ORGANIC LETTERS

2007
Vol. 9, No. 22
4603−4606

Nickel(0) Triethyl Phosphite Complex-Catalyzed Allylic Substitution with Retention of Regio- and Stereochemistry

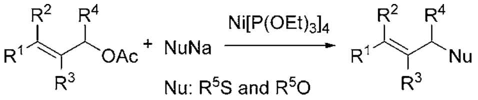
Yasutaka Yatsumonji, Yusuke Ishida, Akira Tsubouchi, and Takeshi Takeda*

Department of Applied Chemistry, Graduate School of Engineering, Tokyo University of Agriculture and Technology, Koganei, Tokyo 184-8588, Japan

takeda-t@cc.tuat.ac.jp

Received August 29, 2007

ABSTRACT



Nickel(0) triethyl phosphite complex-promoted reaction of allylic acetates with thiols produced allylic sulfides with retention of configuration without allylic rearrangement. A similar reaction of allylic acetates with alcohols and phenols also proceeded with retention of regio- and stereochemistry.

Transition metal-catalyzed allylic substitution is one of the most frequently employed transformations in organic synthesis, and a variety of transition metal complexes have been explored as catalysts for the regio- and stereoselective reactions.[1] The reactions catalyzed by these complexes are generally classified into two categories: the branch selective reaction,[1a,2] in which a nucleophile attacks at the more hindered side of the allylic system, and the linear selective reaction, which involves nucleophilic attack at the less substituted allylic terminus.[3] Recently, the regiospecific reactions have also been reported.[4]

The nickel-catalyzed regio- and stereoselective allylic substitution with hard nucleophiles such as the Grignard reagent have been reported.[5] Nickel complexes, however, have retained less attention in allylic substitution with soft nucleophiles. Although Ni(dppb)$_2$[6] and Ni[1,2-bis[*N*-methyl-*N*-(diphenylphosphinoamino)ethane]]$_2$[7]-catalyzed reactions of allylic alcohol derivatives with soft nucleophiles have been investigated, these reactions end up with the formation of regio- and stereoisomeric mixtures. Recently we reported the transformation of alkenyl and aryl halides into sulfides

---

(1) (a) Leahy, D. K.; Evans, P. A. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, Germany, 2005; pp 191−214. (b) Heumann, A. In *Transition Metals for Organic Synthesis*; Beller, M.; Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 1, pp 251−264. (c) Tsuji, J. *Palladium Reagents and Catalysts, New Perspectives for the 21st Century*; John Wiley & Sons: Chichester, UK, 2004. (d) Hegedus, L. S. In *Transition Metals in the Synthesis of Complex Organic Molecules*; Hegedus, L. S., Ed.; University Science Book: Sausalito, CA, 1999; pp 245−286.

(2) For recent examples: [Pd]: (a) Dai, L.-X.; Tu, T.; You, S.-L.; Deng, W.-P.; Hou, X.-L. *Acc. Chem. Res.* **2003**, *36*, 659−667. [W]: (b) Malkov, A. V.; Baxendale, I. R.; Dvořák, D.; Mansfield, D. J.; Kočovský, P. *J. Org. Chem.* **1999**, *64*, 2737−2750. (c) Trost, B. M.; Hung, M.-H. *J. Am. Chem. Soc.* **1983**, *105*, 7757−7759. [Mo]: (d) Belda, O.; Moberg, C. *Acc. Chem. Res.* **2004**, *37*, 159−167. (e) Trost, B. M.; Dogra, K.; Hachiya, I.; Emura, T.; Hughes, D. L.; Krska, S.; Reamer, R. A.; Palucki, M.; Yasuda, N.; Reider, P. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1929−1932. [Rh]: (f) Kazmaier, U.; Stolz, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 3072−3075. (g) Hayashi, T.; Okada, A.; Suzuka, T.; Kawatsura, M. *Org. Lett.* **2003**, *5*, 1713−1715. [Ir]: (h) Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 3139−3143. (i) Helmchen, G.; Dahnz, A.; Dübon, P.; Schelwies, M.; Weihofen, R. *Chem. Commun.* **2007**, 675−691. (j) Polet, D.; Alexakis, A.; Tissot-Croset, K.; Corminboeuf, C.; Ditrich, K. *Chem.−Eur. J.* **2006**, *12*, 3596−3609. (k) Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 15164−15165. (l) Takeuchi, R.; Ue, N.; Tanabe, K.; Yamashita, K.; Shiga, N. *J. Am. Chem. Soc.* **2001**, *123*, 9525−9534. [Ru]: (m) Bruneau, C.; Renaud, J.-L.; Demerseman, B. *Chem.−Eur. J.* **2006**, *12*, 5178−5187. (n) Fernández, I.; Hermatschweiler, R.; Pregosin, P. S.; Albinati, A.; Rizzato, S. *Organometallics* **2006**, *25*, 323−330. (o) Trost, B. M.; Fraisse, P. L.; Ball, Z. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1059−1061.

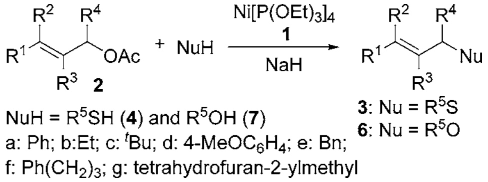
(3) For recent examples, see: [Pd]: (a) Pàmies, O.; Diéguez, M.; Claver, C. *J. Am. Chem. Soc.* **2005**, *127*, 3646−3647. (b) Hilgraf, R.; Pfaltz, A. *Adv. Synth. Catal.* **2005**, *347*, 61−77. (c) Trost, B. M. *Tetrahedron* **1977**, *33*, 2615−2649. [Ru]: (d) Kawatsura, M.; Ata, F.; Wada, S.; Hayase, S.; Uno, H.; Itoh, T. *Chem. Commun.* **2007**, 298−300.

10.1021/ol702122d CCC: $37.00

catalyzed by the less expensive and air-stable Ni[P(OEt)$_3$]$_4$ **1**.[8] Here we report the nickel complex **1**-catalyzed allylic substitution with heteronucleophiles, which proceeds with retention of regio- and stereochemistry.

Allylic sulfides are useful synthetic intermediates, and the regioselective reactions of allylic alcohols and their derivatives with thiols catalyzed by palladium[9] and rhodium[10] have been reported. These facts prompted us to investigate the practical transformation of allylic acetates **2** into sulfides **3** with thiols **4** in the presence of a catalytic amount of **1** (Scheme 1).

Scheme 1



NuH = R^{5}SH (**4**) and R^{5}OH (**7**)
a: Ph; b:Et; c: ^{t}Bu; d: 4-MeOC$_6$H$_4$; e: Bn;
f: Ph(CH$_2$)$_3$; g: tetrahydrofuran-2-ylmethyl

3: Nu = R^{5}S
6: Nu = R^{5}O

After benzenethiol (**4a**, 1.2 equiv) was treated with sodium hydride, the resulting thiolate was treated with (*E*)-3-phenylprop-2-enyl acetate (**2a**) in the presence of **1** (5 mol %) in THF/DMF (2:1) at reflux to produce (*E*)-1-phenyl-3-(phenylthio)propene (**3a**) in 96% yield (Table 1, entry 1). No formation of the (*Z*)-isomer **3c** was observed. Likewise, the reaction of (*Z*)-3-phenylprop-2-enyl acetate (**2b**) with **4a** resulted in the exclusive formation of the (*Z*)-allylic sulfide **3c** without *Z*→*E* isomerization (entry 3). All the reactions of primary allylic acetates with **4a** proceeded with complete retention of regio- and stereochemistry to produce allylic sulfides **3** in high yields. The reactions with ethanethiol (**4b**) and 2-methyl-2-propanethiol (**4c**) at 50 °C revealed the same selectivity.

When the secondary allylic acetate **2f** was subjected to substitution with **4b**, the branched sulfide **3k** was obtained regioselectively by performing the reaction in the dark in the presence of 2,6-di-*tert*-butyl-*p*-cresol (BHT) to prevent the photoisomerization of the product (Table 1, entry 11).[11] In a similar fashion, the reaction of secondary allylic acetates with different substitution patterns resulted in the direct displacement of the acetoxy group with thiolates. Only when the (*E*)-acetate **2g** was treated with **4a** was a mixture of the regioisomers produced (80%, branch:linear = 92:8). The formation of the linear isomer should be attributable to the photoisomerization during workup. Indeed the branched allylic sulfone **5** was produced with little *E*→*Z* isomerization by the in situ oxidation of the initially formed sulfide with MCPBA (entry 13). Some stereoisomerization was also observed when the (*Z*)-secondary acetate **2h** was employed (entry 14).

The present regio- and stereospecific allylic substitution is expected to be extended to the preparation of various allylic compounds. Indeed the allylic ethers **6** were obtained in high yields by the nickel(0) **1**-catalyzed reactions of primary and secondary allylic acetates **2** with alcohols and phenols **7** in the presence of sodium hydride as a base (Table 2). In the reaction of the secondary allylic acetates **2**, only the branched ethers **6** were obtained regioselectively in all cases tested without special care to prevent the isomerization.

To clarify the stereochemical outcome for the nickel(0) **1**-catalyzed allylic substitution, the optically active allylic acetate (*R*)-**2j**[12] was subjected to the substitution (Scheme 2). Thus, the (*R*)-allylic ether (*R*)-**6n** was formed by the

---

(4) [Pd]: (a) Fristrup, P.; Jensen, T.; Hoppe, J.; Norrby, P.-O. *Chem.—Eur. J.* **2006**, *12*, 5352–5360. (b) Lüssem, B. J.; Gais, H.-J. *J. Org. Chem.* **2004**, *69*, 4041–4052. (c) Faller, J. W.; Sarantopoulos, N. *Organometallics* **2004**, *23*, 2179–2185. (d) Gouriou, L.; Lloyd-Jones, G. C.; Vyskočil, Š.; Kočovský, P. *J. Organomet. Chem.* **2003**, *687*, 525–537. (e) Fairlamb, I. J. S.; Lloyd-Jones, G. C.; Vyskočil, Š.; Kočovský, P. *Chem.—Eur. J.* **2002**, *8*, 4443–4453. (f) Lloyd-Jones, G. C.; Stephen, S. C.; Murray, M.; Butts, C. P.; Vyskočil, Š.; Kočovský, P. *Chem.—Eur. J.* **2000**, *6*, 4348–4357. (g) Kočovský, P.; Vyskočil, Š.; Císařová, I.; Sejbal, J.; Tišlerová, I.; Smrčina, M.; Lloyd-Jones, G. C.; Stephen, S. C.; Butts, C. P.; Murray, M.; Langer, V. *J. Am. Chem. Soc.* **1999**, *121*, 7714–7715. (h) Butts, C. P.; Crosby, J.; Lloyd-Jones, G. C.; Stephen, S. C. *Chem. Commun.* **1999**, 1707–1708. (i) Vyskočil, Š.; Smrčina, M.; Hanuš, V.; Polášek, M.; Kočovský, P. *J. Org. Chem.* **1998**, *63*, 7738–7748. (j) Lloyd-Jones, G. C.; Stephen, S. C. *Chem.—Eur. J.* **1998**, *4*, 2539–2549. (k) Lloyd-Jones, G. C.; Stephen, S. C. *Chem. Commun.* **1998**, 2321–2322. (l) Hayashi, T.; Kawatsura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 1681–1687. (m) Hayashi, T.; Kawatsura, M.; Uozumi, Y. *Chem. Commun.* **1997**, 561–562. (n) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1996**, *118*, 235–236. (o) Fiaud, J. C.; Malleron, J. L. *Tetrahedron Lett.* **1981**, *22*, 1399–1402. [W]: (p) Lehmann, J.; Lloyd-Jones, G. C. *Tetrahedron* **1995**, *51*, 8863–8874. (q) Lloyd-Jones, G. C.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1995**, *34*, 462–464. [Mo]: (r) Hughes, D. L.; Palucki, M.; Yasuda, N.; Reamer, R. A.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 2762–2768. [Rh]: (s) Ashfeld, B. L.; Miller, K. A.; Martin, S. F. *Org. Lett.* **2004**, *6*, 1321–1324. (t) Takeuchi, R.; Kitamura, N. *New J. Chem.* **1998**, *22*, 659–660. (u) Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581–5582. (v) Minami, I.; Shimizu, I.; Tsuji, J. *J. Organomet. Chem.* **1985**, *296*, 269–280. [Ru]: (w) Kawatsura, M.; Ata, F.; Hayase, S.; Itoh, T. *Chem. Commun.* **2007**, in press; doi 10.1039/b709218k. [Fe]: (x) Plietker, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 6053–6056. (y) Plietker, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 1469–1473. (z) Xu, Y.; Zhou, B. *J. Org. Chem.* **1987**, *52*, 974–977.

(5) (a) Chung, K.-G.; Miyake, Y.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2725–2729. (b) Didiuk, M. T.; Morken, J. P.; Hoveyda, A. H. *Tetrahedron* **1998**, *54*, 1117–1130. (c) Nomura, N.; RajanBabu, T. V. *Tetrahedron Lett.* **1997**, *38*, 1713–1716. (d) Didiuk, M. T.; Morken, J. P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 7273–7274. (e) Kobayashi, Y.; Ikeda, E. *J. Chem, Soc., Chem. Commun.* **1994**, 1789–1791. (f) Didiuk, M. T.; Morken J. P.; Hoveyda A. H. *Tetrahedron* **1994**, *50*, 1117–1130 and references cited therein.

(6) (a) Bricout, H.; Carpentier, J.-F.; Mortreux, A. *Tetrahedron* **1998**, *54*, 1073–1084. (b) Bricout, H.; Carpentier, J.-F.; Mortreux, A. *Tetrahedron Lett.* **1997**, *38*, 1053–1056.

(7) Bricout, H.; Carpentier, J.-F.; Mortreux, A. *Tetrahedron Lett.* **1996**, *37*, 6105–6108.

(8) Yatsumonji, Y.; Okada, O.; Tsubouchi, A.; Takeda, T. *Tetrahedron* **2006**, *62*, 9981–9987.

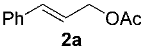
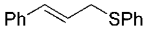
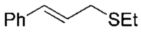
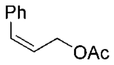
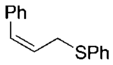
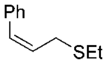
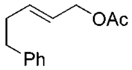
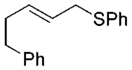
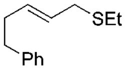
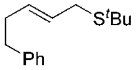
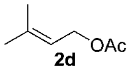
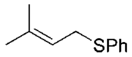
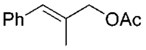
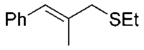
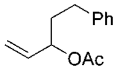
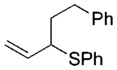
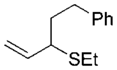
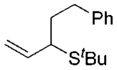
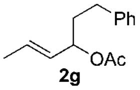
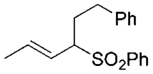
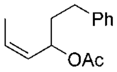
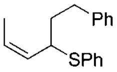
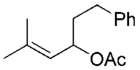
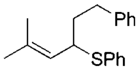
(9) (a) Komine, N.; Sako, A.; Hirahara, S.; Hirano, M.; Komiya, S. *Chem. Lett.* **2005**, *34*, 246–247. (b) Tsutsumi, K.; Yabukami, T.; Fujimoto, K.; Kawase, T.; Morimoto, T.; Kakiuchi, K. *Organometallics* **2003**, *22*, 2996–2999. (c) Frank, M.; Gais, H.-J. *Tetrahedron: Asymmetry* **1998**, *9*, 3353–3357. (d) Goux, C.; Lhoste, P.; Sinou, D. *Tetrahedron* **1994**, *50*, 10321–10330. (e) Kang, S.-K.; Park, D.-C.; Jeon, J.-H.; Rho, H.-S.; Yu, C.-M. *Tetrahedron Lett.* **1994**, *35*, 2357–2360. (f) Goux, C.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* **1992**, *33*, 8099–8102. (g) Deardorff, D. R.; Linde, R. G., II; Martin, A. M.; Shulman, M. J. *J. Org. Chem.* **1989**, *54*, 2759–2762. (h) Auburn, P. R.; Whelan, J.; Bosnich, B. *J. Chem, Soc., Chem. Commun.* **1986**, 146–147. (i) Trost, B. M.; Scanlan, T. S. *Tetrahedron Lett.* **1986**, *27*, 4141–4144.

(10) Kondo, T.; Morisaki, Y.; Uenoyama, S.; Wada, K.; Mitsudo, T. *J. Am. Chem. Soc.* **1999**, *121*, 8657–8658.

(11) A stereoisomeric mixture of the linear sulfide **3f** (*E*:*Z* = 81:19) and the branched isomer **3k** (82%, **3f**:**3k** = 76:24) was obtained by the reaction of the secondary allylic acetate **2f** with **4b** in bright light in the absence of BHT. We found that the branched sulfide **3k** was completely isomerized into the linear isomer **3f** by irradiation with fluorescent light for 12 h.

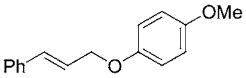
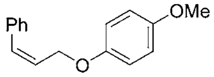
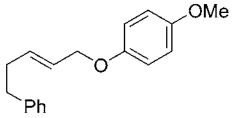
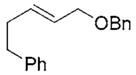
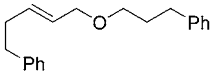
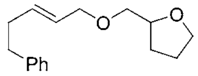
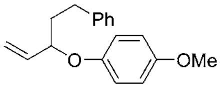
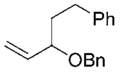
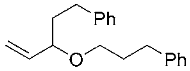
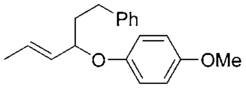
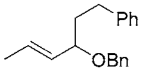
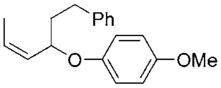
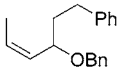
(12) The optically active allylic acetate (*R*)-**2j** was prepared from commercially available (*R*)-oct-1-en-3-ol (ACROS) by acetylation with Ac$_2$O.

Table 1. Nickel(0)-Catalyzed Reaction of Allylic Acetates **2** with Thiols **4**[a]

entry	allylic acetate	NuH	product (yield / %)[b]
1[c]	 **2a**	**4a**	 **3a** (96)
2[d]	**2a**	**4b**	 **3b** (95)
3[c]	 **2b**	**4a**	 **3c** (91)
4[d]	**2b**	**4b**	 **3d** (79)
5[c]	 **2c**	**4a**	 **3e** (90)
6[d]	**2c**	**4b**	 **3f** (91)
7[d]	**2c**	**4c**	 **3g** (88)
8[c]	 **2d**	**4a**	 **3h** (89)
9[d]	 **2e**	**4b**	 **3i** (97)
10[c,e]	 **2f**	**4a**	 **3j** (87)
11[d,e]	**2f**	**4b**	 **3k** (80)
12[d,e]	**2f**	**4c**	 **3l** (78)
13[c,e]	 **2g**	**4a**	 **5** (81)[f] E:Z = 94:6
14[c,e]	 **2h**	**4a**	 **3m** (78) Z:E = 95:5
15[c,e]	 **2i**	**4a**	 **3n** (78)

[a] The reaction was carried out with 1.0 equiv of allylic acetate, 1.2 equiv of thiol, 1.2 equiv of NaH, and 5 mol % of $Ni[P(OEt)_3]_4$. [b] Isolated yield. No formation of the corresponding regioisomer was detected by NMR analysis of the crude reaction mixture. [c] Carried out in THF/DMF at reflux for 20 h. [d] Carried out in THF/DMF at 50 °C for 20 h. [e] Carried out in the presence of a trace amount of BHT. [f] Isolated after oxidation with MCPBA (10 equiv) at room temperature for 1 h.

Table 2. Nickel(0)-Catalyzed Reaction of Allylic Acetates **2** with Alcohols and Phenols **7**[a]

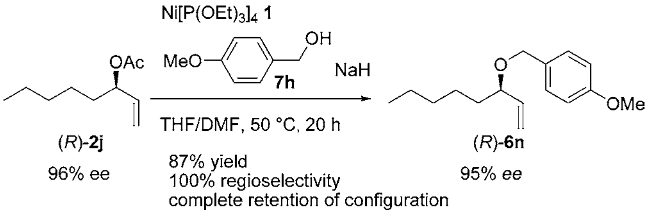
entry	allylic acetate	NuH	product (yield / %)[b]
1	**2a**	**7d**	 **6a** (92)
2	**2b**	**7d**	 **6b** (90)
3	**2c**	**7d**	 **6c** (90)
4	**2c**	**7e**	 **6d** (92)
5	**2c**	**7f**	 **6e** (89)
6	**2c**	**7g**	 **6f** (91)
7	**2f**	**7d**	 **6g** (79)
8	**2f**	**7e**	 **6h** (90)
9	**2f**	**7f**	 **6i** (88)
10	**2g**	**7d**	 **6j** (82)
11	**2g**	**7e**	 **6k** (87)
12[c]	**2h**	**7d**	 **6l** (81) Z:E = 92:8
13	**2h**	**7e**	 **6m** (82) Z:E = 94:6

[a] The reaction was carried out in THF/DMF at 50 °C for 20 h with 1.0 equiv of allylic acetates, 1.2 equiv of alcohol or phenol, 1.2 equiv of NaH, and 5 mol % of $Ni[P(OEt)_3]_4$, unless otherwise noted. [b] Isolated yield. No formation of the corresponding regioisomer was detected by NMR analysis of the crude reaction mixture. [c] Carried out in DMF at 120 °C for 2 h with 1.2 equiv of DBU as a base.

reaction with 4-methoxybenzyl alcohol (**7h**) as a single regioisomer with perfect retention of configuration.[13] Our results demonstrate that $Ni[P(OEt)_3]_4$ is an excellent catalyst that promotes allylic substitution with perfect retention of regiochemistry, complete retention of configuration of the asymmetric center, and excellent retention of configuration of the double bond.

Evans and Nelson have demonstrated that a rhodium complex-catalyzed alkylation of an enantiomerically enriched (*E*)-secondary allylic carbonate proceeded in a regio-, stereo-, and enantiospecific manner through the formation of an *enyl*

Scheme 2



complex.[4u] The present nickel-catalyzed reaction might, therefore, proceed via the similar *enyl* intermediate.

Recently, the highly regio- and stereospecific allylic substitution catalyzed by transition metal complexes has been reported. Iron(II) complex-catalyzed allylic amination[4x] and alkylation[4y] of (*E*)-primary and secondary allylic carbonates proceed with high regioselectivity (up to 98%), leading to the completely selective formation of (*E*)-allylic compounds. Partial racemization was, however, observed in the reactions of optically active (*E*)-secondary allylic carbonates. Until now the reaction with the corresponding (*Z*)-isomers has not appeared. It has also been known that the alkylation of allylic carbonates with sodium malonate catalyzed by $[Rh(CO)_2Cl]_2$ proceeds through the preferential attack at the carbon atom bearing the leaving group irrespective of the structure of the starting carbonates.[4s] Although almost complete regioselectivity was observed in the alkylation of (*Z*)-primary allylic carbonates, the reaction of the secondary (Z)-isomers has not been investigated. The nickel catalyst **1** is suitable for the reaction of allylic acetates having a variety of substitution patterns and gives the product with total retention of regio- and stereochemistry even in the case of (Z)-secondary allylic acetates.[14]

In conclusion, we have developed a practical method for the highly regio- and stereospecific transformation of allylic acetates into sulfides and ethers using the inexpensive and air-stable nickel catalyst. Further study on the nickel(0)-promoted substitutions of allylic compounds with various nucleophiles is now in progress.

Supporting Information Available: Experimental procedures and characterization data of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL702122D

---

(13) The absolute configuration of **6n** was assigned by comparison of the optical rotation of the allylic alcohol obtained by the debenzylation of **6n** (2,3-dichloro-5,6-dicyano-*p*-benzoquinone) with that of the starting allylic alcohol. The enantiomeric excess was determined by GC analysis with a Chiraldex B-DM column for **2j** and HPLC analysis with a CHIRALCEL OD-H column for **6n**.

(14) Palladium(0)-catalyzed regio- and stereospecific allylic substitution with retention of configuration of the allylic chiral center of the (*Z*)-4-phenylbut-3-en-2-yl carbonate has been reported. However, the complete *Z*→*E* isomerization took place when the (*Z*)-pent-3-en-2-yl carbonate was used; Kazmaier, U.; Zumpe, F. L. *Angew. Chem., Int. Ed.* **2000**, *39*, 802−804.