Trends in Chemistry

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Spotlight

Mind the gap! Steric-driven reductive desymmetrisation of malononitriles

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Huang and coworkers recently demonstrated that a cobalt(I)-hydride complex, ligated with a finely tuned chiral bisoxazoline ligand, can selectively reduce disubstituted malononitriles by discriminating between enantiotopic nitrile groups. This reductive desymmetrisation strategy utilises the bulk industrial feedstock malononitrile to access nitrogen-rich enantioenriched products.

Nitrogen-rich fine chemicals are important synthetic intermediates in the agrochemical and material industries, but they are particularly prevalent in pharmaceuticals due to the ubiquity of nitrogen-containing heterocycles [1]. The enantioselective synthesis of amines, preferably from abundant and renewable chemical feedstocks, provides access to unique three-dimensional scaffolds, which are often under-represented in bioactive molecules when compared with their planar heterocyclic counterparts.

Malononitrile is an ideal chemical feedstock due to its high nitrogen content resulting from the presence of two nitrile groups. This dinitrile substrate enables desymmetrisation strategies to be implemented for the synthesis of other useful molecular intermediates. Currently, Liu and coworkers are pioneering the desymmetrisation of disubstituted malononitriles having designed several unique and valuable protocols [2–4]. Yet, many of the resulting products have reduced nitrogen atom content due to the nitrile group being erased by functional group conversions or limited synthetic potential as the nitrogen atom is incorporated within subsequent heterocycles. Liu's desymmetrisation protocols, which give access to highly substituted chemical scaffolds, are notable whilst leaving opportunities for the synthesis of small chiral nitrogen-containing building blocks.

Huang and coworkers have previously focused on the desymmetrisation of 1,3-dicarbonyl compounds, relying on the chelation of a metal centre with bespoke chiral phenolic ligands enabling enantiocontrol [5–8]. Nonetheless, in their most recent work, published in *Nature Chemistry,* Huang and coworkers have tackled a new challenge in the reductive desymmetrisation of disubstituted malononitriles [9]. To accommodate this, they have pivoted towards a new catalytic system that uses a cobalt(I)–hydride complex as the active reductant, reporting the first highly enantioselective protocol of its kind to synthesise enantiopure β-amino nitriles from malononitriles. To achieve this, they employed a mixture of a cobalt salt ($CoBr_2$) and sodium borohydride ($NaBH_4$) with a tailored bisoxazoline ligand **L1**.

The challenge of controlling enantioselectivity in this process is due to the free rotation of the C(sp)-C(sp^3) bond of the complexed nitrile, as this single-point binding mode allows many conformations. Bisoxazoline **L1** creates a spatially differentiated steric environment due to the flanking aryl groups that limits substrate rotation when bound to the cobalt catalyst (Figure 1A). This increases specific conformer recognition and enhances enantiocontrol, primarily driven by the creation of a suitably narrow channel where the unbound nitrile resides (Figure 1C). An experimental investigation demonstrated that the incorporation of a cyclopropyl group in the methylene bridge increased the bite angle, arising from the Thorpe–Ingold effect, and enhanced the enantioselectivity. Additionally, when the four methyl groups were removed (**L2**), a minor decrease in enantioselectivity was observed. On the contrary, increasing the steric bulk (**L3**) further was detrimental for both enantiocontrol and yield as the narrow channel becomes too small for efficient substrate binding.

The employment of trifluoroethanol (TFE) as a co-solvent was necessary for obtaining high yields whilst maintaining excellent levels of enantioselectivity. TFE is proposed to enhance catalyst turnover; however, its full involvement within the reaction is yet to be elucidated. These findings are reiterated with isopropanol (IPA) and hexafluoroisopropanol (HFIP), where these bulkier alcohols exhibit lower rates whilst maintaining the stereoselectivity. Alternatively, methanol facilitates a non-selective background reduction, that leads to a noticeable drop in stereocontrol.

Consideration was also given to the over-reduction of the malononitriles, where a second reduction of the remaining nitrile may be observed after desymmetrisation. Pleasingly, only a minimal amount of diamine was detected (~5%), giving a high *mono-* to *di-* ratio rationalised by the large steric bulk of the attached boronate before workup and its inability to fit the ligand's steric pocket.

The nitrile reduction is commonly followed by amine protection, for which several suitable protecting groups could be incorporated (Boc, Bn, Bz). A diverse range of substituents and substitution patterns were tolerated at the methylene position with no additional reduction observed for aryl ester, nitro, or nitrile substituents. Replacement of either the aryl or benzyl ring for a variety of extended aromatic systems and heteroarenes gave excellent results (**2**), although a small drop in enantioselectivity is observed when the benzyl group is

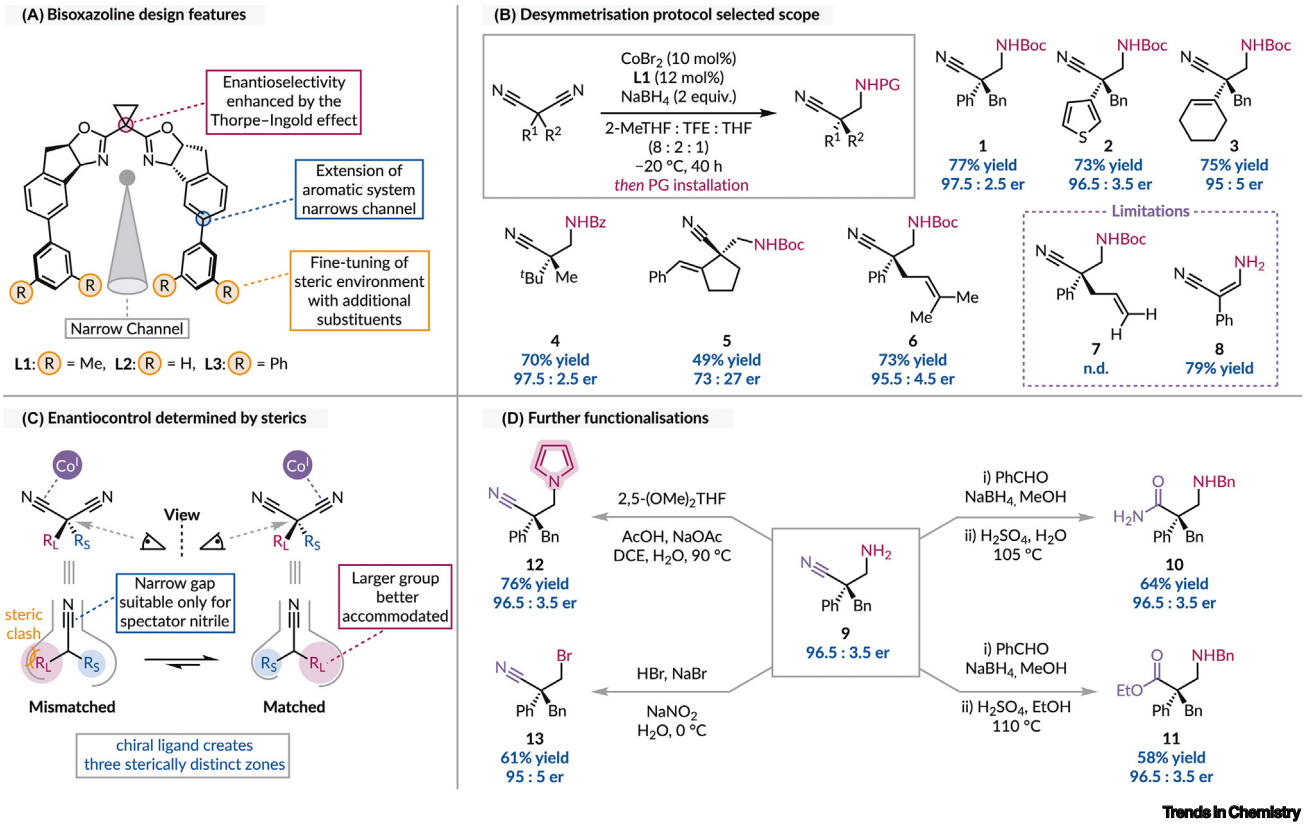

Figure 1. Overview of Huang and colleagues' cobalt-catalysed desymmetrisation of malononitriles.

replaced with short-chain alkyl substituents. This loss of optical purity can be reinstated by switching to extended-chain alkanes. Interestingly, the desymmetrisation of dialkyl substituted malononitriles (**4**) retains excellent enantioselectivity, but an observed limitation was cyclic systems (**5**), which gave both reduced asymmetric induction and yield. The inclusion of an allyl group (**7**) highlights an intolerance for unhindered alkenes as they are reduced to give saturated side chains upon desymmetrisation (Figure 1B). Fortunately, increasing the steric bulk, as exemplified by a trisubstituted olefin (**6**), exclusively leads to the formation of the desymmetrised product with no alkene reduction, including decorated internal cyclic olefins (**3**). Monosubstituted malononitriles are unsuitable substrates, forming acrylonitrile-based compounds instead (**8**).

The resulting products of the desymmetrisation allow for the synthesis of small chiral molecules that can undergo further functional group interconversions to produce synthetically diverse chiral scaffolds (Figure 1D). Treatment of the benzyl-protected desymmetrisation product with either water or ethanol at low pH yields a straightforward route to the corresponding amide (**10**) or ester (**11**). Alternatively, the free amine can be converted to pharmaceutically relevant targets (**12**) or undergo a Sandmeyer reaction to yield an alkyl bromide (**13**), further broadening its synthetic utility.

In summary, Huang and coworkers' report has set the stage for the enantioselective reductive desymmetrisation of disubstituted malononitriles. Their unique approach demonstrates a straightforward modular avenue to produce valuable enantioenriched nitrile compounds whilst illustrating the challenges and limitations, such as the reduction of sensitive decorative groups and the necessity for disubstituted malononitriles. Further extension of this catalytic system to tackle related asymmetric transformations, such as kinetic and dynamic kinetic resolutions of racemic nitrile compounds, represents a promising avenue to enhance the versatility of this protocol. Similarly, the mode of enantiocontrol used here could be adapted to other synthetically useful linear functional groups (allenes, azides, isocyanates). In addition, the reliance on only a single chelating nitrile group unlocks exciting opportunities to investigate substrates containing more distal nitrile groups. Overall, this report sets the foundation for a new catalytic asymmetric desymmetrisation platform, which may

be translatable into distinct areas of enantioselective catalysis.

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Declaration of interests

The authors declare no competing interests.

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