JOC Note

Synthesis of Enantiopure 1-Arylprop-2-en-1-ols and Their *tert*-Butyl Carbonates

Jan Štambaský,[†] Andrei V. Malkov,*[,‡] and Pavel Kočovský*

Department of Chemistry, WestChem, University of Glasgow, Glasgow G12 8QQ, Scotland, U.K.

a.malkov@lboro.ac.uk; pavelk@chem.gla.ac.uk

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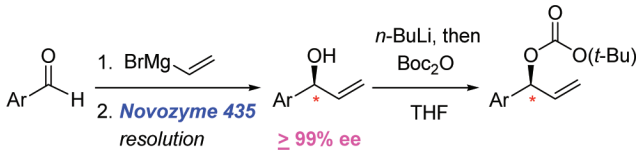
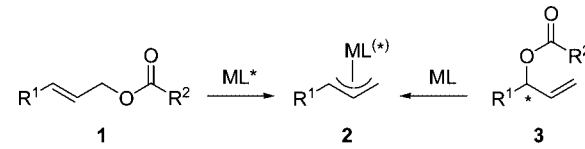


Enantiomerically pure 1-arylpropenols **8** have been prepared by resolution of the corresponding racemates, using the lipase formulation Novozyme 435. Deprotonation of the latter alcohols with *n*-BuLi, followed by derivatization with $(t\text{-BuO})_2CO$, afforded the corresponding carbonates **5**. Optimization of the process is presented.

π-Allyl complexes of transition metals are indispensable intermediates in the stereo- and regiocontrolled allylic substitution (Scheme 1).[1] Nonsymmetrically substituted complexes, such as **2**, which can be generated either from the linear esters **1** or from their branched isomers **3**,[2] are inherently chiral. Therefore, an enantioselective reaction starting with **1** requires the use of a chiral catalyst (with a chiral ligand L*),[3] whereas a nonchiral catalyst is sufficient when the enantiopure branched isomer **3** is employed.[1,4−7] While both ester and carbonate leaving groups have been employed in numerous examples, in some instances,

SCHEME 1. Transition-Metal-Catalyzed Asymmetric Allylic Substitution



the more delicate *tert*-butyl carbonates [R^2 = O-(*t*-Bu)] are required for the catalytic substitution reaction to occur efficiently.[6] Herein, we report on the optimized protocol for the preparation of carbonates **5**, derived from 1-arylpropenols.

Branched alcohols $ArCH(OH)CH{=}CH_2$, where the carbinol atom is flanked by an aromatic ring on one side and a vinyl group on the other, are rather acid-sensitive compounds, prone to the generation of a well-stabilized benzylic/allylic cation. Therefore, both the alcohols and their esters and carbonates have to be handled with care, and their large-scale preparation and storage, especially in a nonracemic form, is not trivial.

The synthesis of branched carbonates (±)-**5** was intended to be carried out according the known one-pot procedure (Scheme 2),[8]in which the starting aryl aldehyde **4** is treated with vinylmagnesium bromide and the resulting magnesium alkoxide is directly derivatized with Boc anhydride. A series of aromatic and heteroaromatic aldehydes **4** were used, but the seemingly straightforward procedure turned out to be complicated by two side reactions, producing carbonates **6** and **7** (Table 1, entries 1−6), not mentioned in the original paper.[8] While the linear byproduct **6** is presumably formed from the primarily generated branched carbonate **5** via a [3,3] sigmatropic rearrangement, carbonate **7** apparently originates from the competing Cannizzaro-like reaction of aldehyde **4**, followed by derivatization with Boc_2O. In some cases, the desired product **5** was not formed at all and only **6** and **7** were detected (entries 8 and 9). Only nicotinic aldehyde **4j** afforded the branched carbonate (**5j**) selectively (entry 7). As the mixtures of carbonates are very difficult to separate, this method was abandoned.[9]

[†] Current address: NovaEnergo, Na Horánku 673, 38411, Netolice, Czech Republic.

[‡] Current Address: Department of Chemistry, University of Loughborough, Leicestershire LE11 3UT, U.K.

(1) For Pd-catalyzed allylic substitution, see: (a) Negishi, E., Ed.; *Handbook of Palladium Chemistry for Organic Synthesis*; J. Wiley: New York, 2002; Vol *2*, p 1663. For an overview of our contribution to Pd-catalyzed allylic substitution, see: (b) Kočovský, P. *J. Organomet. Chem.* **2003**, *687*, 256. For an overview of catalysis by other metals, see: (c) Kočovský, P.; Malkov, A. V.; Vyskočil, Š.; Lloyd-Jones, G. C. *Pure Appl. Chem.* **1999**, *71*, 1425. (d) Kočovský, P.; Malkov, A. V. *Pure Appl. Chem.* **2008**, *80*, 953.

(2) In principle, the two isomeric substrates **1** and **3** should produce the same η^3-complex **2** (ref 1). However, this may not always be the case, as known from the elucidation of the "memory effect": (a) Lloyd-Jones, G. C.; Stephen, S. C.; Murray, M.; Butts, C. P.; Vyskočil; Š.; Kočovský, P. *Chem.—Eur. J.* **2000**, *6*, 4348. (b) Fairlamb, I. J. S.; Lloyd-Jones, G. C.; Vyskočil, Š.; Kočovský, P. *Chem.—Eur. J.* **2002**, *8*, 4443. (c) Gouriou, L.; Lloyd-Jones, G. C.; Vyskočil, Š.; Kočovský, P. *J. Organomet. Chem.* **2003**, *687*, 525.

(3) For overviews, see ref 1 and the following: (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (b) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336. (c) Helmchen, G.; Kudis, S.; Sennhenn, P.; Steinhagen, H. *Pure Appl. Chem.* **1997**, *69*, 513.

(4) In the Pd-catalyzed allylic substitution, the η^3-complex **2** is formed via inversion of configuration (ref 1). For the retention pathway, see: (a) Starý, I.; Kočovský, P. *J. Am. Chem. Soc.* **1989**, *111*, 4981. (b) Farthing, C. N.; Kočovský, P. *J. Am. Chem. Soc.* **1998**, *120*, 6661, and refs cited therein.

(5) In the Mo-catalyzed allylic substitution, the η^3-complex **2** has been shown to arise via retention of configuration: (a) Dvořák, D.; Starý, I.; Kočovský, P. *J. Am. Chem. Soc.* **1995**, *117*, 6130. (b) Lloyd-Jones, G. C.; Krska, S. W.; Hughes, D. L.; Gouriou, L.; Bonnet, V. D.; Jack, K.; Sun, Y.; Reamer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 702.

(6) The Rh- and Ir-catalyzed allylic substitution is known to give products of overall retention of configuration. However, the stereochemistry of the individual steps has not been elucidated: (a) Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581. (b) Evans, P. A.; Leahy, D. K.; Andrews, W. J.; Uraguchi, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4788. (c) Evans, P. A.; Leahy, D. K.; Slieker, L. M. *Tetrahedron: Asymmetry* **2003**, *14*, 3613. (d) Shu, C.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 4794. For a featured article, see: (e) Helmchen, G.; Dahnz, A.; Dübon, P.; Schelwies, M.; Weihofen, R. *Chem. Commun.* **2007**, 675.

(7) The stereochemistry of the formation of the molybdenum complex **2** (M = Mo) from a chiral substrate **3**, carried out in the presence of a chiral ligand, is controlled predominantly by the ligand. An isomerization in the case of a "mismatched" combination of **3** and L* has been demonstrated, so that even a racemic substrate **3** can be converted into a substitution product with high enantioselectivity: Malkov, A. V.; Starý, I.; Gouriou, L.; Lloyd-Jones, G. C.; Langer, V.; Spoor, P.; Vinader, V.; Kočovský, P. *Chem.—Eur. J.* **2006**, *12*, 6910.

(8) Stoner, E. J.; Peterson, M. J.; Allen, M. S.; DeMattei, J. A.; Haight, A. R.; Leanna, M. R.; Patel, S. R.; Plata, D. J.; Premchandran, R. H.; Rasmussen, M. *J. Org. Chem.* **2003**, *68*, 8847–8852.

(9) The published example[8] featured the reaction of 3-quinolinecarboxaldehyde, which is closely related to **4j**, our only successful substrate. As we have now demonstrated, this method is far from being general.

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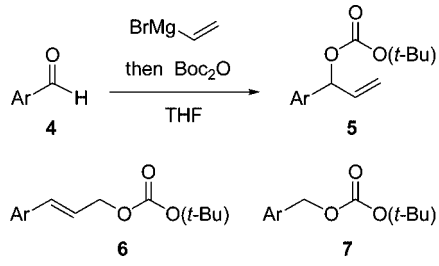
SCHEME 2. One-Pot Sythesis of Racemic Boc Derivatives (for yields, see Table 1)



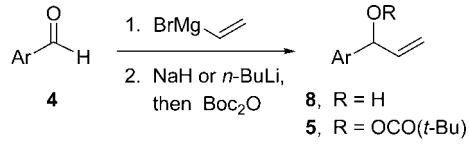
a, Ar = C_6H_5 **g**, Ar = 2,4-$F_2C_6H_3$
b, Ar = 4-Me-C_6H_4 **h**, Ar = 3-MeO-C_6H_4
c, Ar = 3,4-$Me_2C_6H_3$ **i**, Ar = 3,4-$(MeO)_2C_6H_3$
d, Ar = 4-Br-C_6H_4 **j**, Ar = 3-pyridyl
e, Ar = 4-F-C_6H_4 **k**, Ar = 2-furyl
f, Ar = 3-F-C_6H_4 **l**, Ar = 2-thiophenyl

TABLE 1. Synthesis of *tert*-Butyl 1-arylprop-2-en-1-yl Carbonates (Scheme 2)[a]

entry	aldehyde	Ar	products ratio in %[b] **5**:**6**:**7**
1	**4b**	4-Me-C_6H_4	67:27:6[c]
2	**4c**	2,4-$Me_2C_6H_3$	29:64:7[c]
3	**4d**	4-Br-C_6H_4	39:0:61
4	**4f**	3-F-C_6H_4	51:0:49
5	**4g**	2,4-$F_2C_6H_3$	24:0:76
6	**4h**	3-MeO-C_6H_4	68:0:32
7	**4j**	3-pyridyl	100:0:0
8	**4k**	2-furyl	0:97:3
9	**4l**	2-thiophenyl	0:74:26

[a] The reaction was carried out on a 50 mmol scale. [b] The ratio is based on isolated yields. [c] Established by the ^{1}H NMR spectroscopy of the crude reaction mixture.

SCHEME 3. Two-Pot Synthesis of Racemic Boc Derivatives (for Ar and yields, see Table 2)



Since the one-pot procedure essentially failed, a two-step alternative was explored next. The alcohols (±)-**8**, resulting from the reaction of aldehydes **4** with vinylmagnesium bromide in THF (Scheme 3), were first isolated and purified.[10] Their subsequent deprotonation with sodium hydride, followed by treatment with Boc anhydride, proved uneventful and afforded the desired carbonates (±)-**5** in 85−95% yields (Table 2, fifth column). The alternative deprotonation with *n*-BuLi, employed for the enantiopure alcohols **8** (vide infra), proved more efficient (Table 2, last two columns).

The nonracemic 1-arylpropenols **8** were prepared via enzymatic resolution as follows (Scheme 4 and Table 3).[11] The highly active, acrylic resin-supported recombinant lipase formulation Novozyme 435[11b] was added to a suspension of the corresponding 1-arylpropenol **8**, isopropenyl acetate, and 4 Å molecular sieves powder in dry toluene (Scheme 4) and incubated at 40 °C for 16−20 h. The reactions produced mixtures of (*S*)-alcohol (*S*)-**8** and (*R*)-acetate (*R*)-**9** in all cases, which were separated by column chromatography. The acetates were hydrolyzed by KOH in aqueous methanolic solution to afford (*R*)-**8** in practically quantitative yields. The enantiopurities of the (*S*)-alcohols and the ester-liberated (*R*)-alcohols were elucidated by GC and/or HPLC and found to be ≥99% ee in each case. The absolute configuration of **8a** was determined by comparison with the commercially available enantiopure (*S*)-1-phenylpropenol (*S*)-**8a** via chiral GC. The absolute configuration of the remaining members of the series can be assumed to be the same,[11b] which was confirmed via their carbonates **5**.[12]

TABLE 2. Two-Pot synthesis of 1-Arylprop-2-en-1-ols and *tert*-Butyl 1-arylprop-2-en-1-yl Carbonates (Scheme 3)

entry	aldehyde	Ar	(±)-**8** (%)[a]	(±)-**5** (%)[b]	(*S*)-**5** (%)[c]	(*R*)-**5** (%)[c]
1	**4a**	C_6H_5	n/a[d]	95	96	92
2	**4d**	4-Br-C_6H_4	95[e] (74)[f]	85	91	n/a
3	**4e**	4-F-C_6H_4	77[f]	89	n/a	n/a
4	**4f**	3-F-C_6H_4	98[e]	90	97	98
5	**4i**	3,4-$(MeO)_2C_6H_3$	96[e] (78)[f]	n/a	99	n/a

[a] The reactions were carried out on a 80−125 mmol scale. [b] Isolated yield from the NaH method (10−65 mmol scale). [c] Isolated yield from the *n*-BuLi method, using the enantiopure alcohol (*S*)-**8** or (*R*)-**8** (5−30 mmol scale). [d] Commercial. [e] Isolated yield of pure product (without chromatography). [f] Isolated yield after chromatography.

SCHEME 4. Resolution of 1-Arylpropenols 8 (for Ar and yields, see Table 3)

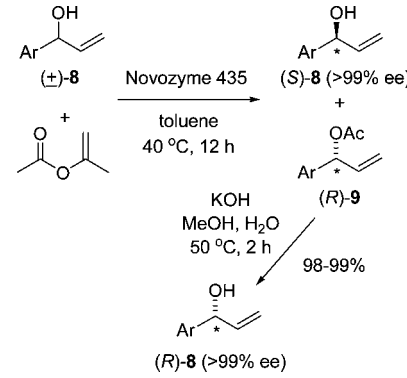


TABLE 3. Resolution of Racemic Alcohols 8 by Novozyme 435 (Scheme 4)[a]

entry	(±)-**8**	(*S*)-**8** (%)	(*R*)-**9** (%)	(*R*)-**8** (%)
1	**8a**	45	47	44
2	**8d**	22	43	42
3	**8f**	40	44	41
4	**8i**	22	46	45

[a] The reactions were carried out on a 40−75 mmol scale.

The synthesis of the corresponding nonracemic carbonates **5** was further optimized, namely, by using *n*-buthyllithium as a base instead of sodium hydride to generate the corresponding

(10) The products purified by chromatography were obtained in 74−78% yield. However, when only a small excess of the Grignard reagent (5−7%) was employed in the reaction, aqueous workup provided products of sufficient purity in 95−98% yield (Table 2, fourth column). These products were contaminated by minute amounts of a colored substance, which however could not even be detected by ^{1}H/^{13}C NMR spectroscopy.

(11) For a review, see: (a) Ghanem, A.; Aboul-Enein, H. Y. *Chirality* **2005**, *17*, 1–15. For more examples see: (b) Ghanem, A.; Schurig, V. *Tetrahedron: Asymmetry* **2003**, *14*, 57–62. (c) Maier, S.; Kazmaier, U. *Eur. J. Org. Chem.* **2000**, *7*, 1241–1251.

(12) The configuration was corroborated by the reaction of the carbonates **5** in a transition-metal-catalyzed allylic substitution with an enantiomerically pure alcohol, whose absolute configuration was known. Details of this chemistry will be revealed in due course. For a preliminary account, see ref 1d.

alkoxide. High yields and excellent purities of the desired products were attained without chromatography separation (Table 2, the last two columns). The main advantage of this procedure over that using NaH is that it allows an accurate dosing of the base (1.05 equiv), together with the use of a very small excess of Boc anhydride (1.01 to 1.02 equiv).

In summary, we have successfully prepared various enantiopure 1-arylpropenols **8** and their carbonates **5**. Several published procedures[8,11] were tested, modified, and optimized. These efforts resulted in the development of a robust synthetic procedure affording enantiopure carbonates **5** that will be utilized as the key starting materials for our novel approach to C-nucleosides.

Experimental Section

(±)-*tert*-Butyl 1-(3′-Fluorophenyl)prop-2-en-1-yl Carbonate (±)-(5f). 1-(3′-Fluorophenyl)prop-2-en-1-ol (±)-**8f** (1.600 g, 10.25 mmol) was added slowly to a suspension of sodium hydride (382 mg, 15.92 mmol, neat) in THF (25 mL) at room temperature, and the mixture was stirred for 15 min. The resulting solution was added slowly to a solution of Boc anhydride (2.460 g, 11.28 mmol) in THF (60 mL) at room temperature, and the mixture was stirred at room temperature overnight. The reaction was quenched with brine (20 mL), the mixture was diluted with ether (250 mL), washed with brine (3 × 50 mL), dried (Na_2SO_4), and evaporated. Chromatography on a column of silica gel (3 × 10 cm) with a mixture of hexanes and ethyl acetate (98.5:1.5) gave (±)-**5f** as a colorless oil (2.325 g, 90%): ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 1.48 (s, 9H, *t*-Bu), 5.25−5.36 (m, 2H, 3-H), 5.99 (ddd, $^3J_{2\text{-H},3\text{-Ha}}$ = 16.1 Hz, $^3J_{2\text{-H},3\text{-Hb}}$ = 10.7 Hz, $^3J_{2\text{-H},1\text{-H}}$ = 6.2 Hz, 1H, 2-H), 6.05 (m, 1H, 1-H), 6.98 (dddd, $^3J_{4'\text{-H,F}}$ = 8.5 Hz, $^3J_{4'\text{-H},5'\text{-H}}$ = 8.5 Hz, $^4J_{4'\text{-H},2'\text{-H}}$ = 2.6 Hz, $^4J_{4'\text{-H},6'\text{-H}}$ = 1.0 Hz, 1H, 4′-H), 7.08 (ddd, $^3J_{2'\text{-H,F}}$ = 9.6 Hz, $^4J_{2'\text{-H},4'\text{-H}}$ = 2.6 Hz, $^4J_{2'\text{-H},6'\text{-H}}$ = 1.0 Hz, 1H, 2′-H), 7.14 (dddd, $^3J_{6'\text{-H},5'\text{-H}}$ = 7.6 Hz, $^4J_{6'\text{-H},2'\text{-H}}$ = 1.0 Hz, $^4J_{6'\text{-H},4'\text{-H}}$ = 1.0 Hz, $^5J_{6'\text{-H,F}}$ = 0.4 Hz, 1H, 6′-H), 7.31 (ddd, $^3J_{5'\text{-H},4'\text{-H}}$ = 8.5 Hz, $^3J_{5'\text{-H},6'\text{-H}}$ = 7.6 Hz, $^4J_{5'\text{-H,F}}$ = 5.8 Hz, 1H, 5′-H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 27.74 (C(CH_3)$_3$), 78.37 (d, $^4J_{CF}$ = 1.9 Hz, CH-1), 82.59 (*C*(CH_3)$_3$), 113.89 (d, $^2J_{CF}$ = 22.4 Hz, CH-2′), 115.05 (d, $^2J_{CF}$ = 21.2 Hz, CH-4′), 117.65 (CH_2-3), 122.52 (d, $^4J_{CF}$ = 3.0 Hz, CH-6′), 130.07 (d, $^3J_{CF}$ = 8.2 Hz, CH-5′), 135.71 (CH-2), 141.35 (d, $^3J_{CF}$ = 7.1 Hz, C-1′), 152.60 (CO carbonate), 162.89 (d, $^1J_{CF}$ = 246.4 Hz, CF-3′); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −113.06.

(*R*)-(+)-*tert*-Butyl 1-(3′-Fluorophenyl)prop-2-en-1-yl Carbonate (*R*)-(+)-(5f). *n*-Butyllithium (16 mL, 32 mmol, 2.0 M solution in pentane) was added to a cold (0 °C) solution of 1-(3-fluorophenyl)prop-2-en-1-ol (*R*)-(−)-**8f** (4.679 g, 30.74 mmol) in THF (30 mL). The resulting solution was stirred at 0 °C for 10 min and then transferred (via cannula) to a solution of Boc anhydride (7.10 g, 32.5 mmol) in THF (100 mL) at 20 °C, and the mixture was stirred at this temperature for 3 h (TLC monitoring). The reaction was quenched with brine (20 mL), the mixture was diluted with ether (300 mL), washed with brine (3 × 100 mL), and dried (Na_2SO_4). Evaporation of the organic phase gave (*R*)-(+)-**5f** as a light yellow oil (7.60 g, 98%): $[\alpha]_D$ +14.2 (*c* 4.43, $CHCl_3$), >99% ee, chiral HPLC (Chiracel OJ-H, hexane/2-propanol 99:1, 0.500 mL·min^{-1}) t_R = 10.20 min ((*R*)-**5f**), t_R = 12.06 min ((*S*)-**5f**).

(*S*)-(−)-*tert*-Butyl 1-(3′-Fluorophenyl)prop-2-en-1-yl Carbonate (*S*)-(−)-(5f). 1-(3-Fluorophenyl)prop-2-en-1-ol (*S*)-(+)-**8f** (4.50 g, 29.6 mmol) was converted into (*S*)-(−)-**5f** (a light yellow oil; 7.24 g, 97%) using the *n*-butyllithium method: $[\alpha]_D$ −14.1 (*c* 3.58, $CHCl_3$), >99% ee.

(±)-1-(3′-Fluorophenyl)prop-2-en-1-ol (±)-(8f). Vinylmagnesium bromide (85 mL, 85 mmol, 1.0 M solution in THF) was added slowly to a cold (−83 °C) solution of 3-fluorobenzaldehyde (9.85 g, 79.4 mmol) in THF (100 mL). The reaction mixture was stirred for an additional 2 h (while the cooling bath was allowed to warm up to 0 °C), and the reaction was quenched with saturated aqueous solution of ammonium chloride (50 mL). The mixture was diluted with ethyl acetate (400 mL), washed with brine (3 × 100 mL), and dried (Na_2SO_4). Evaporation of the organic phase gave crude (±)-**8f** as a yellow oil (11.93 g, 98%): ^{1}H NMR (400.1 MHz, $CDCl_3$) δ 2.40 (d, $^3J_{OH,1\text{-H}}$ = 3.9 Hz, 1H, OH), 5.15−5.18 (m, 1H, 1-H), 5.21 (ddd, $^3J_{3\text{-Ha},2\text{-H}}$ = 10.3 Hz, $^2J_{3\text{-Ha},3\text{-Hb}}$ = 1.3 Hz, $^4J_{3\text{-Ha},1\text{-H}}$ = 1.3 Hz, 1H, 3-Ha), 5.34 (ddd, $^3J_{3\text{-Hb},2\text{-H}}$ = 17.1 Hz, $^2J_{3\text{-Hb},3\text{-Ha}}$ = 1.3 Hz, $^4J_{3\text{-Hb},1\text{-H}}$ = 1.3 Hz, 1H, 3-Hb), 5.99 (ddd, $^3J_{2\text{-H},3\text{-Hb}}$ = 17.1 Hz, $^3J_{2\text{-H},3\text{-Ha}}$ = 10.3 Hz, $^3J_{2\text{-H},1\text{-H}}$ = 6.2 Hz, 1H, 2-H), 6.97 (dddd, $^3J_{4'\text{-H,F}}$ = 8.6 Hz, $^3J_{4'\text{-H},5'\text{-H}}$ = 8.4 Hz, $^4J_{4'\text{-H},2'\text{-H}}$ = 2.6 Hz, $^4J_{4'\text{-H},6'\text{-H}}$ = 0.9 Hz, 1H, 4′-H), 7.09 (ddd, $^3J_{2'\text{-H,F}}$ = 9.9 Hz, $^4J_{2'\text{-H},4'\text{-H}}$ = 2.6 Hz, $^4J_{2'\text{-H},6'\text{-H}}$ = 1.8 Hz, 1H, 2′-H), 7.12 (dddd, $^3J_{6'\text{-H},5'\text{-H}}$ = 7.7 Hz, $^4J_{6'\text{-H},2'\text{-H}}$ = 1.0 Hz, $^4J_{6'\text{-H},4'\text{-H}}$ = 1.0 Hz, $^5J_{6'\text{-H,F}}$ = 0.4 Hz, 1H, 6′-H), 7.30 (ddd, $^3J_{5'\text{-H},4'\text{-H}}$ = 8.0 Hz, $^3J_{5'\text{-H},6'\text{-H}}$ = 7.9 Hz, $^4J_{5'\text{-H,F}}$ = 5.9 Hz, 1H, 5′-H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 74.65 (CH-1), 113.14 (d, $^2J_{CF}$ = 22.1 Hz, CH-2′), 114.44 (d, $^2J_{CF}$ = 21.2 Hz, CH-4′), 115.73 (CH_2-3), 121.79 (d, $^4J_{CF}$ = 2.9 Hz, CH-6′), 129.95 (d, $^3J_{CF}$ = 8.2 Hz, CH-5′), 139.63 (CH-2), 145.06 (d, $^3J_{CF}$ = 6.7 Hz, C-1′), 162.89 (d, $^1J_{CF}$ = 246.0 Hz, CF-3′).

(*R*)-(−)-1-(3′-Fluorophenyl)prop-2-en-1-ol (*R*)-(−)-(8f) and (*S*)-(+)-1-(3′-Fluorophenyl)prop-2-en-1-ol (*S*)-(+)-(8f). Novozyme 435 (2 g) was added to a mixture of a crude (±)-**8f** (11.52 g, 75.7 mmol), isopropenyl acetate (35 mL, 317 mmol), and activated 4 Å molecular sieves powder (10 g) in dry toluene (650 mL), and the resulting suspension was stirred at 40 °C for 20 h. The suspension was then cooled to ambient temperature, filtered, and evaporated. Gradient chromatography of the residue on a column of silica gel (8 × 10 cm) with a mixture of hexanes and ethyl acetate (98:2 to 96:4) gave the corresponding acetate (*R*)-**9f** as a colorless liquid (6.42 g, 44%), followed by (*S*)-**8f** (4.57 g, 40%) as a colorless liquid. The acetate (*R*)-**9f** (6.41 g, 33.0 mmol) was placed in a 100 mL flask and cooled to 0 °C, and a solution of KOH (2.13 g, 38.0 mmol) in MeOH (3.0 mL) was added dropwise. The cooling bath was removed, and the solution was heated at 50 °C for 2 h. The mixture was then cooled to ambient temperature, brine (50 mL) was added, and the resulting solution was extracted with ethyl acetate (3 × 80 mL) and the extract was dried (Na_2SO_4) and filtered. Evaporation of the filtrate furnished (*R*)-**8f** as a colorless liquid (4.76 g, 41%). The combined yield of both enantiomers was 81%. (*R*)-(−)-**8f**: $[\alpha]_D$ −12.25 (*c* 4.57, PhH). Anal. Calcd for C_9H_9FO: C, 71.04; H, 5.96. Found: C, 70.98; H, 6.01. (*S*)-(+)-**8f**: $[\alpha]_D$ +13.13 (*c* 4.53, PhH). Anal. Calcd for C_9H_9FO: C, 71.04; H, 5.96. Found: C, 70.78; H, 5.91.

Acknowledgment. We thank the University of Glasgow for a graduate fellowship to J.Š.

Supporting Information Available: Full experimental section and ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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