The "Non-Oxidative" Pummerer Reaction: Conclusive Evidence for S_N2-Type Stereoselectivity, Mechanistic Insight, and Synthesis of Enantiopure L-α-Trifluoromethylthreoninate and D-α-Trifluoromethyl-*allo*-threoninate[1]

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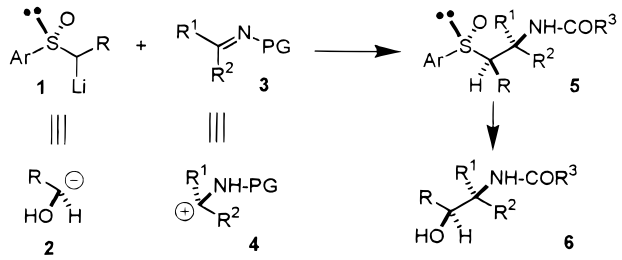
Enantiopure methyl D-α-trifluoromethyl-*allo*-threoninate **18** and L-α-trifluoromethylthreoninate **19** were synthesized using (*R*)-ethyl *p*-tolylsulfoxide as chiral α-hydroxyethyl anion equivalent. The key step was the S_N2-type replacement of the sulfinyl auxiliary with a hydroxy group, via trifluoroacetic anhydride promoted "non-oxidative" Pummerer reaction (NOPR) of the diastereomeric intermediate *β*-sulfinyl amines **14** and **15**, obtained by condensation of (*R*)-ethyl *p*-tolylsulfoxide **13** with the *N*-Cbz imine of methyl trifluoropyruvate **12**. The conclusive evidence for S_N2-type stereoselectivity of the NOPR was achieved by X-ray diffraction of both the starting diastereomer **14** and the *p*-bromobenzoate **25**, obtained from the threoninate **19**. NMR monitoring of the NOPR performed on **15** allowed the detection of a transient intermediate, which was identified as the four membered cyclic *σ*-sulfurane **27**. This intermediate spontaneously rearranged (40 min, rt) into the corresponding sulfenamide **17**, probably via an intramolecular displacement of the sulfinyl by a trifluoroacetoxy group, with inversion of configuration at the carbon stereocenter. The same process occurred for the diastereomeric *β*-sulfinyl amine **14**, but the sulfenamide **16** was formed at a very fast rate, thus precluding NMR detection of the corresponding *σ*-sulfurane intermediate **26**. One-pot treatment of the diastereomeric sulfenamides **16** and **17** with $NaBH_4$ afforded very good yields of the corresponding threoninates **18** and **19**.

Stereochemically defined *β*-amino alcohol units are frequently found in biologically active molecules.[2] We recently developed a new method for the synthesis of these important units.[3] α-Lithium alkyl arylsulfoxides **1** (Scheme 1), used as chiral α-hydroxyalkyl carbanion equivalents **2**, were reacted with *N*-protected imines **3**, synthetic equivalents of α-amino carbocations **4**, to afford the *β*-amino alcohols **6**.

The key step in this strategy is the transformation of the intermediate *β*-sulfinylamines **5**, obtained by stereocontrolled assembling of **1** with **3**, into the targets **6**. This was achieved by means of a highly stereospecific variant of the Pummerer reaction,[4] which results in a one-pot S_N2-type displacement of the sulfinyl auxiliary by a hydroxyl. Previous work from our laboratories[5] showed

Scheme 1



that trifluoroacetoxy sulfenamides **9** (Scheme 2) are the true products of the rearrangement and that these compounds can be in situ transformed into the final *β*-amino alcohols **6**.[6]

Since the original sulfinyl-bearing carbon of sulfenamides **9** has a lower oxidation state than that expected from a classical Pummerer rearrangement product, the process was termed a "non-oxidative Pummerer reaction" (NOPR). The NOPR was shown to be applicable to a wide

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(2) For a detailed list of references see: (a) Volonterio, A.; Vergani, B.; Crucianelli, M.; Zanda, M.; Bravo, P. *J. Org. Chem.* **1998**, *63*, 7236. For a review on *β*-fluoroalkyl-*β*-amino alcohols, see: (b) Bravo, P.; Crucianelli, M.; Ono, T.; Zanda, M. *J. Fluorine Chem.* **1999**, *97*, 27.

(3) Zanda, M.; Bravo, P.; Volonterio, A. In *Asymmetric Fluoro-Organic Chemistry: Synthesis, Applications, and Future Directions*; Ramachandran, P. V. Ed.; American Chemical Society Symposium Series; American Chemical Society: Washington, DC, 1999.

(4) (a) Pummerer, R. *Ber.* **1909**, *42*, 2282. (b) De Lucchi, O.; Miotti, U.; Modena, G. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1991; Vol. 40. (c) Oae, S. *Organic Sulfur Chemistry: Structure and Mechanism*; CRC Press: Boca Raton, 1991; pp 380−400. (d) Padwa, A.; Gunn, D. E., Jr.; Osterhout, M. H. *Synthesis* **1997**, 1353. (e) Kennedy, M.; McKervey, M. In *Comprehensive Organic Chemistry*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 7, pp 193−216.

(5) (a) Arnone, A.; Bravo, P.; Bruché, L.; Crucianelli, M.; Vichi, L.; Zanda, M. *Tetrahedron Lett.* **1995**, *36*, 7301. (b) Arnone, A.; Bravo, P.; Capelli, S.; Fronza, G.; Meille, S. V.; Zanda, M.; Cavicchio, G.; Crucianelli, M. *J. Org. Chem.* **1996**, *61*, 3375. Corrigenda: *J. Org. Chem.* **1996**, *61*, 9635.

(6) In light of this unprecedented reactivity alkyl sulfoxides can be regarded as chiral "chemical chameleons". Indeed, in the first step (C−C bond forming), the sulfinyl group imparts nucleophilic character to the α-carbon, whereas in the second step (the NOPR) it acts as a leaving group transforming the α-carbon in an electrophilic center. A well-established class of "chemical chameleons" are sulfones, according to the definition of Trost: (a) Trost, B. A.; Organ, M. G.; O'Doherty, G. A. *J. Am. Chem. Soc.* **1995**, *117*, 9662.

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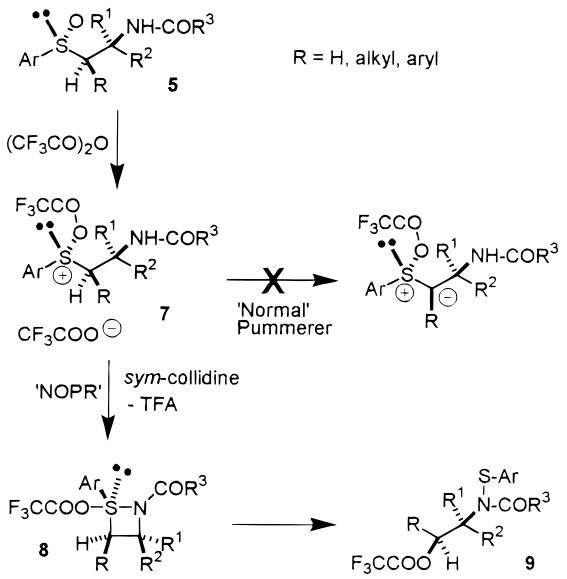
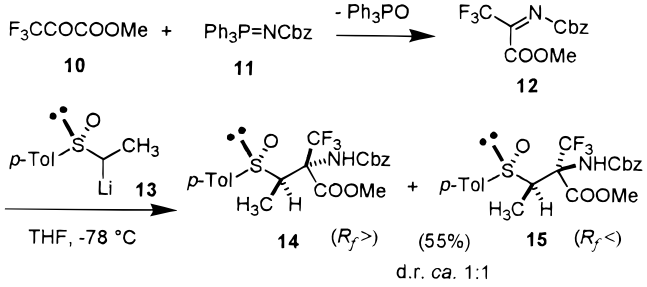
Published on Web 04/15/2000

Scheme 2



Scheme 3



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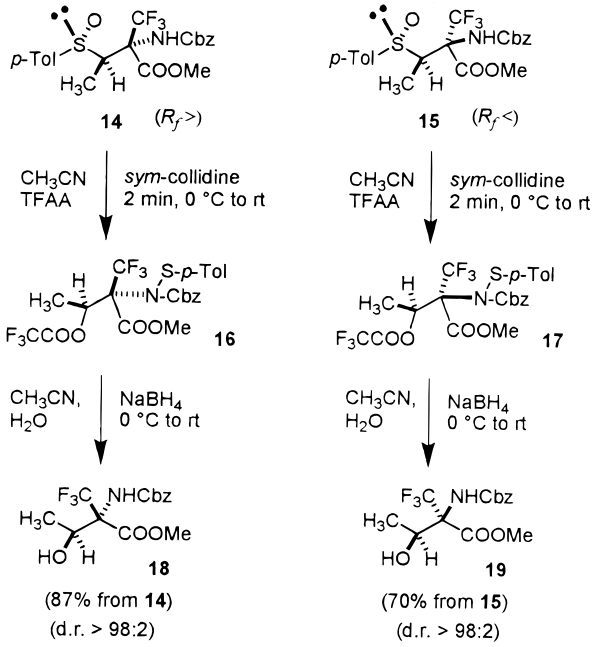


range of β-sulfinylamines, fluorinated and not,[7] provided that the amino group is protected as a monoamide or monocarbamate (NHCOR or NHCOOR, respectively).[8] We would like to emphasize that the NOPR is the first methodology which allows one to preserve and exploit the stereochemical information of an α-sulfinyl stereocenter for the synthesis of sulfur-free molecules, since this is usually lost in the desulfinylation process.[9]

Despite the large number of successful applications of the NOPR, little information about its mechanism is known. This is mainly due to the fact that all the NOPR transformations hitherto explored[7] were found to be very fast processes, therefore precluding the isolation or the spectroscopic detection of any intermediate. The only experimental evidence available was achieved by means of deuterium labeling experiments,[5] which indicated that the "normal" α-sulfinyl proton removal does not take place (Scheme 2). On the basis of these data, we hypothesized that the NOPR might involve intramolecular trapping of the tricoordinate sulfonium cation **7** by the amidic/carbamic β-nitrogen, giving rise to the intermediate chiral σ-sulfurane **8**. This intermediate then undergoes a stereospecific S_N2-type rearrangement providing the final sulfenamide **9**.

In this paper, we present: (a) conclusive evidence for S_N2-type stereoselectivity of the NOPR, based on X-ray diffraction studies of substrate and product; (b) evidence for formation of the sulfurane **8** (Scheme 2), based on NMR spectroscopy; (c) and a novel application of the NOPR for the synthesis of densely functionalized L-α-trifluoromethyl (Tfm)-threoninate and D-α-Tfm-*allo*-threoninate, using lithiated (*R*)-ethyl *p*-tolylsulfoxide **13** (Scheme 3) as a chiral α-hydroxyethyl carbanion equivalent.[10]

Results

The starting β-sulfinylamines **14** and **15** (Scheme 3) were prepared according to known methodology.[11] The Staudinger (aza-Wittig) reaction of methyl trifluoropyruvate **10** with the *N*-Cbz iminophosphorane **11** provided the strongly electrophilic imine **12**,[12] which was reacted in situ with α-lithium (*R*)-ethyl *p*-tolylsulfoxide **13**.

A nearly equimolar ratio of **14** and **15** was produced (55% overall yield), with no trace of the other two possible diastereomers as evidenced by ^{1}H and ^{19}F NMR spec-

(7) (a) Bravo, P.; Capelli, S.; Meille, S. V.; Seresini, P.; Volonterio, A.; Zanda, M. *Tetrahedron: Asymmetry* **1996**, *7*, 2321. (b) Bravo, P.; Cavicchio, G.; Crucianelli, M.; Poggiali, A.; Zanda, M. *Tetrahedron*: *Asymmetry* **1997**, *8*, 2811. (c) Bravo, P.; Farina, A.; Kukhar, V. P.; Markovsky, A. L.; Meille, S. V.; Soloshonok, A. V.; Sorochinsky, A. E.; Viani, F.; Zanda, M.; Zappalà, C. *J. Org. Chem.* **1997**, *62*, 3424. (d) Bravo, P.; Guidetti, M.; Viani, F.; Zanda, M.; Markovsky, A. L.; Sorochinsky, A. E.; Soloshonok, I. V.; Soloshonok, V. A. *Tetrahedron* **1998**, *54*, 12789. (e) Bravo, P.; Corradi, E.; Pesenti, C.; Vergani, B.; Viani, F.; Volonterio, A.; Zanda, M. *Tetrahedron*: *Asymmetry* **1998**, *9*, 3731. (f) Bravo, P.; Capelli, S.; Crucianelli, M.; Guidetti, M.; Markovsky, A. L.; Meille, S. V.; Soloshonok, V. A.; Sorochinsky, A. E.; Viani, F.; Zanda, M. *Tetrahedron* **1999**, *55*, 3025.

(8) NH-PMP β-sulfinylamines were found to behave in a totally different manner when submitted to NOPR conditions: Arnone, A.; Bravo, P.; Bruché, L.; Crucianelli, M.; Zanda, M.; Zappalà, C. *J. Chem. Res.* **1997**, 416.

(9) A stereoselective one-pot displacement of a sulfinyl group via desulfinylative formation of benzyl cations and their subsequent trapping was reported, but that reaction is limited to the case of benzyl sulfoxides: Casey, M.; Manage, A. C.; Murphy, P. J. *Tetrahedron Lett.* **1992**, *33*, 965.

(10) For a preliminary communication, see: (a) Bravo, P.; Zanda, M.; Zappalà, C. *Tetrahedron Lett.* **1996**, *37*, 6005. For an overview on the synthesis of fluorinated threonines, see: (b) Sting, A. R.; Seebach, D. *Tetrahedron* **1996**, *52*, 279 and references therein.

(11) Bravo, P.; Viani, F.; Zanda, M.; Kukhar, V. P.; Soloshonok, V. A.; Fokina, N.; Shishkin, O. V.; Struchkov, Yu. T. *Gazz. Chim. Ital.* **1996**, *126*, 645.

(12) Bravo, P.; Capelli, S.; Meille, S. V.; Viani, F.; Zanda, M.; Kukhar, V. P.; Soloshonok, V. A. *Tetrahedron*: *Asymmetry* **1994**, *5*, 2009.

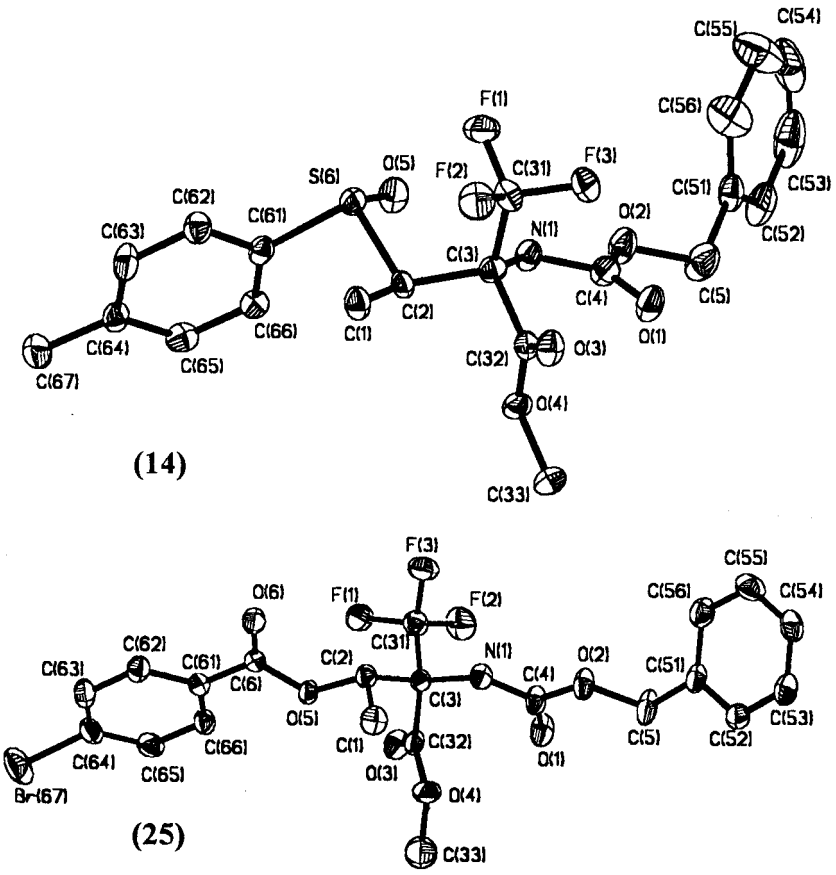
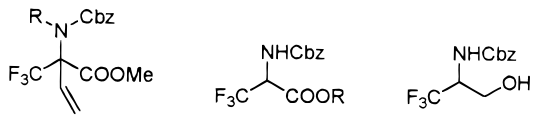


Figure 1. ORTEP view of compounds **14** and **25**, showing the molecular labeling scheme. Displacement ellipsoids are plotted at the 20% probability level.

troscopy of the crude. Diastereomerically pure **14** and **15** were obtained by flash chromatography (FC) and separately treated with trifluoroacetic anhydride (TFAA) (5 equiv) in the presence of *sym*-collidine (3 equiv) at room temperature in acetonitrile, providing the corresponding trifluoroacetoxy sulfenamides **16** and **17** as single diastereomers (Scheme 4).

Interestingly, while the rearrangement of **14** into **16** was instantaneous, in line with all the NOPR previously explored,[7] the transformation of **15** into **17** required ca. 40 min to reach completion (TLC monitoring). Sulfenamides **16** and **17** were separately treated with an excess of $NaBH_4$ (0 °C to room temperature, acetonitrile + 1 drop of water), smoothly affording the α-Tfm-*allo*-threoninate **18** and the α-Tfm-threoninate **19**, respectively.[13] One-pot transformations of **14** into **18** and **15** into **19** were effectively achieved under the same conditions (87% and 70%, respectively). In both cases, a diastereoselectivity >98:2 was observed (the other diastereomer could not be detected in the crude reaction mixture). The only relevant byproducts observed in the crude reaction mixture, under the optimized conditions, were methyl *N*-Cbz α-Tfm-α-vinyl-glycinate **21** and its precursor sulfenamide **20** (<5% overall), which should arise from *β*-elimination of the sulfinyl residue. In contrast, when the reactions of **16** and **17** into **18** and **19** were carried out in the presence of an extra base (usually K_2CO_3) and/or with larger amount of water, extended retro-aldol reaction of **18** and **19** occurred.[14] In that case, methyl *N*-Cbz trifluoroalaninate **22**, *N*-Cbz trifluoroalanine **23**, and their reduced derivative *N*-Cbz trifluoroalaninol **24** were produced in good yields,[5b] together with minor amounts of other uncharacterized side-products.



20 R = S-*p*-Tol
21 R = H

22 R = CH_3
23 R = H

24

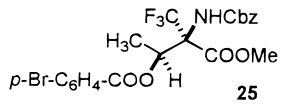
Interestingly, **22**, **23**, and **24** were isolated by FC in nonracemic form. For example, starting from **14**, (*S*)-trifluoroalaninol **24** having ca. 50% ee was obtained, which means that the retro-aldol reaction takes place with at least partial retention of configuration at the amino acid center.[15] To unambiguously assess the absolute configuration of the NOPR products **18** and **19**, and the stereochemical outcome of the transformation, we submitted to X-ray diffraction analysis both the substrate **14** and the *p*-Br-benzoate **25**, prepared from the methyl *N*-Cbz threoninate **19** (Figure 1).

The absolute stereochemistry of **15** was confidentially assigned on the basis of its spectral and physicochemical

(13) The main sulfur-containing product isolated by FC after treatment of the NOPR mixture with $NaBH_4$ was identified as (*p*-Tol-S)$_2$.

(14) For a closely related case, see: Van Hijfte, L.; Heydt, V.; Kolb, M. *Tetrahedron Lett.* **1993**, *34*, 4793.

(15) For other examples of stereospecific fragmentations, see: Park, Y. S.; Beak, P. *J. Org. Chem.* **1997**, *62*, 1574 and references therein. We cannot rule out the hypothesis that the retro-aldol reaction might be highly stereospecific and a partial racemization might occur afterward, under NOPR conditions.



25

similarity with a known molecule, differing only for the protecting group of the amino function (ethoxycarbonyl instead of Cbz).[11]

To achieve a better understanding of the mechanism of the NOPR, both diastereomeric substrates **14** and **15** were submitted to reaction in a NMR tube, under the usual conditions. In agreement with TLC monitoring of the reaction, the addition of neat TFAA (5 equiv) to **14** in the presence of *sym*-collidine (3 equiv in CD_3CN at room temperature) instantaneously produced the expected sulfenamide **16**, along with a small amount of methyl *N*-Cbz α-Tfm-α-vinylglycinate sulfenamide **20**. When submitted to the same experimental conditions, the diastereomer **15** immediately afforded a new compound having a different ^1H NMR spectrum from that of the expected sulfenamide **17** (Figure 2). In particular, the signals at 8.18 ppm that are attributable to the ortho protons of the *p*-tolyl ring (with respect to the sulfur atom) and the vicinal 4-methynic proton at 5.82 ppm both exhibit a downfield shift of 0.47 and 1.47 ppm. This fact clearly points to an increased deshielding about the sulfur atom, which can be ascribed to a more electron-poor character and increased valency.

On the basis of the spectral properties above, this intermediate was assigned as the four-membered cyclic σ-sulfurane **27** (Scheme 5).[16]

Within 30 min at room temperature, a complete transformation of **27** into the sulfenamide **17** was observed by NMR. In this case, a small amount of the unsaturated side product **20** was also detected.

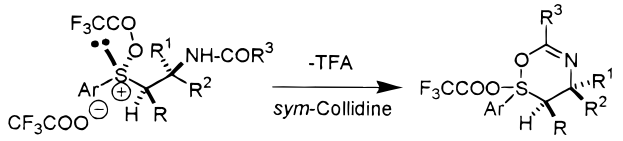
Discussion

The Pummerer reaction is a popular reaction to transform alkyl sulfoxides **28** (Scheme 6) into the corresponding α-substituted sulfides **31**, which can be hydrolyzed to carbonyl compounds **32**.[4]

From the stereochemical point of view, the Pummerer reaction is a self-immolative process, since the stereogenic center migrates from the sulfur atom to the α-carbon. However, relatively few examples of stereospecific Pummerer reactions have been described in the literature.[17] In contrast, many examples of "abnormal" Pummerer reactions are known, some of them with good synthetic usefulness.[4,18] One "abnormal" pathway may occur when the tricoordinate sulfur intermediate **29** (Scheme 6), formed by activation of the sulfinyl oxygen with the electrophile, undergoes reaction with a nucleophile at sulfur, forming a transient σ-sulfurane intermediate **33**. Although nucleophilic attack on tricoordinate sulfur has been reported in a large number of reactions,[19] and the formation of σ-sulfuranes has been often hypothesized in Pummerer-related processes,[20] their isolation or detection by NMR spectroscopy is relatively uncommon.[21] The σ-sulfurane **33** can undergo subsequent fragmentation into the final products, which are usually a sulfide **34** and a trifluoroacetoxy derivative **35**. Such an outcome has been defined earlier as an "interrupted" Pummerer reaction.[22]

The NOPR can be considered a stereospecific intramolecular example of an "interrupted" Pummerer reaction. The complete absence of any products derived from proton removal from the α-sulfinyl position, as was demonstrated by deuterium labeling experiments, is typical of an "interrupted" Pummerer reaction. This evidence, along with the NMR experiments outlined above, strongly supports the picture of kinetic control

(16) The formation of a six-membered σ-sulfurane **38,** via intramolecular trapping of cation **7** by the carbamic oxygen, cannot be ruled out. In that case, the observed sulfenamide products (such as **16, 17**) would arise from rearrangement of **38**. However, we judge such hypothesis quite unlikely, because products having the Ar−S residue attached to the carbamic oxygen have never been either observed or isolated after the NOPR.



7 **38**

(17) (a) Shibata, N.; Matsugi, M.; Kawano, N.; Fukui, S.; Fujimori, C.; Gotanda, K.; Murata, K.; Kita, Y. *Tetrahedron*: *Asymmetry* **1997**, *8*, 303, and references therein. (b) Harwood: L. M.; Lilley, I. A. *Synlett* **1996**, 1010. (c) Abe, H.; Itani, J.; Masunari, C.; Kashino, S.; Harayama, T. *J. Chem. Soc., Chem. Commun.* **1995**, 1197. (d) Craig, D.; Daniels, K.; MacKenzie, A. *Tetrahedron* **1993**, *49*, 11263. (e) Ikeda, M.; Kosaka, K.; Sakakibara, M.; Okano, M. *Heterocycles* **1993**, *35*, 81. (f) Kita, Y.; Shibata, N.; Kawano, N.; Tohjo, T.; Fujimori, C.; Ohishi, H. *J. Am. Chem. Soc.* **1994**, *116*, 5116. (g) Kosugi, H.; Tagami, K.; Takahashi, A.; Kanna, H.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1989**, 935. (h) Ferreira, J. T. B.; Marques, J. A.; Marino, J. P. *Tetrahedron*: *Asymmetry* **1994**, *5*, 641 and references therein. (i) Wolfe, S.; Kazmayer, P.; Auksi, H. *Can. J. Chem.* **1979**, *57*, 2404. (j) Mikolajczyk, M.; Zatorski, A.; Grzejszczak, S.; Costisella, B.; Midura, W. *J. Org. Chem.* **1978**, *43*, 2518. (k) Masuda, T.; Numata, T.; Furukawa, N.; Oae, S. *Chem. Lett.* **1977**, 903. (l) McCormick, J. E.; McElhinney, R. S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 93. (m) Stridsberg, B.; Allenmark, S. *Acta Chem. Scand.* **1976**, *B30*, 219. (n) Numata, T.; Itoh, O.; Oae, S. *Tetrahedron Lett.* **1979**, *20*, 1869. (o) Numata, T.; Itoh, O.; Yoshimura, T.; Oae, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 257. (p) Itoh, O.; Numata, T.; Yoshimura, T.; Oae, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 266. (q) Oae, S.; Itoh, O.; Numata, T.; Yoshimura, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 270. (r) Kita, Y.; Shibata, N. *Synlett* **1996**, 289. (s) Kita, Y.; Shibata, N.; Fukui, S.; Fujita, S. *Tetrahedron Lett.* **1994**, *35*, 9733. (t) Volonterio, A.; Zanda, M.; Bravo, P.; Fronza, G.; Cavicchio, G.; Crucianelli, M. *J. Org. Chem.* **1997**, *62*, 8031. (u) Bravo, P.; Crucianelli, M.; Fronza, G.; Zanda, M. *Synlett* **1996**, 249.

(18) For some recent representative examples, see: (a) Kersey, I. D.; Fishwick, C. W. G.; Findlay, J. B. C.; Ward, P. *Tetrahedron* **1995**, *51*, 6819. (b) Davis, F. A.; Reddy, V. A. *Tetrahedron Lett.* **1996**, *37*, 4349. (c) Pyne, S. G.; Hajipour, A. R. *Tetrahedron* **1994**, *50*, 13501.

(19) See, for example: (a) Bennasar, M. L.; Jiménez, J.-M.; Sufi, B. A.; Bosch, J. *Tetrahedron Lett.* **1996**, *37*, 9105. (b) Sharma, A. K.; Ku, T.; Dawson, A. D.; Swern, D. *J. Org. Chem.* **1975**, *40*, 2758. (c) Wright, S. W.; Abelman, M. M.; Bostrom, L. L.; Corbett, R. L. *Tetrahedron Lett.* **1992**, *33*, 153. (d) Kita, Y.; Shibata, N.; Kawano, N.; Tohjo, T.; Fujimori, C.; Matsumoto, K.; Fujita, S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2045. (e) Amat, M.; Bennasar, M.-L.; Hadida, S.; Sufi, B. A.; Zulaica, E.; Bosch, J. *Tetrahedron Lett.* **1996**, *37*, 5217. (f) Amat, M.; Hadida, S.; Pshenichnyi, G.; Bosch, J. *J. Org. Chem.* **1997**, *62*, 3158. (g) Kawasaki, T.; Suzuki, H.; Sakata, I.; Nakanishi, H.; Sakamoto, M. *Tetrahedron Lett.* **1997**, *38*, 3251. (h) Furukawa, N.; Kawada, A.; Kawai, T.; Fujihara, H. *J. Chem. Soc., Chem. Commun.* **1985**, 1266. (i) Schostarez, H. J.; Schwartz, T. M. *J. Org. Chem.* **1996**, *61*, 8701. (j) Yamamoto, K.; Yamazaki, S.; Murata, I.; Fukuzawa, Y. *J. Org. Chem.* **1987**, *52*, 5239.

(20) See ref 17a and references therein. See also: (a) Numata, T.; Oae, S. *Tetrahedron Lett.* **1977**, *18*, 1337.

(21) See, for example: (a) Hayes, R. A.; Martin, J. C. In *Organic Sulfur Chemistry*; Bernardi, F., Csizmadia, I. G., Mangini, A., Eds.; Elsevier: New York, 1985; pp 408−483. (b) Kaplan, L. J.; Martin, J. C. *J. Am. Chem. Soc.* **1973**, *95*, 793. (c) Adzima, L. J.; Chiang, C. C.; Paul, I. C.; Martin, J. C. *J. Am. Chem. Soc.* **1978**, *100*, 953. For some recent examples: (d) Hornbuckle, S. F.; Livant, P.; Webb, T. R. *J. Org. Chem.* **1995**, *60*, 4153. (e) Zhang, J.; Saito, S.; Koizumi, T. *J. Am. Chem. Soc.* **1998**, *120*, 1631. (f) Szabó, D.; Szendeffy, S.; Kapovits, I.; Kucsman, A.; Czugler, M.; Kálmán, A.; Nagy, P. *Tetrahedron*: *Asymmetry* **1997**, *8*, 2411.

(22) (a) Bates, D. K.; Sell, B. A.; Picard, J. A. *Tetrahedron Lett.* **1987**, *28*, 3535. (b) Bates, D. K.; Winters, R. T.; Picard, J. A. *J. Org. Chem.* **1992**, *57*, 3094. (c) Xia, M.; Chen, S.; Bates, D. K. *J. Org. Chem.* **1996**, *61*, 9289.

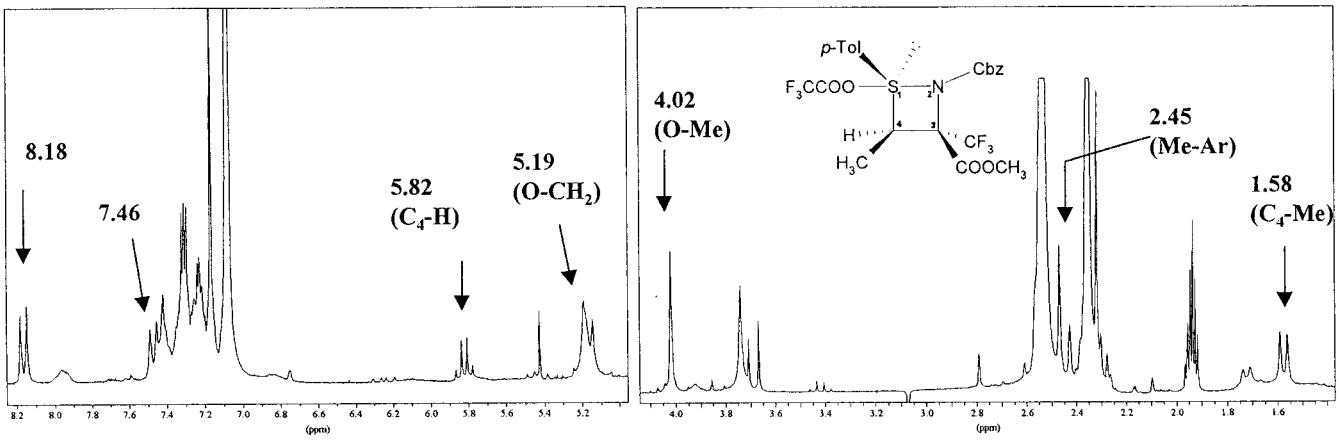
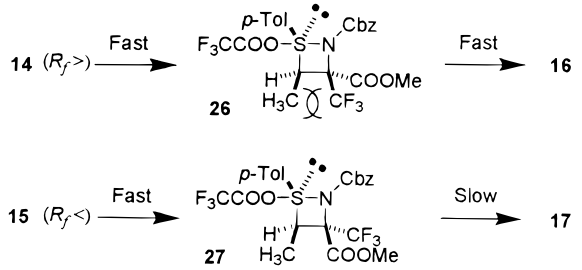


Figure 2. ^{1}H NMR spectrum of **27**.

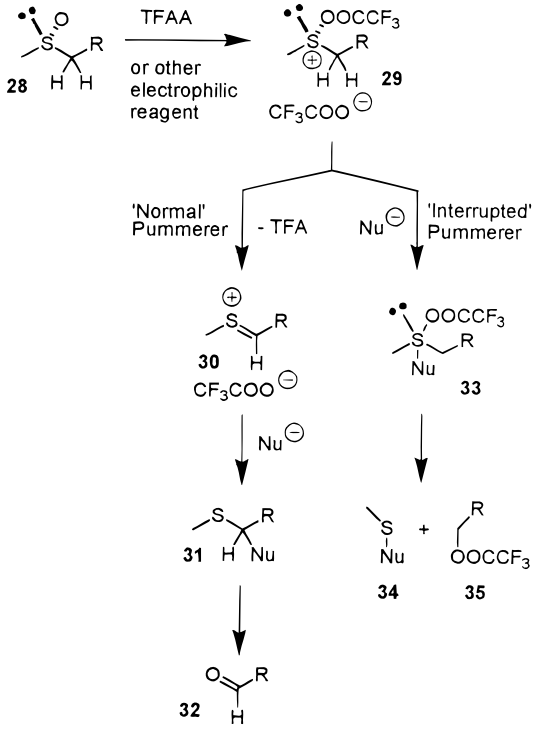
Scheme 5



operating in the NOPR, where the driving force is represented by the fast and irreversible formation of the intermediate four membered σ-sulfuranes, such as **26** and **27**.[23] These intermediates have been shown to undergo a spontaneous rearrangement, in which the O−S bond breaks and the CF_3COO group migrates to the α-sulfinyl carbon producing inversion of configuration and C−S bond breaking. The reasons for the uncommon stability of the σ-sulfurane **27** are presently unclear.[24] However, its high degree of ring substitution, as well as the apparent absence of strain, might slow the rearrangement into **17** for steric reasons. In contrast, the unfavorable cis-interaction experienced by the CH_3 and the stereoelectronically demanding CF_3 group[25] of the diastereomeric σ-sulfurane **26** should force the rearrangement to occur rapidly in order to release the strain.

According to this mechanistic description, the α-stereocenter is never lost during the course of the reaction. This is in agreement with the observation that the stereocontrol depends exclusively on the configuration of the α-sulfinyl carbon. Indeed, if the NOPR would involve a dissociated sulfenium ion, like **30** (Scheme 6), both diastereomeric substrates **14** and **15** should produce the same product.

Scheme 6



Oae et al. demonstrated that σ-sulfuranes can undergo a "ligand coupling reaction" which takes place with retention of configuration at the α-sulfinyl carbon.[26] In contrast, the NOPR takes place with inversion of configuration, which means that a different pathway must be followed (Scheme 7).

The most likely one involves dissociation of the σ-sulfurane (for example **27**) into an intimate ion-pair **36**, which undergoes recombination via S_N2-type attack of the generated trifluoroacetate anion to the sulfur-substituted stereogenic carbon of the resulting sulfonium cation. To obtain some evidence regarding the "intramolecular" nature of the NOPR, we performed a competition experiment using a nucleophilic base instead of *sym*-collidine (Scheme 8).

We reasoned that since the trifluoroacetate anion is a relatively weak nucleophile, if the displacement would

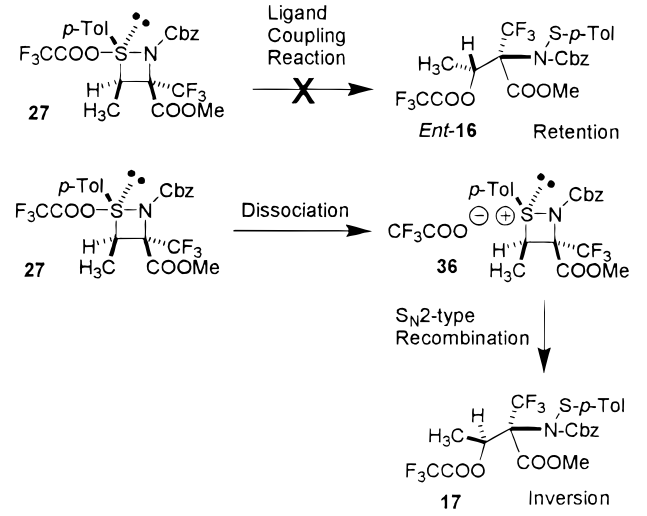
(23) For some examples of four membered cyclic compunds featuring an S−N bond: (a) Tornus, I.; Schaumann, E.; Mayer, R.; Adiwidjaja, G. *Liebigs Ann.* **1995**, 1795. (b) Baxter, N. J.; Laws, A. P.; Rigoreau, L.; Page, M. I. *J. Chem. Soc., Chem. Commun.* **1997**, 2037. (c) Warrener, R. N.; Amarasekara, A. S. *Synlett* **1997**, 167.

(24) σ-Sulfuranes are known to be quite stable when the axial ligands contain highly electronegative heteroatoms. However, under NOPR conditions the transformations β-sulfinylamine → σ-sulfurane → trifluoroacetoxy-sulfenamide were always found to be very fast, with the only remarkable exception of **27** → **17** presented in this work.

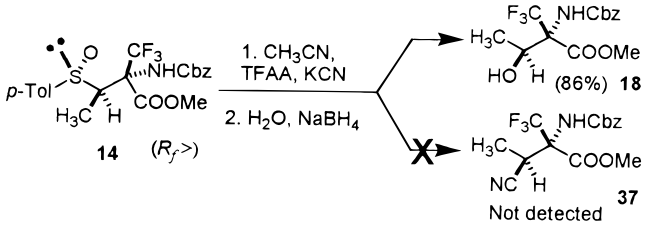
(25) (a) Smart, B. E. In *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E., Tatlow, J. C., Smart, B. E., Eds.; Plenum Press: New York, 1994; pp. 80−81. (b) Nagai, T.; Nishioka, G.; Koyama, M.; Ando, A.; Miki, T.; Kumadaki, I. *Chem. Pharm. Bull.* **1991**, *39*, 233.

(26) Oae, S.; Kawai, T.; Furukawa, N.; Iwasaki, F. *J. Chem. Soc., Perkin Trans. 2* **1987**, 405.

Scheme 7



Scheme 8



not occur within the intimate ion pair **36**, addition of the remarkably more nucleophilic cyanide anion[27] to the reaction mixture should give competitive displacement of the sulfinyl residue, thus producing the corresponding nitrile **37**. In agreement with our "intramolecular" hypothesis, a NOPR experiment using KCN instead of *sym*-collidine as base, afforded the hydroxylated product **18** in very good yields, with no trace of the nitrile **37** detected in the crude mixture. The last question to be answered was how the side products **20,21** are formed during the NOPR. More than likely, **20** and **21** arise from competitive deprotonation of the methyl β-hydrogen of the cyclic sulfonium cation in **36** by trifluoroacetate (or alternatively by *sym*-collidine), resulting in β-elimination. Formation of related unsaturated side-products was observed by Oae in closely related "interrupted" Pummerer reactions.[28]

In summary, this study provides a deeper insight into the mechanism of the NOPR, additional evidence for inversion of configuration at the α-sulfinyl carbon stereocenter, and a further application of the NOPR for the synthesis of densely functionalized and substituted α-Tfm-threoninates. We believe that the NOPR process could open up new synthetic perspectives and lead to new applications of the sulfinyl auxiliary in organic synthesis.

Experimental Section

General Procedure. For general experimental information see ref 29. X-ray diffraction data were collected from colorless crystal platelets (size 0.05 × 0.2 × 1.0 for **14** and 0.08 × 0.3 × 0.06 mm for **25**) with graphite-monochromated Cu Kα radiation (1.541 78 Å). The structures were solved by direct methods using SIR92,[30] and refined by full-matrix least squares on F^2, using SHELXL97.[31] Non-hydrogen atoms were refined anisotropically. All hydrogen atoms were located at calculated positions and refined with group temperature factors.

Synthesis of β-Sulfinylamines (R_S,2*S*,3*R*)-14 and (R_S,2*R*,3*R*)-15. Substrates **14** and **15** were obtained, according to a published method,[11] with an overall yield of 55%, in a nearly equimolar ratio.

(R_S,2*S*,3*R*)-2-Benzyloxycarbonylamino-3-(toluene-4-sulfinyl)-2-trifluoromethylbutyric acid methyl ester (14): mp (*i*-Pr_2O) 144−146 °C; $[\alpha]_D$ +125.6 (*c* 0.83, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.39 (br signal, 1H), 7.70−7.30 (m, 9H), 5.12 (br s, 2H), 3.82 (br s, 3H), 3.38 (qq, J = 7.3, 1.3 Hz, 1H), 2.43 (br s, 3H), 0.89 (dq, J = 7.3, 1.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 164.9, 154.5, 144.0, 138.9, 135.9, 130.3, 130.1, 128.5, 128.2, 126.2, 124.5 (q, J = 289.0 Hz), 68.1 (q, J = 28.0 Hz), 67.4, 61.8, 53.5, 21.6, 11.0; ^{19}F NMR ($CDCl_3$) δ − 69.47 (br s); MS (EI, 70 eV) *m*/*z* 458 (M^+ + 1, 1), 139 (10), 91 (100). Crystal data: $C_{21}H_{22}F_3NO_5S$, fw 457.46; orthorhombic, space group $P2_12_12_1$; a = 6.980(1) Å, b = 10.783(1) Å, c = 29.886(1) Å; V = 2249(2) Å^3; Z = 4; D_c = 1.351 g/cm^3; μ = 1.789 mm^{-1}; F(000) = 952; final R_1 = 11.29, wR_2 (all data) = 21.78, S = 1.001; Flack's parameter[32] = 0.05(5); extinction coefficient = 0.0023(5); largest peak and hole = 0.243 and −0.244 eÅ^{-3}. Some disorder involving the aromatic ring (C51 to C56) together with the poor quality of the crystals results in the relatively high value of the disagreement factor.

(R_S,2*R*,3*R*)-15: oil; $[\alpha]_D$ +55.0 (*c* 0.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.81 (br signal, 1H), 7.70−7.20 (m, 9H), 5.14 and 5.08 (br d, J = 12.2 Hz, 2H), 3.87 (s, 3H), 3.39 (q, J = 7.2 Hz, 1H), 2.42 (br s, 3H), 0.93 (d, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 165.1, 154.6, 143.6, 138.1, 135.5, 130.1, 128.5, 128.3, 128.0, 126.2, 123.7 (q, J = 288.0 Hz), 72.0 (q, J = 30.8 Hz), 67.5, 60.0, 54.2, 21.5, 11.7; ^{19}F NMR ($CDCl_3$) δ − 73.86 (br s); FT IR (cm^{-1}) 3246, 1755, 1739.

(2*S*,3*S*)-2-Benzyloxycarbonyl[*N*-(toluene-4-thio)amino]-3-trifluoroacetoxy-2-trifluoromethylbutyric Acid Methyl Ester (16). This compound was not isolated, but just detected by NMR of crude NOPR of **14**: ^{1}H NMR (CD_3CN) δ 7.40−7.10 (m, 9H), 6.05 (br signal, 1H), 5.20 (br s, 2H), 3.68 (s, 3H), 2.32 (br s, 3H), 1.55 (br signal, 3H); ^{19}F NMR (CD_3CN) δ −63.9 and −72.10 (br s, 6F).

(2*R*,3*S*)-17. To a cooled (0 °C) and stirred solution of **15** (35 mg, 0.076 mmol) in 0.8 mL of acetonitrile were added 31 μL of *sym*-collidine (0.23 mmol), followed by 54 μL of TFAA (0.38 mmol) under nitrogen. After 5 min, the reaction was allowed to stay at rt, under stirring, until TLC analysis (7/3 *n*-hexane/ethyl acetate) showed the disappearance of the starting material (about 40 min). After removal of the solvent, the crude was purified by FC (*n*-hexane/ethyl acetate from 90/10 to 80/20) giving 35 mg of (2*R*,3*S*)-**17** (83% yield): oil; $[\alpha]_D$ −11.5 (*c* 0.57, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.40−7.00 (m, 9H), 5.95 (br q, J = 6.7 Hz, 1H), 5.19 (br s, 2H), 3.73 (s, 3H), 2.32 (br s, 3H), 1.55 (d, J = 6.7 Hz, 3H); ^{19}F NMR ($CDCl_3$) δ −68.20 and −76.40 (br s, 6F).

Nonoxidative Pummerer Reaction of 14 and 15: Synthesis of Methyl *N*-CBz-α-trifluoromethyl-*allo*-threoninate (18) and Methyl *N*-Cbz-α-trifluoromethylthreoninate (19). To a cooled (0 °C) and stirred solution of **14** (250 mg, 0.55 mmol) in 4 mL of acetonitrile, under nitrogen, was added *sym*-collidine (218 μL, 1.64 mmol), followed by TFAA (387 μL, 2.73 mmol). After 2 min at room temperature, TLC analysis (7/3 *n*-hexane/ethyl acetate) showed the disappearance of the starting material. To the reaction mixture, cooled longer at 0 °C, was added one drop of H_2O, and portionwise one drop of water was added at 0 °C, followed by an excess of $NaBH_4$ (about 3 equiv). After 2 min, the reaction was warmed

(27) March. J. *Advanced Organic Chemistry*; Wiley: New York, 1992; pp 348−352.
(28) Uchida, Y.; Oae, S. *Gazz. Chim. Ital.* **1987**, *117*, 649.
(29) Fustero, S.; Navarro, A.; Pina, B.; Asensio, A.; Bravo, P.; Crucianelli, M.; Volonterio, A.; Zanda, M. *J. Org. Chem.* **1998**, *63*, 6210.
(30) Altomare, A.; Cascarano, G.; Guagliardi, A. *J. Appl. Crystallogr.* **1993**, *26*, 343.
(31) Sheldrick, G. M., *SHELXL97*, *Program for crystal structure refinement*; University of Göttingen; Göttingen, Germany, 1997.
(32) Flack, H. D. *Acta Crystallogr.* **1983**, *A 39*, 876.

at rt and stirred for 1.5 h. The mixture was quenched, at 0 °C, with a saturated aqueous solution of NH_4Cl and extracted with ethyl acetate (3 × 5 mL). The collected organic layers were washed twice with a 1 N HCl solution to remove *sym*-collidine and then with aqueous $NaHCO_3$. After routine workup, the crude was purified by FC (80/20 *n*-hexane/ethyl acetate) affording 160 mg of (2*S*,3*S*)-**18** (87% yield).

(2*S*,3*S*)-2-Benzyloxycarbonylamino-3-hydroxy-2-trifluoromethylbutyric acid methyl ester (18): mp (*i*-Pr_2O) 68−70 °C; $[\alpha]_D$ −7.65 (*c* 0.34, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.50−7.20 (m, 5H), 6.26 (br signal, 1H), 5.58 (br d, J = 11.5 Hz, 1H), 5.18 and 5.14 (br d, J = 12 Hz, 2H), 4.65 (dq, J = 11.5, 6.5 Hz, 1H), 3.90 (s, 3H), 1.15 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.3, 156.1, 153.3, 128.6, 128.5, 128.3, 123.5 (q, J = 287.9 Hz), 70.1 (q, J = 27.7 Hz), 68.2, 68.2, 54.7, 18.2; ^{19}F NMR ($CDCl_3$) δ −72.55 (br s); FT IR (cm^{-1}) 3393 (br), 1753, 1710; MS (EI, 70 eV) m/z 335 (M^+, 2), 108 (29), 91 (100).

The same experimental conditions described above (with the exception of longer reaction time in the first step: 40 min at room temperature instead of 2 min) were applied for the synthesis of product (2*R*,3*S*)-**19** obtained, as an oil, in 70% yield.

(2*R*,3*S*)-19: $[\alpha]_D$ −5.64 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.50−7.20 (m, 5H), 5.64 (br signal, 1H), 5.16 (br s, 2H), 4.49 (br q, J = 6.6 Hz, 1H), 3.90 (s, 1H), 3.86 (br s, 3H), 1.36 (dd, J = 6.6, 1.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.0, 155.8, 135.4, 128.6, 128.5, 128.3, 123.4 (q, J = 287.0 Hz), 70.0 (q, J = 27 Hz), 69.0, 68.0, 53.7, 18.5; ^{19}F NMR ($CDCl_3$) δ −70.94 (br s).

2-Benzyloxycarbonyl[*N*-(toluene-4-thio)amino]-2-trifluoromethylbut-3-enoic Acid Methyl Ester (20). Observed by NMR as a byproduct from the crude of the NOPR described above: ^{1}H NMR ($CDCl_3$) δ 7.50−7.00 (m, 9H), 6.16 (m, 1H), 5.43 and 5.42 (m, 2H), 5.19 (br d, 2H), 3.72 (s, 3H), 2.31 (br s, 3H).

2-Benzyloxycarbonylamino-2-trifluoromethylbut-3-enoic Acid Methyl Ester (21). Observed by NMR as a byproduct from the crude of the NOPR described above: ^{1}H NMR ($CDCl_3$) δ 7.50−7.30 (m, 5H), 6.19 (m, 1H), 5.57 (br s, 1H), 5.57 and 5.55 (m, 2H), 5.13 (br s, 2H), 3.86 (s, 3H); ^{19}F NMR ($CDCl_3$) δ −75.71 (br s).

Nonoxidative Pummerer Reaction of Substrates 14 and 15 in the Presence of K_2CO_3: Isolation of Byproducts 22−24. To a stirred solution of **14** (47 mg, 0.103 mmol) and *sym*-collidine (41 μL, 0.308 mmol) in acetonitrile (1 mL) under a nitrogen atmosphere at 0 °C was added dropwise neat TFAA (73 μL, 0.514 mmol). After 2 min at rt, TLC analysis (7/3 *n*-hexane/ethyl acetate) showed the disappearance of starting material. The reaction mixture was slowly added with a 50% aqueous solution of potassium carbonate at 0 °C, until pH 8 was reached. After 10 min, an excess of $NaBH_4$ (about 3 equiv) was added portionwise. After 2 min, the reaction was warmed at room temperature and stirred for 1.5 h. The reaction was quenched and worked up as described above. After purification by FC (*n*-hexane/ethyl acetate from 80/20 to 70/30) the main product isolated was **24** (71% yield) along with minor amounts of **22** and **23**.[5b]

2-Benzyloxycarbonylamino-3,3,3-trifluoropropionic acid methyl ester (22): ^{1}H NMR ($CDCl_3$) δ 7.50−7.30 (m, 5H), 5.67 (br d, J = 9.4 Hz, 1H), 5.16 (br s, 2H), 5.07 (dq, J = 9.4, 7.7 Hz, 1H) 3.86 (s, 3H); ^{19}F NMR ($CDCl_3$) δ − 74.24 (br d, J = 7.7 Hz).

2-Benzyloxycarbonylamino-3,3,3-trifluoropropionic acid (23): ^{1}H NMR ($CDCl_3$) δ 16.65 (br signal, 1H), 7.50−7.20 (m, 5H), 5.70 (d, J = 9.8 Hz, 1H), 5.62 (dq, J = 9.8, 5.5 Hz, 1H), 5.15 (br s, 2H); ^{19}F NMR ($CDCl_3$) δ − 83.05 (br d, J = 5.5 Hz).

(2-Hydroxy-1-trifluoromethylethyl)carbamic acid benzyl ester (24): $[\alpha]_D$ +5.92 (0.41, $CHCl_3$) (ca. 49% ee); ^{1}H NMR ($CDCl_3$) δ 7.50−7.20 (m, 5H), 5.49 (d, J = 9.5 Hz, 1H), 5.15 (br s, 2H), 4.38 (m, 1H), 3.98 and 3.86 (m, 2H); ^{19}F NMR ($CDCl_3$) δ − 75.16 (br d, J = 7.9 Hz). The same reaction performed on the substrate **15** gave **23** as main product (ca. 45% yield).

Synthesis of *p*-Br-Benzoate (2*R*,3*S*)-25. To a solution of **19** (40 mg, 0.119 mmol) and 2 equiv of triethylamine in 2 mL of dichloromethane were added 29 mg of *p*-Br-benzoyl chloride (1.1 equiv) dissolved in 1 mL of CH_2Cl_2 and a catalytic amount of DMAP at room temperature, under stirring. After 45 min, TLC control (7/3 *n*-hexane/ethyl acetate) showed the disappearance of starting material. After removal of solvent, the crude was purified by FC, affording 58 mg (94% yield) of (2*R*,3*S*)-**25**.

(2*R*,3*S*)-4-Bromobenzoic acid 2-benzyloxycarbonylamino-3,3,3-trifluoro-2-methoxycarbonyl-1-methylpropyl ester (25): mp (*i*-Pr_2O) 118−120 °C; $[\alpha]_D$ +31.93 (*c* 0.56, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.85 (d, J = 8.5 Hz, 2H), 7.59 (d, J = 8.5 Hz, 2H), 7.35 (m, 5H), 5.82 (q, J = 6.6 Hz, 2H), 5.73 (br signal, 1H), 5.12 (br s, 2H), 3.85 (br signal, 3H), 1.51 (dd, J = 6.6, 1.2 Hz, 3H); ^{19}F NMR ($CDCl_3$) δ −69.89 (s, 3F). Crystal data: $C_{21}H_{19}BrF_3NO_6$, fw 518.28; monoclinic, space group *C*2; a = 24.665(3) Å, b = 7.336(1) Å, c = 14.690(2) Å, β = 117.78(1)°; V = 2351.7(5) Å^3; Z = 4; D_c = 1.464 g/cm^3; μ = 2.924 mm^{-1}; F(000) = 1048; final R_1 = 9.27, wR_2 (all data) = 18.80, S = 1.076; Flack's parameter[32] = 0.02(4); extinction coefficient = 0.0004(1); largest peak and hole = 0.309 and −0.367 e Å^{-3}.

Nonoxidative Pummerer Reaction Performed on 15 in an NMR Tube To Detect the σ-Sulfurane 27. To a NMR tube containing 65 mg of **15** (0.142 mmol) and 56 μL (0.43 mmol) of *sym*-collidine dissolved in 0.5 mL of CD_3CN were added 98 μL of TFAA (0.71 mmol) at room temperature. After 4 min, ^{1}H and ^{19}F NMR spectra were recorded giving the following signals attributable, as described in the text, to the σ-sulfurane **27**: ^{1}H NMR (CD_3CN) δ 8.18 and 7.46 (m, 4H), 7.40−7.20 (m, 5H), 5.82 (q, J = 7.3 Hz, 1H), 5.19 (br s, 2H), 4.02 (s, 3H), 2.45 (br s, 3H), 1.58 (d, J = 7.3 Hz, 3H); ^{19}F NMR (CD_3CN) δ −63.50 and −72.20 (br s, 6F).

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of compounds **14**, **15**, **18**, and **19** and crystal data of compounds **14** and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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