

ChemComm

Chemical Communications

rsc.li/chemcomm



ISSN 1359-7345

COMMUNICATION

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Cite this: *Chem. Commun.*, 2020, 56, 9094

Received 21st April 2020,
Accepted 29th June 2020

DOI: 10.1039/d0cc02881a

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Conversion of racemic alcohols to optically pure amine precursors enabled by catalyst dynamic kinetic resolution: experiment and computation†

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An unprecedented base metal catalysed asymmetric synthesis of α -chiral amine precursors from racemic alcohols is reported. This redox-neutral reaction utilises a bench-stable manganese complex and Ellman's sulfinamide as a versatile ammonia surrogate. DFT calculations explain the unusual finding of the highly stereoselective transformation enabled by a catalyst that undergoes an unusual dynamic kinetic resolution.

Chiral primary amines are of great importance in the pharmaceutical and agrochemical industries. In fact, at least 40% of the optically active drugs are chiral amines. Biocatalytic kinetic resolution of racemic amines with 50% maximum yield is probably the most widely practiced method for the production of enantiopure primary amines. Additionally, hydrogenation using man-made catalysis (transition-metal catalysis and organo-catalysis), which requires hydrogen gas under high pressure or stoichiometric amounts of a reductant, often involves the use of hard to remove protecting groups. Besides, methods involving chemoenzymatic dynamic kinetic resolution, cascade deracemization of racemic amines, have been reported.¹

The hydrogen autotransfer (HA) strategy has captured much attention during the last few years, mainly due to its synthetic importance as a powerful environmentally benign approach for the construction of C–C and C–N bonds. In this regard, progress has been made in transition-metal catalysed C-alkylations and N-alkylations with non-activated alcohols.

The reactions mainly rely on the production of achiral or racemic products.²

The direct asymmetric amination of alcohols to produce chiral aniline,³ amino alcohols,⁴ oxazolidinones,⁵ and hydrazones⁶ has been demonstrated using ruthenium and iridium catalysis. In contrast, the direct production of chiral primary amines from racemic alcohols is significantly more challenging. In this regard, a ruthenium catalysed protocol was disclosed. However, this noble metal method is limited to the methyl substituted chiral amines.⁷ Apart from metal catalysis, the use of a dual enzymatic system for the direct amination of secondary alcohols has been reported.⁸ Therefore, the development of a new catalytic system, ideally based on a non-precious metal catalyst,⁹ which can transform a broad range of racemic alcohols to enantiopure primary amines, is an elusive goal.¹⁰

Ellman's sulfinamide represents as an industrially relevant reagent, frequently used as an ammonia surrogate in the synthesis of enantiopure primary amines.¹¹ This transformation typically requires three chemical steps, *i.e.*, stoichiometric

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† Electronic supplementary information (ESI) available: Full experimental and computational details and optimised Cartesian coordinates. See DOI: 10.1039/d0cc02881a



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Luis Miguel Azofra loves Quantum Chemistry as much as the sea. The latter was a gift he received for being born in the Canary Islands, the first is a passion he learned during his PhD in Prof. Alkorta's lab (CSIC, Spain). In 2015, Dr Sun and Prof. MacFarlane introduced him to the field of catalysis (Monash University, Australia), and in 2016 he joined Prof. Cavallo's group as an in silico designer (KAUST, Saudi Arabia). Currently, Dr Azofra is an early-career research leader at Universidad de Las Palmas de Gran Canaria, where he combines his efforts as a researcher and lecturer.

oxidation, condensation using stoichiometric titanium reagent and stoichiometric reduction, producing large quantities of waste.

Encouraged by recent studies on metal catalysed hydrogen autotransfer,^{2,12,13} we envisioned that an effective base-metal catalyst might potentially catalyse the oxidative dehydrogenation of the *sec*-alcohols (*rac*-**1**), to form the corresponding ketone and shuttle the abstracted hydrogen required for the stereoselective hydrogenation. The *in situ* formed ketone undergoes condensation with an ammonia equivalent to produce an imine and only water as a by-product. Finally, the imine will be reduced in a stereoselective fashion to produce the desired product. The chemoselectivity of the reaction depends on the potential of the metal catalyst to return the stored hydrogen to the final product.

Herein, we present a new manganese catalysed synthesis of optically active amines from racemic alcohols. Interestingly, our DFT mechanistic study on this stereoselective reaction explains how a racemic catalyst could lead to optically pure product. Notably, we found that the high stereocontrol is enabled by unusual catalyst dynamic kinetic resolution (Scheme 1a). The chiral imine intermediate kinetically discriminates the catalyst racemic mixture (Scheme 1b). While only one enantiomer of the catalyst can be involved in the stereoselective hydrogenation reaction, the ketone intermediate plays the crucial role in the racemisation of the second catalyst enantiomer (Scheme 1a). We are not aware of a literature report with such an unusual observation.

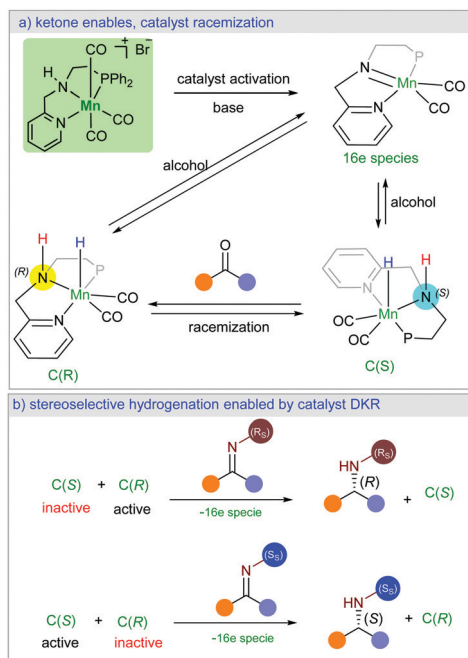
We started our study with the selection of the appropriate base metal catalyst and the optimisation of the suitable reaction parameters. After careful investigations, we found that the use of the air stable PNN-Mn complex (5 mol%) in combination

Table 1 Manganese catalysed asymmetric amination of *sec*-alcohols^a

Product	Yield (%)	dr
(<i>R,R</i>)- 3a	85%	99:1 dr
(<i>R,R</i>)- 3b	80%	98:2 dr
(<i>R,R</i>)- 3c	65%	98:2 dr
(<i>R,R</i>)- 3d^b	74%	97:3 dr
(<i>R,R</i>)- 3e	87%	97:3 dr
(<i>R,R</i>)- 3f	85%	99:1 dr
(<i>R,R</i>)- 3g	83%	98:2 dr
(<i>R,R</i>)- 3h	95%	98:2 dr
(<i>R,R</i>)- 3i^f	70%	95:5 dr
(<i>R,R</i>)- 3j	76%	98:2 dr
(<i>R,R</i>)- 3k^c	84%	94:6 dr
(<i>R,R</i>)- 3l^b	80%	94:6 dr
(<i>R,R</i>)- 3m^{b,d}	86%	97:3 dr
(<i>R,R</i>)- 3n	55%	93:7 dr
(<i>R,R</i>)- 3o^{b,d}	74%	82:18 dr
(<i>R,R</i>)- 3p^c	89%	93:7 dr
(<i>R,R</i>)- 3q	78%	84:16 dr
(<i>R,R</i>)- 3r^{b,d}	86%	96:4 dr
(<i>R,R</i>)- 3s^{b,d}	90%	92:8 dr
(<i>R,R</i>)- 3t^{b,d}	83%	80:20 dr
(<i>R,R</i>)- 3u^{b,d}	65%	95:5 dr

X = S, (*R,R*)-**3s^{b,d}** 90%, 92:8 dr
X = O, (*R,R*)-**3t^{b,d}** 83%, 80:20 dr

^a Reaction conditions: **1** (0.75 mmol), (*R*)-**2a** (0.5 mmol), [Mn] (0.025 mmol) and Cs₂CO₃ (0.05 mmol) in *t*-amyl alcohol (1 mL) were stirred at 140 °C (aluminum block), for 16 h in a glass tube under argon. Yields after column chromatography are given. ^b [Mn] (0.05 mmol), Cs₂CO₃ (0.1 mmol). ^c 48 h. ^d **1** (1 mmol).



Scheme 1 Manganese-catalysed diastereoselective hydrogen autotransfer.

with Cs₂CO₃ (10 mol%) and *t*-amyl alcohol (0.5 M) is the optimal combination for this reaction (see the ESI† for details).

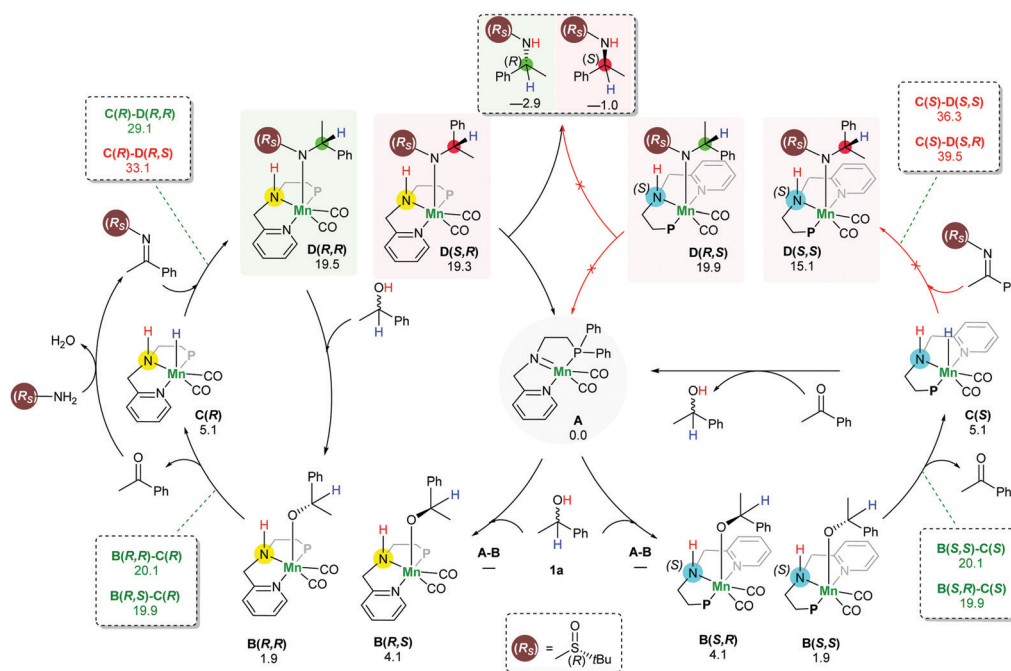
Next, the variability and the applicability of the asymmetric hydrogen autotransfer reaction were investigated (Table 1). We initially explored different racemic benzylic alcohols. The alcohols **1a–1i** bearing different electron donating and electron withdrawing groups were applicable without significant effect on the reactivity or the stereochemical outcome and all desired products **3a–3i** were isolated in very good yields and optical purity. Similarly, the naphthyl substituted sulfinamide (*R,R*)-**3j** was isolated in very good yield and selectivity. Importantly, some of these amines are key intermediates in the synthesis of pharmaceuticals and bioactive molecules. For example, carpropamid,¹⁴ an agriculture fungicide, can be prepared from (*R,R*)-**3b**, whereas the Alzheimer's and Parkinson's drug rivastigmine can be produced using the sulfinylamine (*S,S*)-**3g**.¹⁵ It is noteworthy that the classical synthesis of these α -chiral amines involves the addition of MeLi to *N*-*tert*-butylsulfinyl

aldehydes. However, this reaction often suffers from unfavourable diastereocontrol, even at lower temperature. To our delight, our catalytic system was found not to be limited to the *sec*-phenethyl alcohol derivatives. Thus, 1-tetralol (**1k**) was converted to the desired product in 84% yield. This amine is of relevance as it is used in the synthesis of diverse bio-related compounds.¹⁶ The ethyl substituted alcohol **1l** and the more challenging alcohol **1m** were found to be reactive using the presented catalytic system. With this success, we turned our attention to the more demanding non-benzylic alcohols **1n–1q**. The chiral amines bearing a cyclohexyl substituent (R,R_s)-**3n** and cyclopropyl substituent (R,R_s)-**3p** were produced in a very good diastereomeric ratio as well. Interestingly, the amphetamine, which is used in the treatment of attention deficit hyperactivity disorder, can be obtained from the *rac*-**1q** in 78% yield. Heterocycle-containing alcohols were also tolerated and underwent the reaction to afford the chiral amine precursors (R,R_s)-**3r** to (R,R_s)-**3u** in very good yields and with high diastereoselectivity. Interestingly, despite the importance of the optically pure **3s** and **3r** in the synthesis of HIV protease inhibitors,¹⁷ the asymmetric synthesis of the corresponding primary amines is not yet reported. It is noteworthy that even pyridine containing substrates and products, such as **3u** are tolerated in this manganese catalysed reaction.

In order to understand the origin of the stereoselective hydrogenation, we have carried out DFT modelling for the asymmetric amination of 1-phenylethanol (Scheme 2). The 16e species **A**, which can be generated by treating the manganese pre-catalyst [Mn] with appropriate bases, dehydrogenates the alcohol substrate *rac*-**1a** to produce acetophenone and manganese hydride complex **C**. Based on our DFT results, the

alcohol dehydrogenation step takes place in a stepwise fashion *via* the formation of four different diastereoisomers of manganese alkoxide intermediates **B**, bearing chiral nitrogen and carbon atoms. However, the proton transfer **A–B** is a barrier-less process. The calculated free activation energy for the hydride transfer **B–C** steps are between 19.9 and 20.1 kcal mol⁻¹ at the M06/TZVP level of theory. The β -hydride elimination will lead to the formation of a racemic mixture of the hydrogenated catalyst **C(S)** and **C(R)**.

The condensation reaction between the *in situ* generated ketone and (R_s)-**2** results in the generation of a C=N bond which can be potentially hydrogenated by the action of racemic manganese catalyst **C(S)** and **C(R)**. Similarly, to the alcohol substrate dehydrogenation, we found that the hydrogenation of the imine intermediate takes place *via* a stepwise mechanism. Since the hydrogenated catalyst exists as a racemic mixture, it establishes the possibility of the hydride transfer (**C–D**) to form four different intermediates **D**. Importantly, we found that the hydride transfer step (**C–D**) is the rate determining step as well as the stereodetermining step. When the manganese catalyst **C(R)** was used for the hydrogenation of an imine bearing (R)-sulfinamide group, the computed barrier for the hydride transfer is 29.1 kcal mol⁻¹ for the creation of a new (R) stereogenic centre, while the barrier for the generation of the (S) stereogenic centre is 33.1 kcal mol⁻¹. On the other hand, the barriers for the hydride transfer using the catalyst enantiomer **C(S)** are 39.5 and 36.3 kcal mol⁻¹. Interestingly, when an imine bearing (S)-sulfinamide group is used as a substrate, only the (S) enantiomer of the catalyst is involved in the imine hydrogenation step and creates a new stereogenic centre with the (S) configuration. With this process being controlled by kinetics, it



Scheme 2 Proposed reaction mechanism for the stereoselective manganese catalysed hydrogen autotransfer amination of *rac*-alcohols. Free reaction and activation energies (at 140 °C) are shown in kcal mol⁻¹ at the M06/TZVP level using toluene as a solvent.

supposes a diastereoisomeric ratio equal to 99:1. This is fully in agreement with our experimental results.

The last step involves the proton transfer to the product nitrogen atom. The proton could be internally transferred from the catalyst NH group to generate the product and the 16e species **A**. Alternatively, in the presence of excess *rac*-**1a**, direct proton transfer from the alcohol substrate could take place to produce the desired product and the intermediates **B** without the regeneration of the 16e species **A**.¹⁸ Notably, calculations show that the undesired catalyst enantiomer **C(S)** can be easily racemised with the assistance of the acetophenone intermediate. In other words, the steps **C(S)**–**B(S,R)**, **C(S)**–**B(S,S)**, **B(S,S)**–**A** and **B(S,R)**–**A** are reversible. We are not aware of a previously reported mechanism with a similar observation of the catalyst racemisation assisted by the *in situ* generated intermediate.

In conclusion, we have developed an unprecedented base-metal catalysed stereoselective amination of racemic alcohols using the hydrogen autotransfer strategy. The produced enantiomerically pure sulfinamides could be easily converted to the corresponding α -chiral amine upon stirring in methanolic HCl at room temperature.¹⁹ Notably, the protocol uses an inexpensive earth-abundant manganese complex and readily available substrates. Our DFT calculations demonstrate the origin of high diastereoselectivity which is enabled by an unusual catalyst dynamic kinetic resolution process. We found that the alcohol dehydrogenation and imine hydrogenation reactions occur in a stepwise fashion, while the hydride transfer to the imine intermediate represents the rate and stereodetermining step of the whole reaction. Given the operational simplicity, the presented catalytic system will serve as a basis for further application in the synthesis of relevant optically pure α -chiral amines and heterocycles.

L. M. A. thanks Universidad de Las Palmas de Gran Canaria (ULPGC) for support. Gratitude is also due to the KAUST for use of the supercomputer Shaheen II for providing the computational resources.

Conflicts of interest

There are no conflicts to declare.

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