A Simple *In Situ* ^{31}P NMR Method for the Determination of the Enantiomeric Purity of Aromatic Substrates

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The enantiomeric purity of aromatic substrates can be determined using ^{31}P NMR with chiral rhodium complexes *in situ*.

One of the seemingly subsidiary but important problems in studies involving enantioselective reactions has been the determination of the enantiopurity of the chiral products. During our studies on the asymmetric hydrogenation of α-ethyl styrene, we required a quick and effective method for the determination of the enantiomeric excess of the 2-phenylbutane product **2**. In view of the diversity of optical rotation data for this substrate (at least 3 different recently quoted values[1]) and our failure in separating the enantiomers by GC using a chiral stationary phase (50 m β-cyclodextrin)[2] we developed a simple *in situ* ^{31}P NMR method using a C_2-symmetric rhodium complex, Rh(NBD)[(−)bdpp]ClO_4 (**1**, Fig. 1) to determine the enantiomeric purity of **2**. We subsequently found this method to be applicable to a rather large variety of functionalized chiral aromatic compounds. While chiral GC,[3] HPLC and liquid chromatography on chiral solid phases,[4] and various NMR chiral shift reagents and solvating agents[5] are effective for many of such substrates, the method described here is rapidly and easily performed since it requires no prior derivative formation and uses NMR, a technique accessible to almost all research groups.

Treatment of a solution of **1** [5 mg, (6.7 mmol)] in CD_3OD (0.4 ml) with H_2 at one atmosphere rapidly hydrogenates the norbornadiene ligand to form Rh[(−)bdpp](Solv.)$_2^+$ where Solv. is coordinated methanol.[6] As is well known, such species have a strong affinity for aromatic groups to form stable η^6-arene cationic complexes with an 18 electron configuration.[7] Thus carried out in the presence of the chiral aromatic substrate (0.13 mmol), two diastereoisomeric complexes are produced which may be readily distinguished by ^{31}P NMR, any remaining Rh[(−)bdpp]$(CD_3OD)_2^+$ can be seen as a doublet at δ 51.37 ($J_{P\text{-}Rh}$ 191 Hz). For example at 25 °C the diastereoisomeric 2-phenylbutane complexes so formed each show a sharp doublet ($J_{P\text{-}Rh}$ 194 Hz, $\nu_{1/2}$ = *ca.* 2 Hz), separated by over 0.2 ppm (Fig. 2). For racemic 2-phenylbutane, integration of the resonances yielded a 50:50 ratio demonstrating no diastereoselectivity in binding preference in this case. Identical observations were made, *e.g.* using 1-phenylethanol **3**, 1-(1′-naphthyl)ethanol **4**, 2-methylindoline **5**, *N*-acetylphenylalanine **6**, 1,2-cyclohexylphenylethane **7** (Fig. 1).† We confirmed that the NMR analysis of enantiomerically enriched samples of **3** corresponded well with the values obtained from chiral GC (β-cyclodextrin column) as shown in Fig. 3. It is interesting to note that a wide variety of structures and functional groups are tolerated such as hydroxys, secondary amines, amides, and carboxylates. The chiral centres of **5** and **6** are β to the aromatic ring, showing that the diastereoisomeric complexes can be distinguished even when the phenyl ring becomes increasingly distant from the chiral centre. The ^{31}P resonances are generally clearly separated from other resonances and are found in the region of δ 30–45, with $J_{Rh\text{-}P}$ values of *ca.* 190–200 Hz. Care must be taken however for polyaromatic substrates since Rh may bind to one or other of the arene moities. Hence **4** gives two pairs of well separated doublets resulting from competitive binding of Rh to either of the aromatic rings of the naphthyl group but here analysis is still possible since the diastereoisomeric ratios obtained for each binding mode for racemic **4** are strictly equal. With racemic 1-(2′-naphthyl)ethanol **9**,

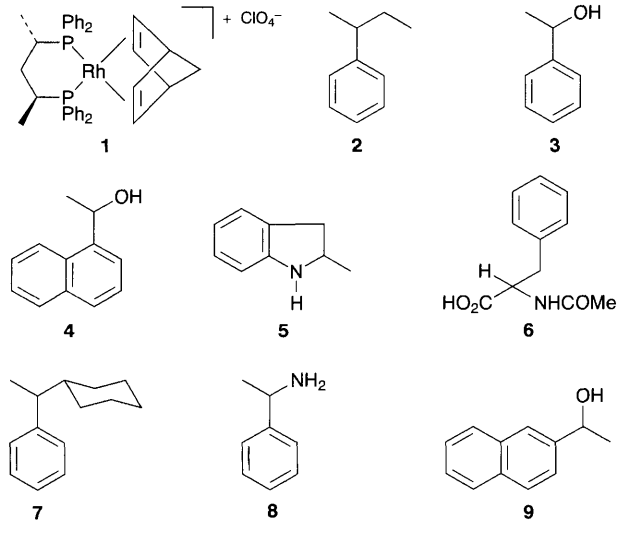

Fig. 1 Chiral rhodium complex and selected aromatic substrates used

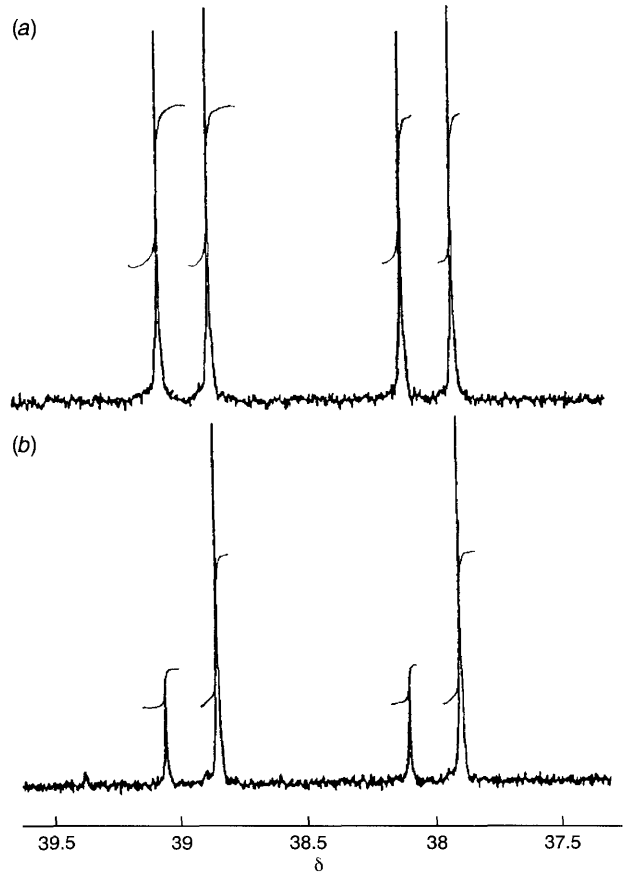

Fig. 2 ^{31}P NMR spectra at 202 MHz of (*a*) racemic **2** and (*b*) **2** with e.e. determined to be 59%

however, only three doublets are observed on binding with the two aromatic rings. In one binding mode (presumably that distant from the chiral centre) only one doublet is observed with no diastereoisomerism being observable. In the second binding mode a pair of resonances are indeed seen but are of different intensities indicating a diastereoisomeric binding preference. Finally it may be anticipated that the method will not be useful if strong binding groups to Rh^{I} (*e.g.* primary amines, phosphines, sulfur donors) are also present in the molecule. Hence the application to 1-phenylethylamine **8** was thwarted as a result of the preferred binding of the primary amine to the rhodium.

The effectiveness of the method depends on the fortuitous values of three parameters i, a relatively strong binding constant of the arene moiety to the Rh^{I} complex, ii, the exchange processes involving arene are slow on the NMR lifetime at 25 °C but iii, the lability of the system on a chemical lifetime which allows equilibration of the Rh complexes in solution. The values obtained are hence concentration independent and even if adventitious impurities are present these will have no bearing on the enantiomeric ratio obtained. This method, as for all NMR methods, is particularly applicable when no diastereochemical binding preferences are present which can easily be tested by use of the racemic substrate.

In conclusion, this ^{31}P NMR method can be used for the determination of the enantiomeric purity of aromatic substrates with the chiral centre either α or β to the phenyl ring. This method is particularly useful for substrates not easily analysed by other means such as those lacking strongly interacting functional groups (such as **2** and **7**). However, given the convenience and simplicity of the method it may also find more general use since it tolerates a relatively wide variety of functional groups and could thereby complement or replace less accessible chiral chromatographic techniques. At first sight it may appear to be an expensive method but based on the cost of the commercially available rhodium complex and the fact that only 5 mg are needed to obtain a spectrum it is cheaper than the deuterated solvent used in the experiment.

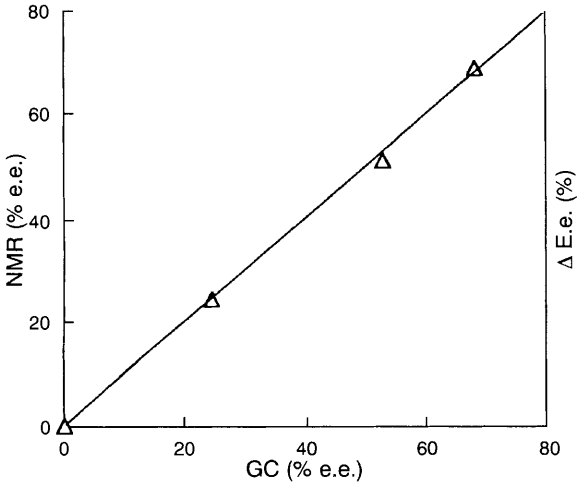

Fig. 3 Comparison of enantiomeric purity of **3** as determined by chiral GC and ^{31}P NMR (with **1**). A Hewlett Packard 5890 Series II Gas Chromatograph fitted with a 30 m × 0.25 mm internal diameter fused silica capillary column with β-cyclodextrin stationary phase (J & W Scientific) was used.

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Footnote

† The chemical shifts of the diastereoisomers formed from **1** and **2**–**7** are as follows: **2**, δ 38.86, 38.65, *J* 194 Hz; **3**, δ 39.01, 38.81, *J* 194 Hz; **4**, δ 34.66, 34.40, *J* 194 Hz, and 34.53, 34.26, *J* 191 Hz; **5**, δ 41.40, 41.11, *J* 201 Hz; **6**, δ 39.43, 39.37, *J* 194 Hz; **7**, δ 38.95, 38.22, *J* 193 Hz.

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