JOC Article

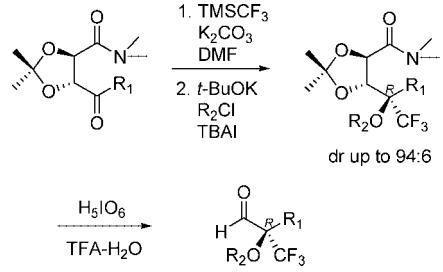
Enantiopure Quaternary α-Trifluoromethyl-α-alkoxyaldehydes from L-Tartaric Acid Derived Ketoamides

Jean Nonnenmacher, Fabien Massicot, Fabienne Grellepois, and Charles Portella*

Université de Reims Champagne-Ardenne, Institut de Chimie Moléculaire de Reims, CNRS UMR 6229, UFR des Sciences Exactes et Naturelles, BP 1039, 51687 Reims Cedex 2, France

charles.portella@univ-reims.fr

Received June 20, 2008



The diastereoselective nucleophilic trifluoromethylation of a range of ketoamides derived from L-tartaric acid has been studied. $TMSCF_3$ in the presence of a catalytic amount of K_2CO_3 in DMF has been identified as the conditions leading to the highest diastereoselectivities. A sequential one-pot reaction trifluoromethylation−etherification of the trifluoromethylcarbinol has been developed. Only one further one-pot reaction, ketal hydrolysis−oxidative cleavage, led to the final α-trifluoromethylated α-alkoxyaldehydes. This procedure was applied to the preparation of a series of enantiopure aryl, heteroaryl, and alkyl α-trifluoromethyl-α-alkoxyaldehydes

Introduction

Organofluorine compounds have found a wide range of applications as pharmaceuticals, agrochemicals, or materials[1] as a result of the beneficial properties brought by the fluorine atom.[2] One of the most important fluorine-containing substituents is the trifluoromethyl group. The latter is relatively large, its van der Waals radius lies between those of *i*Pr and *t*Bu, its electronegativity is similar to that of oxygen, and its hydrophobic parameter is large. Moreover, the trifluoromethyl group often improves biological activity and metabolic stability.[1c,3]

The most useful method to introduce a trifluoromethyl group into organic molecules is certainly the nucleophilic addition of trifluoromethyltrimethylsilane ($TMSCF_3$)[4] on aldehydes, ketones, esters, and activated imines.[5] Organic and inorganic fluorides such as tetraalkylammonium fluorides (TMAF, TBAF), tetrabutylammonium difluorotriphenylsilicate (TBAT), and CsF have been the most widely used nucleophilic initiators to activate $TMSCF_3$ and allow the transfer of the trifluoromethide equivalent to carbonyl groups and related π electrophiles.[5] Over the past few years, considerable efforts have been focused on the development of other sources of initiators, especially nucleophilic catalysts.[5e] Among them metal alkoxides,[6] acetates[7] or carbonates,[8] phosphate salts,[8] amine *N*-oxide,[8,9] phosphines,[10] and carbenes[11] have been described to give the desired CF_3-

(1) (a) Hiyama, T. *Organofluorine Compounds: Chemistry and Applications*; Springer-Verlag: Berlin, 2000. (b) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, 2004. (c) Bégué, J. P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley-VCH: Weinheim, 2008.

(2) O'Hagan, D *Chem. Soc. Rev* **2008**, *37*, 308–319, and references therein.

(3) For reviews on fluorinated molecules in medicinal chemistry and agrochemistry, see: (a) Jeschke, P. *ChemBioChem* **2004**, *5*, 570–589. (b) Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637–640. (c) Thayer, A. M. *Chem. Eng. News* **2006**, *84* (23), 15–24. (d) Thayer, A. M. *Chem. Eng. News* **2006**, *84* (23), 27–32. (e) Isanbor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006**, *127*, 303–319. (f) Bégué, J.-P.; Bonnet-Delpon, D. *J. Fluorine Chem.* **2006**, *127*, 992–1012. (g) Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013–1029. (h) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320–330. (i) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12* (2), 305–321.

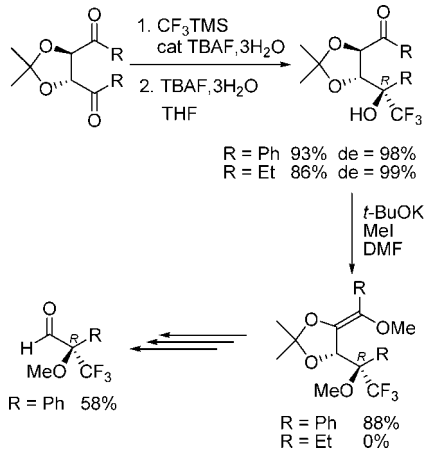
(4) (a) Ruppert, I.; Schlich, K.; Volbach, W. *Tetrahedron Lett.* **1984**, *25*, 2195–2198. (b) Prakash, G. K. S.; Krishnamurti, R.; Olah, G. A. *J. Am. Chem. Soc.* **1989**, *111*, 393–395.

(5) For reviews on nucleophilic trifluoromethylation, see: (a) Prakash, G. K. S.; Yudin, K. *Chem. Rev.* **1997**, *97*, 757–786. (b) Singh, R. P.; Shreeve, J. M. *Tetrahedron* **2000**, *56*, 7613–7632. (c) Prakash, G. K. S.; Mandal, M. *J. Fluorine Chem.* **2001**, *112*, 123–131. (d) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119–6146. (e) Ma, J.-A.; Cahard, D. *J. Fluorine Chem.* **2007**, *128*, 975–996. (f) Bastos, R. S. *Synlett* **2008**, 1425–1426.

(6) (a) Nelson, D. W.; Easley, R. A.; Pintea, B. N. V. *Tetrahedron Lett.* **1999**, *40*, 25–28. (b) Nelson, D. W.; Owens, J.; Hiraldo, D. *J. Org. Chem.* **2001**, *66*, 2572–2582.

10.1021/jo8013403 CCC: $40.75 © 2008 American Chemical Society
Published on Web 09/25/2008

SCHEME 1. Preparation of (*R*)-Mosher Acid Precursor from L-Tartaric Acid Derived Diketones[15d]



adducts in high yields.[12] Very recently, Shibata and Toru reported the first successful Lewis acid catalyzed nucleophilic trifluoromethylation using $TMSCF_3$.[13]

Currently, the asymmetric nucleophilic trifluoromethylation of carbonyl-containing substrates using $TMSCF_3$ is a major synthetic challenge.[5d,e] A few enantioenriched trifluoromethylcarbinols have been prepared by enantioselective trifluoromethylation, in moderate to good enantiomeric excess depending on the substrate and the chiral quaternary ammonium salt used.[14] Meanwhile, the diastereoselective trifluoromethylation of prochiral ketones has emerged as an efficient approach for the preparation of more functionalized α-trifluoromethylated-α-hydroxy (or alkoxy) building blocks.[15]

We recently reported the simultaneous preparation of two enantiopure building blocks from L-tartaric acid derived diketones, one being (*R*)-α-trifluoromethyl-α-alkoxyaldehyde precursors of Mosher's acid analogues (Scheme 1).[15d] A highly chemo- and diastereoselective nucleophilic monotrifluoromethylation of the substrate with $TMSCF_3$ in the presence of tetrabutylammonium fluoride (TBAF) provided the intermediate chiral α-trifluoromethyl carbinol. Only three further steps (protection of the alcohol, ketal hydrolysis, and oxidative cleavage of the resulting diol) were then required to reach the desired chiral building blocks. Unfortunately, this new route to enantiopure α-trifluoromethyl-α-alkoxy aldehydes suffered several drawbacks, including the following: (i) Weinreb diamides, precursors of the starting diketones, required experimental conditions not adapted for scaling up, (ii) hindered and heteroaromatic diketones could not be prepared, and (iii) this sequence was not suitable for the preparation of aliphatic derivatives (the protection step required basic conditions in which substrates containing a residual enolizable ketone proved to be unstable). Consequently, only aromatic α-trifluoromethyl-α-alkoxyaldehydes could eventually be synthesized.

We have now reexamined the synthesis of functionalized α-trifluoromethyl-α-hydroxy (or alkoxy) building blocks from natural L-tartaric acid derivatives.[16] As the residual ketone function seemed to be one of the main factors responsible for the limitations of our previous approach,[15d] we turned our efforts on the diastereoselective trifluoromethylation of tartaric acid derived ketoamides.[17] During the course of this study, we became interested in examining the influences of the ketal protecting group and/or the amide moieties and of the reaction conditions of the key nucleophilic trifluoromethylation step. We also focused our work on rendering this method more versatile and scalable.

Results and Discussion

With the aim of assessing the best tartaric acid derived starting material, we first prepared various model substrates. For this purpose, bis-Weinreb amide derived from tartaric acid in which the diol was protected by an isopropylidene group **1**[18] and bis-dimethylamide derivatives possessing either an isopropylidene group **2**[19] or a benzylidene group **3**[20] have been selected as starting materials. The controlled addition of 1.3−1.5 equiv of phenyl or ethyl Grignard reagent at −10 °C onto diamides **1**−**3**[21] gave selectively the corresponding aryl and alkyl ketoamides **4**−**7** and **9** in good to very good yields (68−95%) except for ethyl ketoamide **8**, which was isolated in lower yield (52%) (Table 1). As the protection of the diol with a benzylidene group introduced a new stereogenic center, the formation of a mixture of diastereomers could be expected for this family of compounds. However, the addition of aryl or alkyl organomagnesium reagent on bis-amide **3** afforded only one diastereomer, the structure of which was determined by NOE measurement (Figure 1).

We then considered various conditions for the nucleophilic trifluoromethylation of phenyl ketoamides **4**−**6** with $TMSCF_3$. Our attention has been focused, in particular, on studying the

(7) (a) Mukaiyama, T.; Kawano, Y.; Fujisawa, H. *Chem. Lett.* **2005**, *34*, 88–89. (b) Kawano, Y.; Fujisawa, H.; Mukaiyama, T. *Chem. Lett.* **2005**, *34*, 422–423. (c) Kawano, Y.; Kaneko, N.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1133–1145.

(8) Prakash, G. K. S.; Panja, C.; Vaghoo, H.; Surampudi, V.; Kultyshev, R.; Mandal, M.; Rasul, G.; Mathew, T.; Olah, G. A. *J. Org. Chem.* **2006**, *71*, 6806–6813.

(9) Prakash, G. K. S.; Mandal, M.; Panja, C.; Mathew, T.; Olah, G. A. *J. Fluorine Chem.* **2003**, *133*, 61–63.

(10) (a) Mizuta, S.; Shibata, N.; Sato, T.; Fujimoto, H.; Nakamura, S.; Toru, T. *Synlett* **2006**, 267–270. (b) Matsukawa, S.; Saijo, M. *Tetrahedron Lett.* **2008**, *49*, 4655–4657.

(11) Song, J. J.; Tan, Z.; Reeves, J. T.; Gallou, F.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2005**, *7*, 2193–2196.

(12) Trifluoromethylation reactions using other nucleophilic initiators such as amines, $AsPh_3$, $SbPh_3$, etc. have also been described but with low yields; see: Hagiwara, T.; Kobayashi, T.; Fuchikami, T. *Main Group Chem.* **1997**, *2*, 13–15.

(13) Mizuta, S.; Shibata, N.; Ogawa, S.; Fujimoto, H.; Nakamura, S.; Toru, T. *Chem. Commun.* **2006**, 2575–2577.

(14) (a) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1994**, *35*, 3137–3138. (b) Caron, S.; Do, N. M.; Arpin, P.; Larivée, A. *Synthesis* **2003**, 1693–1698. (c) Nagao, H.; Yamane, Y.; Mukaiyama, T. *Chem. Lett.* **2007**, *36*, 666–667. (d) Nagao, H.; Kawano, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 2406–2412. (e) Mizuta, S.; Shibata, N.; Akiti, S.; Fujimoto, H.; Nakamura, S.; Toru, T. *Org. Lett.* **2007**, *9*, 3707–3710.

(15) (a) Pedrosa, R.; Sayalero, S.; Vicente, M.; Maestro, A. *J. Org. Chem.* **2006**, *71*, 2177–2180. (b) Kawano, Y.; Kaneko, N.; Mukaiyama, T. *Chem. Lett.* **2006**, *35*, 304–305. (c) Song, J. J.; Tan, Z.; Xu, J.; Reeves, J. T.; Yee, N. K.; Ramdas, R.; Gallou, F.; Kuzmich, K.; DeLattre, L.; Lee, H.; Feng, X.; Senanayake, C. H. *J. Org. Chem.* **2007**, *72*, 292–294. (d) Massicot, F.; Monnier-Benoit, N.; Deka, N.; Plantier-Royon, R.; Portella, C. *J. Org. Chem.* **2007**, *72*, 1174–1180. (e) Enders, D.; Herriger, C. *Eur. J. Org. Chem.* **2007**, 1085–1090.

(16) (a) Gawronski, J.; Gawonskra, K. *Tartaric and Malic Acids in Synthesis: A Source Book of Building Blocks, Ligands, Auxiliaries and Resolving Agents*; Wiley: New York, 1999. (b) Coppola, G. M.; Schuster, H. F. *a-Hydroxy Acids in Enantioselective Syntheses*; Wiley-VCH: Weinheim, 1997.

(17) For examples of total synthesis of natural products from tartaric acid derived ketoamides, see: Prasad, K. R.; Gholap, S. L. *J. Org. Chem.* **2008**, *73*, 2–11, and references therein.

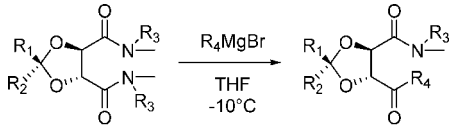
(18) Nugiel, D. A.; Jacobs, K.; Worley, T.; Patel, M; Kaltenbach, R. F.; Meyer, D. T.; Jadhav, P. K.; DeLucca, G. V.; Smyser, T. E.; Klabe, R. M.; Bacheler, L. T.; Rayner, M. M.; Seitz, S. P. *J. Med. Chem.* **1996**, *39*, 2156–2169.

(19) Sho, I.; Tetsudo, T. *Pure Appl. Chem.* **1994**, *66*, 2071–2074.

(20) Kondo, Y.; Green, J. R.; Ho, J. *J. Org. Chem.* **1993**, *58*, 6182–6189.

(21) (a) McNulty, J.; Grunner, V.; Mao, J. *Tetrahedron Lett.* **2001**, *42*, 5609–5612. (b) Prasad, K. R.; Chandrakumar, A. *Tetrahedron* **2007**, *63*, 1798–1805.

TABLE 1. Preparation of Model Ketoamides 4−9



1-3 4-9

bis-amide	R_1	R_2	R_3	R_4	ketoamide	yield (%)
1	Me	Me	OMe	Ph	**4**	80
2	Me	Me	Me	Ph	**5**	96[a]
3	H	Ph	Me	Ph	**6**	95[a,b]
1	Me	Me	OMe	Et	**7**	68
2	Me	Me	Me	Et	**8**	52[c]
3	H	Ph	Me	Et	**9**	94[a,b]

[a] Pure enough after workup. [b] Only one diastereomer. [c] 10% of diketone were isolated.

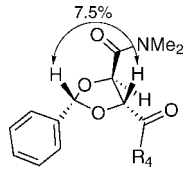
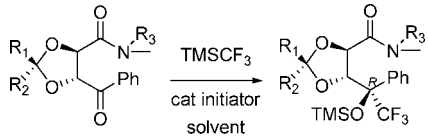


FIGURE 1. NOE on benzylidene protected ketoamides **6** and **9**.

TABLE 2. Screening of Conditions for the Nucleophilic Trifluoromethylation Reaction of Phenyl Ketoamides 4−6



4-6 (*R*)-10 - (*R*)-12 (major)

R_1 = Me R_2 = Me R_3 = OMe
R_1 = Me R_2 = Me R_3 = Me
R_1 = H R_2 = Ph R_3 = Me

entry	ketoamide	initiator/solvent (*T*)	product (*R*:*S*)[a,b,c]
1	**4**	TBAF,3H_2O/THF (−20 °C)	**10** (95:5)
2	**5**	TBAF,3H_2O/THF (−20 °C)	**11** (92:8)
3	**6**	TBAF,3H_2O/THF (−20 °C)	**12**(85:15)
4	**4**	TMAF/THF (−20 °C)	**10** (92:8)
5	**5**	TMAF/THF (−20 °C)	**11**(90:10)
6	**4**	*n*$Bu_4NPh_3SnF_2$/THF (0 °C)	**10** (94:6)
7	**5**	*n*$Bu_4NPh_3SnF_2$/THF (0 °C)	**11** (91:9)
8	**6**	*n*$Bu_4NPh_3SnF_2$/THF (0 °C)	**12**(88:12)
9	**4**	CsF/THF (−20 °C)	**10**(68:32)
10	**5**	CsF/THF (−20 °C)	**11**(66:34)
11	**6**	CsF/THF (−20 °C)	**12**(79:21)
12	**5**	CsF/THF (rt)	**11**(68:32)
13	**5**	CsF/DMF (rt)	**11** (91:9)
14	**5**	KF/DMF (rt)	**11** (92:8)
15	**4**	K_2CO_3/DMF (rt)	**10** (94:6)
16	**5**	K_2CO_3/DMF (rt)	**11** (93:7)
17	**6**	K_2CO_3/DMF (rt)	**12**(87:13)
18	**4**	K_2HPO_4/DMF (rt)	**10** (94:6)
19	**5**	K_2HPO_4/DMF (rt)	**11** (93:7)
20	**5**	AcONa/DMF (rt)	**11** (93:7)
21	**5**	*t*-BuOK/DMF (rt)	**11** (91:9)

[a] Conversion better than 90%. [b] Diastereomeric ratio (dr) determined by ^{19}F NMR of the crude mixture. [c] *R* and *S* refer to the configuration of the new stereocenter.

influence of the structure of ketoamides **4**−**6**, the nucleophilic initiator, and the solvent on the stereochemical course of the reaction. The results are collected in Table 2.

Ketoamides **4**−**6** were converted selectively to the corresponding α-silyloxy-α-trifluoromethyl carbinol **10**−**12** (conversion >90%) within 2 h, whatever the trifluoromethylation conditions. No traces of addition of a trifluoromethyl group onto the amide group have been observed.[5a,b,22,23] By use of TBAF, 3H_2O, TMAF,[24] or *n*-$Bu_4NPh_3SnF_2$,[25] an anhydrous synthetic equivalent of TBAF,[15d] as initiators in THF, the trifluoromethylation reaction occurred with a good diastereoselectivity (up to 95:5 in favor of the *R* isomer; see below for the assignment of stereochemistry) (entries 1−8). No significant variation of the diastereomeric ratio (dr) versus temperature was observed. The disappointing stereoselectivity observed with CsF in THF has been dramatically increased by replacing THF by DMF (dr = 91:9) (entries 9−13). With KF, use of DMF is crucial as no reaction occurred in THF even at room temperature (entry 14). However, with all fluoride salts tested, problems of reproducibility have been highlighted (unpredictable addition of a larger amount of reagents needed and/or formation of desilylated product). These results prompted us to consider various Lewis bases that have been recently described for the activation of $TMSCF_3$ in dipolar aprotic solvent such as DMF or DMSO.[5e] Among them, oxygenated nucleophiles proved to be the most efficient.[6−8] K_2CO_3[8,26] in DMF led to the trifluoromethylated products **10**−**12** with a good stereoselectivity (up to 94:6) (entries 15−17). Similar trends were observed with other oxygen-containing nucleophiles such as K_2HPO_4, AcONa, and *t*-BuOK[8] (entries 18−21).

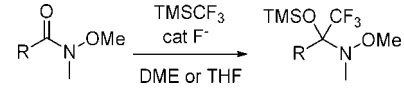
With tetraalkylammonium fluorides or difluorotriphenylstannate as initiators in THF, the good diastereoselectivities observed may be rationalized in term of bulkiness of the counterion.[27] Bulky counterion solvated by DMF might also account for the better diastereoselectivity observed in this solvent. Thus, potassium carbonate in dimethylformamide appeared as being the most useful reaction conditions, which were then systematically used.

The stereoselectivity of the nucleophilic trifluoromethylation can be explained considering a nonchelated Felkin−Anh type of transition state,[15a,d] in which the addition of the trifluoromethide equivalent occurs preferentially on the less hindered *si* face of the prochiral ketone.

We have previously shown that the alcohol function should be protected by a nonlabile protecting group for the next steps of the synthesis (hydrolysis of the ketal function and oxidative cleavage of the resulting diol).[15d] DMF being a solvent of choice for alkylation reactions, the trifluoromethylation and the subsequent conversion of the trimethylsilyl ether group into alkyl ether[28] was performed in a sequential one-pot reaction. Ketoamides were first treated with $TMSCF_3$ (1.2 equiv) in the presence

(22) For the nucleophilic trifluoromethylation of α-ketoamides with $TMSCF_3$ leading exclusively to α-hydroxy α-trifluoromethylated amides, see: Singh, R. J.; Kirchmeier, R. L.; Shreeve, J. M. *J. Org. Chem.* **1999**, *64*, 2579–2581.

(23) It has been previously observed in our group that the reaction of Weinreb benzamide (or bis-Weinreb amide derived from tartaric acid) with $TMSCF_3$ in the presence of a catalytic amount of fluoride gave the corresponding hemiaminal: Monnier-Benoit, N.; Massicot, F.; Portella, C. unpublished results.



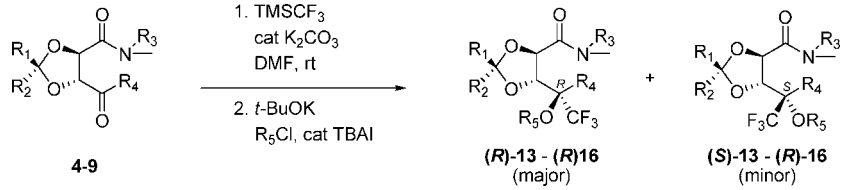
(24) For drying TMAF, 4H_2O, see: Christe, K. O.; Wilson, W. W.; Wilson, R. D.; Bau, R.; Feng, J. *J. Am. Chem. Soc.* **1990**, *112*, 7619–7625.

(25) (a) Gingras, M. *Tetrahedron Lett.* **1991**, *32*, 7381–7384. (b) Gingras, M.; Chabre, Y. M.; Raimundo, J.-M. *Synthesis* **2006**, 182–185.

(26) For the nucleophilic trifluoromethylation of quinones with Et_3SiCF_3 initiated by cat. K_2CO_3 in DMF, see:Stahly, G. P.; Bell, D. R. *J. Org. Chem.* **1989**, *54*, 2873–2877.

(27) Ooi, T.; Maruoka, K. *Acc. Chem. Res.* **2004**, *37*, 526–533.

TABLE 3. Sequential One-Pot Reaction: Nucleophilic Trifluoromethylation−O-Alkylation



entry	ketoamide	R_1	R_2	R_3	R_4	alkylating agent (R_5Cl)	dr (*R*:*S*)[a,b]	major product[c]	isolated yield (%)
1	**4**	Me	Me	OMe	Ph	AllCl	*d,e*		
2	**5**	Me	Me	Me	Ph	AllCl	93:7	**(*R*)-13**	73
3	**6**	H	Ph	Me	Ph	AllCl	86:14	**(*R*)-14**	58
4	**7**	Me	Me	OMe	Et	BnCl	*d,e*		
5	**8**	Me	Me	Me	Et	BnCl	82:18	**(*R*)-15**	67[f]
6	**9**	H	Ph	Me	Et	BnCl	79:21	**(*R*)-16**	53

[a] Diastereomeric ratio (dr) determined by ^{19}F NMR of the crude mixture. [b] *R* and *S* refer to the configuration of the new stereocenter. [c] Diastereomers separated by chromatography on silica gel. [d] Degradation during the alkylation step. [e] Diastereomeric ratio for the intermediate trifluoromethyl silylethers: 94:6 from **4**, 84:16 from **7**. [f] Approximately 10% of the minor diastereomer **(*S*)-15** was also isolated.

of a catalytic amount of K_2CO_3 in DMF as previously optimized. After completion of the trifluoromethyl addition (reaction monitored by GC), *t*-BuOK (1.2 equiv) and the alkylating reagent (1.2 equiv) were then added to the reaction mixture. Several trends emerged from the results depicted in Table 3. With ketoamides **4** and **7** containing a Weinreb-amide residue, a complex mixture was formed during the protection step (entries 1 and 4). These disappointing results were confirmed by carrying both steps separately. However, with ketoamides possessing a dimethylamide moiety and protected either by an isopropylidene group, **5**, **8**, or by a benzylidene group, **6**, **9**, this one-pot procedure provided the corresponding α-alkoxy α-trifluoromethyl compounds **(*R*)-13**−**(*R*)-16** in good yields (entries 2, 3, 5, and 6). As previously noticed, best diastereomeric ratios were obtained with ketoamides protected by an isopropylidene group (up to 93:7). Moreover, better diastereoselectivities have been obtained on phenyl ketones than on ethyl ones whatever the model substrate. The major (*R*) isomers were isolated in optically pure form by chromatography on silica gel.

The last steps of the reaction sequence involved the successive deprotection of the ketal group and oxidative cleavage of the resulting diol (Scheme 2). Contrary to the trifluoromethyl intermediates derived from diketones (Scheme 1),[15d] the ketal moiety of amide derivatives might be removed under acidic conditions. The treatment of **(*R*)-13** with HCl in methanol led to the expected diol **(*R*)-17** (37%) accompanied by the corresponding methyl ester (50%). Therefore the protecting group was preferentially removed by using aqueous trifluoroacetic acid, giving the free-diol **(*R*)-17** (∼85%). Then, the oxidative cleavage of **(*R*)-17** with periodic acid in ether led to the α-trifluoromethyl-α-allyloxyaldehyde **(*R*)-18** (94%). No traces of cleavage of the allyl protective group have been detected in the ^{19}F NMR spectra of the crude mixture. Eventually, the overall process was optimized by carrying out the last two steps in a one-pot and faster process using periodic acid in aqueous trifluoroacetic acid. The reaction was very clean, giving directly the pure aldehyde **(*R*)-18** after workup (94%).

SCHEME 2. Deprotection of (*R*)-13 and Oxidative Cleavage

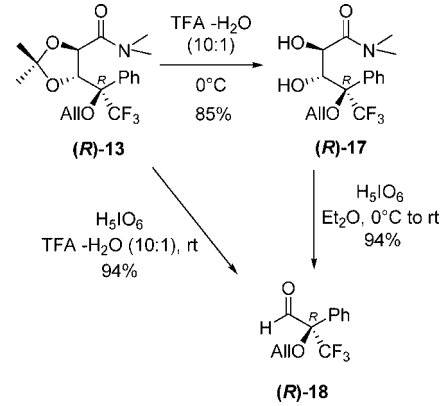
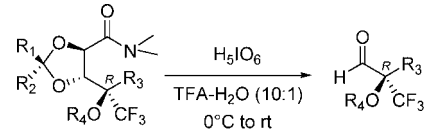


TABLE 4. One-Pot Deprotection−Oxidative Cleavage



entry	CF_3-adduct	R_1	R_2	R_3	R_4	aldehyde	yield (%)[a]
1	**(*R*)-13**	Me	Me	Ph	All	**(*R*)-18**	94
2	**(*R*)-14**	H	Ph	Ph	All	**(*R*)-18**	73
3	**(*R*)-15**	Me	Me	Et	Bn	**(*R*)-19**	71
4	**(*R*)-16**	H	Ph	Et	Bn	**(*R*)-19**	47

[a] Pure isolated compound after workup for entry 1, after chromatography for entries 2−4.

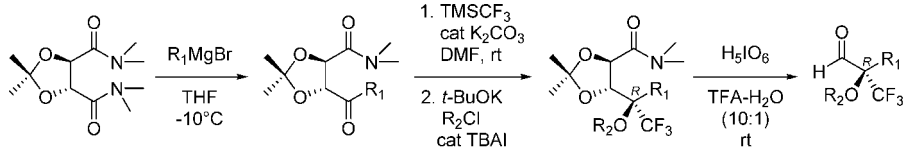
These one-pot reaction conditions were applied to the other model substrates (Table 4). For both phenyl and ethyl substrates, the best yields were obtained in isopropylidene-protected series.

To confirm the configuration of the created pseudo quaternary stereocenter, the aldehyde **(*R*)-18** was converted into the known (*R*)-3,3,3-trifluoro-2-phenylpropane-1,2-diol **(*R*)-21**[29] (Scheme 3). The attempted deallylation of **(*R*)-18** under mild conditions (catalytic amount of Pd(0) in presence of K_2CO_3),[30] resulted in a complex mixture. Consequently, aldehyde **(*R*)-18** was first reduced with sodium borohydride into the corresponding

(28) For various methodologies for converting silyl ethers into alkyl ethers, see: (a) Edwards, L. H.; Turner, C. E.; Thames, S. F. *Tetrahedron Lett.* **1969**, *48*, 4225–4228. (b) Sinhababu, A. K.; Kawase, M.; Borchardt, R. T. *Tetrahedron Lett.* **1987**, *28*, 4139–4142. (c) Sassaman, M. B.; Kotian, K. D.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1987**, *52*, 4314–4319. (d) Saunders, D. G. *Synthesis* **1988**, 377–379. (e) Oriyama, T.; Noda, K.; Yatabe, K. *Synlett* **1997**, 701–703. (f) Iwanami, K.; Yano, K.; Oriyama, T. *Synthesis* **2005**, 2669–2672.

(29) (a) Bennani, Y. L.; Vanhessche, K. P. M.; Sharpless, K. B. *Tetrahedron: Asymmetry* **1994**, *5*, 1473–1476. (b) Moreno-Dorado, F. J.; Guerra, F. M.; Ortega, M. J.; Zubia, E.; Massanet, G. M. *Tetrahedron: Asymmetry* **2003**, *14*, 503–510.

TABLE 5. Preparation of Various Trifluoromethyl Aldehydes from Tartaric Acid Derivative 2

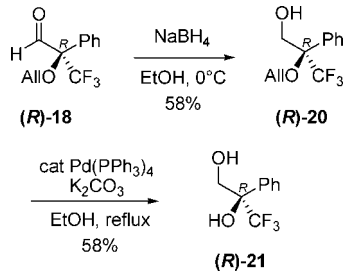


2 **5, 8, 22-27** **(*R*)-13, (*R*)-15 (*R*)-28 - (*R*)-32, 33** **(*R*)-18, (*R*)-19 (R)-34 - (*R*)-38, 39**

entry	R_1	ketoamide	yield (%)	R_2	dr[a] (*R*:*S*)	major CF_3-adduct[b,c]	yield (%)[c]	CF_3-aldehyde	isolated yield (%)
1	phenyl	**5**	96[d]	All	(93:7)	**(*R*)-13**	73	**(*R*)-18**	94[d]
2	ethyl	**8**	52[e]	Bn	(82:18)	**(*R*)-15**	67[f]	**(*R*)-19**	71
3	*o*-methoxyphenyl	**22**	67[e]	All	(79:21)	**(*R*)-28**	53[f]	**(*R*)-34**	43[i]
4	*p*-methoxyphenyl	**23**	67[e]	All	(94:6)	**(*R*)-29**	72	**(*R*)-35**	49
5	*p*-fluorophenyl	**24**	75	All	(91:9)	**(*R*)-30**	22[g]	**(*R*)-36**	93[d]
6	*m*-difluorophenyl	**25**	84	All	(77:23)	**(*R*)-31**	33[g]	**(*R*)-37**	45[i]
7	thiophen-2-yl	**26**	85	All	(89:11)	**(*R*)-32**	72[f]	**(*R*)-38**	73[d]
8	cyclopropyl	**27**	46	Bn	(70:30)	**33**	82[h]	**39**	50[j]

[a] Diastereomeric ratio (dr) determined by ^{19}F NMR in the crude mixture, except for compound **33** (^1H NMR). [b] *R* and *S* refer to the configuration of the new stereocenter. [c] Unless specified, diastereomers separated by flash silica gel chromatography. [d] Pure enough after workup. [e] A minor amount of diketone was also isolated: 10% for **8** and **22**, 23% for **23**. [f] The minor diastereomer was also isolated: 10% of (*S*)-**15**, 14% of (*S*)-**28**, 4% of (*S*)-**32**. [g] Pure major diastereomer isolated by recrystallization. [h] Diastereomers not separated. [i] Partial degradation over silica gel. [j] Mixture of enantiomers (ratio undetermined).

SCHEME 3. Preparation of Known (*R*)-3,3,3-Trifluoro-2-phenylpropane-1,2-diol (*R*)-21



(*R*)-18 **(*R*)-20** **(*R*)-21**

primary alcohol **(*R*)-20**, which was then submitted to the Pd-mediated cleavage reaction to give the diol **(*R*)-21**, the characteristics of which correspond to literature data.[29b] The (*R*) configuration was assigned to the major isomer of the new trifluoromethylated compound **(*R*)-19** by comparison of ^{19}F NMR data, the CF_3 signal of both major isomers appearing at upper field.

The optimized substrate structure type (isopropylidene keto-*N*,*N*-dimethylamide) and reaction conditions (two one-pot processes) were applied to a range of aromatic, heteroaromatic and aliphatic substrates. Results are collected in Table 5.

Ketoamides were prepared by reacting bis-amide **2** with the suitable organomagnesium reagent. Despite the fact that a moderate amount of bis-ketones were obtained with aromatic group bearing an electron-donating substituent (entries 3 and 4), aryl and heteroaryl monoketones **5** and **22**−**26** were isolated in better yield than aliphatic ones **8** and **27**. Keto-amides were then submitted to the one-pot nucleophilic trifluoromethylation−alkylation sequence. The diastereomeric ratio depends on the structure of the ketone, the best one being observed for unsubstituted or para-substituted phenones and thiophenyl derivative. A Felkin−Anh type of transition state governs the orientation of the diastereoselectivity[15d] but seems insufficient to explain its substrate-dependent effectiveness. The *R* configuration of the new created stereocenter in major diastereomers was ascribed by chemical correlation (see above), except for the cyclopropyl derivative **33**. Its two diastereomers exhibit such closed CF_3 NMR signals that we were unable to assign unambiguously the configuration. In most cases, major isomers were isolated in quite good yields by chromatography on silica gel (entries 1−4 and 7). However, **(*R*)-30** and **(*R*)-31** bearing an electron-withdrawing substituent have not been isolated in pure form by chromatography; additional recrystallizations were required, giving lower isolated yields of **(*R*)-30** and **(*R*)-31** (22% and 33%, respectively) (entries 5 and 6). Deprotection of the isopropylidene group and oxidative cleavage of the trifluoromethylated tartaric acid derivatives **(*R*)-28**−**(*R*)-32** and **33** under the previously optimized one-pot conditions provided the corresponding aldehydes **(*R*)-34**−**(*R*)-38** and **39**.

Conclusion

In summary, we have developed a convenient and cost-effective three-step asymmetric synthesis of α-trifluoromethyl α-aryl(alkyl)-α-alkoxyaldehyde, the key step involving the diastereoselective addition of $TMSCF_3$ to a tartaric acid derived ketoamide. Despite the preparation of some intermediates in fair yields, this methodology might be applied to a variety of compounds covering aliphatic, aromatic, and heteroaromatic series, even if the overall process is generally more effective in aromatic series. Moreover, owing to the easy access of the starting material and the convenient reaction conditions, the process is scalable, as illustrated by the preparation of 20 g of aldehyde **(*R*)-18** from 100 g of the commercially available dimethyl tartaric ester.[31]

Experimental Section

General Procedure for the Sequential One-Pot Reaction: Nucleophilic Trifluoromethylation−O-Alkylation. To a solution of ketoamide (1 equiv) and $TMSCF_3$ (1.2−2.4 equiv) in DMF was added, at room temperature under Ar, K_2CO_3 (0.05−0.21 equiv). After complete conversion of starting ketoamide (reaction monitored

(30) Vutukuri, D. R.; Bharathi, P.; Yu, Z.; Rajasekaran, K.; Tran, M.-H.; Thayumanavan, S. *J. Org. Chem.* **2003**, *68*, 1146–1149.

(31) A procedure similar to the one reported in the Experimental Section for the millimolar scale was applied, except for the purification of the ketoamide **5** and the intermediate (**R**)-**13**, which was carried out by crystallization instead of flash chromatography (crystallization solvents were petroleum ether/Et_2O for **5**, petroleum ether for **(*R*)-13**).

by GC), *t*-BuOK (1.2−4.0 equiv), TBAI (0.09−0.10 equiv), and allyl or benzyl chloride (1.2−3.8 equiv) were added. After complete conversion of the intermediate *O*-silyl ether (reaction monitored by GC), the reaction was quenched with saturated aqueous NH_4Cl and extracted thrice with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (PE/Et_2O) to afford the corresponding α-alkoxy-α-trifluoromethyl intermediate.

(−)-(4*R*,5*R*)-5-((*R*)-1-Allyloxy-2,2,2-trifluoro-1-phenylethyl)-2,2-dimethyl-[1,3]dioxolane-4-carboxylic Acid Dimethylamide, (R)-13. According to the general procedure, a mixture of ketoamide **5** (1.04 g, 3.74 mmol), CF_3TMS (0.66 mL, 4.5 mmol, 1.2 equiv), and K_2CO_3 (27 mg, 0.2 mmol, 0.05 equiv) in DMF (40 mL) was stirred for 24 h. Then, *t*-BuOK (564 mg, 4.77 mmol, 1.3 equiv), TBAI (136 mg, 0.37 mmol, 0.10 equiv), and AllCl (0.40 mL, 4.91 mmol, 1.3 equiv) were added, and the reaction was stirred for 3 h. Purification of the residue (mixture of two diastereomers 93:7) by chromatography (PE/EtOAc 90:10) and recrystallization (PE) afforded the major diastereomer **(*R*)-13** (1.06 g, 73%) as a white solid. Mp 91 °C; GC (100 to 250 °C, 10 °C/min) t_R = 11.6 min; $[\alpha]^{20}_D$ −35.0 (*c* 0.97, $CHCl_3$); ^{19}F NMR (235.3 MHz, $CDCl_3$) δ −74.2 (s, 3F, CF_3); ^1H NMR (250 MHz, $CDCl_3$) δ 1.28 (s, 3H), 1.40 (s, 3H), 2.98 (s, 3H), 3.14 (s, 3H), 4.15 (dd, J = 13.0 Hz, J = 4.5 Hz, 1H), 4.26 (dd, J = 13.0 Hz, J = 4.5 Hz, 1H), 4.96 (d, J = 6.0 Hz, 1H), 5.21 (tdd, J = 1.5 Hz, J = 10.5 Hz, J = 3.0 Hz, 1H), 5.37 (tdd, J = 1.5 Hz, J = 17.0 Hz, J = 3.5 Hz, 1H), 5.74 (d, J = 6.0 Hz, 1H), 5.94 (tdd, J = 17.0 Hz, J = 10.5 Hz, J = 4.5 Hz, 1H), 7.39−7.44 (m, 3H), 7.59−7.62 (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 25.5, 26.4, 36.1, 37.2, 67.0, 72.9 (d, J = 2.0 Hz), 78.3, 82.4 (q, J = 26.0 Hz), 111.0, 116.1, 124.3 (q, J = 288.0 Hz, CF_3), 128.2, 129.0, 129.1, 132.6, 134.4, 168.9. HMRS *m*/*z* calcd for $[C_{19}H_{24}NO_4F_3Na]^+$ 410.1555, found 410.1545.

General Procedure for the One-Pot Reaction: Ketal Hydrolysis−Oxidative Cleavage. To a solution of α-alkoxy-α-trifluoromethyl derivative (1 equiv) in a mixture of TFA/H_2O (10:1) was added H_5IO_6 (1.1−1.5 equiv) at room temperature. After completion (GC monitoring), the reaction was quenched with saturated aqueous Na_2CO_3 and extracted thrice with Et_2O. The combined organic layers were washed with brine and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure and chromatography on silica gel (PE/Et_2O) yielded the corresponding 2-alkoxy-2-aryl(alkyl)-3,3,3-trifluoropropanal.

(−)-(*R*)-2-Allyloxy-3,3,3-trifluoro-2-phenylpropanal, (R)-18. According to the general procedure, a solution of **(*R*)-13** (341 mg, 0.88 mmol) and H_5IO_6 (258 mg, 1.13 mmol, 1.3 equiv) in TFA/H_2O (2.0 mL/0.2 mL) was stirred for 2 h. After workup, aldehyde **(*R*)-18** (203 mg, 94%) was obtained as a colorless liquid. GC (from 100 to 250 °C, 10 °C/min) t_R = 3.0 min; $[\alpha]^{20}_D$ −31.7 (*c* 1.06, $CHCl_3$); ^{19}F NMR (235.3 MHz, $CDCl_3$) δ −71.7 (s, 3F, CF_3); ^1H NMR (250 MHz, $CDCl_3$) δ 4.16 (dd, J = 13.0 Hz, J = 5.0 Hz, 1H), 4.24 (dd, J = 13.0 Hz, J = 5.0 Hz, 1H), 5.27 (ddt, J = 1.5 Hz, J = 10.5 Hz, J = 3.0 Hz, 1H), 5.41 (ddt, J = 1.5 Hz, J_s = 17.0 Hz, J = 3.0 Hz, 1H), 5.98 (ddt, J = 5.0 Hz, J = 10.5 Hz, J = 17.0 Hz, 1H), 7.44−7.54 (m, 5H), 9.74 (q, J = 2.0 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 68.1, 85.1 (q, J = 26.5 Hz), 117.6, 123.3 (q, J = 288.5 Hz, CF_3), 128.0, 129.1, 129.8, 130.1, 133.4, 193.2. HRMS (ESI^+): *m*/*z* calcd for $C_{12}H_{12}F_3O_2$ $[M + H]^+$ 245.0790, found 245.0784

Acknowledgment. We thank CNRS and Région Champagne-Ardenne for a fellowship to J.N. This project has been supported (programme GLYCOVAL) by the "Contrat de Plan Etat-Région" (Ministère de la Recherche, Région Champagne-Ardenne, Ville de Reims) and Fondation du Site Paris-Reims. We are grateful to Europol'Agro for the help in the management of this programme. We also express our thanks to Henry Baillia (NMR), Dominique Harakat (Mass Spectrometry), Romain Peresutti (synthesis of some intermediates), and to the group of Prof Tabet (Univ. P. & M. Curie, UMR CNRS 7613) for their help in obtaining some HRMS.

Supporting Information Available: Experimental procedure and full characterization and copies of ^{19}F, ^1H, and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8013403