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A Non-chiral Lithium Aluminate Reagent for the Determination of Enantiomeric Excess of Chiral Alcohols†

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Raúl García-Rodríguez,*[a] Schirin Hanf,[a] Andrew D. Bond[a] and Dominic S. Wright[a]

Here we illustrate a new method for the rapid determination of *ee*'s of chiral alcohols using the thermally-stable, non-chiral lithium aluminate reagent [EtAl(6-Me-2-py)$_3$Li] (1). *In situ* reaction of the alcohols with 1 produces robust dimers in solution, present as diastereomeric pairs (*SS*/*RR* and *RS*) with distinct resonances in their ^{1}H and ^{7}Li NMR spectra. The *ee* can be calculated simply from integration of the ^{1}H and/or ^{7}Li NMR spectra

Chirality plays a major role in many areas of chemistry, from natural products to the design of new materials. The easy of detection of chirality, the study of chiral interactions and (in particular) the evaluation of chiral purity are areas of great research interest.[1] Many methods have been reported for the determination of the chiral purity of a sample, including optical rotation and circular dichroism,[2] gas chromatography (GC) or liquid chromatography (HPLC)[3] with a chiral stationary phase. Methods based on NMR spectroscopy have been at the forefront of this area due to the simplicity and availability of this technique.[4] In the last few decades, considerable effort has gone into developing new methodologies and reagents for the rapid and convenient determination of enantiomeric excess (*ee*) using NMR spectroscopy.[5] Current methods involve the use of enantiomerically-pure compounds as chiral auxiliaries.[6] Chiral derivatizing agents (CDAs)[7] are based on the formation of a covalent bond with the analyte and are perhaps the most commonly used species for determining *ee*'s. However, chiral reagents based on non-covalent interactions are also available, including chiral solvating agents (CSA),[8] chiral lanthanide shift reagents, ion-pairing agents[5c] and liquid crystals.[9] Although these methods rely on the simple principle of forming diastereomeric compounds, in many cases the exact mechanism of the discrimination is not fully understood and is based on empirical observations, such as changes in chemical shift.

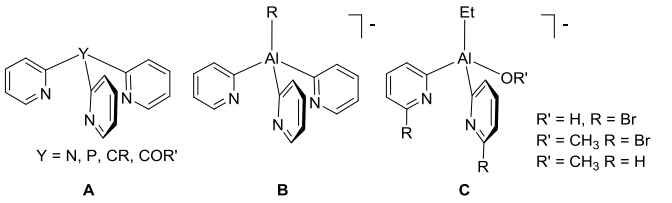
Few examples of the use of achiral reagents for the determination of enantiomeric purity are known.[5b] Such reagents are also less general as they require the covalent bonding of two chiral molecules of analyte to the substrate[10] or the design of complex solvating agents in combination with an excess of the chiral analyte.[5b] A very elegant way of avoiding chiral reagents for the determination of *ee*'s by NMR spectroscopy would be through chiral self-discrimination (i.e., self-association of the chiral molecule). However, only a few analytes have been found to exhibit chiral self-discrimination under specific conditions.[11] In many cases association though hydrogen bonds seems to play a major role.[12] However, due to the relatively weak nature of the bonding, small differences in chemical shift are observed and distinguishing between a racemic mixture and an enantiomerically pure one is not always straightforward, since under fast exchange conditions the same number of signals is observed.[13]

Here we report the use of non-chiral [EtAl(6-Me-2-py)$_3$Li] (**1**) as a convenient reagent for the evaluation of the optical purity of alcohols. The method relies on the fast and selective cleavage of one of the Al-bonded pyridine groups by the chiral alcohol under mild conditions, and subsequent chiral self-discrimination by the association of the chiral aluminate into dimers that are retained in solution. These dimers are easily distinguishable by ^{1}H and ^{7}Li NMR spectroscopy, allowing the fast evaluation of optical purity and the determination of *ee*.

Tris-pyridyl aluminates [RAl(2-Py)$_3$]$^-$ are closely related to the important family of neutral ligands of the type [Y(2-py)$_3$], Y = non-metallic bridgehead atom or group (Scheme 1, A).[14] Aluminate ligands of this type (Scheme 1, B) are unusual in this area in being negatively charged,[15] which results in strong affinity towards a large variety of main group and transition metal ions.[15a,16] Our recent focus in this area has been on the reactivity of these ligands and we have shown that they react selectively with H_2O or MeOH to form stable heteroleptic aluminium complexes (Scheme 1, C).[17]

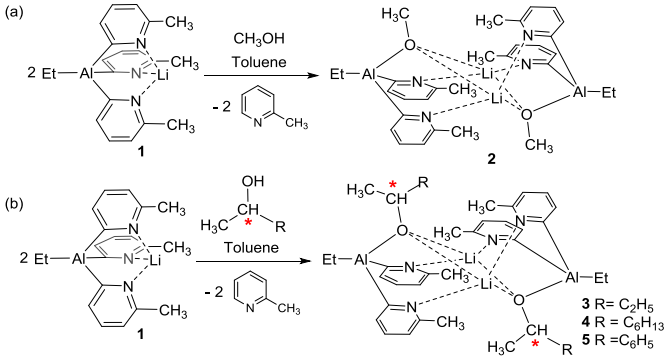
[a] *Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW. E-mail: rg489@cam.ac.uk.*

† Electronic Supplementary Information (ESI) available: Experimental procedures and additional figures. Full details of the syntheses and characterization of the compounds and NMR spectra for all the new compounds including crystallographic data for **2**, **3**-*SS*, **3**-*RR*, **3**-*RS* and **5**-*RS*. See DOI: 10.1039/x0xx00000x



Scheme 1 (**A**) Frameworks found in the family of tris-2-pyridyl ligands, (**B**) anionic tris-2-pyridyl aluminate ligands, and (**C**) heteroleptic aluminium complexes.

In the current study we initially reacted the aluminate [EtAl(6-Me-2-Py)$_3$Li] (**1**), which exists as a monomer in solution (C_6H_6) and in solid state,[17] with one equivalent of CH_3OH in toluene in order to demonstrate the same reactivity pattern as that found for other aluminates of this type (Scheme 2a). The spectroscopic data showed the formation of the expected heteroleptic anion [EtAl(6-Me-2-Py)$_2$(OMe)]$^-$ (**2**), resulting from the cleavage of one pyridine arm. The ^{1}H NMR spectrum showed the presence of OCH_3 as a singlet at δ = 3.24 ppm along with a singlet for the 6-*Me*-Py group at δ = 2.20 ppm, while only one sharp singlet (δ = 2.75 ppm) was observed in the ^{7}Li NMR spectrum (see ESI Fig. S1†). X-ray analysis revealed that **2** forms a centrosymmetric dimer [{EtAl(6-Me-2-py)$_2$(OMe)}Li]$_2$, similar to that found previously for [{EtAl(6-Br-2-py)$_2$(OMe)}Li]$_2$ (see ESI Fig. S2†).[17]



Scheme 2 (a) Reactivity of [EtAl(6-Me-2Py)$_3$Li] towards methanol and (b) chiral alcohols.

We next studied the reactivity of **1** towards racemic mixtures of the chiral alcohols 2-butanol (**3**), 2-octanol (**4**) and 1-phenylethanol (**5**), to form the corresponding heteroleptic aluminate complexes *rac*-**3**, *rac*-**4** and *rac*-**5**, respectively (Scheme 2b).The room-temperature ^{1}H NMR spectra of all of these species were more complicated than expected, showing extensive splitting of the resonances, which depended on the particular alcohol. The largest effect was found for the resonance at the 6-*Me* groups of their pyridine rings (6-*Me*-Py), where four singlets were observed in the ^{1}H NMR spectra of each of the compounds (*rac*-**3**-**5**) (see Figure 1a), in contrast to the singlet observed for the 6-*Me*-Py groups of **2**. The ^{7}Li NMR spectra of *rac*-**3**-**5** were also complicated. For example, in contrast to **2** which gives just one singlet, *rac*-**5** shows three distinctive resonances (see later, Fig 3). When the reactions were carried out using enantiomerically pure alcohols (*R* or *S*), simplification of the ^{1}H, ^{13}C{^{1}H} and ^{7}Li NMR spectra of the aluminates formed (*R*-**3**-**5** or *S*-**3**-**5**) was observed (see ESI, Figs S3-S6† and Figs 1 and 3, later). In all cases, the resonances for the reporter 6-*Me*-Py groups in the ^{1}H NMR spectra were reduced to only two singlets (Fig 1b.).

It is well known that the NMR spectra of either the separate enantiomers or their racemic mixture, under the same conditions, are identical in the presence of an achiral solvent. The mechanism by which the discrimination between racemic and enantiomerically pure alcohols is achieved in our case relies on the formation of robust heteroleptic dimers [EtAl(6-Me-2-Py)$_2$(OR)]$_2$ (scheme 2). In the presence of only one enantiomer of the chiral alcohol, only one homochiral dimer *SS* (or RR) is formed. However, if a racemic alcohol is used, a mixture of the heterochiral dimer (RS) together with the two homochiral counterparts is obtained. The homochiral (chiral) and heterochiral (meso) aluminate dimers are diastereomers and therefore are different spectroscopically. This makes it possible a) to distinguish between a pure enantiomer and the corresponding racemic mixture and b) to determine the ratio of each enantiomer present, i.e., the ee (obtained by integration of the ^{1}H NMR or ^{7}Li spectra, see later).

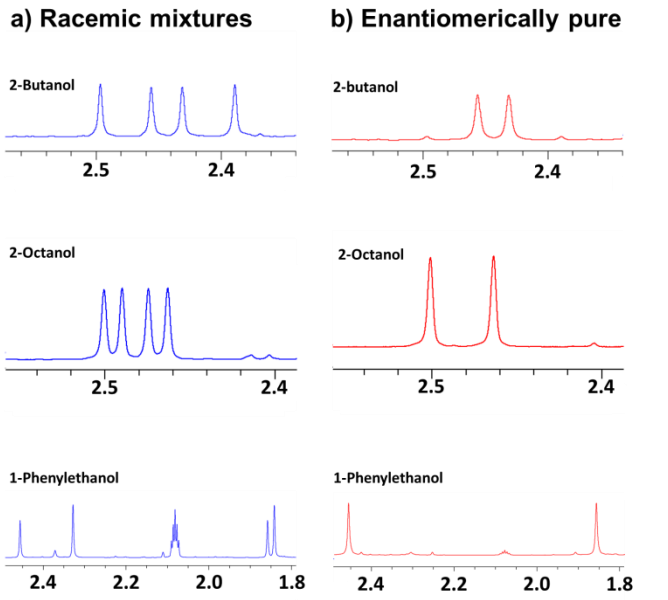


Fig. 1 ^{1}H NMR spectra (298K) in toluene-d$_8$ of the 6-*Me*-Py region resulting from the reaction of **1** with a) racemic alcohols to give the aluminates *rac*-**3**-**5**, and b) enantiomerically pure alcohols to give the corresponding enantiomerically pure aluminates (*R*-**3**-**5** or *S*-**3**-**5**).

The explanation for this discrimination is most clearly seen from X-ray crystallographic analysis of *all* of the possible dimers of **3**: **3**-*SS*, **3**-*RR* and **3**-*RS*, which were obtained as crystals from reactions of **1** in toluene with one equivalent of the corresponding enantiomerically pure or racemic 2-butanol. Fig 2 (left) shows the structure of the chiral aluminate dimer **3**-*SS*. Due to the molecular C_2 symmetry there are two different 6-*Me*-Py environments in **3**-*SS*, two of the 6-*Me*-Py groups facing the alkoxide Me group and two facing the alkoxide Et group (see ESI Fig. S7, pages S16-S17†). The same conclusion can be drawn from the analysis of the solid-state structure of **3**-*RR* (see ESI Figs. S8-S9†), whose ^{1}H NMR resonances are

coincident with its **3**-*SS* enantiomer, explaining the observation of the same two singlets for the 6-*Me*-Py groups in the ^{1}H NMR spectrum for **3**-*S* and **3**-*R* (see Fig 1b, top right), due to the retention of this dimeric structure in solution. The C_2-symmetry of dimers of **3**-*SS* (and **3**-*RR*) also results in two distinct Li environments (as seen in the ^{7}Li NMR spectra, see ESI Figs. S10-S11†).

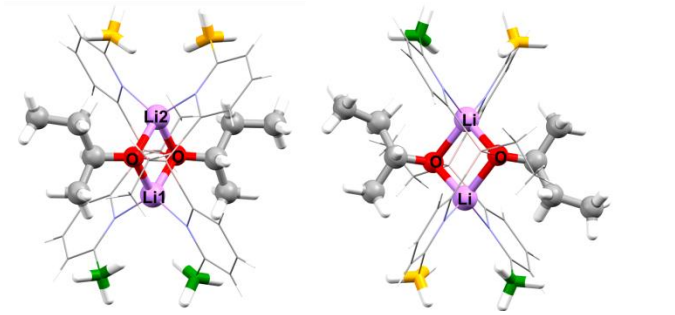


Fig. 2 Solid-state structures of the dimeric complexes **3**-*SS* (left) and **3**-*RS* (right). Both dimers have two different *6-Me*-Py environments, which are highlighted in green and orange. In the case of **3**-*SS* (or the enantiomer **3**-*RR*) both Li atoms are inequivalent, as a result of the C_2 symmetry, in contrast to the hererochiral dimer **3**-*RS* for which both Li atoms are equivalent since the dimer is locally centrosymmetric (effective C_i symmetry).

In the case of the racemic mixture, a further two singlets result in the ^{1}H NMR spectrum from the fact that the heterochiral dimer **3**-*RS* also possesses two inequivalent 6-*Me* groups of the pyridine rings (Fig. 2 (right)) as a result of the effective C_i symmetry. Hence, the ^{1}H NMR spectrum of *rac*-**3** contains four distinct resonances in the 6-*Me*-Py region consisting of those for **3**-*SS*/**3**-*RR* (two resonances for each that are coincident) and **3**-*RS* (two resonances).

For 1-phenylethanol (**5**), the presence of a phenyl group induces a larger difference in the magnetic environments of the 6-*Me* groups, as seen in the ^{1}H NMR spectra at room temperature (Fig. 1, bottom). This can also be seen in the ^{7}Li NMR spectra of *R*-**5** (or *S*-**5**) and *rac*-**5** (Fig 3, left). If one enantiomer of 1-phenylethanol is present (*R* or *S*) then two clearly separated singlets are observed as a result of the two different Li environments of the C_2 symmetric homochiral dimer (**5**-SS or **5**-*RR*). For *rac*-**5**, three singlets are observed in the ^{7}Li NMR spectrum, a central resonance, resulting from the single magnetic environment of **5**-*RS* (which has centrosymmetric C_i symmetry), which is flanked by the resonances for **5**-*SS*/**5**-*RR* (two resonances for each which are coincident) (Fig 5, left). This demonstrates that detection of chirality can be also achieved using ^{7}Li NMR spectroscopy (in addition to ^{1}H NMR).

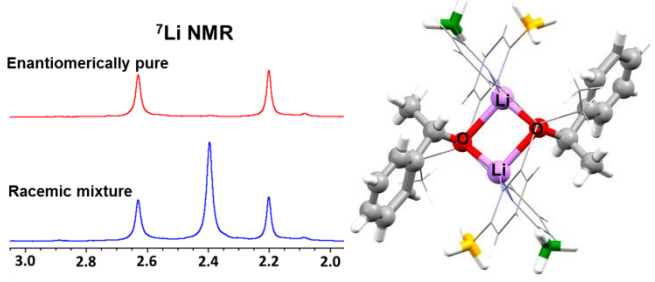


Fig. 3 ^{7}Li NMR stack spectra (left) of enantiomerically pure *R*-**5** or *S*-**5** (above, red) and racemic mixture of **5**, *rac*-**5** (bottom, blue), and solid-state structure of centrosymmetric (C_i symmetry) dimeric **5**-*RS* (right) showing the presence of two 6-Me environment and only one Li.

Having established the basic concept of how **1** can be used to detect chirality, we next moved on to assess its use in the quantitative measurement of ee's. We studied the substoichiometric addition of the alcohols 2-butanol, 2-octanol and 1-phenylethanol of known ee's (typically 0.5 equivalents, ca. 4μL of alcohol),[18] to **1** in air and at room temperature in toluene-d_8. The ^{1}H NMR spectra of each mixture was then recorded at room temperature (see ESI, Figs S12-S13†) and the integration of the homo-(RR+SS) and hetero-(RS) resonances in the 6-Me-Py region was then used to determine the *ee* for comparison with the known, pre-determined values. These data are shown in Table S1† (see ESI).

If the formation of the SS-, RR- and RS-dimers is purely statistical, the calculation of the *ee* (%) is straightforward through eqn (1) (see ESI pages S54-S55 and S57-S59†), in which r = the ratio of the homo- to heterochiral dimers [r = (RR + SS)/RS].

$$ee(\%) = \sqrt{\frac{r-1}{r+1}} \times 100 \quad (1)$$

In a racemic mixture, the same amount of heterochiral (RS) and homochiral (RR+SS) dimers will be expected (50:50). As can be seen from Table S1†, this is the case for 2-butanol (**3**) and 2-octanol (**4**) (first entries), with only a small deviation being observed for the former alcohol.

In the case of **5**, however, there appears to be a preference for the formation of the heterochiral dimer (RS), as shown by the 42:58 distribution found in the reaction of **1** with a racemic mixture of 1-phenylethanol (first entry for **5**). This preference is corrected for by using eqn (2), in which d′ is the ratio of the homo- and hetero-chiral dimers for a racemic mixture of the alcohol. This parameter is easily accessible from the NMR spectroscopic data, i.e., 42/58 = 0.724 using the data for entry 1 for **5**, see Table S1†. Significantly, this simple modification avoids the use of a calibration curve under these circumstances.

$$ee(\%) = \sqrt{\frac{r-d'}{r+d'}} \times 100 \quad (2)$$

As can be seen from the data in Table S1†, our technique for determining ee's works extremely well (i.e., compare the values in column 1 with those determined experimentally in column 4). The procedure is very sensitive at high enantiomeric purities where the effects of diasteroselectivity are negligible, and the presence of the small amount of the minority enantiomer is effectively amplified by the formation of the heterochiral dimer. For instance, Table S1† shows that ee's of 95% are easily discriminated from enantiomerically pure ones since they result in the formation of *ca* 5% of the heterochiral dimer. In this regard, it is worth noting that the 'enantiomerically pure' R-2-butanol acquired commercially (Aldrich) was estimated to contain 93.0±0.5% *ee* using our method (last entry for 3, Table S1†). This agrees well with the *ee* calculated by optical rotation (93.5%, see ESI on page S56†). Due to the nature of the method, the sensitivity for low enantiomeric excesses is lower and only high ee's can be

measured with accuracy of at least 1% (see table S1†). Since the RR/SS- and RS-dimers of **5** can be easily distinguished by ^{7}Li NMR (Fig 3, left), the *ee* can be calculated on the basis of the ^{7}Li NMR integration (see ESI, Fig. S14†). The values obtained agree well with the results obtained from ^{1}H NMR data.

In conclusion, we have reported the use of an achiral aluminate **1** for the rapid evaluation of enantiomeric purity and the determination of *ee*'s of alcohols by NMR spectroscopy.The mechanism by which detection of enantiopurity works is revealed though detailed X-ray and NMR experiments and relies on chiral self-discrimination of the aluminates. Detection of enantiomeric purity is best achieved by ^{1}H NMR spectroscopy through 6-*Me*-Py reporter groups. However, ^{7}Li can also be used as an additional and convenient reporter nucleus. To the best of our knowledge, this is the first time that ^{7}Li NMR spectroscopy has been employed to assess optical purity.

Importantly, the aluminate reagent **1** is ideal for standard laboratory use as it is highly thermally stable and can be stored indefinitely under N_2 at room temperature. This method also avoids the use of optically pure reagents, as *in situ* reaction of the alcohol with aluminate **1** and the formation of robust dimers produces diastereomers.[19] Although the method requires the use of a racemic mixture to evaluate the preference between dimers for any new analyte to be studied (i.e to calculate d' in eqn (2)), it avoids the use of a calibration curve. Since the initial reaction of each enantiomer of the alcohol with **1** proceeds quantitatively and rapidly, errors in the measurement of the *ee* due to slow kinetics are avoided. In addition, only small amounts of the alcohols (*ca.* 4μL) are required since they react immediately and quantitatively at room temperature with **1**. Having established the principle of *ee* determination using **1**, the tailoring of other aluminates to a particular group of analytes should also be possible. We are currently working to extend this new methodology to other chiral analytes with relatively acidic protons, such as carboxylic acids or even amines.

Acknowledgements

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19 The closest precedent is the formation of kinetically labile dimers using an achiral Sn reagent that converted 1,2-diols into dimeric dioxastannolanes (ref 11c). Information of ee was obtained from ^{13}C NMR data on concentrated samples, since analysis of by ^{1}H NMR was impossible due to its complexity, as a result of the complex exchange processes occurring that were temperature and concentration dependent. Self-discrimination occurred under fast-exchange conditions, although details about the exact nature, distribution and geometry of the aggregates were unknown (i.e .possible formation of higher aggregates in addition to dimers could not be ruled out). Duplication of the signals occurred for non-racemic samples and their differences in chemical shifts were related to the ee. However, chemical shifts were strongly dependent on concentration and temperature.

