbon bond formation to occur preferentially via a cyclized alkenylpalladium (II) complex (vide infra, Scheme 4).

A possible mechanistic pathway[28] consistent with the data at hand is presented in Scheme 4. Oxidative addition of the low valent palladium catalyst to the allylic acetate furnishes π-allyl palladium complex **A**. Alkyne complexation and migratory insertion (**B**, **D**) is followed



Scheme 3. Exploring the reactions of heteroleptic organoindiums. Reagents and conditions: (a) 5 mol % $Pd(dba)_2$, DMF, 80 °C, 1 h.

Table 2. Palladium-catalyzed reactions of acetoxy 2,8- and 3,9-enynes with triphenylindium



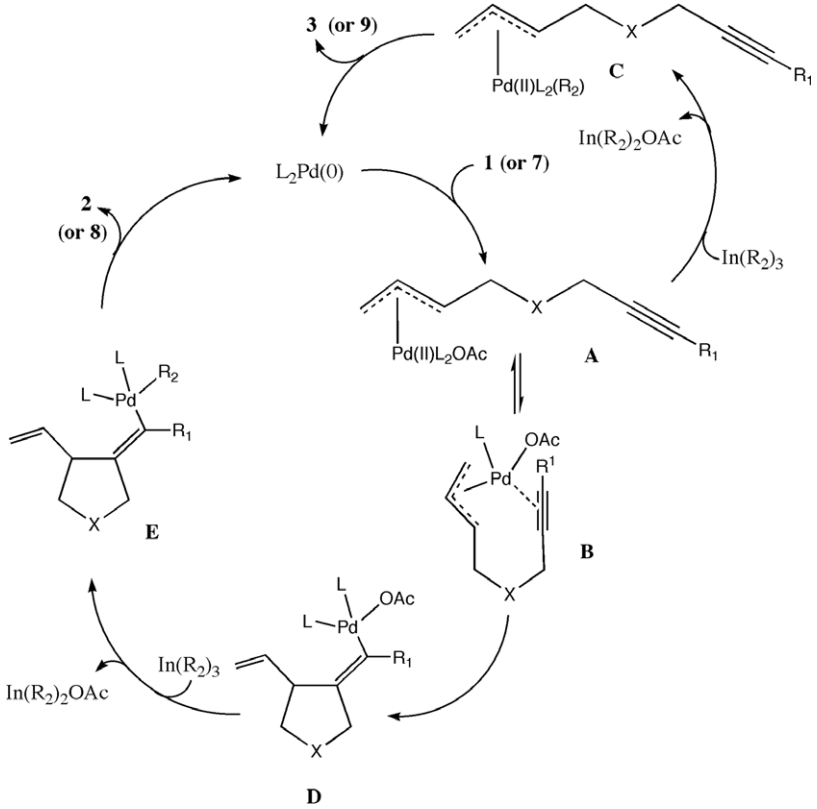
7 **8** **9**

Entry	7	R_1	X	Product ratio[a] **8:9**	Yield[b] (%) (**8**[c] + **9**[d])
1	**a**	H	CH_2	1:10	75
2	**b**	H	$C(CO_2Et)_2$	1:1	68
3	**c**	CH_3	$C(CO_2Me)_2$	2.2:1	55
4	**d**	H	O	1:1.25	85
5	**e**	CH_3	O	1.7:1	78
6	**f**	CH_3	NTs	5:1	90

[a] Product ratios determined by ^{1}H NMR analysis of the crude reaction mixture.
[b] Yields shown are of purified products **8** and **9**, which coelute on column chromatography.
[c] Obtained as 3:1–5:1 mixtures of *E*:*Z* alkene isomers (see Supplementary data).
[d] Ratio of alkene isomers (*E*:*Z*) not determined.

by transmetalation with the organoindium reagent (providing **E**); reductive elimination then gives rise to **2** (or **8**) and regenerates the palladium catalyst. For enynes favoring an extended conformation (e.g., $X = CH_2$, CH_2CH_2, **4a** and **7a**, respectively) or with increased steric bulk at the alkyne terminus (e.g., $R_1 = Et$, $R_1 = SiMe_3$, **1b** and **1f**, respectively), there is a higher energy barrier to migratory insertion, and therefore intermediate **A** may instead directly undergo transmetalation with the organoindium reagent, furnishing intermediate **C**. Reductive elimination (with carbon–carbon bond formation occurring at the less hindered carbon atom of the allyl system) then furnishes acyclic allylic substitution products **3** (or **9**).

In summary, the palladium-catalyzed reactions of acetoxyenynes with triorganoindium reagents proceed to give cyclic and/or acyclic substitution products based substrate structure.[29] Cyclized products may be obtained in high yields from substrates bearing quaternary



Scheme 4. Mechanistic proposal.

centers or heteroatoms in the enyne tether and/or substituents that hinder the palladium π-allyl complex. Acyclic allylic substitution products may be favored for enynes with steric bulk at the alkyne terminus and or with *n*-alkyl tethers. Preliminary results indicate that a practical and more atom-efficient process may be realized by employing stoichiometric amounts of dimethoxyorganoindium reagents. Further studies on the scope and stereoselectivity of this useful reaction are underway and will be reported in due course.

Acknowledgments

We thank the ACS Petroleum Research Fund (No. PRF 45277-B1) and Research Corporation (No. CC6343) for their generous support of our program. We also thank Dr. Paul Shin (CSUN) for helping perform the two-dimensional NMR experiments.

Supplementary data

Complete experimental details and spectroscopic data for all compounds prepared in Tables 1 and 2. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.10.043.

References and notes

1. For reviews on the chemistry of indium, see: (a) Chan, T. H.; Li, C. J.; Lee, M. C.; Wei, Z. Y. *Can. J. Chem.* **1994**, *72*, 1181; (b) Li, C. J. *Chem. Rev.* **1993**, *93*, 2023; (c) Cintas, P. *Synlett* **1995**, 1087; (d) Li, C. J. *Tetrahedron* **1996**, *52*, 5643; (e) Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*; Wiley: New York, 1997; (f) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Thomson Science: Glasgow, Scotland, 1998; (g) Li, C. J.; Chan, T. H. *Tetrahedron* **1999**, *55*, 11149; (h) Li, C. J. *Chem. Rev.* **2005**, *105*, 3095.
2. (a) Perez, I.; Sestelo, J. P.; Sarandeses, L. A. *Org. Lett.* **1999**, *1*, 1267; (b) Perez, I.; Sestelo, J. P.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155; (c) Pena, M. A.; Perez, I.; Perez Sestelo, J.; Sarandeses, L. A. *Chem. Commun.* **2002**, *19*, 2246; (d) Nomura, R.; Miyazaki, S.; Matsuda, H. *J. Am. Chem. Soc.* **1992**, *114*, 2738; (e) Takami, K.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Org. Lett.* **2001**, *3*, 1997; (f) Lee, P. H.; Sung, S.; Lee, K. *Org. Lett.* **2001**, *3*, 3201; (g) Lee, P. H.; Lee, S. W.; Saemoon, D. *Org. Lett.* **2003**, *5*, 4963; (h) Lehmann, U.; Awasthi, S.; Minehan, T. *Org. Lett.* **2003**, *5*, 2405; (i) Pena, M. A.; Sestelo, J. P.; Sarandeses, L. A. *Synthesis* **2005**, *3*, 485.
3. (a) Rodriguez, D.; Sestelo, J. P.; Sarandeses, L. A. *J. Org. Chem.* **2003**, *68*, 2518; (b) Baker, L. A.; Minehan, T. G. *J. Org. Chem.* **2004**, *69*, 3957; (c) Rodriguez, D.; Perez Sestelo, J.; Sarandeses, L. A. *J. Org. Chem.* **2004**, *69*, 8136; (d) Riveiros, R.; Rodriguez, D.; Perez Sestelo, J.; Sarandeses, L. A. *Org. Lett.* **2006**, *8*, 1403.
4. (a) Goeta, A.; Salter, M. M.; Shah, H. *Tetrahedron* **2006**, *62*, 3582; (b) Lee, P. H.; Kim, S.; Lee, K.; Seomoon, D.; Kim, H.; Lee, S.; Kim, M.; Han, M.; Noh, K.; Livinghouse, T. *Org. Lett.* **2004**, *6*, 4825; (c) Kang, S.-K.; Lee, S.-W.; Jung, J.; Lim, Y. *J. Org. Chem.* **2002**, *67*, 4376; (d) Salter, M. M.; Sardo-Inffiri, S. *Synlett* **2002**, 2068; (e) Yanada, R.; Nishimori, N.; Matsumura, A.; Fujii, N.; Takemoto, Y. *Tetrahedron Lett.* **2002**, *43*, 4585; (f) Kang, H.-Y.; Kim, Y.-T.; Yu, Y.-K.; Cha, J. W.; Cho, Y. S.; Koh, H. Y. *Synlett* **2004**, 45; (g) Nair, V.; Ros, S.; Jayan, C. C.; Pillai, B. S. *Tetrahedron* **2004**, *60*, 1959; (h) Takami, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 2993.
5. Price, S.; Edwards, S.; Wu, T.; Minehan, T. G. *Tetrahedron Lett.* **2004**, *45*, 5197.
6. Ihle, N. C.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 560.
7. Prepared by acylation (Ac_2O, pyridine) of the corresponding allylic alcohol: Marshall, J. A.; Piettre, A.; Paige, M. A.; Valeriote, F. *J. Org. Chem.* **2003**, *68*, 1771.
8. Prepared by acylation (Ac_2O, pyridine) of the corresponding allylic alcohol: Trost, B. M.; Lee, D. C. *J. Org. Chem.* **1989**, *54*, 2271.
9. For a discussion of the Thorpe–Ingold effect, see: (a) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080; (b) Bruice, T. C.; Pandit, U. K. *J. Am. Chem. Soc.* **1960**, *82*, 5858; (c) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224; (d) Jung, M. E.; Kiankarimi, M. *J. Org. Chem.* **1998**, *63*, 2968.
10. Cui, D.-M.; Tsuzuki, T.; Miyake, K.; Ikeda, S.; Sato, Y. *Tetrahedron* **1998**, *54*, 1063.
11. Sarandeses also observed the formation of reduced products in palladium-catalyzed cross-couplings of propargylic esters with Bu_3In; see Ref. 3d.
12. Oppolzer, W.; Ruiz-Montes, J. *Helv. Chim. Acta* **1993**, *76*, 1266.
13. A similar result was obtained when tris(phenylethynyl)indium was employed in an attempted palladium-catalyzed allylic substitution of cyclohex-2-enyl acetate: see Ref. 3b.
14. Miura, T.; Shimada, M.; Murakami, M. *J. Am. Chem. Soc.* **2005**, *127*, 1094.
15. Zhang, Q.; Xu, W.; Lu, X. *J. Org. Chem.* **2005**, *70*, 1505.
16. Prepared by acylation (Ac_2O, pyridine) of the corresponding allylic alcohol: Kressierer, C. J.; Mueller, T. J. *Org. Lett.* **2005**, *7*, 2237.
17. For the unique uncatalyzed reaction of **1e**, we hypothesize that triphenylindium-assisted ionization of the allylic acetate of **1e**, concurrent with intramolecular cyclization of the alkyne π bond onto the incipient allylic cation would generate an aryl-stabilized alkenyl cation. The triphenyl(acetoxy)indate complex could then deliver a phenyl ligand to this cation, furnishing **2p**. For triorganoindium-mediated ionization of allylic esters and the nucleophilic reactivity of organoindates, see Ref. 5. Cook has also investigated $InCl_3$-catalyzed atom-transfer cyclization of enynes: Cook, G. R.; Hiyashi, R. *Org. Lett.* **2006**, *8*, 1045.
18. A similar observation has been noted by Sarandeses in his studies of organoindium-mediated substitution reactions of allylic and propargylic halides and esters; see Refs. 3c and 3d.
19. (a) Beachley, O. T.; MacRae, D. J.; Kovalevsky, A. Y.; Zhang, Y.; Li, X. *Organometallics* **2002**, *21*, 4632; (b) Beachley, O. T.; MacRae, D. J.; Churchill, M. R.; Kovalevsky, A. Y.; Robirds, E. S. *Organometallics* **2003**, *22*, 3991; (c) Beachley, O. T.; MacRae, D. J.; Churchill, M. R.; Kovalevsky, A. Y.; Robirds, E. S. *Organometallics* **2003**, *22*, 5152.
20. The sodium methoxide used in the preparation of the aryldimethoxyindium solutions was generated by adding 2 M equiv (relative to indium trichloride) of sodium metal to sufficient methanol to make a 10 M solution; this 10 M methanolic solution was then quantitatively transferred to the THF solution of arylindiumdichloride.

21. Beachley (Ref. 19) suggests that heteroleptic organoindiums ($R_1In(R_2)_2$) exist as an equilibrium mixture of $(R_1)_3In$, $(R_2)_3In$, $R_1In(R_2)_2$, $(R_1)_2InR_2$ in solution.
22. Prepared by acylation (Ac_2O, pyridine) of the corresponding allylic alcohol: Baldwin, J. E.; Chesworth, R.; Parker, J. S.; Russell, A. T. *Tetrahedron Lett.* **1995**, *36*, 9551.
23. Prepared by acylation (Ac_2O, pyridine) of the corresponding allylic alcohol: Lee, H.-Y.; Kim, H. Y.; Tae, H.; Kim, B. G.; Lee, J. *Org. Lett.* **2003**, *5*, 3439.
24. Prepared by reaction of 3-butyn-1-ol with (*Z*)-1-(methansulfonyloxy)-4-(*tert*-butyldimethylsiloxy)-2-butene (NaH, DMF), followed by silyl ether deprotection (3:1:1 HOAc/THF/H_2O) and acylation (Ac_2O, pyridine).
25. Preparation of **7c**: starting from (*Z*)-1-(*tert*-butyldimethylsiloxy)-2-buten-4-ol, oxidation of the primary alcohol (MnO_2, CH_2Cl_2), methyllithium treatment (MeLi, Et_2O, −78 °C), secondary alcohol protection (TBDPS-Cl, imid., CH_2Cl_2), primary silyl ether deprotection (3:1:1 HOAc, H_2O, THF), and mesylation (MsCl, THF, NEt_3) gave 1-(methansulfonyloxy)-4-(*tert*-butyldiphenylsiloxy)-2-pentene as a mixture of *E* and *Z* alkene isomers. Reaction of this compound with the anion of dimethyl-2-(but-3-ynyl)malonate (DMF, NaH, 0 °C), silyl ether deprotection (TBAF, THF), and acetylation (Ac_2O, pyridine) furnished **7c**.
26. Preparation of **7e**: starting with 1-(methansulfonyloxy)-4-(*tert*-butyldiphenylsiloxy)-2-pentene (Ref. 25), reaction with the alkoxide of 3-butyn-1-ol (NaH, DMF, 0 °C), silyl ether deprotection (TBAF, THF), and acetylation (Ac_2O, pyridine) furnished **7e**.
27. Preparation of **7f**: starting with 1-(methansulfonyloxy)-4-(*tert*-butyldiphenylsiloxy)-2-pentene (Ref. 25), reaction with the amide of *N*-tosylbut-3-yn-1-amine (NaH, DMF, 0 °C), silyl ether deprotection (TBAF, THF), and acetylation (Ac_2O, pyridine) furnished **7f**.
28. For a discussion of the mechanism of a related palladium-catalyzed zinc-ene reaction, see: Oppolzer, W.; Schroder, F. *Tetrahedron Lett.* **1994**, *35*, 7939.
29. Typical procedure: to a stirred solution of acetoxyenyne (0.45 mmol) in DMF (1 mL) is added $Pd(dba)_2$ (12 mg, 0.02 mmol). A separately prepared 0.3 M THF solution of Ar_3In (1.6 mL, 0.5 mmol) is then added dropwise and the reaction is placed in an 80 °C bath and stirred for 1 h. The reaction mixture is then cooled to room temperature, quenched by the dropwise addition of methanol (1 mL) and then diluted with ether (20 mL). The solution is washed with two portions (10 mL each) of 0.1 N HCl, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (SiO_2, 1% Et_2O in hexanes) affords the substitution products.