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DETERMINATION OF ABSOLUTE CONFIGURATION OF AXIALLY CHIRAL BIARYLS[1]

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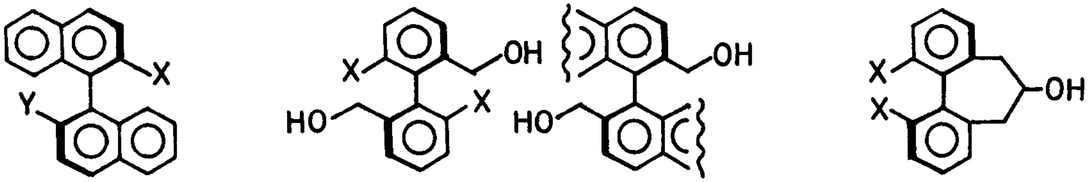
Summary: Absolute configurations of axially chiral biaryls with hydroxyl, amino, and carboxyl groups can be easily determined by pmr spectra using MTPA derivatives and shift reagents.

Recently chiral biaryls have been successfully utilized in the field of asymmetric synthesis[2]. For example, virtually complete enantioselectivity was found in the reduction of phenyl alkyl ketones with lithium aluminum hydride modified by 2,2'-dihydroxy-1,1'-binaphthyl[2c]. The determination of absolute configuration of these biaryls have been performed by several methods; X-ray analysis[3], chemical correlation[3], chiroptical methods[4], and Prelog's synthesis[5] etc. Although recently developed NMR techniques[6] make it possible to determine concommitantly absolute configuration and enantiomeric purity of compounds with centro-chirality,no successful application of the methods has been reported on axially chiral biaryls. We wish to report, in this paper, a convenient NMR methods using MTPA derivatives and lanthanide shift reagents on determination of absolute configuration of chiral biaryls having hydroxyl, amino, or carboxyl group(s). Eleven biaryls were examined. These biaryls can be classified in three types shown in Figure 1 by their structures: (Type 1) binaphthyls with OH or NH_2 attached directly to the aromatic rings; (Type 2) primary alcohols of biaryls; (Type 3) secondary alcohols of bridged biphenyls.



Type 1
1 X=OH, Y=H
2 X=OH, Y=OMe
3 X=Y=OH
4 $X=NH_2$, Y=H
5 $X=Y=NH_2$

Type 2
6 X=Me
7 $X=NO_2$
8 binaphthyl
9 bianthryl

Type 3
10 X=Me
11 $X=NO_2$

Figure 1

A partially active biaryl with hydroxyl or amino group(s) was completely acylated with excess acid chloride of (R)-(+)-α-mehtoxy-α-trifluoromethylphenylacetic acid[7](MTPA, Mosher's Reagent) in the presence of excess 4-dimethylamino pyridine. The ^1H NMR of the resulting diastereomeric

(*R*,*R*) and (*R*,*S*) pair was examined in the presence of a lanthanide shift reagent, $Eu(fod)_3$ or $Eu(dpm)_3$. The MeO signals of MTPA acid moieties were used as the probes and the relative magnitudes of the lanthanide induced shifts(LIS_{OMe}) were correlated to the absolute configurations of the biaryl moieties. Easily accessible di-MTPA derivatives were used for the dihydroxy or diamino biaryls(**3**,**5**,**6**,**7**,**8**,**9**) instead of mono-MTPA derivatives, since these biaryls have C_2 symmetry and two hydroxyl or amino groups, and consequently two MTPA moieties, are equivalent. The results are summerized in the Table.

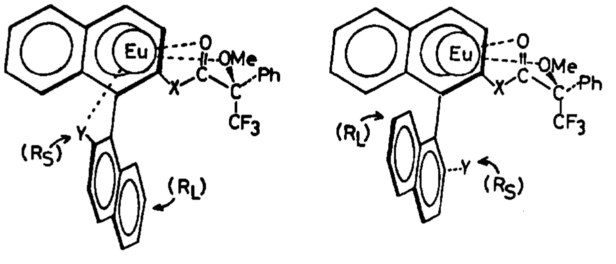
Table Lanthanide Induced Shifts of Methoxyl Group in the Acid Moiety for Diastereomeric (*R*)-(+)-MTPA esters(amides) of Biaryls in the Presence of $Eu(fod)_3$[a]

Biaryls	$LIS^{(R,R)}_{OMe}$	$LIS^{(R,S)}_{OMe}$	ΔLIS_{OMe} $[LIS^{(R,R)}_{OMe}-LIS^{(R,S)}_{OMe}]$	Config. of biaryls with larger LIS_{OMe}
1	5.8	5.1	0.7	(*R*)-(+)[c]
2	2.1	3.6	-1.5	(*S*)-(-)[d]
3	1.6	4.3	-2.7	(*S*)-(-)[d]
4	8.0[b]	4.6	3.4	(*R*)-(-)[e]
5	1.1[b]	2.2	-1.1	(*S*)-(-)[e]
6	3.9	4.3	-0.4	(*S*)-(-)[e,f]
7	1.8	2.3	-0.5	(*S*)-(-)[g]
8	3.6	4.6	-1.0	(*S*)-(-)[e,h]
9	4.2	4.7	-0.5	(*S*)-(+)[e,i]
10	15.2	9.2	6.0	(*R*)-(-)[j,k]
11	12.9	5.9	7.0	(*R*)-(-)[g,k]

[a] Spectra determined at 90 MHz on CCl_4 solutions unless otherwise stated. [b] Shift reagent: $Eu(dpm)_3$, Solvent: $CDCl_3$. [c] Revised configuration. Absolute configuration of **1** has been reported by Akimoto and Yamada as (*R*)-(-) by correlating it chemically to (*S*)-(+)-**5** as follows: (*S*)-(+)-**5** → (*R*)-(-)-**4** → (-)-**1**, reference 3 and note 8. Reexamination of their experiment by us, however, afforded the opposite result: (*R*)-(-)-**5** → (*S*)-(+)-**4** → (-)-**1**. CD spectra of (-)-**1** and (*S*)-(+)-**4** also showed these two biaryls had the same configuration. The configuration of **1**, therefore, must be corrected to (*R*)-(+) which is consistent with the result obtained by the method described in this paper. Details will be published elswhere. [d] J. Jacques et al, *Tetrahedron Lett.*, 4617 (1971). [e] Reference 3. [f] G. Wittig et al, *Chem. Ber.*, **86**, 629 (1953). [g] P. Newman et al, *J. Am. Chem. Soc.*, **80**, 465 (1958). [h] D. M. Hall et al, *J. Chem. Soc.*, 3072 (1951). [i] G. M. Badger et al, *J. Chem. Soc.*, 1837 (1957). [j] K. Mislow et al, *J. Am. Chem. Soc.*, **84**, 1455 (1962). [k] K. Mislow, *Angew. Chem.*, **70**, 683 (1958).

Pertinent observations are as follows: (Type 1, Biaryls **1**-**5**) In the undoped spectra of (*R*)-MTPA derivatives of these, two partially or completely resolved MTPA-MeO signals were observed. However, no definitive correlation was found between the configurations of the biaryls and the chemical shifts nonequivalence of MeO signals of the diastereomeric pairs. By the successive addition of the shift reagent, the MeO signals shifted downfield with different magnitudes, giving two resolved peaks with different areas which represented enantiomeric composition[9] of the original biaryls. A regularity was observed between the relative magnitudes of LIS_{OMe} values and the absolute configurations of the biaryls. Since *R* configuration of the monosubstituted biaryls(1 and 4) is related to S configuration of the di-substituted biaryls(2,3, and 5), the (R)-MTPA derivatives of the binaphthyls with absolute configuration shown in Figure 1 have always larger LIS_{OMe} values than those with opposite configuration. (Type 2; Biaryls 6-9) Notwithstanding larger distance between the probe(MTPA-MeO) and the chiral axis compared to the biaryls of Type 1, the initial single MeO signal was resolved into two peaks by the addition of a shift reagent. The (R,S) isomers have larger LIS_{OMe} values than the (R,R) isomers. The configuration of Type 2 biaryls whose (R)-MTPA derivatives have larger LIS_{OMe} values is shown in Figure 1. As can be seen from the Figure, this configuration corresponds to that of Type 1 biaryls whose (R)-MTPA derivatives have larger LIS_{OMe} values. These primary alcohols are derived from the corresponding carboxylic acids without any detectable racemization, hence the present method can be also applied for the determination of the absolute configuration of the biaryls with carboxyl functions. (Type 3, Biaryls 10-11) The probe(MTPA-MeO) in this series is remotest from the chiral axis among three types of biaryls examined. However, the present method was also applicable to this type of biaryls. The configuration of the biaryls with larger LIS_{OMe} values is shown in the Figure.

The above NMR configurational correlation scheme can be explained by the following empirical models. A model for Type 1 series is represented by Figure 2A and 2B where the aromatic ring and X-C(=O)-C-CF_3 group lie almost on the same plane and the shift reagent coordinates with both O atoms of the carbonyl and MeO groups[10]. As can be seen from the Figure, the substituent(Y) in the diastereomer shown in Figure 2A is located in the vicinity of the shift reagent. Therefore, when Y is polar group(Biaryls 2,3,5), the coordination of Y with the shift reagent seems to be possible in the diastereomer. This additional coordination will increase the concentration of the complex with the shift reagent, affording larger LIS_{OMe} values than those in the alternate diastereomer(Figure 2B), as is observed. On the other hand, when Y is non-polar group, the steric effect may be operative. For the biaryls 1 and 4(Y=H), one can reasonably assume H as R_S and the aromatic ring moiety as R_L. Consequently, the coordination of the shift reagent in 2A must be easier than that in 2B because of lesser steric repulsion between the shift reagent and smaller R_S group, thus giving larger LIS_{OMe} values. For Type 2 series, the larger LIS_{OMe} can be explained by the diasteromer in Figure 3, where the aromatic ring moiety(in 8 and 9; shown in



A X=O, NH B

Figure 2

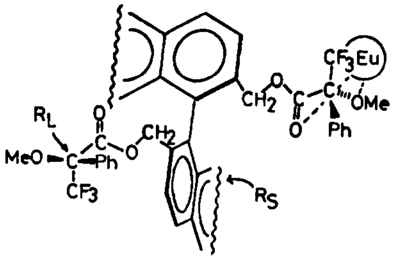
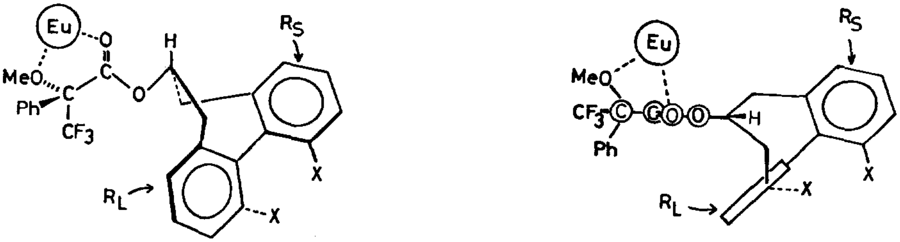


Figure 3

Figure 3) or the substituent (Me or NO_2 group in **6** or **7**; not shown in the Figure) can be designated as R_S and the MTPA ester moiety(MTPA-O-CH_2-) as R_L. In this case, the polar site of the substituent (MTPA-O-CH_2-) is far from the shift reagent and difficult to work as a coordinating group, therefore the steric effect of the substituents seems to be operative. For Type 3 series, the configurational correlation can be made on the basis of the model previously presented for secondary carbinols[10]. The diastereomer having larger LIS_{OMe} can be shown in Figure 4 where carbinyl C-H bond takes eclipsed conformation with carbonyl group[11]. In viewing the molecule from the point above the carbonyl oxygen (Figure 4B), the aromatic ring on the same side of MTPA-MeO group with respect to the plane carrying C-C(=O)-O-C-H group is remote from the probe in comparison with the alternate diastereomer(not shown). Therefore, the ring on this side can be designated as R_S and the other side as R_L. Thus, in the (R,R) diastereomer shown, the shift reagent can approach from the less hindered side, inducing larger LIS_{OMe} values.



A Figure 4 B

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References and Notes

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