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Synthesis of Enantiopure Trifluoromethyl Building Blocks via a Highly Chemo- and Diastereoselective Nucleophilic Trifluoromethylation of Tartaric Acid-Derived Diketones

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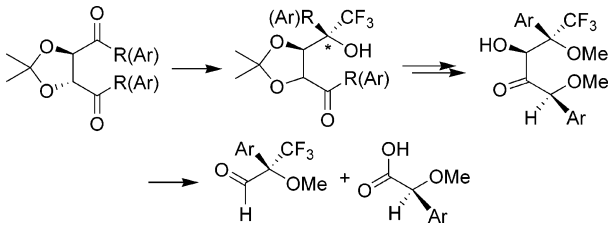

A highly diastereoselective nucleophilic mono(trifluoromethylation) of a tartaric acid-based diketone, using trifluoromethyl(trimethyl)silane, afforded the corresponding γ-keto trifluoromethylcarbinol. The scope and limitation of this reaction was studied. The acidic removal of the acetonide moiety protecting the two hydroxyl groups of the adducts was unsuccessful. Bis(O-methylation) of the aromatic derivatives under basic conditions, followed by acidic hydrolysis and oxidative cleavage, led to two different enantiopure products: an α-aryl-α-methoxy-α-trifluoromethyl ethanal and an α-aryl-α-methoxycarboxylic acid. The overall process is eventually an interesting way to convert one natural chiral raw material into two functionalized enantiopure building blocks including a trifluoromethyl one.

Introduction

In recent years, the synthesis of fluorinated organic compounds has become an important field due to the unique abilities of the fluorine atom to significantly modify their physicochemical and biological properties.[1] Fluoroorganic compounds have shown important applications in different fields, such as material science,[2] agrochemistry, and the pharmaceutical industry.[3,4] Due to its stability, to its hydrophobic and electron-withdrawing character, the trifluoromethyl group can bring interesting properties to a molecule, especially for bioorganic purposes.[5] This explains the continuing interest in developing methods and reagents for the synthesis of trifluoromethyl-substituted compounds. Although various new approaches were recently proposed,[6] trifluoromethyl(trimethyl)silane (TFMTMS) remains the most convenient reagent, for its easy handling and broad

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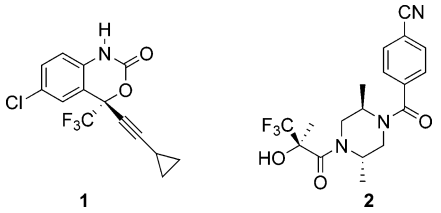

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FIGURE 1. Examples of biologically active molecules with a CF_3-bearing chiral quaternary center.

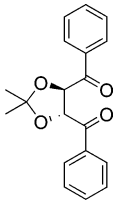


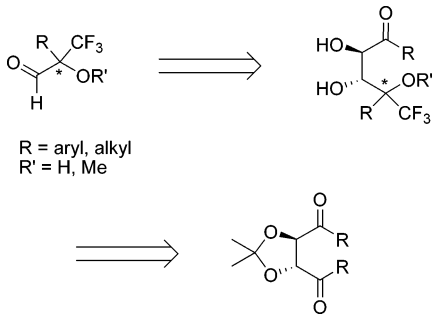
FIGURE 2. Structure of the diketone **3a**.

applicability, at least for trifluoromethylation of carbonyl and carboxyl derivatives.[7] The asymmetric construction of a quaternary[8] stereogenic center bearing a CF_3 group is an important topic, as exemplified by some compounds of pharmaceutical interest. Efavirenz **1** is a potent anti-HIV drug,[9] and several α-alkoxy-α-trifluoromethyl carboxamides such as **2** were reported as antidiabetic[10] products (Figure 1).

The synthesis of such quaternary trifluoromethyl derivatives with a well-defined configuration is still a challenging topic, which has been addressed by several groups. Despite some enantioselective attempts,[11] the diastereoselective approach was much more successful. Apart from the Yamazaki building-block approach,[12] effective diastereoselective trifluoromethylation of prochiral carbonyl compounds with trifluoromethyl(trimethyl)-silane were very recently reported.[13]

These last reports prompted us to disclose our own results in this field. Our approach is based on the nucleophilic trifluoromethylation of L-tartaric acid-derived ketones. Tartaric acid is a chiral pool raw material and an excellent C-2 symmetric

SCHEME 1. Retrosynthesis of α-Alkoxy-α-trifluoromethyl Aldehydes from Tartaric Acid-Derived Diketones



chiral scaffold for the synthesis of enantiopure compounds.[14,15] TADDOLs (α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanols) are among the most famous ligands for various enantioselective reactions.[16] When we attempted to prepare bis(trifluoromethylated) analogues of TADDOLs by trifluoromethylation of the tartaric acid-derived bisphenone **3a** (Figure 2) with TFMTMS, we obtained a very selective mono(trifluoromethylation) reaction.

We then decided to exploit this unexpected and interesting observation to assess the scope and limitations of this reaction as an entry to the preparation of enantiopure trifluoromethylated building blocks. Actually, we report in this paper a methodology that leads to two enantiopure compounds from a unique tartaric acid-based scaffold.

Results and Discussion

A simplified retrosynthetic pathway for the preparation of α-alkoxy-α-trifluoromethyl aldehydes is depicted in Scheme 1.

The tartaric acid derived diketones **3** were prepared via the bis-Weinreb tartramide[17] and its condensation with organomagnesium reagents (Table 1).

Aromatic (entries 1−4) and aliphatic (entries 5 and 6) diketones were obtained in good to excellent yields (72−95%). No reaction occurred with more hindered Grignard reagents (cyclohexyl, β-naphthyl, or *p*-OMe-*m*-Me-phenyl) and with heteroaromatic Grignard reagents (2-pyridyl).

We next studied the trifluoromethylation of diketones **3a**−**f** with TFMTMS. The reaction conditions were investigated by use of diketone **3a** as model substrate. The fluoride initiator, the solvent, the stoichiometry, and the temperature of the reaction were considered, giving the results summarized in Table 2.

The reaction afforded the monoadduct **4a** as the only product, even when an excess of TFMTMS was used (entries 1 and 2), whatever the fluoride initiator used, except for cesium fluoride

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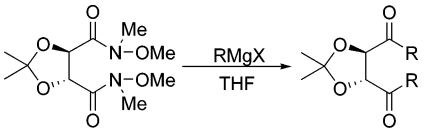
TABLE 1. Preparation of Diketones[a]



3a-f

entry	product	R	temp (°C)	yield[b]
1	**3a**	Ph	0	95
2	**3b**	4-MePh	−10	57
3	**3c**	4-MeOPh	−10	78
4	**3d**	2-MeOPh	−10	55
5	**3e**	Bn	−10	72
6	**3f**	Et	0	75

[a] The reactions were carried out by adding dropwise RMgX (3.5 equiv) to the Weinreb tartramide and stirring for 0.15−3 h. [b] Isolated yield.

(entry 4). The reaction proceeds efficiently with the difluorostannate[18] and the difluorosilicate[19] salts (entries 1 and 2), and with tetramethyl- and tetrabutylammonium fluorides (TMAF and TBAF, respectively) (entries 6 and 7). These fluoride salts may be used in dichloromethane or in tetrahydrofuran (THF). Cesium fluoride behaved differently. In the presence of an excess of CsF, the bisadduct **5a** was the major product (entry 4), the monoadduct **4a** being obtained by use of 1 equiv of reagent (entry 5).

This trifluoromethylation reaction proved to be highly diastereoselective in the formation of the monoadduct for all initiators except for cesium fluoride. The best compromise seemed to be an initiation with TBAF, for which the diastereoselectivity was optimized by lowering the reaction temperature (entry 9). Such conditions are very convenient since the crystalline TBAF trihydrate was used.

Compound **4a** was quantitatively transformed into the corresponding γ-keto trifluoromethylcarbinol **6a** by reaction with *n*-tetrabutylammonium fluoride trihydrate. The major diastereoisomer of both carbinol **6a** and the parent silyl ether **4a** were easily isolated in pure form by crystallization from petroleum ether. Conversion of **3a** into **6a** may be carried out in a one-pot process with a similar yield.

The optimized reaction conditions (one-pot procedure) were applied to the prepared diketones **3a**−**f**, giving the results summarized in Table 3.

The reaction of both aromatic and aliphatic diketones led exclusively to the corresponding monoaddition product. The yields were good to excellent, the lower ones corresponding to less electrophilic aromatic ketones bearing an ortho or para electron-donating substituent (entries 3 and 4) with possible contribution of steric effect (entry 4).

The diastereoselectivity of the nucleophilic addition depends strongly on the structure of the diketones. Substituted aromatic substrates gave the lowest diastereomeric excess (entries 2−4), while we were unable to detect a minor diastereomer from ethylketone **6f** (entry 6). In each case, the major diastereomer could be isolated in pure form. The configuration (*R*) was deduced by chemical correlation (vide infra).

The trifluoromethylation of carbonyl compounds by TFMTMS proceeds through a chain mechanism where the trifluoromethyl group is delivered to the substrate from a stabilized trifluoromethyl "silicate" species.[7a] The origin of the diastereoselectivity may be explained by use of a nonchelated Felkin−Anh[20] transition state model (Figure 3). A similar transition state was proposed for the addition of TFMTMS on chiral imines[21] or carbonyl compounds.[13a,22] The very high degree of stereoselectivity could be due to an additive effect of repulsive electronic interaction between the trifluoromethyl group and the oxygen-rich bulky α-substituent. In some cases such repulsive electronic effects can control the course of the reaction, as in the addition of TFMTMS to carbonylated sugars, where the high diastereoselectivity is opposed to the one predicted by a Felkin−Anh model.[23] It should also be noted that the entering nucleophile is not a naked CF_3 group but is transferred from the bulky hypervalent species mentioned above.

We are not able at the moment to rationalize the chemoselectivity for a mono(trifluoromethylation). The scarce papers regarding the reaction of dicarbonyl compounds with TFMTMS report the formation of a mixture of mono- and bis(trifluoromethylated) products, or the latter alone,[24] except for 1,2-diphenylethane-1,2-dione, but most of these reactions were performed with cesium fluoride as initiator.[24b] A tentative explanation could be a competing intramolecular trapping of the alcoholate resulting from the second nucleophilic addition by the TMS group to form an hypervalent intermediate. Such a process would compete with the chain transfer reaction so that the chain reaction would be effective only for the first addition. The counterion of the alcoholate or silicate intermediates seems to play a crucial role since the reaction with cesium fluoride behaves differently than reactions with ammonium salt-type initiators. Some investigations are underway for a better understanding of this transformation.

Having in hand diastereomerically pure trifluoromethylcarbinols, we then considered the deketalization and oxidative cleavage of diphenyl derivative **6a** as model compound. The isopropylidene-protected compound **6a** proved to be very resistant [aqueous HCl 2 N/THF at reflux, H_5IO_6 (5 equiv)/Et_2O at reflux, trifluoroacetic acid (20 equiv)/Et_2O at reflux] or decomposed [MeOH/HCl 2 N at reflux, picric acid (2 equiv)/Et_2O at reflux, neat trifluoroacetic acid at reflux] under acidic conditions. The stability of isopropylidene-protected tartaric acid derivatives was already observed in TADDOLs chemistry[16] or more recently in total synthesis.[25]

While we intend to alkylate the hydroxy group, to possibly allow the use of stronger acid conditions, interesting unexpected results were observed. Under treatment with an excess of base (2.2 equiv of KO*t*Bu) and methyl iodide, compound **6a** was converted in high yield into the product **8a**, resulting from the methylation of both the alcoholate and the enolate of the ketone moiety (Scheme 2). Formation of the enol ether competes effectively with the methylation of the sterically more demand-

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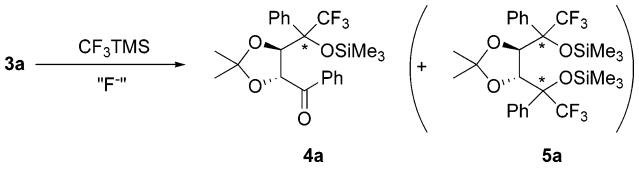
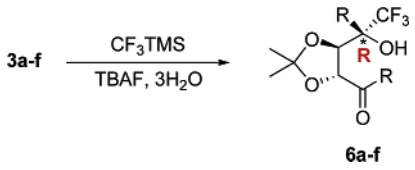
TABLE 2. Nucleophilic Trifluoromethylation of 3a[a]



entry	CF_3TMS (equiv)	fluorine source	reaction conditions	monoaddition product **4a** yield[b] (%)	monoaddition product **4a** de[c]	bisaddition product **5a** yield[b] (%)
1	3	$Bu_4N^+Ph_3SnF_2^-$	CH_2Cl_2, 0 °C, 0.5 h	75	80	
2	3	$Bu_4N^+Ph_3SiF_2^-$	CH_2Cl_2, 0 °C, 0.5 h	99	96	
3	1.5	$Bu_4N^+Ph_3SiF_2^-$	CH_2Cl_2, 0 °C, 1−2 h	99	92	
4	3	CsF	DME, rt, 12 h	9	0[d]	54[e]
5	1.1	CsF	DME, −40 °C, 3 h	90	40	
6	1.05	TMAF	CH_2Cl_2, 0 °C, 0.25 h	95	90	
7	1.05	TBAF·$3H_2O$	CH_2Cl_2, 0 °C, 0.25 h	95	90	
8	1.05	TBAF·$3H_2O$	THF, 0 °C, 0.33 h	90	96	
9	1.05	TBAF·$3H_2O$	THF, −40 °C, 1 h	90	98	

[a] The reactions were carried out by adding 0.08 equiv of fluoride salt to a mixture of CF_3TMS and **3a.** [b] Isolated yield. [c] Determined by GC analysis of the crude reaction mixture. [d] Determined by ^1H NMR analysis of the crude reaction mixture. [e] Ratio of diastereoisomers C_2 symmetrical product/C_2 symmetrical product/C_1 symmetrical product 16/84/0 (^1H NMR).

TABLE 3. Generalization of the Nucleophilic Trifluoromethylation to Various Diketones[a]



entry	product	R	reaction time[b] (h)	yield[c]	de[d]
1	**6a**	phenyl	1	93	98
2	**6b**	4-methylphenyl	3	20	70
3	**6c**	4-methoxyphenyl	3	60	75
4	**6d**	2-methoxyphenyl	3	56	20
5	**6e**	benzyl	3	91	92
6	**6f**	ethyl	1	86	99

[a] The reactions were carried out by adding 0.08 equiv of TBAF, $3H_2O$ at −40 °C to a mixture of CF_3TMS (1.05 equiv) and compounds **3a**−**f** in THF; desilylation of intermediates products were carried out by reaction with TBAF, $3H_2O$ (1 equiv) in CH_2Cl_2 at room temperature for 3 h. [b] Reaction time for trifluoromethylation. [c] Isolated yield. [d] Determined by GC/MS analysis of the crude reaction mixture.

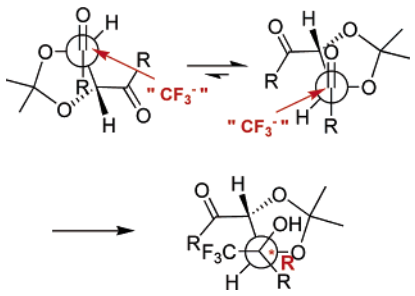
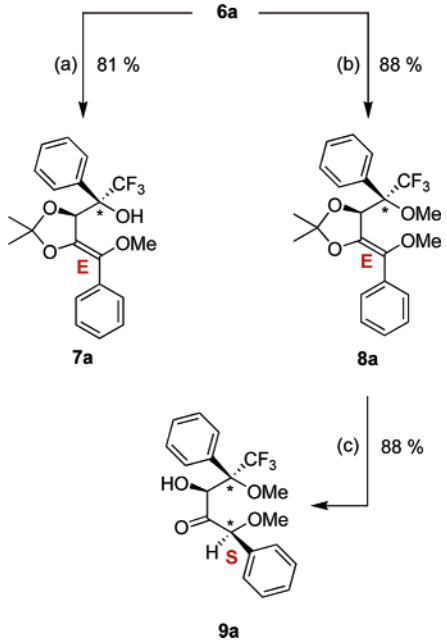


FIGURE 3. Felkin−Anh model for the nucleophilic trifluoromethylation of carbonyl compounds.

ing alcoholate moiety, the nucleophilicity of which is decreased by the strongly electron-withdrawing trifluoromethyl group. Indeed, the treatment with 1 equiv of base led selectively to the enol ether **7a** (Scheme 2).

SCHEME 2. Methylation of 6a under Basic Conditions[a]



[a] Reagents and conditions: (a) tBuOK (1.1 equiv), MeI (1.1 equiv), CH_3CN, 2 h, rt; (b) tBuOK (2.2 equiv), MeI (2.2 equiv), CH_3CN, 3 h, rt; (c) MeOH/HCl 1.4 N, 3 h, 65 °C.

Interestingly, the enol ether formation was totally stereoselective, giving the (*E*) isomer, as demonstrated by NOE measurement (Figure 4) (percentage of NOE transferred: OMe−H = 1%, OMe−OH = 15%).

The observed stereoselectivity can easily be explained by a preferential conformation allowing an αC−H bond parallel to the carbonyl π-system (Figure 5).[26] The IR spectrum exhibits an intramolecular H-bond absorption. However, owing to the absence of a significant shift for the carbonyl band and to the possibility of intramolecular H-bonding with other oxygen atoms

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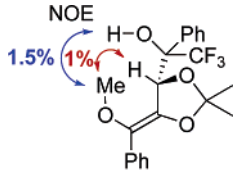


FIGURE 4. Interactions studied by NOE measurements.

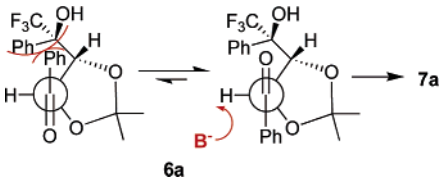


FIGURE 5. Model for the stereoselective formation of enol ether 7a.

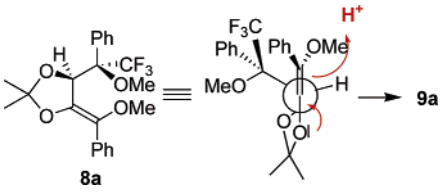


FIGURE 6. Model for the stereoselective protonation of 8a.

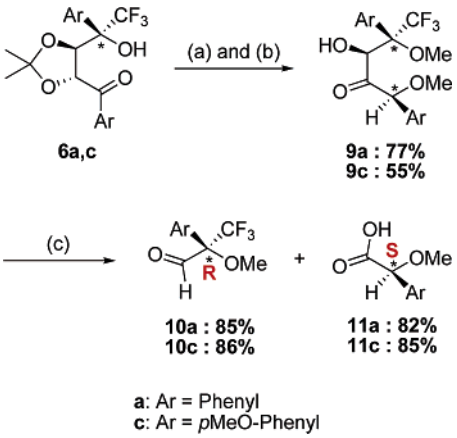
present in the molecule, we are unable to discriminate any contribution of H-bonding to the preferred conformation.

Whereas compound **6a** resisted mild acid hydrolysis, compound **8a** was easily converted with HCl/methanol into the hydroxyketone **9a** with an excellent yield (88%) (Scheme 2). Here again, the reaction occurred with a remarkable stereoselectivity. Only one diastereomer was obtained, which is significant because of a total diastereofacial protonation step, which would occur according to Figure 6, giving a (*S*) configuration, as will be confirmed (vide infra).

Treatment of **9a** with periodic acid in ether at 0 °C produced finally two products: the expected 2-methoxy-2-phenyl-3,3,3-trifluoropropanal (**10a**) and methoxy(phenyl)acetic acid (**11a**) (Scheme 3). Stereochemical integrity was preserved in this oxidative cleavage. The configuration of these enantiopure compounds was confirmed by comparison of optical properties with those reported in the literature.[27] Compound **10a** is the precursor of Mosher acid, a well-known reagent for the determination of enantiomeric excess of alcohols and amines.[28] The acid **11a** was also used as a tool for determination of the absolute configuration of alcohols.[29]

The reaction sequence was applied to some other trifluoromethylcarbinols **6**. It could be extended to the bis(*p*-MeO-phenyl) derivative **6c** (Scheme 3). Unfortunately, under the basic conditions required for the methylation, aliphatic derivatives proved to be unstable.

SCHEME 3. Oxidative Cleavage of 9a and 9c[a]



[a] Reagents and conditions: (a) tBuOK (2.2 equiv), MeI (2.2 equiv), CH_3CN, 3 h, rt; (b) MeOH/HCl 1.4 N, 3 h, 65 °C; (c) H_5IO_6 (1.1 equiv), Et_2O, 2.5 h at 0 °C, then rt.

Conclusion

We have developed a methodology that allows us to prepare two enantiopure building blocks from a unique tartaric acid-derived scaffold. One of these building blocks is an α-aryl-α-methoxy-α-trifluoromethyl ethanal, a potential precursor for a variety of enantiopure functionalized trifluoromethyl derivatives.[10] The second one is an α-aryl-α-methoxycarboxylic acid, not a trivial compound in enantiopure series.[27b,30] Research is underway to develop this approach toward a more versatile and more general method for both fluorinated and nonfluorinated enantiopure derivative production.

Experimental Section

General Procedure for the Preparation of Diketones 3a−f. To a solution of the Weinreb tartramide[17] (1 equiv) in THF (50 mL) at a temperature between 0 and −10 °C under an argon atmosphere was added dropwise the Grignard reagent corresponding to the desired diketone (3.5 equiv). The reaction was monitored by thin-layer chromatography (TLC) until completion. The reaction was quenched with saturated NH_4Cl solution and the mixture was acidified with 1 N HCl and extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with a saturated NaCl solution and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel with petroleum ether/ethyl acetate as eluent and recrystallized in the case of a solid product.

(−)-[(4*R*,5*R*)-5-(2-Methoxybenzoyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-(2-methoxyphenyl)methanone (3d). Reaction temperature was −10 °C; reaction time was 3 h. Purification by preparative centrifugal TLC (petroleum ether/EtOAc 80/20) and recrystallization from petroleum ether/ethyl acetate mixture yielded **3d** as white crystals. Yield 55%; mp 93 °C; $[\alpha]_D^{20}$ −67.9 (*c* 1.07, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) 1.43 (s, 6H), 3.67 (s, 6H), 5.81 (s, 2H), 6.90 (m, 2H), 7.03 (m, 2H), 7.48 (m, 2H), 7.79 (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$) 27.2, 55.2, 82.2, 111.4, 113.2, 120.8, 126.0, 131.2, 134.1, 158.6, 198.7. Anal. Calcd for $C_{21}H_{22}O_6$: C, 68.11; H, 5.95. Found: C, 67.97; H, 6.07. HRMS (ESI^+) *m/z* calcd for $C_{21}H_{23}O_6$ $[M + H]^+$ 371.1495, found 371.1487.

(+)-(4*R*,5*R*)-1-(2,2-Dimethyl-5-phenylacetyl-[1,3]dioxolan-4-yl)-2-phenylethanone (3e). Reaction temperature was −10 °C;

(28) (a) Hundscheid, F. J. A.; Tandon, V. K.; Rouwette P. H. F. M.; van Leusen, A. M. *Tetrahedron* **1987**, *43*, 5073−5088. (b) Moreno−Dorado, F. J.; Guerra, F. M.; Ortega, M. J.; Zubía, E.; Massanet, G. M. *Tetrahedron: Asymmetry* **2003**, *14*, 503−510.

(29) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543−2549.

(30) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 4929−4932.

(31) Prasad, K. R.; Chandrakumar, A. *Tetrahedron: Asymmetry* **2005**, *16*, 1897−1900.

reaction time was 3 h. Purification by preparative centrifugal TLC (petroleum ether/EtOAc 80/20) yielded **3e** as a pale-yellow oil. Yield 72%; $[\alpha]_D^{20}$ +12.5 (*c* 0.32, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) 1.45 (s, 6H), 3.93 (s, 4H), 4.69 (s, 2H), 7.18−7.32 (m, 10H); ^{13}C NMR (62.9 MHz, $CDCl_3$) 26.3, 45.9, 81.0, 112.9, 127.3, 128.8, 129.7, 133.0, 205.8. HRMS (ESI^+) *m*/*z* calcd for $C_{21}H_{22}O_4Na$ $[M + Na]^+$ 361.1416, found 361.1414.

General Procedure for the Synthesis of Trifluoromethyl Alcohols (6a−f). The following experiment is representative of the procedure for the trifluoromethylation of **3a**−**f**: To a solution of the desired diketone **3a**−**f** (1 equiv) and trifluoromethyl(trimethyl)silane (1.05 equiv) in THF (30 mL) at a temperature of −40 °C under an argon atmosphere was added tetra *n*-butylammonium fluoride trihydrate (0.08 equiv). After 1 h, the reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with a saturated NaCl solution and dried ($MgSO_4$), and the solvent was removed under reduced pressure. Except for the silylated product **4a**, which was first purified by preparative centrifugal TLC with a mixture of petroleum ether/ethyl acetate (99/1) and recrystallized from petroleum ether to afford white crystals (yields and de in Table 2, vide supra), the other compounds **4** were directly converted into the corresponding alcohols **6** by reaction of the crude product with tetra *n*-butylammonium fluoride trihydrate (1 equiv) in dichloromethane (30 mL) at room temperature for 3 h. The reaction was washed with water and dried ($MgSO_4$), and the solvent was removed under reduced pressure. Finally, the residue was purified by preparative centrifugal thin-layer chromatography with petroleum ether/ethyl acetate as eluent and recrystallized for the solid compounds.

(−)-[(4*R*,5*R*)-2,2-Dimethyl-5-((*R*)-2,2,2-trifluoro-1-phenyl-1-(trimethylsilanyloxy)ethyl)-[1,3]dioxolan-4-yl]phenylmethanone (4a). Major diastereomer: white crystals; mp 78 °C; $[\alpha]_D^{20}$ −53.7 (*c* 0.45, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) 0.15 (s, 9H), 1.31 (s, 3H), 1.36 (s, 3H), 5.06 (d, $^3J_{HH}$ = 6.1 Hz, 1H), 5.53 (d, $^3J_{HH}$ = 6.1 Hz, 1H), 7.40−7.69 (m, 8H), 8.04 (m, 2H); ^{19}F NMR (235.3 MHz, $CDCl_3$) −74.58 (s, 3F, CF_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) 1.7, 25.6, 26.1, 76.4, 77.2, 111.8, 127.7, 128.0, 128.5, 128.8, 129.3, 133.5, 135.2, 135.5, 195.7. IR (KCl, cm^{-1}) $\upsilon_{C=O}$ = 1693; υ_{max} = 3094, 3008, 2975, 2960, 2899, 1383, 1156, 1176, 1090, 1053, 848, 764. Anal. Calcd for $C_{23}H_{27}O_4F_3Si$: C, 61.06; H, 5.97. Found: C, 61.08; H, 5.89.

(−)-[(4*R*,5*R*)-2,2-Dimethyl-5-((*R*)-2,2,2-trifluoro-1-hydroxy-1-phenylethyl)-[1,3]dioxolan-4-yl]phenylmethanone (6a). Reaction time was 1 h. Purification by preparative centrifugal TLC with a petroleum ether/ethyl acetate mixture (95/5) yielded **6a** as white crystals, yield 93% (de 98%). Major diastereomer: mp 115−117 °C; $[\alpha]_D^{20}$ −39.5 (*c* 0.43, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) 1.22 (s, 3H), 1.38 (s, 3H), 4.20 (d, $^3J_{HH}$ = 6.6 Hz, 1H), 4.78 (d, $^3J_{HH}$ = 6.6 Hz, 1H), 7.41−8.10 (m, 10H); ^{19}F NMR (235.3 MHz, $CDCl_3$) −77.67 (s, 3F, CF_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) 25.5, 26.6, 75.7 (q, $^3J_{CF}$ = 28.2 Hz), 77.7, 79.2, 112.0, 124.9 (q, $^1J_{CF}$ = 285.7. Hz, CF_3), 128.9, 128.1, 128.6, 129.2, 130.2, 134.1, 134.4, 134.8, 200.0. IR (KCl, cm^{-1}) $\upsilon_{C=O}$ = 1687; υ_{max} = 3505, 2997, 2981, 2948, 1451, 1374, 1215, 1165, 1138, 1063, 1011, 985, 851, 724, 706, 688. Anal. Calcd for $C_{20}H_{19}O_4F_3$: C, 63.16; H, 5.00. Found: C, 62.85; H, 4.77. HRMS (ESI^+) *m*/*z* calcd for $C_{20}H_{20}O_4F_3$ $[M + H]^+$ 381.1314, found 381.1313.

(−)-{(4*R*,5*R*)-2,2-Dimethyl-5-[(*R*)-2,2,2-trifluoro-1-hydroxy-1-(4-methylphenyl)ethyl]-[1,3]dioxolan-4-yl}-(4-methylphenyl)-methanone (6b). Reaction time was 3 h. Purification by preparative centrifugal TLC (petroleum ether/EtOAc 95/5) and recrystallization from petroleum ether/ethyl acetate mixture afforded **6b** as white crystals, yield 20% (de 70%). Major diastereomer: mp 136−138 °C; $[\alpha]_D^{20}$ −20 (*c* 0.46, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) 1.21 (s, 3H), 1.39 (s, 3H), 2.38 (s, 3H), 2.41 (s, 3H), 4.28 (s, 1H), 4.74 (d, $^3J_{HH}$ = 6.5 Hz, 1H), 5.16 (d, $^3J_{HH}$ = 6.5 Hz, 1H), 7.20−7.27 (m, 4H), 7.70 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 7.99 (d, $^3J_{HH}$ = 8.1 Hz, 2H); ^{19}F NMR (235.3 MHz, $CDCl_3$) −77.71 (s, 3F, CF_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) 21.1, 21.8, 25.4, 26.2, 75.6 (q, $^2J_{CF}$ = 27.7 Hz), 77.2, 79.2, 111.7, 124.8 (q, $^1J_{CF}$ = 284.1 Hz, CF_3), 127.6, 128.7, 129.2, 130.1, 131.1, 132.2, 138.8, 145.4, 199.5. HRMS (ESI^+) *m*/*z* calcd for $C_{22}H_{24}O_4F_3$ $[M + H]^+$ 409.1627, found 409.1640.

(−)-{(4*R*,5*R*)-2,2-Dimethyl-5-[(*R*)-2,2,2-trifluoro-1-hydroxy-1-(4-methoxyphenyl)ethyl]-[1,3]dioxolan-4-yl}-(4-methoxyphenyl)methanone (6c). Reaction time was 3 h. Purification by preparative centrifugal TLC (petroleum ether/EtOAc 75/25) and recrystallization from petroleum ether/ethyl acetate mixture afforded **6c** as white crystals, yield 60% (de 75%). Major diastereomer: mp 113 °C; $[\alpha]_D^{20}$ −55.6 (*c* 1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) 1.23 (s, 3H), 1.40 (s, 3H), 3.83 (s, 3H), 3.87 (s, 3H), 4.61−4.64 (m, 2H), 5.08 (d, $^3J_{HH}$ = 6.7 Hz, 1H), 6.91−6.95 (m, 4H), 7.74 (d, $^3J_{HH}$ = 8.8 Hz, 2H), 8.11 (d, $^3J_{HH}$ = 8.8 Hz, 2H); ^{19}F NMR (235.3 MHz, $CDCl_3$) −77.97 (s, 3F, CF_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) 25.4, 26.1, 55.2, 55.5, 75.1 (q, $^2J_{CF}$ = 28.2 Hz.), 77.7, 79.6, 111.7, 113.2, 113.7, 124.9 (q, $^1J_{CF}$ = 285.7 Hz, CF_3), 126.0, 127.6, 129.2, 132.8, 160.0, 164.5, 198.6. HRMS (ESI^+) *m*/*z* calcd for $C_{22}H_{24}O_6F_3$ $[M + H]^+$ 441.1525, found 441.1530.

(−)-{(4*R*,5*R*)-2,2-Dimethyl-5-[2,2,2-trifluoro-1-hydroxy-1-(2-methoxyphenyl)ethyl]-[1,3]dioxolan-4-yl}-(2-methoxyphenyl)-methanone (6d and 6d′). Reaction time was 3 h. Purification by preparative centrifugal TLC (petroleum ether/EtOAc 80/20) yielded a mixture of the two diastereomers **6d** and **6d′** (ratio 65/35, de 20%); global yield was 56%. Recrystallization from a petroleum ether/ethyl acetate mixture allowed the separation of the two compounds.

Major Diastereomer: (−)-{(4*R*,5*R*)-2,2-Dimethyl-5-[(*R*)-2,2,2-trifluoro-1-hydroxy-1-(2-methoxyphenyl)ethyl]-[1,3]dioxolan-4-yl}-(2-methoxyphenyl)methanone (6d). White crystals; mp 135−137 °C; $[\alpha]_D^{20}$ −34.00 (*c* 1, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$) 1.25 (s, 3H), 1.40 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 5.46 (d, $^3J_{HH}$ = 5.2 Hz, 1H), 5.59 (d, $^3J_{HH}$ = 5.2 Hz, 1H), 6.92−7.09 (m, 4H), 7.33−7.46 (m, 2H), 7.60−7.63 (m, 1H), 7.71−7.74 (m, 1H); ^{19}F NMR (235.3 MHz, $CDCl_3$) −77.95 (s, 3F, CF_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) 25.8, 26.7, 55.9, 56.6, 78.3, 78.8 (q, $^2J_{CF}$ = 27.1 Hz), 79.9, 111.0, 111.8, 112.9, 120.7, 121.6, 122.6, 125.0 (q, $^1J_{CF}$ = 287.8 Hz, CF_3), 127.6, 130.3, 130.4, 131.0, 133.6, 158.6, 158.7, 200.7. HRMS (ESI^+) *m*/*z* calcd for $C_{22}H_{24}O_6F_3$ $[M + H]^+$ 441.1525, found 441.1529.

Minor Diastereomer: (+)-{(4*R*,5*R*)-2,2-Dimethyl-5-[(*S*)-2,2,2-trifluoro-1-hydroxy-1-(2-methoxyphenyl)-ethyl]-[1,3]dioxolan-4-yl}-(2-methoxyphenyl)methanone (6d′). Pale-yellow oil; $[\alpha]_D^{20}$ +33.8 (*c* 1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) 1.42 (s, 3H), 1.55 (s, 3H), 3.55 (s, 3H), 3.65 (s, 3H), 5.19 (d, $^3J_{HH}$ = 5.3 Hz, 1H), 5.83 (d, $^3J_{HH}$ = 5.3 Hz, 1H), 6.64 (m, 1H), 6.76 (m, 1H), 6.92 (m, 2H), 7.20 (m, 1H), 7.38 (m, 2H), 7.80 (m, 1H); ^{19}F NMR (235.3 MHz, $CDCl_3$) −75.62 (s, 3F, CF_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) 25.9, 27.0, 54.7, 55.2, 77.5, 79.7, 110.8, 111.4, 112.8, 120.3, 120.3, 122.3, 125.2 (q, $^1J_{CF}$ = 288.9 Hz, CF_3), 126.6, 128.9, 130.3, 130.7, 133.6, 156.2, 158.2, 199.2. HRMS (ESI^+) *m*/*z* calcd for $C_{22}H_{24}O_6F_3$ $[M + H]^+$ 441.1525, found 441.1528.

(+)-1-[(4*R*,5*R*)-5-((*R*)-1-Benzyl-2,2,2-trifluoro-1-hydroxyethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-2-phenylethanone (6e). Reaction time was 3 h. Purification by preparative centrifugal TLC (petroleum ether/EtOAc 90/10) afforded **6e** as a pale-yellow oil, yield 91% (de 92%). Major diastereomer: $[\alpha]_D^{20}$ +29.4 (*c* 1.5, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) 1.32 (s, 3H), 1.59 (s, 3H), 3.07(d, $^2J_{HH}$ = 14.3 Hz, 1H), 3.18 (d, $^2J_{HH}$ = 14.3 Hz, 1H), 3.95 (s, 2H), 4.31 (d, $^3J_{HH}$ = 6.4 Hz, 1H), 4.58 (d, $^3J_{HH}$ = 6.4 Hz, 1H), 7.13−7.31 (m, 10H); ^{19}F NMR (235.3 MHz, $CDCl_3$) −78.65 (s, 3F, CF_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) 25, 26.4, 35.8, 46.0, 74.5 (q, $^2J_{CF}$ = 26.2 Hz), 76.4, 80.3, 111.7, 125.4 (q, $^1J_{CF}$ = 287.7 Hz, CF_3), 127.2, 127.2, 128.1, 128.6, 129.6, 131.1, 132.6, 133.6, 209.6. HRMS (ESI^+) *m*/*z* calcd for $C_{22}H_{24}O_4F_3$ $[M + H]^+$ 409.1627, found 409.1633.

(+)-1-[(4*R*,5*R*)-5-[(*R*)-1-Hydroxy-1-(trifluoromethyl)propyl]-2,2-dimethyl-[1,3]dioxolan-4-yl]propan-1-one (6f). Reaction time was 1 h. Purification by flash chromatography (petroleum ether/

EtOAc 95/5) yielded **6f** as a pale-yellow oil. Major diastereomer: yield 86% (de 99%); $[\alpha]_D^{20}$ +23 (*c* 0.4, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) 1.07−1.12 (m, 6H), 1.31 (s, 3H), 1.52 (s, 3H), 1.75−1.92 (m, 2H), 2.70−2.83 (m, 2H), 4.47−4.50 (m, 2H); ^{19}F NMR (235.3 MHz, $CDCl_3$) −78.88 (s, 3F, CF_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) 6.9, 7.0, 23.9, 25.3, 26.4, 32.9, 74.2 (q, $^2J_{CF}$ = 26.3 Hz), 76.8, 80.8, 111.6, 125.8 (q, $^1J_{CF}$ = 287.5 Hz, CF_3), 213.9. HRMS (ESI^+) *m*/*z* calcd for $C_{12}H_{20}O_4F_3$ $[M + H]^+$ 285.1314, found 285.1316.

Methylation of α-Trifluoromethyl Alcohol: (A) With 1.1 Equiv of Base. To a solution of **6a** (1 equiv) and iodomethane (1.1 equiv) in CH_3CN (20 mL) at room temperature (rt) under an argon atmosphere was added potassium *tert*-butylate (1.1 equiv). After being stirred for 2 h, the reaction was quenched with a saturated NH_4Cl solution and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Purification by preparative centrifugal TLC with a petroleum ether/ethyl acetate mixture (95/5) yielded **7a** as a pale-yellow oil, yield 81%.

(−)-(*R*)-2,2,2-Trifluoro-1-{(*S*)-5-[1-methoxy-1-phenylmeth-(*E*)-ylidene]-2,2-dimethyl-[1,3]dioxolan-4-yl}-1-phenylethanol (7a). $[\alpha]_D^{20}$ −300.3 (*c* 1.24, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) 1.25 (s, 3H), 1.39 (s, 3H), 3.49 (s, 3H), 5.40 (s, 1H), 7.17−7.65 (m, 10H); ^{19}F NMR (235.3 MHz, $CDCl_3$) −76.46 (s, 3F, CF_3); ^{13}C NMR (125.7 MHz, $CDCl_3$) 24.7, 25.4, 59.0, 78.1 (q, $^2J_{CF}$ = 26.7 Hz), 79.3, 112.8, 125.1 (q, $^1J_{CF}$ = 286.9 Hz, CF_3), 126.9, 127.4, 127.5, 127.9, 128.3, 128.6, 131.3, 134.8, 135.5, 140.3. HRMS (ESI^+) *m*/*z* calcd for $C_{21}H_{21}O_4F_3Na$ $[M + Na]^+$ 417.1290, found 417.1288.

(B) With 2.2 Equiv of Base. The experimental procedure was the same as above with 2.2 equiv of iodomethane and potassium *tert*-butylate and a reaction time of 3 h. Purification by preparative centrifugal TLC with a petroleum ether/ethyl acetate mixture (97.5/2.5) and recrystallization from a petroleum ether/ethyl acetate mixture yielded **8a** as white crystals, yield 88%.

(−)-(*R*)-4-[1-Methoxy-1-phenylmeth-(*E*)-ylidene]-2,2-dimethyl-5-((*R*)-2,2,2-trifluoro-1-methoxy-1-phenylethyl)-[1,3]dioxolane (8a). Mp 83 °C; $[\alpha]_D^{20}$ −52.38 (*c* 0.62, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) 0.75 (s, 3H), 1.07 (s, 3H), 3.35−3.36 (m, 3H), 3.51 (s, 3H), 5.45 (s, 1H), 7.22−7.56 (m, 10H); ^{19}F NMR (235.7 MHz, $CDCl_3$) −67.68 (s, 3F, CF_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) 24.4, 25.9, 53.9 (q, $^4J_{CF}$ = 2 Hz), 59.2, 78.0, 84.6 (q, $^2J_{CF}$ = 24.3 Hz), 111.4, 125.7 (q, $^1J_{CF}$ = 292.8 Hz, CF_3), 127.4, 127.6, 127.7, 128.6, 128.7, 128.7, 132.2, 133.0, 138.5, 140.4. Anal. Calcd for $C_{22}H_{23}O_4F_3$: C, 64.70; H, 5.63. Found: C, 64.56; H, 5.55.

Deprotection of the Isopropylidene Group. To a solution of MeOH/HCl 1.4 N [prepared by dropwise addition of acetyl chloride (1.5 mL, 21.1 mmol) to 15 mL of dry MeOH at 0 °C] was added **8a** (0.4 mmol). The mixture was refluxed for 3 h. The solvent was then evaporated under reduced pressure and the crude product was dissolved in ethyl acetate (30 mL). The organic layer was washed with a saturated $NaHCO_3$ solution and with brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Purification by preparative centrifugal TLC with a petroleum ether/ethyl acetate mixture (90/10) and recrystallization from a petroleum ether/ethyl acetate mixture yielded **9a** as white crystals, yield 88%.

(+)-(1*S*,3*S*,4*R*)-5,5,5-Trifluoro-3-hydroxy-1,4-dimethoxy-1,4-diphenylpentan-2-one (9a). Mp 116−118 °C; $[\alpha]_D^{20}$ +234.5 (*c* 1.24, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 2.80 (d, $^3J_{HH}$ = 9.6 Hz, 1H), 3.34 (s, 3H), 3.29 (m, 3H), 4.63 (d, $^3J_{HH}$ = 9.6 Hz, 1H), 5.35 (s, 1H), 7.34−7.42 (m, 10H); ^{19}F NMR (235.3 MHz, $CDCl_3$) −69.37 (s, 3F, CF_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) 54.1, 57.1, 72.2, 85.1 (q, $^2J_{CF}$ = 25.2 Hz), 88.5, 124.9 (q, $^1J_{CF}$ = 292.3 Hz, CF_3), 128.0, 128.2, 128.4, 129.1, 129.2, 129.3, 129.4, 134.2, 205.1. HRMS (ESI^+) *m*/*z* calcd for $C_{19}H_{19}O_4F_3Na$ $[M + Na]^+$ 391.1133, found 391.1141.

Methylation and Deprotection of 6c. By the same procedure, product **9c** was obtained as white crystals by preparative centrifugal TLC with a petroleum ether/ethyl acetate mixture (90/10) and recrystallization from a petroleum ether/ethyl acetate mixture. Global yield for the two steps was 55%.

(+)-(1*S*,3*S*,4*R*)-5,5,5-Trifluoro-3-hydroxy-1,4-dimethoxy-1,4-bis(4-methoxyphenyl)pentan-2-one (9c). Mp 85−88 °C; $[\alpha]_D^{20}$ +159.54 (*c* 1.29, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) 2.80 (d, $^3J_{HH}$ = 8.9 Hz, 1H), 3.33 (s, 3H), 3.41 (m, 3H), 3.80 (s, 3H), 3.83 (s, 3H), 4.58 (d, $^3J_{HH}$ = 8.8 Hz, 1H), 5.3 (s, 1H), 6.89−6.94 (m, 4H.), 7.24−7.27 (m, 4H); ^{19}F NMR (235.3 MHz, $CDCl_3$) −69.70 (s, 3F, CF_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) 54.0, 55.2, 55.3, 57.0, 72.1, 85.0 (q, $^2J_{CF}$ = 26.4 Hz), 87.9, 113.6, 114.6, 121.1, 126.1, 128.0 (q, $^1J_{CF}$ = 292.1 Hz, CF_3), 129.5, 129.9, 160.2, 160.3, 205.4. HRMS (ESI^+) *m*/*z* calcd for $C_{21}H_{23}O_6F_3Na$ $[M + Na]^+$ 451.1344, found 451.1339.

Oxidative Cleavage of 9a and 9c. The following experiment is representative of the procedure of oxidative cleavage of **9a** and **9c**: To a solution of **9a** (1 equiv) in diethyl ether (10 mL) at 0 °C was added periodic acid (1.1 equiv). After 0.5 h, the mixture was warmed at room temperature and stirred for 2 h. The crude mixture was washed with a saturated $NaHCO_3$ solution, the organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure. Purification by preparative centrifugal TLC with a petroleum ether/ethyl acetate mixture (99/1) and recrystallization from petroleum ether give **10a** as a pale-yellow oil, yield 85%.

The aqueous layer was acidified at pH = 1 with a 1 N HCl solution and extracted with diethyl ether (2 × 10 mL), and the combined organic layer was dried over $MgSO_4$. Purification by preparative centrifugal TLC with a petroleum ether/ethyl acetate mixture (99/1) and recrystallization from petroleum ether yielded **11a** as white crystals, yield 82%.

(+)-(*R*)-3,3,3-Trifluoro-2-methoxy-2-(4-methoxyphenyl)propionaldehyde (10c). Pale-yellow oil; yield 86%; $[\alpha]_D^{20}$ +8.1 (*c* 0.73, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) 3.41 (s, 3H), 3.75 (s, 3H), 6.89 (d, $^3J_{HH}$ = 8.8 Hz, 2H), 7.33 (d, $^3J_{HH}$ = 8.5 Hz, 2H), 9.61 (q, $^4J_{HF}$ =2.1 Hz, 1H); ^{19}F NMR (235.3 MHz, $CDCl_3$) −71.36 (s, 3F, CF_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) 54.6, 55.3, 114.3, 120.7, 129.5 (q, $^3J_{CF}$ = 1.4 Hz), 160.7, 193.1. Anal. Calcd for $C_{11}H_{11}O_2F_3$: C, 56.89; H, 4.74. Found: C, 56.52; H, 4.65.

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Supporting Information Available: General experimental methods; spectroscopic data for compounds **3a−c,f**, **10a**, and **11a,c**; ^1H NMR, ^{13}C NMR, and ^{19}F NMR spectra of **3a,c,e,f**, **6b−f**, **7a**, **9a,c, 10a,** and **11a**; and NOESY spectra of compound **7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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