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Enantioselective Synthesis of α-Methyl Carboxylic Acids from Readily Available Starting Materials via Chemoenzymatic Dynamic Kinetic Resolution

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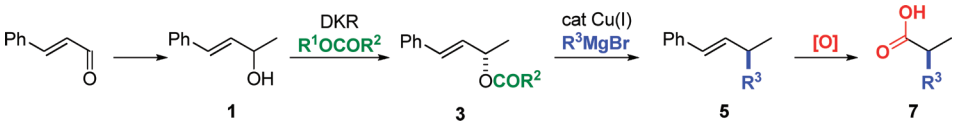

An enantioselective method for the synthesis of α-methyl carboxylic acids starting from *trans*-cinnamaldehyde, a readily available and inexpensive compound, has been developed. Allylic alcohol **1** was obtained via a standard Grignard addition to *trans*-cinnamaldehyde. Dynamic kinetic resolution was applied to allylic alcohol **1** utilizing a ruthenium catalyst and either an (*R*)-selective lipase or an (*S*)-selective protease to provide the corresponding allylic esters in high yield and high ee. A copper-catalyzed allylic substitution was then applied to provide the corresponding alkenes with inversion of stereochemistry. Subsequent C−C double bond cleavage afforded pharmaceutically important α-methyl substituted carboxylic acids in high ee and overall yields of up to 76%.

Introduction

α-Methyl substituted carboxylic acids constitute an important class of compounds and are of the nonsteroidal anti-inflammatory drug (NSAID) family. They can be prepared in high enantiopurity by using dynamic kinetic resolution (DKR) as the enantio-determining step. DKR of secondary alcohols has been thoroughly investigated by our group[1,2] and others,[3−10] and several reviews on enzyme/metal mediated DKR reactions have appeared in the literature.[11−13]

Application of DKR to allylic alcohol **I** with a Ru catalyst and either *Candida antarctica* lipase B (CALB) or Subtilisin Carlsberg as the enzyme would provide either the (*R*)- or (*S*)-ester **II**, respectively (only the (*S*)-ester is shown in Scheme 1). The enantiomerically pure ester can then undergo a copper-catalyzed allylic substitution reaction to give the α-product, olefin **III**. These olefins can then undergo oxidative double bond cleavage to provide α-methyl substituted carboxylic acids **IV**, which are of pharmaceutical interest. In most cases, the (*S*)-enantiomer is active as an NSAID. (*R*)-Flurbiprofen is under clinical trials for the treatment of metastatic prostate cancer and Alzheimer's disease.

We have previously demonstrated the application of this synthetic route starting from *β*-phenyl-cinnamaldehyde (R^1 = Ph).[14] The transformation of this aldehyde via DKR of the alcohol **I** worked smoothly to give the target α-methyl

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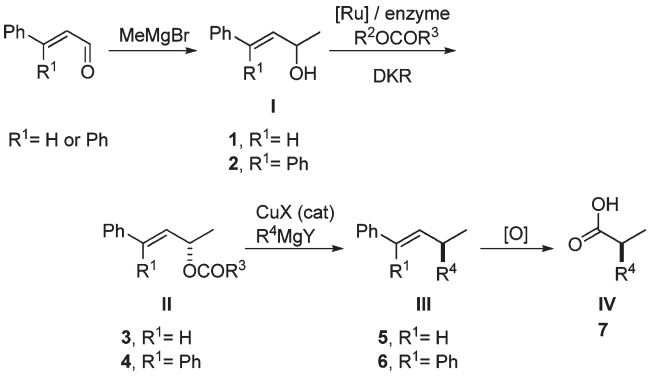
SCHEME 1. Enantioselective Synthesis of α-Methyl Carboxylic Acids via Metal and Enzyme Catalysis



aryl acetic acids (Scheme 1). One drawback with this approach is that β-phenyl-cinnamaldehyde is an expensive starting material, and furthermore, two phenyl groups have to be removed in the oxidative cleavage of the double bond (final step). We report herein our successful efforts to improve the applicability of this method by starting from a readily available and inexpensive compound, *trans*-cinnamaldehyde.[15]

Results and Discussion

Dynamic Kinetic Resolution. First, the allylic alcohol **1** (Scheme 1) was prepared from *trans*-cinnamaldehyde by a standard Grignard addition. Suitable DKR protocols were then needed to obtain both enantiomers of **3**. *Candida antarctica* lipase B (CALB) is an (*R*)-selective enzyme, and the DKR of **1** with CALB as the enzyme and **8** (Figure 1) as the racemization catalyst has previously been reported by our group; (*R*)-**3′** ($R^3 = CH_3$) was obtained in 89% yield and >99% ee.[16]

For the (*S*)-selective reaction, Subtilisin Carlsberg was used as the enzyme in combination with racemization catalyst **8**. The activity of commercially available Subtilisin Carlsberg was enhanced by treatment with surfactants octyl-β-D-glucopyranoside (**9**) and Brij (**10**) (Figure 2).[17] It is possible that coating the enzyme with surfactant results in the formation of reversed micelles, which have the property of solubilizing small amounts of water in their interior, thus providing a stable aqueous microenvironment in nonaqueous media.[18] Surfactant-treated Subtilisin Carlsberg has previously been used in the DKR of alcohols.[2,6] The activation was achieved by dissolving Subtilisin Carlsberg and the surfactants in a phosphate buffer and then lyophilizing the frozen solution. The activation was carried out to provide Subtilisin:**9**:**10** in three different ratios: 8:4:1, 8:1:4, and 4:1:1.

Kinetic resolution (KR) of **1** with surfactant-treated Subtilisin Carlsberg was carried out with acyl donors **11**−**13** (Figure 3), and it was found that acyl donor **11** gave the highest *E* value of 132 (Table 1, entry 3). Since the *E* value was much higher in KR with **11** as the acyl donor it was used in the subsequent reactions. Three different ratios of surfactant-

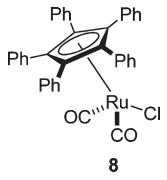


FIGURE 1. Racemization catalyst.

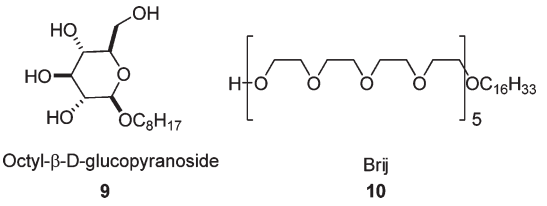


FIGURE 2. Surfactants used in the treatment of Subtilisin Carlsberg.

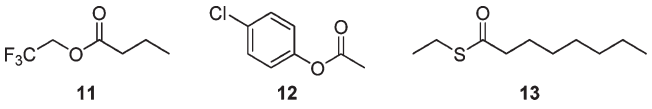
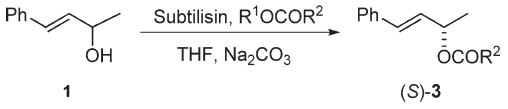


FIGURE 3. Acyl donors tested.

TABLE 1. Kinetic Resolution of 1[a]



entry	Sub:**9**:**10**	acyl donor	time (h)	ee of **1** (%)	ee of **3** (%)	conv (%)[b]	*E*
1	8:1:4	**11**	24	50	97	33	108
2	8:4:1	**11**	24	63	97	39	125
3	4:1:1	**11**	24	67	97	41	132
4	4:1:1	**12**	24	33	90	25	26
5[c]	4:1:1	**13**	24	4	80	5	9

[a]Conditions: 0.5 mmol of **1**, 1.5 equiv of acyl donor, 10 mg of Subtilisin:**9**:**10**, and 1 mmol of Na_2CO_3 in 2 mL of THF at ambient temperature for 24 h [b]Determined by NMR. [c]5 mg of Subtilisin:**9**:**10**.

treated Subtilisin Carlsberg (Subtilisin:**9**:**10**, 8:4:1, 8:1:4, and 4:1:1) were also compared in the KR of **1**, and Subtilisin:**9**:**10** (4:1:1) gave the best results (Table 1, entries 1−3).

Allylic alcohols of this type are known to undergo isomerization reactions under DKR conditions (i.e., in the presence of racemization catalyst **8**),[16,19] where readdition of the putative intermediate hydride occurs in a 1,4-fashion to form the ketone. Previously, the isomerization product was avoided by using sterically hindered, yet expensive, alcohol **2** (Scheme 1).[14] In the route with the less sterically hindered monophenyl substituted alcohol **1**, some isomerization to ketone **14** occurs, but it was possible to minimize the formation of this isomerization product by optimizing reaction conditions such as temperature, and amount of enzyme and acyl donor. DKR was first applied to **1** with Subtilisin:**9**:**10** (4:1:1), 5 mol % **8**, and acyl donor **11** at room temperature; however, the racemization of **1** (79% ee, Table 2, entry 1) was slow relative to acylation, so the reaction temperature was increased to 40 °C. Under these

(15) One kilogram of β-phenyl-cinnamaldehyde costs € 345. One kilogram of *trans*-cinnamaldehyde costs € 19. Prices are based on 100 kg price quotes from Sigma Aldrich.

(16) See ref 1. Saturated ketone formed from rearrangement of the allylic alcohol was observed as a side product.

(17) Bordusa, F. *Chem. Rev.* **2002**, *102*, 4817–4868.

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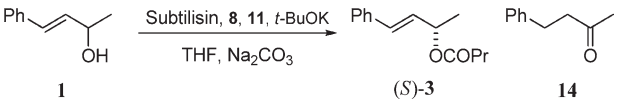
TABLE 2. Dynamic Kinetic Resolution of 1[a]

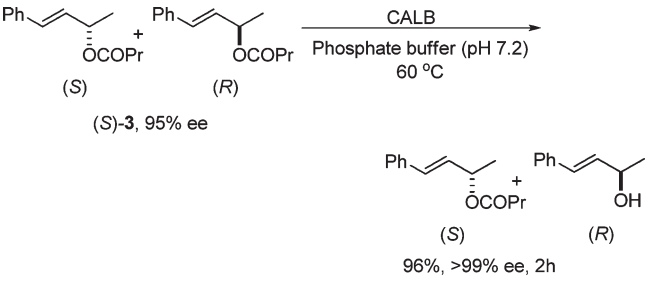


1 (*S*)-**3** **14**

entry	Sub:**9**:**10** (mg/mmol)	acyl donor (equiv)	*T* (°C)	time (h)	ee of **1** (%)	ee of **3** (%)	yield (%)[b]	**14** (%)[b]
1	20	2	rt	48	79	82	79	2
2[c]	20	2	rt	48	35	80	87	4
3[d]	20	2	rt	24	16	67	70	3
4	40	3	40	48	62	95	81 (75)	11
5[e]	40	3	40	45		97	81	19
6[c]	20	3	40	20	18	90	75	9

[a]Conditions: 5 mol % of *t*-BuOK was added to 5 mol % of **8**, Subtilisin:**9**:**10** (4:1:1), and Na_2CO_3 in THF; 6 min later **1** (0.5 or 1.0 mmol) was added, and 4 min later **11** was added. The reaction mixture was heated to 40°C. [b]Determined by NMR, isolated yield in parentheses. [c]6 mol % of *t*-BuOK. [d]7 mol % of *t*-BuOK. [e]20 mg/mmol of Subtilisin: **9**:**10** (4:1:1) added after 24 h.

SCHEME 2. Enantiomeric Excess Enhancement via Hydrolysis of (*R*)-3 with CALB



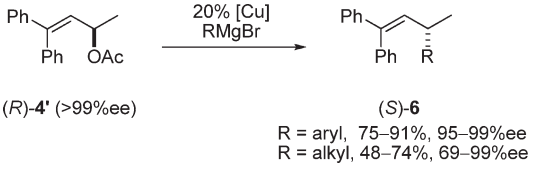
conditions, (*S*)-**3** was obtained in 75% isolated yield and 95% ee, with only 11% isomerization product **14** (Table 2, entry 4). When an additional aliquot of Subtilisin:**9**:**10** was added after 24 h, under otherwise unchanged conditions, (*S*)-**3** was obtained in 81% yield and 97% ee, with 19% **14** (Table 2, entry 5). The number of equivalents of base used to activate the catalyst was also increased to see if there would be a parallel increase in activity; however, a drop in product ee was observed indicating chemical acylation (Table 2, entries 2, 3, and 6).

The enantiomeric purity of the ester obtained from DKR was further improved by hydrolyzing the undesired enantiomer with an (*R*)-selective enzyme. The hydrolysis was carried out in a phosphate buffer solution (pH = 7.2) with CALB as the enzyme to provide (*S*)-**3** in 96% yield and >99% ee in 2 h at 60 °C (Scheme 2).

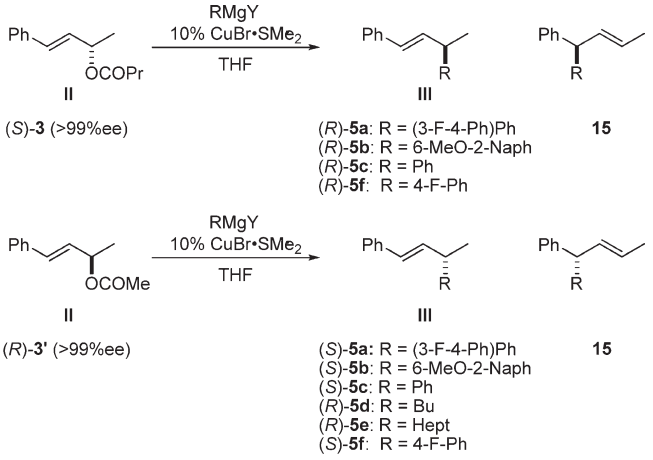
Copper-Catalyzed Allylic Substitution Reactions. Previously, copper-catalyzed allylic substitution reactions have been carried out with allylic ester **4** to provide olefin **6** (Scheme 3).[14] Complete regioselectivity for the α-product was observed when using either aryl or aliphatic Grignard reagents. When aryl Grignard reagents were used **6** was obtained in 75−91% yield and 95−99% ee, and when aliphatic Grignard reagents were used **6** was obtained in 48−74% yield and 69−99% ee (Scheme 3).

A screening of copper salts has previously been carried out for the reaction of (*R*)-**4′**, BuMgBr, and 10% copper catalyst.[20]

SCHEME 3. Copper-Catalyzed Allylic Substitution Reactions with (*R*)-4′ and (*S*)-4 (Only the (*R*)-Enantiomer Is Shown)[14]



SCHEME 4. Copper-Catalyzed Allylic Substitution Reaction with (*S*)-3 and (*R*)-3′



It was found that CuCl and CuBr·SMe_2 gave higher conversion and higher selectivity for the substitution reaction than CuI, CuCN, and Li_2CuCl_4. CuCl and CuBr·SMe_2 gave similar results, where CuCl provided the product in slightly higher ee and CuBr·SMe_2 gave the product in slightly higher yield. Therefore, these two copper catalysts were chosen for the subsequent substitution reactions.

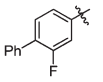
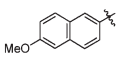
Application of the reaction to monophenyl substituted allylic substrates (*S*)-**3** and (*R*)-**3′** with aryl Grignard reagents provided the olefin products with inversion of stereochemistry in high yields and excellent ee (Scheme 4; Table 3, entries 1−6, 9, and 10). Complete selectivity for the α-product was observed. The substitution of (*S*)-**3** and (*R*)-**3′** could also be carried out with aliphatic Grignard reagents (Table 3, entries 7 and 8). Some loss of stereochemistry and formation of 10−11% γ-product **15** was observed. The loss of stereochemistry could be due to single bond rotation of **16** to **16′** (Scheme 5).[20] When THF was used as the solvent and the reaction was run at −20 °C, (*R*)-**5d** could be obtained in 59% yield and 90% ee (Table 3, entry 7). By changing the solvent to diethyl ether, (*R*)-**5e** was obtained in 65% yield and 96% ee (Table 3, entry 8). On the basis of our current and previous studies,[14,20,21] it was found that in general a lower reaction temperature promoted selectivity for the α-product, while also promoting loss of stereochemistry. Also THF as the solvent provided the product in higher yield than diethyl ether as the solvent, whereas diethyl ether provided the product in higher ee than THF as the solvent.

Oxidative C−C Double Bond Cleavage. The oxidative C−C double bond cleavage of olefins **5a** and **5b** afforded the desired α-methyl substituted carboxylic acids **7a** and **7b**,

(20) Norinder, J.; Bäckvall, J.-E. *Chem.—Eur. J.* **2007**, *13*, 4094–4102.

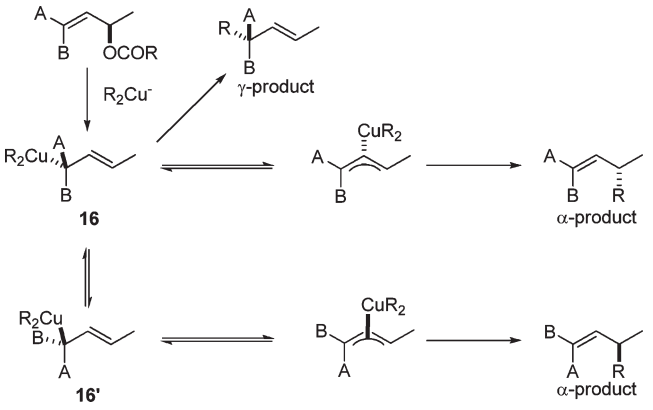
(21) Bäckvall, J. E.; Sellen, M.; Grant, B. *J. Am. Chem. Soc.* **1990**, *112*, 6615–6621.

TABLE 3. Copper-Catalyzed Allylic Substitution Reaction with (*S*)-3 and (*R*)-3′[a]

Entry	II	R	Time	III	5 + 15 (%)[b]	α/γ ratio[b]	ee (%)[c]
1	(*S*)-**3**		5	(*R*)-**5a**	(97)	100:0	> 99
2	(*R*)-**3'**		5	(*S*)-**5a**	99 (92)	100:0	> 99
3	(*S*)-**3**		4	(*R*)-**5b**	99 (99)	100:0	> 99
4	(*R*)-**3'**		4	(*S*)-**5b**	99 (98)	100:0	> 99
5[e]	(*S*)-**3**		4	(*R*)-**5c**	94 (78)	100:0	>99
6	(*R*)-**3'**		6	(*S*)-**5c**	95 (79)	100:0	> 99
7[d,e]	(*R*)-**3'**		24	(*R*)-**5d**	59	89:11	90[f]
8[d,g]	(*R*)-**3'**		16	(*R*)-**5e**	65	90:10	96[f]
9	(*S*)-**3**		4	(*R*)-**5f**	99 (94)	100:0	>99
10	(*R*)-**3'**		4	(*S*)-**5f**	99 (97)	100:0	> 99

[a]Conditions: **3** or **3′** (0.5 mmol) and $CuBr \cdot SMe_2$ were mixed in THF. After cooling to 0 °C, 0.75 mmol of Grignard reagent was added. [b]Determined by NMR using 2-decanol or 2-nonanol as internal standard; isolated yields in parentheses. [c]Determined by HPLC. [d]CuCl. [e]−20 °C. [f]Determined by GC of the corresponding carboxylic acid obtained by Sharpless oxidation. [g]Et_2O.

SCHEME 5. Isomerization of the Allyl Intermediates, Leading to Different Products



which are of pharmaceutical interest. The Sharpless oxidation is a well-known procedure[22] and was previously applied to the oxidation of **6** to provide **7** in high yields and excellent ee.[14] However, these conditions proved too harsh when applied to (*S*)-**5b**, the precursor of Naproxen ((*S*)-**7b**).

C−C double bond cleavage of monophenyl substituted **5** afforded two acids, **7** and benzoic acid (**17**). For **7a** and **7b** the separation of the two acids could be achieved by Kugelrohr distillation. Two oxidation methods were tested to find suitable conditions for the oxidation of **5b**: Lemieux and von Rudloff reagent, and osmium tetroxide with oxone. Application of Lemieux and von Rudloff reagent provided Naproxen ((*S*)-**7b**) in 42% isolated yield and >99% ee (Table 4, entry 4). The low yield is due to byproduct formation. Catalytic amounts of osmium tetroxide in combination with stoichiometric amounts of oxone were also tested and provided (*S*)-**7b** in 51% isolated yield and > 99% ee (Table 4, entry 5). The Lemieux and von Rudloff reagent was also applied to the oxidation of (*S*)-**5a** to afford (*R*)-**7a** (Flurbiprofen) in 44% yield and >99% ee (Table 4, entry 3). Oxidation of (*S*)-**5a** under Sharpless conditions afforded (*R*)-**7a** (Flurbiprofen) in 93% yield and >99% ee (Table 4, entry 1). The optical rotation of known compound (*S*)-(+)-**7a** was compared with literature data to verify the absolute configuration.[23]

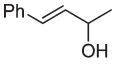
Other starting materials that would increase the atom economy have also been considered. Crotonaldehyde is one such substrate; however, it is probable that the lack of steric hindrance in the γ-position would lead to a higher degree of isomerization product formation in the DKR reaction and a higher degree of γ-product formation in the copper-catalyzed substitution reaction.

Conclusions

We have developed a method for the synthesis of α-methyl carboxylic acids starting from *trans*-cinnamaldehyde, a readily available and inexpensive compound. Allylic alcohol **1** was obtained via a standard Grignard addition to *trans*-cinnamaldehyde. DKR was applied to allylic alcohol **1** to provide both the (*R*)- and (*S*)-enantiomers of **3** in high enantiomeric purity. Copper-catalyzed allylic substitution was then applied to **3** with aryl and aliphatic Grignard reagents, which afforded the corresponding olefins **5** with inversion of stereochemistry. C−C double bond cleavage provided the biologically active α-methyl carboxylic acids **7** in moderate to excellent yields and in high enantiopurity (>99% ee).

Experimental Section

Synthesis of Racemic Alcohol 1.



1

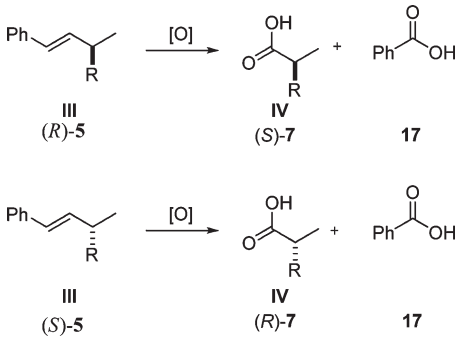
4-Phenyl-3-buten-2-ol (1). Racemic alcohol **2** was prepared by addition of MeMgCl to *trans*-cinnamaldehyde in THF, according to a literature procedure.[24] The ^1H NMR and

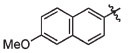
(22) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938.

(23) Guintchin, B.; Bienz, S. *Tetrahedron* **2003**, *59*, 7527–7533.

(24) Dawson, G. J.; Williams, J. M. J.; Coote, S. J. *Tetrahedron: Asymmetry* **1995**, *6*, 2535–2546.

TABLE 4. Oxidation of Olefins (*R*)-5 and (*S*)-5[a]

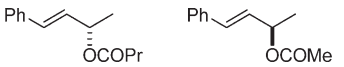


Entry	III	R	[O] method	IV	7 (%)[b]	ee (%)[c]
1	(*S*)- **5a**		A	(*R*)-**7a**	93	>99
2	(*R*)- **5a**		A	(*S*)-**7a**	76	>99
3	(*S*)- **5a**		B	(*R*)-**7a**	44	>99
4	(*R*)- **5b**		B	(*S*)-**7b**	42	>99
5	(*R*)- **5b**		C	(*S*)-**7b**	51	>99

[a]Conditions: [A] **III**, 2 mol % of $RuCl_3$, 4.1 equiv of $NaIO_4$; [B] **III**, 0.5 equiv of $KMnO_4$, 5 equiv of $NaIO_4$, 1 equiv of K_2CO_3; [C] **III**, 5 mol % of OsO_4, 4 equiv of oxone. [b]Isolated yield. [c]Determined by GC.

^{13}C NMR spectral data were in accordance with literature data.[25]

Synthesis of Enantiomerically Pure Esters (*S*)-3 and (*R*)-3′.



(*S*)-**3** (*R*)-**3′**

(*S*)-4-Phenyl-3-buten-2-yl Butanoate ((*S*)-3). Complex **8** (16 mg, 25 μmol), Subtilisin Carlsberg:Brij:octyl-β-glycopyranoside, 4:1:1 (20 mg, prepared as previously reported[3]), Na_2CO_3 (106 mg, 1.0 mmol), and *t*-BuOK (50 μL, 0.5 M in THF) were stirred in toluene (0.5 mL) for 6 min. Thereafter, a solution of racemic alcohol **1** (74.1 mg, 0.50 mmol) in THF (2 mL) was added. After 4 min, trifluoroethylbutyrate (225 μL, 1.5 mmol) was added, and the mixture was stirred at 40 °C under an argon atmosphere. After 48 h, the reaction mixture was filtered through a plug of silica and was washed with ethyl acetate. The crude product was concentrated *in vacuo*, and column chromatography (pentane/EtOAc, 60:1) afforded (*S*)-**3** (75%, 82.2 mg) as a colorless oil in 95% ee. The optical purity was determined by HPLC analysis (OJ column, *i*-hexane/*i*-PrOH, 99:1, $t_R(R)$ = 24.63, $t_R(S)$ = 27.28 min).

Enantiomeric Excess Enhancement via Hydrolysis of (*R*)-4-Phenyl-3-buten-2-yl Butanoate ((*S*)-3). (*S*)-**3** (95% ee, 109.1 mg, 0.5 mmol) and CALB (10 mg) were then suspended in a 0.5 M phosphate buffer (2 mL, pH 7.2) and stirred for 2 h at 60 °C. The mixture was filtered, and the aqueous phase was extracted three times with EtOAc. The organic phases were combined and washed once with 2 M $NaHCO_3$. The organic phase was dried over Na_2SO_4, and the product was concentrated *in vacuo*. Column chromatography (pentane/EtOAc, 60:1) afforded (*S*)-**3** (96%) in >99% ee. The optical purity was determined by HPLC analysis (OJ column, *i*-hexane/*i*-PrOH, 99:1, $t_R(R)$ = 24.63, $t_R(S)$ = 27.23 min). NMR spectral data were in accordance with published data.[26] ^1H NMR (400 MHz, $CDCl_3$): δ 7.43−7.38 (m, 2H), 7.37−7.31 (m, 2H), 7.29−7.24 (m, 1H), 6.62 (d, *J* = 15.9 Hz, 1H), 6.22 (d, *J* = 15.9, 6.8 Hz, 1H), 5.57 (d, *J* = 6.8, 6.5 Hz, 1H), 2.33 (t, *J* = 7.3 Hz, 2H), 1.7 (tq, *J* = 7.3, 7.4 Hz, 2H), 1.43 (d, *J* = 6.5 Hz, 3H), 0.98 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 136.5, 131.5, 129.1, 128.7, 128.0, 126.7, 70.8, 36.7, 20.5, 18.6, 13.8. $[\alpha]^{27}_D$ = −105.8 (*c* 1.0, $CHCl_3$).

4-Phenyl-3-buten-2-yl Acetate ((*R*)-3′). Prepared via DKR according to a literature procedure (89% yield and >99% ee).[16]

General Procedure for the Copper(I)-Catalyzed Allylic Substitution Reactions. (*S*)-5a. The allylic acetate (*R*)-**3′** (190 mg, 1.0 mmol) and $CuBr \cdot SMe_2$ (20.5 mg, 0.1 mmol) were mixed in THF (9 mL) and cooled to 0 °C. A solution of ((3-fluoro-4-phenyl)phenyl)MgBr in THF (3.0 mL, 0.5 M) was added, and the reaction mixture and was stirred at the given temperature. The reaction mixture was quenched after 5 h by addition of $HCl_{(aq)}$ (2 M, 10 mL), followed by addition of 2-nonanol (50 μL, 0.26 mmol) as internal standard. The organic solvent was removed *in vacuo*, and Et_2O (10 mL) was added. The product was extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with H_2O (1 × 10 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* to afford the crude product, which was purified by column chromatography (pentane/EtOAC, 100:0 to 97:3). (*S*)-**5a** was obtained in 92% yield and >99% ee. The optical purity was determined by HPLC analysis (OJ column, *i*-hexane/*i*-PrOH, 85:15; flow 1.0, $t_R(S)$ = 13.6 min, $t_R(R)$ = 18.6 min). NMR spectral data were in accordance with published data.[27] $[\alpha]^{27}_D$ = −39.2 (*c* 1.00, $(CH_3)_2CO$).

General Procedure for Oxidative C−C Double Bond Cleavage. (*S*)-7b. Method [A]. Oxidative cleavage of the olefin (*S*)-**5a** was performed on 1.0 mmol scale according to the Sharpless procedure[13] and as previously described.[14] Olefin (*S*)-**5a** (302 mg, 1 mmol), $RuCl_3 \cdot H_2O$ (4.2 mg, 0.02 mmol), $NaIO_4$ (877 mg, 4.1 mmol), MeCN (2 mL), CCl_4 (2 mL), and H_2O (3 mL) were charged in a 25 mL round-bottom flask and stirred under

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ambient conditions. The reaction was followed by TLC analysis (pentane/EtOAc, 95:5) and upon completion DCM (25 mL) was added. The product was extracted with $NaHCO_3$ (3 × 20 mL). The combined aqueous phase was acidified with 2 M HCl solution, and the product was extracted with DCM (3 × 20 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Benzoic acid was then removed from the mixture by Kugelrohr distillation (80 °C, 0.4 mbar) to afford (*R*)-**7a** in 93% yield and >99% ee. The optical purity was determined by GC analysis (flow rate; 1.5 mL/min. GC program: from 100 to 200 °C at a rate of 10 °C/min, isothermal at 200 °C for 40 min; $t_R(S) = 25.6$, $t_R(R) = 26.3$ min). $[\alpha]^{27}_D = -42.7$ (*c* 0.8, $CDCl_3$). Spectroscopic data were in agreement with the literature data.[28]

Method [B]. According to a literature procedure,[29] the olefin (*R*)-**5** (72.1 mg, 0.25 mmol) was dissolved in acetone (35 mL). Subsequently, Li_2CO_3 (9.2 mg, 0.13 mmol) and H_2O were added (7 mL). The solution was cooled to 0 °C. In a separate flask, $NaIO_4$ (267 mg, 1.25 mmol), $KMnO_4$ (19.8 mg, 0.125 mmol), and Li_2CO_3 (9.2 mg, 0.13 mmol) were dissolved in H_2O (17 mL). The aqueous solution was added dropwise to the olefin solution. The reaction mixture was quenched after 24 h by addition of $HCl_{(aq)}$ (1 M, 5 mL) at 0 °C. $Na_2S_2O_5$ was added until a colorless solution was obtained. The organic solvent was removed *in vacuo*, and Et_2O (5 mL) was added. The pH was adjusted to 10 with $NaHCO_3$, and the product was extracted with sat. $NaHCO_3$ solution (3 × 5 mL). The combined aqueous phase was washed once with Et_2O and then acidified to pH 2 with 2 M HCl. The product was extracted with DCM (3 × 10 mL). The combined organic phase was washed with H_2O (1 × 5 mL) and dried over Na_2SO_4. The solvent was removed *in vacuo* to afford the crude product mixture. Benzoic acid was then removed from the mixture by Kugelrohr distillation (80 °C, 0.4 mbar) to afford (*S*)-**7b** in 42% yield (24.2 mg, 0.11 mmol) and >99% ee. The optical purity (>99% ee) was determined by GC analysis (flow rate; 1.5 mL/min. GC program: from 100 to 200 °C at a rate of 10 °C/min, isothermal at 200 °C for 40 min; $t_R(S) = 28.5$, $t_R(R) = 29.2$ min). $[\alpha]^{27}_D = +60.8$ (*c* 0.5, $CDCl_3$). Spectroscopic data were in agreement with the literature data.[30]

Method [C]. According to a literature procedure,[31] the olefin-(*R*)-**5b** (50.0 mg, 0.173 mmol) was dissolved in DMF (1 mL) and cooled to 0 °C. Oxone (213 mg, 0.695 mmol) and $K_2OsO_4 \cdot 2H_2O$ (3.20 mg, 0.009 mmol) were added to the solution as a solid mixture in one portion. The brown reaction mixture was stirred at 0 °C for 5 h. The reaction was followed by TLC (pentane/EtOAc, 99:1). Upon completion, solid Na_2SO_3 (6 equiv w/w) was added, and the resulting suspension was stirred for 1 h, during which time it becomes slightly yellow (as opposed to deep brown). Subsequently, 1 M HCl was added to dissolve the salts, and the product was extracted with EtOAc (× 3). The combined organic phases were washed with 1 M HCl (× 3) and brine (× 1). The combined organic phase was dried with $MgSO_4$, and the solvent was subsequently removed *in vacuo* to provide a sticky brown oil. The crude product was purified by bulb-to-bulb distillation (80 °C, 0.4−0.5 mmHg) to remove the benzoic acid. The residual brown solid was then subjected to silica gel chromatography (pentane/EtOAc/AcOH, 3:1:0.1) to afford (*S*)-**7b** in 51% yield (20.3 mg, 0.089 mmol) and >99% ee. The optical purity (>99% ee) was determined by GC analysis (flow rate; 1.5 mL/min. GC program: from 100 to 200 °C at a rate of 10 °C/min, isothermal at 200 °C for 40 min; $t_R(S) = 28.5$, $t_R(R) = 29.2$ min). Spectroscopic data were in agreement with the literature data.[30]

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Supporting Information Available: General methods, experimental procedures, copies of NMR spectra, and copies of chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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