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Selective Reductions. 52. Efficient Asymmetric Reduction of α-Acetylenic α'-Fluoroalkyl Ketones with Either *B*-Chlorodiisopinocampheylborane or *B*-Isopinocampheyl-9-borabicyclo[3.3.1]nonane in High Enantiomeric Purity. The Influence of Fluoro Groups in Such Reductions

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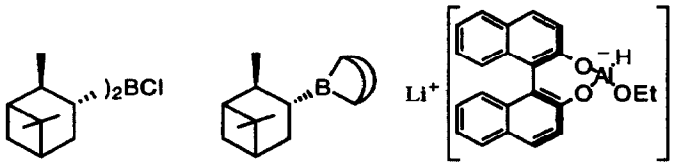
Abstract: A systematic study of the asymmetric reduction of prochiral α-acetylenic α'-fluoroalkyl ketones with (–)-*B*-chlorodiisopinocampheylborane [(–)-DIP-Chloride, **1**] and (–)-*B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane (*R*-Alpine-Borane, **2**) reveals that perfluoroalkyl acetylenic ketones can be reduced in very high ee (92-≥99%) with both of these reagents. For example, 1,1,1-trifluoro-4-phenyl-3-butyn-2-one, 1,1,1,2,2-pentafluoro-5-phenyl-4-pentyn-3-one, and 4,4,5,5,6,6,6-heptafluoro-1-phenyl-1-hexyn-3-one are all reduced with **1** in EE at –25 °C within 0.25-2 h in 98%, 96%, and 94% ee, respectively. The same ketones are reduced with **2** under neat condition, within 1-4 h at rt in 98%, 97%, and 96% ee, respectively. Similarly, 1,1,1-trifluoro-3-octyn-2-one, 1,1,1,2,2-pentafluoro-4-nonyn-3-one, and 1,1,1,2,2,3,3-heptafluoro-5-decyn-4-one are reduced with both **1** and **2** in ≥97% ee. Difluoromethyl and monofluoromethyl acetylenic ketones are reduced with **2** in relatively high ee (78-88% ee) whereas **1** is ineffective for these types of ketones. In all of the above reductions, the fluoroalkyl group acts as the enantiocontrolling group with one exception. A remarkable inversion in selectivity in the reduction of monofluoromethyl acetylenic ketones with **1** is observed as compared to the reduction with **2**, indicating that in the transition state the acetylenic moiety acts as the enantiocontrolling group instead of the anticipated monofluoromethyl group. These results highlight the combined effects of both the electronic and steric influences of the fluorine in controlling both the rate and the enantioselectivity in the asymmetric reduction of prochiral fluorinated acetylenic ketones.

INTRODUCTION

The preparation of fluorinated compounds, especially optically active derivatives has gained considerable attention due to their importance and increasing range of application.[2] The development of excellent chiral reducing agents has made the synthesis of optically active *secondary* alcohols a relatively simple affair.[3] However, the asymmetric reduction of fluoroketones is yet to receive appropriate attention.

Several years ago we introduced *B*-chlorodiisopinocampheylborane (**1**) (Aldrich: DIP-Chloride) as an excellent chiral reducing agent for the reduction of aralkyl ketones and α-hindered ketones.[4] When we tested **1** for a representative set of ten classes of ketones, it proved inefficient, among other classes, for the reduction of α-acetylenic ketones.[3d] However, another organoborane reagent derived from α-pinene, Alpine-Borane (**2**), introduced by Midland prior to our synthesis of **1**, is a superior reagent for the reduction of α-acetylenic ketones.[5] The mechanism of reductions by both **1** and **2** appear to be very similar. Later studies showed that **1** is an efficient reagent for the reduction of hindered acetylenic ketones[6] and α-perfluoroalkyl ketones[7] whereas **2** reacts only slowly with these ketones and provides the alcohols in relatively poor ee.

In the reduction of trifluoromethyl ketones with **1**, the $-CF_3$ group acts as though it is comparable to a *tert*-butyl group, *albeit* for different reasons, in controlling the stereoselectivity of the reduction.[7,8] Based on this we expected an α-acetylenic α'-trifluoromethyl ketone to be reduced with **1** in high ee and decided to test this possibility. A related study comparing the reduction of mono-, di-, and trifluromethyl alkynyl ketones with **2** and another widely used reagent for the reduction of alkynyl ketones, Binal-H (**3**),[9] has been described by Kobayashi and coworkers.[10]

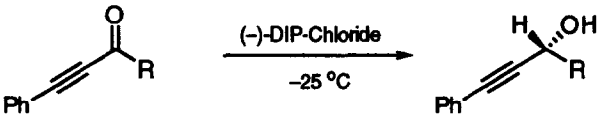


(–)-DIP-Chloride, **1** *R*-Alpine-Borane, **2** Binal-H, **3**

They reported that **2** provided the product alcohols with the anticipated stereochemistry in 74-90% ee.[10] It is known that reagent **2** is inefficient to reduce hindered ketones,[5] including hindered alkynyl ketones,[6] and perfluorinated aryl and alkyl ketones.[7] The reduction of trifluoromethyl acetylenic ketones with **2** shows that the electron-withdrawing acetylenic moiety largely overcomes the rate retarding effect of *t*-butyl and $-CF_3$ groups and facilitates the reaction. Apart from the desire to test the capability of **1** to reduce fluorinated acetylenic ketones, we were curious to know the effect of fluorine containing groups in conjunction with an acetylenic moiety in asymmetric reduction with **1** for comparison of the results with those obtained for reductions with **2**. The results are presented herein.

RESULTS AND DISCUSSION

1,1,1-Trifluoro-4-phenyl-3-butyn-2-one (**4c**) reacts with **1**, in ethyl ether (EE), 1*M*, at –25 °C, within 15 min and the usual diethanolamine workup provides the alcohol **5c** in 81% yield and in 98% ee in the *S*-isomer (eq 1) (The *S*-configuration, a consequence of the Cahn-Ingold-Prelog priority rules, is stereochemically equivalent to the *R*-configuration in the hydrocarbon analogs).[11] This result was expected, given the consistency of reagent **1** in successfully reducing alkyl and aryl trifluoromethyl ketones, with the $-CF_3$ group always acting as the enantiodirector, providing the product alcohols in very high ee.[6] The present result extends this reduction to α-acetylenic α'-trifluoromethyl ketones as well. It is interesting to note that earlier we had obtained poor ee for the reduction of simple acetylenic ketones, such as 4-phenyl-3-butyn-2-one (**4a**) (21% ee, *R*)[4] and very high ee for the reduction of hindered acetylenic ketones, such as 4,4-dimethyl-1-phenyl-1-pentyn-3-one (**4b**) (≥99% ee, *R*)[6] with **1** (eq 1). In the reduction of the hydrocarbon analogues, we correlated the stereocontrol of the reduction in terms of the relative steric requirements of the two groups on either side of the carbonyl moiety. Since an acetylenic moiety acts as a smaller group even when compared with a methyl group,[5] we expected the $-CF_3$ group to act as the larger group unless some major electronic influence intervenes, and the *S*-configuration of the product alcohol obtained supports this assumption.



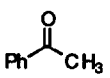
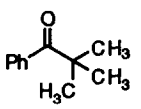
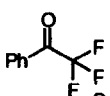
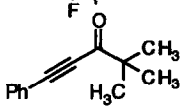
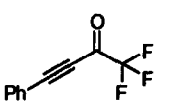
4a R = Me
4b R = *t*-Bu
4c R = CF_3

5a R = Me : 21% ee, *R*
5b R = *t*-Bu : ≥99% ee, *R*
5c R = CF_3 : 98% ee, *S*

(1)

A comparison of the rates of reduction of *tert*-butyl and trifluoromethyl ketones with **1** is worthy of discussion at this point (Table 1). Pivalophenone and α,α,α-trifluoroacetophenone were both reduced by **1**, providing the product alcohols with stereochemistry opposite to that of the product from the reduction of acetophenone itself. However, only 60% of pivalophenone is reduced within 14 d under neat condition at room temperature (rt) whereas the trifluoromethyl ketone is reduced completely within 1 d. This could be attributed to the effect of the electronegativity of the fluorine atoms α- to the carbonyl group. Midland had reported that in these types of reductions the rate is accelerated by electron-withdrawing groups present in the ketone which enhances the rate limiting hydride transfer.[12] Compared to the 14 d for the complete reduction of *tert*-butyl phenyl ketone, *tert*-butyl acetylenic ketone requires only 8 h at rt, due to the acetylenic moiety. When the trifluoromethyl group and the acetylenic group on either side of the carbonyl moiety act concurrently, it requires only 15 min for the reduction even in a 1*M* EE solution at –25 °C.

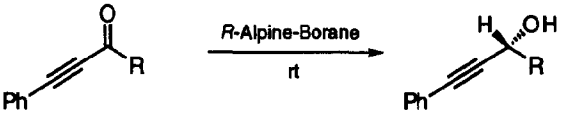
Table 1. Comparison of the Rates, % ee and Configuration of the Product Alcohols from the Reduction of *tert*-Butyl and Trifluoromethyl Ketones with 1 and 2.

ketone	(-)-DIP-Chloride				(*R*)-Alpine-Borane			
	react. cond.	time	% ee	config.	react. cond.	time	% ee	config.
	EE, 1 *M*, –25 °C	3 h	98	*S*[a]	neat, rt	14 d	87	*S*[b]
	neat, rt[c]	14 d	79	*R*[a]	neat, rt	very slow reaction		
	neat, rt	24 h	90	*S*[d,e]	neat, rt	45 d	32	*R*[d,e]
	neat, rt	8 h	98	*R*[f]	neat, rt	14 d[c]	80	*R*[a]
	EE. 1*M*, –25 °C	6 d	≥99	*R*				
	EE, 1 *M*, –25 °C	0.25 h	98	*S*[e]	neat, rt	1 h	98	*S*[e]

[a]Ref. 4. [b]Ref. 5. [c]For 50% reaction. [d]Ref. 7. [e]The *S* and *R* configurations are equivalent to *R* and *S* configurations, respectively in the hydrocarbon analog (ref. 11). [f]Ref. 6.

The chlorine atom present in **1** also plays a role in accelerating the rate of reduction by increasing the Lewis acidity of the reagent.[4] But, a comparison of the reduction of the above ketones with **2** should distinguish the effect of the fluorine atoms on the rate. In contrast to the reduction with **1**, pivalophenone does not undergo

reduction with **2** and phenyl trifluoromethyl ketone is reduced, 90% within 45 d, mostly by the achiral 9-BBN produced by dehydroboration of **2**.[13] Even a *tert*-butyl acetylenic ketone requires 14 d for 50% reduction. Yet, **2** reduces **4c** in 1 h and the product alcohol is obtained in 98% ee (eq 2). Again, a combination of the effects of the acetylenic and the trifluoromethyl groups results in a rapid reaction! The reaction of **2** and a trifluoromethyl alkyl ketone requires several weeks for completion[7] and an α-acetylenic ketone without the α'-trifluoromethyl group requires a relatively longer time for reaction.[6]



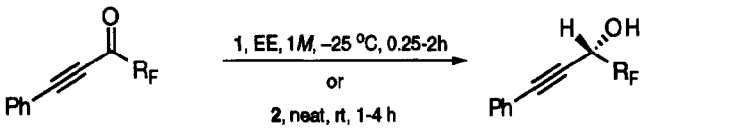
(2)

4a R = Me — **5a** R = Me : 83% ee, *R*

4b R = *t*-Bu — **5b** R = *t*-Bu : 80% ee, *R*

4c R = CF_3 — **5c** R = CF_3 : 98% ee, *S*

To ascertain whether this effect is general for the reduction of α-acetylenic α'-perfluoroalkyl ketones with **1** and **2**, the corresponding α'-pentafluoroethyl and α'-heptafluoropropyl acetylenic ketones, 1,1,1,2,2-pentafluoro-5-phenyl-4-pentyn-3-one (**4d**) and 4,4,5,5,6,6,6-heptafluoro-1-phenyl-1-hexyn-3-one (**4e**), respectively were prepared using a procedure similar to that reported in the literature[14] and reduced with **1** and **2** (eq 3). We observed that **1** reduces these ketones within 2 h providing the alcohols in 96% ee, and 94% ee respectively, and reagent **2** also reduces them within 4 h in 97% ee and 96% ee, respectively (eq 3). Knowing that **1** reduces pentafluoroethyl and heptafluorobutyl phenyl ketones within 3 d providing the *S*-alcohols in 87-92% ee while reagent **2** needs 20 days for only 15-20% reaction providing the *R*-alcohols in 40-48% ee, it follows that once again the combined electron-withdrawing capabilities of the acetylenic and perfluoroalkyl groups might be accelerating the rate and providing the alcohols in high ee with both of these reagents. Based on the analogy of the trifluoromethyl ketones, we expect the *S* isomer for both pentafluoroethyl and heptafluoropropyl alcohols as well.



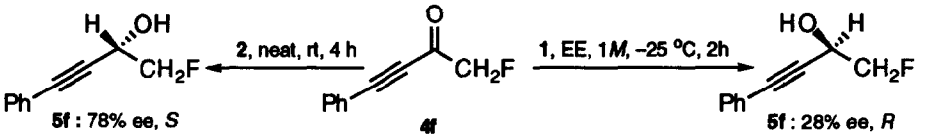
(3)

4c R_F = CF_3 — **5c** R_F = CF_3 : 98% ee, *S*

4d R_F = C_2F_5 — **5d** R_F = C_2F_5 : 96 or 97% ee, *S*

4e R_F = C_3F_7 — **5e** R_F = C_3F_7 : 94 or 96% ee, *S*

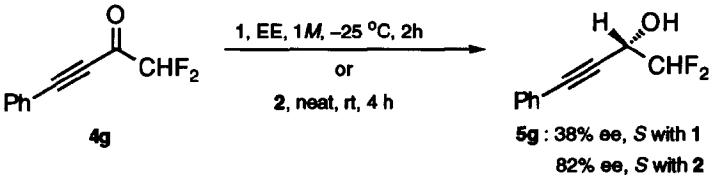
Since the introduction of three fluorine atoms revealed a considerable influence on the enantioselectivity in contrast to the reduction of non-fluorinated acetylenic ketones with **1** (21% –> 98%), it was desirable to examine the effect of the stepwise introduction of the fluorine atoms. Accordingly, the corresponding mono- and difluoromethyl acetylenic ketones, **4f** and **4g** were treated with **1** and **2**. Reduction of the monofluoroalkyl alkynyl ketone **4f** with **1** and **2** provides product alcohols with *opposite* configurations in 28% ee and 78% ee, respectively (eq 4).



(4)

This result is quite unexpected since the proposed transition state for the reduction with **1**, which is very similar to that for the reduction with **2**, considers the acetylenic moiety as the group with smaller steric requirements even when compared with a methyl group. Evidently, the influence of the electronic nature of the CH_2F group interacting with the chlorine of the reagent results in the change of direction of the enantioselectivity (Scheme I).

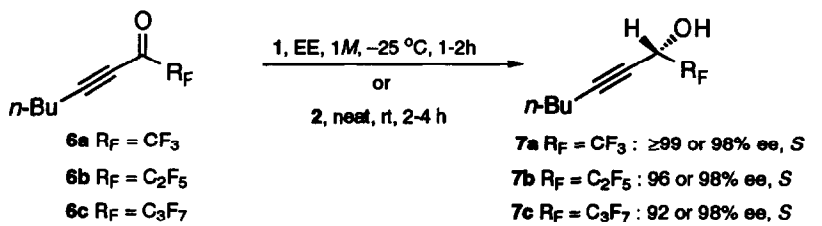
The reduction of **4g** with **1** is complete within 2 h and workup provides the product alcohol, **5g**, in 84% yield and 38% ee, while the reaction with **2** provides 82% ee (eq 5). The gas chromatographic analyses of the α-methoxy α-(trifluoromethyl)phenylacetates (MTPA derivative)[15] of the product alcohols from the above reactions reveal the same major isomer in excess, proving that both of them have the *S*-configuration. The fact that we obtain the same configuration for the alcohols derived from the reduction of the difluoromethyl and trifluoromethyl acetylenic ketones with **1** and **2** and the opposite configuration of the product alcohol from the reduction of the monofluoromethyl ketone adds to the interest of their study.



(5)

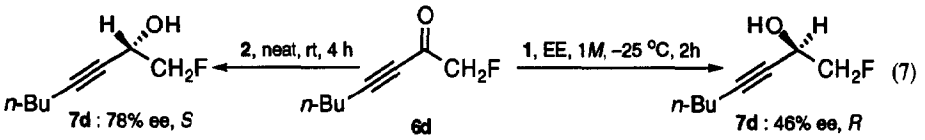
The enigmatic inversion of selectivity in the reduction of monofluoromethyl alkynyl ketone with **1** prompted us to prepare another series of mono-, di- and trifluoromethyl acetylenic ketones by replacing the phenyl group in **4c-g** with an *n*-butyl group, and to study their reductions with both **1** and **2**. This would help in eliminating any electronic influence the phenyl ring might exert on the reduction.

As the following results show, no influence of the phenyl group in the reduction of perfluorinated acetylenic ketones is identified while some effect in the reduction of mono- and difluoromethyl acetylenic ketones with **1** is observed. The trifluoromethyl, pentafluoroethyl and heptafluoropropyl acetylenic ketones (**6a**, **6b**, and **6c**, respectively) are reduced with **1** in 2 h to the *S*-alcohol in high ee (92-≥99%) (eq 6). Reagent **2** reduces them within 2-4 h with the same high enantioselectivity (98% ee), enriched in the *S* isomer. The electronic/steric or their combined effects of the perfluoroalkyl group overtake all other influences in determining the direction of the enantioselection process.



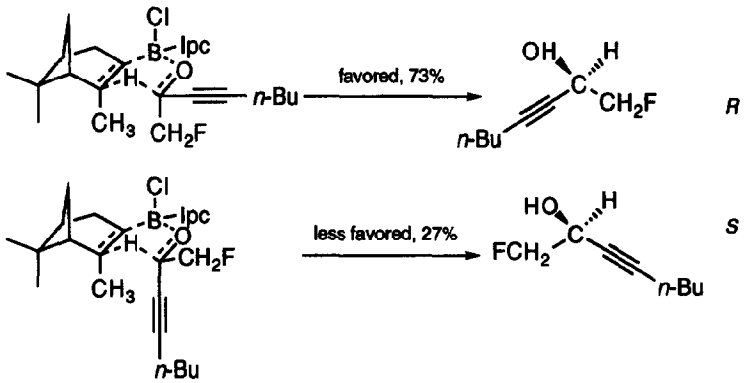
(6)

But, as in the case of **4f**, the monofluoromethyl acetylenic ketone **6d** is also reduced by **1** and **2** to the corresponding propargylic alcohols with *opposite* configurations in 46% ee and 78% ee, respectively (eq 7).



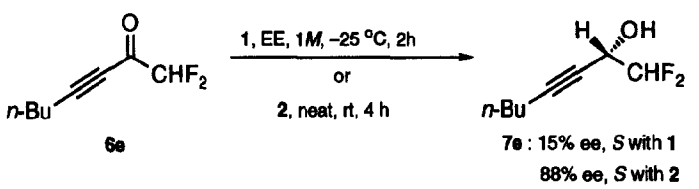
(7)

The electronic and/or steric influence is more pronounced in this case. It is fascinating to observe that 73% of the product is realized *via* a transition state where the acetylenic moiety behaves as though it were a group with larger steric requirements, as compared to the monofluoromethyl group (Scheme I).



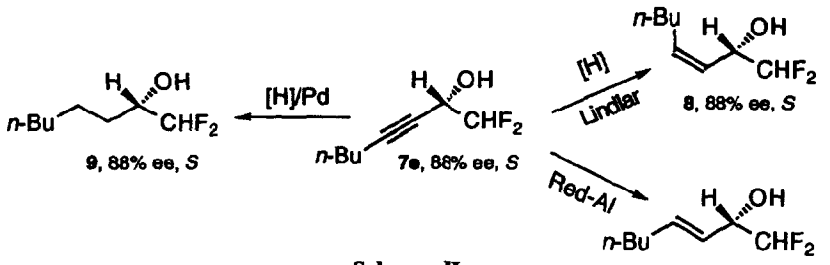
Scheme I

As in the earlier case, the product alcohol of same configuration (*S*) was obtained for the reaction of the difluoromethyl ketone **6e** with **1** (15% ee) and **2** (88% ee) (eq 8). However, the % ee obtained for **6e** (15%) with **1** is lower than that obtained for **4g** with **1** (38%). The change in the direction of asymmetric induction (38% ee, *S* –> 15% ee, *S*) is the same as in the case of monofluoromethyl acetylenic ketones, **4f** and **6d** (28% ee, *R* –> 46% ee, *R*). In both series of acetylenic ketones (**4** and **6**) ~10% more of the *R*-alcohol is formed in the reduction of the monofluoromethyl ketone compared to the difluoromethyl ketone *via* an increasing participation of the acetylenic moiety as the enantiocontrolling group in the transition state. This effect is felt only with the reagent containing the chlorine atom, probably indicating its electronic interactions with the fluorine of the ketone in the transition state. The results are summarized in Table 2.



(8)

The high synthetic utility of these acetylenic alcohols is indicated in the following scheme. As representative examples, we converted **6e** to the corresponding *Z*-enol[16] (**8**) and to the saturated alcohol (**9**) (Scheme II).



Scheme II

While the olefinic alcohols could probably be obtained *via* the reduction of olefinic difluoromethyl ketones, we know that the synthesis of *n*-alkyl difluoromethyl alcohols in high ee *via* the asymmetric reduction of the corresponding ketone is difficult.[17] The olefinic bond can also be converted to other functionalities, such as epoxides which can be functionalized further. All of these make this ready synthesis of fluorinated propargylic alcohols in high ee a desirable development.

Table 2. Asymmetric Reduction of α-Acetylenic α'-Fluoroalkyl Ketones with (–)-DIP-Chloride and (*R*)-Alpine-Borane

ketone	R-C≡C-CO-R_F		DIP-Chloride				Alpine-Borane			
reduced	R	R_F	time h	yield %	ee[a] %	config.[b]	time h	yield %	ee[a] %	config.[b]
4a	Ph	CH_3	2	92	21[c]	*R*	8	82	82[d]	*R*[c]
4f	Ph	CH_2F	2	88	28	*R*	4	91	78	*S*
4g	Ph	CHF_2	2	84	38	*S*	4	87	82	*S*
4c	Ph	CF_3	0.25	81	98	*S*	1	89	98	*S*
4d	Ph	C_2F_5	2	77	96	*S*	4	90	97	*S*
4e	Ph	C_3F_7	2	78	94	*S*	4	88	96	*S*
6d	*n*-Bu	CH_2F	2	79	46	*R*	4	89	78	*S*
6e	*n*-Bu	CHF_2	2	74	15	*S*	4	80	88	*S*
6a	*n*-Bu	CF_3	1	76	≥99	*S*	2	78	98	*S*
6b	*n*-Bu	C_2F_5	2	72	96	*S*	4	80	98	*S*
6c	*n*-Bu	C_3F_7	2	72	92	*S*	4	82	98	*S*

[a]Analyzed as the MTPA ester on a capillary GC. [b]The *R* and *S* configurations of the fluoro alcohols correspond to the *S* and *R* alcohols, respectively derived from the hydrocarbon analogs, such as **4a**. [c]Ref. 4. [d]Ref. 5b.

CONCLUSIONS

We have made a systematic study of the effect of fluoroalkyl groups on the asymmetric reduction of acetylenic ketones with **1** and **2**, both of which proved to be efficient for the reduction of perfluoroalkyl alkynyl ketones. This is the first instance where a particular class of ketone is reduced efficiently with both of these chiral organoborane reagents. In all other cases studied thus far, they are complementary to each other.[4-8] While **1** fails to reduce mono- and difluoromethyl alkynyl ketones efficiently, reagent **2** can be used for the efficient chiral reduction of these ketones. Only reagent **2** is capable of reducing these ketones in high ee since it has been shown that the other commonly used reagent for alkynyl ketones, *viz.* **3** also reduces alkynyl fluoroalkyl ketones in only moderate (19% - 65%) ee.[10]

This study provides an excellent route for the preparation of optically active fluorinated acetylenic alcohols in very high ee, compounds which are readily transformed into various other classes of fluorinated compounds, greatly extending the scope of these reagents. The commercial availability of both isomers of reagents **1** and **2** makes the preparation of either enantiomer of these alcohols simple. Moreover, evidence has been obtained for the electronic influences of the fluorine atom in the enantioselection process in the asymmetric reduction of fluoroalkyl ketones, especially with reagent **1**. It is difficult to provide a rationale for the unexpected inversion in configuration of the product alcohol obtained from the reduction of monofluoromethyl acetylenic ketone with **1** unless the molecular mechanics of the reaction is examined. This suggests that our proposed mechanism is incomplete and provides a subject for further exploration. We are continuing our investigations of the reduction of several other classes of fluoroketones with **1** and **2** and are looking into the molecular mechanics of these reactions.

EXPERIMENTAL SECTION

General Methods. Techniques for handling air-sensitive compounds have been previously described.[18] ^{1}H, ^{13}C, ^{11}B, and ^{19}F NMR (CF_3COOH as external standard at δ –76.5 ppm) spectra were plotted on a Varian Gemini-300 spectrometer and IR spectra were plotted on a Perkin-Elmer 1420 ratio recording spectrophotometer. Mass spectra were recorded with a Finnigan gas chromatograph-mass spectrometer model 4000. GC analyses were done on a OV-3 column (1/8'x6') using a Varian 3400 gas chromatograph having a flame ionization detector and a built-in integrator. Analyses of the MTPA esters were performed on a Hewlett-Packard 5890A gas chromatograph using a Supelcowax glass capillary column (15 m), or a SPB-5 capillary column (30 m), at appropriate temperatures, and integrated using a Hewlett-Packard 3390A integrator. Optical rotations were measured using a Rudolph Autopol III polarimeter.

Materials. Ethyl ether (Mallinckrodt) was used as such. DIP-Chloride, Alpine-Borane, acetaldehyde, ethanolamine, diethanolamine, menthyl chloroformate, ethyl fluoroacetate, ethyl trifluoroacetate, phenylacetylene, 1-hexyne, *n*-butyllithium, borontrifluoride etherate, Lindlar catalyst, and palladium on activated carbon were all obtained from Aldrich Chemical Co. Ethyl difluoroacetate was obtained from Strem Chemicals. Preparation of the ketones are detailed below. α-Methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) was obtained from Aldrich Chemical Co. and converted to the acid chloride using Mosher's procedure.[15]

Preparation of the α-Acetylenic α'-Fluoroalkyl Ketones.

General Procedure.[14] *n*-Butyllithium (100 mmol, 2.0 *M* solution in hexanes) was added to a solution of RC≡CH (100 mmol) in 150 mL dry THF at –78 °C. The solution was stirred for 30 min. at –78 °C, and ethyl fluoroalkylacetate (100 mmol) in THF (200 mL) was added, followed by, 15 mL of BF_3•EE. The reaction mixture was stirred for an additional 1.5 h at –78 °C, warmed to –25 °C, and saturated NH_4Cl (60 mL) was then added. The organic phase was separated, washed with brine, and dried over $MgSO_4$. Removal of the solvents and distillation provided the required α-acetylenic α'-fluoroalkyl ketone.

Preparation of individual ketones and their physical characteristics are detailed below.

1,1,1-Trifluoro-4-phenyl-3-butyn-2-one (4c). Ethyl trifluoroacetate (100 mmol) was treated with 100 mmol of the alkynyllithium prepared from phenylacetylene as described in the general procedure to provide **4c** in 66% yield: bp 97-99 °C/30 mm Hg (lit.[14] bp 93-95 °C/25 mm Hg); IR ν_{max} cm^{-1} (neat): 2198 (C≡C), 1695 (C=O); ^{1}H NMR δ (ppm) ($CDCl_3$): 7.22-7.79 (m, Ph); ^{13}C NMR δ (ppm) ($CDCl_3$): 83.11 (C_3), 100.31 (C_4), 114.96 (q, J = 288.2 Hz, C_1), 117.95 (C_1'), 128.79 (C_3'), 132.39 (C_4'), 133.72 (C_2'), 166.92 (q, J = 42.1 Hz, C_2); ^{19}F NMR δ (ppm) ($CDCl_3$): –78.58 (s).

1,1,1,2,2-Pentafluoro-5-phenyl-4-pentyn-3-one (4d). Ethyl pentafluoropropionate was treated with the alkynyllithium from phenylacetylene as above to provide the ketone **4d** in 83% yield: bp 53-54 °C/ 0.65 mm Hg (lit.[19] bp 92-94 °C/14 mm Hg). IR ν_{max} cm^{-1} (neat): 2196 (C≡C), 1697 (C=O); ^1H NMR δ (ppm) ($CDCl_3$): 7.18-7.75 (m, Ph);^{13}C NMR δ (ppm) ($CDCl_3$): 83.86 (C_4), 101.36 (C_5), 106.63 (qt, J = 265.6, 38.5 Hz, C_2), 118.08 (C_1'), 117.99 (tq, J =286.9, 34.4 Hz, C_1), 128.91 (C_3'), 132.59 (C_4'), 133.89 (C_2'), 169.10 (t, J = 30.2 Hz, C_3); ^{19}F NMR δ (ppm) ($CDCl_3$): –82.08 (s, CF_3), –122.07 (s, CF_2). MS EI: *m/z*: 248 $(M)^+$, 129 $(M–C_2F_5)^+$ (100%); CI: *m/z*: 249 $(MH)^+$ (100%).

4,4,5,5,6,6,6-Heptafluoro-1-phenyl-1-hexyn-3-one (4e). Ethyl heptafluorobutyrate was treated with phenylalkynyllithium as above to provide **4e** in 55% yield: bp 52-54 °C/ 0.4 mm Hg (lit.[20] bp 76 °C/9 mm Hg). Anal calcd. for $C_{12}H_5F_7O$: C, 48.34; H, 1.69. Found: C, 48.53; H, 1.43; IR ν_{max} cm^{-1} (neat): 2194 (C≡C), 1698 (C=O); ^1H NMR δ (ppm) ($CDCl_3$): 7.18-7.82 (m, Ph); ^{13}C NMR δ (ppm) ($CDCl_3$): 84.10 (C_2), 101.42 (C_1), 105.96-111.00 (m, C_4, C_5), 117.65 (tq, J = 287.6, 33.4 Hz, C_6), 118.18 (C_1'), 128.92 (C_3'), 132.6 (C_4'), 133.89 (C_2'), 168.87 (m, C_3); ^{19}F NMR δ (ppm) ($CDCl_3$): –80.87 (t, J =8.6 Hz -CF_2-), –119.54 (q, J = 8.6 Hz, -CO-CF_2-), –126.43 (s, CF_2-CF_3); MS EI: *m/z*: 298 $(M)^+$, 129 $(M–C_3F_7)^+$ (100%); CI: *m/z*: 299 $(MH)^+$ (100%).

1-Fluoro-4-phenyl-3-butyn-2-one (4f). Treatment of ethyl fluoroacetate with the alkynyllithium from Phenylacetylene as described above yields 55% of the ketone **4f**. mp 39-39.5 °C; IR ν_{max} cm^{-1} (nujol): 2205 (C≡C), 1681 (C=O); ^1H NMR δ (ppm) ($CDCl_3$): 5.01 (d, J = 47.2 Hz, 2H, CH_2F), 7.38-7.64 (m, 5 H, C_6H_5); ^{13}C NMR δ (ppm) ($CDCl_3$): 84.09 (C_3), 84.56 (d, J = 187.8, C_1), 95.61 (C_4), 118.72 (C_1'), 128.49 (C_3'), 131.19 (C_4'), 133.01 (C_2'), 181.27 (d, J = 22.5 Hz, C_2); ^{19}F NMR δ (ppm) ($CDCl_3$): –224.91 (t, J = 47.0 Hz); MS EI: *m/z*: 162 $(M)^+$, 129 $(M–CH_2F)^+$ (100%); CI: *m/z*: 163 $(MH)^+$ (100%).

1,1-Difluoro-4-phenyl-3-butyn-2-one (4g). Phenylalkynyllithium was treated with ethyl difluoroacetate to provide **4g** in 75% yield: bp 126-130 °C/25 mm Hg; IR ν_{max} cm^{-1} (neat):2208 (C≡C), 1692 (C=O); ^{19}F NMR δ (ppm) ($CDCl_3$): –125.83 (d, J = 53.9 Hz).

1,1,1-Trifluoro-3-octyn-2-one (6a). This ketone was prepared from 1-hexynyllithium and ethyl trifluoroacetate as described in the general procedure. Yield: 83%; bp 55-57 °C/25 mm Hg; (lit.[14] bp 70 °C/65 mm Hg). IR ν_{max} cm^{-1} (neat): 2163 (C≡C), 1695 (C=O); ^{19}F NMR δ (ppm) ($CDCl_3$): –78.89 (s).

1,1,1-2,2-Pentafluoro-4-nonyn-3-one (6b). This ketone was prepared from 1-hexynyllithium and ethyl pentafluoropropionate as described above. Yield: 70%; bp 63-65 °C/20 mm Hg. Anal calcd. for $C_9H_9F_5O$: C, 47.38; H, 3.98; F, 41.63. Found: C, 47.23; H, 3.84; F, 41.36; IR ν_{max} cm^{-1} (neat): 2215 (C≡C), 1704 (C=O); ^1H NMR δ (ppm) ($CDCl_3$): 0.95 (t, J = 7.2 Hz, 3H, CH_3), 1.40-1.53 (m, 2H, -CH_2-CH_3), 1.59-1.69 (m, 2H, -CH_2-CH_2-CH_3), 2.52 (t, J = 7.2 Hz, 2H, -C≡C-CH_2-); ^{13}C NMR δ (ppm) ($CDCl_3$): 12.76 (C_9), 18.84 (C_6), 21.81 (C_8), 29.22 (C_7), 76.50 (C_4), 105.77 (C_5), 106.49 (qt, J = 265.2, 38.3 Hz, C_2), 118.15 (tq, J = 321.4, 34.6 Hz, C_1), 169.11 (t, J = 29.7 Hz, C_3); ^{19}F NMR δ (ppm) ($CDCl_3$) –82.38 (s, CF_2F_3), –122.37 (s, CF_2CF_3); MS EI: *m/z* : 213 $(M–CH_3)^+$, 109 $(M–C_2F_5)^+$ (100); CI: *m/z*: 229 $(MH)^+$ (100%).

1,1,1,2,2,3,3-Hepatafluoro-5-decyn-4-one (6c). Ethyl heptafluorobutyrate was treated with 1-hexynyllithium as described above to provide **6c** in 60% yield: bp 70-72 °C/20 mm Hg; IR ν_{max} cm^{-1} (neat): 2213 (C≡C), 1705 (C=O); ^1H NMR δ (ppm) ($CDCl_3$): 0.95 (t, J = 7.3 Hz, 3H, -CH_3), 1.40-1.53 (m, 2H, -CH_2-CH_3), 1.58-1.69 (m, 2H, -CH_2-CH_2-CH_3), 2.52 (t, J = 7.0 Hz, 2H, -C≡C-CH_2-); ^{13}C NMR δ (ppm) ($CDCl_3$): 13.06 (C_{10}), 19.01 (C_7), 21.85 (C_9), 29.19 (C_8), 76.95 (C_5), 106.20 (C_6), 105.64-111.07 (m, C_2, C_3), 117.51 (tq, J = 287.6, 32.9 Hz, C_1), 169.05 (t, J = 30.7 Hz, C_4); ^{19}F NMR δ (ppm) ($CDCl_3$): –80.90 (t,

J = 8.7 Hz, CF_3), –119.62 (q, J = 8.7 Hz, $-CF_2-CF_2-CF_3$), 126.47 (s, $CF_2-CF_2-CF_3$). MS EI: *m/z* : 263 $(M-CH_3)^+$, 109 $(M-C_3F_7)^+$ (100);CI: *m/z*: 279 $(MH)^+$, (100%).

1-Fluoro-3-octyn-2-one (6d). This ketone was prepared from 1-hexynyllithium and ethyl fluoroacetate as described in the general procedure. Yield: 42%, bp 108-110 °C/40 mm Hg. Anal. calcd. for $C_8H_{11}FO$: C, 67.59; H, 7.80; F, 13.36. Found: C,67.68; H, 7.97; F, 13.13; IR ν_{max} cm^{-1} (neat): 2210 (C≡C), 1703 (C=O); ^1H NMR δ (ppm) ($CDCl_3$): 0.94 (t, J = 7.2 Hz, 3H, $-CH_3$), 1.38-1.51 (m, 2H, $-CH_2-CH_3$), 1.53-1.64 (m, 2H, $-CH_2-CH_2-CH_3$), 2.43 (dt, J = 6.9, 1.1 Hz, 2H, $CH_2-CH_2-CH_2-CH_3$), 4.88 (d, J = 47.2 Hz, 2H, CH_2F); ^{13}C NMR δ (ppm) (C_6D_6): 13.61 (C_8), 18.86 (C_5), 22.34 (C_7), 30.04 (C_6), 77.73 (C_3), 85.43 (d, J = 186.7 Hz, C_1), 99.49 (C_4), 181.49 (d, J = 21.9 Hz, C_2); ^{19}F NMR δ (ppm) ($CDCl_3$): –225.10 (t, J = 47.3 Hz, CH_2F); MS EI: *m/z* : 122 $(M-HF)^+$, 109 $(M-CH_2F)^+$ (100%);CI: *m/z*: 143 $(MH)^+$ (100%).

1,1-Difluoro-3-octyn-2-one (6e). Ethyl difluoroacetate was treated with 1-hexynyllithium as described in the standard procedure to obtain 71% of **6e**: bp 100-106 °C/ 70 mm Hg (lit.[14] bp 85 °C/60 mm Hg); IR: ν_{max} cm^{-1} (neat): 2213 (C≡C), 1697 (C=O); ^{19}F NMR δ (ppm) ($CDCl_3$): –126.45 (d, J = 54.5 Hz, CHF_2).

Reduction of Acetylenic Ketones With (–)-DIP-Chloride. General Procedure. An oven-dried, 50 mL round-bottom flask equipped with a side-arm, magnetic stirring bar, and a connecting tube was cooled to rt in a stream of nitrogen. (–)-DIP-Chloride (11 mmol) was transferred to the flask in a glove bag and dissolved in EE (10 mL). The solution was cooled to –25 °C, and the ketone (10 mmol) was added using a syringe. The reaction was followed by ^{11}B NMR spectrum after aliquots were methanolyzed at –25 °C at periodic intervals. When the reaction was complete (^{11}B δ: 32 ppm), the mixture was raised to 0 °C and diethanolamine (22 mmol) was added dropwise. The mixture was warmed to rt and left stirred for 2 hours when the boranes precipitated as a complex which was filtered and washed with pentane. The filtrate was concentrated and distilled to collect the α-pinene and the product alcohol in separate flasks. The alcohol was further purified by preparative GC using appropriate columns (SE-30 or Carbowax 20M). The rotation was measured. The MTPA ester of the alcohol was prepared by standard procedure.[15] Racemic alcohols of the ketones were obtained by reducing with $NaBH_4$. All the racemic alcohols were converted to the MTPA esters and analyzed on a capillary GC to obtain the diastereomeric pairs of peaks. Then the optically active esters were analyzed to obtain the enantiomeric excess.

Reduction of Acetylenic Ketones with Alpine-Borane. General Procedure. To a 50-mL round-bottomed flask fitted as usual,[18] 12 mmol of the reagent was added, followed by the acetylenic ketone (10 mmol) and the mixture stirred at rt. The reaction was followed by ^{11}B NMR of an aliquot dissolved in EE. When the reaction was complete (^{11}B δ: 52 ppm), acetaldehyde (3 mmol) was added at 0 °C and stirred at rt for 30 min. EE (20 mL) was then added to the reaction mixture followed by ethanolamine (12 mmol) and stirred for 1 h. The precipitated boron component was filtered and washed with pentane. The filterate was concentrated and distilled to yield the alcohol. The MTPA ester was then prepared and analyzed on an appropriate capillary GC column to determine the % ee.

S-(–)-1,1,1-Trifluoro-4-phenyl-3-butyn-2-ol (5c).

(a) From reduction with 1. Reduction of **4c** with (–)-**1** was complete in 15 min. and workup as described above provided 81% yield of the product alcohol **5c**. bp 70-71 °C/0.5 mm Hg (lit.[21] bp 98-100 °C/5 mm Hg); $[\alpha]_D^{20}$ = –13.1 (*c* 2.6, $CHCl_3$). Analysis of its MTPA derivative on a SPB-5 capillary column showed it to be of 98% ee. ^{19}F NMR: δ($CDCl_3$): –80.01 (d, J = 6.6Hz).

(b) From reduction with 2. A reaction of **4c** with **2** was complete, at rt, within 1 h and the product **5c** was obtained in 89% yield. The MTPA derivative showed the product to be of 98% ee in the same isomer as obtained from the reduction with **1**.

S-(–)-1,1,1,2,2-Pentafluoro-5-phenyl-4-pentyn-3-ol (5d).

(a) From reduction with 1. The reaction of 10 Mmol of **4d** with 11 mmol of (–)-**1** in EE at –25 °C was complete in 2 h. Workup as usual provided **5d** in 77% yield: bp 70-71 °C/ 0.5 mm Hg. Analysis calcd for $C_{11}H_7F_5O$: C, 52.81; H, 2.82; F, 37.98. Found: C, 52.42; H, 2.62; F, 37.62. Analysis of its MTPA ester on a SPB-5 capillary column showed it to be of 96% ee. IR ν_{max} cm^{-1} neat: 3386 (OH), 2241 (C≡C); ^1H NMR δ (ppm) ($CDCl_3$): 2.70 (d, *J* = 5.1 Hz, 1H, CHOH), 4.98-5.08 (m, 1H, CHOH), 7.30-7.51 (m, 5H, C_6H_5); ^{13}C NMR δ (ppm) (CD_3COCD_3): 62.72 (t, *J* = 27.0 Hz, C_3), 82.16 (C_4), 88.36 (C_5), 113.48 (qt, *J* = 258.2, 35.4 Hz, C_2), 120.10 (tq, *J* = 286.7, 35.3 Hz, C_1), 122.34 (C_1'), 129.34 (C_3'), 130.12 (C_4'), 132.56 (C_2'); ^{19}F NMR δ (ppm) ($CDCl_3$): –81.96 (s, CF_3), –128.02 (dd, *J* = 270.2, 13.7 Hz, CFF'-CF_3), –123.31 (dd, *J* = 270.2, 7.9 Hz, CFF'-CF_3); MS EI: *m/z*: 250 M^+, 233 $(M–OH)^+$ 131 $(M–C_2F_5)^+$ (100%); CI: *m/z*: 251 $(MH)^+$, 233 $(MH–H_2O)^+$ (100%).

(b) From reduction with 2. A reaction of **4d** with **2** was complete in 4 h. The usual ethanolamine workup gave the product **5d** in 90% yield. $[\alpha]_D^{21}$ = –7.63 (*c* 1.6, $CHCl_3$). Analysis of the MTPA ester using a capillary GC showed it to be of 97% ee in the same isomer as above.

S-(–)-4,4,5,5,6,6,6-Heptafluoro-1-phenyl-1-hexyn-3-ol (5e).

(a) From reduction with 1. 10 Mmol of **4e** was treated with 11 mmol of (–)-**1** in EE at –25 °C. The reaction was complete in 2 h. Workup as usual provided **5e** in 80% yield: bp 75-76 °C/ 0.55 mm Hg. Analysis calcd for $C_{12}H_7F_7O$: C, 48.01; H, 2.35. Found: C, 48.38; H, 2.62. Analysis of its MTPA ester on a SPB-5 capillary column showed it to be of 94% ee. IR ν_{max} cm^{-1} neat: 3379 (OH), 2238 (C≡C); ^1H NMR δ (ppm) ($CDCl_3$): 3.12 (s, 1H, CHOH), 5.05-5.12 (m, 1H, CHOH), 7.30-7.55 (m, 5H, C_6H_5); ^{13}C NMR δ (ppm) ($CDCl_3$): 62.55 (t, *J* = 27.5 Hz, C_3), 79.84 (C_2), 89.08 (C_1), 106.60-112.00 (m, C_5), 113.50 (tt, *J* = 261.1, 29.3 Hz, C_4), 117.81 (tq, *J* = 287.6, 34.1 Hz, C_6), 120.95 (C_1'), 128.43 (C_3'), 129.54 (C_4'), 131.99 (C_2'); ^{19}F NMR δ (ppm) ($CDCl_3$): –81.78 (t, *J* = 9.7 Hz, CF_3), –121.26 (md, *J* = 277.7 Hz, -CFF'-CF_2-CF_3), –124.95 (md, *J* = 278.7 Hz, -CFF'-CF_2-CF_3), –126.31 (t, *J* = 6.6 Hz, -CF_2-CF_2-CF_3); MS EI: *m/z*: 300 M^+, 131 $(M–C_3F_7)^+$ (100%); CI: *m/z*: 301 $(MH)^+$, 283 $(MH–H_2O)^+$ (100%).

(b) From reduction with 2. A reaction of **4e** with **2** was complete in 4 h, and the usual ethanolamine workup gave the product **5e** in 88% yield. $[\alpha]_D^{21}$ = –4.1 (*c* 2.1, $CHCl_3$). Analysis of the MTPA ester using a capillary GC showed it to be of 96% ee in the same isomer as above.

R-(–)-1-Fluoro-4-phenyl-3-butyn-2-ol (5f). 10 Mmol of **4f** was treated with 11 mmol of (–)-**1** in EE at –25 °C. The reaction was complete in 2 h. Workup as usual provided **5f** in 88% yield: bp 120-22 °C/ 0.55 mm Hg. Analysis calcd for $C_{10}H_9FO$: C, 73.16; H, 5.53; F, 11.57. Found: C, 72.77; H, 5.41; F, 11.36. Analysis of its MTPA ester on a SPB-5 capillary column showed it to be of 28% ee (*R*). IR ν_{max} cm^{-1} neat: 3379 (OH), 2230 (C≡C); ^1H NMR δ (ppm) ($CDCl_3$): 2.57 (d, *J* = 4.6 Hz, 1H, CHOH), 4.56-4.76 (m, 2H, CH_2F), 4.76-4.98 (m, 1H, CHOH), 7.42-7.50 (m, 5H, C_6H_5); ^{13}C NMR δ (ppm) ($CDCl_3$): 62.22 (d, *J* = 23.9 Hz, C_2), 84.37 (d, *J* = 11.9 Hz, C_3), 85.42 (d, *J* = 176.7 Hz, C_1), 86.76 (d, *J* = 1.8 Hz, C_4), 121.77 (C_1'), 128.35 (C_3'), 128.91 (C_4'), 131.83 (C_2'); ^{19}F NMR δ (ppm) ($CDCl_3$) –224.21 (dt, *J* = 47.2, 16.1Hz); MS EI: *m/z*: 164 M^+, 146 $(M–H_2O)^+$, 131 $(M–CH_2F)^+$ (100%); CI: *m/z*: 165 $(MH)^+$, 147 $(MH–H_2O)^+$ (100%).

S-(+)-1-Fluoro-4-phenyl-3-butyn-2-ol (5f). A reaction of **4f** with **2** was complete in 4 h, and the usual ethanolamine workup gave the product **5f** in 91% yield. $[\alpha]_D^{20}$ = +14.89 (*c* 2.5, $CHCl_3$). Analysis of the MTPA ester using a capillary GC showed it to be of 78% ee in the opposite isomer as compared to the product obtained from the reaction with **1**. Since it has been shown that **2** gives the *S*-isomer for the product,[10] the product derived with **1** must be the *R*-alcohol.

S-(–)-1,1-Difluoro-4-phenyl-3-butyn-2-ol (5g).

(a) From reduction with 1. 10 Mmol of **4g** was treated with 11 mmol of (–)-**1** in EE at –25 °C. The reaction was complete in 2 h. Workup as usual provided **5g** in 84% yield: bp 100-101 °C/ 0.50 mm Hg. Analysis calcd for $C_{10}H_8F_2O$: C, 65.93; H, 4.43; F, 20.86. Found: C, 65.80; H, 4.34; F, 20.68. Analysis of its MTPA ester on a SPB-5 capillary column showed it to be of 38% ee (*S*). IR ν_{max} cm^{-1} neat: 3375 (OH), 2236 (C≡C); ^1H NMR δ (ppm) ($CDCl_3$): 2.56 (s, 1H, CHO<u>H</u>), 4.75 (t, *J* = 9.2 Hz, 1H, C<u>H</u>OH), 5.82 (dt, *J* = 55.8, 3.7 Hz, 1H, C<u>H</u>F_2), 7.30-7.50 (m, 5H, C_6<u>H_5</u>); ^{13}C NMR δ (ppm) ($CDCl_3$): 63.46 (t, *J* = 27.5 Hz, C_2), 82.12 (t, *J* = 5.2 Hz, C_3), 87.96 (C_4), 113.72 (t, *J* = 246.97 Hz, C_1), 121.34 (C_1'), 128.40 (C_3'), 129.24 (C_4'), 131.98 (C_2'); ^{19}F NMR δ (ppm) ($CDCl_3$) –128.81 (ddd, *J* = 55.6, 9.9, 4.5 Hz); MS EI: *m/z*: 182 M^+, 165 $(M–OH)^+$, 131 $(M–CHF_2)^+$ (100%); CI: *m/z*: 183 $(MH)^+$, 165 $(MH–H_2O)^+$ (100%).

(b) From reduction with 2. A reaction of **4g** with **2** was complete in 4 h, and the usual ethanolamine workup gave **5g** in 87% yield. $[\alpha]_D^{21}$ = –14.8 (*c* 0.94, $CHCl_3$). Analysis of the MTPA ester using a capillary GC showed it to be of 82% ee in the same isomer as compared to the product obtained from the reaction with **1**. Since it has been shown that **2** gives the *S*-isomer for the product,[10] the product derived with **1** must also be the *S*-alcohol.

S-(–)-1,1,1-Trifluoro-3-octyn-2-ol (7a).

(a) From reduction with 1. Reduction of **6a** with (–)-**1** in EE at 25 °C was complete in 1 h and workup as described above provided 76% yield of **7a**: bp 94-96 °C/5 mm Hg (lit.[21] bp 90-92/4 mm Hg); $[\alpha]_D^{21.5}$ = –13.18 (*c* 3.1, $CHCl_3$). Analysis of its MTPA derivative on a SPB-5 capillary column showed it to be of ≥99% ee. ^{19}F NMR: δ($CDCl_3$): –80.31 (d, *J* = 6.7Hz).

(b) From reduction with 2. A reaction of **6a** with **2** was complete, at rt, within 2 h and the product **7a** was obtained in 78% yield. The MTPA derivative showed the product to be of 98% ee in the same isomer as obtained from the reduction with **1**.

S-(–)-1,1,1-2,2-Pentafluoro-4-nonyn-3-ol (7b).

(a) From reduction with 1. 10 Mmol of **6b** was treated with 11 mmol of (–)-**1** in EE at –25 °C. The reaction was complete in 2 h. Workup as usual provided **7b** in 82% yield: bp 130-31 °C/ 20 mm Hg. Analysis calcd for $C_9H_{11}F_5O$: C, 46.96; H, 4.82. Found: C, 46.66; H, 4.69. Analysis of its MTPA ester on a SPB-5 capillary column showed it to be of 96% ee (*S*). IR ν_{max} cm^{-1} neat: 3376 (OH), 2246 (C≡C); ^1H NMR δ (ppm) ($CDCl_3$): 0.92 (t, *J* = 7.3 Hz, 3H, -C<u>H</u>$_3$), 1.35-1.68 (m, 4H, -C<u>H</u>$_2$-C<u>H</u>$_2$CH$_3$), 2.26 (dt, *J* = 6.8, 1.9 Hz, 2H, C<u>H</u>$_2$-C≡C), 2.56 (br s, 1 H, CHO<u>H</u>), 4.73-4.82 (m, 1H, C<u>H</u>OH); ^{13}C NMR δ (ppm) ($CDCl_3$): 13.21 (C_9), 18.17 (C_6), 21.78 (C_8), 30.67 (C_7), 61.84 (t, *J* = 27.5 Hz, C_3), 71.54 (C_4), 90.59 (C_5), 111.93 (qt, *J* = 258.2, 35.7 Hz, C_2), 118.85 (tq, *J* = 286.7, 35.3 Hz, C_1); ^{19}F NMR δ (ppm) ($CDCl_3$): –81.97 (s, CF_2-C<u>F</u>$_3$), –124.53 (dd, *J* = 270.5 Hz *J* = 7.8 Hz, -C<u>F</u>F'-CF$_3$), –128.72 (dd, *J* = 270.5, 13.0 Hz, -CF<u>F</u>'-CF$_3$); MS EI: *m/z*: 229 $(M–H)^+$, 213 $(M–OH)^+$, 111 $(M–C_2F_5)^+$ (100); CI: *m/z*: 231 $(MH)^+$, 213 $(MH–H_2O)^+$ (100).

(b) From reduction with 2. A reaction of **6b** with **2** was complete in 4 h, and the usual ethanolamine workup gave **7b** in 89% yield. $[\alpha]_D^{21}$ = –4.16 (*c* 3.6, $CHCl_3$). Analysis of the MTPA ester using a capillary GC showed it to be of 98% ee in the same isomer (*S*) as compared to the product obtained from the reaction with **1**.

S-(–)-1,1,1-2,2,3,3-Heptafluoro-5-decyn-4-ol (7c).

(a) From reduction with 1. 10 Mmol of **6c** was treated with 11 mmol of (–)-**1** in EE at –25 °C for 2 h. The usual diethanolamine workup provided **7c** in 82% yield: bp 135-37 °C/20 mm Hg. Analysis calcd for $C_{10}H_{11}F_7O$: C, 42.87; H, 3.96; F, 47.46. Found: C, 42.52; H, 3.84; F, 47.25. Analysis of its MTPA ester on a SPB-5 capillary column showed it to be of 92% ee (*S*). IR ν_{max} cm^{-1} neat: 3375 (OH), 2244 (C≡C); ^1H NMR δ (ppm) ($CDCl_3$): 0.92 (t, *J* = 7.3 Hz, 3H, -C<u>H</u>$_3$), 1.34-1.57 (m, 4H, -C<u>H</u>$_2$-C<u>H</u>$_2$CH$_3$), 2.26 (dt, *J* = 6.9, 1.9 Hz, 2H, C≡C-C<u>H</u>$_2$), 2.40 (br s, 1 H, CHO<u>H</u>), 4.76-4.88 (m, 1H, C<u>H</u>OH); ^{13}C NMR δ (ppm)

($CDCl_3$): 13.27 (C_{10}), 18.22 (C_7), 21.78 (C_9), 30.10 (C_8), 62.04 (t, J = 27.5 Hz, C_4), 71.60 (C_5), 90.44 (C_6), 106.75-112.20 (m, C_2), 113.46 (tt, J = 230.8, 29.4 Hz, C_3), 117.79 (tq, J = 288.5, 33.9 Hz, C_1); ^{19}F NMR δ (ppm) ($CDCl_3$): –81.94 (t, J = 9.8 Hz, CF_3), –121.65 (md, J = 278.1 Hz, -CFF'-CF_2-CF_3), –125.43 (md, J = 278.1 Hz, -CFF'-CF_2-CF_3), –126.43 (t, J = 5.4 Hz, CF_2-CF_2-CF_3); MS EI: *m/z*: 263 $(M–OH)^+$, 111 $(M–C_3F_7)^+$ (100%); CI: *m/z*: 281 $(MH)^+$, 263 $(MH–H_2O)^+$ (100%).

(b) From reduction with 2. A reaction of **6b** with **2** was complete in 4 h, and the usual ethanolamine workup gave **7b** in 82% yield. $[\alpha]_D^{21}$ = –2.95 (*c* 3.3, $CHCl_3$). Analysis of the MTPA ester using a capillary GC showed it to be of 98% ee in the same isomer (*S*) as compared to the product obtained from the reaction with **1**.

R-(–)-1-Fluoro-3-octyn-2-ol (7d). 10 Mmol of **6d** was treated with 11 mmol of (–)-**1** in EE at –25 °C. The reaction was complete in 2 h. Workup as usual provided **7d** in 74% yield. Analysis of its MTPA ester on a SPB-5 capillary column showed it to be of 46% ee (*R*). IR ν_{max} cm^{-1} neat: 3382 (OH), 2238 (C≡C); ^1H NMR δ (ppm) ($CDCl_3$): 0.91 (t, J = 7.2 Hz, 3H, -CH_3), 1.33-1.55 (m, 4H, -CH_2-CH_2CH_3), 2.22 (dt, J 6.9 Hz, 1.9 Hz, 2 H, -CH_2-C≡C), 2.60 (br d, 1 H, CHOH), 4.25-4.57 (m, 2H, CH_2F), 4.56-4.69 (m, 1H, CHOH); ^{13}C NMR δ (ppm) ($CDCl_3$): 13.29 (C_8), 18.10 (C_5), 21.70 (C_7), 30.30 (C_6), 61.58 (d, J = 23.8 Hz, C_2), 75.77 (d, J = 11.9 Hz, C_3), 85.58 (d, J = 175.9, C_1) 87.49 (C_4); ^{19}F NMR δ (ppm) ($CDCl_3$) –223.11 (dt, J = 47.3 Hz, J = 15.0 Hz); MS EI: *m/z*: 127 $(M–OH)^+$, 111 $(M–CH_2F)^+$ (100%); CI: *m/z*: 145 $(MH)^+$, 127 $(MH–H_2O)^+$ (100%).

S-(+)-1-Fluoro-3-octyn-2-ol (7d). A reaction of **6d** with **2** was complete in 4 h, and the usual ethanolamine workup gave **7d** in 89% yield. $[\alpha]_D^{21}$ = +12.97 (*c* 2.5, $CHCl_3$). Analysis of the MTPA ester using a capillary GC showed it to be of 78% ee in the opposite isomer (*S*) as compared to the product obtained from the reaction with **1**.

S(–)-1,1-Difluoro-3-octyn-2-ol (7e).

(a) From reduction with 1. 10 Mmol of **6e** was treated with 11 mmol of (–)-**1** in EE at –25 °C. The reaction was complete in 2 h. Workup as usual provided **7e** in 74% yield. Analysis calcd for $C_8H_{12}F_2O$: C, 59.25; H, 7.46; F, 23.43. Found: C, 58.88; H, 7.58; F, 23.11. Analysis of its MTPA ester on a SPB-5 capillary column showed it to be of 15% ee (*S*). IR ν_{max} cm^{-1} neat: 3367 (OH), 2239 (C≡C); ^1H NMR δ (ppm) ($CDCl_3$): 0.92 (t, J = 7.2 Hz, 3H, -CH_3), 1.34-1.56 (m, 4H, -CH_2-CH_2CH_3), 2.25 (dt, J = 7.0 Hz, 1.9 Hz, 2H, -CH_2-C≡C), 2.97 (br s, 1 H, CHOH), 4.47-4.53 (m, 1H, CHOH), 5.69 (dt, J = 56.0, 3.8 Hz, 1H, CHF_2); ^{13}C NMR δ (ppm) ($CDCl_3$): 13.55 (C_8), 18.35 (C_5), 21.93 (C_7), 30.34 (C_6), 63.03 (t, J = 27.3 Hz, C_2), 73.74 (t, J = 5.3 Hz, C_3), 89.31 (C_4), 114.06 (t, J = 246.4 Hz, C_1); ^{19}F NMR δ (ppm) ($CDCl_3$) –128.52 (ddd, J = 55.7, 9.9, 7.2 Hz).

(b) From reduction with 2. A reaction of **6e** with **2** was complete in 4 h, and the usual ethanolamine workup gave the product **7e** in 80% yield. $[\alpha]_D^{21}$ = –2.52 (*c* 3.4, $CHCl_3$). Analysis of the MTPA ester using a capillary GC showed it to be of 88% ee in the same isomer as compared to the product obtained from the reaction with **1**.

S-(–)-1,1-difluoro-[Z]-oct-3-en-2-ol (8). Semi-hydrogenation of 7e. A solution of the above 1,1-difluoro-3-octyn-2-ol (10 mmol) and Lindlar catalyst (10%) in methanol was stirred under an atmosphere of hydrogen at rt until the rate of hydrogenation dropped (15 min). The suspension was filtered through celite to yield 92% of **8**. Purification of this alcohol by preparative gas chromatography yielded ≥96% stereochemically pure Z-alcohol. $[\alpha]_D^{21}$ = –8.9 (*c* 1.7, $CHCl_3$); Analysis calcd for $C_8H_{14}F_2O$: C, 58.15; H, 8.94; F, 22.91. Found: C, 58.51; H, 8.61; F, 23.14. Analysis of the MTPA ester of this product on an SPB-5 capillary column showed an ee of 88%. IR ν_{max} cm^{-1} neat: 3373 (OH), 1658 (C=C); ^1H NMR δ (ppm) ($CDCl_3$): 0.91 (t, J = 7.2 Hz, 3H, CH_3), 1.26-1.42 (m, 4H, CH_3-CH_2-CH_2-), 2.03 (d, J = 4.4 Hz, 1H, OH), 2.05-2.2 (m, 2H, C_3H_7-

CH_2-), 4.50-4.68 (m, 1H, CH-OH), 5.37-5.86 (m, 3H, CHF_2, -HC=CH-); ^{13}C NMR δ (ppm) ($CDCl_3$): 14.3, 22.72, 28.25, 31.9, 67.96 (t, J = 24.7 Hz, C_2), 116.0 (t, J = 244.5 Hz, C_1), 123.36 (t, J = 3.7 Hz, C_3), 138.73 (C_4), ^{19}F NMR δ (ppm) ($CDCl_3$): –129.41 (dd, J = 56.1, 10.8 Hz); Ms EI: *m/z*: 146 $(M–H_2O)^+$, 57 $(C_4H_9)^+$ (100%); CI: *m/z*: 165 $(MH)^+$, 147 $(MH–H_2O)^+$, 127 $[MH–(H_2O+HF)]^+$ (100%).

S-(–)-1,1-difluoro-2-octanol (9). Hydrogenation of 7e. A solution of 1,1-difluoro-3-octyn-2-ol (25 mmol) in THF was externally hydrogenated in the presence of 5% Pd on activated carbon in a Brown's hydrogenator[22] until no more hydrogen was abosorbed. The suspension was filtered through celite and washed with 20 mL of THF. The combined washings were concentrated to yield 90% of **9**. $[\alpha]_D^{21}$ = –21.63 (*c* 2.0, $CHCl_3$) which corresponds to ≥99% ee based on the reported rotation in the literature[23] $[\alpha]_D^{21}$ = –20.3 (*c* 1.99, $CHCl_3$) for 98% ee. Analysis of the MTPA derivative on a SPB-5 capillary column showed the product to be of 88% ee. ^1H NMR δ (ppm) ($CDCl_3$): 0.89 (t, J = 6.7 Hz, 3H, $-CH_3$), 1.20-1.57 (m, 10H, $-(CH_2)_5-CH_3$), 2.0 (br s, 1H, OH), 3.65-3.80 (m, 1H, CHOH), 5.61 (dt, J = 56.2, 4.2 Hz, 1H, CHF_2-); ^{13}C NMR δ (ppm) ($CDCl_3$): 14.51, 23.04, 25.30, 29.56, 30.48, 32.12, 71.64 (t, J = 23.2 Hz, C_2), 116.87 (t, J =243.5 Hz, C_1); ^{19}F NMR δ (ppm) ($CDCl_3$): –129.75 (ddd, J = 56.3, 11.0, 6.4 Hz).

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