# Highly Enantioselective Metalation–Substitution alpha to a Chiral Nitrile

Carbanion chemistry is extremely important in synthesis, since carbanions act as nucleophiles for efficient carbon–carbon bond formation. Arguably the most-used type of carbanion is an enolate, and enolate alkylation and the aldol reaction play a key role in many synthetic endeavors. As the anion in enolates is delocalized, they adopt a planar structure. Therefore, any stereocenter that was present alpha to the carbonyl is lost on formation of the enolate and it is necessary to use a chiral auxiliary, a chiral electrophile, or a chiral catalyst that is associated with the transition state to induce asymmetry in the resulting alkylated product.

The similarity of nitriles to carbonyls has led the scientific community to consider their reactivity to be related. Indeed, deprotonation of a nitrile to form a carbanion using a base such as LDA provides a carbanion where the lithium ion resides on the nitrogen atom in a dimeric structure.[1] Such a ketenimine, like an enolate, reacts with alkyl halides and carbonyl compounds through the carbon atom thereby leading to C-alkylated products. Therefore, it might be expected that starting from an alpha chiral nitrile the reaction would give, after deprotonation, an achiral metalated intermediate and hence racemic products. Indeed, this is typically the case,[2]
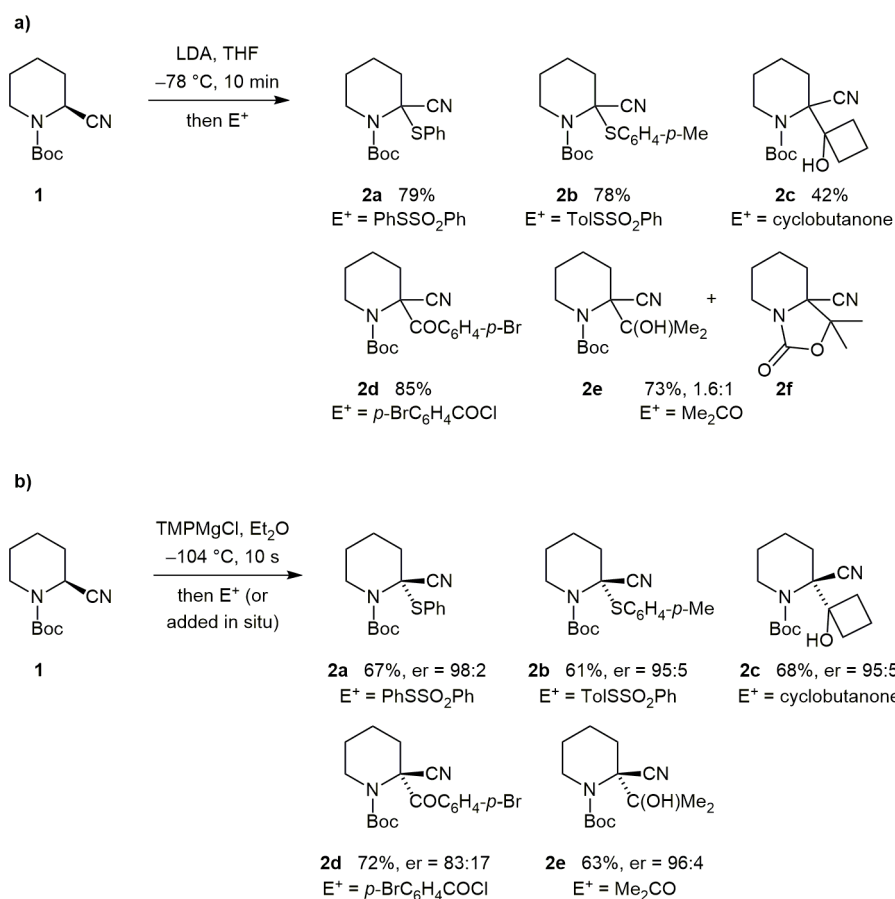
Scheme 1 Deprotonation of chiral nitrile **1**

and the Coldham group at the University of Sheffield (UK) has found that treating the chiral nitrile **1** with LDA followed by addition of electrophiles gives racemic products, such as **2a–f** (Scheme 1a). However, by using the magnesium base TMPMgCl, the products were formed with high enantioselectivity (Scheme 1b).

Professor Coldham explained: "Deprotonation alpha to a nitrile with a magnesium base is likely to lead to a metalated intermediate in which the magnesium ion is attached, at least initially, to the carbon rather than the nitrogen atom.[3] This then provides a chiral metalated intermediate from which it is possible to obtain enantiomerically enriched products. The intermediate organomagnesium compound is not particularly configurationally stable and we found that the half-life for enantiomerization is only about three minutes in Et$_2$O at –104 °C. However, this is sufficient to allow rapid quench either in situ or after a few seconds without significant loss of enantiopurity in many cases." A plot for the loss of enantiomeric excess (at –104 °C, quenching with cyclobutanone and assuming 100% at time zero) is shown in Figure 1. This illustrates that the racemization occurs at low temperature within several minutes. "However, the quench can be conducted without the need for the electrophile to be present in situ to give enantiomerically enriched products," continued Professor Coldham. The electrophilic quench was found to occur with overall retention of configuration, as determined for ketone **2d** by recrystallization to high enantiopurity (er = 99:1 by chiral stationary phase HPLC) and single crystal X-ray analysis.

The reaction was followed by in situ IR spectroscopy (ReactIR) and this demonstrated that at least two equivalents of TMPMgCl were required for full metalation. "The structure of the magnesiated intermediate was studied computationally and DFT calculations suggested that there are two magnesium ions involved, one attached to the carbon atom and one on the nitrogen atom," said Professor Coldham. He continued: "The lowest energy form has the nitrile in an axial location and the carbonyl oxygen chelated with the magnesium attached to the alpha carbon atom. However, rotation of the carbonyl group is likely to be very slow at low temperatures so the rotamer without chelation was also modelled. Although this was higher in energy, it presumably also exists in solution. It is likely that the two rotamers have different rates of enantiomerization but both can lead to enantiomerically enriched products."

Professor Coldham concluded: "This study provides useful insight into the intermediates involved in metalations of nitriles. A magnesiated intermediate does not necessarily lose its configuration immediately on forming, as occurs with enolates, and this methodology could be valuable for the preparation of enantiomerically enriched products starting from chiral nitriles. The combination of experiment and calculations gives us real insight into the molecular basis for the effects we see, giving us confidence that we understand why our approach works the way it does, boding well for its future applicability."

Matteo Zanda

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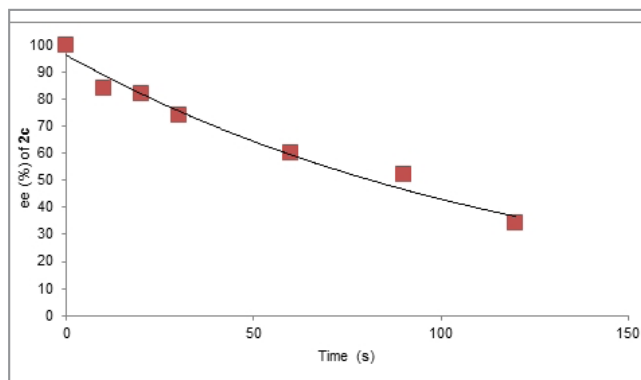
Figure 1 Enantiomeric excess of chiral nitrile **2c** over time using conditions from Scheme 1b

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About the authors

Iain Coldham received his PhD from the University of Cambridge (UK). After postdoctoral research in Austin, Texas (USA), he joined the faculty at the University of Exeter (UK) in 1991. He was a visiting Professor at the University of Miami (USA) in 2001. He moved to the University of Sheffield (UK) in 2003 and was promoted to Professor in 2008. His research is centered on chiral organometallic chemistry and cascade reactions involving dipolar cycloadditions.

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