MTPA (Mosher) Amides of Cyclic Secondary Amines: Conformational Aspects and a Useful Method for Assignment of Amine Configuration

Thomas R. Hoye* and Matthew K. Renner

Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

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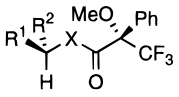
Mosher's MTPA (methoxy(trifluoromethyl)phenylacetyl) technology is a well-known tool used to determine the absolute configuration of chiral alcohols and primary amines. The technique now has been extended to include secondary amines. A number of MTPA amide derivatives have been prepared from cyclic amines. Both piperidines and pyrrolidines have been studied. A detailed discussion of the conformational issues associated with both amide bond rotation and ring flipping is presented. The observed ^{1}H NMR chemical shifts are correlated into a model that allows unambiguous determination of absolute configuration of cyclic secondary amines. While the presence of amide rotamers must be accounted for in the analysis, this is a relatively straightforward process that follows from detailed evaluation of coupling constant data and is often aided by COSY. The exceptionally large $\Delta\delta$ values observed for these MTPA amides make this a valuable and reliable method for assigning amine configuration.

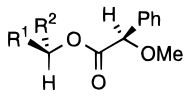
Among techniques employed to determine absolute configuration of organic compounds, Mosher's method is one of the most often used. Mosher proposed[1] that analysis of ^{1}H and ^{19}F NMR spectra of methoxy(trifluoromethyl)phenylacetyl (MTPA) derivatives of chiral alcohols and primary amines could allow one to determine the absolute configuration of that compound. The refined Mosher method,[2] which relies upon the assessment of numerous proton chemical shift differences ($\Delta\delta$s) throughout the molecule, demonstrates the advantages of analysis of the more reliable and numerous proton NMR chemical shifts rather than the sometimes ambiguous ^{19}F shifts.

Recently, three groups have reported the application of MTPA[3] and the related *O*-methylmandelate[4] technology to the analysis of chiral *primary* amines. Kusumi and Kakisawa[3] found that the dominant conformation of the resulting amides was analogous to that of esters of secondary alcohols; that is, the methine proton, the carbonyl oxygen, and the trifluoromethyl groups are coplanar and syn. It has recently been confirmed for some esters by NOE analysis that the trifluoromethyl and carbonyl groups are syn.[5] Thus, in the conformation shown (**1**), protons in R^1 are more highly shielded than those in R^2 for both ester and amide derivatives.

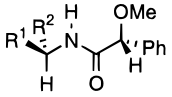


1 X=O, NH

Trost[4a] and Riguera[4b] found that the conformations of *O*-methylmandelamides, on the other hand, are not analogous to those of the *O*-methylmandelate esters. The major conformation for esters **2a** is that in which the methoxy group is syn-coplanar to the carbonyl, while the major conformation for amides **2b** was deduced to have the methoxy group anti-periplanar to the carbonyl. It would seem that this results in smaller differential shielding (or $\Delta\delta$ values) for these *O*-methylmandelamides since the phenyl group is "aimed" away from the R groups (cf. **2b**) rather than toward them (cf. **2a** and **1**).



2a
R^1 shielded by phenyl



2b
R^2 shielded by phenyl

Tavares and Rauk[6] reported NMR studies of a number of MTPA amides derived from the secondary amines *N*,*N*-diisopropylamine, *cis*-2,6-dimethylpiperidine, and (*R*)- and (*S*)-2-methylpiperidine. Their observations and interpretation of the significant chemical shift differences in the individual diastereomeric MTPA amides derived from (*R*)- and (*S*)-2-methylpiperidine (**8** and **9**, *vide infra*) clearly indicate the potential for deducing absolute configuration from this kind of derivative. However, no one has since capitalized on this opportunity. We used a CASOnline substructure search on the fragment FCCC(=O)N to identify literature reports of Mosher amides. While in some cases the % ee of secondary amines has been determined from the MTPA amides, the approach has not subsequently been used to deduce configuration.[7]

Tavares and Rauk[6] also studied in detail a number of conformational and dynamic issues associated with MTPA-

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

(2) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

(3) Kusumi, T.; Fukushima, T.; Ohtani, I.; Kakisawa, H. *Tetrahedron Lett.* **1991**, *32*, 2939.

(4) (a) Trost, B. M.; Bunt, R. C.; Pulley, S. R. *J. Org. Chem.* **1994**, *59*, 4202. (b) Latypov, S. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem* **1995**, *60*, 1538.

(5) Fukushi, Y.; Yajima, C.; Mizutani, J. *Tetrahedron Lett* **1994**, *35*, 9417.

(6) (a) Khan, M. A.; Tavares, D. F.; Rauk, A. *Can. J. Chem.* **1982**, *60*, 2451. (b) Rauk, A.; Tavares, D. F.; Khan, M. A.; Borkent, A. J.; Olson, J. F. *Can. J. Chem.* **1983**, *61*, 2572.

(7) (a) Toshimitsu, A.; Hirosawa, C.; Tanimoto, S.; Uemura, S. *Tetrahedron Lett.* **1992**, *33*, 4017. (b) Agami, C.; Couty, F.; Prince, B.; Puchot, C. *Tetrahedron* **1991**, *47*, 4343. (c) Nakagawa, K.; Somei, M. *Heterocycles* **1991**, *32*, 873. (d) Barrett, A. G. M.; Pilipauskas, D. *J. Org. Chem.* **1990**, *55*, 5170.

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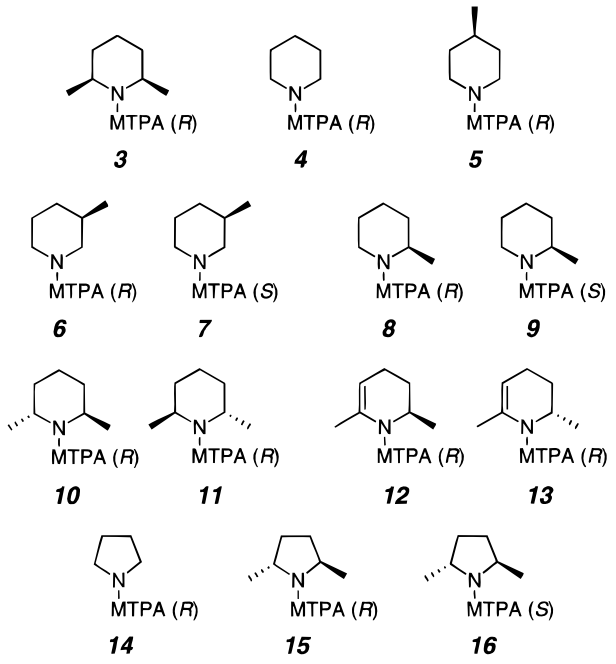
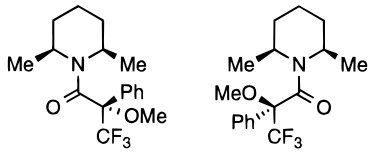
Scheme 1. Piperidine− and Pyrrolidine−MTPA Amides Studied



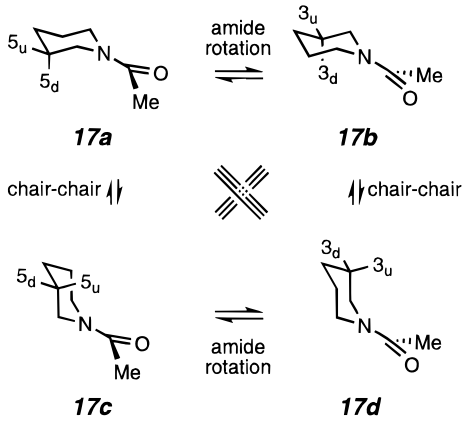
NRR′ molecules. For example, the MTPA amide of *cis*-2,6-dimethylpiperidine exists predominantly in two conformations (**3a** and **3b**). These two conformations are diastereomeric, since in one the methyl substituents are syn to the phenyl and in the other anti. Two distinct ^{1}H NMR spectra are observed under conditions where amide rotation is slow on the NMR time scale.

While this hindered rotation about the amide C(O)−N bond is expected to somewhat complicate the spectral analysis of these amides, it is also true that a single MTPA derivative provides, after deconvolution, two complementary and reinforcing data sets. We report herein analysis methods that are generally applicable to the determination of absolute configuration of cyclic amines.



We have prepared and analyzed a number of MTPA derivatives of simple cyclic amines. Both piperidine and pyrrolidine derivatives (**3**−**13** and **14**−**16**, respectively, Scheme 1) were examined. Samples of the chiral amine precursors used to prepare **6**−**9** and **15**−**16** were of >95% ee of material of known absolute configuration.[8−10] The diastereomeric pairs **10**/**11** and **12**/**13** were prepared from racemic amines and the amides separated by HPLC. Specifically, lutidine was reduced with sodium in ethanol. The tetrahydropyridine products were reacted directly with (*S*)-MTPA-Cl to afford enamides **12** and **13**, which were separable by preparative HPLC. These enamides were reduced with sodium cyanoborohydride and trifluoroacetic acid with greater than 95% selectivity for the trans products **10** and **11** in each case.

Scheme 2. Conformations of the Pair of Amide Rotamers for Each of the Chair Forms of *N*-Acetylpiperidine (17a−d)



In general, the preparation of the Mosher amides can be accomplished by reaction of the substrate amine or amine salt with MTPA acid chloride in the presence of Hunig's base (or Et_3N, pyridine, DMAP, etc.). If the amine substrate is hindered to the extent of, for example, the 2,6-dialkylated piperidines, background reaction between MTPA-Cl and the tertiary amine base can be a problem. In this regard, Hunig's base (DIEA) is preferable to triethylamine (Et_2N−MTPA formation) and pyridine, but even DIEA will slowly react with the MTPA-Cl. Alternatively, if the amine substrate is readily available, it is sometimes convenient to react 2 equiv of the free base with 1 equiv of MTPA acid chloride. DCC coupling with MTPA-OH is possible for unhindered amines, but 2-mono- and 2,6-disubstituted piperidines couple too slowly for this method of preparation to be useful.

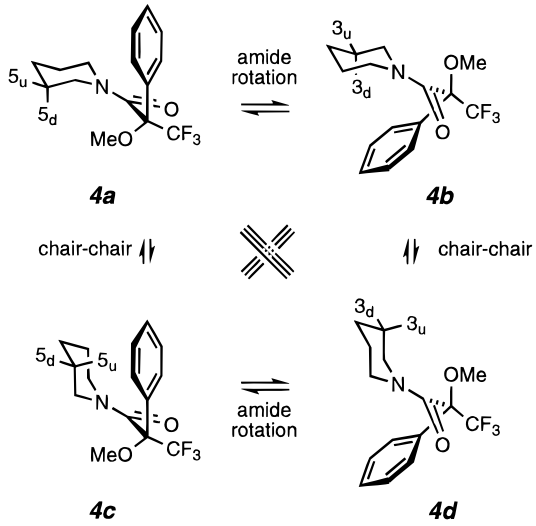
The Discussion section is divided into two parts. The first, Conformational Considerations, contains a detailed analysis of the complex yet tractable issues of conformation that arise from simultaneous ring flipping and amide rotation events. Readers primarily interested in the utility of assigning configuration to stereogenic centers in various secondary amines are directed to the second part of the Discussion, Configurational Assignments from Analysis of MTPA Amides, with reference to the Conformational Considerations part as necessary.

Discussion

Conformational Considerations. Consider *N*-acetylpiperidine (**17**, Scheme 2). Rotation about the amide bond is slow, while chair−chair interconversion of the piperidine ring is rapid. The two amide rotamers of the same chair conformer (i.e., **17a** vs **17b** or **17c** vs **17d**) are enantiomeric, as are the two chair conformers of the same amide rotamer (i.e., **17a** vs **17c** or **17b** vs **17d**). This requires that **17a** is identical with **17d** and that **17b** is identical with **17c**. At ambient temperature the ^{1}H NMR spectrum of **17** shows five 2H multiplets for each of the methylene pairs at C(2) through C(6), respectively. This is consistent with rapid chair−chair interconversion and slow amide rotation. On time-average, the molecule can be thought of as having planar symmetry (achiral) even though this geometry is never adopted because of its high energy.

(8) Bettoni, G.; Duranti, E.; Tortorella, V. *Gazz. Chim. Ital.* **1972**, *102*, 189.
(9) Craig, J. C.; Pinder, A. R. *J. Org. Chem.* **1971**, *36*, 3648.
(10) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231.

Scheme 3. Conformations of the Pair of Amide Rotamers for Each of the Chair Forms of the (*R*)-MTPA Amide of Piperidine (4a−d)

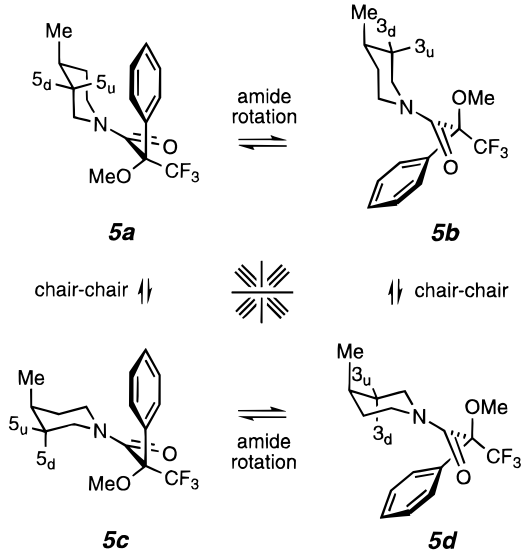


It will be necessary to refer to each of the individual hydrogen atoms in the amine portion of many of the MTPA derivatives. We have used the following convention. With the amine ring oriented as shown in **3** in Scheme 1 (i.e., with the nitrogen atom at the bottom, the ring numbered with C(2) at the lower right, and with the substituent attached to the lowest numbered carbon up) all "up" hydrogens are designated H_u and those "down" are H_d.

Now consider the (*R*)-MTPA amide derivative of piperidine (**4**). Let us view this chiral amide from the four analogous representations **4a**−**d** (Scheme 3). Again the **4a**/**4b** and **4c**/**4d** pairs represent amide rotamers and the **4a**/**4c** and **4b**/**4d** pairs represent chair-flipped conformations of one another. Again **4a** is identical with **4d** and **4b** is identical with **4c**. In this instance, however, because of the stereogenic center in the MTPA moiety **4a** (= **4d**) is *diastereomeric* with **4b** (= **4c**). The ^{1}H NMR spectrum of **4** in toluene-d_8 at ambient temperature is comprised of ten 1H resonances, consistent again with rapid chair−chair interconversion and slow rotation about the Mosher amide bond. In the regime where amide rotation is rapid, one would expect the spectrum to simplify to five 2H resonances since the proton pairs $2_u/6_d$, $2_d/6_u$, $3_u/5_d$, $3_d/5_u$, and $4_u/4_d$ are rendered homotopic. Indeed, at 90 °C the ^{1}H NMR spectrum of **4** shows that several of these pairs have already or have nearly coalesced. At the other extreme, in the regime where piperidine chair−chair interconversion is slow, one would expect to see up to 20 separate ^{1}H resonances all with similar intensity. This is because each of the presumably nearly isoenergetic diastereomers **4a** (= **4d**) and **4c** (= **4b**) has ten unique protons. At −70 °C the spectrum indicates that several of the higher temperature proton resonances have decoalesced. From the set of temperature-dependent spectra, we estimate the $\Delta G^{\ddagger}$ values for amide rotation and chair flip in **4** to be 17.6 ± 0.2 and 9.5 ± 1.0 kcal mol^{-1}, respectively. The former is slightly lower than the barriers of 17.7−18.4 kcal mol^{-1} reported for the 2-methylpiperidine−MTPAs **8** and **9** in DMSO.[6]

The (*R*)-MTPA amide of 4-methylpiperidine (**5a**−**d**) is a chiral amide derived from an achiral amine; thus the (*R*)- and (*S*)-MTPA amide derivatives are enantiomeric. Each of the four conformers of one of the single enantiomers is unique. Unlike piperidine MTPA amide (**4**), the

Scheme 4. Conformations of the Pair of Amide Rotamers for Each of the Chair Forms of the (*R*)-MTPA Amide of 4-Methylpiperidine (5a−d)



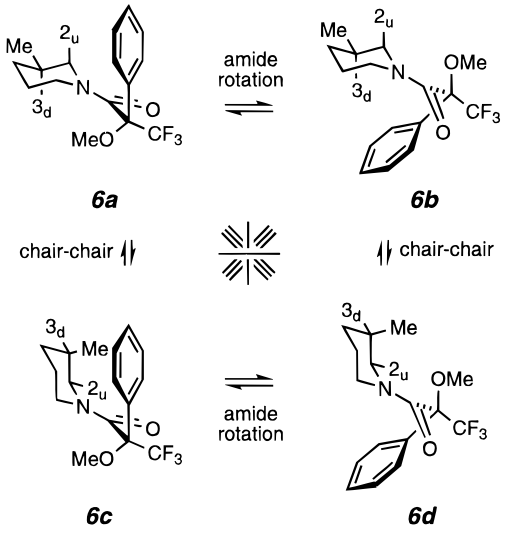
amide rotamers of **5** cannot interconvert by chair−chair flipping (Scheme 4). It is reasonable to assume that those conformations with the 4-Me substituent in the equatorial position (**5a** and **5b**) predominate over those with an axial 4-Me group (**5c** and **5d**) and that the amide rotamers **5a** and **5b** are similar in energy. Conformational searching (Monte Carlo) with the Amber force field suggests that the energies of amide rotamers **5a** and **5b** (as well as **5c** and **5d**) are within 0.25 kcal mol^{-1} of one another. Those with the equatorial methyl group (**5a** and **5b**) are ∼1.5−1.7 kcal mol^{-1} more stable than those with the axial methyl (**5c** and **5d**). These calculated energies are supported by the facts that (i) the coupling constant between $H(3_u)$ and H(4) in **5b**/**d**[11] is ≥12.0 Hz and between $H(5_u)$ and H(4) in **5a**/**c** is ≥10.0 Hz in the spectrum at ambient temperature and (ii) the integrated ratio of pairs of interchangeable protons in the amide rotamers **5a** and **5b** is ∼1.4:1.

Each of the four conformers of the (*R*)-MTPA amide of (*R*)-3-methylpiperidine (**6a**−**d**) is also unique (Scheme 5). This is a chiral amide derived from a chiral amine; therefore the (*R*)- and (*S*)-MTPA amide derivatives **6** and **7** are diastereomeric. Amide **6** is the like (*l*) diastereomer since the configuration of both stereogenic carbon atoms is identical. It is again reasonable to assume that those conformers with the 3-Me substituent in the equatorial position predominate over those with an axial 3-Me group and that the amide rotamers are similar in energy. These assumptions are again supported by the facts that (i) the coupling constant between $H(2_u)$ and $H(3_d)$ in **6a**/**c** = 10.5 Hz and between $H(2_u)$ and $H(3_d)$ in **6b**/**d** = 10.5 Hz in the spectrum at ambient temperature and (ii) the integrated ratio of pairs of interchangeable protons in the amide rotamers **6a** and **6b** is again ∼1.4:1. The ratio of amide rotamers **7a** to **7b** for the unlike (*ul*) diastereomeric (*S*)-MTPA amide of (*R*)-3-methylpiperidine (**7**) is ∼2.5:1.

Expectations change for the Mosher amides derived from 2-methylpiperidine, two of the MTPA amides analyzed by Tavares and Rauk,[6b] because piperidine amides

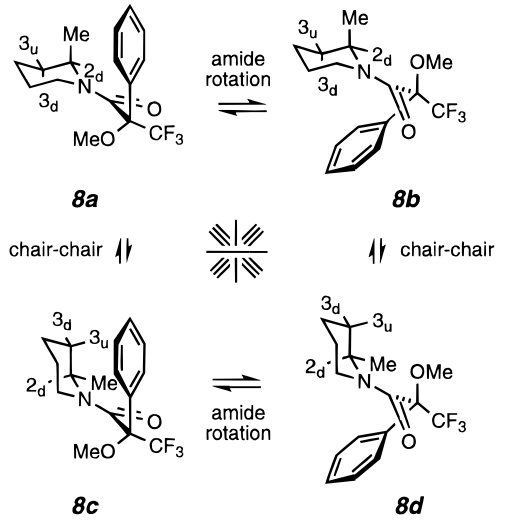
(11) Compound numbers incorporating a slash (**a/c** or **b/d**) represent a rapidly equilibrating pair of chair conformations that gives rise to a single, time-averaged set of chemical shifts and coupling constants.

Scheme 5. Conformations of the Pair of Amide Rotamers for Each of the Chair Forms of the (*R*)-MTPA Amide of (*R*)-3-Methylpiperidine (6a−d)



6a **6b** **6c** **6d**

Scheme 6. Conformations of the Pair of Amide Rotamers for Each of the Chair Forms of the (*R*)-MTPA Amide of (*R*)-2-Methylpiperidine (8a−d)



8a **8b** **8c** **8d**

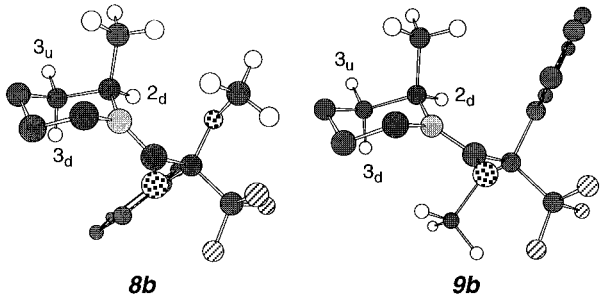
with substituents in the 2-position often favor a conformation in which the substituent is axial and H(2) is equatorial. They concluded that the amide carbonyl oxygen is oriented toward C(2) in order to minimize $A^{1,3}$-strain[6b,12] and that the like (*R*)-MTPA amide of (*R*)-2-methylpiperidine (**8**) is predominated by conformer **8a** in which the methyl group at C(2) is axial and the hindered MTPA α-carbon and its substituents are anti to the branched C(2) (Scheme 6). Most telling is the highly shielded resonance at δ 0.49 ppm (vs 1.65 for **8a**) for the C(3) axial proton [$H(3_d)$] in the minor, syn-amide[13] rotamer **8b** (rotamer ratio of 2.6:1). The unlike diastereomer **9** has a highly shielded C(2) methyl group (δ 0.31) in the syn-amide rotamer, consistent again with the predominance of **9a** over **9b** (2.5:1 ratio).

Configurational Assignments from Analysis of MTPA Amides. Described below is how MTPA amides can be used to assign absolute configuration of chiral secondary amines. The Tavares and Rauk[6b] analysis of the set of diastereomeric Mosher amides of (*R*)-2-methylpiperidine (**8** and **9**) serve as a very instructive example. The ^{1}H NMR data (in $CDCl_3$) extracted for each of the amide rotamers for each of these diastereomers are summarized in Table 1.

Table 1. Chemical Shifts (ppm in $CDCl_3$) and $\Delta\delta$ Values for the Individual Rotamers of (*R*)- and (*S*)-MTPA Amides of (*R*)-2-Methylpiperidine (8 and 9, Respectively)

H	**8a/c**	**8b/d**	**9a/c**	**9b/d**	$\Delta\delta =$ $\delta_S - \delta_R$ (*a/c*)	$\Delta\delta =$ $\delta_S - \delta_R$ (*b/d*)
2_d	4.93	4.14	5.06	4.35	0.13	0.21
3_d	1.65	0.49	1.5	1.65	~-0.15	1.16
3_u	1.6	0.80	1.6	1.4	~0	0.6
4_u	1.5	1.5	1.5	1.57	0	~0.07
4_d	a	a	1.3	a	a	a
5_d	1.35	1.35	0.32	1.4	-1.03	~0.05
5_u	1.5	1.6	1.00	1.72	-0.5	~0.12
6_u	2.17	2.76	2.92	2.68	0.75	-0.08
6_d	3.70	4.58	3.74	4.57	0.04	-0.01
Me	1.14	1.20	1.21	0.31	0.07	-0.89

[a] Chemical shift could not be identified with certainty.



8b **9b**

Figure 1. 3D representation[15] of the diastereomers of the syn-amide rotamers[13] of (*R*)- and (*S*)-MTPA derivatives of (*R*)-2-methylpiperidine, (**8b** and **9b**, respectively).

Chem3D renderings for the two syn-amide rotamers **8b** and **9b** (Figure 1) facilitate rationalization of the ^{1}H NMR data in Table 1**.** Each of the rotamers has its methyl group at C(2) in an axial orientation and was identified as the minimum energy geometry via Monte Carlo searching with the Amber force field in MacroModel (although the fluorine atoms are not properly parameterized). From these views, the greatest difference between the syn-amides **8b** and **9b** would be expected for the chemical shift of the 2-methyl substituent. Clearly, the methyl group in **9b** will experience greater shielding than the methyl group in **8b**.[6b] This expectation is borne out by the NMR data: the $\Delta\delta_{Me}$ ($\delta_S - \delta_R$) is −0.89 ppm. Recognize that the magnitude of this $\Delta\delta$ value is enormous when compared with those from, e.g., Mosher esters. The latter rarely exceed 0.3 ppm and often are meaningful even when they are as small as a few hundredths of a ppm.[2,14]

In the analysis of these Mosher amides the signs of the $\Delta\delta$ values do not follow the usual simple pattern that all protons in, say, the right "half" of the molecule will

(12) (a) Lunazzi, L.; Macciantelli, D.; Tassi, D.; Dondoni, A. *J. Chem. Soc., Perkin Trans. 2* **1980**, 717. (b) Chow, Y. L.; Colon, C. J.; Tam, J. N. S. *Can. J. Chem.* **1968**, *46*, 2821.

(13) The syn-amide rotamer is defined throughout as the one having the α-carbon of the acid moiety of the amide syn to the lowest numbered, substituted carbon on the amine moiety [C(2) for unsymmetrically substituted cyclic amines].

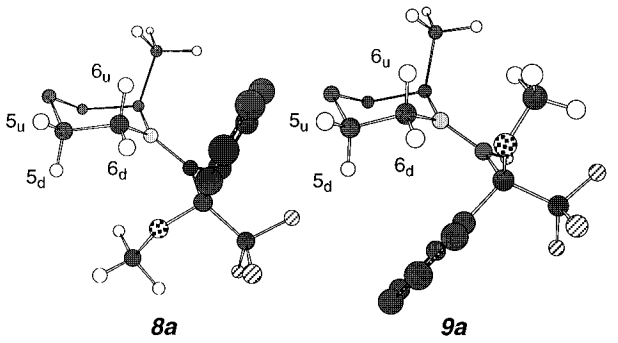


Figure 2. 3D representation of the diastereomers of the anti-amide rotamers of (*R*)- and (*S*)-MTPA derivatives of (*R*)-2-methylpiperidine (**8a** and **9a**, respectively).

be of one sign while those in the left "half" will be of the opposite sign. For example, the sign of the nearby H(2) shows a $\Delta\delta = +0.21$, opposite in sign to that of the C(2) methyl group. This is entirely reasonable when one carefully considers the spatial relationships among the protons in question and the phenyl groups of **8b** and **9b**.[6b] Both the axial and equatorial protons at C(3) [$H(3_d)$ and $H(3_u)$, respectively] in **8b/d** and **9b/d** have extremely large, positive $\Delta\delta$ values (+1.16 and +0.6 ppm, respectively), consistent again with the geometries shown in the Chem 3D renderings of **8b** and **9b**. Thus, the differential anisotropy in the two diastereomers is even greater at the more remote C(3) than for the protons at the closer C(2). The remaining $\Delta\delta$ values are relatively small, consistent with their remote location from the phenyl ring in either **8b** or **9b**.

Additional information can be gleaned from examination of the minimized, major, anti-amide rotamers (Figure 2). In structure **8a** the phenyl group is aimed at the axial proton at C(6) [$H(6_u)$], while in **9a**, the phenyl is oriented toward both protons at C(5). Again, these observations are supported by the NMR data. The $\Delta\delta$ value for the $H(6_u)$ proton in **8a/c** and **9a/c** is +0.75 ppm, while the $\Delta\delta$ values for $H(5_d)$ and $H(5_u)$ are −1.0 and −0.5, respectively. In contrast the $\Delta\delta$ value for $H(6_d)$ is quite small (+0.04) since it "bisects" the shielding regions of the phenyl rings in **8a** and **9a**. While one might expect that small changes in rotation about the phenyl to α-carbon bond (phenyl rotamers) could lead to significant changes in the resulting orientation of the phenyl's shielding region, it is noteworthy that the depicted minimum energy geometries nicely rationalize the experimental $\Delta\delta$ values and are not accompanied by additional phenyl rotamers of similar energy.

Several of the effects observed for the case of the 2-methylpiperidine amides **8** vs **9** are general and applicable to MTPA amides of other substituted piperidines. The prediction can be made that for any given amide rotamer the phenyl group will be principally oriented toward the axial proton at C(3) [or C(5)] in one diastereomer or toward an axial substituent present at C(2) [or C(6)] for the other diastereomer. For example, in the syn rotamers of (*R*)-2-methylpiperidine (**8b/d** and **9b/d**), the phenyl is directed toward the axial methyl group at C(2) in **9b/d** ($\delta = 0.31$ ppm) and toward the axial proton

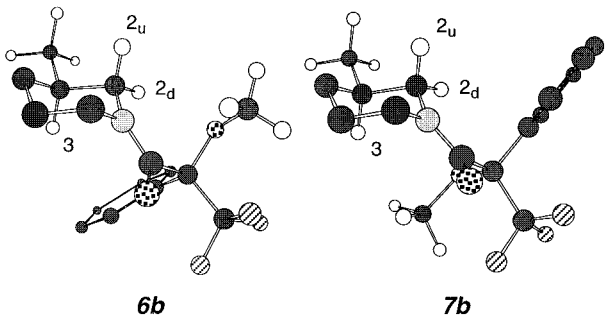


Figure 3. 3D representation of the diastereomers of the syn-amide rotamers of (*R*)- and (*S*)-MTPA derivatives of (*R*)-3-methylpiperidine (**6b** and **7b**, respectively).

Table 2. Chemical Shifts (ppm in $CDCl_3$) and $\Delta\delta$ Values for the Individual Rotamers of (*R*)- and (*S*)-MTPA Amides of (*R*)-3-Methylpiperidine (6 and 7, Respectively)

H	**6a/c**	**6b/d**	**7a/c**	**7b/d**	$\Delta\delta = \delta_S - \delta_R$ (**a/c**)	$\Delta\delta = \delta_S - \delta_R$ (**b/d**)
2_u	2.43	2.34	2.24	1.82	-0.19	-0.52
2_d	4.40	3.88	4.55	3.72	0.15	-0.16
3	1.5	0.35	1.5	1.5	~0	1.15
4_u	0.99	0.91	0.95	0.98	-0.04	0.07
4_d	1.74	1.5	1.7	1.5	~-0.04	~0
5_u	1.3	1.5	1.05	1.7	~-0.25	~0.2
5_d	1.3	1.3	0.35	1.5	~-0.95	~0.2
6_u	2.28	2.47	2.74	2.53	0.46	0.06
6_d	3.69	4.69	3.87	4.61	0.18	-0.08
Me	0.93	0.38	0.89	0.66	-0.04	0.28

$H(3_d)$ in **8b/d** ($\delta = 0.49$ ppm). In the anti rotamers $H(6_u)$ is shielded to $\delta = 2.17$ in **8a/c** and $H(5_d)$ to $\delta = 0.32$ in **9a/c**.

The ^1H NMR data for the MTPA amides of 3-methylpiperidine (**6** and **7**, Table 2) follow the above expectations. The largest observed shielding effects are for H(3) in the syn (or **b/d**) case ($\Delta\delta = +1.15$ ppm) and $H(5_d)$ in the anti (or **a/c**) case ($\Delta\delta = -0.95$ ppm). Both of these protons are axial in the predominant conformation, which has the 3-methyl substituent equatorial (Figure 3). The axial protons at C(2) and C(6) are also indicative. For example, $H(6_u)$ in the **a/c** case ($\Delta\delta = +0.46$ ppm) and $H(2_u)$ in the **b/d** case ($\Delta\delta = -0.52$ ppm) show significant $\Delta\delta$ values, although not as large as for the 2-methyl substituent in **9b/d** ($\Delta\delta = -0.89$ ppm), which is oriented closer to the center of the phenyl shielding region.

The 3-methyl group in **6** and **7** shows, not surprisingly, a very small $\Delta\delta$ (= −0.04 ppm) for the anti rotamers but a larger, more diagnostic $\Delta\delta$ for the syn amide rotamers ($\delta_{\mathbf{7b/d}} - \delta_{\mathbf{6b/d}} = +0.28$ ppm). The positive sign of this $\Delta\delta$ reinforces the fact that one cannot simply assume that protons on the "top half" of the molecule will be more highly shielded when the phenyl ring of the MTPA moiety is oriented "up". Namely, in conformers **7b** both the 3-methyl and phenyl groups are "up" while in **6b** one is "up" the other "down". However, from the Amber-derived structures (Figure 3) we conclude that the phenyl ring in **7b** is actually farther away from the methyl (average methyl carbon to phenyl carbon distance = 5.92 Å) than

(14) Rieser, M. J.; Hui, Y.-H.; Rupprecht, J. K.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L.; Hanson, P. R.; Zhuang, Z.-P.; Hoye, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 10203.

(15) Selected protons have been removed for clarity in this and all subsequent figures.

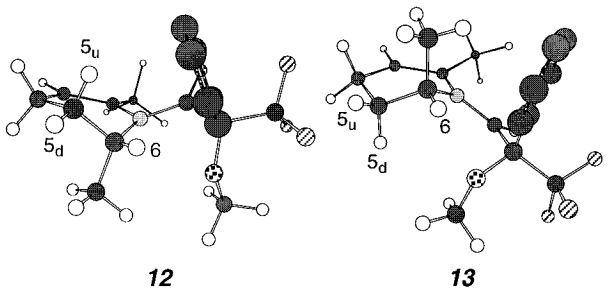
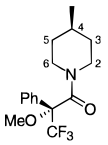
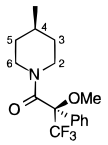


Figure 4. 3D representation of the diastereomers of the (*R*)-MTPA Amides of (6*R*)- and (6*S*)-2,6-dimethyl-1,4,5,6-tetrahydropyridine (**12** and **13**, Respectively).

Table 3. Chemical Shifts (ppm in $CDCl_3$) for the Individual Amide Rotamers of the (*R*)-MTPA Amide of 4-Methylpiperidine (5)

H	 **5a/c**	 **5b/d**
2_d	2.59	2.18
2_u	4.69	3.80
3_d	1.65	1.4
3_u	1.0	1.0
4	1.4	1.4
5_u	-0.02	1.10
5_d	1.0	1.74
6_u	3.92	4.62
6_d	2.79	2.62
Me	0.76	0.91

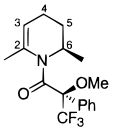
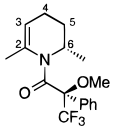
in **6b** (average distance = 4.68 Å). Therefore, the methyl experiences more shielding in **6b**. This emphasizes the importance of evaluating specific geometric relationships within appropriate models of the MTPA amides in question.

The (*R*)- and (*S*)-amides of 4-methylpiperidine are enantiomeric, and only the former, **5**, was prepared. The ^{1}H NMR data for the diastereomeric amide rotamers of **5** is summarized in Table 3 and serves to reinforce the chemical shift trends described. Thus, in one rotamer the axial proton at C(5) should be strongly shielded [i.e., $\delta_{H(5u)}$ in **5a/c** = −0.02], and in the other rotamer the axial proton at C(2) should be highly shielded [i.e., $\delta_{H(2d)}$ in **5b/d** = 2.18].

Diastereomers **12** and **13**, tetrahydropyridine−MTPA derivatives, were prepared as precursors to the *trans*-2,6-dimethylpiperidine derivatives. These compounds are dominated by a single conformation in which the amide carbonyl is syn to the allylic methyl group (to minimize allylic strain) and with the 6-methyl group in an axial-like orientation (Figure 4). This is supported by Amber calculations and the fact that the width at half-height of H(6) in the ^{1}H NMR spectrum of each of **12** and **13** is ∼27 Hz, consistent with its equatorial orientation. That is, ∼21 Hz arises from coupling to the 6-methyl group so the remaining J values must both be small.[16]

(16) Hoye, T. R.; Hanson, P. R.; Vyvyan, J. R. *J. Org. Chem.* **1994**, *59*, 4096.

Table 4. Chemical Shifts (ppm in $CDCl_3$) and $\Delta\delta$ Values for the (*R*)-MTPA Amides of (6*R*)- and (6*S*)-2,6-Dimethyl-1,4,5,6-tetrahydropyridine (12 and 13, Respectively)

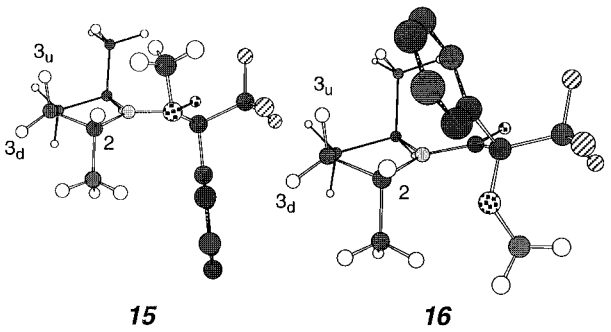
H	 **12**	 **13**	$\Delta\delta =$ $\delta_S - \delta_R$
3	5.18	5.12	-0.06
4_u	1.9	2.0	0.1
4_d	1.9	2.0	0.1
5_u	1.03	1.57	0.54
5_d	0.95	1.83	0.88
6	4.04	4.38	0.34
Me(2)	2.10	2.16	0.06
Me(6)	1.07	0.10	-0.97

Although the presence of the double bond somewhat distorts the ring conformation, the established chemical shift trends also apply to these molecules (Table 4). The methyl substituent at C(6) in **13** is greatly shielded ($\Delta\delta$ = −0.97 ppm), consistent with a single rotamer in which the MTPA phenyl and C(6)-Me are nearly always in close proximity. The diastereomer **12** is shielded most at the C(5) methylene protons [$\Delta\delta$ = +0.88 ppm for H(5_d) and +0.54 for H(5_u)]. Note that the $\Delta\delta$ values for the side of the molecule anti to the MTPA moiety are very small, again consistent with the predominance of one amide rotamer. Recall that the diastereomers **12** and **13** were prepared from racemic amine and then separated chromatographically. Thus, the configuration at C(6) in each has not been independently established but, rather, has been deduced from analysis of the MTPA data *vis-a-vis* those for **8** and **9**. The remarkably large $\Delta\delta$ values, when taken in conjunction with the conformational rules established above, demand the conclusion that **12** bears the *R* configuration at C(6) and **13** the *S*.

The MTPA amide of *cis*-2,6-dimethylpiperidine **3**[6]also derives from an achiral amine precursor (like the amide of 4-methylpiperidine) and follows the chemical shift trends (Table 5). For example, the methyl substituent at C(2) is greatly shielded (δ = 0.28 ppm) in rotamer **3a/c**. In rotamer **3b/d** the axial proton H(5_d) has a chemical shift of 0.56 ppm, while the equatorial proton H(5_u) has a chemical shift of 0.88 ppm.

For the diastereomeric amides **10** and **11** the individual amide rotamers are not distinguishable by ^{1}H NMR analysis because, as is the case for the parent piperidine compound **4**, the two amide rotamers can interconvert by ring-flipping (see Conformational Considerations). Nonetheless, the large $\Delta\delta$ values for the methyl group at C(2) and for H(2), syn to the MTPA α-carbon, allow the assignment of the (2*R*,6*R*) configurations in **10** and **ent-11**. Thus, the configuration independently deduced for the **10** and **11** diastereomeric pair is the same as those for their precursor pair, **12** and **13**.

MTPA amides of pyrrolidines are also useful. Table 6 contains the chemical shift data assigned to the amides derived from pyrrolidine itself (**14**) and from (2*R*,5*R*)-2,5-dimethylpyrrolidine (**15** and **16**), whose configuration is unambiguously known.[10] Again, individual amide rotamers are not observed because rapid ring-conformational



15 ***16***

Figure 5. 3D representation of the diastereomers of the (*R*)- and (*S*)-MTPA amides of (2*R*,5*R*)-2,5-dimethylpyrrolidine (**15** and **16**, respectively).

Table 5. Partial Listing of Chemical Shifts (ppm in $CDCl_3$) and $\Delta\delta$ Values for the Individual Rotamers of *cis*-2,6-Dimethylpiperidine−(*S*)-MTPA Amide (3a and 3b) and the (*R*)-MTPA Amides of (2*R*,6*R*)-2,6-Dimethylpiperidine and (2*S*,6*S*)-2,6-Dimethylpiperidine (10 and 11)

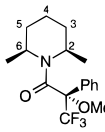
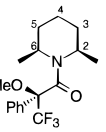
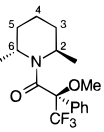
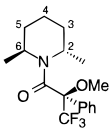
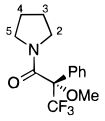
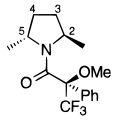
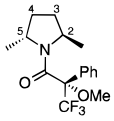
H	 ***3a/c***	 ***3b/d***	 ***10***	 ***11***	$\Delta\delta =$ $\delta_S - \delta_R$ ($\delta_{ent\text{-}11} - \delta_{10}$)
2	5.03	4.50	3.93	4.37	0.40
6	4.01	4.82	3.65	4.13	0.48
5_u		0.88			
5_d		0.56			
Me(2)	0.28	1.31	1.20	0.21	-0.99
Me(6)	1.23	1.24	1.54	1.40	-0.14

Table 6. Chemical Shifts (ppm in $CDCl_3$) and $\Delta\delta$ Values for the MTPA Amide of Pyrrolidine (14) and the (*R*)- and (*S*)-MTPA Amides of (2*R*,5*R*)-2,5-Dimethylpyrrolidinee (15 and 16)

H	 ***14***	 ***15***	 ***16***	$\Delta\delta =$ $\delta_S - \delta_R$ ($\delta_{16} - \delta_{15}$)
2_u	2.64	-	-	-
2_d	3.27	3.19	4.43	1.24
3_u	1.54	1.25	1.5	0.2
3_d	1.54	1.60	2.05	0.45
4_u	1.7	2.06	2.05	-0.01
4_d	1.7	1.42	1.5	0.1
5_u	3.6	4.30	4.33	0.03
5_d	3.6	-	-	-
Me(2)	-	1.09	0.10	-0.99
Me(5)	-	1.32	1.30	-0.02

changes render the two rotamers identical. The largest $\Delta\delta$ values for these pyrrolidines are observed for the methylene, methine, and methyl protons attached to C(2), syn to the α-carbon. A smaller, but still meaningful, $\Delta\delta$ is seen for the C(3) methylene protons. These trends are consistent with the geometries shown in Figure 5 for **15** and **16**. To summarize, for the piperidine−MTPA amides, the largest $\Delta\delta$ values are found for protons four bonds removed from the amide carbonyl carbon [i.e., H(3) or Me(2)]. For pyrrolidines, the ring protons at C(3) (four bonds removed) are less affected than those attached to C(2) (three bonds), but substituent protons at C(2) (four bonds) still have large $\Delta\delta$ values. One should be able to assign chiral pyrrolidines of unknown configuration with confidence.

Presented above is a reliable and powerful method for unambiguously determining the absolute configuration of chiral secondary amines based on Mosher amide technology. It should prove to be general. Additional applications showing the use of this information to confirm and/or deduce the configuration of various natural and synthetic chiral amines will be reported elsewhere.

Experimental Section

Method 1. General Procedure for Preparation of MTPA Amides with No External Amine Base. MTPA-Cl (1 equiv) was added to a stirred solution of the amine (2.1 equiv) in methylene chloride (0.1−0.25 M) under a nitrogen or argon atmosphere. The mixture was stirred at ambient temperature until TLC indicated disappearance of the amine. The mixture was concentrated under reduced pressure, and the residue was loaded onto a microcolumn and purified by flash chromatography.

(*R*)-Piperidine−MTPA Amide (4). Piperidine (29 mg, 0.34 mmol) was dissolved in methylene chloride (1 mL) at room temperature. (*S*)-MTPA-Cl (32 μL, 0.17 mmol) was added, and the reaction mixture was stirred for 1 h. The mixture was concentrated under reduced pressure and purified by flash chromatography (5:1 hexanes/EtOAc) to yield a white solid (48 mg, 94%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.52 (d, 2H, J = 5.0 Hz), 7.37−7.39 (m, 3H), 3.85 (ddd, 1H, J = 3.5, 6.5, and 12.5 Hz), 3.40 (ddd, 1H, J = 4.0, 8.5, and 12.5 Hz), 3.67 (s, 3H), 3.22 (ddd, 1H, J = 4.5, 5.5, and 13.5 Hz), 3.19 (ddd, 1H, J = 3.5, 8.0, and 13.5 Hz), 1.6 (m, 2H), 1.48 (m, 2H), 1.16 (m, 1H), and 0.77 (m, 1H); IR (thin film) 2940 (m), 1654 (s), 1259 (s), 1180 (s), and 1157 (s) cm^{-1}; MS (EI) m/z 301 (1, M$^+$), 189 [4, Ph(OMe)C$^+$(CF$_3$)], 112 (100, M$^+$− 189), and 69 (28). Anal. Calcd for $C_{15}H_{18}F_3NO_2$: C, 59.79; H, 6.02. Found: C, 59.57; H, 5.86.

Method 2. General Procedure for Preparation of MTPA Amides with DIEA Base. MTPA-Cl (1.2 equiv) was added to a stirred solution of the amine (1 equiv) and Hunig's base (1.5 equiv) in methylene chloride (0.1−0.25 M) under an argon or nitrogen atmosphere. The reaction mixture was stirred at ambient temperature until TLC indicated disappearance of the substrate amine. The mixture was concentrated under reduced pressure, and the residue was taken up in 1 M NH_4Cl and extracted into methylene chloride. The combined organic extracts were dried over $MgSO_4$ and purified by flash chromatography.

(*R*)-Piperidine−MTPA Amide (4). Piperidine (1.3 mg, 0.015 mmol) and Hunig's base (2.4 mg, 0.018 mmol) were dissolved in methylene chloride (150 μL). (*R*)-MTPA-Cl (4 mg, 0.016 mmol) was added to the stirred reaction mixture, which was stirred overnight and concentrated under reduced pressure. An aqueous solution of 1 M NH_4Cl was added, and the resulting slurry was agitated for 30 min. Extraction with methylene chloride, drying over $MgSO_4$, and purification by flash chromatography (5:1 hexanes/EtOAc) provided **4** as a clear oil (3.8 mg, 80%).

Method 3. General Procedure for Preparation of MTPA Amides from Substrate Amine·HCl and Excess IPEA Base. MTPA-Cl (1.2 equiv) was added to a stirred solution of the amine hydrochloride salt (1 equiv) and Hunig's base (2.2 equiv) in methylene chloride (0.1−0.25 M) under an argon or nitrogen atmosphere. The reaction mixture was stirred at ambient temperature until TLC indicated disappearance of the amine. The mixture was concentrated under reduced pressure. The residue was taken up in 1 M NH_4Cl and extracted into methylene chloride. The combined organic

extracts were dried over $MgSO_4$ and purified by flash chromatography.

(*R*)-Piperidine−MTPA Amide (4). (*S*)-MTPA-Cl (4.8 mg, 0.019 mmol, 1.1 equiv) was added to a stirred suspension of piperidine hydrochloride (2.2 mg, 0.018 mmol) and Hunig's base (5 mg, 0.038 mmol, 2.2 equiv) in methylene chloride (150 μL). The reaction mixture was stirred at ambient temperature overnight and concentrated under reduced pressure. An aqueous solution of 1 M NH_4Cl was added, and the resulting slurry was agitated for 30 min. Extraction with methylene chloride, drying over $MgSO_4$, and purification by flash chromatography (5:1 hexanes/EtOAc) gave **4** as a clear oil (3.4 mg, 63%).

Spectral Data for MTPA Amides 5−16 (in the ^{1}H NMR data for 5−9, resonances associated with the major amide rotamer are indicated with *, those for the minor amide rotamer with **; resonances comprising protons from both rotamers bear no asterisk).

4-Methylpiperidine−(*R*)-MTPA amide (5): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.54−7.55* (m, 2H), 7.44** (m, 2H), 7.36−7.39 (m, 6H), 4.69* (dddd, 1H, J = 2.5, 2.5, 4.0, and 13.0 Hz), 4.62** (dddd, 1H, J = 2.0, 3.0, 4.5, and 13.0 Hz), 3.92* (dddd, 1H, J = 2.5, 2.5, 4.5, and 14.0 Hz), 3.80** (dddd, 1H, J = 2.5, 3.0, 4.0, and 13.5 Hz), 3.74** (q, 3H, J = 2 Hz), 3.67* (q, 3H, J = 2.0 Hz), 2.79* (ddd, 1H, J = 3.0, 12.5, and 14.0 Hz), 2.62** (ddd, 1H, J = 3.0, 12.0, and 13.0 Hz), 2.59* (ddd, 1H, J = 3.0, 12.5, and 13.0 Hz), 2.18** (ddd, 1H, J = 3.0, 12.5, and 13.0 Hz), 1.74** (dddd, 1H, J = 3.0, 3.0, 6.0, and 13.5 Hz), 1.65* (dddd, 1H, J = 3.0, 3.5, 5.0, and 13.5 Hz), 1.41−1.47 (m, 2H), 1.10** (dddd, 1H, J = 4.5, 11.0, 12.5, and 13.5 Hz), 0.96−1.08 (m, 3H), 0.91** (d, 3H, J = 7.0 Hz), 0.76* (d, 3H, J = 6.5 Hz), and −0.02* (dddd, 1H, J = 4.0, 12.0, 12.5, and 13.5 Hz); IR (thin film) 2952 (m), 1653 (s), 1258 (s), 1180 (s), and 1155 (s) cm^{-1}; MS (EI) m/z 315 (1, M^+), 189 [4, $Ph(OMe)C^+(CF_3)$], 126 (100, M^+ − 189), 105 (6), and 55 (29).

(3*R*)-3-Methylpiperidine−(*R*)-MTPA amide (6): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.55−7.60* (m, 2H), 7.48−7.53** (m, 2H), 7.36−7.42 (m, 6H), 4.69* (dd, 1H, J = 3 and 13 Hz), 4.40** (dd, 1H, J = 3 and 13.5 Hz), 3.88* (dd, 1H, J = 2 and 12 Hz), 3.77** (q, 3H, J = 1.5 Hz), 3.69** (m, 1H), 3.68* (q, 3H, J = 1.5 Hz), 2.47* (ddd, 1H, J = 3, 13, and 13 Hz), 2.43** (dd, 1H, J = 10.5 and 13 Hz), 2.34* (dd, 1H, J = 10.5 and 13.5 Hz), 2.28** (ddd, 1H, J = 4, 10.5, and 13.5 Hz), 1.74** (m, 1H), 1.57−1.68 (m, 3H,), 1.32−1.41 (m, 3H), 0.99** (m, 1 H), 0.93** (d, 3H, J = 6.5 Hz), 0.91* (m, 1H), 0.38* (d, 3H, J = 5 Hz), and 0.35* (m, 1H); IR (thin film) 2851 (w), 1654 (s), 1260 (s), 1180 (s), and 1157 (s) cm^{-1}; MS (EI) m/z 315 (1, M^+), 296 (1), 189 [4, $Ph(OMe)C^+(CF_3)$], 126 (100, M^+ − 189), 105 (6), and 83 (15). Anal. Calcd for $C_{16}H_{20}F_3NO_2$: C, 60.94; H, 6.39. Found: C, 61.06; H, 6.38.

(3*R*)-3-Methylpiperidine−(*S*)-MTPA amide (7): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.54−7.56* (m, 2H), 7.48−7.51** (m, 2H), 7.37−7.39 (m, 6H), 4.61** (dd, 1H, J = 1.5 and 13.5 Hz), 4.55* (dddd, 1H, J = 2, 2, 4, and 13 Hz), 3.87* (dd, 1H, J = 2 and 13.5 Hz), 3.73** (q, 3H, J = 1.5 Hz), 3.72** (m, 1H), 3.68* (q, 3H, J = 1.5 Hz), 2.74* (ddd, 1H, J = 2.5, 13.5, and 13.5 Hz), 2.53** (ddd, 1H, J = 3.5, 12.5, and 13.5 Hz), 2.24* (dd, 1H, J = 11 and 13 Hz), 1.82** (dd, 1H, J = 11 and 13 Hz), 1.73−1.78 (m, 2H), 1.42−1.63 (m, 4H), 1.05* (ddddd, 1H, J = 3.5, 3.5, 3.5, 3.5, and 13.5 Hz), 0.98** (dddd, 1H, J = 3.5, 12.5, 12.5, and 12.5 Hz), 0.95* (dddd, 1H, J = 4, 12, 12, and 12 Hz), 0.89* (d, 3H, J = 6.5 Hz), 0.66** (d, 3H, J = 6.5 Hz), and 0.35* (ddddd, 1H, J = 4, 4, 12.5, 12.5, and 12.5 Hz); IR (thin film) 2851 (w), 1654 (s), 1260 (s), 1180 (s), and 1157 (s) cm^{-1}; MS (EI) m/z 315 (1, M^+), 296 (1), 189 [5, $Ph(OMe)C^+(CF_3)$], 126 (100, M^+ − 189), 105 (5), and 83 (15).

(2*R*)-Methylpiperidine−(*R*)-MTPA amide (8):[6b,17] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.53−7.59 (m, 4H), 7.30−7.43 (m, 6H), 4.93* (dq, 1H, J = 5 and 7 Hz), 4.58** (bd, 1H, J = 13.5 Hz), 4.14** (dq, 1H, J = 5 and 7 Hz), 3.76* (q, 3H, J = 1.5 Hz), 3.71** (q, 3H, J = 1.5 Hz), 3.70** (m, 1H), 2.76** (ddd, 1H, J = 2.5, 12.5, and 13.5 Hz), 2.17* (ddd, 1H, J = 3, 13, and 13.5 Hz), 1.3−1.7 (m, 10H), 1.20** (d, 3H, J = 6.5 Hz), 1.14* (d, 3H, J = 7.5 Hz), 0.80** (dddd, 1H, J = 2.5, 2.5, 5, and 13.5 Hz), and 0.49** (dddd, 1H, J = 5, 5, 13.5, and 13.5 Hz); IR (thin film) 2942 (m), 1651 (s), 1182 (m), and 1157 (m) cm^{-1}; MS (EI) m/z 315 (1, M^+), 189 [11, $Ph(OMe)C^+(CF_3)$], 126 (100, M^+ − 189), 105 (9), and 83 (10); HRMS calcd for $C_{16}H_{20}F_3NO_2$ (315.1446), found 315.1461.

(2*R*)-2-Methylpiperidine−(*S*)-MTPA Amide (9):[6b] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.53−7.57 (m, 4H), 7.32−7.43 (m, 6H), 5.06* (dq, 1H, J = 5 and 7 Hz), 4.57** (bd, 1H, J = 14 Hz), 4.35** (dq, 1H, J = 5 and 7 Hz), 3.79** (q, 3H, J = 1.5 Hz), 3.74* (bd, 1H, J = 14 Hz), 3.65* (q, 3H, J = 1.5 Hz), 2.92* (ddd, 1H, J = 3, 13.5, and 14 Hz), 2.68** (ddd, 1H, J = 3, 13.5, and 13.5 Hz), 1.72** (bd, 1H, J = 13.5 Hz), 1.35−1.68 (m, 9H), 1.21* (d, 3H, J = 7 Hz), 1.00* (bd, 1H, J = 14 Hz), 0.32* (ddddd, 1H, J = 5, 5, 12, 13, and 13 Hz), and 0.31** (d, 3H, J = 7 Hz); IR (thin film) 2942 (m), 1651 (s), 1182 (m), and 1157 (m) cm^{-1}; MS (EI) m/z 315 (1, M^+), 189 [11, $Ph(OMe)C^+(CF_3)$], 126 (100, M^+ − 189), 105 (9), and 83 (10); HRMS calcd for $C_{16}H_{20}F_3NO_2$ (315.1446), found 315.1433.

(2*R*, 6*R*)-2,6-Dimethylpiperidine−(*R*)-MTPA Amide (10). Enamide **12** (11 mg, 0.034 mmol) was dissolved in methylene chloride (2 mL). To this stirred solution was added sodium cyanoborohydride (15 mg, 0.24 mmol, 7 equiv), and the reaction mixture was stirred at ambient temperature for 10 min. The mixture was then cooled to −42 °C, and trifluoroacetic acid (28 μL, 41 mg, 0.36 mmol, 11 equiv) was added over ∼1 min. The reaction mixture was stirred at −42 °C for 3.5 h, and the reaction was quenched with THF/saturated $NaHCO_3$ (1.5 mL). Once warmed to room temperature, the layers were separated, and the aqueous layer was extracted with methylene chloride (3 × 3 mL). The combined extracts were dried over $MgSO_4$ and concentrated to a clear oil [10 mg, 91%, a trace (<5%) of the cis isomer **3** was observed by GC/MS and ^{1}H NMR analysis]. The oil was further purified by preparative HPLC (96:4 hexanes/EtOAc) to give **10** as a white solid (6 mg, 55%); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.61 (m, 2H), 7.37−7.40 (m, 3H), 3.93 (br s, 1H), 3.73 (q, 3H, J = 1.5 Hz), 3.66 (br s, 1H), 1.68 (br s, 2H), 1.55 (br s, 2H), 1.54 (d, 3H, J = 6.5 Hz), 1.20 (d, 3H, J = 6.5 Hz), and 0.87 (br s, 2H); MS (EI) m/z 189 [14, $Ph(OMe)C^+(CF_3)$], 140 (100, M^+ − 189), 97 (25), 70 (10), and 55 (45).

(2*S*,6*S*)-2,6-Dimethylppiperidine−(*R*)-MTPA Amide (11). Diastereomer **11** was prepared from **13** in a procedure analogous to the preparation of **10** from **12** (6.1 mg, 48%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.58−7.60 (m, 2H), 7.36−7.39 (m, 3H), 4.37 (br s, 1H), 4.13 (br s, 1H), 3.74 (q, 3H, J = 1.5 Hz), 1.91 (m, 1H), 1.84 (m, 1H), 1.66 (m, 2H), 1.51 (m, 2H), 1.40 (d, 3H, J = 6.5 Hz), and 0.21 (d, 3H, J = 6 Hz); MS (EI) m/z 189 [18, $Ph(OMe)C^+(CF_3)$], 140 (100, M^+ − 189), 119 (7), 97 (27), 70 (10), and 55 (43).

(6*R*)-2,6-Dimethyl-1,4,5,6-tetrahydropyridine−(*R*)-MTPA Amide (12) and −(*S*)-MTPA Amide (13). 2,6-Lutidine (13 g, 0.121 mol) was dissolved in dry ethanol (225 mL) and cooled in an ice bath. Sodium (spheres, washed with hexanes) was added to the solution over 10 min. The reaction mixture was warmed to room temperature and the mixture was stirred for 36 h. The reaction was quenched with water and the solution steam distilled. The distillate was concentrated under reduced pressure, basified with aqueous NaOH, and extracted with chloroform. The solvent was removed under reduced pressure to afford several grams of a crude mixture of products. A portion of this (50 mg) was dissolved in THF (500 μL) and stirred while (*S*)-MTPA-Cl (45 μL, 0.23 mmol) was added. The reaction mixture was stirred at room temperature for 15 h and concentrated under reduced pressure. The resulting mass of solid and oil was loaded onto a SiO_2 microcolumn and eluted with EtOAc to obtain a mixture of amides as pale yellow oils (38 mg). Enamides **12** and **13** were isolated by preparative HPLC (89:11 hexanes/EtOAc), with **12** (t_R = 10.0 min) eluting before **13** (t_R = 11.7 min). **12**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.58−7.60 (m, 2H), 7.38−7.42 (m, 3H), 5.18 (m, 1H), 4.04 (m, 1H), 3.79 (q, 3H, J = 1.5 Hz), 2.10 (s, 3H), 1.89−1.92 (m, 2H), 1.07 (d, 3H, J = 6.5 Hz), 1.03 (dddd, 1H, J = 4, 9.5, 9.5, and 9.5 Hz), and 0.95 (m, 1H); IR (thin film) 2960 (w), 1677 (s), 1658 (s), 1401 (m), 1181 (s), and 1163 (s); LRMS (EI, 70 eV) m/z (rel int) 327 (22, M^+), 189 [36,

(17) The CAS name for this compound is [*R*-(*R**,*R**)]-2-methyl-1-(3,3,3-trifluoro-2-methoxy-1-oxo-2-phenylpropyl)piperidine.

Ph(OMe)$C^+(CF_3)$], 139 (7), 138 (41), 105 (11), and 96 (100). **13**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56−7.58 (m, 2H), 7.37−7.43 (m, 3H), 5.12 (br s, 1H), 4.38 (m, 1H), 3.77 (q, 3H, J = 1.5 Hz), 2.16 (s, 3H), 1.93−2.06 (m, 2H), 1.83 (dddd, 1H, J = 4, 7.5, 12.5, and 12.5 Hz), 1.57 (m, 1H), and 0.10 (d, 3H, J = 7 Hz); IR (thin film) 2961 (w), 1675 (m), 1654 (s), 1403 (m), 1180 (s), and 1158 (s) cm^{-1}; MS (EI) m/z 327 (20, M^+), 189 [36, Ph(OMe)$C^+(CF_3)$], 138 (41), 105 (11), and 96 (100).

Pyrrolidine−MTPA amide (**14**): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.52−7.53 (m, 2H), 7.37−7.38 (m, 3H), 3.66 (s, 3H), 3.56−3.62 (m, 2H), 3.27 (m, 1H), 2.64 (ddd, J = 4.5, 7.0, and 11.0 Hz, 1H), 1.70−1.79 (m, 3H), and 1.54 (m, 1H); IR (thin film) 2940 (w), 1654 (s) 1263 (s), and 1175 (m) cm^{-1}; MS (EI) m/z 189 [5, Ph(OMe)$C^+(CF_3)$], 105 (8), 98 (100, $M^+ - 189$), and 55 (45).

(2*R*,5*R*)-2,5-Dimethylpyrrolidine−(*R*)-MTPA amide (**15**): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.53 (m, 2H), 7.36−7.40 (m, 3H), 4.30 (dq, 1H, J = 8 and 6 Hz), 3.66 (q, 3H, J = 2 Hz), 3.19 (dq, 1H, J = 6.5 and 6.5 Hz), 2.06 (dddd, 1H, J = 6, 8.5, 12.5, and 14 Hz), 1.60 (dddd, 1H, J = 6.5, 6.5, 12, and 13.5 Hz), 1.42 (dd, 1H, J = 6 and 12 Hz), 1.32 (d, 3H, J = 6.5 Hz), 1.25 (dd, 1H, J = 6 and 12.5 Hz), and 1.09 (d, 3H, J = 6.5 Hz); IR (thin film) 2967 (w), 1644 (s), 1387 (m), 1257 (m), 1178 (s), 1160 (s) cm^{-1}; MS (EI) m/z 189 [13, Ph(OMe)$C^+(CF_3)$], 126 (100, $M^+ - 189$), 105 (8), 83 (50), and 55 (29).

(2*R*,5*R*)-Dimethylpyrrolidine−(*S*)-MTPA amide (**16**): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.63 (m, 2H), 7.36 (m, 3H), 4.43 (dq, 1H, J = 6.5 and 6.5 Hz), 4.33 (dq, 1H, J = 8 and 6.5 Hz), 3.68 (q, 3H, J = 2 Hz), 2.03−2.07 (m, 2H), 1.46−1.49 (m, 2H), 1.30 (d, 3H, J = 6.5 Hz), and 0.09 (d, 3H, J = 6.5 Hz); MS (EI) m/z 189 [10, Ph(OMe)$C^+(CF_3)$], 126 (100, $M^+ - 189$), 105 (9), 83 (55), and 55 (22).

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