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(*S*)-2-[(*R*)-Fluoro(phenyl)methyl]oxirane: A General Reagent for Determining the ee of α-Chiral Amines

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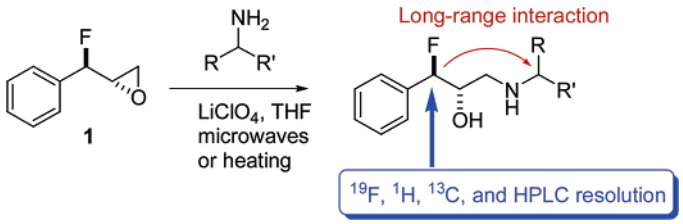
ABSTRACT



(*S*)-2-[(*R*)-Fluoro(phenyl)methyl]oxirane is a new, synthetic, yet enantiopure, chiral resolution reagent, readily obtained from enantiopure (2*S*,3*S*)-phenylglycidol, that reacts with a variety of α-chiral primary and secondary amines in a straightforward manner through a regioselective ring-opening. Diastereomeric products are easily identified and quantified by ^{19}F, ^{1}H, and ^{13}C NMR and by HPLC, which makes this fluorinated compound a most versatile reagent for the analysis of scalemic mixtures of amines.

Since enantiopure compounds are increasingly important in the chemical and pharmaceutical sciences due to their particular properties, and especially because one enantiomer usually behaves differently than its counterpart when interacting with a biological system,[1,2] the need to develop fast and efficient methods to determine the enantiomeric composition of a synthetic scalemic mixture is in demand. Chiral chromatographic methods (HPLC, GC) have simplified and quickened the analysis of many products,[3] but chiral stationary phases are expensive and much more sensitive to physical and chemical agression than regular chromatography columns. Moreover, their use always implies trial-and-error iterations to optimize the phase and separation conditions, whenever it is possible to separate the compounds. Therefore, the classical use of resolution reagents chemically bonded to the individual components of the mixture to be analyzed is still in use.[4] These methods are very reliable and can be adapted to several common techniques such as NMR or HPLC with no need of any modification. In some cases, it is even possible to determine the absolute configuration of the new compound.[4d] Thus, the development of new resolution reagents with improved properties is of practical interest.

It is generally admitted that resolution reagents should fulfill the following requisites in order to achieve general interest: (a) straightforward preparation to make it easily accessible to most chemists, (b) fast and clean reactivity toward the substrate to be analyzed, and (c) absence of kinetic

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(1) (a) *Chirality in Industry*; Collins, A. N., Sheldrake, G. N., Crosby, J., Eds.; John Wiley and Sons: Chichester, 1992. (b) *Chirality in Industry II*; Collins, A. N., Sheldrake, G. N., Crosby, J., Eds.; John Wiley and Sons: Chichester, 1997.

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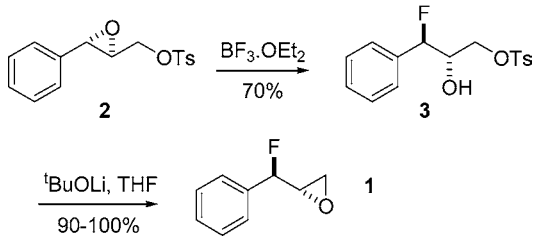
Scheme 1. Preparation of Resolution Reagent **1** from (2*S*,3*S*)-Phenylglycidyl *p*-Toluenesulfonate (**2**)



resolution to ensure that the enantiomeric ratio determined corresponds to that of the original sample. Moreover, the more techniques that are able to distinguish the diastereomers formed, the easier the determination will be. In this respect it is desirable that NMR-active heteroatoms, such as ^{19}F, are embedded in the structure in addition to ^{1}H and ^{13}C in order to facilitate the analysis by NMR techniques.[5] In much the same manner, the presence of UV-active groups (aromatic rings) that allow simple detection in conventional HPLC is also an advantage.

In this paper, we present a new derivatization reagent, (*S*)-2-[(*R*)-fluoro(phenyl)methyl]oxirane (**1**),[6] that can be readily prepared from (2*S*,3*S*)-phenylglycidyl tosylate (**2**) which, in turn, ultimately arises from the Sharpless epoxidation of cinnamyl alcohol with inexpensive natural tartrate ligands.

Regioselective and stereospecific ring opening of **2** with BF_3 yielded (2*S*,3*R*)-3-fluoro-2-hydroxy-3-phenylpropyl *p*-toluenesulfonate (**3**),[7] which was converted into **1** in essentially quantitative yield by intramolecular nucleophilic displacement induced by lithium *tert*-butoxide (Scheme 1). This procedure allows for the preparation of enantiopure **1** on a multigram scale without any difficulty.[8,9] To our knowledge, **1** is the first chiral derivatizing agent introduced through the ring-opening of an epoxide that has been successfully tested.

With fluoroepoxide **1** in hand, the ring-opening of the epoxide with α-chiral primary amines was next tested. This class of amines is present in many natural substances and in active pharmaceutical ingredients, so that the development of methods for the easy and reliable determination of their enantiomeric composition is a matter of interest. We found (Scheme 2) that either upon conventional heating or microwave irradiation the epoxide ring opening with *rac*-α-methyl benzylamine (**4a**) took place in excellent yield and with complete regioselectivity using lithium perchlorate as a promoter[10] and THF as the solvent. Microwave irradiation consistently afforded higher yields, and few decomposition

Scheme 2. Reaction of **1** with α-Chiral Amines

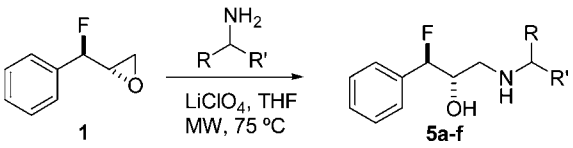
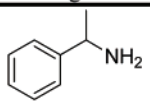
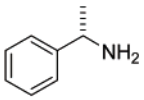
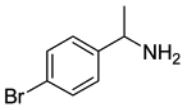
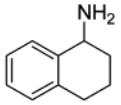
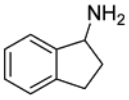
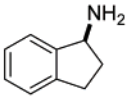
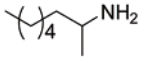
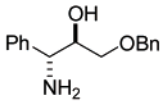
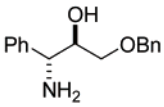
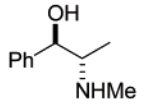
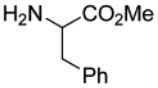
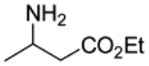


Table 1. Yields and Main NMR Signals Associated to the CHF Group of Diastereomers Obtained by Reaction with the Derivatization Reagent **1**

	starting amine	product (yield [%][a])	δ [ppm]
rac-**4a**		**5a** (92)	^{19}F: -186.8; -188.8 ^{1}H: 5.38; 5.33 ^{13}C: 95.8; 95.7
(*S*)-**4b**		(*S*)-**5a** (92)	^{19}F: -186.8 ^{1}H: 5.33 ^{13}C: 95.7
rac-**4b**		**5b** (83)	^{19}F: -185.8; -188.2 ^{1}H: 5.35; 5.32 ^{13}C: 95.8; 95.6
rac-**4c**		**5c** (77)	^{19}F: -187.1; -188.6 ^{1}H: 5.49; 5.45 ^{13}C: 95.8; 95.6
rac-**4d**		**5d** (80)	^{19}F: -187.3; -187.9 ^{1}H: 5.45; 5.40 ^{13}C: 95.9; 95.7
(*S*)-**4d**		(*S*)-**5d** (83)	^{19}F: -187.9 ^{1}H: 5.45 ^{13}C: 95.7
rac-**4e**		**5e** (50)	^{19}F: -187.6; -187.7 ^{1}H: 5.30[b] ^{13}C: 95.80; 95.78
rac-**4f**		**5f** (74)	^{19}F: -183.5; -186.0 ^{1}H: 5.43; 5.33 ^{13}C: 95.8; 95.4
(1*R*, 2*R*)-**4f**		(**1*R*, 2*R***)-**5f** (75)	^{19}F: -186.5 ^{1}H: 5.33 ^{13}C: 95.8
rac-**4g**		**5g** (60)[c]	^{19}F: -185.2; -185.9 ^{1}H: 5.19; 5.17 ^{13}C: 95.3; 95.2
rac-**4h**		**5h** (70)	^{19}F: -188.9; -189.1 ^{1}H: 5.31; 5.22 ^{13}C: 95.4; 95.3
rac-**4i**		**5i** (72)	^{19}F: -187.0; -187.1 ^{1}H: 5.38; 5.37 ^{13}C: 95.9; 95.8

[a] Isolated yield after flash chromatography. [b] No signal separation. [c] Experimental conditions: 10 mol % of $Cu(BF_4)_2 \cdot 6H_2O$, acetonitrile, 2 h, 75 °C (MW).

byproducts were observed compared to the thermal reaction; therefore, this activation was preferentially used thereafter.

The optimized procedure for complete conversion of the amine under scrutiny consisted, thus, in irradiating with microwaves the mixture of 0.7 equiv of racemic amine (**4**), 1 equiv of enantiopure terminal epoxide, and 1 equiv of $LiClO_4$ in THF at for 90 min, with the maximum temperature set at 75 °C, in a pressure tube. We applied this procedure to a family of structurally diverse racemic amines and recorded in all cases ^{1}H, ^{13}C, and ^{19}F NMR spectra in order

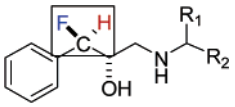


Figure 1. Most suitable nuclei for diastereomeric composition estimation in amines **5**.

to find out the most convenient way to determine the diastereomeric composition (Table 1).

Very interestingly, all three distinct nuclei present at the fluorine bearing chiral center were differentially perturbed by the chiral center α to nitrogen, which is located four bonds away, and originated different sets of signals for each diastereomer (Figure 1).

^{19}F NMR was superior in all cases, since only two sets of clearly separated signals, remote from those due to the initial fluoroepoxide, appeared in the spectra. These signals allowed easy integration and, hence, a simple evaluation of diastereomeric (enantiomeric) composition. As mentioned above, the ^{1}H and ^{13}C NMR spectra also presented sets of signals corresponding to the methyne moiety showing good line separation and making their integration feasible.

We have collected in Table 1 a summary of the studied amines (**4a**−**i**) and the chemical shifts for the ^{19}F, ^{1}H, and ^{13}C signals corresponding to the considered center in the two diastereomers formed by the ring-opening reaction. As an example of signal separation, the regions of the ^{1}H, ^{13}C, and ^{19}F NMR spectra of interest for analytical purposes of **5a** obtained from racemic **4a** and from (*S*)-**4a** are shown in Figure 2.

From a preparative point of view, the reaction worked nicely for both acyclic (**4a**,**b**) and cyclic (**4c**,**d**) primary amines, somewhat lower yields being recorded with long-chain amines (**4e**). Even a more functionalized substrate like **4f**, also containing an alcohol and ether functions,[11] could be successfully used in the ring-opening of **1**. Racemic ephedrine **4g** could be used as substrate as well, showing how secondary amines with extra functional groups (alcohol) are able to react with fluoroepoxide **1**. Phenylalanine methyl

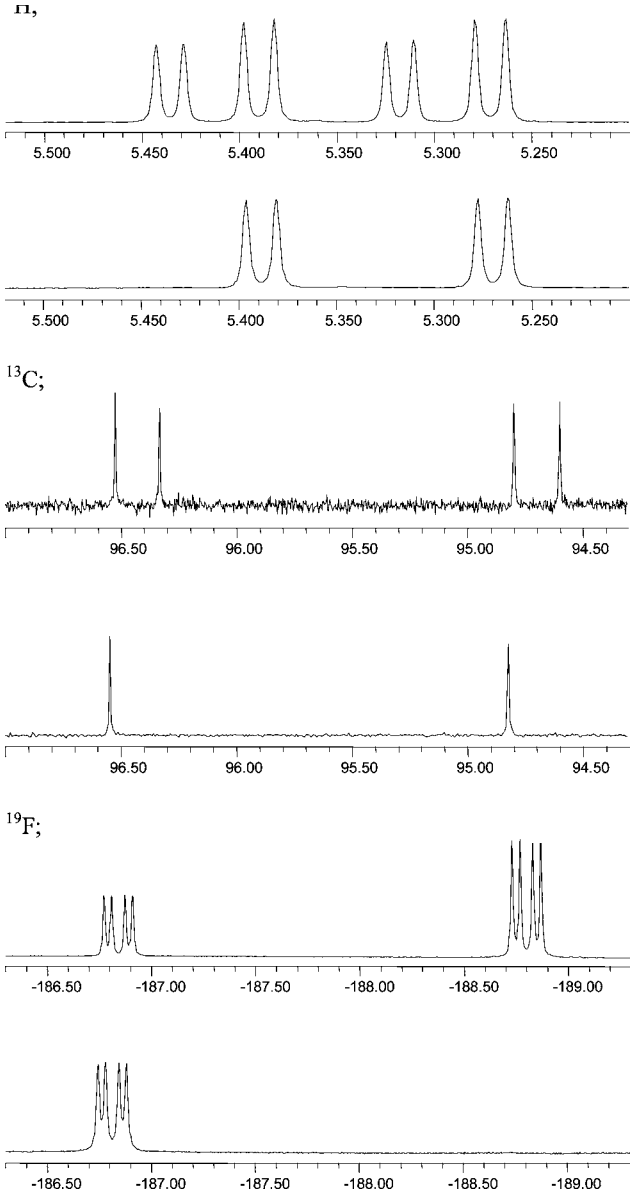


Figure 2. NMR spectra of the CHF region of the α-methyl benzylamine compound, **5a** (partially resolved after flash chromatography), and (*S*)-**5a**.

ester and *β*-amino butanoic acid methyl ester (products **5h** and **5i**) were suitable substrates as well. In this way, the enantiomeric composition of a wide variety of nitrogen-containing compounds could be analyzed using the present method.

To ensure that no kinetic resolution happened while the reaction was in course, the reaction crudes were analyzed at different conversion levels for α-methyl benzylamine. In all cases, the ring-opening product was a perfect 1:1 mixture of diastereomers. In addition, the use of either enantiopure or racemic amines led to the same yields of ring-opening products under identical conditions.

It must be pointed out that other NMR signals are also suitable for the determination of the diastereomeric (enan-

(5) For key references on some F-containing chiral derivatizating agents, see the following. MTPA: (a) Dale, L. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143. CFTA and CFPA: (c) Takeuchi, Y. *J. Fluorine Chem.* **2000**, *105*, 215 and references therein. AFPA: (d) Apparu, M.; Ben Tiba, Y.; Léo, P.-M.; Hamman, S.; Coulombeau, C. *Tetrahedron: Asymmetry* **2000**, *11*, 2885 and references therein. (e) Hamman, S.; Barrelle, M.; Tetaz, F.; Beguin, C. G. *J. Fluorine Chem.* **1987**, *37*, 85. ATEA: (f) Pirkle, W. H.; Simmons, K. A. *J. Org. Chem.* **1981**, *46*, 3239. TFLA: (g) Kubota, T.; Kanega, J.; Katagiri, T. *J. Fluorine Chem.* **1999**, *97*, 213.

(6) Patent pending

(7) Islas-González, G.; Puigjaner, C.; Vidal-Ferran, A.; Moyano, A.; Riera, A.; Pericàs, M. A. *Tetrahedron Lett.* **2004**, *45*, 6337.

(8) Methods to prepare *rac*-**1**: (a) Chehidi, I.; Chaabouni, M. M.; Baklouti, A. *Tetrahedron Lett.* **1989**, *30*, 3167. (b) Gabriel, B.; Gounelle, Y.; Jullien, J. *Bull. Soc. Chim. Fr.* **1969**, 521.

(9) A method to prepare enantiopure **1** using a chiral auxiliary: Bravo, P.; Piovosi, E.; Resnati, G. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1201.

(10) Chini, M.; Crotti, P.; Flippin, L. A.; Gardelli, C.; Giovani, E.; Macchia, F.; Pineschi, M. *J. Org. Chem.* **1993**, *58*, 1221.

(11) Puigjaner, C.; Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1999**, *64*, 7902.

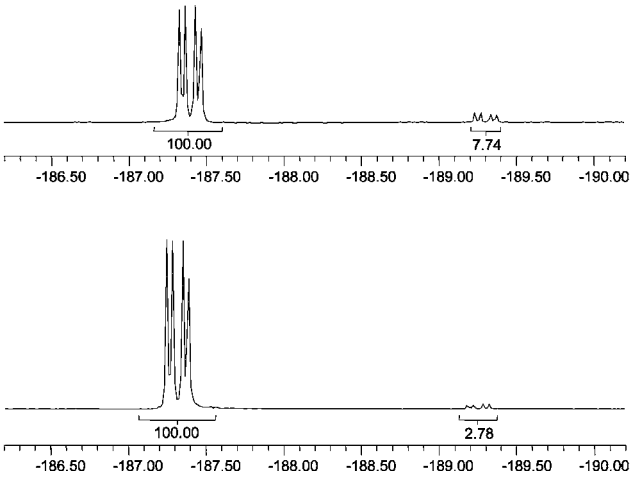


Figure 3. ^{19}F NMR spectra of **5a** obtained from (top) 85% and (bottom) 95% ee (*S*)-α-methyl benzylamine, **4a**.

tiomeric) composition, but the CHF signals already discussed are in general more separated, appear in a cleaner zone of the spectra, and are much easier to assign.

In practice, the analytical use of **1** involves greatly simplified conditions. Once it has been established that no kinetic resolution is taking place during the ring opening of **1** by primary amines, and since the diagnostic ^{19}F NMR signals of the diastereomeric amines **5** occur in a clean spectral region, it is not necessary to use stoichiometric amounts of fluoroepoxide **1** with respect to the amine to be analyzed. When 20 mol % of fluoroepoxide is used, the chiral derivatizing reagent is completely consumed within 15 min and the reaction crude can be directly submitted to ^{19}F NMR analysis, without any intermediate purification. In this way, enantiomeric purities up to 95% on **4a** have been easily determined with less than 1% error, as shown in Figure 3 and Table 2.

In addition to the NMR-based determinations of diastereomeric composition, it is also generally possible to separate the diastereomers of **5a**−**h** by HPLC, using a commercial Zorbax-Sil column and a UV−vis detector. The HPLC retention times for the diastereomers of the prepared ring-opening products are also provided in the Supporting Information.

Table 2. Comparison of Analysis Methods on the 95% and 85% ee Samples of **4a**

method	95% ee	85% ee
weighting (α-methylbenzylamine)	95.7	86.6
GC[a] (α-methyl benzylamine)	96.0	87.3
mean	**95.9**	**87.0**
HPLC[b] (**5a**)	95.7	85.0
^{19}F NMR (**5a**)	94.6	85.6
mean	**95.2**	**85.3**

[a] Supelco β-DEX column. [b] Zorbax-Sil column.

Although we have devoted a considerable computational effort to the analysis of the conformational preferences of the diastereomers of **5**, the precise reasons for the excellent signal separation observed in most cases cannot be fully accounted for at this moment. However, the structures of the lowest energy conformers of **5a** calculated by DFT (B3LYP hybrid functional with 6-31G* basis set) strongly suggest that intramolecular hydrogen bonding between the fluorine atom, the hydroxyl, and/or the amine can help in freezing the conformational flexibility of these compounds and, hence, facilitate analytical differentiation.

In summary, the readily available enantiopure fluoroepoxide **1** has been shown to be a most convenient reagent for the fast and reliable determination of enantiomeric composition of α-chiral primary amines. The reaction involved in the analysis, the nucleophilic ring-opening of an epoxide, has not been used before in this context and could, in principle, be extended for the determination of the enantiomeric composition of other chiral nucleophiles. Further work in this area, now in progress in our laboratories, will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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