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# NMR Determinations of the Absolute Configuration of α-Chiral Primary Amines

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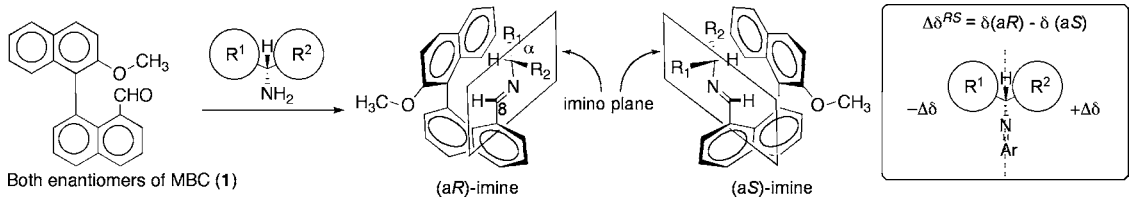
## ABSTRACT




**We have established a methodology to determine the absolute configuration of α-chiral primary amines by derivatization to the corresponding imines with each enantiomer of 2′-methoxy-1,1′-binaphthalene-8-carbaldehyde (1). This methodology proceeds on the basis of modified Mosher's method, and sufficiently large $\Delta\delta^{RS}$ values can be obtained to elucidate the stereochemistry of the amines.**

Determination of the absolute configurations of chiral molecules is very important in organic chemistry, especially in asymmetric synthesis and in structure elucidation of natural products. A couple of physical methods, namely, the exciton chirality method[1] and X-ray crystallography,[2] can fulfill these needs, but they have some limitations. There are also several chemical methods for determining the absolute configuration of organic compounds. Among them, modified Mosher's method[3] and Trost's method,[4] which use α-methoxy-(α-trifluoromethyl)phenylacetic acid (MTPA) and α-methoxyphenylacetic acid (MPA), respectively, as chiral derivatizing agents (CDAs), are the most convenient and widely used approaches. In these methods, the chiral substrate is derivatized with each enantiomer of the CDA, and the $^1$H NMR spectra of the two resulting diastereomers are compared. Interpretation of the chemical shift difference based on the representative conformations of the diastereomers allows the absolute configuration of the chiral substrate to be assigned. Currently, the methods are widely applied to elucidate the absolute configuration of chiral alcohols, amines, diols, and sulfoxides.[5]

Our group has developed chiral binaphthalene compounds as CDAs. In our studies, we found that NOE correlations of the derivatized compounds are powerful tools to determine the stereochemistry of chiral substrates. By using this NOE method, we have developed an approach to determine the absolute configuration of cyclic chiral alkenes,[6] chiral 1,2- and 1,3-diols,[7] and *β*-chiral primary alcohols.[8]

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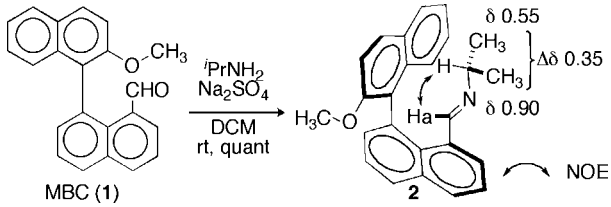
Chiral amines, including amino acids, have a central importance in both chemistry and biology. Several CDAs have been developed to determine the absolute configuration of the amines,[9] but MTPA[10] and MPA[11] are the two most frequently used reagents. Because of the complexity of the conformational distribution, however, the amides derived from these reagents have small $\Delta\delta^{RS}$ values in general, and the development of more efficient CDAs is required. To solve this difficulty, more effective CDAs have been developed with bigger $\Delta\delta^{RS}$ by taking advantage of intramolecular hydrogen bonds[12] or chelation control via metals.[13] Here, we report that 2′-methoxy-1,1′-binaphthalene-8-carbaldehyde (MBC, **1**),[14] which converts the chiral amine substrates to corresponding imines, is a useful CDA for chiral amines that produces sufficiently greater $\Delta\delta^{RS}$ values because the prospective conformations of the imines are more simple than those of the amides.

**Scheme 1.** NMR Analysis of the Imine Derivative (**2**) from Racemic **1** and 2-Propylamine




To obtain preliminary data, imine **2** was prepared from racemic **1** and *iso*-propylamine and analyzed by $^1$H NMR spectroscopy (Scheme 1) and X-ray crystallography (see Supporting Information (SI)). The derivatization proceeded in quantitative yield, and the resultant imine **2** was sufficiently stable for analysis in $CDCl_3$. From the X-ray crystallography data of **2** and the large chemical shift differences ($\Delta\delta$ 0.35 ppm) between each methyl in the *iso*-propyl group of **2** in $CDCl_3$, the *iso*-propyl group faces the naphthalene ring, as shown in Scheme 1. In addition, NOE correlations between the α-proton and the imino proton Ha suggested that the imine in **2** has an *E*-geometry and, predominantly, an eclipsed conformation in solution.

On the basis of this result, configurational correlation models of the (a*R*)- and (a*S*)-imines are depicted in Figure 1A. The intensity of the shielding effects is strongly dependent on the distance from the naphthalene ring that faces each proton. Due to the diamagnetic effect of the naphthalene ring, the $^1$H NMR signals of the $R^1$ group in the (a*R*)-imine derivative should appear at higher field relative to those of the $R^1$ group in the (a*S*)-imine derivative, and vice versa for the $R^2$ group. Therefore, when the chemical shifts of the amine moiety of the imines are compared, the $\Delta\delta^{RS}$ ($= \delta aR - \delta aS$) values of the left side of the imino plane, which includes C-8, C═N, and the α-carbon of the amine moiety, must have negative values ($\Delta\delta^{RS} < 0$), whereas the $\Delta\delta^{RS}$ values of the right side must be positive ($\Delta\delta^{RS} > 0$), as shown in Figure 1B. Now, modified Mosher's method[3] can be applied to our methodology. The absolute values of $\Delta\delta^{RS}$ must be proportional to the distance from the chiral center in the modified Mosher's method, however, whereas these values are affected by distance from the naphthalene ring in our methodology.

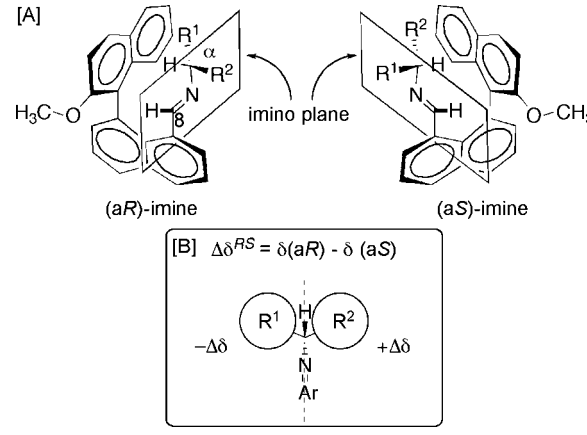



**Figure 1.** (A) Configurational correlation models of both diastereomers of the imine derivatives. (B) $\Delta\delta^{RS}$ values should be opposite on both sides of the imino plane.

To verify our methodology, several imines (**3**−**7**) were prepared from each enantiomer of **1** and the corresponding chiral amines, for which the absolute configurations are known. All $^1$H NMR signals of the imines were assigned, and the chemical shifts were compared for both diastereomers to obtain $\Delta\delta^{RS}$ values, as shown in Figure 2. The $\Delta\delta^{RS}$ values show opposite signs on both sides of the imino plane, and the absolute configurations determined for each amine moiety corresponded to the known ones.

Next, this methodology was applied to several amino acid derivatives, whose absolute configurations are also known.

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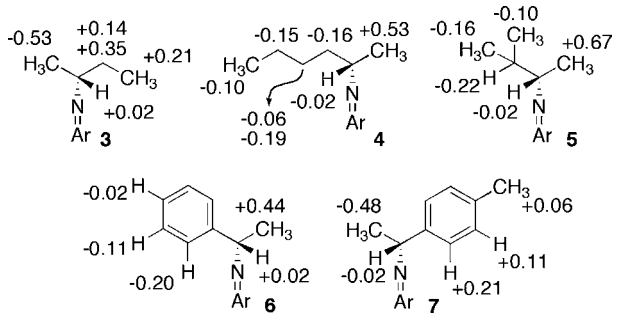

**Figure 2.** Chemical shift differences ($\Delta\delta^{RS} = \delta aR - \delta aS$) of imine derivatives (**3**−**7**) from **1** and (*R*)-2-butylamine (**3**), (*S*)-3-methyl-2-butylamine (**4**), (*S*)-2-hexylamine (**5**), (*S*)-1-phenylethylamine (**6**), and (*R*)-1-(*p*-tolyl)ethylamine (**7**).

The $\Delta\delta^{RS}$ values of the amino acid moieties of **8**−**11** and the absolute configurations determined for the amino acid substrates correspond to the known ones (Figure 3).

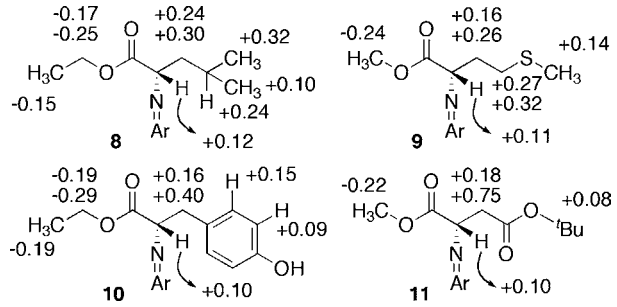

**Figure 3.** Chemical shift differences ($\Delta\delta^{RS} = \delta aR - \delta aS$) of imine derivatives (**8**−**11**) from **1** and L-leucine ethyl ester (**8**), L-methionine methyl ester (**9**), L-tyrosine ethyl ester (**10**), and L-aspartic acid *β-tert*-butyl α-methyl diester (**11**).

Lastly, cyclic chiral amines, whose absolute configurations were also known, were applied to our methodology. The absolute configuration of the amine moiety of **12** was deduced from its $\Delta\delta^{RS}$ values as depicted in Figure 4 and corresponded to the known one. In contrast, the $\Delta\delta^{RS}$ values of **13**, **14**, and **15**, which were prepared from **1** with (+)-bornylamine, (1*R*, 2*S*, 5*R*)-menthylamine,[15] and (−)-oseltamivir,[16] respectively, were complicated. Therefore, the absolute configuration of **13** was analyzed, as described below, by using the $\Delta\delta^{RS}$ values and configurational models.

If each enantiomer of bornylamine was derived to the corresponding imines by using (a*R*- or a*S*)-MBC (**1**), assumed configurational correlation models of the imine derivatives would be as depicted in Figure 5. Owing to steric hindrance from the 10-methyl group, the amine moiety of (a*R*,*S*)-**13**, which was derived from (a*R*)-**1** and (+)-bornylamine, lies

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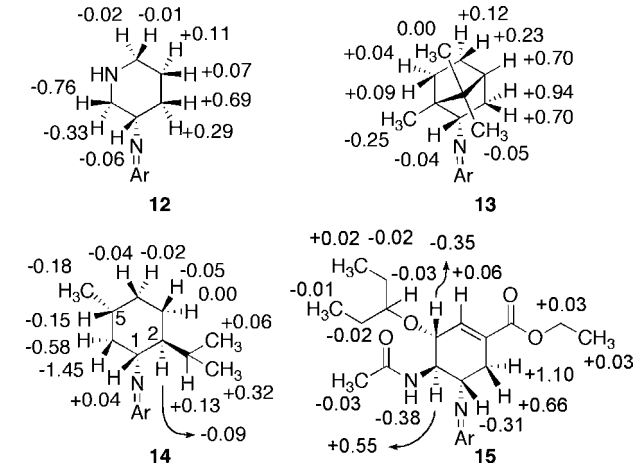

**Figure 4.** Chemical shift differences ($\Delta\delta^{RS} = \delta aR - \delta aS$) of imine derivatives (**12**−**15**) from **1** and (*S*)-3-aminopiperidine (**12**), (+)-bornylamine (**13**), (1*R*, 2*S*, 5*R*)-menthylamine (**14**), and (−)-oseltamivir (**15**).

further from the naphthalene ring than that of (a*S*,*S*)-**13** from (a*S*)-**1** and (+)-bornylamine. Therefore, the $\Delta\delta^{RS}$ value of 10-Hs in **13** should be negative, and that of 3-Hs should be positive. On the other hand, if (−)-bornylamine had been used as a chiral amine, the $\Delta\delta^{RS}$ value of 10-Hs in **13** should be positive, and those of 3-Hs should be negative. The resulting $\Delta\delta^{RS}$ values of 10-Hs, which are negative ($\Delta\delta^{RS} = -0.25$), and 3-Hs, which are positive ($\Delta\delta^{RS} = +0.97$ and $+0.70$), as shown in Figures 5 and 6, are sufficient to elucidate that the absolute configuration of the C-2 position of (+)-bornylamine is *S*. Therefore, we proposed the hypothesis that comparison of the $\Delta\delta^{RS}$ values of protons around the derivatized position may be enough to determine

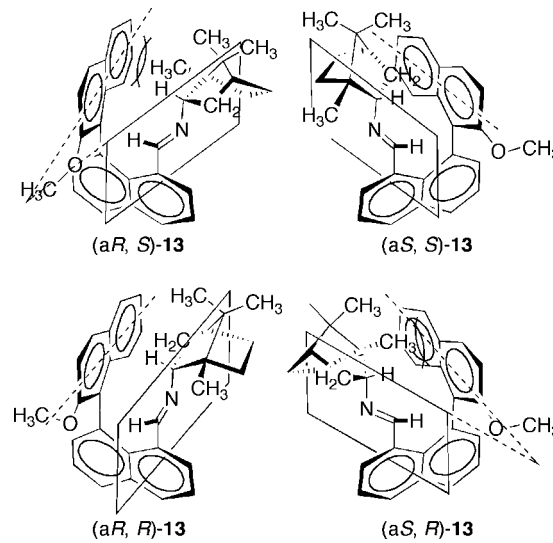

**Figure 5.** Configurational correlation models for (a*R*,*S*)-**13**, which was generated from (a*R*)-**1** and (+)-bornylamine, and other diastereomers.

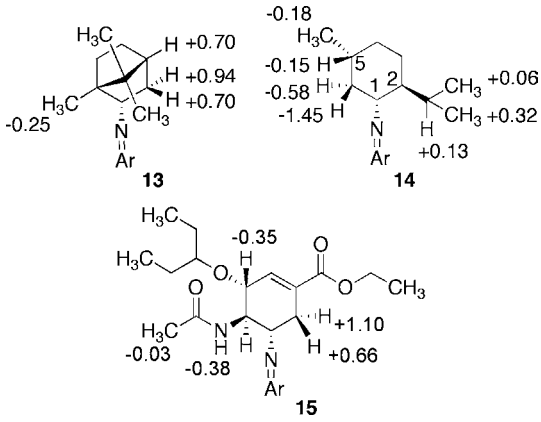


**Figure 6.** Selected $\Delta\delta^{RS}$ values of **13**, **14**, and **15**.

the absolute configuration of cyclic amines, and we applied this hypothesis to (1*R*,2*S*,5*R*)-menthylamine and (−)-oseltamivir. From the results depicted in Figure 6, well-ordered $\Delta\delta^{RS}$ values are observed around the derivatized position in **14** and **15**, and the absolute configurations of the amine moiety can be determined from these values. In short, we can summarize the methodology for the determination of the absolute configurations of cyclic chiral amines as follows: (i) compare the $\Delta\delta^{RS}$ values of the proton of the $\beta$-position of the imine; (ii) if a functional group is attached to the $\beta$-position, the protons of the functional group should be considered; (iii) if a functional group is attached to the $\beta$-position, the proton of the $\beta$-position should **not** be considered; (iv) next, compare the $\Delta\delta^{RS}$ values of the proton of the $\gamma$-position; (v) finally, if a small functional group (such as a methyl group) is attached to the $\gamma$-position, the protons may be considered. In this case, the proton of the $\gamma$-position should be considered.

As described above, we have established a methodology to determine the absolute configuration of α-chiral primary amines by derivatization to the corresponding imines with each enantiomer of MBC (**1**). The imines obtained are easily hydrolyzed to recover **1** and amines. Therefore, this methodology can be said to be a highly recyclable method to confirm the stereochemistry of α-chiral primary amines.

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**Supporting Information Available:** Synthetic details and spectroscopic data for MBC (**1**), **2**−**15**, and crystallographic data for **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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