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α-Methoxyphenyl acetic acid (MPA) for the configurational assignment of aromatic–heteroaromatic carbinols by ^{1}H NMR spectroscopy

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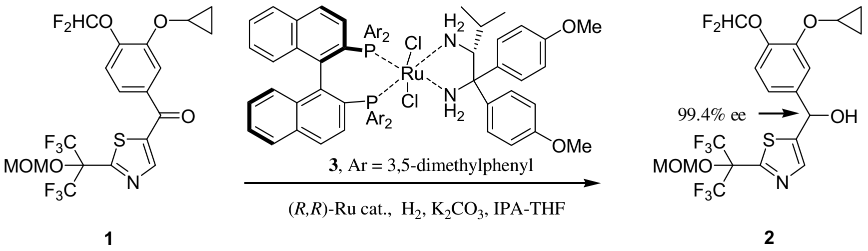
Abstract—Configurational assignment for a wide array of aromatic–heteroaromatic carbinols using NMR method employing α-methoxyphenyl acetic acid (MPA) as a convenient and reliable anisotropic agent is described.

We have recently published a work on the highly enantioselective hydrogenation of aromatic–heteroaromatic ketones using a catalyst pioneered by Noyori et al. to give the corresponding alcohols in excellent yield and enantiomeric purity (ee).[1] For example, asymmetric hydrogenation of the ketone **1** afforded the alcohol **2** quantitatively in 99.4% ee (Scheme 1).[1] The structural uniqueness of this compound did not allow us to determine its absolute configuration by comparison to other chiral substrates studied. A simple chemical derivatization of the alcohol to chiral molecules with known configuration was not conceivable either. With additional aromatic–heteroaromatic carbinols obtained in high ee using this methodology, we were prompted to seek a reliable method for determining their absolute configuration. Among many methods developed, we chose to assign the absolute configuration by ^{1}H NMR spectroscopy. The absolute configuration of secondary alcohols bearing a β-hydrogen next to the chiral centre can be readily deduced from ^{1}H NMR by esterification of both alcohol enantiomers with several α-substituted phenyl acetic acids.[2] The application of the protocol to bis-aromatic alcohols that lack a β-hydrogen, however, is not well precedented in the literature.[3] Herein, we report that a simple acid, (*R*)- or (*S*)-α-methoxyphenyl acetic acid (MPA), serves as an excellent derivatizing reagent to induce anisotropic effect on these carbinols allowing for the ready assignment of their absolute configuration in a reliable manner.

Our first attempt to derivatize alcohol **2** involved the use of α-methoxy-α-trifluoromethylphenyl acetic acid



Scheme 1.

Keyword: Absolute configuration.

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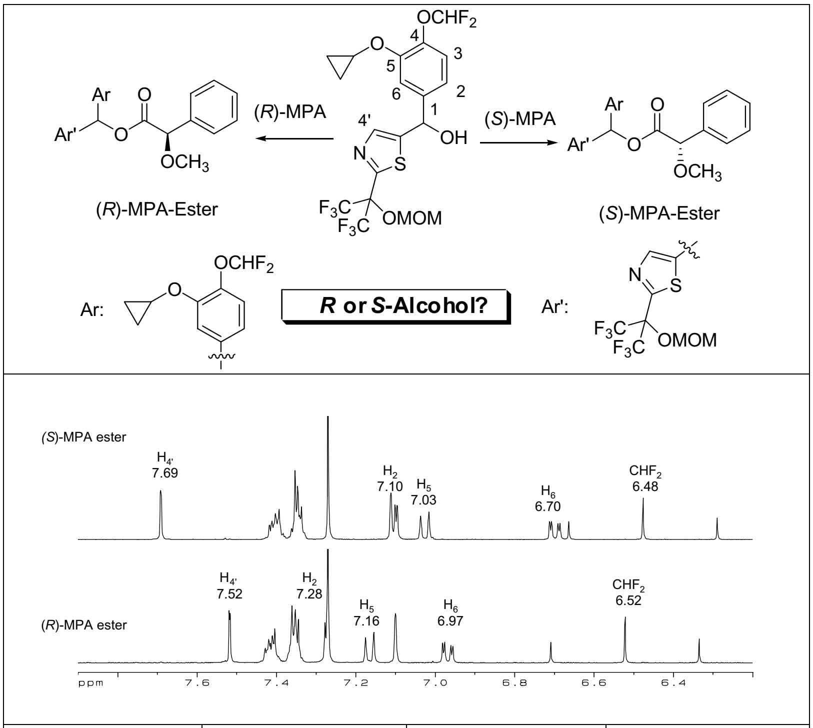
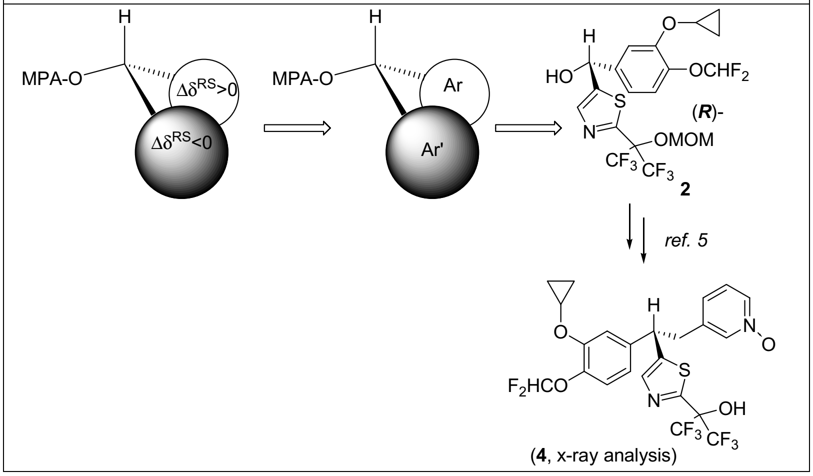
(MTPA), which is commonly employed as an effective chiral derivatizing agent for NMR spectroscopy.[2,4] The experiment, however, turned out to be quite disappointing since very little differentiation in chemical shifts was observed between the (*R*)- and (*S*)-MTPA esters. As such, we were not confident that these data could be used to assign the absolute configuration for **2**. We reasoned that the interaction of the phenyl group in MTPA and the aromatic moieties in **2** was not strong enough to generate substantial anisotropic effect, presumably due the steric bulkiness of the MTPA. We were delighted to find that the NMR experiment using a sterically less demanding agent such as α-methoxyphenyl acetic acid (MPA) and the same substrate (**2**) worked remarkably well (Scheme 2). In the actual experiment, alcohol **2** was converted to its (*R*) and (*S*)-MPA esters via an EDCI mediated coupling. Both diastereoisomers were isolated by preparative TLC and their NMR spec-



		δ(*R*)-MPA ester	δ(*S*)-MPA ester	$\Delta\delta_R - \Delta\delta_S$
Ar	CHF_2	6.52	6.48	$\Delta\delta$ Ar>0
	H_2	7.28	7.10	
	H_5	7.16	7.03	
	H_6	6.90	6.70	
Ar'	$H_{4'}$	7.52	7.69	$\Delta\delta$ Ar'<0



Scheme 2. Determination of absolute configuration of alcohol **2**.

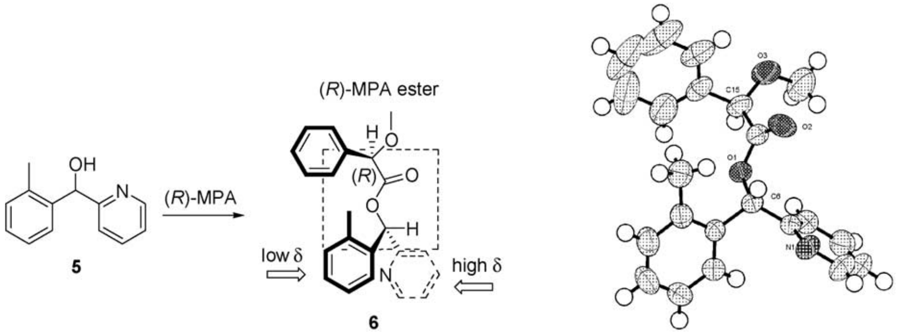


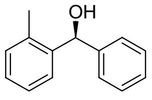
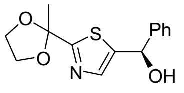
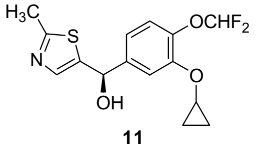
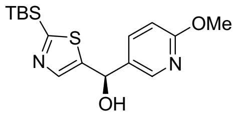
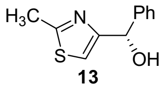
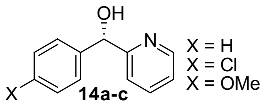
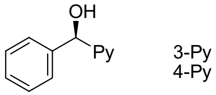
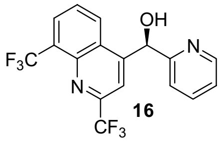
Figure 1. Correlation of the NMR experiment with the X-ray analysis.

tra were recorded. The chemical shifts of these two diastereoisomers were highly distinguishable, allowing us to assign the absolute configuration of the alcohol (**2**) as the (*R*)-MPA ester based on the reported protocol.[2] Thus, this NMR method is valid for this bis-aromatic carbinol since the alcohol was subsequently converted to a potent PDE4 inhibitor (**4**) whose absolute configuration was unambiguously established by X-ray analysis.[5]

Having secured the assignment for the absolute configuration of alcohol **2**, we turned our attention to *o*-tolyl pyridyl carbinol (**5**), which was prepared by hydrogenation of the corresponding ketone in 98.7% ee.[1] Alcohol **5** was derivatized to its (*R*)- and (*S*)-MPA esters and based on the working scheme depicted above, we readily assigned the absolute stereochemistry as the *S*-isomer. A single crystal of the (*R*(MPA),*S*)-isomer (**6**) was later obtained, which confirmed the results of the NMR experiment (Fig. 1).

The accuracy of our method for the assignment of the absolute configuration by NMR was further validated by the application of this protocol to a wide array of these biaryl alcohols (Table 1). We again demonstrated the simplicity in deducing the absolute configuration of a known substrate, *o*-tolyl phenyl carbinol (**9**). The (*S*)-enantiomer was prepared according to Noyori's method[6] and the absolute configuration of this compound was determined by Watanabe et al.[7] employing both chemical correlation and X-ray analysis. We reasoned that a simple derivatization of the alcohol using MPA will lead to assignment of the absolute configuration. Indeed, the NMR methods elaborated above allowed us to assign the absolute configuration as (*S*) in a very straightforward manner. Absolute configurations were assigned for compounds **10**–**13** based on the NMR experiment and these results were confirmed by X-ray analyses. Alternatively, the NMR assignments for compounds **14**–**16** were confirmed by comparison of optical rotation to that of the authentic material.

Table 1. Validation of the NMR methods

Alcohols	Absolute configuration (this work)	Confirmation
 **9**	*S*	Refs. 6 and 7
 **10**	*R*	X-ray analysis[1]
 **11**	*R*	X-ray analysis[1]
 **12**	*R*	X-ray analysis[1]
 **13**	*S*	X-ray analysis[1]
 **14a-c** X = H X = Cl X = OMe	*R*	Optical rotation[1,8]
 **15a,b** 3-Py 4-Py	*S*	Optical rotation[1,8]
 **16**	*R*	Optical rotation[9]

In summary, we have demonstrated that α-methoxyphenyl acetic acid (MPA) serves as an effective resolving agent for aromatic heteroaromatic carbinols. The significant anisotropic effect allows for the determination of the absolute configuration of these structurally interesting alcohols in a very reliable manner. Moreover, MPA is an inexpensive and readily available reagent with robust reactivity towards secondary alcohols. We believe that the method described should be routinely used for these alcohol derivatives.

References and notes

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3. α-Cyano-α-fluoro-*p*-tolyl acetic acid (CFTA) was used for the determination of absolute configuration of chiral secondary alcohols by ^{1}H NMR spectroscopy. To our knowledge, this is the first example to deduce the absolute configuration of chiral benzhydrols. See: Takeuchi, Y.; Fujisawa, H.; Noyori, R. *Org. Lett.* **2004**, *6*, 4607–4610.
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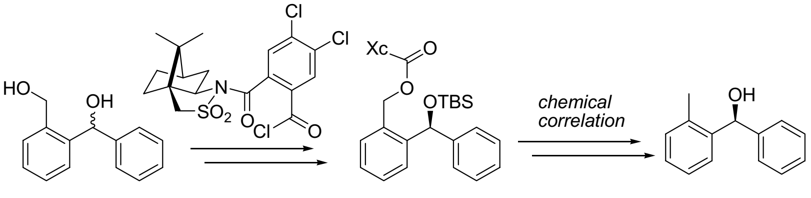
7. A summary of Watanabe's work: racemic (2-hydroxymethyl)pheylphenylemethanol (**7**) was enantioresolved by the chiral phthalic acid to afford two diastereoisomers. The absolute configuration of one of the diastereoisomers was unambiguously assigned based on the X-ray crystallography. Chemical correlation of the other diastereoisomer (**8**) to *o*-tolyl phenyl carbinol (**9**) thus assigned the absolute configuration of the latter. This work was rather labour intensive in that both chemical correction and X-ray analysis were employed. See: Watanabe, M.; Kuwahara, S.; Harada, N.; Koizumi, M.; Ohkuma, T. *Tetrahedron: Asymmetry* **1999**, *10*, 2075–2078.



7 **8** **9**

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