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Asymmetric transfer hydrogenation of \( \alpha \)-ketoamides; highly enantioselective formation of malic acid diamides and \( \alpha \)-hydroxyamides

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**ABSTRACT:** The asymmetric transfer hydrogenation (ATH) of \( \alpha \)-keto-1,4-diamides using a tethered Ru/TS-DPEN catalyst was achieved in high ee. Studies on derivatives identified the structural elements which lead to the highest enantioselectivities in the products. The \( \alpha \)-keto amide reduction products have been converted to a range of synthetically valuable derivatives.

The asymmetric transfer hydrogenation (ATH) of ketones using Noyori-Ikariya catalysts, including their tethered derivatives, has been widely reported, notably for acetophenone derivatives, and acetylenic and fluorinated ketones.\(^1\) In contrast, the ATH of \( \alpha \)-keto amides has not been explored in detail,\(^6\) even though they are useful intermediates towards pharmaceutical targets and ligands for asymmetric catalysis.\(^7\) A report by Bhanage and Mishra, using the 3C tethered catalyst 2, demonstrated a practical approach to the synthesis of asymmetric mandelineimides,\(^8\) (Figure 2A). ATH of \( \alpha \)-keto/enol lactams, coupled to dynamic kinetic resolution (DKR), using catalyst 3, gave products in high dr and ee (Figure 2B).\(^9\) Other catalytic methods have also been used for the asymmetric reduction of \( \alpha \)-keto amides, including biocatalysis,\(^10\) Cu-catalysed hydrosilylation,\(^11\) and asymmetric hydrogenation.\(^12\) ATH of the closely-related \( \alpha \)-ketoimides in high ee, using Noyori-Ikariya catalysts (Figure 2C) was reported by Liu et al.\(^13\) The ATH of analogous \( \alpha \)-ketoesters, using the same class of catalyst, has also been reported in detail.\(^14\)

**Figure 1.** Noyori-Ikariya catalysts used in Asymmetric Transfer Hydrogenation (ATH) of ketones and imines.

Given the limited work in this area and noting that previous studies have largely focused on aromatic or cyclic substrates, we investigated the ATH of \( \alpha \)-keto-1,4-diamides (Figure 2D). Apart from being a novel class of substrate for ATH, the second amide group provides a useful function for further elaboration of the ATH products. This led to the development of a practical enantioselective synthesis of malic acid diamides, determination of which structural features of the substrate were required for high enantioselectivities, and the extension to related non-aromatic \( \alpha \)-ketoamide reductions.

Substrates were prepared by addition of lihiated amides to oxoacetates (see the Supporting Information). In several cases, the substrates were enol/keto mixtures. For ATH reactions, formic acid:triethylamine 5:2 azetropere (FA/TEA) was used as the reducing agent, with reactions carried out at rt using 1.5 mol% of catalyst, with dichloromethane (DCM) to improve substrate solubility.\(^1\) In the first series, for consistency, the distal amide was the \( N \)-methyl-\( \text{V} \)-phenyl derivative in most cases (Figure 3). With a NMePh on each amide, the product (5) was

**Figure 2.** Previous reports on the reduction of \( \alpha \)-keto amides, and close derivatives, to alcohols using ATH, and the work in this report. FA/TEA = 5.2 Formic acid:triethylamine azetropere.
essentially racemic, however changing one amide to NMeBn resulted in formation of product 6 in an improved 77% ee, whilst with NMeBn on each amide, the ee rose to 94% (7). Use of NMe2 on the proximal amide gave product 8 in just 76% ee whereas replacement with NMeCy gave a better result, with product 9 formed in 79% ee. Introduction of NMeCy on both amides gave a product 10 of 95% ee, indicating that the NMePh distal amide was not optimal. Allyl and propargyl derivatives gave products of 77% ee (11) and 88% ee (12) respectively, with an improved 94% ee for the product 13 with an N-allyl on both amides. A substrate with a diphenylamide gave a very poor result of just 31% ee for product 14. An improvement to the ee was observed using a secondary aromatic amide proximal to the ketone (15; 91% ee), and a thioamide derivative of this was also compatible (16; 89% ee). The homogenated analogue of 5, i.e. 17, was formed in a low ee of just 16%, revealing the importance of each amide group. Deletion of the methyl group from the distal amide, gave a ketone that was reduced to product 18 in a further improved 95% ee, indicating a further element for substrate optimisation. The absolute configuration (R) of the product in this case was found to be opposite (by chiral HPLC) to the compound formed from commercially available (S)-malic acid. The configuration of the other products were assigned by analogy with 18. Finally, it was shown that ester derivatives of the compounds were also compatible with the reductions, although reduced in slightly lower enantioselectivity; 77% ee (19) and 84% ee (20) respectively.

The absolute configuration of (R)-18 serves to confirm the configuration of the product. Extension of this approach to further substrates (Figure 6, products 21-25) was formed in just 76% ee whereas replacement with NMePh gave a product of essentially racemic, however changing one amide to NMeBn resulted in formation of product 6 in an improved 77% ee, whilst with NMeBn on each amide, the ee rose to 94% (7). Use of NMe2 on the proximal amide gave product 8 in just 76% ee whereas replacement with NMeCy gave a better result, with product 9 formed in 79% ee. Introduction of NMeCy on both amides gave a product 10 of 95% ee, indicating that the NMePh distal amide was not optimal. Allyl and propargyl derivatives gave products of 77% ee (11) and 88% ee (12) respectively, with an improved 94% ee for the product 13 with an N-allyl on both amides. A substrate with a diphenylamide gave a very poor result of just 31% ee for product 14. An improvement to the ee was observed using a secondary aromatic amide proximal to the ketone (15; 91% ee), and a thioamide derivative of this was also compatible (16; 89% ee). The homogenated analogue of 5, i.e. 17, was formed in a low ee of just 16%, revealing the importance of each amide group. Deletion of the methyl group from the distal amide, gave a ketone that was reduced to product 18 in a further improved 95% ee, indicating a further element for substrate optimisation. The absolute configuration (R) of the product in this case was found to be opposite (by chiral HPLC) to the compound formed from commercially available (S)-malic acid. The configuration of the other products were assigned by analogy with 18. Finally, it was shown that ester derivatives of the compounds were also compatible with the reductions, although reduced in slightly lower enantioselectivity; 77% ee (19) and 84% ee (20) respectively.

The established absolute configurations indicate that reduction takes place through an approach which places the amide adjacent to the ketone close in proximity to the \( \eta^1 \)-arene ring of the catalyst. Stabilisation of this approach through a hydrogen bond, as indicated in Figure 5, would be in agreement with what has been speculated for the cyclic substrate reduction in Figure 2B, and for a previously-reported ATH of a cyclic ketone containing an amide group.15 This approach would also accommodate the most bulky groups, which would be able to rotate away from the complex.

![Figure 3](image3.png) **Figure 3.** Products of ATH of diamides (Figure 2D) where the distal amide is NMePh in most cases. The configuration (R) of 18 was established by comparison to a sample from (S)-malic acid, and configurations of the other products were assigned by analogy. Configuration not assigned to 5, 14 and 17 due to low ee.

A second series of compounds, in this case with a piperidine at the distal amide, were investigated next (Figure 4). These gave ATH products of generally high ee, with products of exceptionally high ee in the best cases (24-30). Again, substrates containing secondary amides with either an aromatic or an alkyl group proximal to the ketone gave products of highest ee. Extension of the chain in the substrate by one carbon gave a product in slightly lower ee (31; 94% ee). The highest enantioselectivity (99% ee) was observed for product 27 containing a hindered amide, indicating that a combination of steric and electronic factors were important. A small range of other ATH catalysts were tested in the formation of 27 and gave products in lower ee than (R)-2 (see the Supporting Information). The absolute configuration of (R)-25 was determined by X-ray crystallography (Supporting Information). The ester derivative 32 was also formed in a high 98% ee and high yield.

The use of a hindered amide adjacent to the ketone was extended to further substrates (Figure 6, products 33-37). A substrate with an ester in the position of the more distal amide, i.e. 33, gave a similar result (98% ee). An X-ray crystal structure of 33 (Supporting information) served to confirm the configuration of the product. Extending the chain to the ester reduced the ee to 68% (product 34). Product 35 containing a butyl chain was formed in 96% ee, and a substrate with a benzyl group was reduced to 36 in a remarkable 98% ee, although a β-Ph product (37) was formed in just 23% ee. Ester-containing products were formed in good range of 90-93% ee in cases where the proximal tertiary amide was piperidine or morpholine-derived or contained an N-benzyl group (39-42), but much lower for an NMePh-derived amide (38) only 54% ee. The N-propyl product 42 which was formed in 90% ee, is a potential intermediate in the synthesis of CA074, a ligand used to obtain an X-ray structure of a cysteine protease linked to a parasitic disease.15 To prepare the required enantiomer for this application, (S)-42 was formed, using catalyst (S,S)-2. Other products containing a linear alkyl side chain were also formed from the NHPh amide (43; 93% ee), the NHEt amide (44; 90% ee) and Weinreb amide (45; 81% ee) with a gradually decreasing enantioselectivity across this series. Finally, an analogous ester-controlled comparator reduction gave a product (46) of 80% ee whilst a very challenging substrate with equidistant ester vs amide directing groups, gave a product (47) of just 4% ee.
Figure 6. Extended range of ATH products (Figure 2D). The optical rotation of (R)-46 matched that reported. Other configurations were assigned by analogy with the X-ray structure of 33 and the results in Figures 3 and 4. Product 42 was formed using (S,S)-2. Configuration not assigned to 37 due to low ee.

The application was found to be to some extent extendable to ATH/DKR of a range of substrates. Whilst the product drs were not high, in some cases the ees were (Figure 7). These results represent a complex picture and are the subject of ongoing studies.

Figure 7. ATH/DKR products, formed using catalyst (R,R)-2, with 5:2 formic acid:triethylamine azeotrope (FA/TEA).

Using amino acid derivative 51 for the formation of 52, ketoamide substrate 53 was prepared. From this, a precursor (54) of a ring-opened form of a cathepsin L inhibitor 55 \(^1\) was prepared using the ATH methodology (Figure 8A). Catalyst (S,S)-2 gave an excellent result in terms of dr, as the directing effects of catalyst and substrate are matched. In contrast the (R,R)-catalyst gave a less selective result; a 18:82 dr mixture was formed.

Curtius rearrangements of the reduction products were investigated (Figure 8B). TBS-protected 33, was hydrolysed to the acid, however a significant amount of what appeared to be the cyclic oxazolidinone product was formed in the attempt at the Curtius reaction. We reasoned that a tertiary amide would be less likely to cyclise. The acid from 38 was formed in racemic form and was converted to the Curtius product in 25% yield (see the Supporting Information). Alcohol 39 (90% ee) was converted, via 56, to the Boc-containing Curtius product 57 in three steps in 89% ee. TBS derivatives of 40 and 41 were also prepared, however attempts at hydrolysis led to decomposition.

The reduction of a number of derivatives gave dihydroxy amines and one dihydroxy amide using LiAlH\(_4\) and NaBH\(_4\) respectively (Figure 8C). LiAlH\(_4\) gave full reduction with minimal loss of ee in the cases tested, furnishing a range of diamines in high ee. There was no need to protect the alcohol groups. Derivatives of 60 have been reported in studies of anti-Alzheimer’s agents. \(^14\) The reduction of (R)-33 (98% ee) to the aminodiol, using LiAlH\(_4\), was also successful but the ee could not be determined.

In conclusion, we report a practical and enantioselective asymmetric transfer hydrogenation (ATH) of \(\alpha\)-keto-1,4-diamides to malic acid diamides in high ee. Variation of the substrate structure permitted the identification of which structural features are required for the highest enantioselectivities, and these observations allowed the extension of the methodology to a wider range of \(\alpha\)-keto amides, which are relatively under-reported as ATH targets. To our knowledge, these results represent the first reports of ATH of the substrates studies.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, NMR spectra, X-ray crystallographic data for CCDC 2100850 and 2100851, and HPLC data (PDF).

Data sharing statement. The research data (and/or materials) supporting this publication can be accessed at http://wrap.warwick.ac.uk/TBA.

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Notes
The authors declare no competing financial interests.
ACKNOWLEDGMENT

We thank The Royal Society (UK) and the Science and Engineering Research Board (SERB, India) for funding VKV through an SERB-Newton International Fellowship (NIF/R1/180142). We thank Warwick University for a Chancellor’s International Scholarship (to SKG). Crystallographic data were collected using an instrument (described in the Supporting Information) purchased through support from Advantage West Midlands (AWM) and the European Regional Development Fund (ERDF). The authors thank Johnson Matthey (Cambridge) for a gift of catalyst (R)- and (S)-2.

Keywords: Asymmetric catalysis • ketone reduction • alcohols • ruthenium – malic acid diamides - α-keto-1,4-diamides.

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