Highly enantioselective metallation–substitution alpha to a chiral nitrile†

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We report the deprotonation of a chiral nitrile and reaction of the resulting chiral organometallic species with a variety of electrophiles to give highly enantioomerically enriched 2-substituted nitrile products. The nitrile was treated with TMPMgCl and the resulting anion, an asymmetric alpha cyano Grignard species, was found to be configurationally stable at low temperature for a short time (half-life several minutes at $-104 \, ^\circ\text{C}$).

Introduction

Metallated nitriles are well-used intermediates in synthetic chemistry due to their excellent reactivity as nucleophiles. The formation of the organometallic species and its reaction with an electrophile such as an alkyl halide or aldehyde allows a high-yielding preparation of the desired substituted nitrile that can then be converted readily to other functional groups. The most common method to prepare the metallated nitrile is to treat the nitrile with a base such as lithium diisopropylamide (LDA) and this is known to give the lithiated nitrile in which the lithium ion normally resides on the nitrogen atom. Although this gives a reactive nitrile anion, one of its drawbacks is that this provides an achiral organometallic species (e.g. Fig. 1), even starting from a chiral, enantiomerically enriched nitrile. Therefore it would be expected that achiral products would result from using chiral enantiomerically enriched nitrile starting materials and this is typically the case. Remarkably, however, Takeda and co-workers reported recently that it is possible in certain cases at low temperature with in situ reactive electrophiles to trap the intermediate anions to give enantioenriched products. At about the same time, we began to explore this possibility but by using magnesiated nitriles.† The idea that magnesiated nitriles may allow asymmetric reaction through a chiral organometallic species 1 rather than 2 (Fig. 2) was based on results from several groups including that of Carlier and co-workers, who reported the first metallated nitrile with macroscopic configurational stability, albeit a cyclopropyl derivative 3 (prepared by Br-Mg exchange). In addition, Fleming and co-workers had found opposing selectivities for reactions of lithiated and magnesiated nitriles and surmised that the magnesium cation has a preference for location on carbon.

If the metal atom is located on the carbon atom, as illustrated by the contact ion pair 1 (or its related solvent-separated ion pair in which the metal cation is nearby), then the metallated nitrile is chiral and has the possibility to transfer its chirality to the product on reaction with an electrophile. However, very little is known about the rate of enantiomerisation of such nitrile anions. The importance of nitrogen-containing heterocycles in natural products and medicinal compounds led us to explore the metallation of nitrile 4 with the aim to determine whether the deprotonation–electrophilic quench would be feasible and how fast the intermediate magnesiated nitrile undergoes racemisation. Herein, we describe the first high yielding, highly enantioselective metallation–substitutions of a chiral ε-amino-nitrile by using a simple magnesium base.

Results and discussion

The carboxylic acid N-Boc-pipecolic acid is commercially available as the (S) enantiomer and this was converted to (S)-N-Boc-2-
To optimise the reaction we carried out in situ IR studies and found that only partial conversion occurs with one equivalent of TMPMgCl (Fig. 3a). However, almost complete conversion occurs with two equivalents and full conversion with three equivalents of TMPMgCl (Fig. 3b).

Several bases were tested under these optimised conditions (Scheme 1). The bases CuO(Bu)3, mesityl copper, or TMPZnCl·MgCl2 were unsuccessful. The method developed by Takeda and co-workers with NaHMDS (and 4-BrC6H4COCl in situ) did give the product 5g but the enantioselectivity was poor (71% yield, er 53 : 47). With the magnesium base iPrMgCl the yield was low (10% yield of product 5a with PhSSO2Ph as the in situ electrophile, not determined). However the base TMPMgCl was much more successful and a good yield and er of the product 5g was obtained (68% yield 5g, er 81 : 19).

We therefore selected TMPMgCl as the most suitable base. The enantioselectivity was not optimal and we were aware that Carlier and co-workers had found that a magnesiated cyclopropynitrile racemises more rapidly in THF than in Et2O. Therefore we conducted kinetic experiments to determine the rate of enantiomerisation of this organomagnesium species in THF/Et2O (1 : 1) and in Et2O (see ESI† and Fig. 4). At −104 °C the intermediate organomagnesium compound was trapped after various time periods to give the product 5a or 5f and the er was measured by CSP HPLC or GC respectively. These gave good first order plots and revealed rates for inversion k ~ 6.5 × 10^{-3} s^{-1} in THF/Et2O (see ESI†) and k ~ 4 × 10^{-3} s^{-1} in Et2O (Fig. 4). The kinetic data demonstrate a slightly slower rate for inversion of the intermediate organomagnesium species in Et2O. In the case of the magnesiated nitrile 4, the enantiomerisation half-life t_{1/2} ~ 3 min in Et2O and only ~2 min in THF/Et2O, presumably as THF helps to solvate the magnesium cation. Therefore, we carried out the deprotonation in pure Et2O and were pleased to find that this improved the enantioselectivity of the metallation-electrophilic quench reaction (Scheme 2). The optimised conditions involved rapid addition of three equivalents of TMPMgCl (prepared from i-PrMgCl and TMPH in Et2O) to the nitrile 4 in Et2O at −104 °C, either with the electrophile added in situ pre-mixed with the nitrile 4 (in the case of the S-aryl benzenesulfonates) or with the electrophile added after about 10 s (for the carbonyl electrophiles). High enantioselectivities of the arylthio derivatives 5a–c were obtained by the in situ method. With the ortho-methoxy compound 5e, the electrophile was only partially soluble in pure Et2O, so this reaction was carried out with some THF and this may account for the reduced selectivity. The organomagnesium intermediate has sufficient configurational stability to allow its formation followed by electrophilic quench without the need for in situ product isolation.

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Fig. 3 In situ IR spectroscopy of the deprotonation of 4 with TMPMgCl in THF/Et2O at −104 °C with time in h:min:sec. (a) One equiv. TMPMgCl added at time 12 min (ν_C=O 1707 cm⁻¹, ν_C=O metalled 4 1627 cm⁻¹). (b) three equiv. TMPMgCl added at time 16 min (ν_C=O 4 1703 cm⁻¹, ν_C=O metalled 4 1626 cm⁻¹).

![Scheme 1](image)

Scheme 1 Metallation-quench of nitrile 4 with various bases.
for an \textit{in situ} electrophile. Benzaldehyde provided racemic product 5d, possibly due to single electron transfer. However, acetone gave highly enantioenriched alcohol 5e and cyclobutanone gave the alcohol 5f also with excellent ee. The electrophile \textit{p}-bromobenzoyl chloride gave the nitrile 5g with ee 83 : 17 after 10 s quench and similar selectivity with \textit{in situ} quench.

Recrystallisation of the nitrile 5g gave essentially enantiopure compound (ee 99 : 1 by CSP-HPLC) and the absolute configuration was determined by single crystal X-ray analysis (Fig. 5).† This demonstrated that the electrophilic quench occurred with retention of configuration. To determine the absolute configuration of the sulﬁdes, we carried out sulfur–magnesium exchange with \textit{i-PrMgCl}. This transformation has not to our knowledge been reported with an enantioenriched sulﬁde and it was intriguing to discover whether it would be possible to transfer chirality by this method. Addition of \textit{i-PrMgCl} to the sulﬁde 5c in Et₂O at \(-104 \, ^\circ\text{C}\) followed by addition of \textit{p}-bromobenzoyl chloride gave the product 5g in moderate yield and only partial loss of enantioselectivity (Scheme 3). The major enantiomer of the product 5g had the same configuration as that obtained by the direct addition of \textit{p}-bromobenzoyl chloride, thereby demonstrating that the sulﬁde 5c (and hence also likely the sulﬁdes 5a and 5b) has the stereochemistry as shown, and was formed by reaction with retention of conﬁguration. We have not been able to determine the absolute conﬁgurations of the alcohols 5e and 5f, but these are likely to be as shown with reaction by retention of configuration, and this would be in line with other known electrophilic quenches of metallated \textit{N}-Boc-piperidines.7 A similar reaction was carried out, in which sulfur–magnesium exchange was followed, after 10 s, by addition of the electrophile PhSSO₂Ph to give the product 5a (Scheme 3). This was formed in moderate yield without signiﬁcant loss of enantio purity, together with what appeared to be an alkene by-product from elimination.

The impressive enantioselectivities that can be obtained with the simple \textit{N}-Boc-2-cyanopiperidine 4 and base TMPMgCl demonstrate that this method has potential for asymmetric synthesis. The magnesium metal likely has a preference for attachment to the carbon atom at least initially. A possible
intermediate, supported by analogy to that proposed by Carlier and co-workers for magnesiated cyclopropylnitriles, would have two magnesium atoms, one on the carbon atom and one on the nitrile nitrogen atom, connected by a bridging chloride. Dimeric magnesium amides with bridging chloride ligands are well known.\(^1\)\(^,\)\(^2\)

To investigate this further, Density Functional Theory (DFT) calculations were performed \([6-311G(d,p)\) basis set with B3LYP functional\] and their ChemDraw representations. (a) 6, chelated structure. (b) 7 non-chelated structure. All hydrogens have been removed for reasons of clarity.

higher energy structures. Fig. 6a (structure 6) has chelation of the C=O group to the magnesium. Fig. 6b (structure 7) derives from the other rotamer without this chelation and this structure is 62 \(\text{kJ mol}^{-1}\) higher in Gibbs energy than 6. As the Boc group is not rotating at low temperature, both species should be present in solution and able to react with the electrophiles as shown earlier.

The organomagnesium species 6 and 7 could racemise by breakage of the C-Mg bond followed by carbanion inversion and reattachment of the magnesium to the opposite face. Alternatively racemisation could take place by formation of the \(N\)-magnesiated ketene imine type structure. However, by whatever mechanism racemisation occurs, the experimental data show that the C-magnesiated intermediates have sufficient lifetime at low temperature for addition of an electrophile and reaction to give highly enantiomerically enriched products.

Experimental

A representative method for the deprotonation and quench of nitrile 4 is given below. For further details and all data, see ESI.†

\[\text{TMPMgCl (1.6 mL, 0.75 mmol) was added to the nitrile 4 (54 mg, 0.25 mmol) in Et}_2\text{O (1 mL) at } -104^\circ\text{C. After 10 s, cyclobutanone (0.056 mL, 0.75 mmol) was added. After 30 min, saturated aqueous NH}_3\text{Cl (0.3 mL) was added. The mixture was allowed to warm to room temperature and was extracted with Et}_2\text{O (3 × 1 mL), dried (MgSO}_4\text{) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (9 : 1), gave the alcohol 5f (47 mg, 68%); [\(\alpha\text{D}^25\] \(-25.7\) (c 0.4, CHCl\text{}3); er 95 : 5 by CSP-GC.\] Computed methods

All calculations were performed using the D.01 version of Gaussian 09.\(^20\) Density functional theory was used throughout using the B3LYP\(^21\) functional including dispersion interactions \(\text{via}\) the GD3-BJ\(^22\) correction. All calculations used the 6-311G(d,p)\(^23\) basis set. Solvent was included \(\text{via}\) the PCM method\(^24\) as implemented in Gaussian with the default parameters for \(\text{Et}_2\text{O}\). Frequency calculations were performed on all optimized structures to confirm that these were all true minima as evidenced by the absence of imaginary frequencies. No complete conformational search for any added \(\text{Et}_2\text{O}\) molecule was performed. Instead, the calculations were all started with \(\text{Et}_2\text{O}\) in the conformation of its free molecule. All Gibbs energies were evaluated at 298.15 K.

Conclusions

In conclusion, the base TMPMgCl can be used at low temperatures to deprotonate a chiral nitrile without significant loss of enantiopurity even in the absence of an \textit{in situ} electrophile. The intermediate magnesiated nitrile can be trapped with a variety of electrophiles to give enantiomerically enriched substituted nitrile products with overall retention of configuration. The organomagnesium intermediate racemises fairly rapidly and the half-life is slightly slower in the presence of the
less polar solvent Et₂O than in THF. In addition we have shown that sulfur–magnesium exchange can occur with retention of configuration. Calculations support the experimental that two magnesium ions are present in the intermediate complexes. These results suggest that, despite their general lack of use for asymmetric synthesis, chiral nitrile anions can be valuable intermediates that do not always lose their configuration but can be converted to highly enantiomerically enriched products.

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Notes and references


