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A Very Reliable Method for Determination of Absolute Configuration of Chiral Secondary Alcohols by ^{1}H NMR Spectroscopy

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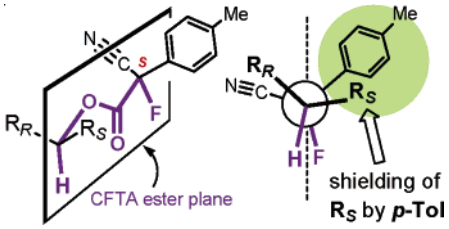
ABSTRACT



Surprisingly stable synperiplanar conformers of CFTA esters have led us to develop a new and very reliable method for assigning absolute configurations of even secondary alcohols having minimal structural differences, such as chiral benzhydrols and α-monodeuterated benzyl alcohols.

The determination of the absolute configuration of chiral molecules is an essential tool for modern organic chemistry. This is particularly true in the areas of asymmetric synthesis and in structural studies of complex natural products. There have been, however, no practical methods generally applicable to noncrystalline compounds and/or for samples available only in very small quantities. In an important approach to this problem using NMR spectroscopy,[1] the modified Mosher's method[2] uses α-methoxy-α-trifluoromethylphenylacetic acid (MTPA, **1**)[3] as a chiral derivatizing agent (CDA). However, a substantial number of cases have been reported where the MTPA procedure fails either because of the low reactivity of MTPA chloride (MTPA-Cl, **2**)[4] or because of the complex mixture of conformers observed in the MTPA derivatives.[5]

To overcome these limitations, we have developed the much more reactive α-cyano-α- fluorophenylacetic acid (CFPA, **3**)[6] and related compounds as CDAs that possess a unique structure with the fluorine atom located at the stereogenic center.[7] As a result of this work, we describe here the development of the first very reliable and yet

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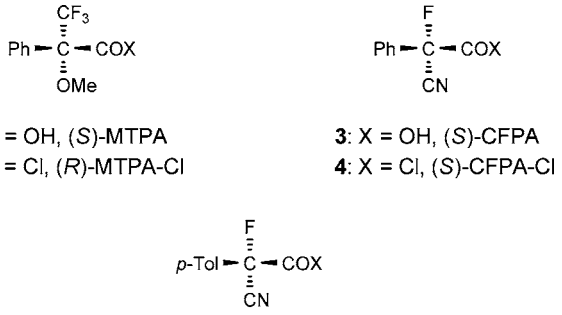
operationally facile procedure for the determination of absolute configurations of chiral secondary alcohols through the use of straightforward ^{1}H NMR spectroscopy.

We originally developed CFPA (**3**) for ee determinations of optically enriched molecules through ^{19}F NMR spectroscopy of CFPA diastereomers. We found that CFPA chloride (CFPA-Cl, **4**), in contrast to MTPA-Cl (**2**), reacts even with sterically hindered nucleophiles.[8] The CFPA moiety in a molecule allows the ^{19}F NMR differentiation of diastereomers having a stereogenic center up to several bonds removed from the attachment point of the CFPA residue.[6] To further exploit CFPA-based methods as a general procedure for chiral differentiation, including the method for absolute stereochemical assignment, we prepared and examined several CFPA analogues.[9]

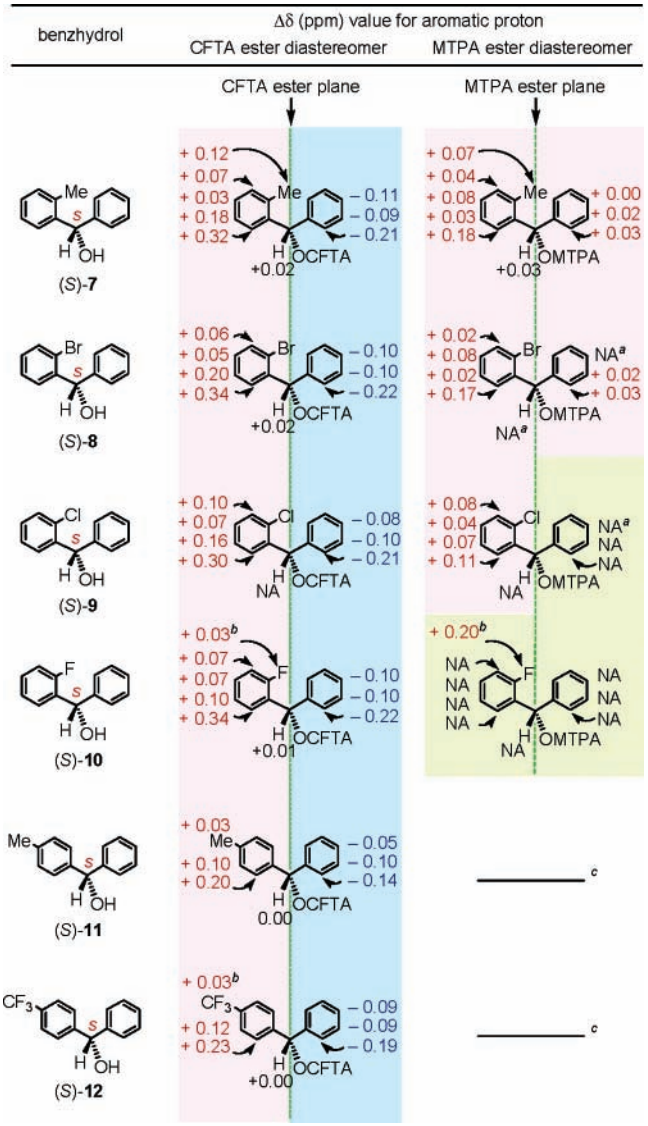
This research led to our development of α-cyano-α-fluoro-*p*-tolylacetic acid (CFTA, **5**),[10] a compound closely related to CFPA, as the agent of choice for the development of our procedure. This agent retains all of the structural merits of CFPA (**3**), including high reactivity of the corresponding chloride (CFTA-Cl, **6**), but is much more readily prepared.[11] We also found the ^{1}H NMR data for the CFTA derivatives to be more readily analyzed and characterized than were the CFPA derivatives (Scheme 1).[12]

Scheme 1



1: X = OH, (*S*)-MTPA
2: X = Cl, (*R*)-MTPA-Cl
3: X = OH, (*S*)-CFPA
4: X = Cl, (*S*)-CFPA-Cl
5: X = OH, (*S*)-CFTA
6: X = Cl, (*S*)-CFTA-Cl

Table 1. Δδ Values for CFTA and MTPA Ester Diastereomers of Some (*S*)-Benzhydrols



[a] NA = not assignable. [b] Data from ^{19}F NMR. [c] Derivatives not obtained.

Preliminary results showing a consistent relationship between stereochemistry of chiral alcohols and chemical shifts of the diastereomeric CFTA esters strongly suggested the formation of an unusually stable conformer having an all-synperiplanar F−Cα−CO−O−C−H array[13] on the "CFTA ester plane" as a predominant rotamer of the CFTA esters,[14] even in $CDCl_3$ on the NMR time scale.[13] To validate the rationale of our CFTA-based procedure for absolute stereochemical assignment, we examined some chiral benzhydrols of known absolute configurations.[15] These secondary carbinols have two very similar aromatic substituents. Each (*S*)-benzhydrol **7**−**12** was condensed with both (*S*)- and (*R*)-CFTA-Cl (**6**) to give (*S*)- and (*R*)-CFTA ester diastereomers, respectively. All aromatic proton signals for each of the (*S*)- and (*R*)-CFTA diastereomers were assigned by means of COSY and other NMR techniques, and the chemical shift

(8) Takeuchi, Y.; Itoh, M.; Koizumi, T. *J. Chem. Soc., Chem. Commun.* **1992**, 1514−1515 (see also *Chem. Ind.* **1992**, 874).

(9) Takeuchi, Y.; Iwashita, H.; Yamada, K.; Gotaishi, M.; Kurose, N.; Koizumi, T.; Kabuto, K.; Kometani, T. *Chem. Pharm. Bull.* **1995**, *43*, 1668−1673. Some of the CFPA analogues prepared were examined with respect to their abilities to differentiate enantiomers based on NMR analysis.

(10) Takeuchi, Y.; Konishi, M.; Hori, H.; Takahashi, T.; Kometani, T.; Kirk, K. L. *Chem. Commun.* **1998**, 365−366.

(11) (a) Takeuchi, Y.; Konishi, M.; Hori, H.; Takahashi, T.; Kirk, K. L. *Enantiomer* **1999**, *4*, 339−344. (b) Fujiwara, T.; Sasaki, M.; Omata, K.; Kabuto, C.; Kabuto, K.; Takeuchi, Y. *Tetrahedron: Asymmetry* **2004**, *15*, 555−563.

(12) It should be noted that assigning each proton in the ^{1}H NMR spectrum of the *p*-Tol group is much easier than that of the Ph group (because of the simple AB quartet of *p*-Tol), especially for those chiral alcohols having more than one aromatic residue.

(13) Takahashi, T.; Fukushima, A.; Tanaka, Y.; Takeuchi, Y.; Kabuto, K.; Kabuto, C. *Chem. Commun.* **2000**, 787−788.

(14) Abraham, R. J.; Tormena, C. F.; Rittner, R. *J. Chem. Soc., Perkin Trans. 2* **2001**, 815−820.

(15) Ohkuma, T.; Koizumi, M.; Ikehira, H.; Yokozawa, T.; Noyori, R. *Org. Lett.* **2000**, *2*, 659−662.

differences ($\Delta\delta$ values)[16] for each protons were obtained. When the benzhydrol esters are depicted in a manner such that the two aromatic substituents are in the plane of Table 1 and the carbinyl protons are coming out of the plane, the protons having positive $\Delta\delta$ values (written in red) are invariably on the left side of the CFTA ester plane and those having negative $\Delta\delta$ values (written in blue) are on the right side of the plane. These results are shown in the middle column of Table 1. From these results, we conclude that our procedure is consistent even for chiral secondary alcohols such as these, which have quite subtle structural differences. To date we have found no exception to this pattern, including the other chiral alcohols shown as the preliminary data.[12]

In contrast, the MTPA method of stereochemical assignment gives very inconsistent results for this set of chiral secondary alcohols, as shown in the right-hand column of Table 1. For **7** and **8**, the $\Delta\delta$ values for the protons on both the left and right sides of the MTPA ester plane[2,17] are positive.[18] For **9** and **10**, some of the proton shifts cannot be assigned.[12] Furthermore, in the case of **11** and **12**, the reliability of the procedure could not be investigated because the corresponding MTPA derivatives could not be prepared, presumably as a result of the poor reactivity of MTPA-Cl (**2**).[4] These results reveal that the modified Mosher's procedure[1] is not applicable to this series of chiral benzhydrols.

To account for the observed patterns in the ^{1}H NMR of CFTA esters, we propose a synperiplanar (sp) F−Cα−CO−O−C−H conformation, as shown by Figure 1. Indeed, there

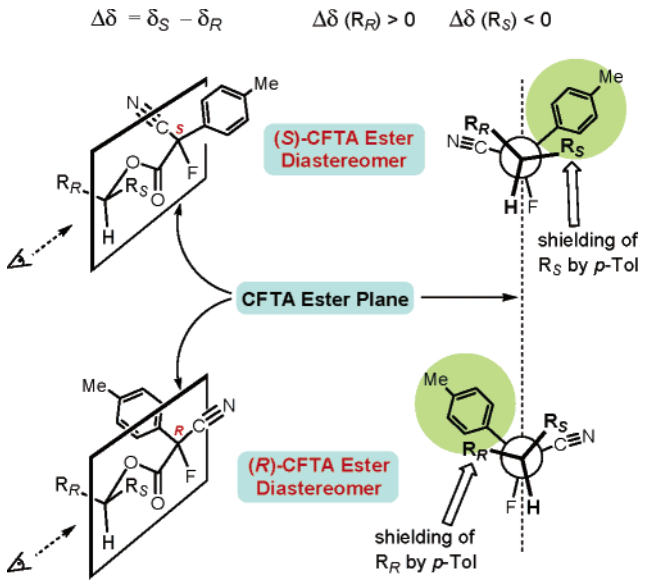
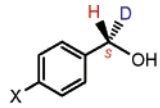
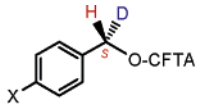


Figure 1. Conformations of (*S*)- and (*R*)-CFTA esters of chiral secondary alcohols R_SR_RCHOH.

are spectral data and calculations reported that support a sp F−Cα−CO−X conformation as the most stable rotamer, for a highly conformational preference for various α-fluoro carbonyl compounds (X = OMe, OH, Cl, R).[14,19] This structural hypothesis is also supported by the X-ray crystallographic structure of neomenthyl CFTA ester and by the ab initio calculations on menthyl CFPA ester.[13]

Steric arguments can be invoked to explain the proposed sp conformation that we use to rationalize the observed $\Delta\delta$ values (Figure 1). To view the diastereomeric CFTA esters of chiral alcohol (R_SR_RCHOH)[20] from the left side via an "extended Newman projection", the intervening ester linkages are omitted for convenience. Conformational arguments are used to explain the algebraic signs of the $\Delta\delta$ values. In the (*S*)-CFTA diastereomer, the shifts of the protons of the R_S substituent that eclipses the *p*-Tol group should always be upfield, relative to the shifts in the nonderivatized alcohol, as a result of the anisotropic shielding of the aromatic ring. In contrast, for the (*R*)-diastereomer, the protons of the R_R group are shielded and therefore should appear upfield. Reinforcing these differences, the CN group induces the anisotropic deshielding effect[21] on the proximate R_R and R_S groups in the (*S*)- and (*R*)-CFTA diastereomers, respectively.





compound	X	Δδ (ppm) = δS − δR	
		$\Delta\delta_H$	$\Delta\delta_D$
(*S*)-**13**	H	+ 0.03	− 0.03
(*S*)-**14**	CH_3	+ 0.05	− 0.05
(*S*)-**15**	OCH_3	+ 0.03	− 0.02
(*S*)-**16**	CF_3	+ 0.02	− 0.02
(*S*)-**17**	Br	+ 0.02	− 0.01

Figure 2. $\Delta\delta_H$ and $\Delta\delta_D$ values for CFTA esters of (*S*)-d_α-benzyl alcohols.

Accordingly, the $\Delta\delta$ ($= \delta_S - \delta_R$) values for the protons in the R_R group, namely, those for all of the protons on the left side of the CFTA ester plane, should be positive, and those

(16) The $\Delta\delta$ values are defined as $\delta_S - \delta_R$, where δ_S and δ_R are the chemical shifts of the corresponding protons in the (*S*)- and (*R*)-CFTA esters, respectively.

(17) The term "MTPA ester plane" is used in a same manner as the term "CFTA ester plane".

(18) (a) Seco, J. M.; Quinoa, E.; Riguera, R. *Tetrahedron: Asymmetry* **2000**, *11*, 2781−2791. (b) Kusumi, T.; Fujita, Y.; Ohtani, I.; Kakisawa, H. *Tetrahedron Lett.* **1991**, *32*, 2923−2926. (c) Rieser, M. J.; Hui, Y.; Rupprecht, J. K.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L.; Hanson, P. R.; Zhuang, Z.; Hoye, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 10203−10213. (d) Duret, P.; Waechter, A.; Figadere, B.; Hocquemiller, R.; Cave, A. *J. Org. Chem.* **1998**, *63*, 4717−4720.

(19) (a) Nieminen, J.; Pettersson, M.; Rasanen, M. *J. Phys. Chem.* **1993**, *97*, 10925−10936. (b) Durig, J. R.; Phan, H. V.; Hardin, J. A.; Little, T. S. *J. Chem. Phys.* **1989**, *90*, 6840−6851. (c) Amin, M. R.; Harper, D. B.; Moloney, J. M.; Murphy, C. D.; Howard, J. A. K.; O'Hagan, D. *Chem. Commun.* **1997**, 1471−1472.

(20) In a formula, the "pro-*S* group R" and the "pro-*R* group R" are written as R_S and R_R, respectively.

(21) Noe, C. R.; Knollmuller, M.; Oberhauser, B.; Steinbauer, G.; Wagner, E. *Chem. Ber.* **1986**, *119*, 729−743.

in the R_S group, namely, those for all of the protons on the right side of the plane, should be negative.

To look further at the scope and limitation of our technique, we next investigated the CFTA esters of several chiral α-monodeuterated benzyl alcohols **13**−**17**.[22] The stereogenic carbon in these structures carries two substituents that chemically and sterically are almost identical. The $\Delta\delta_H$ values for the benzylic protons are always positive, and the $\Delta\delta_D$ values for the benzylic deuteriums are always negative (Figure 2).[23] Because the stereochemistry of the proton and the deuterium in each compound is reversed, the $\Delta\delta_D$ values obtained by ^{2}D NMR should be reversed from the $\Delta\delta_H$ values obtained by ^{1}H NMR, yet as observed, their absolute values should be the same within the instrumental errors in measurement.

In the conformational equilibria shown in Figure 3, there should be two sp conformers, A and B, and C and D, for the (*S*)- and (*R*)-CFTA ester diastereomers, respectively. The positions of the two equilibria will be essentially the same, because the proton and deuterium are essentially the same, both chemically and sterically. Only the designated deuterium and proton shown in the structures A and C, respectively, will be subjected to the shielding effect of the *p*-Tol group, and therefore the $\Delta\delta_D$ and $\Delta\delta_H$ values for **13**−**17** should be always negative and positive, respectively. All the data shown in Figure 2 are in good agreement with these considerations based on steric factors.

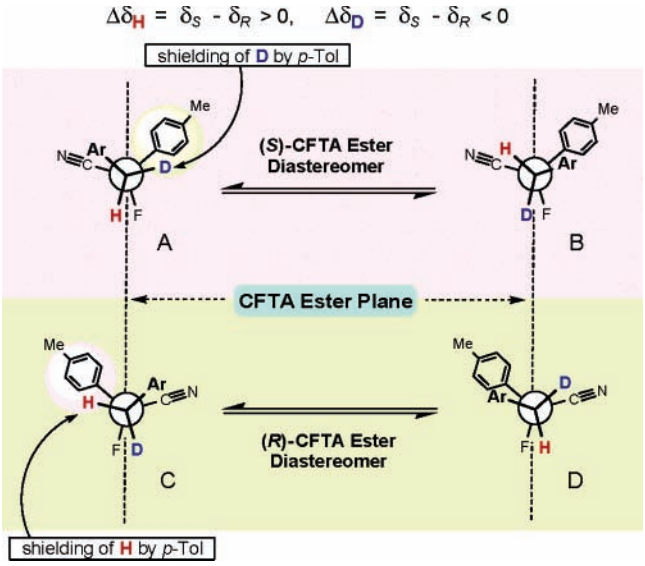


Figure 3. Conformational equilibria for (*S*)- and (*R*)-CFTA esters of (*S*)-d_α-benzyl alcohols.

The theoretical basis for the surprisingly stable sp conformation will be thoroughly investigated and clarified in the future. It seems reasonable at this time to propose that structures having both F and CN groups on the α-position of aryl acetate lend themselves to creating the specific stereoelectronic environment that produces this sp conformation.

In summary, because of the robust reactivity of CFTA chloride (**6**) and the consistency in the signs of the $\Delta\delta$ values for the derivatized chiral secondary alcohols so far examined, the CFTA procedure appears to be much more reliable than any of the other existing methods.[24] We stress that this method is especially suitable for examining sterically hindered secondary alcohols. The method can also be routinely applied to very small amounts of material. Further clarification of the theoretical basis for the above results and acquisition of additional data to study the generality of the CFTA procedure are objectives of our ongoing investigations.

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Supporting Information Available: Experimental details of the synthesis and characterization of **7**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Yamada, I.; Noyori, R. *Org. Lett.* **2000**, *2*, 3425−3427.

(23) The ^{1}H NMR data of the corresponding MTPA esters showed no consistent relationship between the signs of the $\Delta\delta_H$ values and stereochemistry.

(24) Both enantiomers of the CFTA agent are now being commercially developed.