Stereoselective Synthesis of Trifluoromethylated Compounds: Nucleophilic Addition of Formaldehyde *N*,*N*-Dialkylhydrazones to Trifluoromethyl Ketones

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The nucleophilic 1,2-addition of formaldehyde *N*,*N*-dialkylhydrazones **1**, **2**, and **7**−**10** to trifluoromethyl ketones **3a**−**e** takes place in the absence of any catalyst or promoter to afford a series of α-hydroxy-α-trifluoromethylhydrazones (**4**, **5**, and **11**−**14**) in good-to-excellent yields. From the several reagents studied, optimal results were achieved using 1-(methyleneamino)pyrrolidine (**2**) for the synthesis of racemic adducts and (*S*)-1-(methyleneamino)-2-[1-(methoxy)diphenyl-methyl]-pyrrolidine (**10**) for the asymmetric version of the reaction. The resolving properties of the chiral auxiliary carried by **10** allowed an easy chromatographic (flash) separation of any obtained diastereomeric mixture. Thus, a single operation rendered moderate-to-good amounts (42−75%) of optically pure adducts (*S*,*S*)-**14** (de ≥ 98%) by combining excellent chemical (82−92%) and moderate optical (51−81%) yields. Hydrazones **5** and (*S*,*S*)-**14** were protected by benzylation [→ **16** and (*S*,*S*)-**18**] and then transformed into benzyl-protected α-trifluoromethyl cyanohydrins **21** by MMPP oxidative cleavage and into α-benzyloxy-α-trifluoromethyl aldehydes **22** by ozonolysis. Alternatively, adducts **5** and (*S*,*S*)-**14** were methylated [→ **19** and (*S*,*S*)-**20**] and transformed into the corresponding α-methoxy-α-trifluoromethyl carboxylic acids **24** by successive ozonolysis and in situ oxidation ($NaClO_2$, ^tBuOH, isobutene) of the crude α-methoxyaldehydes.

Introduction

The introduction of one or more fluorine atoms into specific positions on organic molecules strongly modifies their physicochemical properties, increasing, for example, stability and lipophilicity. Much of the chemical behavior of these compounds can be rationalized in terms of the high electronegativity of the fluorine atom (4.0 on Pauling's electronegativity scale), the high carbon−fluorine bond strength (108 kcal/mol), and remarkable particularities such as the low tendency to participate in hydrogen bonds.[1] In many other cases, however, the overall influence by fluorine atoms is poorly understood. The term "flustrates" (*flu*orine-containing sub*strates*) coined by Seebach[2] reflects the difficulties encountered in predicting the reactivity and biological activity of these compounds. However, many bioactive compounds in which one or more hydrogen atoms have been replaced by fluorine present modified biological activities that have attracted much interest in medicinal chemistry[3] and agrochemistry.[4] Additionally, many fluorinated compounds present interesting optoelectronic properties that have found applications in materials science, in particular for the synthesis of dyes,[5] polymers,[6] and liquid crystals.[7] The growing scientific and economic interest in these compounds, on one hand, and the lack of natural sources,[8] on the other, have evoked the development of new methods for their synthesis. In this context, trifluoromethyl ketones play an important role, as they have been used not only as inhibitors of hydrolytic enzymes including proteases,[9] but their availability[10] has also stimulated their extensive use in the synthesis of other trifluoromethyl-containing compounds. In particular, the retrosynthetic analysis for α-hydroxy-α-trifluoromethyl carbonyl compounds depicted in Scheme 1 suggests the use of these substrates as electrophilic targets for the attack of d^1 reagents, but this approach has been scarcely investigated.[11]

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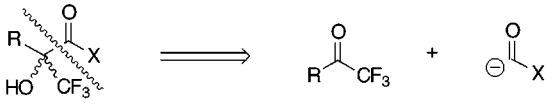
Scheme 1



Scheme 2

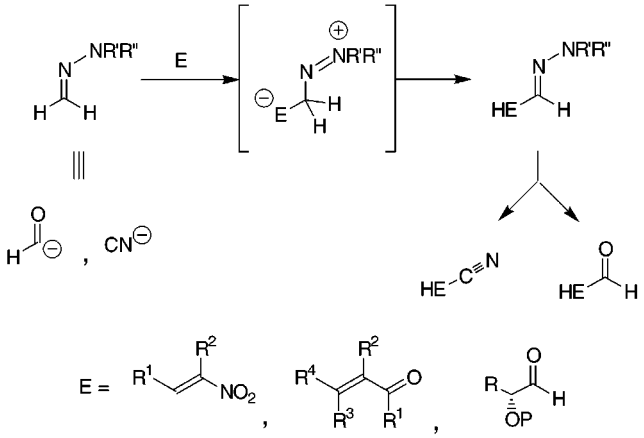
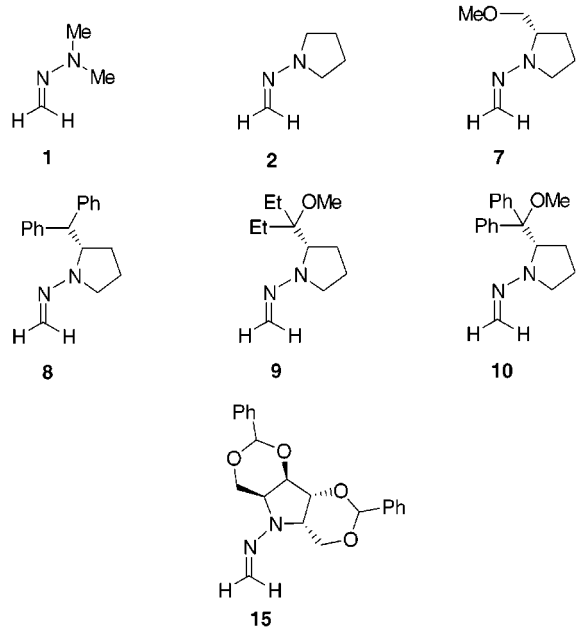


Chart 1



We have been studying during the past few years a new approach for the umpolung of formaldehyde. The strategy is based on the aza-enamine character of aldehyde dialkylhydrazones (FDAHs), first discussed in the pioneering studies by Brehme,[12] who demonstrated a weak nucleophilicity of the azomethine carbon atom of aldehyde dialkylhydrazones toward strong electrophilic species. As a result of minimal steric hindrance around the azomethine carbon, formaldehyde derivatives have been found to present an enhanced nucleophilic reactivity, and this fact has been exploited for the formylation of several electrophilic substrates, including nitroalkenes,[13] α-alkoxyaldehydes,[14] and conjugated enones (Scheme 2).[15] These processes present some remarkable features to be highlighted. First, the reaction with reactive substrates such as nitroalkenes or α-alkoxyaldehydes takes place spontaneously, by just mixing reactants under *neutral* conditions in the absence of any additives. Second, chiral reagents of this type are easily available from D- or L-proline, so that asymmetric formylations to yield products having the desired configuration are feasible in theory. Third, the hydrazone moiety is not only key for further C−C bond-forming reactions (such as the stereocontrolled α-functionalization of their azaenolates by the well established SAMP/RAMP methodology,[16] the addition of organometallics to their CN bond,[17] the addition of nucleophilic radicals,[18] etc.) but can also be easily transformed into aldehydes (ozonolysis, hydrolysis), nitriles,[19] and dithioketals.[20] Therefore, taking into account the particularities described above and the interest in the expected targets, we decided to explore the nucleophilic 1,2-addition of both achiral and optically pure formaldehyde *N*,*N*-dialkylhydrazones to trifluoromethyl ketones, with the results described herein.[21]

Results and Discussion

Addition of Achiral Formaldehyde Hydrazones to Trifluoromethyl Ketones. The synthesis of racemic forms of α-hydroxy-α-trifluoromethyl hydrazones by addition of achiral *N*,*N*-dialkylhydrazones to trifluoromethyl ketones was investigated first. The simplest formaldehyde dimethylhydrazone **1**[22] and the pyrrolidine-containing analogue **2** (Chart 1), conveniently prepared in one step from commercial *N*-nitrosopyrrolidine ($LiAlH_4$, then paraformaldehyde, 85%), were made to react with a variety of differently substituted trifluoromethyl ketones **3a**−**g** (Chart 2). For all types (aliphatic, aromatic, and heteroaromatic) of simple ketones **3a**−**e**, the expected 1,2-addition reaction to the carbonyl took place smoothly to afford α-trifluoromethyl-α-hydroxy hydrazones **4**,**5a**−**e** in good-to-excellent yields (Scheme 3, Table 1, entries 1−9). By contrast, the reaction with 1,3-

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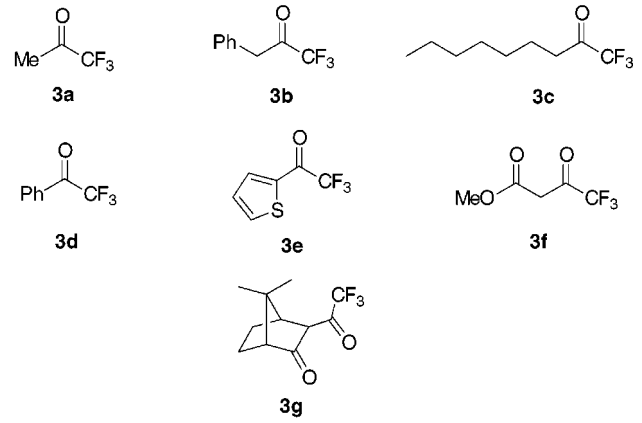
Chart 2



Scheme 3

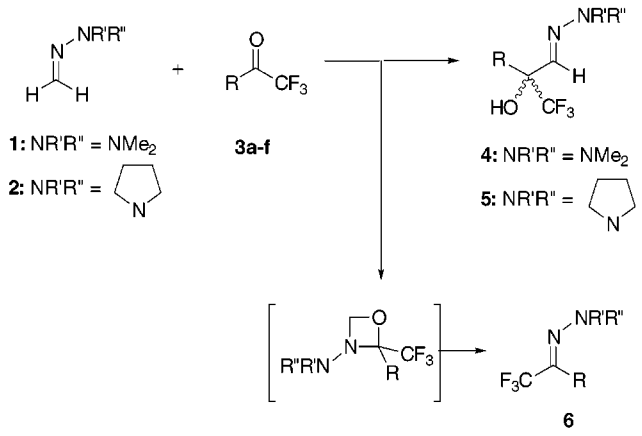


Table 1. Synthesis of Racemic α-Hydroxy-α-trifluoromethyl Hydrazones 4 and 5

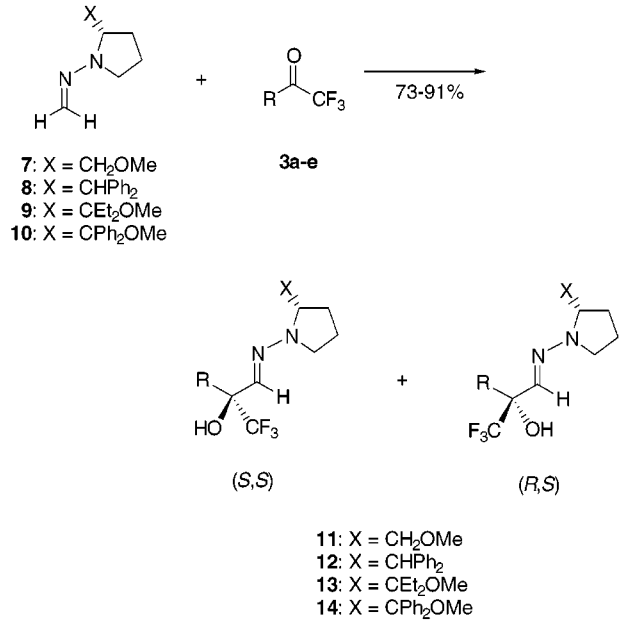
entry	ketone	R	hydrazone	solvent	prod.	time	yield (%)[a]
1	**3a**	Me	**2**	CH_2Cl_2	**5a**	15 h	90
2	**3b**	Bn	**1**	CH_2Cl_2	**4b**	14 h	28
3	**3b**	Bn	**2**	CH_2Cl_2	**5b**	75 min	81
4	**3c**	n-C_7H_{15}	**2**	CH_2Cl_2	**5c**	3 d	73
5	**3c**	n-C_7H_{15}	**2**	**3c**[b]	**5c**	21 h	80
6	**3d**	Ph	**1**	CH_2Cl_2	**4d**	30 d	61
7	**3d**	Ph	**2**	CH_2Cl_2	**5d**	46 h	87
8	**3d**	Ph	**2**	**3d**[b]	**5d**	16 h	74
9	**3e**	2-thienyl	**2**	CH_2Cl_2	**5e**	8 d	66
10	**3f**	$MeOCOCH_2$	**2**	CH_2Cl_2	**5f**	8 h	23
11	**3g**	camphor-3-yl	**2**	CH_2Cl_2	**5g**	24 h	35

[a] Isolated yield. [b] Excess recovered by bulb-to-bulb distillation.

dicarbonylic substrates **3f**,**g** afforded more complex mixtures, from which the adducts **5f**,**g** could be isolated in low yields (entries 10 and 11). This difference in behavior is most probably associated with the high content of the tautomeric enolic form in this kind of substrate.[23]

The comparative analysis of the results collected in Table 1 clearly indicates that hydrazone **2** is a much more efficient reagent than the acyclic *N*,*N*-dimethyl analogue **1**, as evidenced by the higher yields of compounds **5** and the faster reactions observed (compare entries 2,3 and 6,7). The higher reactivity of the pyrrolidine-containing system **2** with respect to **1** can be explained, as in the case of related enamines,[24] by considering the lower demand of energy needed to reach the planarity required for effective conjugation. Additionally, the use of **1** resulted in some cases in the formation of small amounts of hydrazo transfer byproducts **6**, as observed earlier for its addition to α-alkoxyaldehydes.[14] The formation of these byproducts has been classically explained by assuming the catalytic effect of trace amounts of water present in the medium, which hydrolyze the C=N bond of the hydrazone and allow the subsequent condensation of the liberated hydrazine with the ketone. However, experimental conditions such as the rigorous exclusion of water, as well as theoretical ab initio MO calculations,[25] suggest an alternative mechanism consisting of the successive [2 + 2] and retro-[2 + 2] cycloaddition reactions depicted in Scheme 3. Finally, the long reaction times needed for completion of the addition to less reactive trifluoromethyl ketones **3c**,**d** could be shortened to reasonable levels by using the ketones themselves as solvents (entries 5 and 8). The excess of ketone **3** was effectively recovered (75−85%) in high purity by bulb-to-bulb distillation of the reaction crudes.

Scheme 4



Addition of Chiral Formaldehyde Hydrazones Derived from Proline. The interest in the optically pure forms of these trifluoromethyl-containing quaternary adducts prompted us to investigate the asymmetric version of the addition reaction. The preliminary experiments were carried out using (*S*)-1-methyleneamino-2-(methoxymethyl)pyrrolidine **7**, which was chosen as the reagent on the basis of its availability[13d,26] and the high reactivity associated with the presence of the pyrrolidine ring. In full analogy with the achiral version, the addition of **7** to trifluoromethyl ketones **3a**−**e** (Scheme 4) was again a clean and high-yielding reaction (Table 2, entries 1, 4, and 10). However, the diastereoselectivities were disappointing, and the diastereomeric mixtures **11** could not be separated by flash or medium-pressure chroma-

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(26) Compound **7** is commercially available from Merck-Schuchardt, Hohenbrunn, Germany.

Table 2. Synthesis of α-Hydroxy-α-trifluoromethyl Hydrazones 11−14

entry	ketone	hydrazone	X	R	adduct	yield (%)[a]	optically pure[b] adducts, (%)	dr[c]
1	**3a**	**7**	CH_2OMe	Me	**11a**	81		64:36[d]
2	**3a**	**9**	CEt_2OMe	Me	**13a**	77		66:34[d]
3	**3a**	**10**	CPh_2OMe	Me	**14a**	90	(*S*,*S*)-**14a**, 63 (*S*,*R*)-**14a**, 27	70:30
4	**3b**	**7**	CH_2OMe	Bn	**11b**	84		54:46[d]
5	**3b**	**8**	$CHPh_2$	Bn	**12b**	70		64:36[d]
6	**3b**	**9**	CEt_2OMe	Bn	**13b**	70		71:29[d]
7	**3b**	**10**	CPh_2OMe	Bn	**14b**	92	(*S*,*S*)-**14b**, 75 (*S*,*R*)-**14b**, 17	81:19
8	**3c**	**10**	CPh_2OMe	n-C_7H_{15}	**14c**	85[e]	(*S*,*S*)-**14c**, 49 (*S*,*R*)-**14c**, 36	62:38
9	**3c**	**10**	CPh_2OMe	n-C_7H_{15}	**14c**	30[f]		82:18
10	**3d**	**7**	CH_2OMe	Ph	**11d**	79		60:40[d]
11	**3d**	**9**	CEt_2OMe	Ph	**13d**	81		51:49[d]
12	**3d**	**10**	CPh_2OMe	Ph	**14d**	90[e]	(*S*,*S*)-**14d**, 52 (*S*,*R*)-**14d**, 38	58:42
13	**3e**	**10**	CPh_2OMe	2-thienyl	**14e**	82[e,g]	(*S*,*S*)-**14e**,[h]42 (*S*,*R*)-**14e**,[h]40	51:49

[a] Isolated yield. [b] de ≥ 98%. [c] Determined by ^{13}C and ^1H NMR spectroscopy of unpurified reaction mixtures. [d] Inseparable mixture of diastereomers. [e] Solvent-free reaction; excess of ketone **3** was recovered by bulb-to-bulb distillation [f] In the presence of $ZnCl_2$ as promoter. [g] Reaction carried out at 80 °C. [h] Configuration assigned tentatively.

tography. Assuming that the diastereoselectivity should be a consequence of steric interactions, we decided to explore the behavior of sterically more demanding reagents which, to keep the reactivity as high as possible, maintain the presence of the pyrrolidine ring as a common characteristic. Hence, readily available compounds **8**−**10**, carrying bulkier substituents in position 2′ of the pyrrolidine ring, were considered as candidates. Compound **8** was prepared from (*S*)-1-aza-2-oxo-3-oxa-4,4-diphenyl-bicyclo[3.3.0]octane[27] by hydrogenolysis (Pd/C, H_2), nitrosation (^{t}BuONO, THF), reduction ($LiAlH_4$, THF), and condensation with paraformaldehyde (51%, overall). Compounds **9** and **10** were prepared from their corresponding hydrazines[28] by reaction with paraformaldehyde and purified by distillation and flash chromatography, respectively. The influence effected by these tuned auxiliaries was analyzed using ketone **3b** as the model substrate. The analysis of the results collected in Table 2 (entries 4−7) indicated a direct correlation between the size of the residues on position 2′ of the pyrrolidine ring and the observed selectivity. Thus, benzhydryl-containing reagent **8** gave the corresponding adduct **12b** with slightly better results (dr 64:36) than **7**, while the asymmetric inductions effected by **9** and **10**, having bigger (quaternary) substituents, were higher (dr 71:29 and 81:19 for **13b** and **14b**, respectively). Nevertheless, crystalline derivative **10** proved to be the reagent of choice for practical reasons: with this reagent, both diastereomers (*S*,*S*)- and (*R*,*S*)-**14b** could be easily separated by flash chromatography. The interesting properties as resolving agent exhibited by the (*S*)-1-amino-2-(1-methoxy-1,1-diphenylmethyl)-pyrrolidine auxiliary proved to be a uniform behavior and led to the easy chromatographic separation of *all diastereomeric mixtures* and, hence, to the isolation of both diastereomers (*S*,*S*)- and (*R*,*S*)-**14a**−**e** in optically pure form from each studied reaction (Table 2, entries 3, 7, 8, 12, and 13). Shortening of reaction times and/or improvement of selectivity by addition of $ZnCl_2$ as a promoter[29] were investigated. Although some significant effect on rate and selectivity was observed in some cases, the yield dramatically dropped under these conditions (entry 9).

An important solvent effect was found in the case of hindered reagents (**9**, **10**). Thus, it was observed that the use of nonpolar solvents such as cyclohexane or toluene considerably shortened the reaction times and practically suppressed the formation of hydrazo-transfer byproducts.[30] As in the racemic version, the addition of **10** to ketones **3c**−**e** was accelerated by carrying out the reactions under solvent-free conditions. The overall result for these additions can be considered as satisfactory; the combination of excellent chemical yields, moderate inductions, and easy chromatographic separations result in moderate-to-good yields (42−75%) of the major (*S*,*S*)-**14a**−**e** diastereomers as optically pure compounds (de > 98%) in a single step.

Finally, the use of C_2-symmetric reagents based on 2,5-disubstituted pyrrolidines was not considered a good alter native in this context, as the planar geometry presumed in the transition state for the aza-enamine-like reactivity was expected to be sterically hindered in these substrates. Nevertheless, we decided to confirm this hypothesis by reacting compound **15**[31] with ketone **3b**. Even in this case, where the small and conformationally rigid methylene groups in positions 2 and 5 were expected to effect a minimum steric inhibition of conjugation, no reaction was observed, even after 48 h at 80 °C.

Cleavage of the Hydrazone Moiety. Preliminary experiments carried out for the cleavage of the hydrazone moiety to aldehydes confirmed the expected lack of stability frequently observed for such α-hydroxycarbonyl compounds. Therefore, the newly created hydroxy group of racemic and optically enriched α-hydroxy-*N*,*N*-dialkylhydrazones **5**, **13**, and (*S*,*S*)-**14** was protected first. For

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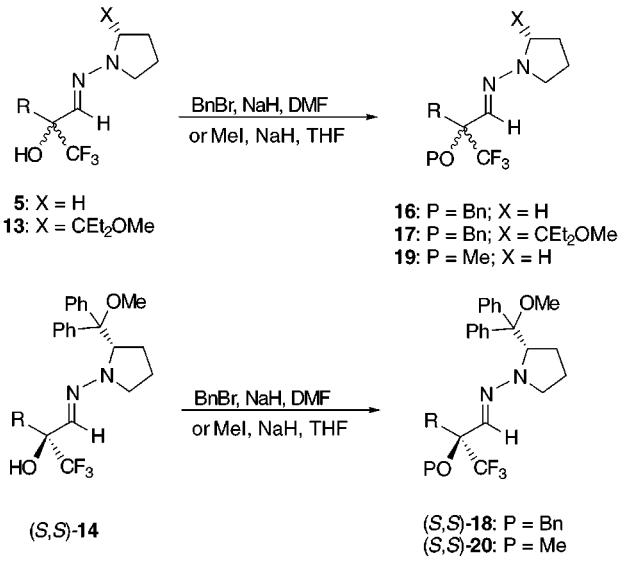
(29) In a parallel study on the activation of simple aldehydes for the addition of formaldehyde *N*,*N*-dialkylhydrazones, $ZnCl_2$ was found to be particularly effective: Pareja, C.; Martín-Zamora, E.; Fernández, R.; Lassaletta, J. M., unpublished results.

(30) As an illustrative example, use of Et_2O for the reaction of **3b** and **10** resulted in the isolation of (*S*)-**6b** (R = Bn, NR′R″ = 2-(diphenylmethoxymethyl)pyrrolidine) in 22% yield, together with only 66% yield of the expected adduct **14d**.

(31) Obtained from the parent known hydrazine (Defoin, A.; Brouillard-Poichet, A.; Streith, J. *Helv. Chim. Acta* **1991**, *74*, 103) by condensation with paraformaldehyde: Díez, E.; Martín-Zamora, E.; Ferrete, A.; Fernández, R.; Lassaletta, J. M., unpublished results.

Scheme 5



5: X = H
13: X = CEt_2OMe

16: P = Bn; X = H
17: P = Bn; X = CEt_2OMe
19: P = Me; X = H

(*S*,*S*)-**14**

(*S*,*S*)-**18**: P = Bn
(*S*,*S*)-**20**: P = Me

Table 3. Synthesis of α-Benzyloxy-α-trifluoromethyl Hydrazones 16−18 and α-Methoxy-α-trifluoromethyl Hydrazones 19−20

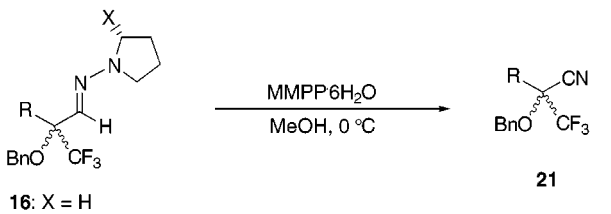
			benzylation		methylation	
starting material	R	X	product	yield (%)[a]	product	yield (%)[a]
5a	CH_3	H	**16a**	81	**19a**	65
(*S*,*S*)-**14a**	CH_3	CPh_2OMe	(*S*,*S*)-**18a**	87	(*S*,*S*)-**20a**	85
5b	CH_2Ph	H	**16b**	89	**19b**	77
13b[b]	CH_2Ph	CEt_2OMe	**17b**[b]	83		
(*S*,*S*)-**14b**	CH_2Ph	CPh_2OMe	(*S*,*S*)-**18b**	89	(*S*,*S*)-**20b**	87
5c	*n*-C_7H_{15}	H	**16c**	75	**19c**	69
(*S*,*S*)-**14c**	*n*-C_7H_{15}	CPh_2OMe	(*S*,*S*)-**18c**	72	(*S*,*S*)-**20c**	83
5d	Ph	H	**16d**	92	**19d**	80
(*S*,*S*)-**14d**	Ph	CPh_2OMe	(*S*,*S*)-**18d**	82	(*S*,*S*)-**20d**	73
5e	2-thienyl	H	**16e**	79		

[a] Isolated yield. [b] A 71:29 mixture of (*S*,*S*) and (*R*,*S*) diastereomers.

the synthesis of the corresponding α-trifluoromethyl aldehydes and for the oxidative cleavage to cyanohydrins we decided to prepare the corresponding benzyl ethers; the benzylation reactions were performed under standard conditions (NaH, BnBr, DMF) to obtain the protected α-benzyloxy-α-trifluoromethyl hydrazones **16**−**18** in good yields (Scheme 5). For the synthesis of α-trifluoromethylated carboxylic acids, however, we decided to avoid the use of benzyl protecting groups because the final oxidation conditions to the neopentyl-type product could eventually be incompatible with them. Methylation was then envisaged considering the higher stability of methyl ethers against oxidation and the direct applications found for some of the derivatives available from them (see below). Therefore, methylation of adducts **5** and (*S*,*S*)-**14** (MeI, NaH, THF) to the corresponding α-methoxy-α-trifluoromethyl hydrazones **19** and **20**, respectively, was carried out in the usual way (Scheme 5). The results for the synthesis of compounds **16**−**20** are summarized in Table 3.

The oxidative cleavage of the racemic α-benzyloxy-α-trifluoromethyl *N*,*N*-dialkylhydrazones **16** to the corresponding nitriles **21** (Scheme 6) was accomplished using methanolic magnesium monoperoxyphthalate hexahydrate (MMPP·$6H_2O$) under mild conditions according to the method previously described.[19b] The reaction was again a fast, clean, and high-yielding process, as deduced from the results collected in Table 4. Unfortunately this

Scheme 6



16: X = H
17: X = CEt_2OMe

21

Table 4. Synthesis of α-Benzyloxy-α-trifluoromethyl Nitriles 21

entry	hydrazone	X	R	nitrile **21**	time	yield (%)
1	**16a**	H	CH_3	**21a**	35 min	93
2	**16b**	H	CH_2Ph	**21b**	45 min	86
3	**17b**[a]	CEt_2OMe	CH_2Ph	**21b**[b]	5 h	83
4	**16c**	H	*n*-C_7H_{15}	**21c**	10 min	88
5	**16d**	H	Ph	**21d**	40 min	91
6	**16e**	H	2-thienyl	**21e**	40 min	70

[a] A 71: 29 mixture of (*S*,*S*) and (*R*,*S*) diastereomers. [b] Optically enriched mixture of enantiomers.

procedure was ineffective for the optically pure methoxydiphenylmethyl-substituted analogues (*S*,*S*)-**18**; the starting hydrazones were recovered unaltered after several hours, even at higher temperatures. Alternatively, other reagents such as MCPBA or hydrogen peroxide in the presence of catalytic amounts of methyltrioxorhenium (MTO)[32] were also unsuccessfully essayed. This result may be explained considering the mechanism proposed[19b] for the reaction: the presence of the bulky methoxydiphenylmethyl group near to the amino nitrogen prevents the initial *N*-oxidation required and, therefore, effectively inhibits the process. By contrast, the slightly less hindered substrate **17b** was deprotected by MMPP to afford the optically enriched nitrile **21b**, although a longer reaction time was required than for the C-2′ unsubstituted hydrazone **16b** (Table 4, entries 2 and 3).

According to several literature reports[33] and our own experience,[13,15] cleavage of the dialkylhydrazone moiety to the corresponding aldehydes was efficiently performed by ozonolysis (CH_2Cl_2, −78 °C; MeS_2). This racemization-free method was appropriate for the deprotection of both the pyrrolidine- and the 2-(1-methoxy-1,1-diphenylmethyl)-pyrrolidine-derived analogues **16** and (*S*,*S*)-**18**, respectively (Scheme 7). In this way, both racemic α-benzyloxy-α-trifluoromethyl aldehydes *rac*-**22** and their corresponding optically pure forms (*S*)-**22** were satisfactorily synthesized, according to the results collected in Table 5. One of the advantages associated with the use of ozone for the cleavage of the hydrazone moiety is the possibility of recovering the chiral auxiliary.[34] In fact, the *N*-nitroso-2-(1-methoxy-1,1-diphenylmethyl)pyrrolidine **23**, obtained as byproduct in the synthesis of aldehydes (*S*)-**22**, could be easily recycled into the formylating reagent **10** by sequential reduction ($LiAlH_4$) and in situ condensation of the resulting hydrazine with paraformaldehyde (65−85%).

(32) Very recently, two different groups have independently reported on the cleavage of *N*,*N*-dimethylhydrazones into nitriles using this system: (a) Stankovic, S.; Espenson, J. H. *Chem. Commun.* **1998**, 1579. (b) Rudler, H.; Denise, B. *Chem. Commun.* **1998**, 2145.

(33) (a) Erickson, R. E.; Andrulis, P. J., Jr.; Collins, J. C.; Lungle, M. L.; Mercer, G. D. *J. Org. Chem.* **1969**, *34*, 2961. (b) Enders, D.; Kipphart, H.; Fey, P. *Org. Synth.* **1987**, *65*, 183.

(34) Enders, D.; Eichenauer, H. *Chem. Ber.* **1979**, *121*, 2933.

Scheme 7

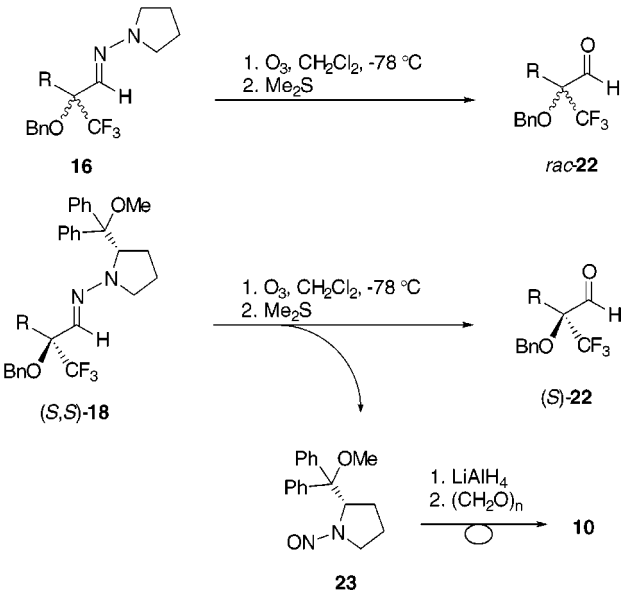
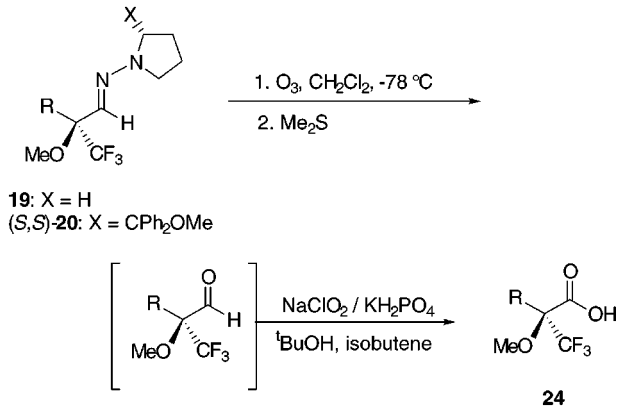


Table 5. Synthesis of α-Benzyloxy-α-trifluoromethyl Aldehydes 22

entry	starting material	R	product **22**	yield (%)
1	**16a**	CH_3	*rac*-**22a**	54
2	(*S*,*S*)-**18a**	CH_3	(*S*)-**22a**	63
3	**16b**	CH_2Ph	*rac*-**22b**	82
4	(*S*,*S*)-**18b**	CH_2Ph	(*S*)-**22b**	77
5	**16c**	*n*-C_7H_{15}	*rac*-**22c**	79
6	(*S*,*S*)-**18c**	*n*-C_7H_{15}	(*S*)-**22c**	74
7	(*S*,*S*)-**18d**	Ph	(*S*)-**22d**	77
8	**16e**	2-thienyl	*rac*-**22e**	44

Scheme 8



Finally, α-methoxy-α-trifluoromethyl carboxylic acids **24** were also synthesized from hydrazones **19** and **20** by ozonolysis followed by oxidation ($NaClO_2$, ^{t}BuOH, isobutene, KH_2PO_4) of the intermediate α-methoxy-α-trifluoromethyl aldehydes (Scheme 8, Table 6). It should be stressed here that the intermediate methylated aldehydes do not have to be isolated and can be used directly in the final oxidation step. The use of methyl protecting groups, however, proved to be inappropriate for the preparation of the corresponding aldehydes, as the low boiling points of these compounds strongly complicated the separation from the solvents used for the chromatographic purification.

Some of the methyl derivatives synthesized have direct applications. For instance, (*S*)-**24d** [(*S*)-MPTA] has been widely used as a chiral derivatizing reagent for the determination of the absolute configuration of alcohols and amines,[35] and (*S*)-**24a** has been used as derivatizing reagent for GC separation of enantiomeric amino acids.[36] In addition, optically pure, long-chain trifluoromethylated compounds such as (*S*)-**24c** possess promising structures as precursors of liquid crystals.

Table 6. Synthesis of α-Methoxy-α-trifluoromethyl Carboxylic Acids 24

starting hydrazone	X	R	product **24**	yield (%)
(*S*)-**20a**	CPh_2OMe	CH_3	(*S*)-**24a**	89
19b	H	CH_2Ph	*rac*-**24b**	72
(*S*)-**20b**	CPh_2OMe	CH_2Ph	(*S*)-**24b**	72
19c	H	*n*-C_7H_{15}	*rac*-**24c**	81
(*S*)-**20c**	CPh_2OMe	*n*-C_7H_{15}	(*S*)-**24c**	80
(*S*)-**20d**	CPh_2OMe	Ph	(*S*)-**24d**	72

The absolute configuration of the newly created quaternary center of the minor isomer (*R*,*S*)-**14a** was unequivocally determined by X-ray diffraction analysis,[21] and that of (*S*)-**24d** was assigned by comparison of their optical rotation [$[\alpha]^{20}_D$ −71.6 (*c* 2, MeOH)] with that of commercial Mosher's acid [(*S*)-MPTA, $[\alpha]^{20}_D$ −73.0 (*c* 2, MeOH)]. The absolute configuration of **b**- and **e**-series compounds has been assigned by analogy. Of course, use of *ent*-**10**, available from D-proline, would afford products with the opposite absolute configuration.

Conclusions

In summary, the spontaneous addition of formaldehyde *N*,*N*-dialkylhydrazones to trifluoromethyl ketones, followed by standard hydrazone cleavage, opens a short entry to several useful fluorinated α-alkoxycarbonyl compounds and derivatives, including α-trifluoromethyl-α-alkoxy-hydrazones, -aldehydes, -carboxylic acids, and -nitriles. Readily available chiral reagents bearing tunable proline-derived auxiliaries can be used in the same way, leading to a variety of enantiomerically pure trifluoromethyl-containing compounds. Despite the moderate inductions observed, the high chemical efficiency, the extremely simple workup associated with the absence of promoters or additives in the reaction mixtures, the easy separation of diastereomers, and the recycling of the chiral auxiliary after ozonolysis constitute interesting characteristics for eventual large-scale preparations. Concerning the generality of the method, it appears to be appropriate for simple aliphatic, aromatic and heteroaromatic substrates, while poorer results were observed for easily enolizable 1,3-dicarbonyl substrates.

Experimental Section

General Experimental Data. Melting points were determined using a metal block and are uncorrected. Optical rotations were measured at room temperature. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ with either TMS (0.00 ppm ^{1}H, 0.00 ppm ^{13}C) or $CDCl_3$ (7.26 ppm ^{1}H, 77.00 ppm ^{13}C) as an internal reference. FT-IR spectra were recorded for KBr pellets or films. Mass spectra (EI) were recorded at 70 eV, using an ionizing current of 100 μA, an accelerating voltage of 4 kV, and a resolution of 1000 or 10 000 (10% valley

(35) (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (c) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143.

(36) Yasuhara, F.; Takeda, M.; Ochiai, Y.; Miyano, S.; Yamaguchi, S. *Chem. Lett.* **1992**, 251.

definition). The reactions were monitored by TLC. Purification of the products was carried out by flash chromatography (silica gel, 0.063−0.200 nm). The light petroleum ether (PE) used had a boiling range of 40−65 °C. Tetrahydrofuran (THF) was distilled from sodium−benzophenone ketyl inmediately prior to use. Compounds **1**[22] and **7**[13d] were prepared according to the literature. Trifluoromethyl ketones **3a**,**b**,**d**−**g** were obtained from commercial suppliers.

1-(Methyleneamino)pyrrolidine (2). A three-necked round-bottom flask equipped with an addition funnel and a cooler was charged under argon with $LiAlH_4$ (0.6 mol) and dry Et_2O (1 L). A solution of commercial *N*-nitrosopyrrolidine (0.3 mol) in dry Et_2O (190 mL) was then added dropwise, at a rate that maintained the mixture under reflux. After completion of the addition, the mixture was cooled to 0 °C, and a saturated Na_2SO_4 solution was added until the excess of $LiAlH_4$ was destroyed. More Et_2O (300 mL) and paraformaldehyde (0.39 mol) were added, and the mixture was stirred overnight at room temperature. The ethereal layer was separated, and the remaining solid was washed several times with Et_2O. The combined organic layer was dried (Na_2SO_4) and concentrated to a volume of ca. 50 mL and purified by fractional distillation (50−55 °C, 200 mmHg) to yield 25 g (80% yield) of **2** as a colorless liquid: bp 122−124 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.86−1.89 (m, 4H), 3.16−3.18 (m, 4H), 5.96 (d, 1H, J = 11.7 Hz), 6.02 (d, 1H, J = 11.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.2, 50.2, 120.9; IR (film, cm^{-1}) 1574, 1539.

1-Methyleneamino-2-(diphenylmethyl)pyrrolidine (8). (*S*)-[3.3.0]-1-Aza-2-oxo-3-oxa-4,4-diphenylbicyclooctane (15.1 g, 54 mmol) was catalytically hydrogenated (10% Pd/C, H_2) as described.[27] The catalyst was filtered off, and the filtrate was evaporated. The residue was redissolved in THF (30 mL), and ^{t}BuONO (135 mmol) was added. The mixture was refluxed overnight, concentrated, and poured on suspended $LiAlH_4$ (4.31 g, 108 mmol) in THF (30 mL). After completion of the reduction (ca. 15 min, TLC), the mixture was cooled to 0 °C, treated with a saturated solution of Na_2SO_4 (50 mL), and extracted several times with Et_2O. The ethereal phase was concentrated, redissolved in CH_2Cl_2, and paraformaldehyde (81 mmol) was added. The mixture was stirred overnight and purified by flash chromatography to give 7.32 g (51%) of crystalline **8**: mp 32−34 °C; $[\alpha]^{28}_D$ −172.1° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.16−1−38 (m, 1H), 1.70−1.88 (m, 2H), 2.00−2.10 (m, 1H), 2.76−2.85 (m, 1H), 3.15−3.21 (m, 1H), 4.27−4.35 (m, 1H), 4.57 (d, 1H, J = 5.2 Hz), 5.94 (d, 1H, J = 11.7 Hz), 6.03 (d, 1H, J = 11.7 Hz), 7.13−7.32 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.1, 26.9, 47.9, 53.8, 66.3, 119.6, 125.9, 126.0, 127.8, 128.0, 128.3, 129.0, 129.5, 142.2, 142.7; IR (film, cm^{-1}) 1562; MS *m*/*z* (rel intensity) 264 M$^+$ (1%), 97 (100). Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60. Found: C, 81.58; H, 7.74; N, 10.51.

1-Methyleneamino-2-(1′-ethyl-1′-methoxpropyl)pyrrolidine (9). To a cooled (0 °C) solution of (*S*)-(−)-1-amino-2-(1-ethyl-1-methoxypropyl)pyrrolidine (SAEP)[28] (27 mmol) in CH_2Cl_2 (50 mL) was added paraformaldehyde (32.4 mmol), and the mixture was stirred at room temperature until TLC (Et_2O−PE, 1:1) indicated total consumption of the starting material. The reaction mixture was concentrated, and the residue was purified by flash chromatography (Et_2O−PE, 1:6) to afford 4.15 g (76%) of **9** as an oil: $[\alpha]^{29}_D$ +56.7° (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84−0.89 (m, 6H), 1.51−1.58 (m, 2H), 1.60−1.69 (m, 2H), 1.72−1.77 (m, 1H), 1.79−1.86 (m, 1H), 1.87−1.93 (m, 1H), 1.96−2.03 (m, 1H), 2.76−2.82 (m, 1H), 3.23 (s, 3H), 3.24−3.32 (m, 1H), 3.65 (dd, 1H, J = 2.5, 9.4 Hz), 5.93 (d, 1H, J = 11.6 Hz), 6.07 (d, 1H, J 11.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.8, 8.1, 23.5, 23.7, 24.3, 26.0, 49.8, 50.7, 68.7, 80.8, 120.0; IR (film, cm^{-1}) 1568; MS *m*/*z* (rel intensity) 198 M$^+$ (1%), 97 (100); *m*/*z* calcd for $C_{11}H_{22}N_2O$ 198.1732, found 198.1727.

1-Methyleneamino-2-(1′-methoxy-1′,1′-diphenylmethyl)pyrrolidine (10). (*S*)-(−)-1-Amino-2-(1-methoxy-1,1-diphenylmethyl)-pyrrolidine (SAPP)[28] was treated as described above for **9**. Flash chromatography (Et_2O−PE, 1:30) gave 4 g (56%) of crystalline **10**: mp 79−80 °C; $[\alpha]^{20}_D$ −57.5° (*c* 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.13−0.27 (m, 1H), 1.36−1.46 (m, 1H), 1.82−1.89 (m, 1H), 1.93−2.07 (m, 1H), 2.56−2.67 (m, 1H), 2.77−2.83 (m, 1H), 3.03 (s, 3H), 4.83 (dd, 1H, J = 1.7, 9.4 Hz), 5.89 (d, 1H, J = 11.8 Hz), 6.0 (d, 1H, J = 11.8 Hz), 7.15−7.43 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.9, 26.1, 49.5, 51.3, 67.4, 85.8, 119.5, 126.9, 127.1, 127.3, 129.5, 129.9, 140.8, 141.6; IR (film, cm^{-1}) 1577; MS *m*/*z* (rel intensity) 294 M$^+$ (1%), 97 (100). Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.48; H, 7.41; N, 9.65.

Synthesis of Racemic 2-Hydroxy-2-trifluoromethyl *N*,*N*-Dialkylhydrazones 4 and 5. General Procedure. To a cooled (0 °C) solution of the hydrazone **1** or **2** (3 mmol) in CH_2Cl_2 was added dropwise the trifluoromethyl ketone **3** (6 mmol). The mixture was stirred at room temperature until TLC indicated total comsumption of the starting hydrazone. The mixture was then concentrated and purified by flash chromatography. Representative spectral and analytical data for compounds **4d** and **5a** are as follows.

2-Hydroxy-2-phenyl-3,3,3-(trifluoro)propanal *N*,*N*-Dimethylhydrazone (4d). From **3d** and **1** in CH_2Cl_2 (0.5 mL); flash chromatography (1:20 → 1:9 Et_2O−PE) gave 468 mg (61%) of crystalline **4d**: mp 36−38 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.90 (s, 6H), 5.25 (s, 1H), 6.80 (s, 1H), 7.35−7.44 (m, 3H), 7.65−7.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 42.7, 75.2 (q, J = 29.0 Hz), 124.5 (q, J = 284.2 Hz), 126.1, 126.3, 128.3, 128.4, 137.1; IR (film, cm^{-1}) 3401, 1595; MS *m*/*z* (rel intensity) 264 M$^+$ (44), 177 (100). Anal. Calcd for $C_{11}H_{13}F_3N_2O$: C, 53.66; H, 5.32; N, 11.38. Found: C, 53.52; H, 5.25; N, 11.32.

1-[2-Hydroxy-2-(trifluoromethyl)propyleneamino]-pyrrolidine (5a). From **3a** and **2** in CH_2Cl_2 (0.5 mL); flash chromatography (1:9 Et_2O−PE) gave 568 mg (90%) of **5a** as an oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.49 (s, 3H), 1.90−2.03 (m, 4H), 3.19−3.29 (m, 4H), 4.54 (s, 1H), 6.36 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.8, 23.3, 60.9, 72.4 (q, J = 28.9 Hz), 125.2 (q, J = 283.9 Hz), 126.5; IR (film, cm^{-1}) 3443, 1593; MS *m*/*z* (rel intensity) 210 M$^+$ (46), 195 (27); *m*/*z* calcd for $C_8H_{13}F_3N_2O$ 210.0980, found 210.0979.

(2*S*,2′*S*)- and (2*S*,2′*R*)-1-[2′-Hydroxy-3′-phenyl-2′-(trifluoromethyl)propyleneamino]-2-(1″methoxy-1″,1″-diphenyl)pyrrolidine (14b). To a cooled (0 °C) solution of **10** (883 mg, 3 mmol) in dry cyclohexane (5 mL) was added Et_3N (0.45 mL) and **3b** (2.2 mL, 12 mmol) under an argon atmosphere. The mixture was stirred at room temperature for 6 h 30 min and concentrated, and the resulting residue was purified by flash chromatography (1:30 Et_2O−PE) to give 246 mg (17%) of (*S*,*R*)-**14b** as an oil and 1.08 g (75%) of crystalline (*S*,*S*)-**14b**.

(*S*,*S*)-**14b**: mp 89−90 °C; $[\alpha]^{26}_D$ −38.6° (*c* 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.21−0.27 (m, 1H), 1.36−1.42 (m, 1H), 1.85−1.91 (m, 2H), 2.44−2.50 (m, 1H), 2.73−2.77 (m, 1H), 2.92 (s, 3H), 2.98 (d, 1H, J = 13.7 Hz), 3.15 (d, 1H, J = 13.7 Hz), 3.75 (s, 1H), 4.43 (m, 1H), 6.16 (s, 1H), 7.19−7.38 (m, 15H)); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.3, 25.7, 39.0, 49.3, 51.5, 67.9, 75.1 (q, J = 27.5 Hz), 85.5, 123.2, 125.1 (q, J = 287.5 Hz), 126.6, 127.0, 127.1, 127.2, 127.5, 127.6, 129.4, 129.8, 130.9, 134.4, 138.5, 140.2; IR (film, cm^{-1}) 3450−3430, 1593; MS *m*/*z* (rel intensity) 482 M$^+$ (0.2), 285 (100). Anal. Calcd for $C_{28}H_{29}F_3N_2O_2$: C, 69.69; H, 6.06; N, 5.81. Found: C, 69.91; H, 5.84; N, 6.12.

(*S*,*R*)-**14b**: $[\alpha]^{26}_D$ −198.3° (*c* 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ (−0.16)−(−0.09) (m, 1H), 1.18−1.25 (m, 1H), 1.82−1.87 (m, 2H), 2.42−2.52 (m, 2H), 2.72 (s, 3H), 2.79 (d, 1H, J = 13.8 Hz), 3.03 (d, 1H, J = 13.8 Hz), 3.69 (s, 1H), 4.51−4.54 (m, 1H), 5.83 (s, 1H), 6.73−7.27 (m, 15H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.9, 25.4, 38.8, 48.5, 51.5, 67.9, 75.2 (q, J = 27.7 Hz), 85.3, 121.8, 125.1 (q, J = 275.0 Hz), 126.5, 126.8, 127.1, 127.3, 127.4, 127.7, 129.3, 129.9, 130.5, 134.4, 137.7, 139.6; IR (film, cm^{-1}) 3450−3430, 1593; MS *m*/*z* (rel intensity) 482 M$^+$ (0.1), 285 (100); *m*/*z* calcd for $C_{28}H_{29}F_3N_2O_2$ 482.2181, found 482.2172.

Synthesis of α-Benzyloxy-α-trifluoromethyl Hydrazones 16−18. General Procedure. To a cooled (0 °C) solution of the α-hydroxy-α-trifluoromethylhydrazone **5**, **13**, or **14** (1 mmol) in DMF (2 mL) was added NaH (60% in parafine, 100 mg, 2.5 mmol) and benzyl bromide (0.23 mL, 2 mmol) under

an argon atmosphere. The mixture was stirred at room temperature until TLC (1:6 Et_2O−PE) indicated total consumption of the starting material (ca. 1 h 30 min). A solution of MeONa (1 M in dry MeOH, 1.5 mL) was added, and the suspension was stirred for 15 min. The mixture was then diluted with Et_2O and washed with a saturated solution of NH_4Cl and H_2O. The organic layer was dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography. Representative spectral and analytical data for compounds **16a** and (*S*,*S*)-**18d** are as follows.

1-[2′-Benzyloxy-2′-(trifluoromethyl)propyleneamino]-pyrrolidine (16a). From *rac*-**5a**; flash chromatography (1:30 Et_2O−PE) gave 243 mg (81%) of **16a** as an oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.57−1.59 (m, 3H), 1.88−1.92 (m, 4H), 3.15−3.23 (m, 4H), 4.53 (m, 2H), 6.26 (s, 1H), 7.25−7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.1, 23.4, 50.4, 64.9, 79.2 (q, J = 27.7 Hz), 127.1 (q, J = 284.1 Hz), 127.2, 128.2, 138.6; IR (film, cm^{-1}) 1580; MS *m*/*z* (rel intensity) 300 M$^+$ (29), 194 (56), 174 (14), 91 (100), 70 (41). Anal. Calcd for $C_{15}H_{19}F_3N_2O$: C, 59.99; H, 6.38; N, 9.33. Found: C, 59.52; H, 6.32; N, 9.29.

(2*S*,2′*S*)-1-[2′-Benzyloxy-2′-phenyl-3′,3′,3′-(trifluoro)-propyleneamino]-2-(1″-methoxy-1″,1″-diphenyl)pyrrolidine [(*S*,*S*)-18d]. From (*S*,*S*)-**14d**; flash chromatography (1:20 Et_2O−PE) gave 458 mg (82%) of (*S*,*S*)-**18d** as an oil: $[\alpha]^{24}_D$ -106.7° (*c* 1.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.09−0.19 (m, 1H), 1.32−1.42 (m, 1H), 1.86−1.95. (m, 1H), 1.98−2.07 (m, 1H), 2.37−2.48 (m, 1H), 2.67−2.81 (m, 1H), 2.88 (s, 3H), 4.67−4.76 (m, 2H), 4.81 (dd, 1H, J = 1.2, 9.2 Hz), 6.39 (s, 1H), 7.18−7.69 (m, 20H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 26.1, 49.1, 51.2, 65.8, 66.4, 82.4 (q, J = 26.5 Hz), 85.5, 124.4 (q, J = 262.0 Hz), 124.8, 126.6, 126.8, 127.0, 127.1, 127.3, 127.5, 127.8, 128.2, 128.4, 129.9, 129.5, 129.6, 135.8, 139.4, 141.0, 141.9; IR (film, cm^{-1}) 1458; MS *m*/*z* (rel intensity) 361 (100). Anal. Calcd for $C_{34}H_{33}F_3N_2O_2$: C, 73.10; H, 5.95; N, 5.01. Found: C, 73.11; H, 6.00; N, 5.01.

Synthesis of α-Methoxy-α-trifluoromethylhydrazones 19 and (*S*,*S*)-20. General Procedure. To a cooled (0 °C) solution of the α-hydroxy-α-trifluoromethylhydrazone **5** or (*S*,*S*)-**14** (1 mmol) in dry THF (5 mL) was added NaH (60% in parafine, 120 mg, 3 mmol) and methyl iodide (0.19 mL, 3 mmol) dropwise under an argon atmosphere. The mixture was stirred at room temperature until TLC (1:6 Et_2O−PE) indicated total consumption of the starting material. A solution of MeONa (1 M in dry MeOH, 1.5 mL) was added, and the suspension was stirred for 15 min. The mixture was then diluted with Et_2O and washed with saturated NH_4Cl solution and H_2O. The organic layer was dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography. Representative spectral and analytical data for compounds **19d** and (*S*,*S*)-**20c** are as follows.

1-[2′-Methoxy-2′-phenyl-3′,3′,3′-(trifluoro)propyleneamino]pyrrolidine (19d). From **5d**; flash chromatography (1:30 Et_2O−PE) gave 229 mg (80%) of **19d** as an oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.87−1.99 (m, 4H), 3.24−3.34 (m, 4H), 3.36 (s, 3H), 6.47 (s, 1H), 7.34−7.61 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.4, 50.5, 52.3, 82.1 (q, J = 26.8 Hz), 124.4 (q, J = 285.0 Hz), 124.6, 127.7, 128.4, 129.1, 134.3; IR (film, cm^{-1}) 1585; MS *m*/*z* 286 M$^+$ (42), 217 (100). Anal. Calcd for $C_{14}H_{17}F_3N_2O$: C, 58.73; H, 5.99; N, 9.79. Found: C, 58.30; H, 6.10; N, 9.67.

(2*S*,2′*S*)-1-[2′-Methoxy-2′-(trifluoromethyl)nonyleneamino]-2-(1″-methoxy-1″,1″-diphenyl)pyrrolidine [(*S*,*S*)-20c]. From (*S*,*S*)-**14c**; flash chromatography (1:30 Et_2O−PE) gave 419 mg (83%) of (*S*,*S*)-**20c** as an oil: $[\alpha]^{22}_D$ −118.1° (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.21−0.29 (m, 1H), 0.91−0.94 (m, 3H), 1.27−1.41 (m, 10H), 1.44−1.49 (m, 1H), 1.65−1.71 (m, 1H), 1.79−1.98 (m, 1H), 1.98−2.11 (m, 2H), 2.66−2.71 (m, 1H), 2.78−2.82 (m, 1H), 3.01 (s, 3H), 3.30 (s, 3H), 4.86 (dd, 1H, J = 1.9, 9.0 Hz), 6.09 (s, 1H), 7.26−7.44 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 21.3, 22.2, 22.6, 25.8, 29.0, 30.1, 31.8, 48.9, 51.1, 51.3, 66.7, 72.8 (q, J = 25.9 Hz), 85.6, 124.4, 125.5 (q, J = 285.7 Hz), 127.0, 127.1, 127.3, 129.4, 129.8, 140.1, 141.3; IR (film, cm^{-1}) 1593; MS *m*/*z* (rel intensity) 307 (100). Anal. Calcd for $C_{29}H_{39}F_3N_2O_2$: C, 69.02; H, 7.79; N, 5.55. Found: C, 68.91; H, 7.69; N, 5.61.

Synthesis of α-Benzyloxy-α-trifluoromethyl Nitriles 21. General Procedure. To a cooled (0 °C) solution of the benzyloxy hydrazone **16**,**17** (1 mmol) in MeOH (3 mL) was added dropwise a cooled (0 °C) solution of magnesium monoperoxyphthalate hexahydrate (2.5 mmol) in MeOH (6 mL). The mixture was stirred at 0 °C until TLC (Et_2O−PE) indicated total consumption of the starting hydrazone. CH_2Cl_2 and H_2O were added, and the organic layer was washed with brine and H_2O, dried (Na_2SO_4), and concentrated. The resulting residue was purified by flash chromatography. Representative spectral and analytical data for compound **21d** are as follows.

2-Benzyloxy-3,3,3-trifluoro-2-phenylpropionitrile (21d). From **16d**; flash chromatography (1:20 Et_2O−PE) gave 265 mg (91%) of **21d** as an oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.54 (d, 1H, J = 10.5 Hz), 4.81 (d, 1H, J = 10.5 Hz), 7.36−7.44 (m, 5H), 7.59−7.63 (m, 3H), 7.74−7.75 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 69.8, 80.7 (q, J = 32.5 Hz), 113.3, 121.2 (q, J = 284.2 Hz), 127.6, 127.8, 128.5, 128.6, 128.8, 129.1, 131.2, 135.0. IR (film, cm^{-1}) 1972, 1495; MS (rel intensity) *m*/*z* 291 M$^+$ (4), 185 (100). Anal. Calc for $C_{16}H_{12}F_3NO$: C, 65.98; H; 4.15; N, 4.81. Found: C, 66.08; H, 4.42; N, 4.96.

Synthesis of α-Benzyloxy-α-trifluoromethylaldehydes 22. Dry ozone was bubbled through a cooled (−78 °C) solution of the α-benzyloxy-α-trifluoromethylhydrazone **16** or (*S*,*S*)-**18** (1 mmol) in CH_2Cl_2 (3 mL) until the appearance of a permanent blue-green color (ca. 5−10 min). After addition of Me_2S (0.37 mL, 5 mmol), the mixture was allowed to warm to room temperature and concentrated, and the residue was purified by flash chromatography. Representative spectral and analytical data for compounds *rac*-**22b** and (*S*)-**22a** are as follows.

2-Benzyl-2-benzyloxy-3,3,3-trifluoropropanal (*rac*-22b). From **16b**; flash chromatography (1:20 Et_2O−PE) gave 253 mg (82%) of *rac*-**22b** as an oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.29−3.40 (m, 2H), 4.76−4,84 (m, 2H), 7.22−7.38 (m, 10H), 9.58−9.61 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.5, 68.9, 84.1 (q, J = 24.6 Hz), 123.8 (q, J = 288.8 Hz), 127.3, 127.4, 127.9, 128.3, 130.6, 131.9, 136.8, 196.6; IR (film, cm^{-1}) 1696, 1458; MS (rel intensity) *m*/*z* 212 M$^+$ (5), 91 (100); *m*/*z* calcd for $C_{17}H_{15}F_3O_2$ 308.1024, found 308.1044.

(2*S*)-2-Benzyloxy-3,3,3-trifluoro-2-methylpropanal ((*S*)-22a). From (*S*,*S*)-**18a**; flash chromatography (1:20 Et_2O−PE) gave 146 mg (63%) of (*S*)-**22a** as an oil: $[\alpha]^{25}_D$ −38.5° (*c* 1.2, $CHCl_3$);^{1}H RMN ($CDCl_3$, 300 MHz) δ 1.58 (s, 3H), 4.64 (d, 1H, J = 11.1 Hz), 4.73 (d, 1H, J = 11.0 Hz), 7.36−7.40 (m, 5H), 9.65−9.66 (m, 1H); ^{13}C RMN ($CDCl_3$, 75 MHz) δ 13.3, 67.6, 81.7 (q, J = 27.2 Hz), 123.7 (q, J = 287.4 Hz), 127.5, 128.1, 128.5, 136.6, 195.4; IR (film, cm^{-1}) 1748, 1456; MS (rel intensity) *m*/*z* 232 M$^+$ (2), 91 (100). Anal. Calcd for $C_{11}H_{11}F_3O_2$: C, 56.90; H, 4.77. Found: C, 56.61; H, 5.05.

1-Nitroso-2-(1′-methoxy-1′,1′-diphenyl)pyrrolidine (23). After complete elution of the products (*S*)-**22** obtained by ozonolysis, the column was further eluted (1:3 Et_2O−PE) to obtain compound **23** (65−85%) as an oil: $[\alpha]^{27}_D$ −190.5° (*c* 1.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.27−0.44 (m, 1H), 1.34−1.57 (m, 1H), 2.10−2.21 (m, 1H), 2.26−2.41 (m, 1H), 2.77−2.86 (m, 1H), 3.07 (s, 3H), 3.42−3.53 (m, 1H), 5.80 (d, 1H, J 8.9 Hz), 7.21−7.39 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.4, 26.5, 46.6, 51.2, 63.0, 84.8, 126.3, 127.5, 127.8, 127.9, 129.1, 139.5, 140.6; IR (film, cm^{-1}) 1664; MS (CI) *m*/*z* (rel intensity) 297 M$^+$ + 1 (60), 197 (100); *m*/*z* calcd for $C_{18}H_{21}N_2O_2$ 297.1603, found 297.1590.

Synthesis of α-Methoxy-α-trifluoromethylcarboxylic Acids 24. General Procedure. Dry ozone was bubbled through a cooled (−78 °C) solution of the α-methoxy-α-trifluoromethylhydrazone **19** or (*S*,*S*)-**20** (1 mmol) in CH_2Cl_2 (15 mL) until appearance of a permanent green color (ca. 5−10 min). After addition of Me_2S (0.075 mL, 1 mmol), the mixture was allowed to reach room temperature. To the resulting solution was added ^{t}BuOH (12 mL) and 2-methyl-2-butene (10 mL). After the mixture cooled to 0 °C, a solution of $NaClO_2$ (10 mmol) and KH_2PO_4 (9 mmol) in H_2O (12 mL) was added dropwise, and the mixture was stirred for 16 h at room temperature. The solvent was removed, and the residue was treated with 1 M NaOH and extracted with Et_2O. The aqueous layer was acidified to pH 1 (HCl) and extracted with ethyl

acetate. The combined organic layer was then concentrated and purified by flash chromatography (toluene−AcOEt−AcOH, 40:20:1.5). Representative spectral and analytical data for compounds *rac*-**24c** and (*S*)-**24d** are as follows.

2-Methoxy-2-(trifluoromethyl)nonanoic Acid (*rac*-24c). From **19c**; flash chromatography gave 208 mg (81%) of *rac*-**24c** as an oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85−0.95 (m, 3H), 1.27−1.40 (m, 8H), 1.65−1.78 (m, 2H), 1.93−2.10 (m, 1H), 3.56 (s, 3H), 8.20−8.83 (br. s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.4, 22.4, 28.8, 29.5, 30.0, 32.3, 54.1, 82.4 (q, J = 28.6 Hz), 123.5 (q, J = 288 Hz), 169.6; IR (film, cm^{-1}) 1740; MS (rel intensity) *m*/*z* 236 (3), 211 (100); *m*/*z* calcd for $C_{10}H_{18}F_3O$ 211.1310, found 211.1297.

(2*S*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoic Acid [(*S*)-24d]. From (*S*,*S*)-**20d**; flash chromatography gave 169 mg (72%) of (*S*)-**24d** as an oil: $[\alpha]^{21}_D$ −63.0° (*c* 1.6, MeOH). Spectral and analytical data were in good agreement with literature data.[11b]

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Supporting Information Available: The experimental procedures and/or spectral and analytical data for compounds **3c**, **4b**, **5b**−**g**, **6c**, **11a**,**b**,**d**, **12b**, **13a**,**b**,**d**, **14a**,**c**−**e**, **16b**−**e**, **17b**, (*S*,*S*)-**18a**−**c**, **19a**−**c**, (*S*,*S*)-**20a**,**b**,**d**, **21a**−**c**,**e**, *rac*-**22a**,**c**,**e**, (*S*)-**22b**−**d**, *rac*-**24b**, and (*S*)-**24a**−**c** and the ^{13}C NMR spectra for compounds **2**, **3c**, **5a**,**c**,**g**, **6c**, **9**, **11a**,**b**,**d**, **13a**,**d**, (*S*,*S*)-**14a**,**c**,**e**, (*R*,*S*)-**14b**,**d**,**e**, **16d**,**e**, **17b**, (*S*,*S*)-**18a**,**b**, **19a**,**b**, (*S*,*S*)-**20b**, **21a**,**c**,**e**, **22b**,**c**,**e**, **23**, and **24b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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