

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

Yohei Kiyotsuka and Yuichi Kobayashi*

Department of Biomolecular Engineering, Tokyo Institute of Technology, B52, Nagatsuta-cho 4259, Midori-ku, Yokohama 226-8501, Japan

ykobayas@bio.titech.ac.jp

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To establish allylic substitution of secondary allylic alcohol derivatives with alkynyl copper reagents, allylic esters bearing the (2-pyridine)CO₂-, (2-pyrazine)CO₂-, (EtO)₂PO₂-, C₆F₅CO₂-, o-(Ph₂P)- $C_6H_4CO_2$ -, MeOCO₂-, or AcO- group were examined. First, picolinate (R¹ = Me, R² = CH₂OPMB) was subjected to reaction with (TMS-C=C)₂CuLi·LiBr at 0 °C. Although no substitution took place, MgBr₂ (3 equiv) was found to promote the reaction to produce the anti $S_N 2'$ 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 MgBr₂ were less reactive ((2-pyrazine)CO₂-) or marginally reactive (other cases). Generality of the substitution using picolinates was established with five picolinates ($R^1 = Me$, Ph(CH₂)₂, PMBO(CH₂)₃; $R^2 = Me$, CH₂OPMB, CH₂OTBS, C₅H₁₁, *c*-C₆H₁₁) and seven alkynyl copper reagents ($R^3 = TMS$, Ph, p-TBSOC₆H₄, p- and o-MeOC₆H₄, p-MeC₆H₄, p-FC₆H₄), 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 (sp³-C) copper reagents, less reactive aryl and alkenyl (sp²-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 $S_N 2'$ displacement with a broad range

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of sp²-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 1,4addition 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

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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-C=C)₂CuLi·LiBr.^{8,9}



FIGURE 1. Substrates for the present investigation.

Although no esters underwent the substitution, rac-1a was found to be activated by MgBr₂ 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)

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TABLE 1. Preliminary Study Using Racemic Substrates^a

L OPMB	TMS———Li (31) (2 equiv)	OPMB	
rac.1a 4-9	⊂ CuBr⋅Me₂S (1 equiv) THF, 0 °C, 1 h	TMS	
(racemic)	[additive (3 equiv)]	rac- 3a	rac- 32

entry	substrate	L	additive ^a	yield	<i>rac</i> -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	$(EtO)_2 P(O)O$	0 2	nr^e	
7	5	$(EtO)_{2}P(O)O$	MgBr ₂	12^{f}	nd ^g
8	5	$(EtO)_{2}P(O)O$	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 ₂ P)C ₆ H ₄ CO ₂		0^h	
13	7	o-(Ph ₂ P)C ₆ H ₄ CO ₂	MgBr ₂	0^h	
14	7	o-(Ph ₂ P)C ₆ H ₄ CO 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	

Three equivalents. ^bDetermined by ¹H NMR spectroscopy. ^cAlcohol **30** was obtained. ^dUnidentified products were coproduced. ^eNo reaction after 18 h at rt. ^fAllylic bromides **33a** and **33b** were produced in 88% NMR yield ($J_{\text{olefinic-H}} = 15 \text{ Hz}$). ^gNot determined. ^hThe 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 transformation¹⁰ of the epoxy chlorides to propargylic alcohol **15**.^{3c} In the present investigation, we used the asymmetric hydrogen transfer reaction developed by Noyori¹¹ 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)₂CuLi·LiBr, which had been prepared

from TMS-C=CLi (31) (2 equiv) and CuBr·Me₂S (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 reagents¹³⁻¹⁵ 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 oxide¹⁶ (entry 12). We then envisioned participation(s) of MgBr₂ and ZnBr₂ 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 sp³- and sp²-C reagents.¹⁷ In practice, MgBr₂ (3 equiv) was found to assist the substitution of picolinate rac-1a (1 equiv) and (TMS-C≡C)₂CuLi·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

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⁽¹⁸⁾ Attempted reaction in the presence of MgBr₂ without CuBr·Me₂S afforded alcohol 30.

temperatures of -20 and -60 °C merely retarded the reaction without improving the regioselectivity. Pyrazinecarboxylate **4** was activated by MgBr₂ 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 MgBr₂ 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 MgBr₂ (entries 10, 13, 16, 18). In contrast to the above results, ZnBr₂ (3 equiv) did not promote substitution of picolinate *rac*-1a and other substrates **5**–**7** with (TMS-C=C)₂CuLi · 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).



Next, substitution of *trans* allylic picolinate **34** with (TMS- $C \equiv C)_2$ CuLi·LiBr was investigated in the presence of MgBr₂ to afford a mixture of *rac*-**3a** and the regioisomer **35** (eq 1). Another copper reagent, TMS- $C \equiv CCu \cdot LiBr$, also produced a mixture of the regioisomers.



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_N 2-type product), whereas the S_N 2-type product in the previous substitution of picolinates with Ph₂CuMgBr (sp²-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% CT²⁰) with (TMS-C=C)₂CuLi·LiBr, giving anti S_N2' product (S)-3a²¹ 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·Me₂S 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

SCHEME 3. Synthesis of Racemic Allylic Esters



efficiency is attained without precise measurement of $CuBr \cdot Me_2S$ for preparation of the copper reagent.

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·Me₂S. On the basis of these results we used CuBr·Me₂S 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 CH₂OR group attached to the allylic moiety did not interfere with the MgBr₂-promoted substitution with (TMS-C=C)₂CuLi·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, $(Ph-C=C)_2CuLi \cdot LiBr$, prepared from Ph-C=CLi (36, 2 equiv) and $CuBr \cdot Me_2S$ (1 equiv), was found to be less reactive than $(TMS-C=C)_2$ - $CuLi \cdot LiBr$, and 18% of picolinate (*R*)-1a was recovered after 1 h at 0 °C. This problem was operationally solved with

⁽²³⁾ I repared by the following method:



⁽¹⁹⁾ Bromination of *rac*-1a with CuBr·Me₂S (0.5 equiv) and MgBr₂ (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 ($J_{\text{olefinic-H}} = 15$ Hz).

⁽²⁰⁾ CT, defined as (% ee of product/% ee of substrate) \times 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 CH₃, 4.1 (s) for CH₂OPMB, 5.5–5.6 (m) for CH=CH). (23) Prepared by the following method:

entry

1

2

CT, %

99

99

TABLE 2. Reaction of (R)-1a with 31/CuBr \cdot Me₂S/MgBr₂^{*a*}



94:6:0:0 3 2/0.5/3 91:5:4:0 81 nd^e ^aIn the absence of MgBr₂, reactions in entries 1-3 gave alcohol **30** in 13%, 23%, and 45% yields, respectively. ^bDetermined by ¹H NMR spectroscopy. ^cIsolated yield of (S)-3a and 32. ^dDetermined by chiral HPLC analysis. ^eNot determined.

TABLE 3. Effect of CuX on Substitution⁴

entry	CuX	ratio of (S)-3a:32:30:(R)-1a	yield, % ^b	CT, % ^{<i>c</i>}
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

^aReactions of (R)-1a with copper reagents derived from 31 (2 equiv) and CuX (1 equiv) were examined in the presence of MgBr₂ (3 equiv) at 0 °C for 1 h. ^bIsolated yield of (S)-3a and 32. ^cDetermined by chiral HPLC analysis. ^dAllylic bromides 33a and 33b were coproduced. ^end: 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-)₂CuLi·LiBr (entry 5). Similarly, (Ar−C≡C)₂CuLi·LiBr $(Ar = p-TBSOC_6H_4, p-MeOC_6H_4, o-MeOC_6H_4, p-MeC_6H_4, p-MeC_6H_6, p-MeC_6H_6, p-MeC_6H_6, p-MeC_6H_6, p-MeC_6H_6, p-MeC_$ p-FC₆H₄) 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 Bu₄NF 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 any 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 reaction²⁶ of (S)-42 with azide 48 afforded triazole

(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 Bu₄NF gave a mixture of products.

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SCHEME 4. Transformations of (S)-3a



(S)-49 in high yield. On the other hand, copper-catalyzed reaction²⁷ with p-NH(Ac)C₆H₄SO₂N₃ (50) followed by further reaction with EtOH afforded imidate (*R*)-51 in 81% yield.²⁸

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



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TABLE 4. Substitution of Picolinates with Alkynyl Copper Reagents^a

isolated yield ^{b,c}	selec- tivity ^{b,d} CT ^k
83	97 98
80	98 98
89	94 98
66	86 nd ¹
70	95 96
	00 05
01 07	93 95
0/	92 97
89	97 97
04	94 97
	66 70 61 67 89 84 88

^{*a*}Reactions in entries 1–4 were carried out with **31** (2 equiv), CuBr·Me₂S (1 equiv), and MgBr₂ (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·Me₂S (1.5 equiv), and MgBr₂ (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. ^{*c*}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 MgBr₂ 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(sp³) 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 MgBr₂ (1.60 mL, 0.20 M in THF, 0.320 mmol) and CuBr·Me₂S (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 NH₄Cl 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 MgSO₄, 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): $[\alpha]_{D}^{26}$ +57.8 (*c* 0.816, CHCl₃); IR (neat) 2172, 1514, 1250, 843 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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; $t_{\rm R}$ (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 ($J_{\text{olefinic-H}} = 11$ Hz) was determined. See Supporting Information.

JOC Article

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



(*R*,*E*)-1-[(2-Ethylpent-3-enyloxy)methyl]-4-methoxybenzene (52). To a suspension of CuBr·Me₂S (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 NH₄Cl 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 MgSO₄, 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, CHCl₃); IR (neat) 1612, 1513, 1248, 1096, 1038 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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 Hz, 1 H), 3.33 (dd, J=9, 7 Hz,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); ¹³C NMR (75 MHz, CDCl₃) 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; $t_{\rm R}$ (min) = 67.3 (R), 73.8 (S).

(*R*)-2-(4-Methoxybenzyloxymethyl)butan-1-ol (54). A stream of O₃ in O₂ was gently bubbled into a solution of 52 (25.7 mg, 0.110 mmol) in MeOH at -78 °C for 5 min. Excess O₃ remaining in the solution was purged by bubbling argon at -78 °C, and NaBH₄ (41 mg, 1.08 mmol) was added. After 1 h at -78 °C, saturated NH₄Cl was added to the solution, and the resulting mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over MgSO₄, 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 ([α]²⁷_D +13 (*c* 0.238,

CHCl₃)) was opposite to that of the (S)-enantiomer³⁰ ($[\alpha]^{25}_{D}$ -12.8 (c 1.0, CHCl₃)), 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 H₂ 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%): $[\alpha]^{28}{}_{\rm D}$ -7.2 (c 0.166, CHCl₃); IR (neat) 1612, 1513, 1248, 1094, 1038 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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; $t_{\rm R}$ (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 Bu₄NF (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 NH₄Cl. The layers were separated, and the aqueous layer was extracted with EtOAc twice. The combined extracts were washed with brine, dried over MgSO₄, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/ EtOAc) to afford (S)-42 (73.0 mg, 95%): $[\alpha]_{D}^{27}$ +54.2 (c 0.542, CHCl₃); IR (neat) 3292, 1612, 1513, 1249, 1100, 1036 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₅H₁₈O₂ (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(PPh₃)₃ (21 mg, 0.0227 mmol).³¹ The solution was stirred at rt for 20 h under H₂ 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.

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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.