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The use of Mosher derivatives for the determination of the absolute configuration of substituted isoxazolidines

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ABSTRACT

Isoxazolidines serve as intermediates in the synthesis of natural products. In addition, they can display significant biological activity, much of which derives from their ability to act as nucleoside analogues. As a result, considerable effort has been applied toward the asymmetric synthesis of isoxazolidines. However, a rapid and straightforward method for determination of the absolute configuration of isoxazolidines has not yet been reported. Herein we report the application of Mosher derivatives for the determination of the absolute configuration of substituted isoxazolidines. The Mosher derivatives exhibit conformational behavior similar to the Mosher derivatives of cyclic secondary amines. Interpretation of the chemical shift anisotropy, with these conformational biases in mind, can be used for the assignment of the absolute configuration of substituted isoxazolidines.

1. Introduction

Isoxazolidines have proven to be particularly useful synthetic intermediates for a variety of natural products,[1–4] and serve as biologically active compounds, such as antifungal,[5] anti-tuberculosis,[6] antiviral,[7] and cytotoxic[8] agents. As highly desirable synthetic targets, substantial effort has been invested toward the asymmetric synthesis of isoxazolidines. The 1,3-dipolar cycloaddition of nitrones with alkenes is a powerful approach, which provides isoxazolidine cycloadducts with predictable regioselectivity and excellent control of relative stereochemistry.[9] The introduction of chiral nitrones,[10,11] chiral dipolarophiles,[12–14] and chiral Lewis acid catalysts[15–18] provides isoxazolidine cycloadducts with high enantioselectivity. Other approaches include a stereoselective Pd-catalyzed ring-closing carbonylative amidation,[19] and Pd-catalyzed carboetherification of *N*-butenylhydroxylamines.[20] The determination of the absolute configuration of substituted isoxazolidines has involved one of two approaches: X-ray crystallography[12,13,18,21,22] or conversion of the isoxazolidine into a compound for which the sign of specific rotation is known.[14]

The use of Mosher's amide derivatives for determination of the absolute configuration of amines has been applied principally to primary amines. A comparative analysis of the ^{1}H and/or the ^{19}F NMR spectra of the analyte, which has been derivatized with each enantiomer of α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA), using an empirical model can be used to reliably predict the absolute configuration.[23,24] The dominant conformation of the amides (Fig. 1) is such that the α-protons of the amine, the carbonyl oxygen, and the trifluoromethyl groups are coplanar and *syn*.[25,26] Chemical shift differences result from the different anisotropic effects experienced by the two diastereomeric derivatives. In the (*S*)-MTPA amide, the protons of the R^1 group will be shielded relative to the (*R*)-MTPA derivative (Fig. 1). In this conformation, the α-CF_3 group experiences anisotropic deshielding by the amide carbonyl. However, if R^1 is bulky, the α-CF_3 group is forced out of coplanarity with the carbonyl oxygen and consequently, will no longer experience this deshielding effect. As a result, the chemical shift for the ^{19}F signal of the (*S*)-MTPA amide will be lower compared with the (*R*)-MTPA amide.[27]

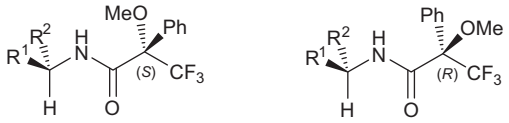

Figure 1. (*S*)-MTPA amide and (*R*)-MTPA amide.

With respect to cyclic amines, the use of Mosher derivatives has been largely limited to the determination of enantiomeric ratio, with only a handful of reports describing the use of Mosher derivatives for the assignment of absolute configuration. Among the latter, a few have applied an empirical model similar to that used for primary amines. Instead, these reports involve the acquisition of an X-ray crystal structure of the derivative,[28–31] analysis of NOESY spectra,[32,33] or comparison with derivatives of known configuration[34,35] and Vidal et al.[36] reported the assignment of the absolute configuration of 2-substituted pyrrolidines based on the

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ring conformation of the Mosher derivatives. Mosher amide derivatives of cyclic amines can exist as two slowly interconverting and unequally populated diastereomeric amide rotamers, which are often observed as two distinct species in the ^{1}H and ^{19}F NMR spectra (Fig. 2).[36–40] Similar to the acyclic amine derivatives, the α-CF_3 is biased toward an eclipsed arrangement with the amide C=O. This bias, combined with the planar geometry imposed by the amide group, positions the phenyl group on opposite sides of the mean plane of the ring in the two rotamers. The chemical shift differences of the ring substituents enforced by shielding of the substituents on the same face of the ring as the α-phenyl group allow the reliable assignment of the absolute configuration either when the derivative appears as two discreet rotamers or as an average of two conformations. This reasoning has been applied to the assignment of the absolute configuration of the solenopsins,[41] a suite of piperidine derivatives, as well as several pyrrolidine derivatives.[39,42,43]

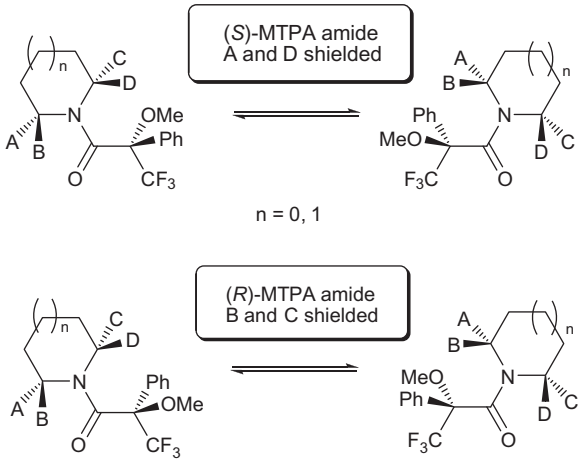


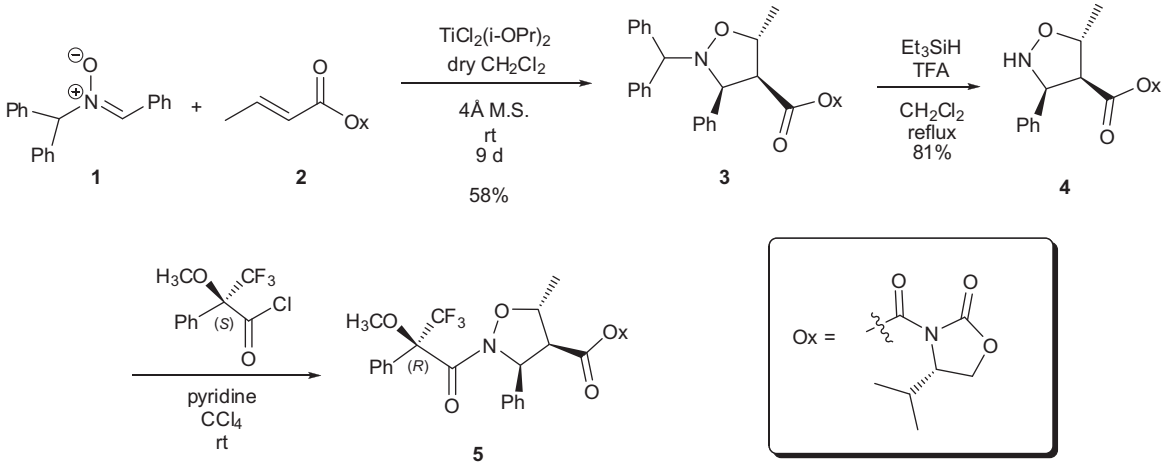
Figure 2. Two diastereomeric amide rotamers of cyclic (*S*)-MTPA and (*R*)-MTPA amides.

A single example of the use of Mosher derivatives of isoxazolidines to determine the enantiomer ratio has been reported.[44] However, the use of Mosher derivatives for the assignment of the absolute configuration of chiral isoxazolidines has not been described. As part of our interest in the synthesis of isoxazolidines, we wished to develop a model for the determination of the absolute configuration of isoxazolidines using the Mosher derivatives. We reasoned that these derivatives would behave in a fashion similar to the Mosher derivatives of cyclic amines.

2. Results and discussion

N-Benzylidene-1,1-diphenylmethanamine oxide **1** and oxazolidinone **2** were prepared according to published methods[18,45] and the 1,3-dipolar cycloaddition was performed using Ti(*i*-OPr)$_2$Cl$_2$ as the catalyst. The dipolarophile may approach in an *endo* fashion resulting in the *trans* relative configuration between substituents at the 3- and 4-positions of the isoxazolidine ring. Alternatively, an *exo* approach will provide the *cis*-relative configuration. The *exo*/*endo* selectivity dictating the relative configuration of the newly formed carbon–carbon bond is influenced by the coordination of the dipolarophile to a Lewis acid catalyst.[13,14,17,46] As anticipated on the basis of earlier studies, using Ti(*i*-OPr)$_2$Cl$_2$ as the catalyst favored the *exo* approach, providing a 3:1 mixture of *exo* to *endo* cycloadducts after 9 days, as determined by ^{1}H NMR spectroscopy. After chromatographic separation, the *exo* cycloadduct **3** was obtained in 58% yield (Scheme 1). Two diastereotopic *exo* adducts may be produced, resulting from an attack on the diastereotopic faces of the dipolarophile **2**. The ^{1}H NMR spectra of the purified *exo* adduct **3** suggested the formation of a single diastereomer. Oxazolidinone chiral auxiliaries provide high diastereofacial discrimination in a wide variety of reactions including 1,3-dipolar cycloadditions.[13,14,17,21,47–49] Based on these earlier studies, it can be reliably predicted that the cycloadduct resulting from the C_α-*Si* face approach is preferred since it arises from attack of the nitrone on the dipolarophile from the face opposite the directing group. Therefore, product **3** can be predicted to have (3*S*,4*S*,5*R*)-absolute configurations in the isoxazolidine ring (Scheme 1).[13,21,48] After deprotection using Et_3SiH, the cycloadduct was converted into the (*R*)-MTPA amide derivative by treatment with (*S*)-MTPA-Cl (Scheme 1). Two peaks were observed in the ^{19}F NMR spectra of **5** in $CDCl_3$, with a ratio of 1 to 2 (Fig. 3A). There are two possible explanations for this observation. The first possibility is that there are two different diastereomers. The other explanation is that a single isomer exists as two slowly interconverting rotamers, consistent with the coexistence of *syn*- and *anti*-rotamers of the MTPA derivatives of cyclic amines, such as piperidines and pyrrolidines.[36–40]

With the acquisition of the ^{19}F NMR spectrum in acetone-d_6, the peak ratio changed to 1 to 4 (Fig. 3B). Since the diastereomer ratio



Scheme 1. 1,3-Dipolar cycloaddition of nitrone **1** with chiral dipolarophile **2,** deprotection and preparation of (*R*)-MTPA amide [because of a change in priority, the (*S*)-MTPA-Cl becomes the (*R*)-MTPA amide].

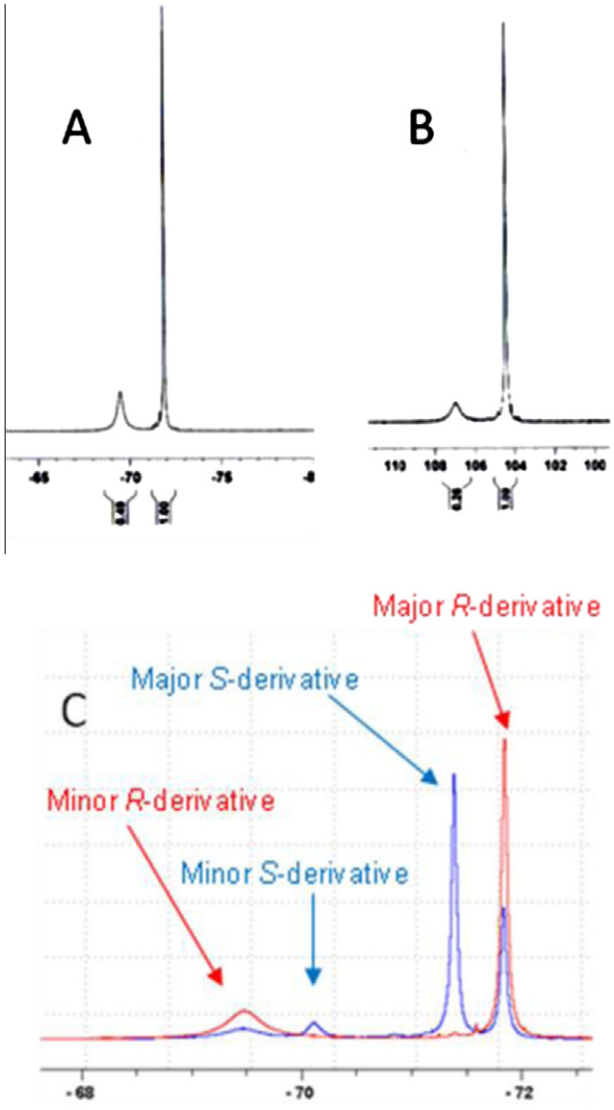


Figure 3. ^{19}F NMR spectra of MTPA amides of **4**; (A) ^{19}F NMR spectra of (*R*)-MTPA amide acquired in $CDCl_3$; (B) ^{19}F NMR spectra of (*R*)-MTPA amide acquired in d_6-acetone; (C) ^{19}F NMR spectra of (*R*)-MTPA amide (red) and racemic MTPA amides (blue) acquired in $CDCl_3$.

would not be solvent dependent, we concluded that the two peaks represented slowly equilibrating amide rotamers. Furthermore, partial coalescence of the two peaks was observed when the ^{19}F NMR was acquired at 45 °C in $CDCl_3$. This observation, that there were only two equilibrating rotamers, also suggested the presence of a single *exo*-diastereomer. The deprotected *exo* adduct **4** was also derivatized with racemic Mosher's acid chloride for comparison of the ^{19}F and ^{1}H NMR spectra. The ^{19}F NMR spectra of the Mosher derivative prepared from racemic MTPA showed four peaks, two of which were coincident with those observed in the (*R*)-MTPA amide obtained from the reaction of **4** with (*S*)-MTPA-Cl (Fig. 3C) and two new peaks belonging to the (*S*)-MTPA amide produced by the reaction of **4** with (*R*)-MTPA-Cl.

In order to better understand the conformational properties of the Mosher derivatives of these isoxazolidines, a Monte Carlo conformational search of both (*R*)- and (*S*)-Mosher derivatives of **4** using the AMBER force field with the programs MacroModel (v. 6.5) and Batchmin (v. 6.5)[50] was performed. Within a 25 kJ/mol energetic window, the isoxazolidine ring adopts a single envelope conformation in which C-4, bearing the largest group, is the out of plane atom and the oxazolidinone group is in a pseudo-equatorial position. As observed with the piperidine and pyrrolidine MTPA amides, and supported by our ^{19}F NMR spectra, these calculations predict the existence of two major families of rotamers (*E* and *Z*) with the *E*-rotamers being favored over the *Z* rotamers (Fig. 4). The *E*- and *Z*-forms are assigned, in our case, on the basis of the relationship between the C=O and the N–O bonds. Within three of these four groups [*Z*- and *E*-rotamers of the (*R*)- and (*S*)-derivatives], the lowest energy conformer has the trifluoromethyl group eclipsed with the amide carbonyl. The single exception is the *E*-rotamer of the (*R*)-MTPA derivative, in which the methoxy group eclipsed by the amide carbonyl is favored by 1.43 kcal/mol.

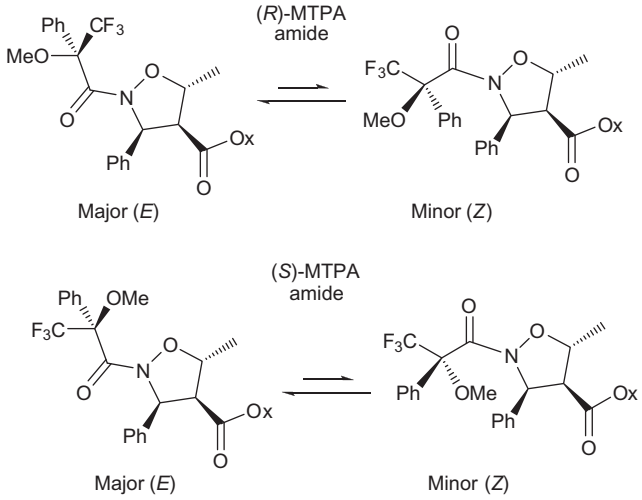


Figure 4. Conformational preferences of (*S*)- and (*R*)-MTPA amides of **4**.

On the basis of these computational results, the relative chemical shifts of diagnostic signals in the ^{19}F, ^{1}H NMR of (*R*)- and (*S*)-MTPA amides may be predicted, resulting in the assignment of the absolute configuration. The diagnostic peaks (Fig. 5C) in the ^{1}H NMR were assigned on the basis of ^{1}H COSY experiments.

According to our calculations, the MTPA-phenyl group of the *E*-rotamers of both (*R*)- and (*S*)-MTPA amides is on the same side of the isoxazolidine ring. This results from the preference for the α-OCH_3 of the *E*-rotamer of the (*R*)-MTPA amide to adopt an eclipsed arrangement with the C=O double bond, whereas the *E*-rotamer of the (*S*)-MTPA amide adopts the more typical conformation in which the α-CF_3 is eclipsed with the C=O double bond. Due to the preference for different conformations, the protons on the isoxazolidine ring in both the (*R*)- and (*S*)-derivatives experience similar anisotropic shielding effects of the phenyl group. It is therefore not informative to examine the relative chemical shifts of the ring protons of the *E*-rotamers in order to determine the absolute configuration. However, the chemical shifts of methoxy and trifluoromethyl groups may be affected by the phenyl substitutent of the isoxazolidine ring. The predicted and observed chemical shifts for the α-CF_3 and the OCH_3 for the *E*-rotamers of the (*R*)- and (*S*)-derivatives are shown in Table 1. In the *E*-rotamer of the (*R*)-MTPA amide, the α-CF_3 is shielded by the phenyl of the isoxazolidine and the methoxy group experiences anisotropic deshielding by the amide carbonyl. These groups on the (*S*)-MTPA amide *E*-rotamer experience opposite effects. The α-CF_3 group experiences anisotropic deshielding by the amide carbonyl and the methoxy group is shielded by the phenyl of the isoxazolidine. This analysis suggests that the chemical shift for the ^{19}F α-CF_3 signal of the (*R*)-MTPA amide must be lower when compared with the (*S*)-MTPA amide and the chemical shift of the methoxy protons of the (*R*)-MTPA amide must be higher than in

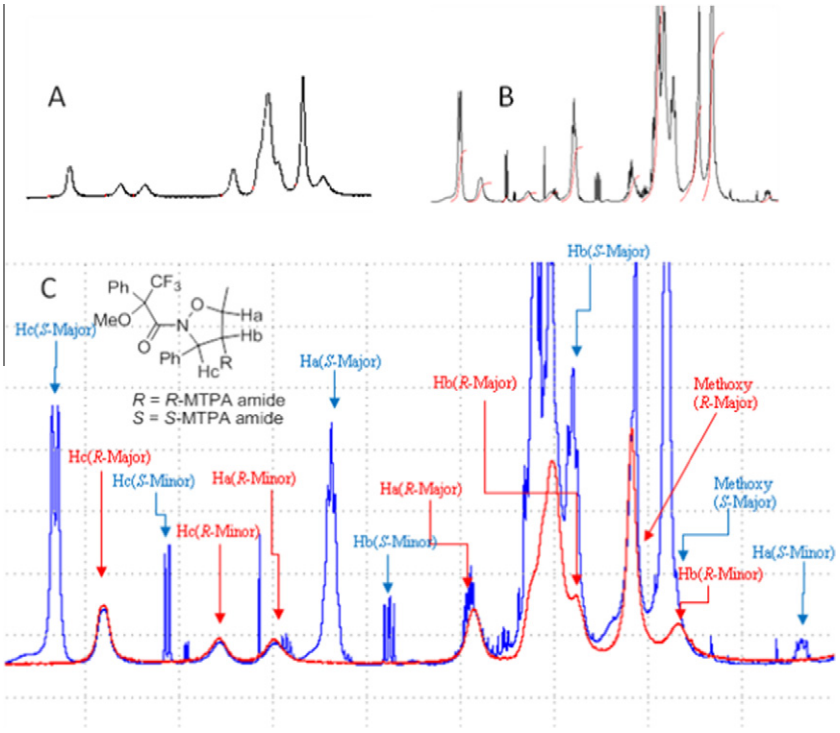
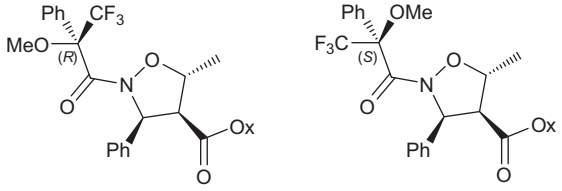


Figure 5. ^{1}H NMR spectra of the MTPA amides of **4**; (A) ^{1}H NMR spectrum of the (*R*)-MTPA amide of **4**; (B) ^{1}H NMR spectra of the product of racemic MTPA amides; (C) Superimposed ^{1}H NMR spectra of (*R*)-MTPA amide (red) and racemic (blue) MTPA amides of **4**.

Table 1
Analysis of the anisotropic effects of the C=O and isoxazolidine-Ph on the CF_3 and OCH_3 groups of the major *E*-rotamers of MTPA amides of **4**



	(*R*)-MTPA amide		(*S*)-MTPA amide	
	CF_3	OCH_3	CF_3	OCH_3
C=O	Not affected	Deshielded	Deshielded	Not affected
Isoxazolidine-Ph	Shielded	Not affected	Not affected	Shielded
δ ppm (expected)	Lower	Higher	Higher	Lower
δ ppm (observed)	−71.9	3.67	−71.4	3.52

the (*S*)-MTPA. We observed these results in the ^{19}F NMR spectra (Fig. 3C) and ^{1}H NMR spectra (Fig. 5C and summarized in Table 1). If *exo* cycloadduct **3** arose from attack of the dipole on the C_α-*Re* face, the relative chemical shift differences of α-CF_3 and methoxy groups of the *E* rotamers should be opposite of what is observed. This demonstrated that **3** has (3*S*,4*S*,5*R*)-absolute configurations in the isoxazolidine ring.

The conformational bias and chemical shift differences of the α-CF_3 and methoxy groups are strongly influenced by the isoxazolidine phenyl substituent. In the absence of this substituent, it is not clear that this analysis would be generally applicable to isoxazolidines. However, inspection of the minor *Z*-rotamers of the (*R*)- and (*S*)-MTPA isoxazolidine amides is perhaps more informative and generally applicable. The conformation of the *Z*-rotamers of both the (*R*)- and (*S*)-MTPA derivatives is more similar to that of acyclic amides and so a similar analysis may be applied. In the (*R*)-MTPA derivative of the *Z*-rotamer, H_b and H_c of the isoxazolidine ring are shielded by the MTPA-phenyl group, whereas in the (*S*)-MTPA derivative, only H_a is shielded by the MTPA-phenyl (Table 2). In addition, because the bulky MTPA-phenyl and isoxazolidine-phenyl are on the same side of the isoxazolidine ring in the *Z*-rotamer of the (*S*)-MTPA amide, the α-CF_3 will therefore be shifted away from co-planarity with the C=O, and will not be subjected to the anisotropic deshielding of the C=O group to the same degree as the (*R*)-MTPA amide. The chemical shift for the ^{19}F α-CF_3 signal of the (*S*)-MTPA amide must be lower when compared with the (*R*)-MTPA amide, that is, the relative chemical shifts of the α-CF_3 groups of the *Z*-rotamers should be opposite to those of the *E*-rotamers. These predictions were observed in ^{1}H NMR spectra (Fig. 5C) and ^{19}F NMR spectra (Fig. 3C) If the *exo*-cycloadduct **3** arose from attack of the dipole on the C_α-*Re* face, the relative chemical shift differences of α-CF_3 and H_a, H_b, and H_c of the *Z* rotamers should be the opposite of what is observed.

3. Conclusion

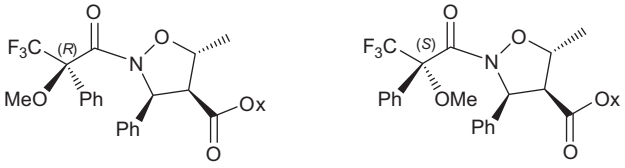
In conclusion we have demonstrated the application of Mosher derivatives of isoxazolidines for the assignment of absolute configurations. Similar to secondary cyclic amines, isoxazolidine derivatives can exist as a pair of slowly equilibrating rotamers. As a result, the assignment of configuration can be performed using either rotamer by interpretation of chemical shift anisotropy in a manner similar to that of secondary cyclic amines.

4. Experimental

4.1. General

Unless otherwise noted, reagents purchased from Sigma–Aldrich or Acros chemical companies were used without further

Table 2
Analysis of the anisotropic effects of the C=O and α-Ph on the CF_3 and isoxazolidine protons of the minor (*Z*) rotamers of MTPA amides of **4**



	(*R*)-MTPA amide				(*S*)-MTPA amide			
	H_a	H_b	H_c	CF_3	H_a	H_b	H_c	CF_3
α-Ph		Shielded	Shielded		Shielded			
C=O				De-shielded				
δ ppm (expected)	Higher	Lower	Lower	Higher	Lower	Higher	Higher	Lower
δ ppm (observed)	5.17	3.48	5.39	−69.5	2.96	4.68	5.61	−70.1

purification. Radial chromatography was performed on a chromatotron (Harrison Research Corp.) using plates coated with silica gel 60 PF_{254} containing gypsum. NMR spectra were recorded on a Bruker Avance spectrometer (400 MHz for proton). ^{1}H NMR spectra were referenced internally to the residual proton resonance in $CDCl_3$ (d = 7.26 ppm), or with tetramethylsilane (TMS, δ = 0.00 ppm) as the internal standard. Chemical shifts are reported as parts per million (ppm) in the δ scale downfield from TMS. ^{13}C NMR spectra were recorded with continuous proton decoupling. Chemical shifts are reported in ppm from TMS with the solvent as the internal reference ($CDCl_3$, δ = 77.0 ppm).

4.2. Synthesis of 3 and 4 and preparation of Mosher derivatives

4.2.1. (*S*)-3-((3*S*,4*S*,5*R*)-2-Benzhydryl-5-methyl-3-phenylisoxazolidine-4-carbonyl)-4-isopropyloxazolidin-2-one 3

To a 100 ml flame-dried flask were added *N*-benzylidene-benzhydrylamine *N*-oxide (0.2834 g, 0.99 mmol), (*S*,*E*)-3-but-2-enoyl-4-isopropyloxazolidin-2-one (0.2356 g, 1.20 mmol), powered 4 Å molecular sieve (215.6 mg), and dry CH_2Cl_2 (5 ml). The flask was then flushed with N_2 gas and sealed by a rubber septum, which was fitted with a nitrogen balloon. Next, $TiCl_2$(i-OPr)$_2$ (2 M in CH_2Cl_2, 0.12 ml) was added via syringe. The resulting suspension was stirred at room temperature for 9 days. A mixture of 20% methanol and 80% CH_2Cl_2 (25 ml) was added and the cloudy solution was then filtered through one layer of Celite (top) and one layer of silica gel (bottom), followed by a wash of the solids with CH_2Cl_2 (20 ml), after which the solvent was evaporated in vacuo. Radial chromatography (5:1 hexane/EtOAc) afforded the pure *exo* adduct **3** as a white solid (0.2770 g, 58% yield). Mp 82–85 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37–7.01 (m, 15H), 4.97 (m, 1H), 4.86 (s, 1H), 4.56 (d, 1H, J = 10.8 Hz), 4.16–3.97 (m, 4H), 1.53 (m, 1H), 1.27 (d, 3H, J = 6.0 Hz), 0.61 (d, 3H, J = 6.8 Hz), −0.01 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.3, 153.4, 141.0, 140.3, 130.0, 129.1, 128.4, 128.0, 127.9, 127.7, 127.6, 127.1, 126.8, 75.2, 72.7, 70.3, 63.3, 59.8, 58.6, 28.3, 18.1, 13.9. HR-MS (ESI/APCI) calcd for: $C_{30}H_{33}N_2O_4$ (MH^+): 485.2435, found: 485.2444.

4.2.2. (*S*)-4-Isopropyl-3-((3*S*,4*S*,5*R*)-5-methyl-3-phenylisoxazolidine-4-carbonyl)oxazolidin-2-one 4

A 100 ml flask was charged with (*S*)-3-((3*S*,4*S*,5*R*)-2-benzhydryl-5-methyl-3-phenylisoxazolidine-4-carbonyl)-4-isopropyloxazolidin-2-one **3** (0.0896 g, 0.19 mmol), dry CH_2Cl_2 (8 ml), TFA (2 ml), and triethylsilane (0.0596 g, 0.51 mmol). The flask was flushed with N_2 and equipped with a reflux condenser fitted with a rubber septum and a balloon. The reaction mixture was refluxed for 3 h and then cooled to room temperature. The flask was placed into an ice bath after which saturated $NaHCO_3$ was added dropwise until the solution became slightly basic. The solution was extracted with CH_2Cl_2 (3 × 30 ml) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Radial chromatography (2:1 hexane/EtOAc then 1:1 hexane/EtOAc) provided the N-unsubstituted isoxazolidine **4**. White solid; 81% yield (0.0479 g); mp 120–123 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24 (m, 5H), 4.99 (d, 1H, J = 9.6 Hz), 4.70 (dq, 1H, J = 6.0 Hz, J = 8.0 Hz), 4.32 (dd, 1H, J = 9.6, 8.0 Hz), 4.19 (m, 1H), 4.12 (t, 1H, J = 8.8 Hz), 4.01 (dd, 1H, J = 8.8, 2.4 Hz), 1.59 (m, 1H), 1.39 (d, 3H, J = 6.0 Hz), 0.64 (d, 3H, J = 6.8 Hz), 0.00 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0, 153.5, 135.0, 128.7, 128.6, 128.5 128.3, 83.0, 68.5, 63.1, 59.0, 58.5, 28.3, 18.6, 18.0, 13.7. HR-MS (ESI/APCI) calcd for: $C_{17}H_{23}N_2O_4$ (MH^+): 319.1652, found: 319.1662.

4.2.2.1. Preparation of Mosher derivatives. To a 25 ml flask equipped with a magnetic stirrer bar were added N-unsubstituted isoxazolidine **4** (0.15 mmol), CCl_4 (1 ml), pyridine (6 drops), and Mosher acid chloride (0.18 mmol). The reaction mixture was stirred for 24 h and then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (25 ml) and washed with H_2O (3 × 25 ml) and a saturated $NaHCO_3$ solution (3 × 25 ml) to remove excess Mosher acid chloride. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude Mosher amide.

4.2.3. (*S*)-4-Isopropyl-3-((3*S*,4*S*,5*R*)-5-methyl-3-phenyl-2-((*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)isoxazolidine-4-carbonyl)oxazolidin-2-one, (*R*)-Mosher amide 5

Purified by radial chromatography (2:1 hexane/EtOAc); 55% yield. Mp 235–238 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) Major rotamer (*E*) δ 7.63–7.14 (m, 10H), 5.87 (br, 1H), 4.33 (br, 1H), 4.00 (br, 2H), 3.91 (1H), 3.67 (br, 3H), 2.71 (br, 1H), 1.35 (1H), 1.09 (br, 3H), 0.52 (d, 3H, J = 7.2 Hz), 0.15 (br, 3H); Minor rotamer (*Z*) δ 7.63–7.14 (m, 10H), 5.39 (br, 1H), 5.17 (br, 1H), 4.00 (4H), 3.67 (br, 1H), 3.48 (br, 1H), 2.71 (1H), 1.35 (1H), 1.19 (3H), 0.52 (3H), 0.15 (3H). ^{19}F NMR ($CDCl_3$, 376 MHz) Major rotamer (*E*) δ −71.9; Minor rotamer (*Z*) δ −69.5. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.6, 160.1, 153.4, 135.1, 134.0, 132.7, 129.9, 128.7, 128.6, 128.2, 127.5, 126.7, 84.4, 84.1, 63.8, 58.7, 57.8, 56.0, 28.4, 18.0, 17.0, 14.5.

4.3. Computational methods

Monte Carlo conformational sampling, minimization and structure comparisons were performed of both Mosher derivatives of **4** using the AMBER force field with the programs MacroModel (v. 6.5) and Batchmin (v. 6.5). Dihedral angles were varied randomly within a range of 0 to ±180°. A ring closure distance of 2.0

angstroms was used. The user-directed structure selection technique was employed where the least used structure is the starting geometry for a new Monte Carlo search. Up to seven torsions were varied at one time. Minimizations using the conjugate gradient method were performed with up to 500 iterations for each conformer. The Monte Carlo search was continued until each conformer had been identified several times.

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