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Formation of Chiral C(sp^3)−C(sp) Bond by Allylic Substitution of Secondary Allylic Picolinates and Alkynyl Copper Reagents

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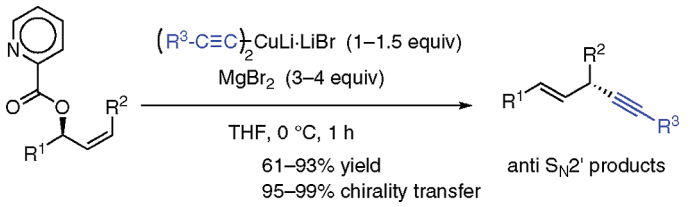

To establish allylic substitution of secondary allylic alcohol derivatives with alkynyl copper reagents, allylic esters bearing the (2-pyridine)CO_2-, (2-pyrazine)CO_2-, $(EtO)_2PO_2$-, $C_6F_5CO_2$-, *o*-(Ph_2P)-$C_6H_4CO_2$-, $MeOCO_2$-, or AcO- group were examined. First, picolinate (R^1 = Me, R^2 = CH_2OPMB) was subjected to reaction with $(TMS\text{-}C{\equiv}C)_2CuLi \cdot LiBr$ at 0 °C. Although no substitution took place, $MgBr_2$ (3 equiv) was found to promote the reaction to produce the anti S_N2' product in 93% yield with 94% regioselectivity and 99% chirality transfer. In contrast, substitution of the other esters with the copper reagent in the presence of $MgBr_2$ were less reactive ((2-pyrazine)CO_2-) or marginally reactive (other cases). Generality of the substitution using picolinates was established with five picolinates (R^1 = Me, $Ph(CH_2)_2$, $PMBO(CH_2)_3$; R^2 = Me, CH_2OPMB, CH_2OTBS, C_5H_{11}, *c*-C_6H_{11}) and seven alkynyl copper reagents (R^3 = TMS, Ph, *p*-$TBSOC_6H_4$, *p*- and *o*-$MeOC_6H_4$, *p*-MeC_6H_4, *p*-FC_6H_4), furnishing anti S_N2' products in 61−93% yields with high regioselectivity (usually >90%) and high chirality transfer (usually >95%). In addition, transformation of the products was briefly studied.

Introduction

Allylic substitution of secondary allylic alcohol derivatives with organocopper reagents is an attractive method of forming a C−C bond on chiral carbons.[1] Although good leaving groups to attain high levels of regioselectivity and chirality transfer have been established for alkyl (sp^3-C) copper reagents, less reactive aryl and alkenyl (sp^2-C) copper reagents generally give lower efficiencies except for the case where substrates are activated or sterically biased.[2] To overcome this limitation, we have introduced the picolinates **1**, which undergo anti S_N2' displacement with a broad range of sp^2-C copper reagents to afford **2** highly efficiently (Scheme 1).[3] We then switched our attention to allylic substitution with alkynyl (sp-C) copper reagents. Generally, the sp-C copper reagents are poor nucleophiles for 1,4-addition to enones,[4] though methods to accomplish the addition have been published.[5] Probably for the same reason, allylic substitution with sp-C reagents was reported once using racemic secondary allylic bromides,[6] which are generally more reactive than allylic esters. However, the

(1) (a) Negishi, E.; Liu, F. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 1. (b) Kar, A.; Argade, N. P. *Synthesis* **2005**, 2995–3022.

(2) (a) Didiuk, M. T.; Morken, J. P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 7273–7274. (b) Yamazaki, T.; Umetani, H.; Kitazume, T. *Tetrahedron Lett.* **1997**, *38*, 6705–6708. (c) Spino, C.; Beaulieu, C. *J. Am. Chem. Soc.* **1998**, *120*, 11832–11833. (d) Belelie, J. L.; Chong, J. M. *J. Org. Chem.* **2002**, *67*, 3000–3006. (e) Perrone, S.; Knochel, P. *Org. Lett.* **2007**, *9*, 1041–1044.

(3) (a) Kiyotsuka, Y.; Acharya, H. P.; Katayama, Y.; Hyodo, T.; Kobayashi, Y. *Org. Lett.* **2008**, *10*, 1719–1722. (b) Kiyotsuka, Y.; Kobayashi, Y. *Tetrahedron Lett.* **2008**, *49*, 7256–7259. (c) Kiyotsuka, Y.; Katayama, Y.; Acharya, H. P.; Hyodo, T.; Kobayashi, Y. *J. Org. Chem.* **2009**, *74*, 1939–1951.

(4) (a) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210–7211. (b) House, H. O.; Umen, M. J. *J. Org. Chem.* **1973**, *38*, 3893–3901. (c) Corey, E. J.; Floyd, D.; Lipshutz, B. H. *J. Org. Chem.* **1978**, *43*, 3418–3420.

(5) (a) Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 3244–3245. (b) Knöpfel, T. F.; Zarotti, P.; Ichikawa, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 9682–9683. (c) Pellegrinet, S. C.; Goodman, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 3116–3117.

(6) Matveeva, E. D.; Yerin, A. S.; Kurts, A. L. *Russ. J. Org. Chem.* **2000**, *36*, 15721576; *Zh. Org. Khim.* **2000**, *36*, 1619−1623.

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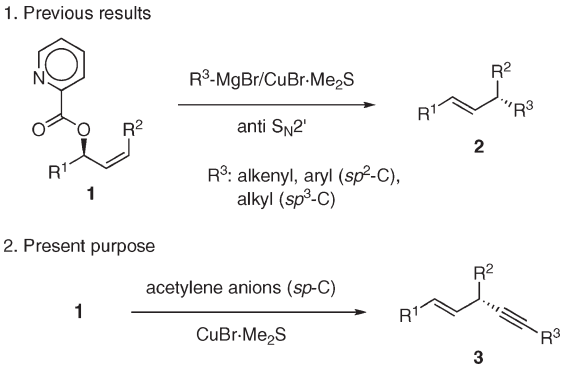
SCHEME 1. Allylic Substitution: Previous Results and Present Purpose



regioselectivity in the report is uncertain. Furthermore, the method suffers from low regioselectivity in the preparation of the bromides and seems difficult to apply to optically active bromides. On the other hand, substitution of 1-halo-2-alkenes and 3-halo-1-alkenes takes place at the primary carbon.[6,7] To establish the substitution at secondary carbons, we examined the reaction of picolinate *rac*-**1a** and other esters **4**−**9** (Figure 1) with $(TMS\text{-}C{\equiv}C)_2CuLi\cdot LiBr$.[8,9]

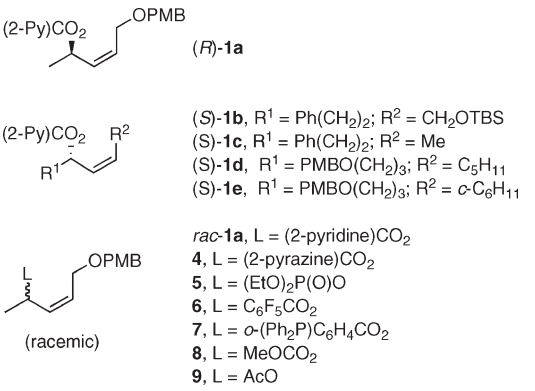


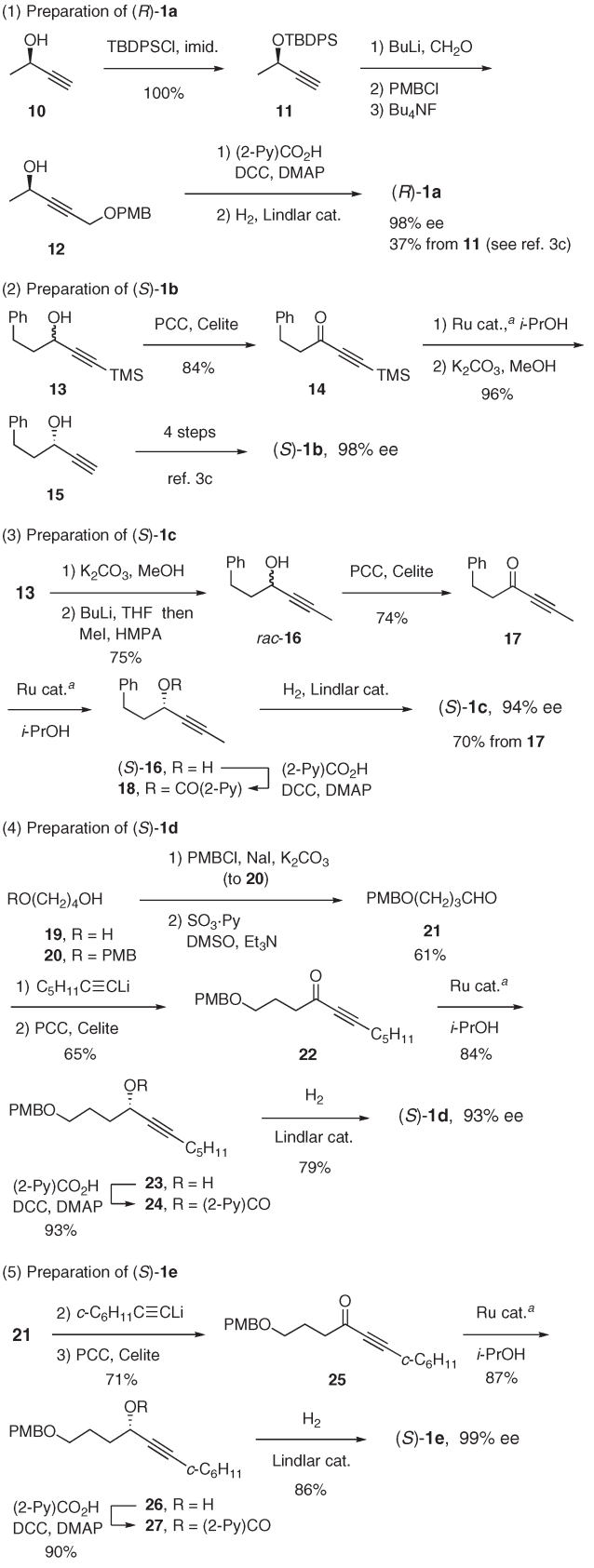
FIGURE 1. Substrates for the present investigation.

Although no esters underwent the substitution, *rac*-**1a** was found to be activated by $MgBr_2$ to produce **3a** with high levels of regio- and stereoselectivities. Herein, we present the results obtained with picolinates (*R*)-**1a** and (*S*)-**1b**−**1e**.

Results and Discussion

Preparation of Allylic Esters. Optically active allylic picolinates (*R*)-**1a** and (*S*)-**1b**−**1e** were prepared by methods delineated in Scheme 2. The optically active propargylic alcohol **10**, kindly gifted from a company, was converted to the TBDPS ether **11**, which was transformed to the most

SCHEME 2. Synthesis of Allylic Esters[a]



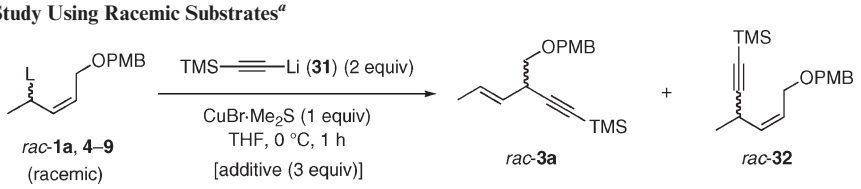
[a]Ru cat. = Ru[(*S*,*S*)-TsDPEN](*p*-cymene)

(7) (a) Jeffery, T. *Tetrahedron Lett*. **1989**, *30*, 2225–2228. (b) Mignani, G.; Chevalier, C.; Grass, F.; Allmang, G.; Morel, D. *Tetrahedron Lett*. **1990**, *31*, 5161–5164. and references therein.

(8) Asymmetric formation of $C(sp^3)-C(sp)$ bond by using substitution at propargylic carbon: (a) Inada, Y.; Nishibayashi, Y.; Uemura, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 7715–7717. (b) Smith, S. W.; Fu, G. C. *J. Am. Chem. Soc*. **2008**, *130*, 12645–12647. (c) Idem *Angew. Chem., Int. Ed.* **2008**, *47*, 9334–9336. (d) Rubenbauer, P.; Herdtweck, E.; Strassner, T.; Bach, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 10106–10109.

(9) Other reactions to create racemic $C(sp^3)-C(sp)$ bonds: (a) Shirakura, M.; Suginome, M. *J. Am. Chem. Soc*. **2008**, *130*, 5410–5411. (b) Idem *Org. Lett*. **2009**, *11*, 523–526. (c) Rayabarapu, D. K.; Tunge, J. A. *J. Am. Chem. Soc*. **2005**, *127*, 13510–13511.

TABLE 1. Preliminary Study Using Racemic Substrates[a]



entry	substrate	L	additive[a]	yield	*rac*-**3a**:**32**[b]
1	*rac*-**1a**	(2-Py)CO_2		0[c]	
2	*rac*-**1a**	(2-Py)CO_2	$MgBr_2$	88	94:6
3	*rac*-**1a**	(2-Py)CO_2	$ZnBr_2$	0[c]	
4	**4**	(2-pyrazine)CO_2		0[c]	
5	**4**	(2-pyrazine)CO_2	$MgBr_2$	51[d]	92:8
6	**5**	$(EtO)_2P(O)O$		nr[e]	
7	**5**	$(EtO)_2P(O)O$	$MgBr_2$	12[f]	nd[g]
8	**5**	$(EtO)_2P(O)O$	$ZnBr_2$	nr[e]	
9	**6**	$C_6F_5CO_2$		nr[e]	
10	**6**	$C_6F_5CO_2$	$MgBr_2$	nr[e]	
11	**6**	$C_6F_5CO_2$	$ZnBr_2$	nr[e]	
12	**7**	*o*-$(Ph_2P)C_6H_4CO_2$		0[h]	
13	**7**	*o*-$(Ph_2P)C_6H_4CO_2$	$MgBr_2$	0[h]	
14	**7**	*o*-$(Ph_2P)C_6H_4CO_2$	$ZnBr_2$	0[h]	
15	**8**	$MeOCO_2$		nr[e]	
16	**8**	$MeOCO_2$	$MgBr_2$	nr[e]	
17	**9**	AcO		nr[e]	
18	**9**	AcO	$MgBr_2$	nr[e]	

[a]Three equivalents. [b]Determined by ^{1}H NMR spectroscopy. [c]Alcohol **30** was obtained. [d]Unidentified products were coproduced. [e]No reaction after 18 h at rt. [f]Allylic bromides **33a** and **33b** were produced in 88% NMR yield ($J_{olefinic\text{-}H}$ = 15 Hz). [g]Not determined. [h]The corresponding phosphine oxide was produced.

frequently examined substrate (*R*)-**1a** with 98% ee according to the method published by us.[3c] Previously, (*S*)-**1b** and -**1c** were prepared in ca. 90% ee through the Yadav's transformation[10] of the epoxy chlorides to propargylic alcohol **15**.[3c] In the present investigation, we used the asymmetric hydrogen transfer reaction developed by Noyori[11] to deliver (*S*)-**1b** and -**1c** with higher ee of 98% and 94%, respectively. Similarly, asymmetric reduction of ketones **22** and **25** furnished (*S*)-**1d** and -**1e** with 93% and 99% ee, respectively. The overall yields of (*S*)-**1c**−**1e** were 30−33%.

For preliminary investigation, racemic picolinate *rac*-**1a** and **4** were prepared by applying the above method to the racemic alcohol *rac*-**12** (Scheme 3). In contrast, Lindlar reduction of *rac*-**12** to the *cis* alcohol **30** followed by esterification delivered **5**−**9** in good yields.[12]

Preliminary Study of Allylic Substitution Using Racemic Substrates. Initially, substitution was investigated in THF at 0 °C using racemic picolinate *rac*-**1a** and a related substrate **4** with (TMS-C≡C)$_2$CuLi·LiBr, which had been prepared from TMS-C≡CLi (**31**) (2 equiv) and CuBr·Me_2S (1 equiv) (Table 1). Unfortunately, these substrates underwent nucleophilic attack to the carbonyl group (entries 1 and 4). Substitution was also examined using esters **5**−**7** possessing leaving groups that are suited to sp^2-C and/or sp^3-C reagents[13−15] and esters **8** and **9** with the standard leaving groups. No reaction took place with **5**, **6**, **8**, and **9** (entries 6, 9, 15, 17), while **7** was changed to the corresponding phosphine oxide[16] (entry 12). We then envisioned participation(s) of $MgBr_2$ and $ZnBr_2$ in the reaction, as a Lewis acid to activate the leaving groups and/or as a source to generate $[R_2Cu]^-MBr^+$ (M = Mg, Zn), which was expected to be more reactive than lithium cuprate on the analogy of the substitution with sp^3- and sp^2-C reagents.[17] In practice, $MgBr_2$ (3 equiv) was found to assist the substitution of picolinate *rac*-**1a** (1 equiv) and (TMS-C≡C)$_2$CuLi·LiBr (1 equiv), furnishing *rac*-**3a** in 88% yield with 94% regioselectivity over its regioisomer *rac*-**32** after 1 h at 0 °C (entry 2).[18] Use of lower

(10) Yadav, J. S.; Deshpande, P. K.; Sharma, G. V. M. *Tetrahedron* **1990**, *46*, 7033–7046.

(11) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738–8739.

(12) Attempted Lindlar reduction of the phosphate of *rac*-**12** produced deoxygenated compound, while the carbonate and the acetate of *rac*-**12** produced saturated compounds.

(13) Phosphates: (a) Yanagisawa, A.; Nomura, N.; Noritake, Y.; Yamamoto, H. *Synthesis* **1991**, 1130–1136. (b) Torneiro, M.; Fall, Y.; Castedo, L.; Mourino, A. *J. Org. Chem.* **1997**, *62*, 6344–6352. (c) Calaza, M. I.; Hupe, E.; Knochel, P. *Org. Lett.* **2003**, *5*, 1059–1061. (d) Piarulli, U.; Daubos, P.; Claverie, C.; Roux, M.; Gennari, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 234–236. (e) Soorukram, D.; Knochel, P. *Org. Lett.* **2004**, *6*, 2409–2411. (f) L. Belelie, J.; Chong, J. M. *J. Org. Chem.* **2001**, *66*, 5552–5555. (g) Whitehead, A.; McParland, J. P.; Hanson, P. R. *Org. Lett.* **2006**, *8*, 5025–5028. (h) Niida, A.; Tanigaki, H.; Inokuchi, E.; Sasaki, Y.; Oishi, S.; Ohno, H.; Tamamura, H.; Wang, Z.; Peiper, S. C.; Kitaura, K.; Otaka, A.; Fujii, N. *J. Org. Chem.* **2006**, *71*, 3942–3951.

(14) Pentafluorobenzoates: (a) Harrington-Frost, N.; Leuser, H.; Calaza, M. I.; Kneisel, F. F.; Knochel, P. *Org. Lett.* **2003**, *5*, 2111–2114. (b) Calaza, M. I.; Yang, X.; Soorukram, D.; Knochel, P. *Org. Lett.* **2004**, *6*, 529–531. (c) Leuser, H.; Perrone, S.; Liron, F.; Kneisel, F. F.; Knochel, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 4627–4631. (d) Soorukram, D.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3686–3689. (e) Soorukram, D.; Knochel, P. *Org. Lett.* **2007**, *9*, 1021–1023. (f) See ref 2e.

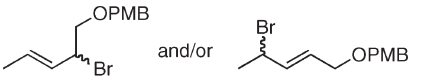
(15) *o*-Diphenylphosphinobenzoates: (a) Breit, B.; Demel, P. *Adv. Synth. Catal.* **2001**, *343*, 429–432. (b) Demel, P.; Keller, M.; Breit, B. *Chem.—Eur. J.* **2006**, *12*, 6669–6683. (c) Breit, B.; Herber, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3790–3792. (d) Herber, C.; Breit, B. *Chem.—Eur. J.* **2006**, *12*, 6684–6691. (e) Herber, C.; Breit, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 5267–5269.

(16) Nieto, S.; Metola, P.; Lynch, V. M.; Anslyn, E. V. *Organometallics* **2008**, *27*, 3608–3610.

(17) For example: (a) Breit, B.; Demel, P.; Studte, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3786–3789. (b) Breit, B.; Demel, P.; Grauer, D.; Studte, C. *Chem. Asian J.* **2006**, *1*, 586–597. See also refs 2a, 3, and 14a.

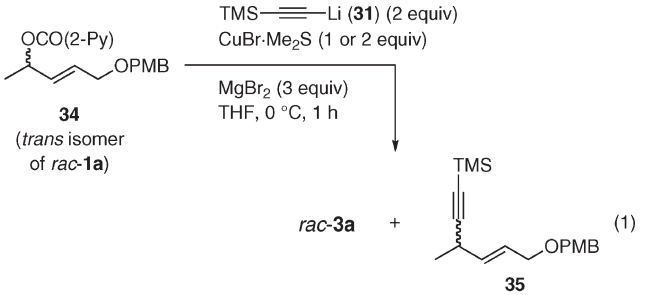
(18) Attempted reaction in the presence of $MgBr_2$ without CuBr·Me_2S afforded alcohol **30**.

temperatures of −20 and −60 °C merely retarded the reaction without improving the regioselectivity. Pyrazinecarboxylate **4** was activated by $MgBr_2$ as well, but to somewhat low extent, producing *rac*-**3a** in 51% yield with unidentified products (entry 5), whereas substitution of phosphate **5** was marginally promoted by $MgBr_2$ at 0 °C for 1 h, and further reaction at room temperature for 18 h produced *rac*-**3a** in 12% yield and a regioisomeric mixture of allylic bromides **33a**/**33b** (1:1)[19] in 88% yield (entry 7). No other substrates **6**−**9** were activated by $MgBr_2$ (entries 10, 13, 16, 18). In contrast to the above results, $ZnBr_2$ (3 equiv) did not promote substitution of picolinate *rac*-1a and other substrates **5**−**7** with $(TMS\text{-}C{\equiv}C)_2CuLi\cdot LiBr$ at 0 °C for 1 h, and further reactions at room temperatures resulted in production of alcohol **30** from *rac*-**1a**, recovery of **5** and **6**, oxidation of **7**, respectively (entries 3, 8, 11, and 14).



33a **33b**

Next, substitution of *trans* allylic picolinate **34** with $(TMS\text{-}C{\equiv}C)_2CuLi\cdot LiBr$ was investigated in the presence of $MgBr_2$ to afford a mixture of *rac*-**3a** and the regioisomer **35** (eq 1). Another copper reagent, $TMS\text{-}C{\equiv}CCu\cdot LiBr$, also produced a mixture of the regioisomers.

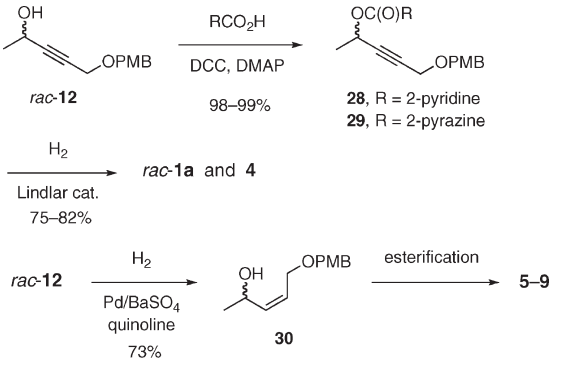


31/Cu (2 : 1) *rac*-**3a** / **35** = 64 : 36
31/Cu (1 : 1) *rac*-**3a** / **35** = 64 : 36

In addition to the different regioselectivities observed above with *rac*-**1a** (*cis* isomer) and **34** (*trans* isomer), we note that the *cis* geometry of *rac*-**1a** is retained in the regioisomer **32** (S_N2-type product), whereas the S_N2-type product in the previous substitution of picolinates with $Ph_2CuMgBr$ (sp^2-C copper reagent) is the *trans* olefin.[3] Presently, we are trying to find results to support these differences.

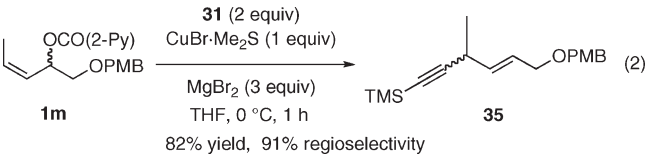
Substitution Using Optically Active Picolinates. The optimal reaction conditions were applied to (*R*)-**1a** (98% ee), which attained near perfect chirality transfer (99% CT[20]) with $(TMS\text{-}C{\equiv}C)_2CuLi\cdot LiBr$, giving anti S_N2' product (*S*)-**3a**[21] and the regioisomer **32** in 94:6 and in 93% combined yield (Table 2, entry 2). Copper reagents consisting of lithium acetylide **31** and $CuBr\cdot Me_2S$ in other ratios of 1:1 and 4:1 showed reactivity and selectivity comparable to those of the above 2:1 reagent (entries 1 and 3). These results implies an operational advantage of that the high efficiency is attained without precise measurement of $CuBr\cdot Me_2S$ for preparation of the copper reagent.

SCHEME 3. Synthesis of Racemic Allylic Esters



Alkynyl copper reagents derived from lithium acetylide **31** and other copper salts (CuCl, CuBr, CuI, CuCN) in the 2:1 ratio produced (*S*)-**3a** as well (Table 3). However, the efficiency in terms of product selectivity over bromides **3a** and **3b**, isolated yield, and/or CT was slightly lower than that obtained with **31** and $CuBr\cdot Me_2S$. On the basis of these results we used $CuBr\cdot Me_2S$ as a copper source in the following reactions.

The above substitution was applied to a range of allylic picolinates and other alkynyl coppers to assess reactivity, regioselectivity, and CT (Table 4).[22] Various methylene units and/or CH_2OR group attached to the allylic moiety did not interfere with the $MgBr_2$-promoted substitution with $(TMS\text{-}C{\equiv}C)_2CuLi\cdot LiBr$, producing anti S_N2' products (*R*)-**3b**−**d**[21] efficiently from (*S*)-**1b**−**d** (entries 1−3). In contrast, a more bulky *c*-hexyl group at the olefinic carbon of (*S*)-**1e** reduced efficiency in selectivity and yield (entry 4). An additional entry is the reaction of racemic picolinate **1m**[23] to produce **35**, which is the regioisomer of *rac*-**3a** (eq 2).



Phenylacetylenic copper, $(Ph{-}C{\equiv}C)_2CuLi\cdot LiBr$, prepared from $Ph{-}C{\equiv}CLi$ (**36**, 2 equiv) and $CuBr\cdot Me_2S$ (1 equiv), was found to be less reactive than $(TMS\text{-}C{\equiv}C)_2CuLi\cdot LiBr$, and 18% of picolinate (*R*)-**1a** was recovered after 1 h at 0 °C. This problem was operationally solved with

(19) Bromination of *rac*-**1a** with $CuBr\cdot Me_2S$ (0.5 equiv) and $MgBr_2$ (3 equiv) at rt proceeded slowly to afford, after 18 h, *trans* allylic bromides **33a** and **33b** in a 2:3 ratio by ^1H NMR spectroscopy ($J_{olefinic\text{-}H} = 15$ Hz).

(20) CT, defined as (% ee of product/% ee of substrate) × 100, was determined by chiral HPLC.

(21) Acetylenes (*S*)-**3a** and (*R*)-**3b** were transformed to the known compounds, respectively, and their $[\alpha]_D$ values were compared to determine their absolute configurations. See the Experimental Section for the former and the Supporting Information for the latter. Other products were assigned by analogy.

(22) Signals corresponding to the regioisomers of the products shown in Table 4 are assigned by analogy to those for **32** (mostly δ 1.3 (d) for CH_3, 4.1 (s) for CH_2OPMB, 5.5−5.6 (m) for CH=CH).

(23) Prepared by the following method:

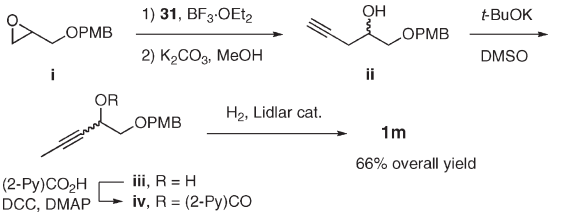
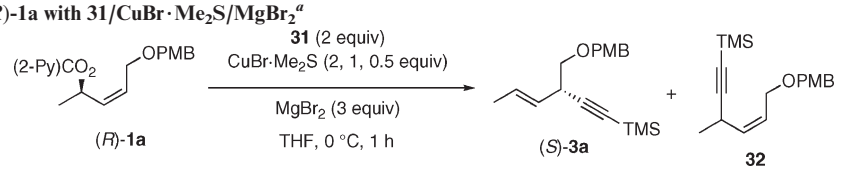


TABLE 2. Reaction of (*R*)-1a with 31/CuBr·Me_2S/$MgBr_2$[a]



entry	**31**/CuBr·Me_2S/$MgBr_2$, equiv	ratio[b] of (*S*)-**3a**:**32**:**30**:(*R*)-**1a**	yield, %[c]	CT, %[d]
1	2/2/3	93:7:0:0	86	99
2	2/1/3	94:6:0:0	93	99
3	2/0.5/3	91:5:4:0	81	nd[e]

[a]In the absence of $MgBr_2$, reactions in entries 1−3 gave alcohol **30** in 13%, 23%, and 45% yields, respectively. [b]Determined by ^1H NMR spectroscopy. [c]Isolated yield of (*S*)-**3a** and **32**. [d]Determined by chiral HPLC analysis. [e]Not determined.

TABLE 3. Effect of CuX on Substitution[a]

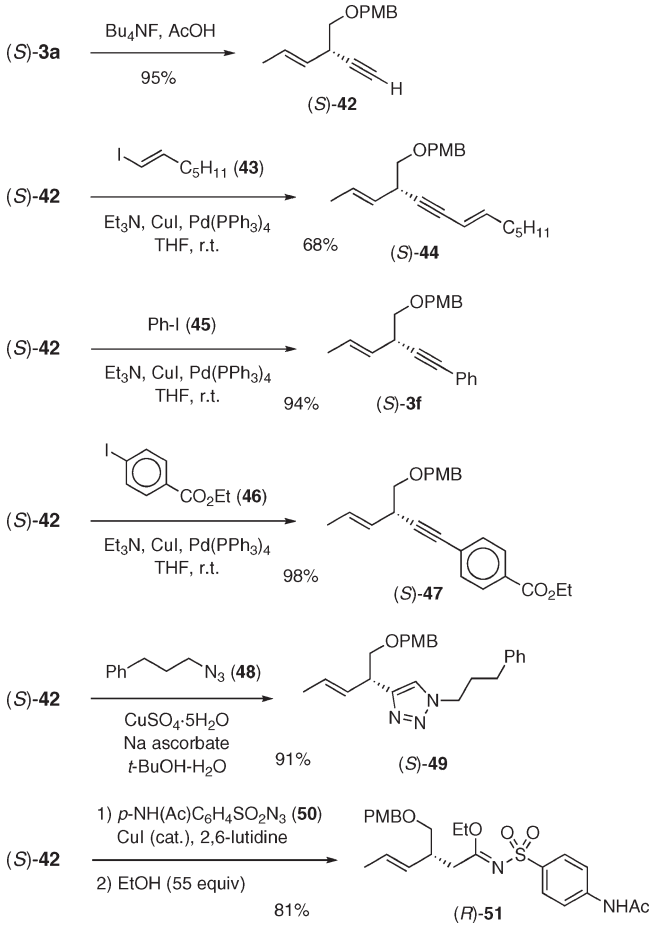
entry	CuX	ratio of (*S*)-**3a**:**32**:**30**:(*R*)-**1a**	yield, %[b]	CT, %[c]
1	CuBr	93:7:0:0	74[d]	96
2	CuCl	86:6:0:8	57[d]	95
3	CuI	94:6:0:0	83	91
4	CuCN	81:6:6:7	nd[e]	nd[e]

[a]Reactions of (*R*)-**1a** with copper reagents derived from **31** (2 equiv) and CuX (1 equiv) were examined in the presence of $MgBr_2$ (3 equiv) at 0 °C for 1 h. [b]Isolated yield of (*S*)-**3a** and **32**. [c]Determined by chiral HPLC analysis. [d]Allylic bromides **33a** and **33b** were coproduced. [e]nd: not determined.

the use of 1.5 times more reagent to afford (*S*)-**3f** in 70% yield with selectivity comparable to that obtained with (TMS-C≡C-)$_2$CuLi·LiBr (entry 5). Similarly, (Ar−C≡C)$_2$CuLi·LiBr (Ar = *p*-TBSOC$_6$H$_4$, *p*-MeOC$_6$H$_4$, *o*-MeOC$_6$H$_4$, *p*-MeC$_6$H$_4$, *p*-FC$_6$H$_4$) derived from lithium acetylides **37**−**41** produced (*S*)-**3g**−**k** in good yields with high selectivity (entries 6−10). It should be noted that electron-withdrawing and -donating factors on the aromatic ring did not affect the reactivity nor selectivity of the present reaction.[24]

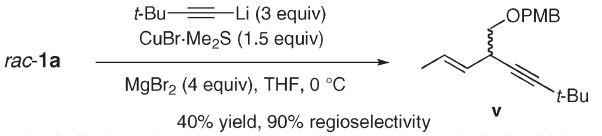
Transformation of Products. Use of the products in various ways was investigated briefly. As delineated in Scheme 4, removal of the TMS group from (*S*)-**3a** with Bu_4NF and AcOH (1:1) in THF produced acetylene (*S*)-**42** in 95% yield.[25] Sonogashira reaction of (*S*)-**42** with iodides **43** and **45** under the standard conditions afforded (*S*)-**44** and -**3f** in 68% and 94% yields, respectively. Although the latter product is synthesized directly by the present substitution using PhC≡CH (Table 4, entry 5), the Sonogashira route would be useful for aryl and alkenyl iodides bearing a carbonyl group(s) as is seen in the synthesis of (*S*)-**47** from acetylene (*S*)-**42** and iodide **46**. Copper-catalyzed 1,3-dipolar reaction[26] of (*S*)-**42** with azide **48** afforded triazole

SCHEME 4. Transformations of (*S*)-3a



(*S*)-**49** in high yield. On the other hand, copper-catalyzed reaction[27] with *p*-NH(Ac)C$_6$H$_4$SO$_2$N$_3$ (**50**) followed by further reaction with EtOH afforded imidate (*R*)-**51** in 81% yield.[28]

(24) Presently, reaction of racemic picolinate *rac*-**1a** with (*t*-BuC≡C)$_2$-CuLi·LiBr afforded S_N2' product **v** in moderate yield.



(25) Similarly, (*R*)-**3b** was converted to acetylene alcohol, which was further transformed to the known compound for determination of the absolute structure of (*R*)-**3b** as described in Supporting Information. On the other hand, reaction with Bu_4NF gave a mixture of products.

(26) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599.

(27) Cho, S. H.; Yoo, E. J.; Bae, I.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 16046–16047.

(28) A similar reaction of *rac*-**42** with azide **50** in aqueous *t*-BuOH gave amide **vi** in 47% yield.

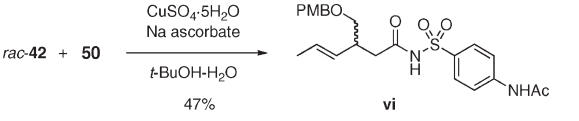
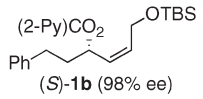
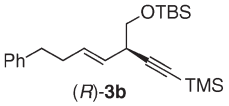
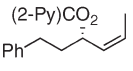
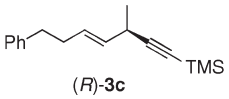
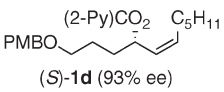
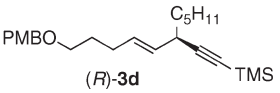
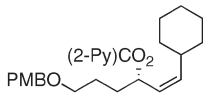
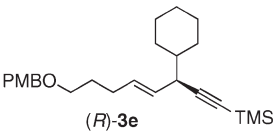
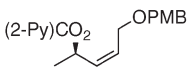
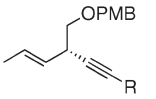


TABLE 4. Substitution of Picolinates with Alkynyl Copper Reagents[a]

entry	picolinate	ArC≡CLi (equiv)	CuBr·Me_2S (equiv)	$MgBr_2$ (equiv)	product	isolated yield[b,c]	regio-selectivity[b,d]	CT[b,e]
1	 (*S*)-**1b** (98% ee)	TMSC≡CLi (**31**) (2)	1	3	 (*R*)-**3b**	83	97	98
2	 (*S*)-**1c** (94% ee)	**31** (2)	1	3	 (*R*)-**3c**	80	98	98
3	 (*S*)-**1d** (93% ee)	**31** (2)	1	3	 (*R*)-**3d**	89	94	98
4	 (*S*)-**1e** (99% ee)	**31** (2)	1	3	 (*R*)-**3e**	66	86	nd[f]
5	 (*R*)-**1a** (98% ee)	PhC≡CLi (**36**) (3)	1.5	4	 (*S*)-**3f** (R = Ph)	70	95	96
6	(*R*)-**1a** (98% ee)	*p*-$TBSOC_6H_4C$≡CLi (**37**) (3)	1.5	4	(*S*)-**3g** (R = *p*-$TBSOC_6H_4$)	61	93	95
7	(*R*)-**1a** (98% ee)	*p*-$MeOC_6H_4C$≡CLi (**38**) (3)	1.5	4	(*S*)-**3h** (R = *p*-$MeOC_6H_4$)	67	92	97
8	(*R*)-**1a** (98% ee)	*o*-$MeOC_6H_4C$≡CLi (**39**) (3)	1.5	4	(*S*)-**3i** (R = *o*-$MeOC_6H_4$)	89	97	97
9	(*R*)-**1a** (98% ee)	*p*-MeC_6H_4C≡CLi (**40**) (3)	1.5	4	(*S*)-**3j** (R = *p*-MeC_6H_4)	84	94	97
10	(*R*)-**1a** (98% ee)	*p*-FC_6H_4C≡CLi (**41**) (3)	1.5	4	(*S*)-**3k** (R = *p*-FC_6H_4)	88	95	98

[a]Reactions in entries 1−4 were carried out with **31** (2 equiv), CuBr·Me_2S (1 equiv), and $MgBr_2$ (3 equiv) in THF at 0 °C for 1 h. Reactions in entries 5−10 were carried out with Ar-C≡CLi (3 equiv), CuBr·Me_2S (1.5 equiv), and $MgBr_2$ (4 equiv) in THF at 0 °C for 1 h. [b]In percent. [c]Combined yield of the regioisomers. [d]Determined by ^1H NMR spectroscopy. [e]Determined by chiral HPLC analysis. [f]HPLC signals on several chiral columns were separated incompletely.

Conclusions

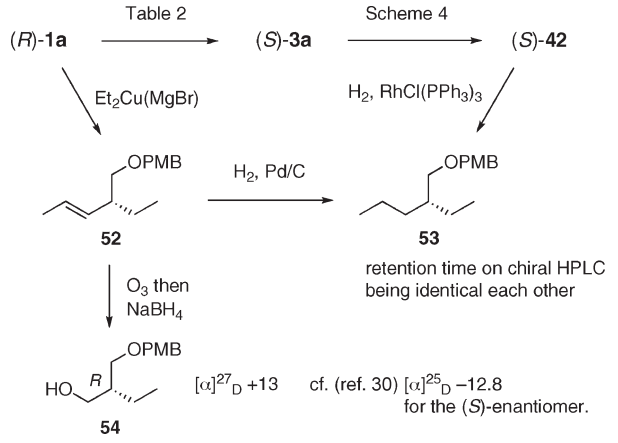
We have attained allylic substitution with alkynyl copper reagents using picolinates **1** as allylic esters in the presence of $MgBr_2$ to produce the anti S_N2' products in 61−93% yields with high regioselectivity (usually >90%) and high chirality transfer (usually >95%). The picolinates were prepared by several methods as shown in Scheme 2 using Lindlar hydrogenation to construct the requisite *cis* olefins, which are also prepared by Wittig reaction.[3] Thus, the present substitution offers a convenient and efficient method for construction of enantiomerically enriched C(sp)−C(sp^3) bond. In addition, transformation of the products was briefly studied.

Experimental Section

General Procedure of Allylic Substitution. (Table 2, entry 2) To an ice-cold solution of trimethylsilylacetylene (0.032 mL, 0.231 mmol) in THF (0.4 mL) was added BuLi (0.13 mL, 1.60 M in hexane, 0.208 mmol) dropwise. After 30 min at 0 °C, a solution of $MgBr_2$ (1.60 mL, 0.20 M in THF, 0.320 mmol) and CuBr·Me_2S (21.6 mg, 0.105 mmol) was added to the solution. The resulting mixture was stirred at 0 °C for 30 min, and a solution of (*R*)-**1a** (34.1 mg, 0.105 mmol, 98% ee) in THF (1 mL) was added to it dropwise. The mixture was stirred at 0 °C for 1 h and diluted with EtOAc and saturated NH_4Cl with vigorous stirring. The layers were separated, and the aqueous layer was extracted with EtOAc twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford a 94:6 mixture of (*S*)-**3a** and **32**[29] (29.5 mg, 93%, 94% regioselectivity): $[\alpha]^{26}_D$ +57.8 (*c* 0.816, $CHCl_3$); IR (neat) 2172, 1514, 1250, 843 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.17 (s, 9 H), 1.71 (ddd, *J* = 7, 2, 2 Hz, 3 H), 3.28−3.39 (m, 1 H), 3.42 (dd, *J* = 9, 7 Hz, 1 H), 3.51 (dd, *J* = 9, 6 Hz, 1 H), 3.80 (s, 3 H), 4.51 (s, 2 H), 5.43 (ddq, *J* = 15, 6, 2 Hz, 1 H), 5.78 (ddq, *J* = 15, 2, 7 Hz, 1 H), 6.88 (d, *J* = 9 Hz, 2 H), 7.27 (d, *J* = 9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.23 (−), 17.9 (−), 36.4 (−), 55.3 (−), 72.7 (+), 72.9 (+), 87.7 (+), 105.6 (+), 113.8 (−), 127.3 (−), 127.7 (−), 129.3 (−), 130.4 (+), 159.2 (+); HRMS (FAB) calcd for $C_{18}H_{26}O_2SiNa$ [(M + Na)$^+$] 325.1600, found 325.1598. The enantiomeric information (97% ee, 99% CT) was determined by chiral HPLC analysis: Chiralcel AS-H; hexane/*i*-PrOH = 98/2, 0.2 mL/min, rt; t_R (min) = 27.6 (*R*), 38.9 (*S*).

(29) The substitution was repeated several times to collect enough quantity of the minor isomer for ^1H NMR spectroscopy, by which the structure **32** including *cis* olefin ($J_{olefinic\text{-}H}$ = 11 Hz) was determined. See Supporting Information.

Determination of the Absolute Configuration of (*S*)-3a.



(*R*,*E*)-1-[(2-Ethylpent-3-enyloxy)methyl]-4-methoxybenzene (52). To a suspension of $CuBr \cdot Me_2S$ (23.8 mg, 0.116 mmol) in THF (3 mL) was added EtMgBr (0.23 mL, 1.00 M in THF, 0.23 mmol) slowly at −60 °C. After 30 min at −60 °C, a solution of (*R*)-**1a** (37.7 mg, 0.116 mmol, 98% ee) in THF (1 mL) was added to the mixture dropwise. The mixture was allowed to warm to −50 °C for 1 h and was diluted with EtOAc and saturated NH_4Cl with vigorous stirring. The layers were separated, and the aqueous layer was extracted with EtOAc twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **52** (23.4 mg, 86%): $[\alpha]^{25}_D$ −6.4 (*c* 0.346, $CHCl_3$); IR (neat) 1612, 1513, 1248, 1096, 1038 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, J = 8 Hz, 3 H), 1.12−1.38 (m, 1 H), 1.46−1.63 (m, 1 H), 1.67 (dd, J = 6, 2 Hz, 3 H), 2.11−2.25 (m, 1 H), 3.30 (dd, J = 9, 7 Hz, 1 H), 3.33 (dd, J = 9, 7 Hz, 1 H), 3.80 (s, 3 H), 4.43 (s, 2 H), 5.23 (ddq, J = 15, 8, 2 Hz, 1 H), 5.48 (ddq, J = 15, 1, 6 Hz, 1 H), 6.87 (d, J = 9 Hz, 2 H), 7.25 (d, J = 9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.5 (−), 18.2 (−), 24.6 (+), 44.6 (−), 55.3 (−), 72.6 (+), 73.8 (+), 113.7 (−), 126.2 (−), 129.2 (−), 130.9 (+), 132.6 (−), 159.1 (+); HRMS (FAB) calcd for $C_{15}H_{22}O_2Na$ [$(M + Na)^+$] 257.1517, found 257.1522. The enantiomeric information (98% ee, 100% CT) was determined by chiral HPLC: Chiralcel OB-H; hexane/*i*-PrOH = 98/2, 0.2 mL/min, 40 °C; t_R (min) = 67.3 (*R*), 73.8 (*S*).

(*R*)-2-(4-Methoxybenzyloxymethyl)butan-1-ol (54). A stream of O_3 in O_2 was gently bubbled into a solution of **52** (25.7 mg, 0.110 mmol) in MeOH at −78 °C for 5 min. Excess O_3 remaining in the solution was purged by bubbling argon at −78 °C, and $NaBH_4$ (41 mg, 1.08 mmol) was added. After 1 h at −78 °C, saturated NH_4Cl was added to the solution, and the resulting mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to obtain a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to give **54** (19.6 mg, 79%). The ^1H NMR spectrum of **54** was identical with the data reported.[30] The specific rotation of **54** ($[\alpha]^{27}_D$ +13 (*c* 0.238, $CHCl_3$)) was opposite to that of the (*S*)-enantiomer[30] ($[\alpha]^{25}_D$ −12.8 (*c* 1.0, $CHCl_3$)), thus confirming the (*R*) chirality for **54**.

(*R*)-1-[(2-Ethylpentyloxy)methyl]-4-methoxybenzene (53) from 52. To a solution of **52** (17.4 mg, 0.0743 mmol) in EtOAc (1 mL) was added 10% Pd/C (8 mg). The mixture was stirred at rt for 1 h under H_2 atmosphere and filtered through a pad of Celite. The filtrate was concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **53** (12.2 mg, 69%): $[\alpha]^{28}_D$ −7.2 (*c* 0.166, $CHCl_3$); IR (neat) 1612, 1513, 1248, 1094, 1038 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, J = 8 Hz, 3 H), 0.86 (t, J = 8 Hz, 3 H), 1.18−1.64 (m, 7 H), 3.31 (d, J = 6 Hz, 2 H), 3.81 (s, 3 H), 4.42 (s, 2 H), 6.88 (d, J = 9 Hz, 2 H), 7.26 (d, J = 9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.1 (−), 14.6 (−), 20.1 (+), 24.0 (+), 33.3 (+), 39.6 (−), 55.4 (−), 72.7 (+), 73.0 (+), 113.8 (−), 129.2 (−), 131.1 (+), 159.1 (+). Chiralcel OB-H; hexane/*i*-PrOH = 96/4, 0.4 mL/min, 40 °C; t_R (min) = 27.8 (*S*), 34.9 (*R*).

(*S*,*E*)-1-[(2-Ethynylpent-3-enyloxy)methyl]-4-methoxybenzene ((*S*)-42). To an ice-cold solution of (*S*)-**3a** (101 mg, 0.334 mmol) in THF (0.5 mL) was added a solution of Bu_4NF (0.67 mL, 1.0 M in THF, 0.67 mmol) and AcOH (0.038 mL, 0.664 mmol) in THF (0.5 mL). The resulting solution was stirred at rt overnight and diluted with EtOAc and saturated NH_4Cl. The layers were separated, and the aqueous layer was extracted with EtOAc twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford (*S*)-**42** (73.0 mg, 95%): $[\alpha]^{27}_D$ +54.2 (*c* 0.542, $CHCl_3$); IR (neat) 3292, 1612, 1513, 1249, 1100, 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.70 (ddd, J = 6, 2, 2 Hz, 3 H), 2.23 (d, J = 2 Hz, 1 H), 3.26−3.37 (m, 1 H), 3.43 (dd, J = 9, 7 Hz, 1 H), 3.50 (dd, J = 9, 7 Hz, 1 H), 3.81 (s, 3 H), 4.51 (s, 2 H), 5.43 (ddq, J = 15, 6, 2 Hz, 1 H), 5.81 (ddq, J = 15, 2, 6 Hz, 1 H), 6.88 (d, J = 9 Hz, 2 H), 7.27 (d, J = 9 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9 (−), 35.2 (−), 55.3 (−), 71.3 (+), 72.7 (+), 72.8 (+), 83.5 (+), 113.8 (−), 126.9 (−), 128.1 (−), 129.4 (−), 130.2 (+), 159.3 (+); HRMS (FAB) calcd for $C_{15}H_{18}O_2$ (M^+) 230.1307, found 230.1308.

(*R*)-1-[(2-Ethylpentyloxy)methyl]-4-methoxybenzene (53) from (*S*)-42. To a solution of (*S*)-**42** (26.3 mg, 0.114 mmol) in benzene (1 mL) was added $RhCl(PPh_3)_3$ (21 mg, 0.0227 mmol).[31] The solution was stirred at rt for 20 h under H_2 atmosphere, and filtered through a pad of Celite. The filtrate was concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford **53** (19.4 mg, 72%). Retention time for **53** was identical with that derived from **52**.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.

Supporting Information Available: Experimental procedures for the preparation of allylic picolinates, determination of the absolute configuration of (*R*)-**3b**, and spectral data of compounds described herein. This material is available free of charge via the Internet at http://pubs.acs.org.

(30) Yadav, J. S.; Nanda, S. *Tetrahedron: Asymmetry* **2001**, *12*, 3223–3234.

(31) Hydrogenation of (*S*)-**42** with 10% Pd/C in EtOAc resulted in partial racemization.