Molecules **2015**, *20*, 12880-12900; doi:10.3390/molecules200712880

OPEN ACCESS

molecules

ISSN 1420-3049

www.mdpi.com/journal/molecules

Article

Characteristic Conformation of Mosher's Amide Elucidated Using the Cambridge Structural Database

Akio Ichikawa [1,*], Hiroshi Ono [2] and Yuji Mikata [3]

[1] Division of Insect Sciences, National Institute of Agrobiological Sciences, Tsukuba, Ibaraki 305-8634, Japan

[2] Analytical Science Division, National Food Research Institute, Tsukuba, Ibaraki 305-8642, Japan; E-Mail: ono@affrc.go.jp

[3] Department of Chemistry, Biology, and Environmental Science, Faculty of Science, Nara Women's University, Kita-Uoya Nishi-machi, Nara 630-8506, Japan; E-Mail: mikata@cc.nara-wu.ac.jp

* Author to whom correspondence should be addressed; E-Mail: ichikawa@affrc.go.jp; Tel.: +81-29-838-6267; Fax: +81-29-838-6028.

Academic Editor: Derek J. McPhee

Received: 23 June 2015 / Accepted: 10 July 2015 / Published: 16 July 2015

Abstract: Conformations of the crystalline 3,3,3-trifluoro-2-methoxy-2-phenylpropanamide derivatives (MTPA amides) deposited in the Cambridge Structural Database (CSD) were examined statistically as R_{acid}-enantiomers. The majority of dihedral angles (48/58, *ca.* 83%) of the amide carbonyl groups and the trifluoromethyl groups ranged from –30° to 0° with an average angle θ^1 of −13°. The other conformational properties were also clarified: (1) one of the fluorine atoms was antiperiplanar (*ap*) to the amide carbonyl group, forming a staggered conformation; (2) the MTPA amides prepared from primary amines showed a *Z* form in amide moieties; (3) in the case of the MTPA amide prepared from a primary amine possessing secondary alkyl groups (*i.e.*, Mosher-type MTPA amide), the dihedral angles between the methine groups and the carbonyl groups were *syn* and indicative of a moderate conformational flexibility; (4) the phenyl plane was inclined from the O–C_{chiral} bond of the methoxy moiety with an average dihedral angle θ^2 of +21°; (5) the methyl group of the methoxy moiety was *ap* to the *ipso*-carbon atom of the phenyl group.

Keywords: chiral recognition; chirality; crystal engineering; Mosher's method; MTPA

1. Introduction

NMR using chiral resolving agents is a powerful technique, along with X-ray crystallography and circular dichroism, for assignment of the absolute configuration of organic compounds [1]. Mosher *et al*. developed 3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid (MTPA, **1**, Figure 1) and constructed the conformational model of the MTPA amide and the MTPA ester derived from a primary amine and a secondary alcohol, respectively (Figure 2a) [2–4]. Considering the shielding effect of the phenyl ring, the relative stereochemistry of the MTPA amide and the MTPA ester could be elucidated based on a mutual comparison of the ^{1}H-NMR chemical shifts of their diastereomers; namely, upfield shifts are observed in substituent L^2. Therefore, the absolute configuration of the amine moieties and the alcohol moieties could be clarified using stereochemistry of the MTPA moiety as an internal standard. Kusumi *et al*. modified this method using two-dimensional NMR spectroscopy [5–8].

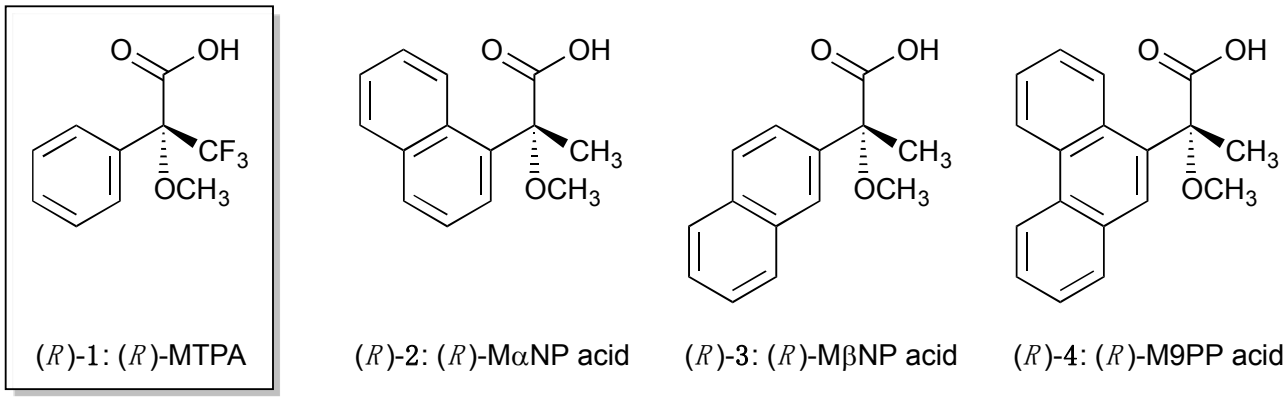


Figure 1. Structures of chiral resolving agents.

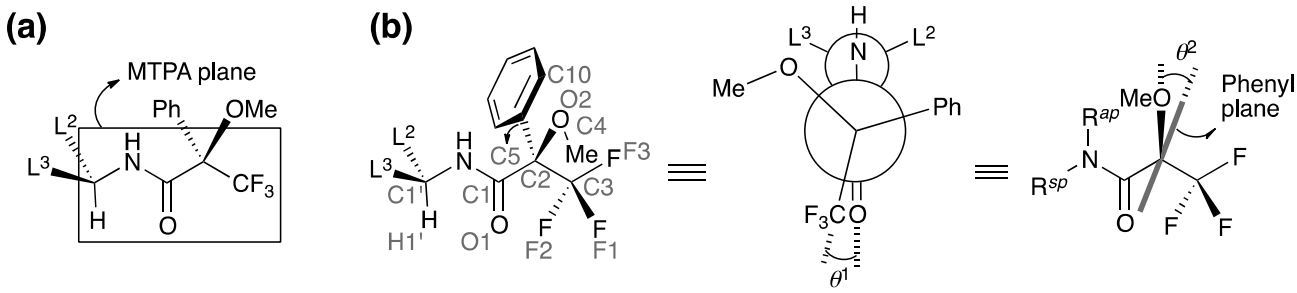


Figure 2. Major conformation of (R_{acid})-MTPA amide proposed in (**a**) previous studies and (**b**) this study. The Newman-like projection originally proposed by Mosher *et al*. [3] was modified in (**b**). Three covalent bonds separate the two chiral centers C1′ and C2; therefore, L^3–C1′–L^2 moiety is more flat in this projection. The MTPA ester exhibited the equivalent conformation with substitution of NH for O [9].

We studied on three chiral resolving agents [*i.e.*, MαNP acid (**2**), MβNP acid (**3**), and M9PP acid (**4**)] based on their enantioresolution of chiral alcohols and elucidation of absolute configurations [10–24]. The resolving ability of **2** is superior to that of **1** in normal phase HPLC. The diastereomeric MαNP esters also exhibit large chemical shift differences (Δδ values) in ^{1}H-NMR spectroscopy [12,18].

In 2013, we elucidated the crystal structure of Mosher's salt prepared from (*R*)-**1** and (*R*)-1-phenylethylamine using X-ray crystallography [9]; Mosher *et al*. prepared this compound via the enantioresolution of *rac*-**1** in ethanol as a less soluble salt [2]. In the course of this study, we found that a number of crystal structures of MTPA amides and MTPA esters were deposited in the CSD.

Each molecular structure is influenced by packing force in crystal [25]. However, statistical analyses of the crystal structures elucidated the relative stability of each conformer [25]. Therefore, we reported statistical analyses of the crystal structures of MTPA esters [9].

The properties of the major conformation of the crystalline MTPA ester are as follows [9]: (1) the ester carbonyl group is synperiplanar (*sp*, dihedral angle 0° to ±30°) [26] to the trifluoromethyl group; (2) the trifluoromethyl group is in the staggered conformation; (3) the methine group of the alcohol moiety is *syn* to the carbonyl group; (4) the phenyl plane is inclined from the O–C_{chiral} bond of the methoxy moiety; (5) the methyl group of the methoxy moiety is antiperiplanar (*ap*, dihedral angle ±150° to 180°) [26] to the *ipso*-carbon atom of the phenyl group. Thus, our database study proposed a modified conformational model of the MTPA ester.

In this report, we perform the statistical analyses of the crystal conformations of MTPA amides deposited in the CSD [27–66]. The conformational data of the crystalline MTPA amide moiety (a total of 58), which had been prepared from: (i) primary amines; (ii) secondary amines; (iii) aniline derivatives [tetrakis-MTPA amides of ruthenium(II) porphyrin complexes]; (iv) diethyl 1-aminoalkylphosphonate derivatives; (v) benzotriazole; (vi) an oxazolidine-2-selone derivative; (vii) a thiocarbamide derivative; and (viii) a *p*-toluenesulfonamide derivative, were statistically analyzed as R_{acid}-enantiomers.

Conformational features of the MTPA amide moiety were similar to those of the MTPA esters, with less diversity (Figure 2b). The features of the major conformation of crystalline MTPA amides are as follows: (1) the amide carbonyl group is *sp* to the trifluoromethyl group with an average dihedral angle θ^1 of −13°; (2) the trifluoromethyl group is in the staggered conformation; (3) the amide moiety of the secondary MTPA amide is in the *Z* form (*i.e.*, R^{ap} = H, R^{sp} = alkyl group); (4) H1′ of the amine moiety is *syn* to the carbonyl carbon atom C1; (5) the phenyl plane is inclined from the O2–C2 bond with an average dihedral angle θ^2 of +21°; (6) the methyl group of the methoxy moiety is *ap* to C5 of the phenyl group.

Structural elucidation of chiral amines is important, because a considerable number of biologically active natural products and pharmaceuticals contain key chiral amine moieties [67–69]. The number of entries in the CSD is increasing rapidly; therefore, the crystal database is important for structural chemistry. The statistical analyses of crystal data have increased our understanding on the properties of acid **1** and have established valuable insights for Mosher's method and crystal engineering [70,71] of MTPA derivatives.

2. Results and Discussion

2.1. Crystal Structures of MTPA Amides Deposited in the CSD

The crystal structures of the MTPA amide moieties were searched in the CSD using ConQuest software. Table 1 shows the original dihedral angles of (R_{acid})- and (S_{acid})-MTPA amides [27–64].

Table 1. Dihedral angles of crystalline MTPA amides [a].

No.	CCDC Number [b]	Reference	Chirality of MTPA [a]	Amine Moiety	R^{sp}	R^{ap}	O1–C1–C2–C3 (θ^1)	C1–C2–C3–F3	C1'–N–C1–O1	X1″–N–C1–O1 [c]	H1′–C1′–N–C1	O2–C2–C5–C10 (θ^2)	C1–C2–O2–C4
1 [d]	199868	[27]	*R*	Primary amine	Secondary alkyl group	H	−13.1(2)	−172.0(1)	7.1(2)	−172.9	−47.4	23.3(2)	54.2(2)
2 [d]	199868	[27]	*R*	Primary amine	Secondary alkyl group	H	−7.3(2)	−174.6(1)	6.3(2)	−173.7	−51.5	29.4(2)	50.4(2)
3 [d]	222942	[28]	*R*	Primary amine	Secondary alkyl group	H	30.3(3) [e]	175.6(2)	−4.2(5)	169(4)	47.0	11.2(7)	−44.4(4)
4 [d]	603055	[29]	*S*	Primary amine	Secondary alkyl group	H	35.0(4) [e]	165.9(3)	0.5(5)	−179.5	15.2	−43.7(4)	−72.0(3)
5	651954	[30]	*R*	Primary amine	Primary alkyl group	H	−26(2)	−168(1)	−6(2)	173	–	24(2)	72(1)
6	651954	[30]	*R*	Primary amine	Primary alkyl group	H	−25(2)	−166(1)	8(2)	−172	–	22(2)	60(2)
7 [d]	678252	[31]	*R*	Primary amine	Secondary alkyl group	H	−22.6(4)	−171.7(3)	9.5(5)	−170.6	29.6	19.7(4)	58.4(3)
8 [d]	678252	[31]	*R*	Primary amine	Secondary alkyl group	H	−14.4(5)	−173.2(3)	5.2(6)	−174.8	28.3	22.5(4)	54.2(4)
9 [d,f]	703912	[32]	*R*	Primary amine	Secondary alkyl group	H	−67.7(6) [e]	−174.6(5)	3.7(9)	170(5)	−22.5	−58.9(7)	−162.7(5)
10	734247	[33]	*R*	Primary amine	Primary alkyl group	H	−29.1(5)	−168.3(3)	−2.9(6)	177.0	–	24.2(5)	62.9(4)
11	739753	[34]	*R*	Primary amine	Primary alkyl group	H	−36.0(2) [e]	−164.7(2)	7.1(3)	−172.9	–	49.8(2)	64.5(2)
12 [d]	1218697	[35]	*R*	Primary amine	Secondary alkyl group	H	−9.8(3)	−176.9(2)	−3.0(4)	171(2)	1.3	12.0(3)	55.5(3)
13 [d]	1229820	[36]	*R*	Primary amine	Secondary alkyl group	H	−31(1) [e]	−169.2(8)	15(2)	136	−7	21	64
14 [d]	1277744	[37]	*R*	Primary amine	Secondary alkyl group	H	−28.4(3)	−170.3(2)	3.9(4)	−176.0	−14.4	26.9(3)	65.2(3)
15 [g]	140352	[38]	*R*	Secondary amine	Secondary alkyl group	Primary Alkyl group	−4.7(5)	−175.4(3)	5.3(6)	−174.7(4)	20.4(6)	27.5(5)	53.4(4)
16 [g]	167289	[39]	*S*	Secondary amine	Secondary alkyl group	Primary alkyl group	5.2(2)	177.7(1)	−0.5(2)	−177.4(2)	10(2)	−11.7(2)	−45.0(2)
17 [g]	241708	[40]	*S*	Secondary amine	Secondary alkyl group	Primary alkyl group	6.9(2)	176.0(1)	−1.7(2)	169.5(1)	48.1	−15.4(2)	−45.1(2)
18 [g]	251663	[41]	*R*	Secondary amine	Secondary alkyl group	Primary alkyl group	−12.4(2)	−172.3(1)	1.8(2)	−168.2(1)	24.3	24.5(2)	56.7(2)
19	288331	[42]	*S*	Secondary amine	Secondary alkyl group	Secondary alkyl group	7.7(3)	176.5(2)	8.7(3)	174.0(2)	−1.3	−14.0(3)	−50.1(3)
20	296547	[43]	*R*	Secondary amine	Primary alkyl group	Primary alkyl group	−13.4(8)	−171.7(5)	−0.9(9)	−170.9(6)	–	12.6(7)	47.4(7)
21 [g]	604432	[44]	*R*	Secondary amine	Secondary alkyl group	Primary alkyl group	−4.1(5)	−176.3(3)	8.7(5)	−170.3(3)	17.1	15.3(4)	51.7(4)
22 [g]	605818	[45]	*R*	Secondary amine	Secondary alkyl group	Primary alkyl group	−15.6(2)	−174.1(1)	5.8(2)	−164.3(1)	−58.3	6.9(2)	52.1(1)
23	638938	[46]	*R*	Secondary amine	Primary alkyl group	Primary alkyl group	−6.2(5)	−173.8(3)	−1.8(5)	−173.7(3)	–	27.7(4)	51.2(4)
24 [g]	675390	[47]	*R*	Secondary amine	Secondary alkyl group	Primary alkyl group	−14.6(2)	−174.7(1)	10.1(3)	−164.8(2)	−56.5	9.2(2)	50.4(2)
25 [g]	706349	[48]	*R*	Secondary amine	Secondary alkyl group	Primary alkyl group	−13.7(4)	−172.3(3)	5.9(5)	−168.6(3)	19(2)	19.3(4)	59.4(4)

Table 1. *Cont.*

No.	CCDC Number [b]	Reference	Chirality of MTPA [a]	Amine Moiety	R^{sp}	R^{ap}	O1–C1–C2–C3 (θ^1)	C1–C2–C3–F3	C1′–N–C1–O1	X1′′–N–C1–O1 [c]	H1′–C1′–N–C1	O2–C2–C5–C10 (θ^2)	C1–C2–O2–C4
26 [h]	707825	[49]	*S*	Secondary amine	Me	Secondary alkyl group	8.6(3)	173.1(2)	0.1(3)	173.6(2)	–	−12.7(3)	−50.0(3)
27 [h]	707825	[49]	*S*	Secondary amine	Me	Secondary alkyl group	4.0(3)	176.7(2)	0.3(3)	−174.7(2)	–	−14.1(3)	−51.0(2)
28 [h]	707825	[49]	*S*	Secondary amine	Me	Secondary alkyl group	1.1(3)	178.0(2)	1.3(3)	−176.7(2)	–	−18.4(3)	−48.3(3)
29 [h]	707825	[49]	*S*	Secondary amine	Me	Secondary alkyl group	3.6(3)	177.1(2)	1.2(3)	−179.7(2)	–	−9.4(3)	−46.0(3)
30	766837	[50]	*S*	Secondary amine	Primary alkyl group	Primary alkyl group	9.4(2)	175.1(1)	2.0(2)	177.8(1)	–	−14.7(2)	−44.7(1)
31 [g]	830079	[51]	*R*	Secondary amine	Tertiary alkyl group	Primary alkyl group	−18(1)	−173.1(6)	−1(1)	−178.3(7)	–	20(1)	55.8(9)
32	1104875	[52]	*R*	Secondary amine	Primary alkyl group	Primary alkyl group	−2.2(2)	−176.5(2)	−5.2(3)	−176.7(2)	–	27.1(2)	45.2(2)
33	1105464	[53]	*R*	Secondary amine	Primary alkyl group	Primary alkyl group	−8.2(8)	178.4(5)	−0.7(9)	−172.4(6)	–	12.0(8)	46.6(8)
34	1105464	[53]	*R*	Secondary amine	Primary alkyl group	Primary alkyl group	–9.0(8)	–175.6(5)	–6.1(9)	–168.0(6)	–	13.7(8)	45.8(7)
35 [g]	1267150	[54]	*S*	Secondary amine	Secondary alkyl group	Primary alkyl group	7.1(6)	176.2(4)	−3.0(7)	−179.1(4)	19.5	−15.3(6)	−42.6(5)
36 [g]	1267151	[54]	*R*	Secondary amine	Secondary alkyl group	Primary alkyl group	−14.0(7)	−170.3(4)	8.4(7)	−163.3(5)	24.4	29.7(7)	59.7(6)
37 [g]	1280861	[55]	*R*	Secondary amine	Secondary alkyl group	Primary alkyl group	−15.6(6)	−170.9(4)	11.4(7)	−174.1(4)	−15.1	28.5(7)	50.1(6)
38 [g]	1280861	[55]	*R*	Secondary amine	Secondary alkyl group	Primary alkyl group	−5.5(6)	−177.6(4)	7.8(7)	−177.4(4)	−17.0	25.0(6)	41.3(6)
39	1294281	[56]	*R*	Secondary amine	Primary alkyl group	Primary alkyl group	−6(1)	−175.0(7)	1(1)	−172.0(7)	–	26(1)	44.0(9)
40	1294281	[56]	*R*	Secondary amine	Primary alkyl group	Primary alkyl group	−15(1)	−172.9(7)	1(1)	−163.7(8)	–	14(1)	47(1)
41 [i]	113953	[57]	*R*	Aniline derivative	*ortho*-Substituted phenyl group	H	−17(1)	−174.9(6)	−11(1)	178.6	–	8(1)	54.6(8)
42 [i]	113953	[57]	*R*	Aniline derivative	*ortho*-Substituted phenyl group	H	−28(1)	−168.0(7)	−1(1)	−170.3	–	47.7(9)	65.9(8)
43 [f,i]	113953	[57]	*R*	Aniline derivative	*ortho*-Substituted phenyl group	H	−58.4(9) [e]	−175.1(6)	−1(1)	176.4	–	−56.4(9)	−153.6(6)
44 [i]	113953	[57]	*R*	Aniline derivative	*ortho*-Substituted phenyl group	H	−15(1)	−170.8(6)	6(1)	175.4	–	36.1(9)	57.7(8)
45 [i]	1310848	[58]	*R*	Aniline derivative	*ortho*-Substituted phenyl group	H	−2(2)	−172(1)	−5(3)	–	–	35(2)	51(2)

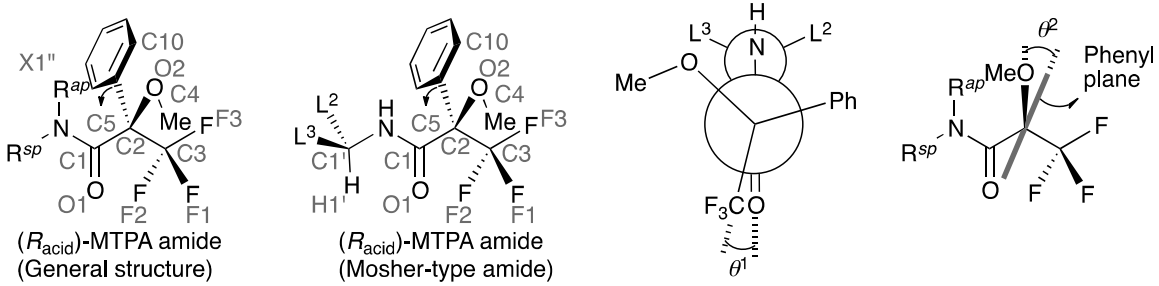
Table 1. *Cont.*

No.	CCDC Number [b]	Reference	Chirality of MTPA [a]	Amine Moiety	R^{sp}	R^{ap}	O1–C1–C2–C3 (θ^1)	C1–C2–C3–F3	C1′–N–C1–O1	X1′′–N–C1–O1 [c]	H1′–C1′–N–C1	O2–C2–C5–C10 (θ^2)	C1–C2–O2–C4
46 [f,i]	1310848	[58]	*R*	Aniline derivative	*ortho*-Substituted phenyl group	H	−60(2) [e]	179(2)	3(3)	–	–	−34(2)	−172(2)
47 [i]	1310848	[58]	*R*	Aniline derivative	*ortho*-Substituted phenyl group	H	−41(2) [e]	−169(2)	0(3)	–	–	13(2)	71(2)
48 [f,i]	1310848	[58]	*R*	Aniline derivative	*ortho*-Substituted phenyl group	H	−51(2) [e]	−165(2)	−1(3)	–	–	85(2)	−154(2)
49	655554	[59]	*R*	Benzotriazole	*ortho*-Substituted phenyl group	N	−9.3(1)	−175.21(7)	−2.8(1)	178.81(8)	–	25.7(1)	46.6(1)
50 [f]	1142231	[60]	*S*	Diethyl 1-aminoalkylphosphonate derivative	1-(Diethoxyphophoryl)alkyl group	H	57(3) [e]	169(2)	9(4)	–	−14	77(2)	148(2)
51	1142231	[60]	*S*	Diethyl 1-aminoalkylphosphonate derivative	1-(Diethoxyphophoryl)alkyl group	H	24(3)	172(2)	4(3)	–	−12	−35(2)	−65(2)
52	1236701	[61]	*R*	Diethyl 1-aminoalkylphosphonate derivative	1-(Diethoxyphophoryl)alkyl group	H	−23.1(5)	−171.5(3)	−3.1(6)	176.6	19.2	7.3(5)	59.3(4)
53	1236702	[61]	*R*	Diethyl 1-aminoalkylphosphonate derivative	1-(Diethoxyphophoryl)alkyl group	H	−19.4(6)	−174.3(4)	−3.2(7)	177.2	18.8	5.8(6)	55.8(5)
54	1236703	[61]	*R*	Diethyl 1-aminoalkylphosphonate derivative	1-(Diethoxyphophoryl)alkyl group	H	−24(2)	−166(1)	4(2)	−173	11	31(2)	59(2)
55	1236703	[61]	*R*	Diethyl 1-aminoalkylphosphonate derivative	1-(Diethoxyphophoryl)alkyl group	H	−24(2)	−166(1)	9(2)	−171	−14	35(2)	57(1)

Table 1. *Cont.*

No.	CCDC Number [b]	Reference	Chirality of MTPA [a]	Amine Moiety	R^{sp}	R^{ap}	O1–C1–C2–C3 (θ^1)	C1–C2–C3–F3	C1′–N–C1–O1	X1″–N–C1–O1 [c]	H1′–C1′–N–C1	O2–C2–C5–C10 (θ^2)	C1–C2–O2–C4
56	1216345	[62]	*R*	Oxazolidine-2-selone derivative	Selenoxo group	Secondary alkyl group	−15.9(4)	−172.9(2)	24.5(4)	−147.8(3)	–	18.5(4)	56.6(3)
57	630372	[63]	*R*	Thiocarbamide derivative	*N*-Substituted thiocarbamoyl group	Secondary alkyl group	−16.7(3)	−174.1(2)	11.2(4)	−152.6(2)	–	24.8(3)	57.7(3)
58	143886	[64]	*R*	*p*-Toluene-sulfonamide derivative	*p*-Toluene-sulfonyl group	Primary alkyl group	−5.4(6)	−177.4(3)	7.4(5) [j]	−177.6(4)	–	18.2(6)	37.8(5)

[a] The original dihedral angles were cited for both (R_{acid})- and (S_{acid})-MTPA amides. In the following sections, (S_{acid})-MTPA amides were processed as (R_{acid})-MTPA amides with plus/minus sign reversal. [b] The same CCDC numbers stand for multiple conformers in a lattice or bis- and tetrakis-MTPA amides. [c] X1″ stands for the atom at the α-position of substituent R^{ap} in the amine moiety. [d] Mosher-type MTPA amides prepared from primary amines possessing secondary alkyl groups. [e] These ten entries were omitted from the calculation of the average dihedral angle θ^1. [f] The minor conformer in which the amide carbonyl group and the methoxy group were *anti*. [g] The tertiary amides exhibiting *Z* forms ($R^{sp} > R^{ap}$). All precursors of these *Z* amides were the cyclic secondary amines. We refer to *Z* and *E* as the forms in which the larger *N*-substituent is *sp* and *ap* to the carbonyl oxygen atom, respectively [72]. [h] The four conformers of CCDC 707825 (*N*-methylamide derivative) only exhibited *E* forms ($R^{sp} < R^{ap}$) in the amide moieties [49]. [i] The tetrakis-MTPA amides of ruthenium(II) porphyrin complexes. [j] The dihedral angle of S–N–C1–O1 was cited.



All obtained MTPA amide moieties (a total of 58) were processed as R_{acid}-enantiomers in the following sections; that is, the dihedral angles of (S_{acid})-MTPA amides cited in Table 1 were substituted by those of the mirror images (*i.e.*, R_{acid}-enantiomers) with plus/minus sign reversal. Despite the various structures of the amine moiety, the MTPA amide moieties showed little conformational diversity. Therefore, the conformations of all MTPA amide moieties were processed together, excluding the dihedral angle H1′–C1′–N–C1, which was specific to the MTPA amides prepared from amines possessing a secondary alkyl group (see Section 2.6.).

2.2. Dihedral Angles of Amide Carbonyl Group and Trifluoromethyl Group: O1–C1–C2–C3

The distribution of the dihedral angles O1–C1–C2–C3 (θ^1) exhibited a concentration of entries between −30° and 0° (Figure 3). All dihedral angles ranged from −70° to +40°; the median angle was −14.5°. These data confirmed Mosher's hypothesis that the carbonyl and trifluoromethyl groups of the MTPA amide are *syn* [3]. In addition, the majority of dihedral angles θ^1 (48/58, *ca.* 83%) ranged from −30° to 0° with the average angle θ^1 of −13°. That is, the carbonyl group was close to the phenyl group. This phenomenon was also observed for the MTPA esters and MTPA salt; we observed the short contacts between the two oxygen atoms and the *ortho*-hydrogen atoms of phenyl group in the MTPA anion [9].

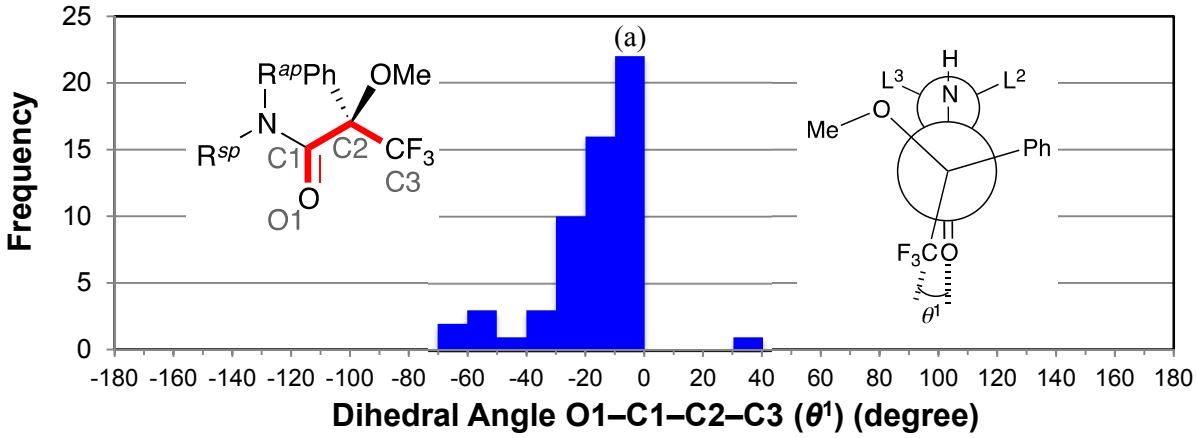


Figure 3. Histogram for dihedral angles between the amide carbonyl and trifluoromethyl groups of all MTPA amides. [(a)] The bar indicates the frequency of $-10 < \theta^1 \leq 0$; and the same is true for the others.

All the outliers were the dihedral angles θ^1 of the secondary amides. An irregular θ^1 of +30.3(3)° represents CCDC 222942 [28] in which the intramolecular aromatic C–H···π interactions and N–H···O hydrogen bond were observed.

The five entries around −60° were indicative of a minor conformer in which the amide carbonyl group and the methoxy group were *anti* [*i.e.*, CCDC 703912 [32], −67.7 (6)°; CCDC 1142231 [60], −57(3)° as R_{acid}-enantiomer; CCDC 113953 [57], −58.4(9)°; CCDC 1310848 [58], −60(2)° and −51(2)°] (see Sections 2.7 and 2.8). The amine moiety of CCDC 703912 has a linear conjugated diene structure. In the case of CCDC 1142231, the phenyl group of the MTPA moiety formed an intramolecular C–H···O hydrogen bond [73] with the oxygen atom of the amine moiety. The other minor *anti* conformers

(*i.e.*, CCDC 113953 and CCDC 1310848) were the tetrakis-MTPA amide derivatives of ruthenium(II) porphyrin complexes.

The tetrakis-MTPA amide derivative CCDC 1310848 also exhibited another irregular θ^1 of −41(2)°. CCDC 739753 [34] showed an irregular θ^1 of −36.0(2)°; the methoxy group of the MTPA moiety formed an intramolecular aromatic C–H···π interaction with the phenyl group of the amine moiety. CCDC 122980 [36] also exhibited an irregular θ^1 of −31(1)°; the methoxy group of the MTPA moiety formed an intramolecular C–H···O hydrogen bond with the oxygen atom of the amine moiety. In addition, CCDC 603055 [29] showed an irregular θ^1 of −35.0(4)° as R_{acid}-enantiomer; the amine moiety possessed a sulfonamide moiety and a phenyl group.

Previously, the dihedral angle θ^1 was discussed in relation to the steric repulsion between the phenyl group and L^2 or L^3 substituents of the amine moiety; it was estimated that the larger repulsion resulted in a lager dihedral angle θ^1, and a smaller deshielding of the fluorine atoms by the amide or ester carbonyl groups [4]. However, Kusumi *et al.* observed the inaccuracies of the MTPA method using ^{19}F-NMR spectroscopy [5,8]. In 2007, Brand *et al*. reported that the origin of the *sp* conformation is the hyperconjugative interactions between the carbonyl group and the electronegative trifluoromethyl group [74].

2.3. Staggered Conformation of Trifluoromethyl Group: C1–C2–C3–F3

The distribution of the dihedral angle C1–C2–C3–F3 showed a concentration of entries around −180° (Figure 4). The median angle was −174°. This was suggestive of the staggered conformation of the trifluoromethyl group [9]; that is, the two oxygen atoms O1 and O2 were as far as possible from the fluorine atoms.

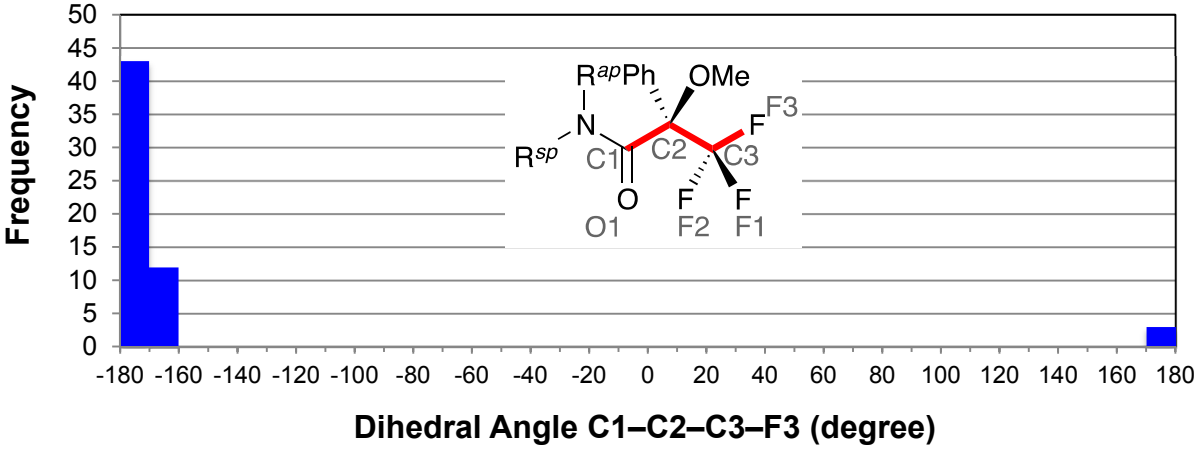


Figure 4. Histogram for dihedral angles C1–C2–C3–F3 of all MTPA amides. F3 is the fluorine atom *ap* to C1. The possible range of the dihedral angle C1–C2–C3–F3 is from −180° to −120° and from +120° to +180°.

Khan *et al*. reported the nonequivalence of three fluorine atoms of the MTPA amide prepared from secondary amines on the ^{19}F-NMR spectra at low temperatures [75]. They also reported that barriers to the hindered rotation on the C2–C3 bonds were in the range of 36–46 kJ/mol. This suggested the severe steric crowding of the MTPA moiety.

2.4. Resonance Effects of Amide Bond: C1′–N–C1–O1

The distribution of the dihedral angle C1′–N–C1–O1 exhibited a concentration of entries around 0° (Figure 5). The average angle and the median angle were +2° and +0.8°, respectively. This represents the resonance effects of the amide bond (Figure 6). Similar planarity was observed in the ester moieties of the crystalline MTPA esters [9].

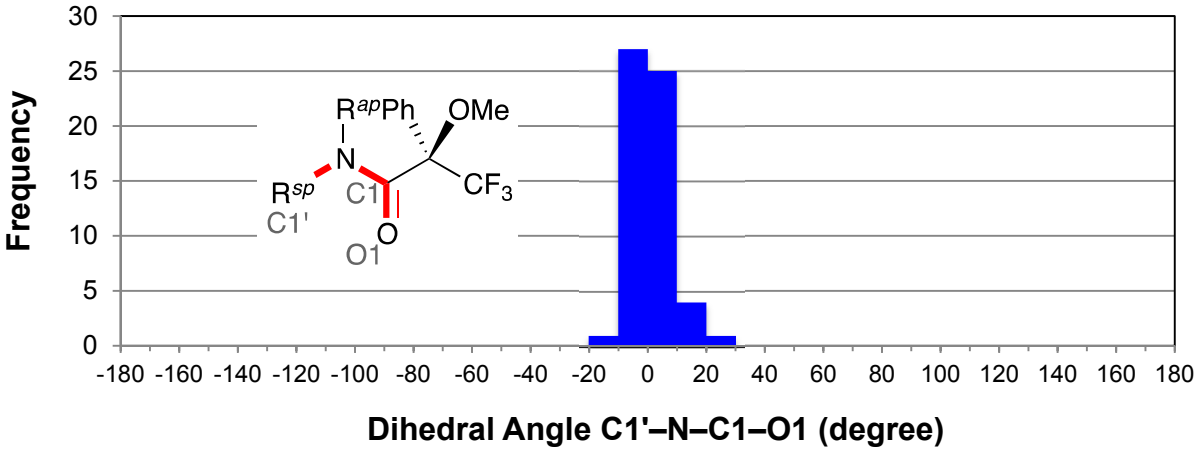


Figure 5. Histogram for the dihedral angles C1′–N–C1–O1 of all MTPA amides. The α-carbon atom of substituent R^{sp}, which is *sp* to the amide carbonyl group, was defined as C1′. The possible range of the dihedral angle C1′–N–C1–O1 is from −90° to +90°.

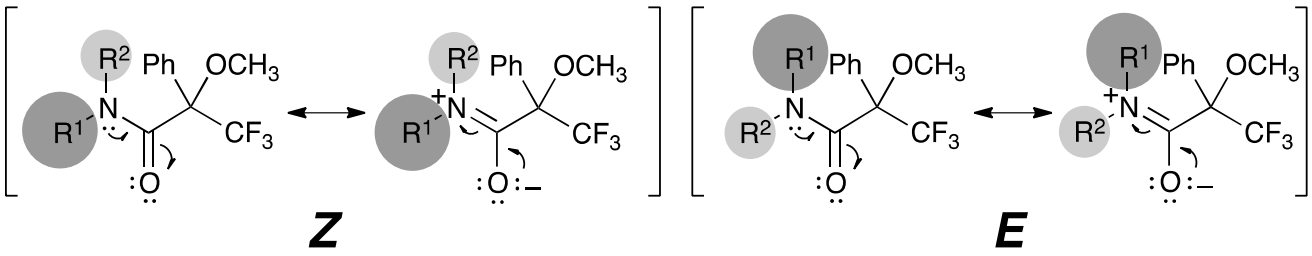


Figure 6. *Z*/*E* forms and their resonance hybrids of MTPA amides. R^1 indicates the substituents with higher Cahn–Ingold–Prelog (CIP) priority (e.g., secondary alkyl group); R^2 indicates the substituents with lower CIP priority (e.g., hydrogen atom and methyl group).

The trivalent nitrogen atom afforded the *Z* and *E* forms in the amide moiety (Figure 6). All crystalline secondary MTPA amides prepared from primary amines exhibited the *Z* form, in which the *N*-substituent was *sp* to the amide carbonyl group (Figure 2 and Table 1).

In the case of tertiary MTPA amide moieties prepared from secondary amines, the ratio of *Z*/*E* forms was 13:4 (Table 1). The MTPA amide moieties prepared from cyclic secondary amines exhibited the *Z* forms (*i.e.*, CCDC 140352 [38], CCDC 167289 [39], CCDC 241708 [40], CCDC 251663 [41], CCDC 604432 [44], CCDC 605818 [45], CCDC 675390 [47], CCDC 706349 [48], CCDC 830079 [51], CCDC 1267150 [54], CCDC 1267151 [54], and the two conformers of CCDC 1280861 [55]).

The four conformers of an *N*-methyl MTPA amide exhibited the *E* forms (*i.e.*, CCDC 707825 [49]). It is noteworthy that the two aromatic rings of the larger secondary alkyl group R^1 were bound to the

MTPA's phenyl groups via the aromatic C–H···π and π···π interactions [73,76], respectively. By contrast, Nakagawa and Somei reported the *Z* form of a crystalline *N*-methyl MTPA amide in the course of the total synthesis of ergot alkaloids [65].

It is possible that the application of Mosher's method using ^{1}H-NMR could be expanded to the cyclic secondary amines [77,78]. In 1996, Hoye and Renner applied the MTPA method for assignment of the absolute configuration in chiral cyclic amines; they observed equilibrium mixtures of the *Z* and *E* forms of amide moieties in the ^{1}H-NMR spectra [77]. Similar peptidyl-prolyl isomerization is a key issue in protein chemistry [79]. In 2001, Azumaya reported the *E*-preference of aromatic *N*-methylamides (e.g., *N*-methylbenzanilide) [80].

2.5. Resonance Effects of Amide Bond: X1″–N–C1–O1

The distribution of the dihedral angle X1″–N–C1–O1 also exhibited a concentration of entries around −180° (Figure 7). The median angle was −174°. This also represents for the resonance effects of the amide bond (see above).

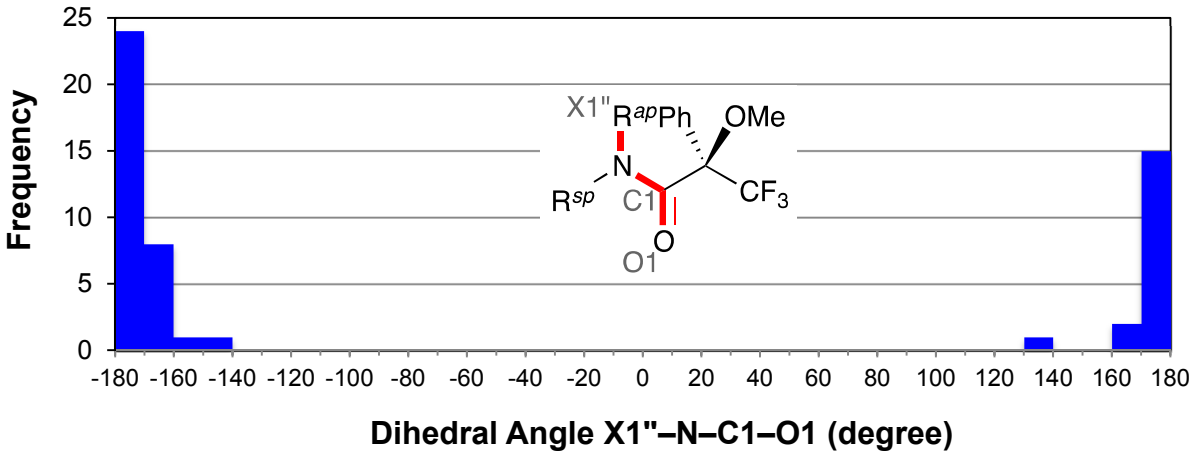


Figure 7. Histogram for dihedral angles X1″–N–C1–O1 of all MTPA amides. X1″ is the α-atom of R^{ap}, which is *ap* to the amide carbonyl group. The possible range of the dihedral angle X1″–N–C1–O1 is from −180° to −90° and from +90° to +180°.

2.6. Conformation of the Amine Moiety: H1′–C1′–N–C1

The distribution of the dihedral angle H1′–C1′–N–C1 was examined in the case of the ten crystalline MTPA amides prepared from the primary amines possessing secondary alkyl groups (*i.e.*, Mosher-type MTPA amides). All dihedral angles were distributed between −60° and +50° with an average angle of −5° (Figure 8). Besides, the median angle was −11°. These data agree with Mosher's hypothesis of the MTPA plane [3,5]. In addition, the broad distribution of dihedral angles was indicative of a moderate conformational flexibility of the C1′–N bond. The same is true for the C1′–O bond of the crystalline MTPA esters prepared from secondary alcohols [9].

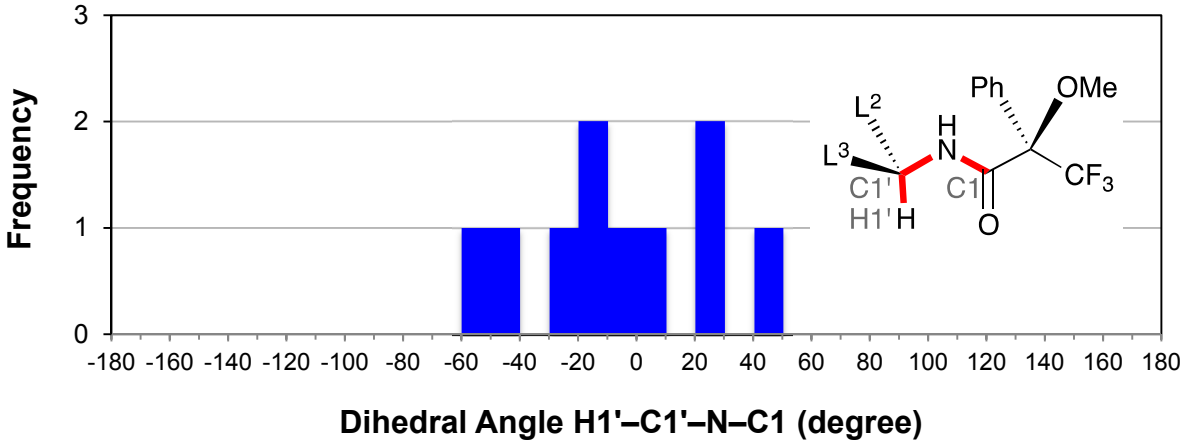


Figure 8. Histogram for dihedral angles H1′–C1′–N–C1 of the MTPA amides prepared from primary amines possessing a secondary alkyl group.

Rzepa analyzed the relationship between the dihedral angle H–N–C=O and the distance from H1' of the amine moiety to the carbonyl oxygen atom in the crystalline secondary amides (a total of 619); that is, the major conformer exhibited a *syn*-co-planar alignment of the C–H bond with the plane of the C=O bond in the *Z* form [81].

2.7. Dihedral Angle between the Methoxy Group and Phenyl Group: O2–C2–C5–C10

The distribution of the dihedral angles O2–C2–C5–C10 (θ^2) exhibited a concentration of entries around +20° (Figure 9). The majority of dihedral angles (53/58, *ca.* 91%) ranged from 0° to +50°; the average angle of these major 53 conformers was +21°. Besides, the median angle for all 58 conformers was +20°.

These data confirmed Mosher's hypothesis of MTPA amide, in which the (R_{acid})-MTPA's phenyl group shields the amine's substituent L^2 (Figure 2a) [3]. Figure 9 also suggested that the substituent L^2 is not just above the phenyl ring. We reported that the phenyl group was inclined by +19° in the MTPA ester [9].

The other five entries exhibited the minor conformer in which the amide carbonyl group and the methoxy group were *anti* (see Sections 2.2. and 2.8.). The crowded tetrakis-MTPA amides of ruthenium(II) porphyrin complexes (CCDC 113953 [57] and CCDC 1310848 [58]) exhibited the irregular dihedral angles θ^2 [*i.e.*, −56.4(9)°, −34(2)°, and +85(2)°]. One of the conformer of CCDC 1142231 [60], in which the MTPA's phenyl group forms the C–H···O hydrogen bond with the ethoxy oxygen atom of amine moiety, also exhibited an irregular dihedral angle θ^2 [*i.e.*, −77(2)° as R_{acid}-enantiomer]. The rest was CCDC 703912 [32] [*i.e.*, −58.9(7)°], which contains the linear conjugated diene in the amine moiety.

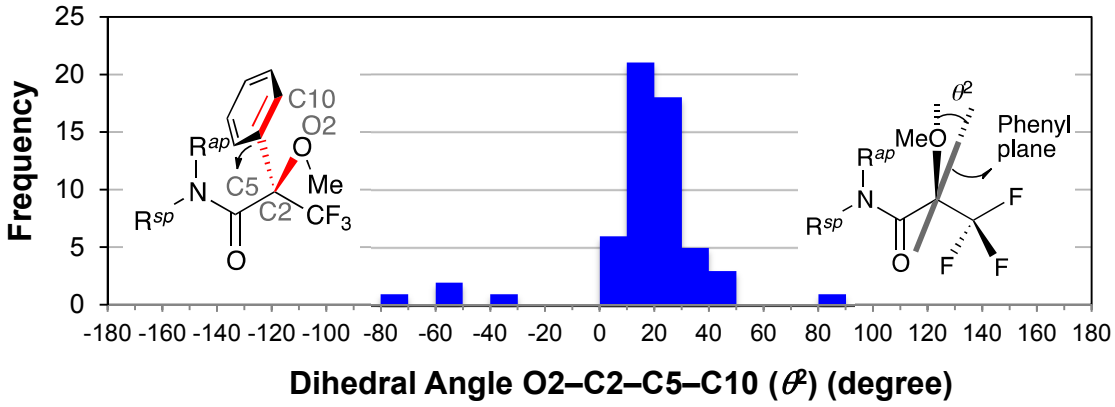


Figure 9. Histogram for dihedral angles O2–C2–C5–C10 (θ^2) of all MTPA amides. C10 is the *ortho*-carbon atom that provides a smaller absolute value. The possible range of the dihedral angle O2–C2–C5–C10 (θ^2) is from −90° to +90°.

The dihedral angle θ^2 has a significant influence on shielding by the phenyl group according to ^{1}H-NMR spectroscopy. The dihedral angle θ^2 also influenced the crystallization, because the intramolecular interactions (e.g., C–H···π and π···π interactions) are crucial for chiral recognition by the resolving agents [71].

2.8. Conformation of the Methoxy Group: C1–C2–O2–C4

The distribution of the dihedral angles C1–C2–O2–C4 exhibited a concentration of entries around +50° (Figure 10). The majority of dihedral angles (52/58, *ca*. 90%) ranged between +30° and +80°; the average dihedral angle for the major 52 conformers was +54°. Besides, the median angle for all 58 conformers was +51°. That is, the methyl group of the methoxy moiety was *ap* to the phenyl group. This extended form was also observed as the major conformer in the MTPA esters, along with the other minor conformers [9]. Khan *et al*. reported that θ^2 was relaxed to +50° using the MNDO method in the case of (*R*)-*N*,*N*′-dimethyl-3,3,3-trifluoro-2-methoxy-2-phenylpropanamide [75].

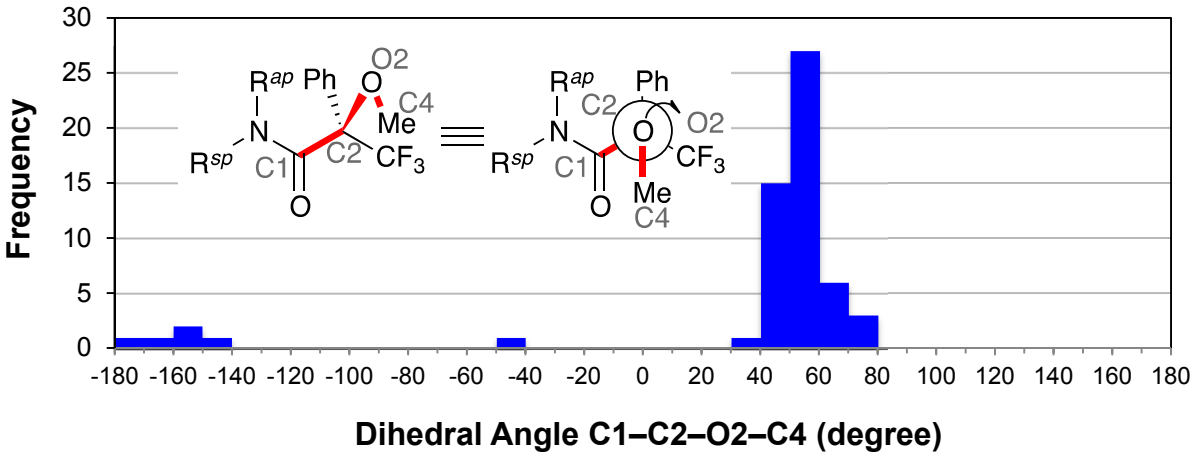


Figure 10. Histogram for dihedral angles between the methoxy and phenyl groups of all MTPA amides.

An irregular dihedral angle −44.4(4)° was observed in the conformer of CCDC 222942 [28], in which the phenyl group of the amine moiety formed the C–H···π interactions with the MTPA's methoxy moiety (see Section 2.2.). Similar C–H···π interactions were observed in CCDC 739753 [34] and CCDC 1104875 [52]. It is possible that the methoxy moiety could interact with the amine moieties through weak intramolecular interactions (e.g., C–H···π interaction and C–H···O hydrogen bond) [9,73,76].

The tetrakis-MTPA amides of ruthenium(II) porphyrin complexes again yielded the irregular dihedral angles (*i.e.*, CCDC 113953 [57], −153.6(6)°; CCDC 1310848 [58], −172(2)°, and −154(2)°). The MTPA amide of CCDC 703912 [32], which has a linear conjugated diene moiety in the amine's substituent L^2, exhibited another irregular dihedral angle of −162.7(5)°. One of the conformers of CCDC 1142231 [60] also exhibited the irregular dihedral angle (*i.e.*, −148(2)° as R_{acid}-enantiomer); these represent the minor conformer in which the amide carbonyl group and the methoxy group were *anti*.

It is noteworthy that Saigo reported that agreement of the molecular lengths is important for the successful resolution via the diastereomeric salt formation method [71]. We reported that the agreement of the molecular lengths of acid/alcohol moieties is important for the crystallization of MαNP esters [16].

The crystal structures of CCDC 199868 [27] and CCDC 678252 [31] contain the typical conformations of Mosher-type MTPA amides.

3. Experimental Section

3.1. Database Study of MTPA Amide

The accessible 41 crystal structures of MTPA amides reported from 1985 to 2011 [27–66] were examined. The original dihedral angles of (R_{acid})- and (S_{acid})-MTPA amides were shown in Table 1. In this study, all MTPA amides were processed as (R_{acid})-MTPA amides; that is, the dihedral angles of (S_{acid})-MTPA amides cited in Table 1 were substituted by those of the mirror images (*i.e.*, R_{acid}-enantiomers) with plus/minus sign reversal [82]. Each of bis- and tetrakis-MTPA amides (*i.e.*, CCDC 1280861 [55], CCDC 113953 [57], and CCDC 1310848 [58]), as well as the different conformers in a lattice (*i.e.*, CCDC 199868 [27], CCDC 651954 [30], CCDC 678252 [31], CCDC 707825 [49], CCDC 1105464 [53], CCDC 1142231 [60], CCDC 1236703 [61], and CCDC 1294281 [56]), was processed individually. This procedure yielded 58 of (R_{acid})-MTPA amide moieties. These MTPA amide moieties were prepared from various amine moieties; that is, primary amines (a subtotal of 14), secondary amines (26), aniline derivatives [tetrakis-MTPA amides of ruthenium(II) porphyrin complexes] (8), benzotriazole (1), diethyl 1-aminoalkylphosphonate derivatives (6), an oxazolidine-2-selone derivative (1), a thiocarbamide derivative (1), and a *p*-toluenesulfonamide derivative (1). The dihedral angles were obtained using Mercury software (Ver. 3.5.1) [83] from the CIF files. The CIF files listed in Table 1 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033; E-mail: deposit@ccdc.cam.ac.uk).

3.2. Caution

Acylation of an amine with (*S*)-MTPA chloride yields (R_{acid})-MTPA amide. In the same way, acylation of an amine with (*R*)-MTPA chloride yields (S_{acid})-MTPA amide. This nominal change in the absolute configuration has often caused confusion. The same is true for MTPA esters.

4. Conclusions

We conducted a database study of the crystal structures of MTPA amides deposited in the CSD. The properties of the major conformation of the MTPA amide elucidated from our database study confirmed Mosher's empirical model on the conformation of MTPA amide; that is, the methine group of the amine moiety, the amide carbonyl group, and the trifluoromethyl group are on the MTPA plane. All secondary MTPA amides prepared from the primary amines exhibited the *Z* form in the amide moiety. The ratio of *Z*/*E* forms of amide moieties was 13:4 in the case of the tertiary MTPA amides prepared from the secondary amines; the cyclic secondary amines yielded the *Z* forms, whereas the *N*-methyl amines yielded the both *Z* and *E* forms. The amide carbonyl group was *sp* to the trifluoromethyl group with the average dihedral angle θ^1 of −13°. The trifluoromethyl group was in the staggered conformation. In addition, the C1′–N bond of the amine moiety exhibited moderate conformational flexibility. The phenyl plane was inclined by θ^2 = +21° from the O–C_{chiral} bond of the methoxy moiety. This dihedral angle θ^2 was suggestive of the inefficient shielding of the phenyl ring. Finally, the methyl group of the methoxy moiety was *ap* to the *ipso*-carbon atom of the phenyl group. These conformational properties were similar to those of the crystalline MTPA ester. Besides, the minor conformer of the crystalline MTPA amides was observed in which the amide carbonyl group and the methoxy group were *anti*. Mosher's method using NMR spectroscopy is crucial for the structural elucidation of chiral amines in combination with X-ray crystallography. This report increases our understanding of Mosher's method and acid **1** and can be used for crystal engineering of MTPA derivatives.

Acknowledgments

We would like to express our gratitude to the late H. S. Mosher (Stanford University), T. Kusumi (Tokyo Institute of Technology), and the other predecessors who contributed to the development of the MTPA method.

Author Contributions

A.I. designed research and performed the database study; H.O. and Y.M. participated in the discussion of the results; Y.M. also searched the crystal structures of the MTPA amides in the CSD.

Conflicts of Interest

The authors declare no conflict of interest.

References and Notes

1. Seco, J.M.; Quiñoá, E.; Riguera. R. Assignment of the absolute configuration of polyfunctional compounds by NMR using chiral derivatizing agents. *Chem. Rev.* **2012**, *112*, 4603–4641.
2. Dale, J.A.; Dull, D.L.; Mosher, H.S. α-Methoxy-α-trifluoromethylphenylacetic acid, a versatile reagent for the determination of enantiomeric composition of alcohols and amines. *J. Org. Chem.* **1969**, *34*, 2543–2549.
3. Dale, J.A.; Mosher, H.S. Nuclear magnetic resonance enantiomer reagents. Configurational correlations via nuclear magnetic resonance chemical shifts of diastereomeric mandelate, *O*-methylmandelate, and α-methoxy-α-trifluoromethylphenylacetate (MTPA) esters. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.
4. Sullivan G.R.; Dale, J.A.; Mosher, H.S. Correlation of configuration and ^{19}F chemical shifts of α-methoxy-α-trifluoromethylphenylacetate derivatives. *J. Org. Chem.* **1973**, *38*, 2143–2147.
5. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. High-field FT NMR application of Mosher's method. The absolute configurations of marine terpenoids. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.
6. Kusumi, T.; Fukushima, T.; Ohtani, I.; Kakisawa, H. Elucidation of the absolute configurations of amino acids and amines by the modified Mosher's method. *Tetrahedron Lett.* **1991**, *32*, 2939–2942.
7. Ohtani, I. I.; Hotta, K.; Ichikawa, Y.; Isobe M. Application of modified Mosher's method to *α*-aromatic secondary alcohols. Exception of the rule and conformational analyses. *Chem. Lett.* **1995**, *24*, 513–514.
8. Kusumi, T. Determination of the absolute configuration of organic compounds by means of NMR spectroscopy—Modified Mosher's method. *J. Syn. Org. Chem. Jpn.* **1993**, *51*, 462–470.
9. Ichikawa, A.; Ono, H.; Mikata Y. Crystal structures of Mosher's salt and ester elucidated by X-ray crystallography. *CrystEngComm* **2013**, *15*, 8088–8096.
10. Harada, N. Determination of absolute configurations by X-ray crystallography and ^{1}H NMR anisotropy. *Chirality* **2008**, *20*, 691–723.
11. Kuwahara, S.; Naito, J.; Yamamoto, Y.; Kasai, Y.; Fujita, T.; Noro, K.; Shimanuki, K.; Akagi, M.; Watanabe, M.; Matsumoto, T.; Watanabe, M.; Ichikawa, A.; Harada, N. Crystalline-state conformational analysis of MαNP esters, powerful resolution and chiral ^{1}H NMR anisotropy tools. *Eur. J. Org. Chem.* **2007**, 1827–1840, doi:10.1002/ejoc.200601088.
12. Kasai, Y.; Sugio, A.; Sekiguchi, S.; Kuwahara, S.; Matsumoto, T.; Watanabe, M.; Ichikawa, A.; Harada, N. Conformational analysis of MαNP esters, powerful chiral resolution and ^{1}H NMR anisotropy tools—Aromatic geometry and solvent effects on Δδ values. *Eur. J. Org. Chem.* **2007**, 1811–1826, doi:10.1002/ejoc.200600856.
13. Ichikawa, A.; Ono, H.; Mikata, Y. Naphthyl groups in chiral recognition: structures of salts and esters of 2-methoxy-2-naphthylpropanoic acids. *Chem. Asian J.* **2012**, *7*, 2294–2304.
14. Ichikawa, A.; Ono, H.; Echigo, T.; Mikata, Y. Crystal structures and chiral recognition of the diastereomeric salts prepared from 2-methoxy-2-(1-naphthyl)propanoic acid. *CrystEngComm* **2011**, *13*, 4536–4548.
15. Ichikawa, A.; Ono, H.; Takenaka, M.; Mikata, Y. Crystal conformations and molecular packing of (*S*)-2-methoxy-2-(1-naphthyl)propanoic acid and a diastereomeric amide prepared from (*R*)-2-methoxy-2-(1-naphthyl)propanoic acid. *CrystEngComm* **2010**, *12*, 2261–2268.

16. Ichikawa, A.; Ono, H.; Mikata, Y. Characteristic conformations and molecular packings in crystal structures of diastereomeric esters prepared from (*S*)-2-methoxy-2-(1-naphthyl)propanoic acid. *Tetrahedron Asymmetry* **2008**, *19*, 2693–2698.
17. Ichikawa, A.; Ono, H. Preparation of single-enantiomer biofunctional molecules with (*S*)-2-methoxy-2-(1-naphthyl)propanoic acid. *Biosci. Biotechnol. Biochem.* **2008**, *72*, 2418–2422.
18. Ichikawa; A.; Ono, H. Preparation of Single-enantiomer 2-methyl-4-heptanol, a pheromone of *Metamasius hemipterus*, using (*S*)-2-methoxy-2-(1-naphthyl)propionic acid. *J. Chromatogr. A* **2006**, *1117*, 38–46.
19. Ichikawa, A.; Ono, H. Preparation of single-enantiomer semiochemicals using 2-methoxy-2-(1-naphthyl)propionic acid and 2-methoxy-2-(9-phenanthryl)propionic acid. *Tetrahedron Asymmetry* **2005**, *16*, 2559–2568.
20. Ichikawa, A.; Ono, H.; Harada, N. Stereochemical studies of chiral resolving agents, M9PP and H9PP acids. *Chirality* **2004**, *16*, 559–567.
21. Ichikawa, A.; Ono, H.; Harada, N. Synthesis and analytical properties of (*S*)-(+)-2-methoxy-2-(9-phenanthryl)propionic acid. *Tetrahedron Asymmetry* **2003**, *14*, 1593–1597.
22. Ichikawa, A.; Ono, H.; Hiradate, S.; Watanabe, M.; Harada, N. Absolute configurations of 2-methoxy-2-(1-naphthyl)propionic acid and 2-methoxy-2-(2-naphthyl)propionic acid as determined by the phenylglycine methyl ester (PGME) method. *Tetrahedron Asymmetry* **2002**, *13*, 1167–1172.
23. Ichikawa, A.; Hiradate, S.; Sugio, A.; Kuwahara, S.; Watanabe, M.; Harada, N. Absolute configuration of 2-methoxy-2-(2-naphthyl)propionic acid as determined by the ^{1}H NMR anisotropy method. *Tetrahedron Asymmetry* **2000**, *11*, 2669–2675.
24. Ichikawa, A.; Hiradate, S.; Sugio, A.; Kuwahara, S.; Watanabe, M.; Harada, N. Absolute configuration of 2-hydroxy-2-(1-naphthyl)propionic acid as determined by the ^{1}H NMR anisotropy method. *Tetrahedron Asymmetry* **1999**, *10*, 4075–4078.
25. Hirayama, N. Chapter 10: Comparison of Structures. In *Introduction to X-ray Analysis for Chemistry and Pharmacy*, 2nd ed.; Maruzen Publishing Co. Ltd.: Tokyo, Japan, 2006; pp. 95–106.
26. Definitions of dihedral angle are as follows: 0° to ±30°, synperiplanar (*sp*); ±150° to 180°, antiperiplanar (*ap*). IUPAC. *Compendium of Chemical Terminology*, 2nd ed. (the "Gold Book"); McNaught, A.D., Wilkinson, A., Eds; Blackwell Scientific Publications: Oxford, UK, 1997. XML on-line corrected version: http://goldbook.iupac.org (2006-) Created by Nic, M.; Jirat, J.; Kosata B. Updates compiled by Jenkins, A.
27. CCDC 199868: Haberhauer, G.; Rominger, F. Straightforward synthesis of a novel class of rigid bicyclic dipeptidomimetics from simple dipeptides: Fused imidazole amino acids. *Synlett* **2003**, 780–784, doi:10.1055/s-2003-38737.
28. CCDC 222942: Dondoni, A.; Massi, A.; Minghini, E.; Bertolasi, V. Multicomponent Hantzsch cyclocondensation as a route to highly functionalized 2- and 4-dihydropyridylalanines, 2- and 4-pyridylalanines, and their *N*-oxides: preparation via a polymer-assisted solution-phase approach. *Tetrahedron* **2004**, *60*, 2311–2326.
29. CCDC 603055: Lindsley, C.W.; Zhao, Z.; Leister, W.H.; O'Brien, J.; Lemaire, W.; Williams, D.L., Jr.; Chen, T.B.; Chang, R.S.L.; Burno, M.; Jacobson, M.A.; *et al*. Design, synthesis, and *in vivo* efficacy of glycine transporter-1 (GlyT1) inhibitors derived from a series of [4-phenyl-1-(propylsulfonyl) piperidin-4-yl]methyl benzamides. *ChemMedChem* **2006**, *1*, 807–811.

30. CCDC 651954: Busto, E.; Gotor-Fernández, V.; Montejo-Bernardo, J.; García-Granda, S.; Gotor, V. First desymmetrization of 1,3-propanediamine derivatives in organic solvent. Development of a new route for the preparation of optically active amines. *Org. Lett.* **2007**, *9*, 4203–4206.
31. CCDC 678252: Soto-Cairoli, B.; de Pomar, J.J.; Soderquist, J.A. Enantiomerically pure α-amino aldehydes from silylated α-amino acids. *Org. Lett.* **2008**, *10*, 333–336.
32. CCDC 703912: Lauzon, S.; Tremblay, F.; Gagnon, D.; Godbout, C.; Chabot, C.; Mercier-Shanks, C.; Perreault, S.; DeSève, H.; Spino, C. Sterically biased 3,3-sigmatropic rearrangement of chiral allylic azides: application to the total syntheses of alkaloids. *J. Org. Chem.* **2008**, *73*, 6239–6250.
33. CCDC 734247: Busto, E.; Gotor-Fernández, V.; Montejo-Bernardo, J.; García-Granda, S.; Gotor, V. Development of a chemoenzymatic strategy for the synthesis of optically active and orthogonally protected polyamines. *Tetrahedron* **2009**, *65*, 8393–8401.
34. CCDC 739753: Reznichenko, A.L.; Hampel, F.; Hultzsch, K.C. Kinetic resolution of aminoalkenes by asymmetric hydroamination: a mechanistic study. *Chem. Eur. J.* **2009**, *15*, 12819–12827.
35. CCDC 1218697: Enders, D.; Nübling, C.; Schubert, H. Asymmetric synthesis of primary amines by nucleophilic addition of alkyllithium compounds to aldehyde SAMP/RAMP hydrazones. *Liebigs Ann.* **1997**, 1089–1100, doi:10.1002/jlac.199719970608.
36. CCDC 1229820: Enders, D.; Funk, R.; Klatt, M.; Raabe, G.; Hovestreydt, E.R. Enantioselective synthesis of α-amino acetals and α-amino acids by nucleophilic 1,2-addition to diethoxyacetaldehyde SAMP hydrazone. *Angew. Chem. Int. Ed.* **1993**, *32*, 418–421.
37. CCDC 1277744: Port, A.; Virgili, A.; Alvarez-Larena, A.; Piniella, J.F. Preparation of enantiomers of 1-(1-naphthyl)-2,2-dimethylpropylamine and their behaviour as chiral solvating agents: Study of diastereochemic association by Job's plots and intermolecular NOE measurements. *Tetrahedron Asymmetry* **2000**, *11*, 3747–3757.
38. CCDC 140352: Tietze, L.F.; Zhou, Y.; Töpken, E. Synthesis of simple enantiopure tetrahydro-β-carbolines and tetrahydroisoquinolines. *Eur. J. Org. Chem.* **2000**, 2247–2252, doi:10.1002/1099-0690(200006)2000:12<2247::AID-EJOC2247>3.0.CO;2-4.
39. CCDC 167289: Golubev, A.S.; Schedel, H.; Radics, G.; Sieler, J.; Burger, K. Stereoselective syntheses of 4-fluoro- and 4,4-difluoropipecolic acids. *Tetrahedron Lett.* **2001**, *42*, 7941–7944.
40. CCDC 241708: Cordes, M.; Franke, D. Studies toward nitrogen-containing natural products using radical cyclizations of chiral vinylogous amides. *Synlett* **2004**, 1917–1920, doi:10.1055/s-2004-830859.
41. CCDC 251663: Roszkowski, P.; Wojtasiewicz, K.; Leniewski, A.; Maurin, J.K.; Lis, T.; Czarnocki, Z. Enantioselective synthesis of 1-substituted tetrahydro-β-carboline derivatives via the asymmetric transfer hydrogenation. *J. Mol. Catal. A Chem.* **2005**, *232*, 143–149.
42. CCDC 288331: Peltier, H.M.; Ellman, J.A. *N*-Sulfinyl metalloenamine conjugate additions: Asymmetric synthesis of piperidines. *J. Org. Chem.* **2005**, *70*, 7342–7345.
43. CCDC 296547: Peeters, O.M.; Polavarapu, P.L.; Zhang, P.; Gera L.; Gal, J. (+)-1-[(*R*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropionyl]-4-(4-{[(2*R*,4*S*)-2-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy}phenyl)piperazine methanol solvate. *Acta Cryst.* **2006**, *E62*, o191–o192.
44. CCDC 604432: Roszkowski, P.; Maurin, J.K.; Czarnocki, Z. Enantioselective synthesis of (*R*)-(−)-praziquantel (PZQ). *Tetrahedron Asymmetry* **2006**, *17*, 1415–1419.

45. CCDC 605818: Gribkov, D.V.; Hultzsch, K.C.; Hampel, F. 3,3′-Bis(trisarylsilyl)-substituted binaphtholate rare earth metal catalysts for asymmetric hydroamination. *J. Am. Chem. Soc.* **2006**, *128*, 3748–3759.
46. CCDC 638938: Laurent, S.A.L.; Boissier, J.; Coslédan, F.; Gornitzka, H.; Robert, A.; Meunier, B. Synthesis of "trioxaquantel"® derivatives as potential new antischistosomal drugs. *Eur. J. Org. Chem.* **2008**, 895–913, doi:10.1002/ejoc.200700975.
47. CCDC 675390: Zhang, Z.; Bender, C.F.; Widenhoefer, R.A. Gold(I)-catalyzed dynamic kinetic enantioselective intramolecular hydroamination of allenes. *J. Am. Chem. Soc.* **2007**, *129*, 14148–14149.
48. CCDC 706349: Nicolaou, K.C.; Dalby, S.M.; Li, S.; Suzuki, T.; Chen, D.Y.K. Total synthesis of (+)-haplophytine. *Angew. Chem. Int. Ed.* **2009**, *48*, 7616–7620.
49. CCDC 707825: Zhong, Y.L.; Krska, S.W.; Zhou, H.; Reamer, R.A.; Lee, J.; Sun, Y.; Askin, D. Catalytic asymmetric synthesis of an HIV integrase inhibitor. *Org. Lett.* **2009**, *11*, 369–372.
50. CCDC 766837: Zhu, H.; Plewe, M.B.; Rheingold, A.L.; Moore, C.; Yanovsky, A. (3a*S*,7a*S*)-5-[(*S*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoyl]-2,3,4,5,6,7-hexahydro-1*H*-pyrrolo-[3,4-*c*]pyridin-3(2*H*)-one monohydrate. *Acta Cryst.* **2010**, *E66*, o175–o176.
51. CCDC 830079: Chapurina,Y.; Ibrahim, H.; Guillot, R.; Kolodziej, E.; Collin, J.; Trifonov, A.; Schulz, E.; Hannedouche, J. Catalytic, enantioselective intramolecular hydroamination of primary amines tethered to di- and trisubstituted alkenes. *J. Org. Chem.* **2011**, *76*, 10163−10172.
52. CCDC 1104875: Nishi, T.; Ishibashi, K.; Nakajima, K.; Iio, Y.; Fukazawa, T. An efficient synthesis of enantiomerically pure 2-[(2*R*)-arylmorpholin-2-yl]ethanols, key intermediates of tachykinin receptor antagonist. *Tetrahedron Asymmetry* **1998**, *9*, 3251–3262.
53. CCDC 1105464: Nishi, T.; Nakajima, K.; Iio, Y.; Ishibashi, K.; Fukazawa, T. Practical methods for the preparation of spiro[benzo[*c*]thiophene-1(3*H*),4′-piperidine]-(2*S*)-oxide by resolution and asymmetric sulfoxidation. *Tetrahedron Asymmetry* **1998**, *9*, 2567–2570.
54. CCDC 1267150, CCDC 1267151: Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. Asymmetric transfer hydrogenation of imines. *J. Am. Chem. Soc.* **1996**, *118*, 4916–4917.
55. CCDC 1280861: Fleischhauer, J.; Raabe, G.; Santos, A.G.; Schiffer, J.; Wollmer, A. Determination of the absolute configuration of 1,5-diaza-*cis*-decalin by comparison of measured and calculated CD-spectra. *Z. Naturforsch.* **1998**, *53a*, 896–902.
56. CCDC 1294281: Takemoto, T.; Nakajima, K.; Iio, Y.; Tamura, M.; Nishi, T. Asymmetric synthesis of enantiomerically pure spiro[((2*S*)-hydroxy)indane-1,4′-piperidine]. *Tetrahedron Asymmetry* **1999**, *10*, 1787–1793.
57. CCDC 113953: Morice, C.; Maux, P.L.; Simonneaux, G.; Toupet, L. Chiral recognition of amino esters by ruthenium porphyrin complexes and crystal structure of {5,10,15,20-tetrakis[*o*-(3,3,3-trifluoro-2-methoxy-2-phenylpropanoylamino)phenyl]porphyrin}bis(L-valine methyl ester)ruthenium(II) (α,α,β,β isomer). *J. Chem. Soc. Dalton Trans.* **1998**, 4165–4172, doi:10.1039/A804704I.
58. CCDC 1310848: Maux, P.L.; Bahri, H.; Simonneaux, G.; Toupet, L. Enantioselective oxidation of racemic phosphines with chiral oxoruthenium porphyrins and crystal structure of [5,10,15,20-tetrakis[*o*-((2-methoxy-2-phenyl-3,3,3-trifluoropropanoyl)amino)phenyl]porphyrinato](carbonyl) (tetrahydrofuran) ruthenium(II) (α,β,α,β isomer). *Inorg. Chem.* **1995**, *34*, 4691–4697.

59. CCDC 655554: Katritzky, A.R.; Mohapatra, P.P.; Fedoseyenko, D.; Duncton, M.; Steel, P.J. 1-Benzotriazol-1-yl-3,3,3-trifluoro-2-methoxy-2-phenylpropan-1-ones: Mosher-Bt reagents. *J. Org. Chem.* **2007**, *72*, 4268–4271.
60. CCDC 1142231: Huber, R.; Knierzinger, A.; Obrecht, J.P.; Vasella, A. Nucleophilic additions to *N*-glycosylnitrones. Asymmetric synthesis of α-aminophosphonic acids. *Helv. Chim. Acta* **1985**, *68*, 1730–1747.
61. CCDC 1236701, CCDC 1236702, CCDC 1236703: Yager, K.M.; Taylor, C.M.; Smith III, A.B. Asymmetric synthesis of α-aminophosphonates via diastereoselective addition of lithium diethyl phosphite to chelating imines. *J. Am. Chem. Soc.* **1994**, *116*, 9377–9378.
62. CCDC 1216345: Peng, J.; Barr, M.E.; Ashburn, D.A.; Lebioda, L.; Garber, A.R.; Martinez, R.A.; Odom, J.D.; Dunlap, R.B.; Silks III, L.A. Synthesis and characterization of acylated chiral oxazolidine-2-selones: Selone chiral derivatizing agents for the detection and quantitation of remotely disposed chiral centers. *J. Org. Chem.* **1995**, *60*, 5540–5549.
63. CCDC 630372: Garcia-Saez, I.; DeBonis, S.; Lopez, R.; Trucco, F.; Rousseau, B.; Thuéry, P.; Kozielski, F. Structure of human Eg5 in complex with a new monastrol-based inhibitor bound in the *R* configuration. *J. Biol. Chem.* **2007**, *282*, 9740–9747.
64. CCDC 143886: Enders, D.; Janeck, C.F.; Raabe, G. Asymmetric β-aminoethylation of ketones and nitriles with tosylaziridines employing the SAMP-hydrazone method. *Eur. J. Org. Chem.* **2000**, 3337–3345, doi:10.1002/1099-0690(200010)2000:19<3337::AID-EJOC3337>3.0.CO;2-V.
65. CCDC 1261296: Mercury software could not load the CIF file: Nakagawa, K.; Somei, M. Ergot alkaloids: The first and five step total syntheses of (−)-and (+)-6,7-secoagroclavines, and syntheses of (−)- and (+)-6-nor-6-propyl-6,7-secoagroclavines ((−)-and (+)-KSU 1415). *Heterocycles* **1991**, *32*, 873–878.
66. CCDC1241198: Mercury software could not load the CIF file: Eberle, M.K.; Keese, R.; Stoeckli-Evans, H. New synthesis and chirality of (−)-4,4,4,4′,4′,4′-hexafluorovaline. *Helv. Chim. Acta* **1998**, *81*, 182–186.
67. Thayer, A.M. Centering on chirality. *Chem. Eng. News* **2007**, *85*, 11–19.
68. Amine Based Pharmaceutical Drugs. Available online: https://www.jacobs-university.de/ses/tnugent/research/chiralamines/drugs (accessed on 3 June 2015).
69. Hutt, A.J.; Valentová, J. The chiral switch: The development of single enantiomer drugs from racemates. *Acta Fac. Pharm. Univ. Comen.* **2003**, *Tomus L*, 7–22.
70. Desiraju, G.R. Crystal engineering: from molecule to crystal. *J. Am. Chem. Soc.* **2013**, *135*, 9952–9967.
71. Saigo, K.; Sakai, K. Toward efficient optical resolution by diastereomeric salt formation. *J. Syn. Org. Chem. Jpn.* **2011**, *69*, 499–505.
72. IUPAC Gold Book recommends that the terms *s*-cis and *s*-trans should not be applied to the *N*-alkyl amides. IUPAC. *Compendium of Chemical Terminology*, 2nd ed. (the "Gold Book"); McNaught, A.D., Wilkinson, A., Eds; Blackwell Scientific Publications: Oxford, UK, 1997. XML on-line corrected version: http://goldbook.iupac.org (2006-) Created by Nic, M.; Jirat, J.; Kosata, B. Updates compiled by Jenkins, A.
73. Desiraju, G.R. Hydrogen bridges in crystal engineering: Interactions without borders. *Acc. Chem. Res.* **2002**, *35*, 565–573.

74. Brand, D.J.; Steenkamp, J.A.; Brandt, E.V.; Takeuchi, Y. Conformational studies of (−)-epicatechin-Mosher ester. *Tetrahedron Lett.* **2007**, *48*, 2769–2773.
75. Khan, M.A.; Tavares, D.F.; Rauk, A. Magnetic non-equivalence of fluorine atoms of a trifluoromethyl group. *Can. J. Chem.* **1982**, *60*, 2451–2455.
76. Nishio, M. Chapter 6: CH/π hydrogen bonds. In *New Edition: Introduction to Intermolecular Forces in Organic Chemistry*; Kodansha Scientific: Tokyo, Japan, 2008; pp. 42–55.
77. Hoye, T.R.; Renner, M.K. Application of MTPA (Mosher) Amides of secondary amines: Assignment of absolute configuration in chiral cyclic amines. *J. Org. Chem.* **1996**, *61*, 8489–8495.
78. Kang, C.Q.; Guo, H.Q.; Qiu, X.P.; Bai, X.L.; Yao, H.B.; Gao, L.X. Assignment of absolute configuration of cyclic secondary amines by NMR techniques using Mosher's method: A general procedure exemplified with (−)-isoanabasine. *Magn. Reson. Chem.* **2006**, *44*, 20–24.
79. Anslyn, E.V.; Dougherty, D.A. Chapter 6: Stereochemistry. In *Modern Physical Organic Chemistry*; University Science Books: Sausalito, CA, USA, 2005; pp. 297–350.
80. Azumaya, I. Discovery of *cis*-preference of aromatic *N*-methylamides and its application to molecular constructions. *Yakugaku Zasshi* **2001**, *121*, 117–129.
81. The Conformational Preference of s-*cis* Amides. Available online: http://www.ch.imperial.ac.uk/rzepa/blog/?p=9459 (accessed on 4 June 2015).
82. Shinitzky reviewed the slight differences of physico-chemical properties between enantiomers in certain cases, and reported the concept of space asymmetry. Shinitzky, M. Space asymmetry as a possible grobal feature. *Chirality* **2013**, *25*, 308–311.
83. Macrae, C.F.; Bruno, I.J.; Chisholm, J.A.; Edgington, P.R.; McCabe, P.; Pidcock, E.; Rodriguez-Monge, L.; Taylor, R.; van de Streek, J.; Wood, P.A. Mercury CSD 2.0—New features for the visualization and investigation of crystal structures. *J. Appl. Cryst.* **2008**, *41*, 466–470.

Sample Availability: Not available.