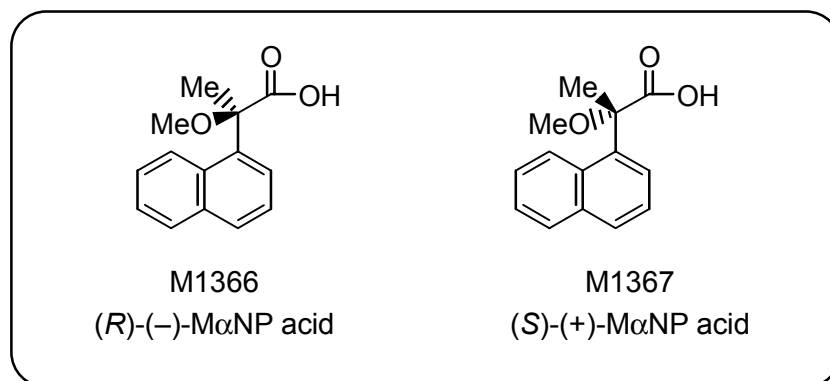


Powerful Chiral Auxiliaries

for enantioresolution of alcohols and determination of
their absolute configurations
by the ^1H NMR anisotropy method



Most biologically active compounds including pharmaceuticals have chiral molecular structures consisting of several chiral stereogenic centers. As exemplified in the case of thalidomide, the absolute configuration of pharmaceuticals carries great importance for their biological activity. It is often found that one enantiomer has medicinal activity while the other enantiomer has no activity. In some cases the opposite enantiomer gives rise to adverse and harmful effects.

The hydroxyl group is one of the most popular functional groups found in pharmaceuticals and natural products. For this reason, it is of great significance to obtain enantiopure alcohols, to determine their absolute configurations, and also to determine their enantiomeric excess.

Recently, Harada and co-workers have developed the MαNP acid method, which is very powerful for the resolution of alcohols. The MαNP acid is also useful for determining the absolute configuration of chiral alcohols by the ^1H NMR anisotropy method. For example, the (*S*)-(+)-MαNP acid is allowed to react with racemic 2-butanol to yield a mixture of diastereomeric esters. These diastereomers are almost base-line separated by HPLC on silica gel (hexane/EtOAc 20:1): $\alpha=1.15$ and $R_s=1.18$. The MαNP acid has thus a great ability to recognize the small difference between methyl and ethyl groups. It is well known that chiral discrimination between methyl and ethyl groups is the most difficult. Therefore, the MαNP acid is a promising tool for the enantioresolution of various alcohols.

The MαNP acid moiety shows a strong anisotropy effect in ^1H NMR spectra, which enables one to determine the absolute configuration of chiral alcohols. The following is an example of the method applied to (+)-2-butanol. (+)-2-Butanol was allowed to react with (*R*)-(-)-MαNP and (*S*)-(+)-MαNP acid to yield (*R*)- and (*S*)-ester, respectively, whose ^1H NMR spectra were measured and all peaks were fully assigned. The $\Delta\delta$ values [$\Delta\delta=\delta(R)-\delta(S)$] were determined for each proton, where $\delta(R)$ is the proton chemical shift of alcohol moiety of (*R*)-MαNP acid ester, and $\delta(S)$ is that of (*S*)-MαNP acid ester. The data are shown in Table 1.

Table. 1

(*S*)-(+)-2-butanol

alcohol moiety		$\delta(R)$	$\delta(S)$	$\Delta\delta$
methyl (a)		0.87	1.11	-0.24
methine (b)		4.85	4.82	+0.03
methylene (c)		1.39	1.21	+0.18
methyl (d)		0.73	0.27	+0.46

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According to the sector rule, when the M α NP ester group and the methine proton of a secondary alcohol are fixed in the down/front and down/rear sides, respectively, as shown in Figure 1, protons with a positive $\Delta\delta$ value are placed on the right side and those with a negative $\Delta\delta$ value on the left side, leading to the conclusion that (+)-2-butanol has (*S*) absolute configuration.

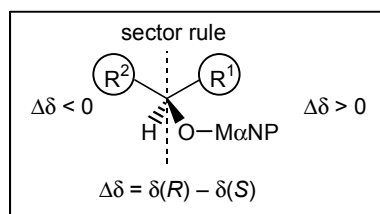


Fig. 1. The sector rule for determining the absolute configuration of chiral secondary alcohols using (*R*)-(-)- and (*S*)-(+)-M α NP acids.

Since the α -position of the carboxylic acid is fully substituted, the M α NP acid has an advantage not to racemize. Furthermore, the naphthalene moiety brings stronger anisotropy effect leading to larger $\Delta\delta$ values. These characteristics of M α NP acid are shown in Figure 2 together with those of conventional chiral acids, e.g., Trost's MPA, Mosher's MTPA, and new Mosher's acids.

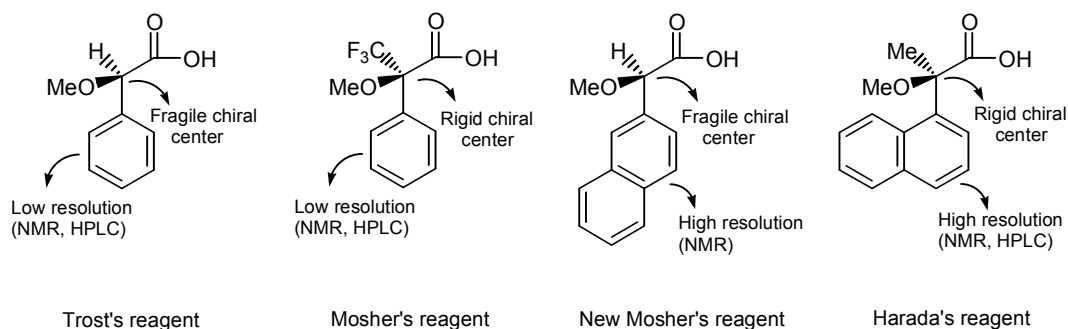


Fig. 2. comparison of the properties of chiral auxiliaries.

The new chiral auxiliaries, (*R*)-(-)-M α NP and (*S*)-(+)-M α NP acids, are thus superior to Trost's, Mosher's, and new Mosher's reagents in the ability to separate enantiomers and also to determine their absolute configurations.

M1366	(<i>R</i>)-(-)-2-Methoxy-2-(1-naphthyl)propionic Acid	100mg
M1367	(<i>S</i>)-(+)-2-Methoxy-2-(1-naphthyl)propionic Acid	100mg

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