JOC Article

Highly Diastereoselective Reductive Coupling of 2-Bromo-2,3,3,3-tetrafluoropropanamide with Aldehydes Promoted by Triphenylphosphine−Titanium(IV) Isopropoxide. An Efficient Route to the Synthesis of *erythro*-α-Fluoro-α-(trifluoromethyl)-*β*-hydroxy Amides

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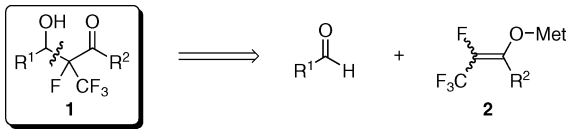
The reductive coupling reaction of *N*-methoxy-*N*-methyl-2-bromo-2,3,3,3-tetrafluoropropanamide (Weinreb amide) with various aldehydes under the influence of the combined reagent, 1.2 equiv each of triphenylphosphine and titanium(IV) isopropoxide, took place smoothly at ambient temperature to give the corresponding α-fluoro-α-(trifluoromethyl)-*β*-hydroxy amides in a highly *erythro*-selective manner. The high *erythro* selectivity was also obtained even by employing a combination of triphenylphosphine (1.2 equiv) and a catalytic amount of titanium(IV) isopropoxide.

Introduction

The introduction of fluorine atom(s) into an organic molecule often dramatically alters its chemical properties and pharmacological profiles, especially in the case of biologically active compounds. As a consequence, many efforts have been put forth toward the development of new synthetic routes to various classes of fluorinated compounds.[1] Out of the diversity of fluorinated compounds, α-fluoro-α-(trifluoromethyl)-*β*-hydroxy carbonyl compounds **1** (Scheme 1), involving two successive stereocenters, are recognized as one of the most important synthetic units in organofluorine chemistry as well as in organic synthesis because the nonfluorinated counterparts are frequently found in the frameworks of naturally occurring substances. To synthesize such a compound **1** stereoselectively, as shown in Scheme 1, the aldol reaction of the metal enolate **2** bearing α-fluoro and α-trifluoromethyl (CF_3) groups with aldehydes would be a general and powerful tool, in view of the extensive studies in the nonfluorinated enolate chemistry.[2] However, the literature has embraced merely quite limited studies on such a reaction of **2**, this being largely because the generation of this type of enolate **2** is often hampered by its decomposition through a fluoride ion elimination.[3] Additionally, the enolate **2** is less reactive than the nonfluorinated counterpart since the electron density at the reactive carbon decreases owing to the electron withdrawal of the CF_3 group.

SCHEME 1



Over the past two decades, intense attempts have been made to realize the proper reaction conditions or means which facilitate the aldol reaction in question without fluoride ion elimination. A few modified means for the aldol reaction have been developed successfully. For example, treating a mixture of ethyl 2,3,3,3-tetrafluoropropanoate and various carbonyl compounds in THF with LDA at −90 to −70 °C (called as the electrophile-coexisting aldol reaction) gives the corresponding *β*-hydroxy esters **1** in 66−80% yields, but with almost no diastereoselectivity.[4] 1-Substituted 1-perfluoroalkenyl phosphates are subjected to reductive dephosphorylation with diisobutylaluminum hydride to generate the corresponding aluminum enolates, which react smoothly with various aldehydes to give rise to the corresponding *β*-hydroxy ketones **1** as diastereomeric mixtures in good yields.[5,6] On the other hand, the highly stereoselective aldol reaction between 2,3,3,3-tetrafluoropropanamides and aldehydes is effected by using Bu_2BOTf and Et_3N, in which the in situ formed boron enolates react with various aldehydes to provide the *threo* isomers of the corresponding *β*-hydroxy amides **1** exclusively.[7,8]

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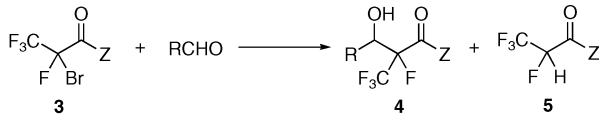
SCHEME 2



a: Z = N(OMe)Me
b: Z = NBu_2
c: Z = OBn

During the course of our studies on the chemistry of this type of enolates **2** and their aldol and related reactions, we have successfully attained an efficient and convenient means for the highly stereoselective aldol reaction of the enolate derived from 2-bromo-2,3,3,3-tetrafluoropropanamide **3a** (Z = N(OMe)Me, Scheme 2). Herein, we wish to describe the results of the reductive coupling reactions between the amides or ester **3** and various aldehydes promoted by a combination of triphenylphosphine and Lewis acid. The reaction of **3a** is the first example of the *erythro*-selective aldol reaction of the type of enolate **2** and can be complementary to the boron enolate-mediated aldol reaction reported previously.[8]

Results and Discussion

Phosphine/Lewis Acid-Mediated Reductive Coupling Reaction of 3. Recent literature has disclosed the original applications of the combination system of phosphine/Lewis acid to the aldol-type reaction.[9,10] Thus, this combined reagent has the characteristic ability of reducing α-halo carbonyl compounds to generate the corresponding enolate, which reacts smoothly with various carbonyl compounds, affording the coupling products in good yields with high stereoselectivity. These results strongly stimulated us to apply the combined reagent to fluorinated α-bromo carbonyl compounds.

We initiated our research for optimal conditions of the reaction between 2-bromo-2,3,3,3-tetrafluoropropanamide **3a** (called as Weinreb amide), prepared readily from the corresponding acid chloride, and the combined reagent. Thus, to a solution of 1.2 equiv of BF_3·Et_2O in CH_2Cl_2 was added 1.2 equiv each of benzaldehyde and triphenylphosphine in this order. After the above reaction mixture was stirred for 10 min at 0 °C, **3a** was added and the whole was stirred for 24 h at ambient temperature (Scheme 3). As a result, the desired α-fluoro-α-(trifluoromethyl)-*β*-hydroxy amide **4aa** was obtained in 37% yield as a diastereomeric mixture of the *erythro*- and *threo*-isomers[11] in a ratio of 67:33, respectively, together with the debrominated product **5a** in 44% (Table 1, entry 1). A number of Lewis acids were examined to improve the yield and diastereoselectivity. Neither zinc triflate nor zinc iodide gave the desired adduct at all (entries 2 and 3), and aluminum Lewis acids, such as Et_2AlCl and $EtAlCl_2$, effected the reaction with low diastereoselectivity to give a mixture of the *erythro*- and *threo*-isomers in 84% and 66% yield, respectively (entries 4 and 5). Changing the Lewis acid from Et_2AlCl to $TiCl_2(O\text{-}i\text{-}Pr)_2$ resulted in a substantial decrease in the yield (26%), and the *erythro* selectivity was profoundly increased from 67% to 96%, though a large amount of **5a** (65% yield) was produced (entry 7). Very interestingly, when $Ti(O\text{-}i\text{-}Pr)_4$ was employed as Lewis acid in place of $TiCl_2(O\text{-}i\text{-}Pr)_2$, significant improvement of the yield was realized without any decrease of the diastereoselectivity; the coupling product **4aa** was obtained in 84% yield with 97% *erythro* selectivity (entry 8). Other reaction conditions were further examined by using $Ti(O\text{-}i\text{-}Pr)_4$ as Lewis acid. As can be seen in entries 10−13, the amounts and the sorts of phosphine used were found to affect both chemical yield and diastereoselectivity. Thus, the use of tributylphosphine furnished a mixture of the *erythro*- and *threo*-isomers in a ratio of 43:57 (entry 10). On decreasing the amount of triphenylphosphine from 120 to 20 or 0 mol %, the chemical yield was decreased to 16% and 0%, respectively (entries 11 and 12). It should be noted that the reactions in polar solvents, such as acetonitrile and THF, took place in a highly *erythro*-selective manner, whereas the reaction did not in a nonpolar solvent such as toluene (entries 14−16).

With the optimized reaction conditions (Table 1, entry 8), the reductive coupling reaction of 2-bromo-2,3,3,3-tetrafluoropropanamide **3a** with various aldehydes was examined. The results are summarized in Table 2.

As in the reaction with benzaldehyde, various aromatic aldehydes, such as *p*-methylbenzaldehyde, *p*-methoxybenzaldehyde, and *p*-fluorobenzaldehyde, underwent the reaction with high diastereoselectivity to afford preferentially the corresponding *erythro* products **4a** in high yields (entries 1−4). The reaction with α,*β*-unsaturated aldehydes, such as crotonaldehyde and cinnamaldehyde, also efficiently proceeded in a highly diastereoselective fashion (entries 5 and 6). The bulkiness of the aldehyde was observed to affect the efficiency of the reaction. When the substituent R in aldehyde was changed from *n*-propyl to isopropyl or *tert*-butyl, the yield of **4a** was decreased from 72% to 65% or 53% yield, respectively, but the diastereoselectivity was obtained with a satisfactorily high level (entries 7−9).

To expand the scope of this reductive coupling reaction, the reactions of related amide **3b** (Z = NBu_2) and ester **3c** (Z = OBn) with benzaldehyde were examined similarly.

In sharp contrast to the reaction of the Weinreb amide **3a**, $Ti(O\text{-}i\text{-}Pr)_4$ did not efficiently promote the reaction of **3b** and **3c** (entries 1 and 6). Then, a variety of Lewis acids, such as $TiCl_4$, $Zn(OTf)_2$, Et_2AlCl, and $EtAlCl_2$, were reexamined for the reactions both of **3b** and of **3c**. As summarized in Table 3, Et_2AlCl was very effective for the reaction of **3b** with benzaldehyde, in which the coupling product **4ba** was afforded in 90% yield, but with low diastereoselectivity. On the other hand, $TiCl_4$ was found to be a good promoter for the reaction of **3c** with benzaldehyde, the desired product **4ca** being produced in 60% yield with high *erythro* selectivity.

From the results mentioned above, it can be assumed that the use of the Weinreb amide **3a** and the combined reagent, $PPh_3/Ti(O\text{-}i\text{-}Pr)_4$, is most favorable for the present

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(11) The relative stereochemical nomenclature proposed by Noyori et al. is applied. See: Noyori, R.; Ishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1983**, *105*, 1598.

SCHEME 3

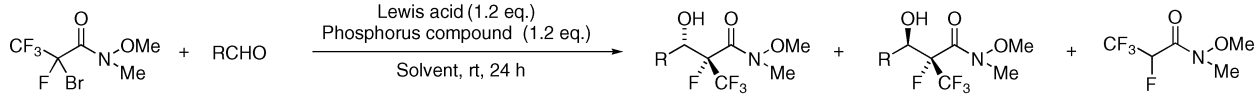


TABLE 1. Reductive Coupling Reaction of 3a with Benzaldehyde (R = Ph) under Various Reaction Conditions

entry	Lewis acid	compd	solvent	yield[a]/% of **4aa**	isomer ratio[a] *erythro*-**4aa**/*threo*-**4aa**	yield[a]/% of **5a**	recovery[a]/% of **3a**
1	$BF_3{\cdot}OEt_2$	PPh_3	CH_2Cl_2	37	67:33	44	0
2	$Zn(OTf)_2$	PPh_3	CH_2Cl_2	5	68:32	80	5
3	ZnI_2	PPh_3	CH_2Cl_2	0		86	0
4	Et_2AlCl	PPh_3	CH_2Cl_2	84	67:33	7	0
5	$EtAlCl_2$	PPh_3	CH_2Cl_2	66	60:40	4	1
6	$TiCl_4$	PPh_3	CH_2Cl_2	*b*		16	0
7	$TiCl_2(O\text{-}i\text{-}Pr)_2$	PPh_3	CH_2Cl_2	26	96:4	65	0
8	$Ti(O\text{-}i\text{-}Pr)_4$	PPh_3	CH_2Cl_2	84	97:3	15	0
9	$Ti(O\text{-}i\text{-}Pr)_4$	$P(OEt)_3$	CH_2Cl_2	0		29	0
10	$Ti(O\text{-}i\text{-}Pr)_4$	Bu_3P	CH_2Cl_2	30	43:57	43	45
11[c]	$Ti(O\text{-}i\text{-}Pr)_4$	Ph_3P	CH_2Cl_2	16	95:5	6	43
12	$Ti(O\text{-}i\text{-}Pr)_4$	none	CH_2Cl_2	0		0	91
13	none	Ph_3P	CH_2Cl_2	3		82	0
14	$Ti(O\text{-}i\text{-}Pr)_4$	Ph_3P	MeCN	61	98:2	25	0
15	$Ti(O\text{-}i\text{-}Pr)_4$	Ph_3P	THF	45	96:4	20	21
16	$Ti(O\text{-}i\text{-}Pr)_4$	Ph_3P	toluene	7		34	44

[a] Determined by ^{19}F NMR. [b] Complex mixture. [c] A catalytic amount of PPh_3 (0.2 equiv) was used.

TABLE 2. Diastereoselective Reductive Coupling Reaction of 3a with Various Aldehydes

entry	R	yield[a]/% of **4a**		isomer ratio[a] *erythro*-**4a**/*threo*-**4a**	yield[a]/% of **5a**	recovery[a]/% of **3a**
1	Ph	84 (73)	**4aa**	97:3	15	0
2	$p\text{-}MeC_6H_4$	79 (73)	**4ab**	98:2	12	0
3	$p\text{-}MeOC_6H_4$	77 (61)	**4ac**	96:4	22	0
4	$p\text{-}FC_6H_4$	82 (76)	**4ad**	97:3	13	0
5	MeCH=CH	74 (63)	**4ae**	95:5	15	0
6	PhCH=CH	76 (68)	**4af**	95:5	17	0
7	*n*-Pr	72 (60)	**4ag**	96:4	27	0
8	*i*-Pr	65 (53)	**4ah**	95:5	22	0
9	*t*-Bu	53 (43)	**4ai**	95:5	25	0

[a] Determined by ^{19}F NMR. Values in parentheses are of isolated yield.

coupling reaction leading to α-fluoro-α-(trifluoromethyl)-β-hydroxy carboxylic acid moiety with high diastereoselectivity in good yield.

Phosphine/Lewis Acid-Catalyzed Reductive Coupling Reaction of 3a. Next, we investigated the possibility of the phosphine/Lewis acid-catalyzed reaction of **3a**.[12] Table 4 summarizes the results of the reactions with benzaldehyde. As shown in entries 1−3, changing the amount of Lewis acid $Ti(O\text{-}i\text{-}Pr)_4$ from 120 mol % to 10 mol % did not cause any substantial difference in the yields of **4aa** and diastereoselectivities. However, the reaction in the presence of only 5 mol % of $Ti(O\text{-}i\text{-}Pr)_4$ resulted in a slight decrease of the yield, though the diastereoselectivity still remained excellent (entry 4).

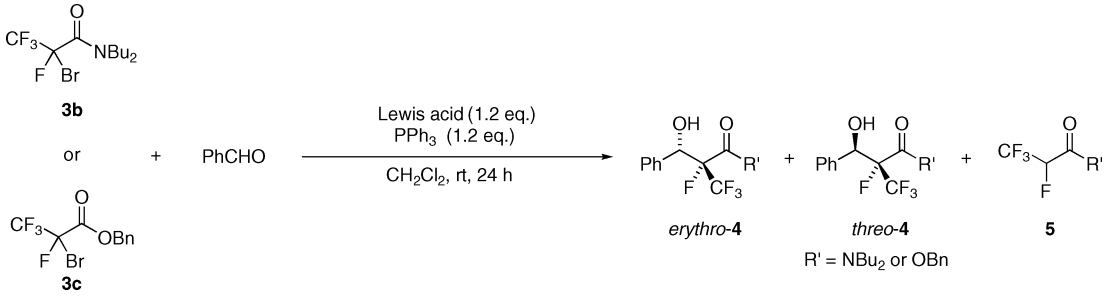
With these optimized reaction conditions in hand (Table 4, entry 3), we carried out the phosphine/Lewis acid-catalyzed reaction between **3a** and various aldehydes. These results are tabulated in Table 5. For the reaction with aromatic aldehydes, as shown in entries 1−4, no difference between the stoichiometric and the catalytic Lewis acid system was observed in view of the yields as well as the diastereoselectivities. In the case of α,β-unsaturated aldehydes and *n*-butyraldehyde, the yields of the corresponding **4a** were still high but the diastereoselectivities were decreased to a slight extent (entries 5−7). Moreover, the reaction with bulky aldehydes, such as isobutyraldehyde and pivalaldehyde, led to a significant decrease in the yields of the products (entries 8 and 9).

Stereochemical Assignment and Plausible Reaction Mechanism. The stereochemical assignment of the coupling products **4a** was made as follows. The X-ray structural analysis was carried out for the major isomer of **4ac** obtained from the reaction of **3a** with *p*-methoxybenzaldehyde.[13] The data permitted its stereochemical assignment to the *erythro*-isomer. ^{19}F NMR analysis of **4ac** indicated that the CF_3 resonance due to the *erythro*-isomer appeared at higher field than that of the *threo*-isomer.[14] This tendency to the relative resonances for the two diastereoisomers is also observed for the aldol

(12) It has been disclosed that a stoichiometric combination of triphenylphosphine and Lewis acid is crucial to facilitate the aldol-type reaction of α-bromo carbonyl compounds, which are limited to *N*,*N*-diphenyl amide, thioesters, and ketones. See ref 9.

(13) For details regarding the X-ray crystal structure of **4ac**, see the Supporting Information.

TABLE 3. Reductive Coupling Reaction of Amide 3b or Ester 3c with Benzaldehyde



entry	Lewis acid	3	yield[a]/% of 4		isomer ratio[a] *erythro*-4/*threo*-4	yield[a]/% of 5	recovery[a]/% of 3
1	$Ti(O\text{-}i\text{-}Pr)_4$	**3b**	8	**4ba**		61	16
2	$TiCl_4$	**3b**	51	**4ba**	62:38	32	0
3	$Zn(OTf)_2$	**3b**	16	**4ba**	78:22	65	3
4	Et_2AlCl	**3b**	90	**4ba**	63:37	9	0
5	$EtAlCl_2$	**3b**	44	**4ba**	70:30	52	0
6	$Ti(O\text{-}i\text{-}Pr)_4$	**3c**	14	**4ca**	49:51	31	13
7	$TiCl_4$	**3c**	60	**4ca**	89:11	26	3
8	$Zn(OTf)_2$	**3c**	6	**4ca**	50:50	40	1
9	Et_2AlCl	**3c**	19	**4ca**	64:36	64	2
10	$EtAlCl_2$	**3c**	15	**4ca**	50:50	61	2

[a] Determined by ^{19}F NMR.

TABLE 4. Effect of the Amount of Lewis Acid

entry[a]	$Ti(O\text{-}i\text{-}Pr)_4$ (mol %)	yield[b]/% of **4aa**	isomer ratio[b] *erythro*-**4aa**/*threo*-**4aa**	yield[b]/% of **5a**	recovery[b]/% of **3a**
1	120	84	97:3	15	0
2	20	91	97:3	8	0
3	10	87	96:4	7	0
4	5	67	96:4	17	1

[a] In all reactions, 1.2 equiv of PPh_3 was employed. [b] Determined by ^{19}F NMR.

products obtained from the boron enolates of *N*,*N*-dialkyl-2,3,3,3-tetrafluoropropanamides.[8] On the basis of such relative resonances for the isomers, examining the ^{19}F NMR spectra of other products **4a** made it possible to assign their major isomers as the *erythro*-isomer.

The present reaction probably involves the generation of a titanium enolate which may take part in a six-membered transition state, as depicted in Scheme 4. Thus, both carbonyl oxygen and phosphorus atom could coordinate $Ti(O\text{-}i\text{-}Pr)_4$ simultaneously and the ensuing bromine transfer occurs intramolecularly through a closed chairlike transition state. Under this consideration, the *E*-enolate may be disfavored owing to a nonbonded repulsive interaction between a CF_3 group and phenyl substituent of PPh_3 (TS-1 vs TS-2), so that the *Z*-enolate may be formed preferentially via TS-2. The subsequent coordination of titanium atom to the carbonyl oxygen of aldehyde may lead to a six-membered chairlike transition state TS-4, where the substituent R occupies the equatorial position due to a 1,3-diaxial repulsion (TS-3 vs TS-4). Consequently, the *erythro*-isomer of the product **4a** is produced preferentially.

(14) It was observed that the rotational isomerism in the unsymmetrical (*N*-methoxy, *N*-methyl) amide caused broadening of the resonances in the ^1H, ^{13}C, and ^{19}F NMR of **3a** and **4a**. In particular, the methoxy protons for **3a** appeared at 3.974 and 3.978 ppm as two peaks, corresponding to the two amide rotamers. Fortunately, the broadening of peaks did not complicate the analysis of diastereomeric distributions of **4a** by using the CF_3 resonance peaks.

Conclusion

In summary, we have investigated the reductive coupling reaction between 2-bromo-2,3,3,3-tetrafluoropropanamides or ester **3a**−**c** and various aldehydes under the influence of the combined reagent $PPh_3/Ti(O\text{-}i\text{-}Pr)_4$ and found that the reaction of *N*-methoxy-*N*-methyl-2-bromo-2,3,3,3-tetrafluoropropanamide (**3a**) with various aldehydes in the presence of 1.2 equiv each of PPh_3 and $Ti(O\text{-}i\text{-}Pr)_4$ furnished the corresponding α-fluoro-α-(trifluoromethyl)-*β*-hydroxy amides **4a** in high yields with high *erythro* selectivities. Additionally, even use of a catalytic amount of $Ti(O\text{-}i\text{-}Pr)_4$ for the combined reagent was found to facilitate the reaction efficiently with high *erythro* selectivities.

Experimental Section

General Methods. Infrared spectra (IR) were recorded on a Shimadzu FTIR-8200A (PC) spectrophotometer. ^1H (500.13 MHz) and ^{13}CNMR (125.75 MHz) spectra were measured with a Bruker DRX 500 NMR spectrometer in a chloroform-*d* ($CDCl_3$) solution with tetramethylsilane (Me_4Si) as an internal reference. A JEOL JNM-EX90A (84.21 MHz, FT) NMR spectrometer was used for determining ^{19}F NMR spectra in a $CDCl_3$ solution with $CFCl_3$ as an internal standard. Mass spectra (MS) and high-resolution mass spectra (HRMS) were taken on a Hitachi M-80B and/or JEOL JMS-700 mass spectrometer by an electron impact (EI), chemical ionization (CI), or FAB (Cs+) method using *m*-nitrobenzyl alcohol as a matrix. Elemental analyses were conducted with a Yanaco CHN CORDER MT-5 instrument.

Materials. 2-Bromo-2,3,3,3-tetrafluoropropanoyl chloride was purchased from Pinnacle Chemicals Ltd. and was used without any purification. Dichloromethane (CH_2Cl_2) was distilled over calcium hydride under argon. All chemicals were of reagent grade and, if necessary, were purified in the usual manner prior to use. Thin-layer chromatography (TLC) was done with Merck silica gel $60F_{254}$ plates, and column chromatography was carried out with Wakogel C-200. All reactions were conducted under an atmosphere of argon.

Preparation of *N*-Methoxy-*N*-methyl-2-bromo-2,3,3,3-tetrafluoropropanamide (3a). To a solution of *N*,*O*-di-

TABLE 5. Diastereoselective Catalytic Reductive Coupling Reaction of 3a with Various Aldehydes

entry[a]	RCHO	yield[b]/% of **4a**		isomer ratio[b] *erythro*-**4a**/*threo*-**4a**	yield[b]/% of **5a**	recovery[b]/% of **3a**
1	Ph	87 (82)	**4aa**	96:4	7	0
2	*p*-MeC_6H_4	84 (66)	**4ab**	96:4	9	0
3	*p*-$MeOC_6H_4$	91 (83)	**4ac**	95:5	5	0
4	*p*-FC_6H_4	83 (81)	**4ad**	97:3	16	0
5	MeCH=CH	91 (83)	**4ae**	89:11	12	3
6	PhCH=CH	87 (62)	**4af**	87:13	9	1
7	*n*-Pr	84 (68)	**4ag**	90:10	11	0
8	*i*-Pr	50 (46)	**4ah**	86:14	37	0
9	*t*-Bu	20 (5)	**4ai**	87:13	37	3

[a] In all reactions, 1.2 equiv of PPh_3 and 0.1 equiv of $Ti(O\text{-}i\text{-}Pr)_4$ were employed. [b] Determined by ^{19}F NMR. Values in parentheses are of isolated yield.

methylhydroxylamine hydrochloride (2.15 g, 11 mmol) in CH_2Cl_2 (30 mL) was added pyridine (3.48 g, 22 mmol) at 0 °C under an argon atmosphere. After being stirred for 30 min, to this reaction mixture was dropwise added a solution of 2-bromo-2,3,3,3-tetrafluoropropanoyl chloride (4.87 g, 10 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The whole mixture was then stirred at room temperature for 2 h and the reaction was quenched with a saturated aqueous $NaHCO_3$ solution (50 mL). The resultant mixture was extracted with CH_2Cl_2 (50 mL × 5), and the organic layers were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The solvents were removed in vacuo, and the residue was purified by silica gel column chromatography (hexane/diethyl ether, 5:1) to afford analytically pure amide **3a** (2.41 g, 9.0 mmol, 90% yield). The amide **3b** (2.2 equiv of Bu_2NH, rt, 3 h, THF) and ester **3c** (1.1 equiv of benzyl alcohol, 1.5 equiv of Et_3N, rt, 3 h, ether) were prepared in a similar manner.

***N*-Methoxy-*N*-methyl-2-bromo-2,3,3,3-tetrafluoropropanamide (3a):** IR (neat) 2947, 1693, 1461, 1292, 1222, 1188, 1103, 956, 902 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.30 (br, 3H), 3.974 and 3.978 (s, 3H, rotational isomer); ^{13}C NMR ($CDCl_3$) δ 33.6, 61.4, 90.6 (qd, J = 32.3, 283.9 Hz), 119.9 (dq, J = 29.8, 283.6 Hz), 159.8; ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −77.3 (d, J = 8.8 Hz, 3F), −139.0 (br, 1F); MS (EI^+) m/z (rel intensity) 266 (M^+, 39), 178 (47), 128 (12), 88 (30), 58 (100); HRMS (M^+) m/z found 266.9515, calcd for $C_5H_6{}^{79}BrF_4NO_2$ 266.9518.

***N*,*N*-Dibutyl-2-bromo-2,3,3,3-tetrafluoropropanamide (3b):** 93% yield; IR (neat) 2939, 2877, 1674, 1434, 1288, 1222, 1184, 1095, 1033, 945, 902, 702, 675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, J = 7.5 Hz, 3H), 0.91 (t, J = 7.5 Hz, 3H), 1.25−1.35 (m, 4H), 1.45−1.70 (m, 4H), 3.08−3.25 (m, 2H), 3.45−3.56 (m, 1H), 3.60−3.72 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.5, 13.6, 19.8, 19.9, 28.6, 30.7, 47.2, 48.2, 48.3, 91.9 (qd, J = 33.4, 284.6 Hz), 112.0 (dq, J = 30.3, 283.7 Hz), 159.5 (d, J = 20.3 Hz); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −77.0 (d, J = 8.7 Hz, 3F), −133.2 to −132.5 (m, 1F); HRMS (M^+ + H) m/z found 336.0583, calcd for $C_{11}H_{18}{}^{79}BrF_4NO_2$ 336.0586.

Benzyl 2-bromo-2,3,3,3-tetrafluoropropanoate (3c): 90% yield; IR (neat) 1774, 1501, 1457, 1304, 1265, 1192, 1134, 1018, 918, 741 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.16 (s, 2H), 7.20 (s, 5H); ^{13}C NMR ($CDCl_3$) δ 69.7, 88.8 (dq, J = 272.3, 57.5 Hz), 119.7 (dq, J = 29.5, 284.0 Hz), 128.3, 128.7, 129.0, 133.5, 160.5 (d, J = 26.5 Hz); ^{19}F NMR ($CDCl_3$) δ −78.0 (d, J = 8.8 Hz, 3F), −135.2 (q, J = 8.8 Hz, 1F); MS (FAB) m/z (rel intensity) 314 (M^+, 100); HRMS (FAB) m/z found 313.9573, calcd for (M^+) $C_{10}H_7BrF_4O_2$ 313.9566. Anal. Calcd for $C_{10}H_7BrF_4O_2$; C, 38.12; H, 2.24. Found: C, 38.02; H, 2.28.

Typical Procedure for the Reductive Coupling Reaction of 3a with Benzaldehyde. To a solution of $Ti(O\text{-}i\text{-}Pr)_4$ (0.154 g, 0.54 mmol) in CH_2Cl_2 (2 mL) were successively added solutions of benzaldehyde (0.057 g, 0.54 mmol) in CH_2Cl_2 (1 mL), PPh_3 (0.142 g, 0.54 mmol) in CH_2Cl_2 (1 mL), and **3a** (0.121 g, 0.45 mmol) in CH_2Cl_2 (1 mL) at room temperature under an argon atmosphere. After being stirred at the same temperature for 24 h, the reaction mixture was quenched with aqueous 10% HCl (10 mL). The resultant mixture was extracted with CH_2Cl_2 (20 mL × 5), and the organic layers were washed with brine followed by drying over anhydrous Na_2SO_4 and filtration. The solvents were removed in vacuo, and the residue was purified by silica gel column chromatography (hexane/diethyl ether, 5:1) to afford analytically pure product **4aa** (0.971 g, 0.329 mmol, 73% yield).

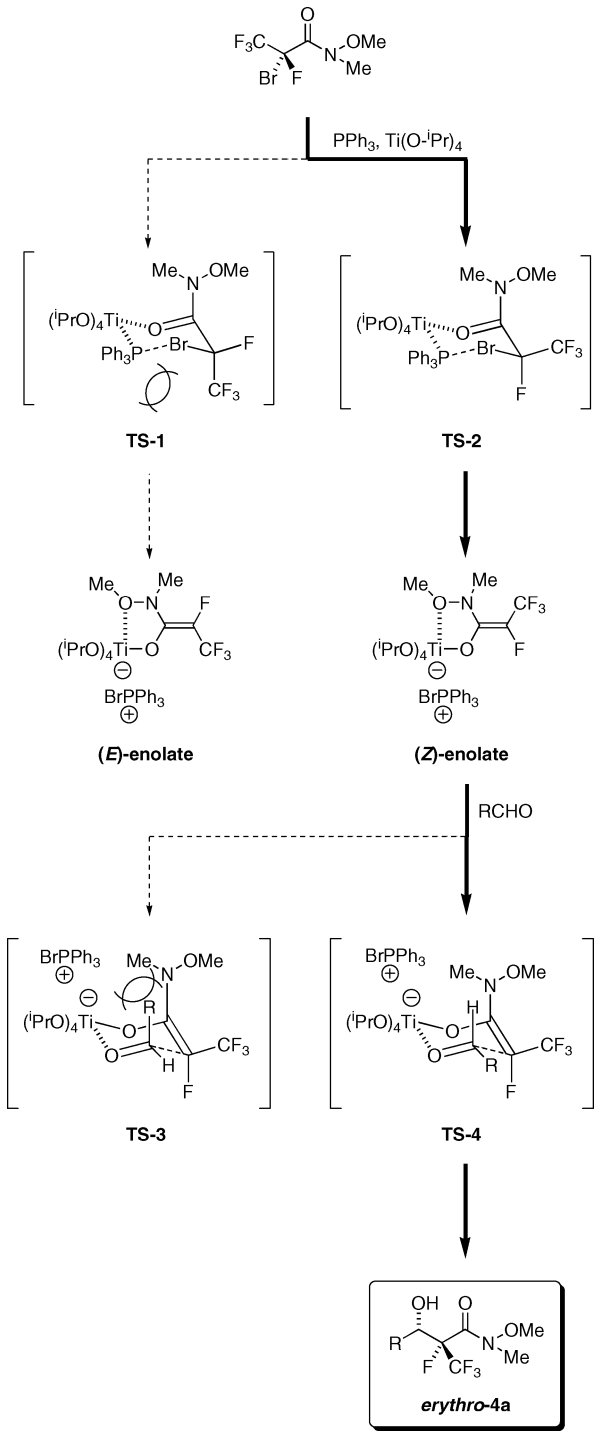
***erythro*-*N*-Methoxy-*N*-methyl-2-fluoro-3-hydroxy-3-phenyl-2-(trifluoromethyl)propanamide (4aa):** mp 80−82 °C; IR (KBr) 3344, 2943, 1651, 1288, 1196, 999, 968, 810, 748, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.22 (br, 3H), 3.53 (s, 3H), 4.35 (br, 1H), 5.29 (d, J = 15.5 Hz, 1H), 7.32−7.45 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 33.9, 61.8, 73.7 (d, J = 22.7 Hz), 93.5−96.0 (m), 121.3 (dq, J = 37.5, 286.8 Hz), 127.8, 128.1, 128.8, 136.4, 164.0 (m); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −73.8 (d, J = 8.8 Hz, 3F), −175.0 to −183.0 (m, 1F); HRMS (FAB^+) m/z found 296.0914, calcd for (M^++ H) $C_{12}H_{14}F_4NO_3$ 296.0910. Anal. Calcd for $C_{12}H_{14}F_4NO_3$: C, 48.82; H, 4.44; N, 4.74. Found: C, 48.63; H, 4.38; N, 4.72.

***erythro*-*N*-Methoxy-*N*-methyl-2-fluoro-3-hydroxy-3-(4-methylphenyl)-2-(trifluoromethyl)propanamide (4ab):** mp 131−133 °C; IR (KBr) 3337, 2943, 1643, 1288, 1200, 1134, 1003, 968 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.35 (s, 3H), 3.23 (br, 3H), 3.56 (s, 3H), 4.10 (br, 1H), 5.26 (dd, J = 8.0, 16.5 Hz, 1H), 7.12−7.20 (m, 2H), 7.27−7.34 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.1, 33.0, 62.0, 73.8 (d, J = 23.7 Hz), CF_3CF could not be detected. 121.4 (dq, J = 28.2, 286.9 Hz), 127.7, 128.9, 133.4, 138.7, a carbonyl carbon could not be detected; ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −73.9 (d, J = 6.6 Hz, 3F), −174.0 to −182.0 (m, 1F); HRMS (FAB^+) m/z found 310.1071, calcd for (M^+ + H) $C_{13}H_{15}F_4NO_3$ 309.1066. Anal. Calcd for $C_{13}H_{15}F_4NO_3$: C, 50.49; H, 4.89; N, 4.53. Found: C, 50.12; H, 4.94; N, 4.42.

***erythro*-*N*-Methoxy-*N*-methyl-2-fluoro-3-hydroxy-3-(4-methoxyphenyl)-2-(trifluoromethyl)propanamide (4ac):** mp 96−97 °C; IR (KBr) 3337, 2943, 2846, 1651, 1516, 1288, 1238, 1188, 999, 968, 787 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.24 (br, 3H), 3.57 (s, 3H), 3.796 and 3.799 (s, 3H, rotational isomers), 4.16 (br, 1H), 5.26 (d, J = 17.5 Hz, 1H), 6.85−6.92 (m, 2H), 7.30−7.37 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 34.0, 55.2, 61.7, 73.4 (d, J = 23.2 Hz), CF_3CF could not be detected. 113.5, 121.3 (dq, J = 28.2, 286.7 Hz), 128.4, 129.0, 159.9, a carbonyl carbon could not be detected; ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −73.9 (d, J = 6.6 Hz, 3F), −174.0 to −183.0 (m, 1F); HRMS (FAB^+) m/z found 326.1019, calcd for (M^+ + H) $C_{13}H_{16}F_4NO_4$ 326.1015. Anal. Calcd for $C_{13}H_{15}F_4NO_4$: C, 48.00; H, 4.65; N, 4.31. Found: C, 47.94; H, 4.99; N, 4.23.

***erythro*-*N*-Methoxy-*N*-methyl-3-(4-fluorophenyl)-2-fluoro-3-hydroxy-2-(trifluoromethyl)propanamide (4ad):** IR (neat) 3422, 2943, 1655, 1512, 1393, 1285, 1203, 999, 849 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.24 (br, 3H), 3.57 (s, 3H), 4.2−4.6 (br, 1H), 5.31 (dd, J = 7.0, 17.5 Hz, 1H), 7.04−7.07 (m, 2H), 7.38−7.41 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 33.7, 62.0, 73.2 (d, J = 23.2 Hz), 93.0−96.0 (m), 115.1 (d, J = 21.7 Hz), 121.3 (dq, J = 28.1, 286.9 Hz), 129.6−129.8 (m), 132.2, 163.0 (d, J = 248.0 Hz), 163.0−164.2 (m); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −73.9 (d, J = 6.6 Hz, 3F), −113.0 to −113.6 (m, 1F), −174.0 to −183.0 (m, 1F); HRMS (FAB^+) m/z found 314.0819, calcd for (M^+ + H)

SCHEME 4



$C_{12}H_{13}F_5NO_3$ 314.0816. Anal. Calcd for $C_{12}H_{12}F_5NO_3$: C, 46.01; H, 3.86; N, 4.47. Found: C, 45.68; H, 3.69; N, 4.32.

***erythro*-*N*-Methoxy-*N*-methyl-2-fluoro-3-hydroxy-2-(trifluoromethyl)-4-(*E*)-hexenamide (4ae):** mp 85−87 °C; IR (neat) 3356, 2943, 1659, 1443, 1458, 1211, 1192, 1142, 991, 968 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.76 (d, J = 7.0 Hz, 3H), 3.33 (br, 4H), 3.74 (s, 3H), 4.67 (dd, J = 7.2, 17.5 Hz, 1H), 5.57 (dd, J = 7.2, 15.3 Hz, 1H), 5.90 (dq, J = 6.7, 15.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 17.8, 34.0, 61.7, 73.0 (d, J = 23.8 Hz), 93.0∼97.0 (m), 121.3 (dq, J = 27.9, 286.6 Hz), 125.5, 132.4, A carbonyl carbon could not be detected.; ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −73.6 (br s, 3F), −176.0 to −186.0 (m, 1F); HRMS (FAB) m/z found 260.0913, calcd for (M^+ + H) $C_9H_{14}F_4NO_3$ 260.0913. Anal. Calcd for $C_9H_{13}F_4NO_3$: C, 41.70; H, 5.06; N, 5.40. Found: C, 41.85; H, 5.33; N, 5.34.

***erythro*-*N*-Methoxy-*N*-methyl-2-fluoro-3-hydroxy-5-phenyl-2-(trifluoromethyl)-4-(*E*)-pentenamide (4af):** IR (neat) 3422, 2943, 1663, 1427, 1389, 1285, 1200, 1142, 968, 694, 664 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.30 (br, 4H), 3.71 (s, 3H), 4.92 (dd, J = 7.0, 17.0 Hz, 1H), 6.26 (dd, J = 7.0, 16.0 Hz, 1H), 6.77 (d, J = 16.0 Hz, 1H), 7.25∼7.41 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 33.9, 61.9, 73.0 (d, J = 23.8 Hz), 93.0∼96.4 (m), 121.3 (dq, J = 27.9, 286.6 Hz), 123.30, 126.8, 128.3, 128.6, 135.1, 135.9, 164.0 (m); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −73.5 (br s, 3F), −177.0 to −184.0 (m, 1F); HRMS (FAB$^+$) m/z found 322.1069, calcd for (M^+ + H) $C_{14}H_{16}F_4NO_3$ 322.1066. Anal. Calcd for $C_{14}H_{15}F_4NO_3$: C, 52.34; H, 4.71; N, 4.36. Found: C, 52.37; H, 5.07; N, 4.31.

***erythro*-*N*-Methoxy-*N*-methyl-2-fluoro-3-hydroxy-2-(trifluoromethyl)hexanamide (4ag):** IR (neat) 3345, 2966, 2878, 1663, 1466, 1389, 1285, 1200, 968 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.97 (t, J = 7.0 Hz, 3H), 1.39−1.49 (m, 1H), 1.52−1.75 (m, 3H), 3.32 (br, 4H), 3.75 (s, 3H), 4.18 (ddt, J = 2.0, 16.0, 10.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 18.7, 32.9, 34.0 (m), 62.0 (m), 71.9 (d, J = 24.7 Hz), 121.6 (dq, J = 28.2, 286.7 Hz), CF_3CF and C=O could not be detected; ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −74.0 (d, J = 6.6 Hz, 3F), −174.0 to −183.0 (m, 1F); HRMS (FAB$^+$) m/z found 262.1060, calcd for (M^+ + H) $C_9H_{16}F_4NO_3$ 262.1066.

***erythro*-*N*-Methoxy-*N*-methyl-2-fluoro-3-hydroxy-4-methyl-2-(trifluoromethyl)pentanamide (4ah):** IR (neat) 3460, 2974, 2943, 1663, 1389, 1281, 1204, 964 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.98−1.07 (m, 6H), 2.00−2.10 (m, 1H), 3.31 (br, 4H), 3.76 (s, 3H), 3.96 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 16.6, 20.7, 30.0, 33.9 (m), 61.9 (m), 75.6 (d, J = 22.6 Hz), 95.0−97.5 (m), 122.2 (dq, J = 28.5, 286.9 Hz), 164.0∼165.0 (m); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −74.4 (br, 3F), −172.0 to −183.0 (m, 1F); HRMS (FAB$^+$) m/z found 262.1068, calcd for (M^+ + H) $C_9H_{16}F_4NO_3$ 262.1066. Anal. Calcd for $C_9H_{15}F_4NO_3$: C, 41.38; H, 5.79; N, 5.36. Found: C, 41.02; H, 5.61; N, 5.08.

***erythro*-*N*-Methoxy-*N*-methyl-2-fluoro-3-hydroxy-4,4-dimethyl-2-(trifluoromethyl)pentanamide (4ai):** IR (neat) 3460, 2962, 1651, 1470, 1389, 1276, 1207, 1080, 961 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.01 (d, J = 2.5 Hz, 9H), 3.08−3.62 (m, 3H), 3.77 (s, 3H), 3.08 (dd, J = 8.0, 11.0 Hz, 1H), 4.00−4.62 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 27.0, 34.2 (m), 36.2, 62.2 (m), 78.5 (d, J = 23.9 Hz), 121.9 (dq, J = 28.8, 288.3 Hz), CF_3CF and C=O could not be detected; ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −75.2 (br s, 3F), −168.0 to −176.5 (m, 1F); HRMS (FAB$^+$) m/z found 276.1225, calcd for (M^+ + H) $C_{10}H_{18}F_4NO_3$ 276.1223.

***N*,*N*-Dibutyl-2-fluoro-3-hydroxy-3-phenyl-2-(trifluoromethyl)propanamide (4ba):** IR (neat) 3444, 2935, 2877, 1635, 1458, 1380, 1288, 1180, 1134, 1072, 1029, 1002, 945, 825, 740, 702 cm^{-1}; HRMS (FAB$^+$) m/z found 364.1905, calcd for (M^+ + H) $C_{10}H_{18}F_4NO_3$ 364.1900.

Erythro isomer: ^{1}H NMR ($CDCl_3$) δ 0.78 (t, J = 7.5 Hz, 3H), 0.90 (t, J = 7.5 Hz, 3H), 1.00−1.46 (m, 8H), 2.80−3.40 (m, 4H), 5.10−5.18 (m, 1H), 5.20−5.30 (m, 1H), 7.28−7.43 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.5, 19.6, 20.0, 29.0, 31.1, 47.3, 47.8, 49.0, 73.9 (d, J = 25.0 Hz), 93.7 (qd, J = 27.9, 213.5 Hz), 121.7 (dq, J = 28.0, 287.1 Hz), 127.6−127.8 (m), 128.0, 128.6, 137.0, 163.5 (d, J = 18.2 Hz); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −74.8 (d, J = 8.8 Hz, 3F), −170.5 to −169.5 (m, 1F).

Threo isomer: ^{1}H NMR ($CDCl_3$) δ 0.80 (t, J = 6.5 Hz, 3H), 0.87 (t, J = 7.0 Hz, 3H), 0.88−1.45 (m, 8H), 2.80−3.40 (m, 4H), 5.20−5.30 (m), 5.59 (d, J = 24.0 Hz, 1H), 7.28−7.43 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.5, 19.6, 20.0, 28.8, 31.2, 47.4, 47.9, 49.0, 74.2 (d, J = 18.7 Hz), 97.9 (qd, J = 28.1, 220.2 Hz), 122.1 (dq, J = 30.5, 287.0 Hz), 128.0, 128.1, 128.8, 136.3, 162.5 (d, J = 18.0 Hz); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −72.3 (d, J = 4.4 Hz, 3F), −186.8 to −186.0 (m, 1F).

Benzyl 2-fluoro-3-hydroxy-2-(trifluoromethyl)-3-phenylpropanoate (4ca): IR (neat) 3471, 3075, 3039, 2958, 1770, 1496, 1458, 1377, 1276, 1195, 1137, 1087, 1041 cm^{-1}; HRMS (EI) m/z found 342.0870, calcd for (M^+) $C_9H_{16}F_4NO_3$ 342.0878.

Erythro isomer: ^{1}H NMR ($CDCl_3$) δ 2.82 (br, 1H), 5.31 (s, 2H), 5.28−5.38 (m, 1H), 7.09−7.37 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 68.7, 73.2 (d, J = 19.2 Hz), 94.6 (qd, J = 29.9, 210.9 Hz), 120.6 (dq, J = 28.2, 286.1 Hz), 127.7−127.8 (m), 128.2, 128.4, 128.6, 128.7, 129.3, 134.1, 135.5, 163.7 (d, J = 25.2 Hz); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −74.2 (d, J = 7.6 Hz, 3F), −187.1 (dq, J = 7.6, 21.2 Hz, 1F).

Thero isomer: ^{1}H NMR ($CDCl_3$) δ 2.65 (br, 1H), 5.04 (s, 2H), 5.28−5.38 (m, 1H), 7.09−7.37 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 68.4, 73.2 (d, J = 19.2 Hz), 94.8 (qd, J = 29.9, 210.9 Hz), 121.2 (dq, J = 29.8, 286.9 Hz), 127.6−127.7 (m), 128.2, 128.4, 128.5, 128.7, 129.3, 133.6, 135.3, 162.9 (d, J = 23.8 Hz); ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ −73.5 (d, J = 5.9 Hz, 3F), −191.6 (dq, J = 5.9, 24.2 Hz, 1F).

X-ray Crystal Structure for 4ac. A colorless prismatic crystal (from hexane−diethyl ether) of approximate dimensions of 0.50 × 0.20 × 0.10 mm was mounted on a glass fiber with epoxy cement. Data were collected on a Rigaku AFC7R diffractometer with graphite-monochromated Cu Kα radiation and a rotating anode genetator. The material crystallized in the monoclinic space group $C2/c$ with a = 8.270(4) Å, b = 12.122(4) Å, c = 8.071(2) Å, b = 97.32(3) Å, V = 744.9(4) Å^3, and Z = 2. Data collection, reduction, solution, and refinement were all carried out using the 'teXsan' crystallographic software package from Molecular Structure Corp. All non-H atoms were refined anisotropically; 3566 observations, 398 variables; R_1 = 0.076 for $F_2 > 4\sigma(F2)$ and wR_2 = 0.183 for all F_2.

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Supporting Information Available: ORTEP drawing of *erythro*-**4ac**, NMR spectra, and ^{19}F NMR chemical shift data. This material is available free of charge via the Internet at http://pubs.acs.org.

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