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Use of a diamagnetic lanthanide complex for extending the scope of NMR determination of absolute configuration by the modified Mosher's method

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Abstract—The reversal of the relative position of ^{1}H NMR signals observed for diastereomeric MTPA esters and amides upon addition of La(hfaa)$_3$ can be used for verification of the validity of the correlation model employed in the modified Mosher's method. This verification extends the scope of the determination of absolute configurations using the Mosher method to substrates having only a few proton probes. © 2002 Published by Elsevier Science Ltd.

1. Introduction

To date, various NMR methods for the determination of absolute configuration using chiral derivatizing agents (CDAs) have been proposed.[1–8] Of these methods, the modified Mosher's method has often been employed to determine the absolute configuration of secondary alcohols from natural sources.[9–12] In this method, a chiral compound with unknown configuration is derivatized with (*R*)- and (*S*)-MTPA (MTPA = α-methoxy-α-trifluoromethylphenylacetic acid) to yield a pair of diastereomeric derivatives. The chemical shifts of ^{1}H NMR signals of this pair of diastereomers are then compared. The absolute configuration is assigned using the correlation model based on the *sp* conformation in which the C–CF$_3$ bond is *synperiplanar to* the C=O bond of the ester carbonyl group (Fig. 1).

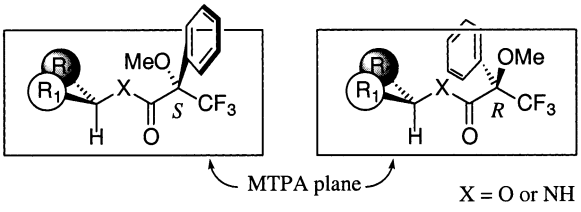

Figure 1. Models for assignment of absolute configuration in the modified Mosher's method.

In the *sp* conformation of (*S*)-MTPA derivative, the protons in the R$_1$ group located in front of the MTPA plane[†] are shielded by the phenyl group of MTPA, thus resonating at a higher field relative to those in the R$_1$ group of the (*R*)-isomer to give negative $\Delta\delta_0^{S,R}$ values ($\Delta\delta_0^{S,R} = \delta_S - \delta_R$: *S* and *R* denote the configuration of MTPA). While in the same conformation of the (*R*)-MTPA derivative, the R$_2$ group located behind the MTPA plane is shielded and the signals due to the R$_2$ protons appear at higher field relative to the signals due to the (*S*)-isomer to give positive $\Delta\delta_0^{S,R}$ values.

The validity of the correlation model can be judged by examining the signs of $\Delta\delta_0^{S,R}$ for as many protons as possible.[‡] If the signs are consistent within each substituent and those observed for the R$_1$ and the R$_2$ are opposite, the model applies. However, if a substrate does not have sufficient protons, or one of the two α-substituents has very few or no protons, the validity

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[†] The atoms in H-C-X-C(=O)-C (X = O or NH) moiety are in the same plane. For convenience we call this plane the MTPA plane.

[‡] Latypov et al. pointed out the conformational complexity of MTPA esters, which might render the prediction of absolute configuration risky. See Ref. 13.

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of the model cannot be verified.[14,15] In such cases another method for verifying the validity of the correlation model is required.

An intriguing method was reported for determining the absolute configuration of chiral primary amines and alcohols using only one of two diastereomeric α-methoxy-α-phenylacetic acid (MPA) derivatives.[16–18] It utilizes the chemical shift change caused by chelation of the CH_3O and the C=O groups of the substrate to Ba^{2+} ion in acetonitrile-d_3. We noted that this method included verification of the validity of the correlation model and were interested in whether this approach could be useful for those MTPA derivatives that have been most widely used. We tested $Ba(ClO_4)_2$ with (*R*)- and (*S*)-MTPA esters of (1*R*,2*S*,5*R*)-menthol and also of (*S*)-2-phenylethanol in acetonitrile-d_3, and found that it did not afford noticeable shifts in the signals of the esters.

In the study presented herein, we found a simple method utilizing $La(hfaa)_3$ (hfaa = hexafluoroacetylacetonate) as a chelating agent to verify the validity of the correlation model employed in the modified Mosher's method. This new method of verification extends the applicability of the modified Mosher's method to secondary alcohols and primary amines that have a limited number of protons. Since the MTPA moiety does not have an acidic hydrogen on its stereogenic α-carbon, it is suitable as a CDA for use with the Lewis acid of a chelating agent.

The method is illustrated in Fig. 2. Added chelating agent forms a chelate with the CH_3O and the C=O of the MTPA moiety and increases the population of the *sp′* conformation. With this conformational change, the phenyl group in each diastereomer moves to the other side of MTPA plane from its original position.

Accordingly, the phenyl group of the (*S*)-isomer shields R_2 to give positive $\Delta\delta_M^{S,R}$ ($\Delta\delta_M = \delta_S - \delta_R$: in the presence of metal ion), while that of the (*R*)-isomer shields the R_1 group to give negative $\Delta\delta_M^{S,R}$ values. Thus, a reversal in the relative position will be observed for the diastereomer signals from protons on both the R_1 group and for signals due to those on the R_2 group. The reversal of the relative position of corresponding diastereomer signals described above is summarized in Fig. 2(b). The signs of $\Delta\delta_0^{S,R}$ and $\Delta\delta_M^{S,R}$ for R_1 located on the left side of MTPA plane are negative and positive, respectively, while the signs of $\Delta\delta_0^{S,R}$ and $\Delta\delta_M^{S,R}$ for R_2 located on the right side of the MTPA plane are opposite to those for R_1. Since this reversal of the relative signal position by a chelating agent indicates that the conformation in the absence of the reagent is *sp*, it can be used for verifying the applicability of the modified Mosher's method.

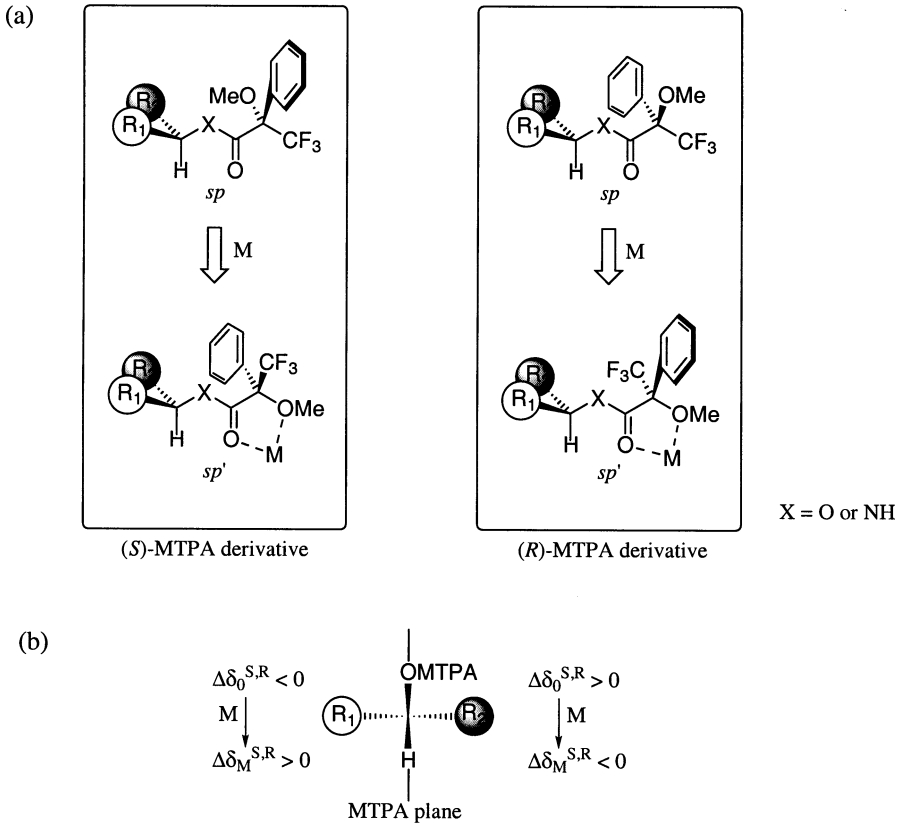
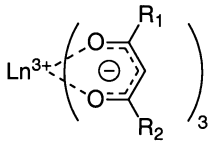


Figure 2. (a) Conformational changes of (*R*)- and (*S*)-MTPA esters and amides on chelation of a metal ion. (b) The signs of $\Delta\delta_0^{S,R}$ and $\Delta\delta_M^{S,R}$ at the right and left sides of the MTPA plane.

2. Results and discussion

2.1. Chelating agent

Chelating agents effective in $CDCl_3$ were first sought. Since the NMR shift reagent $Eu(fod)_3$ (fod = 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-dionate) was known to chelate with the CH_3O and the C=O of MTPA esters,[19] we considered use of similar complexes of diamagnetic lanthanide ions (La^{3+} and Lu^{3+}).



R_1 = *t*-Bu, R_2 = C_3F_7 (fod)
R_1 = R_2 = CF_3 (hfaa)

$Eu(fod)_3$, which induces paramagnetic shift, is not suitable because the method is based on the chemical shift nonequivalence induced by diamagnetic anisotropy of the phenyl group.

In order to avoid overlap of the ligand signals with those from the substrates, it is desirable that the ligand has no or few protons. We therefore chose hfaa since it has only one proton as a ligand. In addition, the electronegative fluorine atoms in this ligand were expected to increase the Lewis acidity of the central metal ion and facilitate chelate formation. $La(hfaa)_3$ and $Lu(hfaa)_3$[20] were tested for the diastereomeric MTPA esters of 1-phenylethanol in $CDCl_3$ and it was revealed that $La(hfaa)_3$ was more effective than $Lu(hfaa)_3$.[§] We therefore chose $La(hfaa)_3$ as the chelating agent in this study. Unlike $Ba(ClO_4)_2$, $La(hfaa)_3$ can be handled easily, since it is not explosive.

2.2. Reversal of the relative signal position of diastereomer signals by $La(hfaa)_3$

The reversal in relative positions of the corresponding signals due to diastereomeric MTPA derivatives was examined upon addition of $La(hfaa)_3$ for nine secondary alcohols and three primary amines. The results are summarized in Fig. 3.

Typical shift behavior of diastereomer signals can be seen in the case of MTPA esters of (*S*)-2-butanol ((*R*)- and (*S*)-**1**: where *R* and *S* denote the configuration of MTPA). In the absence of $La(hfaa)_3$, the $CH_3{}^a$ signals of (*S*)-**1** and (*R*)-**1** are located at 1.25 and 1.34 ppm ($\Delta\delta_0^{S,R} = -0.09$ ppm), respectively (Fig. 4). Upon the addition of $La(hfaa)_3$, the former signal stayed at almost the original position instead of shifting downfield as expected, while the latter signal shifted upfield (Fig. 4).

Consequently, the initial relative position of these signals was reversed as expected ($\Delta\delta_{La}^{S,R} = 0.07$ ppm at 1.5 molar ratio of $La(hfaa)_3$ for **1**). Similarly, reversal of the relative positions was also observed for $CH_3{}^b$ signals, where the signal due to (*R*)-**1** stayed at almost the original position, while the signal due to (*S*)-**1** shifted upfield.

The unexpected shift behavior of the $CH_3{}^a$ signal of (*S*)-**1** and the $CH_3{}^b$ signal of (*R*)-**1** suggests that these groups are shielded by group(s) other than MTPA–Ph. This shielding effect is probably due to the hfaa ligand, which cancels out downfield shift of these signals by the conformational change from *sp* to *sp'*. This is supported by the observed upfield shifts of the signals due to the protons on C-6 and C-7 of (1*R*,2*S*,5*R*)-menthyl methoxyacetate **13** having no aromatic group in the acid moiety (Fig. 5).

The upfield shifts of the MTPA–MeO signals[¶] of (*R*) and (*S*)-**1** (Fig. 4) are of similar magnitude. These upfield shifts are in marked contrast to the downfield shift[21] observed for the MeO signal of **13**, consistent with the expectation of decrease in electron density of the ether oxygen caused by its coordination with the La^{3+} ion. The upfield shifts of similar magnitude for (*R*)- and (*S*)-**1** suggest that formation of a complex by these diastereomers with $La(hfaa)_3$ occurs to a similar extent.

Similar shift behavior of diastereomer signals with the addition of $La(hfaa)_3$ was observed for the diastereomeric MTPA esters **2**–**9** and the amides **10**–**12**. For the esters **5**–**8**, the shift behavior was examined for the signals of all protons. The reversal of the relative position of the corresponding signals was generally seen for all protons in **5**–**7** located on the left and the right sides of the MTPA plane as expected. In **6** and **7**, both having equatorial ester groups, the border between positive and negative $\Delta\delta_0^{S,R}$ is the line connecting C-1 and C-4, indicating that these compounds take the ideal conformations shown in Fig. 1. On the other hand, in **8** having the axial OMTPA group, the border between positive and negative $\Delta\delta_0^{S,R}$ exists between C-2 and C-3. This suggests the conformation of the axial OMTPA groups in **8** differs somewhat from the ideal. Hitherto, the modified Mosher's method has not been considered suitable for determining the absolute configuration for compounds such as **8**,[3,14] however, in addition to the regular

[§] Addition of 1.5 equiv. of $La(hfaa)_3$ decreased the initial chemical shift difference of −0.06 ppm to 0.02 ppm, whereas addition of the same amount of Lu(hfaa) had almost no effect on the chemical shift difference.

[¶] A possible interpretation of this upfield shift is as follows: In the *sp*' conformation of each diastereomer depicted in Fig. 2(a), to avoid steric repulsion from the CF_3 group, the CH_3 group of MTPA–MeO is likely to adopt a position *syn* to the Ph group with respect to rotation around the O–C_α bond and is located in the shielding region of the aromatic ring.

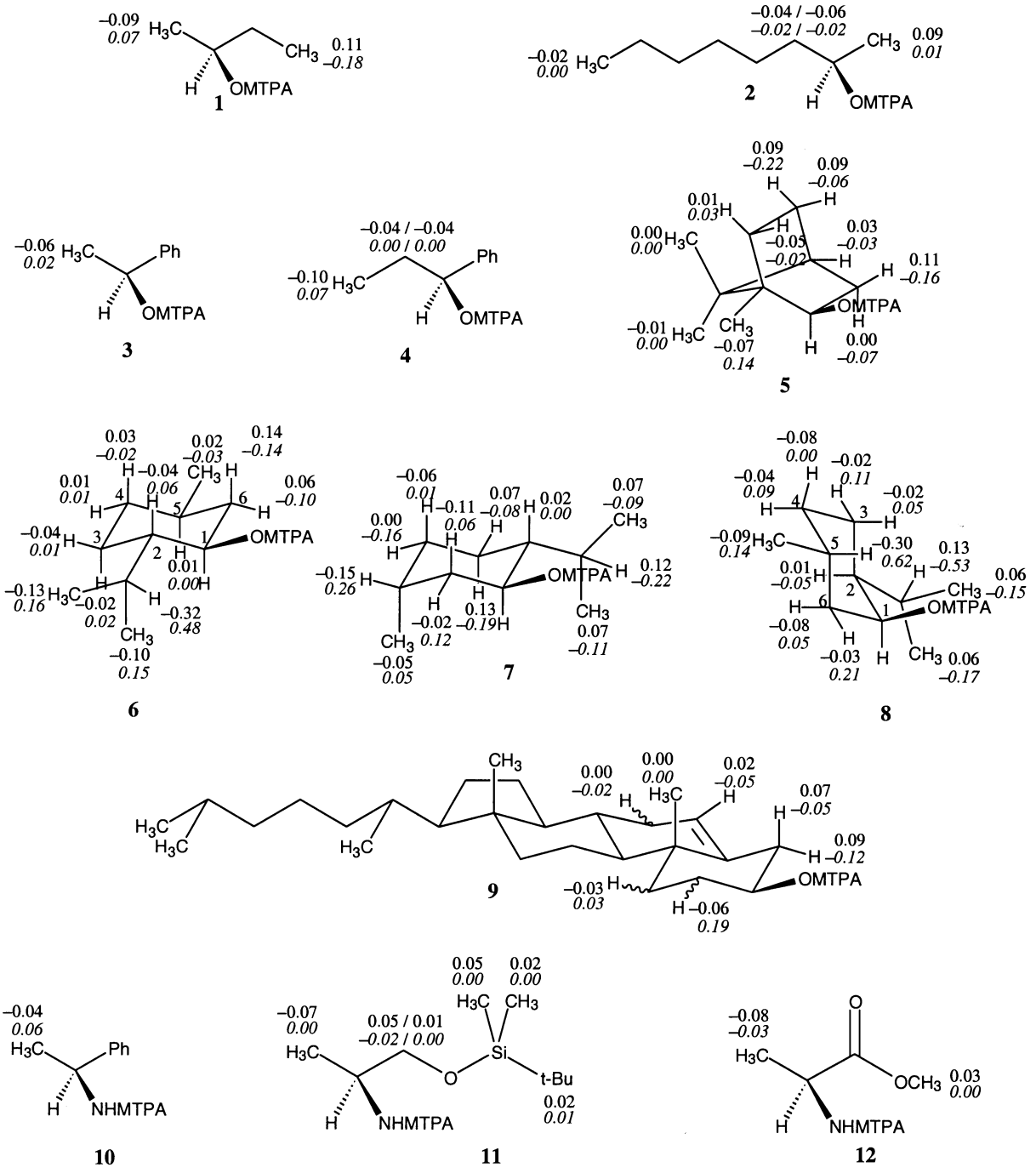


Figure 3. $\Delta\delta_0^{S,R}$ and $\Delta\delta_{La}^{S,R}$ values (ppm) for MTPA esters and amides ($\Delta\delta_0^{S,R}$: normal type, $\Delta\delta_{La}^{S,R}$: *italic*, the values at $[La(hfaa)_3]/[substrate] = 1.5$).

arrangement of sign of $\Delta\delta_0^{S,R}$ values. The observed reversal of the relative positions of the corresponding diastereomer signals upon the addition of $La(hfaa)_3$ strongly supports the application of the modified Mosher's method to **8**, even though it deviates somewhat from the ideal *sp* conformation.

For **2** and **12**, the reversal of relative position of signals due to diastereomers was observed on neither side of the MTPA plane in the presence of a 1.5 molar ratio of $La(hfaa)_3$ to the substrates. However, the absolute values of $\Delta\delta_{La}^{S,R}$ apparently decreased with addition of $La(hfaa)_3$, indicating that the change in relative positions of these signals was on the way to reversal. Further addition of the reagent was prevented due to its solubility limitation.

It must be mentioned that, unlike $Ba(ClO_4)_2$, $La(hfaa)_3$ cannot be employed for determining the absolute configuration of a single diastereomer, since such a

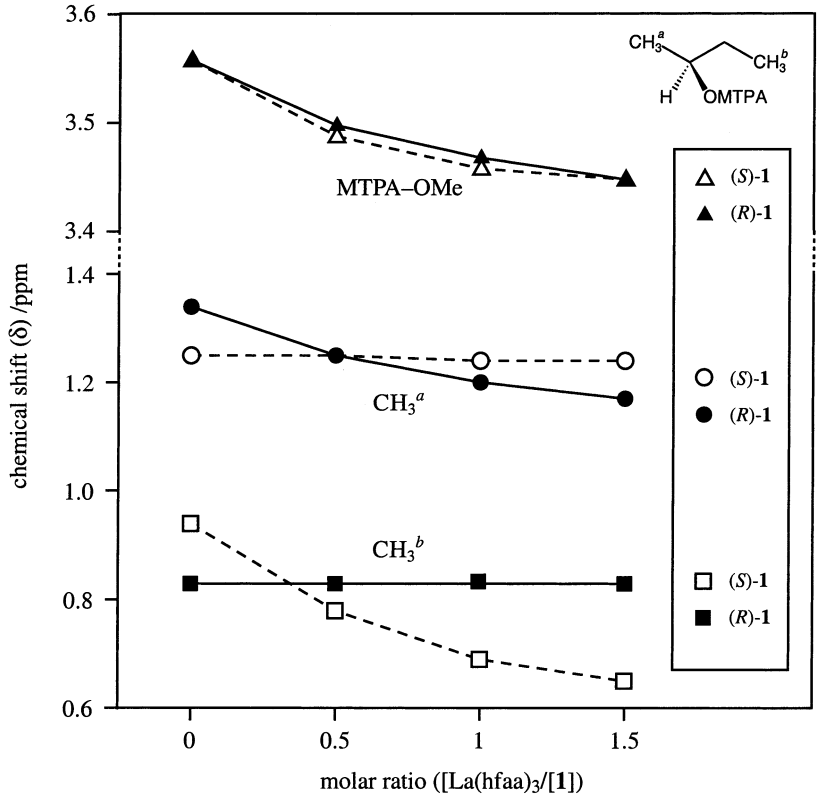


Figure 4. Chemical shift changes observed for the signals of (*R*)- and (*S*)-**1** with the addition of La(hfaa)$_3$.

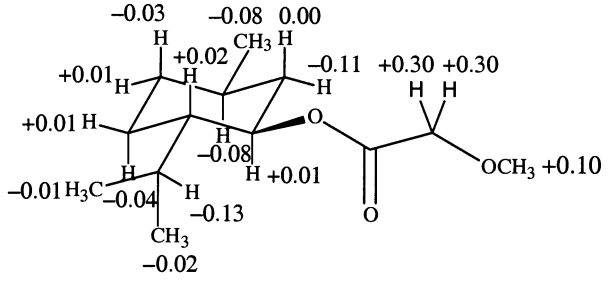


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Figure 5. Chemical shift change [$\Delta\delta_{La}$–$\Delta\delta_0$ (ppm)] of the signals due to the protons of **13** with the addition of La(hfaa)$_3$ (1.5 molar equiv.).

determination requires both upfield shifts for signals from either R_1 or R_2, and downfield shifts for the signals from the other.[16,18] However, upfield shifts were observed for most signals from both R_1 and R_2 groups in the present method.

3. Conclusion

We observed the reversal of relative position of diastereomer signals on MTPA derivatives upon the addition of La(hfaa)$_3$. This reversal reflects the conformational change on moving from the *sp* to the *sp′* caused by chelate formation between a substrate and La(hfaa)$_3$ and can be used for verification of the correlation model of the modified Mosher's method, that is, of the *sp* conformations of MTPA esters and amides. This verification considerably increases the reliability of assignment by the MTPA method. Therefore, the method we have presented must be useful for determining the absolute configuration of substrates in which probe protons are insufficient for reliable assignment and/or are localized on only one substituent (R_1 or R_2) around the stereogenic center.

4. Experimental

4.1. General

The NMR spectra were recorded on a JEOL GSX-400 spectrometer in $CDCl_3$ containing tetramethylsilane as internal standard. Lanthanum chloride heptahydrate and lutetium nitrate *n*-hydrate were purchased from WAKO Pure Chemical. Hhfaa was available from Tokyo Kasei and used without any further purification. (*R*)- and (*S*)-MTPACl were purchased from Aldrich and distilled prior to use. Solvents used in acylation reactions were distilled from CaH_2 under Ar. Column chromatography was performed with Merck Kieselgel 60 (230–400 mesh).

4.2. Chelating agents

Lanthanum tris(hexafluoroacetylacetonate)(La(hfaa)$_3$) was prepared by the method of Richardson et al.[20] It was dried at 60°C overnight in vacuo before use. Colorless crystals. Anal. calcd for $C_{15}H_3F_{18}LaO_6{\cdot}3H_2O$, C, 22.03, H, 1.11%; found: C, 22.06, H, 1.13%. Lutetium tris(hexafluoroacetylacetonate)(Lu(hfaa)$_3$) was also pre-

pared by the same method from $Lu(NO_3)_3 \cdot nH_2O$. Colorless crystals. Anal. calcd for $C_{15}H_3F_{18}LuO_6 \cdot 2H_2O$, C, 21.65; H, 0.85%; found: C, 21.65; H, 0.89%.

4.3. MTPA esters and amides

MTPA esters and amides were prepared using MTPA chlorides and alcohols or amines as reported.[22]

4.3.1. (*S*)-2-Butyl (*R*)-α-methoxy-α-trifluoromethylphenylacetate, (*R*)-1. ^{1}H NMR (400 MHz, $CDCl_3$) 0.83 (3H, t, $J=6.7$ Hz), 1.34 (3H, d, $J=6.4$ Hz), 1.57–1.68 (2H, m), 3.56 (3H, q, $J=1.2$ Hz), 5.08 (1H, brsext, $J=6.3$ Hz), 7.35–7.43 (3H, m), 7.45–7.58 (2H, m).

4.3.2. (*S*)-2-Butyl (*S*)-α-methoxy-α-trifluoromethylphenylacetate, (*S*)-1. ^{1}H NMR (400 MHz, $CDCl_3$) 0.94 (3H, t, $J=6.7$ Hz), 1.25 (3H, d, $J=6.4$ Hz), 1.63–1.77 (2H, m), 3.56 (3H, q, $J=1.2$ Hz), 5.08 (1H, brsext, $J=6.3$ Hz), 7.35–7.43 (3H, m), 7.45–7.58 (2H, m).

4.3.3. (*S*)-2-Octyl (*R*)-α-methoxy-α-trifluoromethylphenylacetate, (*R*)-2. ^{1}H NMR (400 MHz, $CDCl_3$) 0.88 (3H, brt, $J=7.1$ Hz), 1.19–1.34 (8H, m), 1.27 (3H, d, $J=6.6$ Hz), 1.55 (1H, m), 1.68 (1H, m), 3.55 (3H, brd, $J=1.3$ Hz), 5.14 (1H, qt, $J=7.4$, 6.3 Hz), 7.35–7.41 (3H, m), 7.51–7.54 (2H, m).

4.3.4. (*S*)-2-Octyl (*S*)-α-methoxy-α-trifluoromethylphenylacetate, (*S*)-2. ^{1}H NMR (400 MHz, $CDCl_3$) 0.86 (3H, brt, $J=7.0$ Hz), 1.15–1.28 (8H, m), 1.33 (3H, d, $J=6.6$ Hz), 1.51 (1H, m), 1.61 (1H, m), 3.57 (3H, q, $J=1.3$ Hz), 5.14 (1H, qt, $J=6.6$, 5.2 Hz), 7.33–7.44 (3H, m), 7.51–7.58 (2H, m).

4.3.5. (*S*)-1-Phenylethyl (*R*)-α-methoxy-α-trifluoromethylphenylacetate, (*R*)-3. ^{1}H NMR (400 MHz, $CDCl_3$) 1.64 (3H, d, $J=6.7$ Hz), 3.56 (3H, brd, $J=1.3$ Hz), 6.13 (1H, q, $J=6.7$ Hz), 7.23–7.27 (2H, m), 7.27–7.32 (3H, m), 7.32–7.39 (3H, m), 7.39–7.43 (2H, m).

4.3.6. (*S*)-1-Phenylethyl (*S*)-α-methoxy-α-trifluoromethylphenylacetate, (*S*)-3. ^{1}H NMR (400 MHz, $CDCl_3$) 1.58 (3H, d, $J=6.7$ Hz), 3.47 (3H, q, $J=1.1$ Hz), 6.13 (1H, q, $J=6.7$ Hz), 7.29–7.41 (8H, m), 7.42–7.46 (2H, m).

4.3.7. (*S*)-1-Phenylpropyl (*R*)-α-methoxy-α-trifluoromethylphenylacetate, (*R*)-4. ^{1}H NMR (400 MHz, $CDCl_3$) 0.94 (3H, t, $J=7.4$ Hz), 1.88 (1H, dqd, $J=13.7$, 7.4, 6.7 Hz), 2.01 (1H, ddq, $J=13.7$, 7.8, 7.4 Hz), 3.54 (3H, q, $J=1.3$ Hz), 7.17–7.26 (2H, m), 7.26–7.32 (5H, m), 7.32–7.41 (3H, m).

4.3.8. (*S*)-1-Phenylpropyl (*S*)-α-methoxy-α-trifluoromethylphenylacetate, (S)-4. ^{1}H NMR (400 MHz, $CDCl_3$) 0.84 (3H, t, $J=7.3$ Hz), 1.84 (1H, dqd, $J=14.9$, 7.3, 6.1 Hz), 1.97 (1H, ddq, $J=15.0$, 7.9, 7.3 Hz), 3.45 (3H, brs), 5.90 (1H, dd, $J=7.9$, 6.1 Hz), 7.25–7.36 (8H, m), 7.36–7.43 (2H, m).

4.3.9. [(1*S*)-*endo*]-Bornyl (*R*)-α-methoxy-α-trifluoromethylphenylacetate, (*R*)-5. ^{1}H NMR (400 MHz, $CDCl_3$) 0.88 (3H, s), 0.89 (3H, s), 0.93 (3H, s), 1.00 (1H, dd, $J=14.0$, 3.6 Hz), 1.12 (1H, m), 1.27 (1H, m), 1.73 (1H, m), 1.77 (1H, m), 1.83 (1H, m), 2.45 (1H, dddd, $J=14.0$, 9.6, 4.4, 3.6 Hz), 3.49 (3H, brs), 5.07 (1H, ddd, $J=9.6$, 3.2, 2.4 Hz), 7.38–7.43 (3H, m), 7.50–7.55 (2H, m).

4.3.10. [(1*S*)-*endo*]-Bornyl (*S*)-α-methoxy-α-trifluoromethylphenylacetate, (*S*)-5. ^{1}H NMR (400 MHz, $CDCl_3$) 0.81 (3H, s), 0.88 (3H, s), 0.93 (3H, s), 1.11 (1H, dd, $J=14.0$, 3.2 Hz), 1.21 (1H, m), 1.28 (1H, m), 1.70 (1H, m), 1.74 (1H, m), 1.82 (1H, ddd, $J=12.8$, 9.6, 4.4 Hz), 2.45 (1H, dddd, $J=14.0$, 9.6, 4.4, 3.2 Hz), 3.50 (3H, brs), 5.11 (1H, ddd, $J=10.0$, 3.2, 2.0 Hz), 7.38–7.43 (3H, m), 7.53–7.58 (2H, m).

4.3.11. (1*S*,2*R*,5*S*)-Menthyl (*R*)-α-methoxy-α-trifluoromethylphenylacetate: (*R*)-6. ^{1}H NMR (400 MHz, $CDCl_3$) 0.87 (3H, d, $J=7.1$ Hz), 0.86 (1H, m), 0.86 (3H, d, $J=6.8$ Hz), 0.91 (3H, d, $J=6.6$ Hz), 0.98 (1H, q, $J=12.0$), 1.06 (1H, m), 1.45 (1H, dddd, $J=12.2$, 10.9, 3.1, 2.8 Hz), 1.52 (1H, m), 1.69 (1H, m), 1.71 (1H, m), 1.88 (1H, m), 2.07 (1H, dddd, $J=12.0$, 6.0, 3.0, 1.7 Hz), 3.53 (3H, q, $J=1.2$ Hz), 4.88 (1H, td, $J=11.0$, 4.4 Hz), 7.38–7.43 (3H, m), 7.48–7.55 (2H, m).

4.3.12. (1*S*,2*R*,5*S*)-Menthyl (*S*)-α-methoxy-α-trifluoromethylphenylacetate, (*S*)-6. ^{1}H NMR (400 MHz, $CDCl_3$) 0.67 (3H, d, $J=7.1$ Hz), 0.74 (3H, d, $J=6.8$ Hz), 0.89 (1H, m), 0.93 (3H, d, $J=6.6$ Hz), 1.04 (1H, qd, $J=6.6$, 3.4 Hz), 1.11 (1H, q, $J=11.2$ Hz), 1.42 (1H, dddd, $J=12.5$, 11.0, 3.6, 2.8 Hz), 1.53 (1H, m), 1.56 (1H, m), 1.67 (1H, m), 1.70 (1H, m), 2.13 (1H, dddd, $J=12.0$, 3.6, 3.0, 2.0 Hz), 3.58 (3H, q, $J=1.4$ Hz), 4.90 (1H, td, $J=11.0$, 4.4 Hz), 7.36–7.42 (3H, m), 7.51–7.56 (3H, m).

4.3.13. (1*S*,2*R*,5*R*)-Isomenthyl (*R*)-α-methoxy-α-trifluoromethylphenylacetate, (*R*)-7. ^{1}H NMR (400 MHz, $CDCl_3$) 0.82 (3H, d, $J=7.0$ Hz), 0.89 (3H, d, $J=7.1$ Hz), 0.94 (3H, d, $J=6.8$ Hz), 1.23 (1H, m), 1.38 (1H, m), 1.42 (1H, m), 1.45 (1H, m), 1.47 (1H, m), 1.62 (1H, m), 1.64 (1H, m), 1.66 (1H, m), 1.87 (1H, m), 3.57 (3H, q, $J=1.1$ Hz), 5.29 (1H, td, $J=7.4$, 4.1 Hz), 7.37–7.41 (3H, m), 7.52–7.55 (2H, m).

4.3.14. (1*S*,2*R*,5*R*)-Isomenthyl (*S*)-α-methoxy-α-trifluoromethylphenylacetate, (*S*)-7. ^{1}H NMR (400 MHz, $CDCl_3$) 0.89 (3H, d, $J=7.3$ Hz), 0.89 (3H, d, $J=7.3$ Hz), 0.96 (3H, d, $J=6.8$ Hz), 1.17 (1H, dtd, $J=13.2$, 8.8, 4.4 Hz), 1.40 (1H, m), 1.42 (1H, m), 1.51 (1H, m), 1.54 (1H, m), 1.58 (1H, m), 1.64 (1H, m), 1.72 (1H, m), 1.76 (1H, m), 3.54 (3H, q, $J=1.0$ Hz), 5.30 (1H, td, $J=5.9$, 3.2 Hz), 7.24–7.41 (3H, m), 7.51–7.54 (2H, m).

4.3.15. (1*S*,2*S*,5*R*)-Neomenthyl (*R*)-α-methoxy-α-trifluoromethylphenylacetate, (*R*)-8. ^{1}H NMR (400 MHz, $CDCl_3$) 0.81 (3H, d, $J=6.8$ Hz), 0.83 (3H, d, $J=6.0$ Hz), 0.86 (3H, d, $J=6.7$ Hz), 0.90 (1H, m), 0.96 (1H, dddd, 12.1, 9.9, 3.7, 2.2 Hz), 1.15 (1H, ddd, $J=14.7$, 12.6, 2.4 Hz), 1.22 (1H, m), 1.23 (1H, m), 1.60 (1H, m),

1.74 (2H, m), 2.05 (1H, dddd, $J=14.7$, 3.7, 3.2, 2.3 Hz), 3.54 (3H, q, $J=1.2$ Hz), 5.46 (1H, brq, $J=2.4$ Hz), 7.38–7.46 (3H, m), 7.53–7.60 (2H, m).

4.3.16. (1*S*,2*S*,5*R*)-Neomenthyl (*S*)-α-methoxy-α-trifluoromethylphenylacetate, (*S*)-8. ^{1}H NMR (400 MHz, $CDCl_3$) 0.77 (3H, d, $J=6.6$ Hz), 0.87 (3H, d, $J=6.4$ Hz), 0.89 (3H, d, $J=6.4$ Hz), 0.86 (1H, m), 0.98 (1H, dddd, $J=12.5$, 9.5, 3.7, 2.5 Hz), 1.07 (1H, ddd, $J=14.7$, 13.0, 2.5 Hz), 1.20 (1H, qd, $J=13.0$, 3.4 Hz), 1.30 (1H, m), 1.36 (1H, m), 1.66 (1H, dddd, $J=13.0$, 5.7, 3.6, 3.4 Hz), 1.72 (1H, m), 2.02 (1H, dq, $J=14.4$, 3.4 Hz), 3.54 (3H, q, $J=1.0$ Hz), 5.41 (1H, brd, $J=2.0$ Hz), 7.36–7.46 (3H, m), 7.53–7.52 (2H, m).

4.3.17. Choresteryl (*R*)-α-methoxy-α-trifluoromethylphenylacetate, (*R*)-9. ^{1}H NMR (400 MHz, $CDCl_3$) 0.67 (3H, s), 0.86 (3H, d, $J=6.8$ Hz), 0.86 (3H, d, $J=6.9$ Hz), 0.91 (3H, d, $J=6.6$ Hz), 0.92–1.04 (3H, m), 1.00 (3H, s), 1.04–1.19 (6H, m), 1.19–1.42 (5H, m), 1.42–1.63 (6H, m), 1.72 (1H, m), 1.83 (1H, tdd, $J=13.2$, 9.4, 5.9 Hz), 1.89 (1H, dt, $J=13.8$, 3.8 Hz), 2.34 (2H, m), 3.56 (3H, q, $J=1.1$ Hz), 4.88 (1H, tdd, $J=10.3$, 7.8, 4.6), 5.4 (1H, m), 7.36–7.42 (3H, m), 7.52–7.55 (2H, m).

4.3.18. Choresteryl (*S*)-α-methoxy-α-trifluoromethylphenylacetate, (*S*)-9. ^{1}H NMR (400 MHz, $CDCl_3$) 0.68 (3H, s), 0.86 (3H, d, $J=6.2$ Hz), 0.87 (3H, d, $J=6.2$ Hz), 0.91 (3H, d, $J=6.6$ Hz), 0.94–1.50 (3H, m), 1.00 (3H, s), 1.05–1.23 (6H, m), 1.23–1.40 (4H, m), 1.41–1.69 (8H, m), 1.82 (1H, ddd, $J=13.2$, 9.6, 5.6 Hz), 1.83–1.92 (2H, m), 1.98 (1H, dtd, $J=12.8$, 5.2, 2.4 Hz), 2.04 (1H, m), 2.35–2.50 (2H, m), 3.57 (3H, q, $J=1.1$ Hz), 4.88 (1H, dtd, $J=11.4$, 6.0, 2.0 Hz), 5.41 (1H, m), 7.42–7.46 (3H, m), 7.53–7.61 (2H, m).

4.3.19. *N*-(*S*)-1-Phenylethyl-(*R*)-α-methoxy-α-trifluoromethylphenylacetamide, (*R*)-10. ^{1}H NMR (400 MHz, $CDCl_3$) 1.55 (3H, d, $J=7.2$ Hz), 3.41 (3H, q, $J=1.2$ Hz), 5.18 (1H, quint, $J=6.8$ Hz), 6.98 (1H, brd, $J=6.8$ Hz), 7.23–7.39 (8H, m), 7.42 (2H, brd, $J=7.6$ Hz).

4.3.20. *N*-(*S*)-1-Phenylethyl-(*S*)-α-methoxy-α-trifluoromethylphenylacetamide, (*S*)-10. ^{1}H NMR (400 MHz, $CDCl_3$) 1.51 (3H, d, $J=6.8$ Hz), 3.37 (3H, q, $J=1.6$ Hz), 5.20 (1H, quint, $J=6.8$ Hz), 6.97 (1H, brd, $J=6.8$ Hz), 7.27–7.39 (5H, m), 7.40–7.44 (3H, m), 7.55 (2H, m).

4.3.21. *N*-[(*S*)-1-(*tert*-Butyldimethylsilyloxy)-2-propyl]-(*R*)-α-methoxy-α-trifluoromethylphenylacetamide, (*R*)-11. ^{1}H NMR (400 MHz, $CDCl_3$) −0.01 (3H, s), 0.03 (3H, s), 0.87 (9H, s), 1.22 (3H, d, $J=6.8$ Hz), 3.39 (3H, q, $J=1.3$ Hz), 3.55 (1H, dd, $J=10.0$, 3.3 Hz), 3.62 (1H, dd, $J=10.0$, 3.7 Hz), 4.12 (1H, m), 7.02 (1H, brd, $J=6.8$ Hz), 7.36–7.53 (3H, m), 7.40–7.56 (2H, m).

4.3.22. *N*-[(*S*)-1-(*tert*-Butyldimethylsilyloxy)-2-propyl]-(*S*)-α-methoxy-α-trifluoromethylphenylacetamide, (*S*)-11. ^{1}H NMR (400 MHz, $CDCl_3$) 0.062 (3H, s), 0.064 (3H, m), 0.90 (9H, s), 1.16 (3H, d, $J=6.9$ Hz), 3.42 (3H, q, $J=1.2$ Hz), 3.57 (1H, dd, $J=10.1$, 3.3 Hz), 3.70 (1H, dd, $J=10.1$, 3.9 Hz), 4.12 (1H, m), 7.38–7.44 (3H, m), 7.56–7.62 (2H, m).

4.3.23. *N*-[(*R*)-α-Methoxy-α-trifluoromethylphenylacetyl]-L-alanine methyl ester, (*R*)-12. ^{1}H NMR (400 MHz, $CDCl_3$) 1.48 (3H, d, $J=7.3$ Hz), 3.38 (3H, q, $J=1.4$ Hz), 3.75 (3H, s), 4.64 (1H, quint, $J=7.3$ Hz), 7.36–7.45 (4H, m), 7.53–7.58 (2H, m).

4.3.24. *N*-[(*S*)-α-Methoxy-α-trifluoromethylphenylacetyl]-L-alanine methyl ester, (*S*)-12. ^{1}H NMR (400 MHz, $CDCl_3$) 1.41 (3H, d, $J=7.1$ Hz), 3.52 (3H, q, $J=1.5$ Hz), 3.78 (3H, s), 4.66 (1H, quint, $J=7.0$ Hz), 7.19 (1H, brd, $J=7.2$ Hz), 7.38–7.43 (3H, m), 7.51–7.57 (2H, m).

4.3.25. (1*S*,2*R*,5*S*)-Menthyl methoxyacetate, 13. ^{1}H NMR (400 MHz, $CDCl_3$) 0.77 (3H, d, $J=6.9$ Hz), 0.89 (3H, d, $J=7.1$ Hz), 0.89 (1H, m), 0.91 (3H, d, $J=6.6$ Hz), 1.02 (1H, td, $J=12.0$, 11.3 Hz), 1.06 (1H, m), 1.40 (1H, ddt, $J=12.3$, 10.8, 3.1 Hz), 1.50 (1H, m), 1.64–1.74 (2H, m), 1.84 (1H, sepd, $J=6.9$, 3.0 Hz), 2.01 (1H, dddd, $J=11.7$, 4.5, 3.4, 2.0 Hz), 3.45 (3H, s), 3.99 (1H, d, $J=16.1$ Hz), 4.02 (1H, d, $J=16.1$ Hz), 4.81 (1H, td, $J=10.8$, 4.4 Hz).

4.4. NMR measurement of MTPA derivatives in the presence of La(hfaa)$_3$

To an NMR tube containing a $CDCl_3$ solution (0.65 ml) of the MTPA derivative (0.01 mmol), was added finely powdered La(hfaa)$_3$ (4.1 mg, 0.5 equiv.) and the mixture was shaken to dissolve the reagent. Slight warming or ultrasonication helped to facilitate dissolution. NMR spectra were observed on addition of 0, 0.5, 1.0, and 1.5 equiv. of the agent at ambient temperature.

References

1. For a review, see: Uray, G. In *Houben-Weyl*: *Methods in Organic Chemistry*; Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds.; Thieme: Stuttgart/NewYork, 1995; Vol. 1, pp. 253–292.
2. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.
3. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.
4. Trost, B. M.; Belletire, J. K.; Godleski, S.; McDougal, P. G.; Balkovec, J. M. *J. Org. Chem.* **1986**, *51*, 2370–2374.
5. Kusumi, T.; Takahashi, H.; Xu, P.; Fukushima, T.; Asakawa, Y.; Hashimoto, T.; Kan, Y.; Inouye, Y. *Tetrahedron Lett.* **1994**, *35*, 4397–4400.
6. Seco, J. M.; Latypov, Sh. K.; Quiñoá, E.; Riguera, R. *Tetrahedron Lett.* **1994**, *35*, 2921–2924.
7. Takahashi, T.; Fukushima, A.; Tanaka, Y.; Takeuchi, Y.; Kabuto, K.; Kabuto, C. *Chem. Commun.* **2000**, 788–789.
8. Harada, N.; Watanabe, M.; Kuwahara, S.; Sugio, A.; Kasai, Y.; Ichikawa, A. *Tetrahedron: Asymmetry* **2000**, *11*, 1249–1253.
9. Kubota, T.; Tsuda, M.; Kobayashi, J. *Org. Lett.* **2001**, *3*, 1363–1366.
10. Morohashi, A.; Satake, M.; Nagai, H.; Oshima, Y.; Yasumoto, T. *Tetrahedron* **2000**, *56*, 8995–9001.
11. Chang, L. C.; Chávez, D.; Song, L. L.; Farnsworth, N. R.; Pezzutto, J. M.; Kinghorn, D. *Org. Lett.* **2000**, *2*, 515–518.

12. Murata, M.; Matsuoka, S.; Matsumori, N.; Paul, G. K.; Tachibana, K. *J. Am. Chem. Soc.* **1999**, *121*, 870–871.
13. Latypov, S. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1996**, *61*, 8569–8577.
14. Seco, J. M.; Quiñoá, E.; Riguera, R. *Tetrahedron: Asymmetry* **2000**, *11*, 2781–2791.
15. Shi, X.; Attygalle, A. B.; Liwo, A.; Hao, M.; Meinwald, J.; Dharmaratne, H. R. W.; Wanigasekera, W. M. A. P. *J. Org. Chem.* **1998**, *63*, 1233–1238.
16. Lopez, B.; Quiñoá, E.; Riguera, R. *J. Am. Chem. Soc.* **1999**, *121*, 9274–9275.
17. Earle, M. A.; Hultin, P. G. *Tetrahedron Lett.* **2000**, *41*, 7855–7858.
18. Garcia, R.; Seco, M. J.; Vázquez, S. A.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **2002**, *67*, 4579–4589.
19. Yamaguchi, S.; Yasuhara, F.; Kabuto, K. *Tetrahedron* **1976**, *32*, 1363–1367.
20. Richardson, M. F.; Wagner, W. F.; Sands, D. E. *J. Inorg. Nuclear. Chem.* **1968**, *30*, 1275–1289.
21. Shull, B. K.; Sakai, T.; Koreeda, M. *J. Am. Chem. Soc.* **1996**, *118*, 11690–11691.
22. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.