Pd-Catalyzed Substitution Reactions with Organoindium Reagents *in situ* Generated from Indium and Allyl or Propargyl Halides

Phil Ho Lee,* Eunkyong Shim, Kooyeon Lee, Dong Seomoon, and Sundae Kim

Department of Chemistry, Kangwon National University, Chunchon 200-701, Korea. *E-mail: phlee@kangwon.ac.kr
Received November 20, 2004

Allylindium and propargylindium reagents *in situ* generated from the reactions of indium with allyl halides and propargyl halides could participate as nucleophiles in Pd-catalyzed substitution reactions of allyl carbonates to produce 1,5-dienes and 1,5-enynes in good yields. β-Hydride elimination products were produced in case of carbonates having β-hydrogens. Because organoindium reagents obtained from allyl or propargyl halides and indium have previously not been used to Pd-catalyzed allylic and propargylic substitution reactions, these results should provide more opportunities for the development of new C-C bond forming reactions.

Key Words : Allylation, Propargylation, Indium, Palladium, Substitution
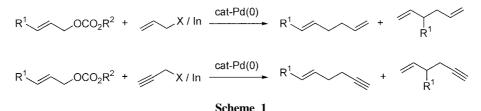
Introduction

The Pd-catalyzed nucleophilic substitution reactions of allyl esters and carbonates with a variety of nucleophiles are very important transition metal-catalyzed processes.[1] Although the stabilized carbanions[2] and various transmetalating agents (Sn, Al, Zr, Li, and Mg)[3] have been reported for metal-catalyzed nucleophilic substitution reactions, development of easily available allyl and propargyl transmetalating agents is still needed due to further functionalization of C-C multiple bonds in products.[4] The use of allyl- and propargyl-stannanes as coupling partners has attracted much attention as a result of their availability and air- and moisture-stability, as well as compatibility with a variety of functional groups.[5] Preparation of allyl- and propargylstannanes is generally accessible, whereas such procedures are sometimes inadequate and the requisite allylmetals and propargylmetals are difficult to obtain. Ideally, allylmetals and propargylmetals must be prepared *in situ* from the reaction of metals with allyl and propargyl halides. The major advantage of organomagnesium and organolithium compounds as coupling partners is their availability.[6] However, these reagents show low functional group tolerance and β-hydride eliminations occurred due to their basicity. Therefore, the development of new allylmetals and propargylmetals in Pd-catalyzed nucleophilic substitution reactions was explored to overcome these difficulties. Our interest applying indium metal to organic synthesis[7] has led us to investigate the participation of indium organometallics in metal-catalyzed reactions.[8] In this paper, we report that *in situ* generated allylindium and propargylindium reagents can be applicable to allylic and propargylic substitution reactions of allyl carbonates catalyzed by Pd (0) as nucleophiles (Scheme 1).[9]

Results and Discussion

Reactions of Allyl Carbonates with *in situ* Generated Allylindiums from Indium and Ally Halides. At the outset, the catalytic activity of several palladium complexes was examined in the reaction of *trans*-cinnamyl methyl carbonate with allylindium, which was *in situ* generated from the reaction of allyl bromide and indium. Among the catalysts studied, 1 mol % of Pd$_2$dba$_3$CHCl$_3$ showed high catalytic activity. Other palladium complexes, such as Pd(CH$_3$CN)$_2$Cl$_2$, Pd(PhCN)$_2$Cl$_2$, PdCl$_2$, BnPd(PPh$_3$)$_2$Cl, and Pd(PPh$_3$)$_4$ produced *trans*-1-phenyl-1,5-hexadiene in low yields. Among the ligands studied, tri-*o*-tolylphosphine gave the best results. Of the catalytic systems examined, the best results were obtained with 1 mol % of Pd$_2$dba$_3$CHCl$_3$ and 8 mol % of (*o*-Tolyl)$_3$P in THF at 65 °C under a nitrogen atmosphere, producing 1-phenyl-1,5-hexadiene in 90% yield with regioselectivity. Also, allylindium reagent obtained from the reaction of 1 equiv of indium with 1.5 equiv of allyl bromide gave the best result as a coupling partner. The use of less than 1 equiv of indium and less than 1.5 equiv of allyl bromide resulted in sluggish reaction and gave lower yields.

To demonstrate the efficiency and scope of the present method, we applied this catalytic system to a variety of allyl halides and allyl carbonates. The results are summarized in Table 1. For the allyl halides as precursor of nucleophile, the presence of various substituents at the α and γ position effected on product yields. When allylindium derived from

Scheme 1

Table 1. Pd-catalyzed allylic substitution reactions of allyl carbonates with allylindium reagents

Entry	Allyl Carbonates	Allyl Halides	Products	Yield (%)[a]
1	Ph⌒OCO₂Me	⌒I	Ph⌒⌒⌒	80
2		⌒Br	Ph⌒⌒⌒	90
3		(cyclohexenyl)Br	Ph⌒⌒(cyclohexene) + (Ph-CH=CH-)(cyclohexene)	83 (1 : 1)[b]
4		EtO₂C⌒⌒Br	Ph⌒⌒⌒ / CO₂Et	44
5	Ph-C(OCO₂Et)=CH₂	⌒I	Ph⌒⌒⌒ / (Ph branched)	81[c] (4 : 1)[b]
6		⌒Br	Ph⌒⌒⌒ / (Ph branched)	81[d] (2.5 : 1)[b]
7		(cyclohexenyl)Br	Ph⌒⌒(cyclohexene) / (Ph)(cyclohexene)	57[c] (2 : 1)[b]
8	Ph⌒C(OCO₂Et)Ph	⌒I	Ph⌒⌒(Ph)⌒	78
9		⌒Br	Ph⌒⌒(Ph)⌒	90
10		(cyclohexenyl)Br	Ph⌒⌒(Ph)(cyclohexene)	84 (1.4 : 1)[e]

[a]Reactions performed in the presence of 1 mol % of Pd₂dba₃CHCl₃ and 8 mol % of (o-Tolyl)₃P in THF at 65 °C, unless otherwise noted. [b]Isomeric ratio. [c][2,6-(MeO)₂Ph]₃P was used as ligand. [d]Ph₃As was used as ligand. [e]Diastereomeric ratio.

the reaction of allyl iodide with indium reacted with *trans*-cinnamyl methyl carbonate in the presence of Pd(0) catalyst, the desired product was obtained in 80% (entry 1). *trans*-Cinnamyl methyl carbonate was treated with 3-bromocyclohexene and indium to provide 3-*trans*-cinnamyl cyclohexene and 3-(1'-phenyl-2'-propenyl)-1-cyclohexene in 83% yield (isomeric ratio = 1 : 1) which were produced from the proximal and distal attack of indium reagent to the oxygen substituent (entry 3). The reaction of *trans*-cinnamyl methyl carbonate with γ-ethoxycarbonyl allylindium gave 4-ethoxycarbonyl-1-phenyl-1,5-hexadiene in 44% yield due to low nucleophilicity of the stabilized indium reagent (entry 4). Although allyl acetates are commonly used for the various types of Pd-catalyzed substitution reactions, the reactions of allyl acetate with allylindium did not proceed. Allyl carbonates derived from phenyl vinyl ketone (entries 5-7) and chalcone (entries 8-10) produced the desired 1,5-dienes in good yield under the present conditions. Although the methyl carbonate from 1-phenyl-4-penten-3-ol and geraniol reacted with allyl halide (Br and I) and indium, the desired product was not obtained and a complicated TLC was obtained.

Reactions of Allyl Carbonates with *in situ* Generated Propargylindiums from Indium and Propargyl Halides. On the bases of allylic substitution reactions, we studied reactions of *trans*-cinnamyl methyl carbonate with *in situ* generated propargylindium reagent derived from propargyl bromide and indium. The results are summarized in Table 2.

THF was the solvent of choice among the reaction media tested (entries 4 *vs* 5). Of the catalytic systems examined, the best results were obtained with 2 mol % of Pd₂dba₃CHCl₃ and 16 mol % of (o-Tolyl)₃P in the presence of LiCl as an additive in THF at 65 °C for 1 h under a nitrogen atmosphere to furnish regioselectively *trans*-6-phenyl-5-hexen-1-yne in

Table 2. Reaction optimization of propargylic substitution reactions[a]

Ph⌒OCO₂Me + ⌒Br / In →(cat-Pd(0))→ Ph⌒⌒≡
　　1　　　　　　　2　　　　　　　　　

Entry	1	2	In	Additive	Solvent	Temp (°C)	Time (hr)	Yield (%)[b]
	(equiv)							
1	1	1.5	1		THF	65	18	0
2	1	1.5	1		DMF	100	18	0
3	1	3	2		THF	65	18	0
4	1	1.5	1	LiCl	THF	65	18	71(23)
5	1	1.5	1	LiCl	DMF	100	15	0
6[c]	1	1.5	1	LiCl	THF	65	18	58(39)
7	1	3	2	LiCl	THF	65	18	78(16)
8[d]	1	1.5	1	LiCl	THF	65	18	82(15)
9[d]	1	3	2	LiCl	THF	65	1	95(92)[e]

[a]Reaction performed in the presence of 1 mol % of Pd₂dba₃CHCl₃ and 8 mol % of (o-Tolyl)₃P, unless otherwise noted. [b]GC yields were obtained on the basis of an internal standard (dodecane). Numbers in parenthesis indicate recovered GC yield of starting material. [c]4 mol % of Pd(PPh₃)₄ was ued. [d]2 mol % of Pd₂dba₃CHCl₃ and 16 mol % of (o-Tolyl)₃P was used. [e]Isolated yield.

Table 3. Pd-catalyzed propargylic substitution reactions of allyl carbonates with propargylindium reagents[a]

Entry	Carbonates	Propagyl Halides	Time (hr)	Products	Yield (%)[b]
1	Ph $\diagup$ OCO$_2$Me	$\equiv$ Br	1	Ph $\diagup$ $\equiv$	92
2		$\equiv$ Br	3	Ph $\diagup$ $\equiv$	74
3		Ph $\diagup$ $\equiv$ Br	4	Ph $\diagup$ $\equiv$ Ph	72
4	OCO$_2$Me Ph	$\equiv$ Br	2	Ph $\diagup$ $\equiv$	88
5		$\equiv$ Br	5	Ph $\diagup$ $\equiv$	65
6		Ph $\equiv$ Br	10	Ph $\diagup$ $\equiv$ Ph	63
7	OCO$_2$Me Ph	$\equiv$ Br	1	Ph $\diagup$ $\equiv$ Ph $\equiv$	88 (1 : 1)[c]
8		$\equiv$ Br	1	Ph $\diagup$ $\equiv$ Ph $\equiv$	81 (1 : 2)[c]
9	OCO$_2$Me	$\equiv$ Br	3		78
10	OCO$_2$Me *n*-C$_8$H$_{17}$	$\equiv$ Br	1	*n*-C$_7$H$_{15}$ $\diagup$	85

[a]Reactions performed in the presence of 1 equiv of carbonate, 3 equiv of propargyl bromide, 2 equiv of In, 3 equiv of LiCl, 2 mol % of Pd$_2$dba$_3$CHCl$_3$, and 16 mol % of (*o*-Tolyl)$_3$P in THF at 65 °C, unless otherwise noted. [b]Isolated yields. [c]Isomeric ratio.

92% yield *via* proximal attack of indium reagent (entry 9). No allenic substitution product is formed in any reactions. The use of lithium chloride was critically important for successful reactions (entries 3 *vs* 9). Also, propargylindium reagent obtained from the reaction of 2 equiv of indium with 3 equiv of propargyl bromide gave the best result as a coupling partner (entries 8 *vs* 9).

With these results in hand, *trans*-cinnamyl methyl carbonate reacted with organoindium reagent derived from 3-bromo-1-butyne and indium to give *trans*-3-methyl-6-phenyl-5-hexen-1-yne in 74% yield *via* proximal attack to the oxygen substitution (entry 2 in Table 3). *trans*-3,6-Diphenyl-5-hexen-1-yne was regioselectively produced in 72% yield in case of 3-bromo-3-phenyl-1-propyne (entry 3). Treatment of the methyl carbonate from 1-phenyl-2-propen-1-ol with propargylindium reagents gave the desired product *via* distal attack due to the steric hindrance (entry 4). Organoindium reagents *in situ* generated from 3-bromo-1-butyne and 3-bromo-3-phenyl-1-propyne and indium produced 1,5-enynes in 65% and 63% yields, respectively (entries 5 and 6). Reaction of methyl carbonate of *trans*-1-phenyl-1,4-pentadien-3-ol with propargylindium reagent provided *trans*-6-phenyl-4-vinyl-5-hexen-1-yne and *trans*-

4-phenyl-5,7-octadien-1-yne in 88% yield (isomeric ratio = 1 : 1, entry 7). Subjecting this carbonate to 3-bromo-1-butyne and indium afforded a 27% yield of *trans*-3-methyl-6-phenyl-4-vinyl-5-hexen-1-yne and a 54% yield of *trans*-3-methyl-4-phenyl-5,7-octadien-1-yne (entry 8). Contrary to results above, when methyl carbonates of geraniol and 1-vinyl-1-nonanol were treated with propargylindium, 1,3-dienes were produced *via* β-hydride elimination (entries 9 and 10).

Although the mechanism of the reaction of allylindiums and propargylindiums with allyl carbonates in the presence of Pd(0) catalyst is not clear at the present moment, we assume that organoindium reagents play the similar role to soft nucleophiles of Trost-Tsuji reaction.[1] This and other plausible mechanistic pathways are under investigation.

In conclusion, we have demonstrated that allylindium and propargylindium reagents *in situ* generated from the reaction of indium with allyl halides and propargyl halides could participate in Pd-catalyzed substitution reactions of allyl carbonates to produce 1,5-dienes and 1,5-enynes. β-Hydride elimination products were produced in case of carbonates having β-hydrogens. Because organoindium reagents derived from allyl and propargyl halides and indium have previously

not been applied to Pd-catalyzed substitution reactions of carbonates, these results should provide more opportunities for the development of new C-C bond forming reactions.

Experimental Section

Typical Experimental Procedure for Allylic Substitution Reactions. To a solution of Pd$_2$dba$_3$CHCl$_3$ (5.2 mg, 1 mol %) and tri-*o*-tolylphosphine (12.2 mg, 8 mol %) in THF (1 mL) was added *trans*-cinnamyl methyl carbonate (96 mg, 0.5 mmol) at room temperature under a nitrogen atmosphere. After 15 min, allylindium reagent *in situ* generated from allyl bromide (91 mg, 0.75 mmol) and indium (57 mg, 0.5 mmol) in THF (1 mL) was added and the mixture was stirred at 65 °C for 24 h. The reaction mixture was quenched with saturated aqueous NaHCO$_3$. The aqueous layer was extracted with ether (3 × 15 mL), and the combined organic layers were washed with water and brine, dried with MgSO$_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using *n*-hexane to give *trans*-1-phenyl-1,5-hexadiene (71 mg, 90%): ^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.34 (2H, d, J = 7.4 Hz), 7.29 (2H, t, J = 7.9 Hz), 7.19 (1H, t, J = 7.1 Hz), 6.41 (1H, d, J = 15.9 Hz), 6.23 (1H, dt, J = 15.7, 6.6 Hz), 5.88 (1H, tt, J = 10.4, 6.6 Hz), 5.06 (1H, d, J = 17.2 Hz), 4.99(1H, d, J = 9.7 Hz), 2.33-2.23 (4H, m); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 138.1, 137.8, 130.2, 130.1, 128.5, 126.9, 125.9, 114.9, 33.6, 32.4; HRMS (EI) calcd for C$_{12}$H$_{14}$ 158.1096, found 158.1095.

Typical Experimental Procedure for Propargylic Substitution Reactions. To a solution of Pd$_2$dba$_3$CHCl$_3$ (10.4 mg, 2 mol %), tri-*o*-tolylphosphine (24.4 mg, 16 mol %) and lithium chloride (63.6 mg, 1.5 mmol) in THF (1 mL) was added *trans*-cinnamyl methyl carbonate (96 mg, 0.5 mmol) at room temperature under a nitrogen atmosphere. After 10 min, propargylindium reagent *in situ* generated from propargyl bromide (166 mg, 1.5 mmol) and indium (114.8 mg, 1 mmol) in THF (1.5 mL) was added and the mixture was stirred at 65 °C for 1 h. The reaction mixture was quenched with saturated aqueous NaHCO$_3$. The aqueous layer was extracted with ether (3 × 15 mL), and the combined organic layers were washed with water and brine, dried with MgSO$_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using *n*-hexane to give *trans*-6-phenyl-5-hexen-1-yne (72 mg, 92%): ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.4-7.1 (5H, m), 6.46 (1H, d, J = 15.9 Hz), 6.26 (1H, dt, J = 15.8, 6.5 Hz), 2.5-2.3 (4H, m), 1.99 (1H, t, J = 2.5 Hz) ^{13}C NMR (CDCl$_3$, 100 MHz) δ 137.8, 131.6, 128.9, 128.8, 127.6, 126.5, 84.2, 69.3, 32.4, 19.1.

References

1. (a) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley & Sons: Chichester, 1995; pp 290-422. (b) Godleski, S. A. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p 585. (c) Tsuji, J. *Tetrahedron* **1986**, *42*, 4361. (d) Trost, B. M. *Tetrahedron* **1977**, *33*, 2615. (e) Heumann, A. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VHC: Weinheim, 1998; Vol. 1, p 251.

2. (a) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385. (b) Wade, P. A.; Morrow, S. D.; Hardinger, S. A. *J. Org. Chem.* **1982**, *47*, 365. (c) Tsuji, J. *Pure Appl. Chem.* **1986**, *58*, 869. (d) Tsuji, J.; Minami, L. *Acc. Chem. Res.* **1987**, *20*, 140.

3. (a) Castanet, Y.; Petit, T. *Tetrahedron Lett.* **1979**, *20*, 3221. (b) Temple, J. S.; Schwartz, J. *J. Am. Chem. Soc.* **1980**, *102*, 7381. (c) Hayashi, T.; Konishi, M.; Yokota, K.; Kumada, M. *Chem. Commun.* **1981**, 313. (d) Matsushita, H.; Negishi, E. *J. Am. Chem. Soc.* **1981**, *103*, 2882. (e) Godleski, S. A.; Gundlach, K. B.; Ho, H. Y.; Keinan, E.; Frolow, F. *Organometallics* **1984**, *3*, 21. (f) Hayashi, T.; Konishi, M.; Kumada, M. *Chem. Commun.* **1984**, 107.

4. (a) Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, *21*, 2595. (b) Godschalx, J.; Stille, J. K. *Tetrahedron Lett.* **1980**, *21*, 2599. (c) Goliaszewski, A.; Schwartz, J. *J. Am. Chem. Soc.* **1984**, *106*, 5028. (d) Goliaszewski, A.; Schwartz, J. *Tetrahedron* **1985**, *41*, 5779. (e) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (f) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

5. (a) Farina, V.; Krishnamurthy, V.; Scott, W. J. *The Stille Reaction*; Wiley: New York, 1998. (b) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, 25, 508. (c) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771. (d) Mitchell, T. N. *Synthesis* **1992**, 803. (e) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1. (f) Pereyre, M.; Quintard, J.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: London, 1987.

6. Geissler, H. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weomheim, 1998; Chapter 2.10.

7. (a) Lee, P. H.; Lee, K.; Sung, S.-Y.; Chang, S. *J. Org. Chem.* **2001**, *66*, 8646. (b) Lee, P. H.; Lee, K.; Kim, S. *Org. Lett.* **2001**, *3*, 3205. (c) Iwasawa, N.; Miura, T.; Kiyota, K.; Kusama, H.; Lee, K.; Lee, P. H. *Org. Lett.* **2002**, 4463. (d) Lee, P. H.; Seomoon, D.; Lee, K.; Heo, Y. *J. Org. Chem.* **2003**, *68*, 2510. (e) Miura, T.; Kiyota, K.; Kusama, H.; Lee, K.; Kim, H.; Kim, S.; Lee, P. H.; Iwasawa, N. *Org. Lett.* **2003**, *5*, 1725. (f) Lee, K.; Kim, H.; Miura, T.; Kiyota, K.; Kusama, H.; Kim, S.; Iwasawa, N.; Lee, P. H. *J. Am. Chem. Soc.* **2003**, *125*, 9682. (g) Damle, S. V.; Seomoon, D.; Lee, P. H. *J. Org. Chem.* **2003**, *68*, 7085. (h) 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. (i) Lee, P. H.; Kim, H.; Lee, K.; Seomoon, D.; Kim, S.; Kim, H.; Kim, H.; Lee, M.; Shim, E.; Lee, S.; Kim, M.; Han, M.; Noh, K.; Sridhar, M. *Bull. Korean Chem. Soc.* **2004**, *25*, 1687.

8. (a) Lee, P. H.; Sung, S.-Y.; Lee, K. *Org. Lett.* **2001**, *3*, 3201. (b) Lee, P. H.; Sung, S.-Y.; Lee, K.; Chang, S. *Synlett* **2002**, 146. (c) Lee, K.; Seomoon, D.; Lee, P. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3901. (d) Lee, K.; Lee, J.; Lee, P. H. *J. Org. Chem.* **2002**, *67*, 8265. (e) Lee, P. H.; Lee, S. W.; Lee, K. *Org. Lett.* **2003**, *5*, 1103. (f) Lee, P. H.; Lee, S. W.; Seomoon, D. *Org. Lett.* **2003**, *5*, 4963. (g) Lee, S. W.; Lee, K.; Seomoon, D.; Kim, S.; Kim, H.; Kim, H.; Shim, E.; Lee, M.; Lee, S.; Kim, M.; Lee, P. H. *J. Org. Chem.* **2004**, *69*, 4852. (h) Lee, P. H.; Seomoon, D.; Lee, K.; Kim, S.; Kim, H.; Kim, H.; Shim, E.; Lee, M.; Lee, S.; Kim, M.; Sridhar, M. *Adv. Synth. Catal.* **2004**, *346*, 1641. (i) Lee, P. H.; Seomoon, D.; Lee, K. *Org. Lett.* **2005**, *7*, 343.