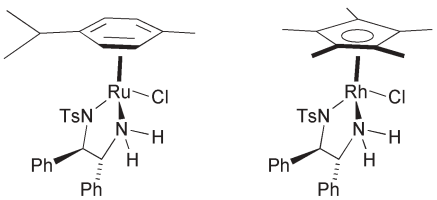
One-pot formation of nitrogen-containing heterocyclic ring systems using a deprotection–cyclisation–asymmetric reduction sequence†‡

Glynn D. Williams,[a] Charles E. Wade[b] and Martin Wills*[a]

Received (in Cambridge, UK) 1st July 2005, Accepted 2nd August 2005
First published as an Advance Article on the web 26th August 2005
DOI: 10.1039/b509231k

A one-pot sequence of amine deprotection, intramolecular C=N bond formation and subsequent asymmetric reduction may be promoted by a ruthenium catalyst.

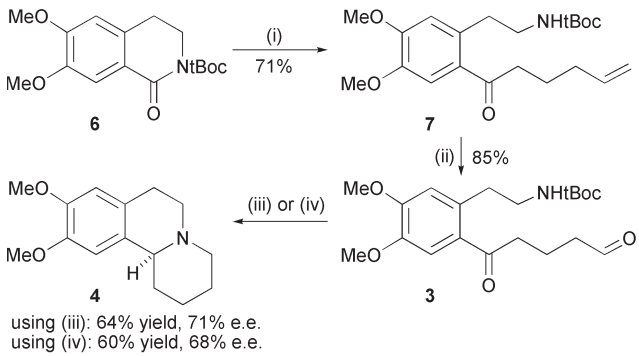
The catalytic asymmetric reduction of C=N bonds represents a highly practical and efficient method for the synthesis of enantiomerically pure amines.[1] Previously reported methods for this process include hydrogenation (*i.e.* with hydrogen gas),[2] hydrosilylation[3a,3b] and reduction with borane.[3c] In the mid-1990s, Noyori reported the efficient asymmetric reduction of cyclic imines using ruthenium–TsDPEN complex **1**.[4] In 1999, Baker reported that structurally-related Rh(III) complexes **2** could also be successfully employed in this application.[5] Since these early reports, many other groups have reported synthetic applications of asymmetric transfer hydrogenation (ATH) of C=N bonds.[6] Whilst the majority of the interest in this area is focused on Ru(II) complexes, the Rh(III) derivatives have been developed commercially by Avecia.[7]



R,R-**1** *R,R*-**2**

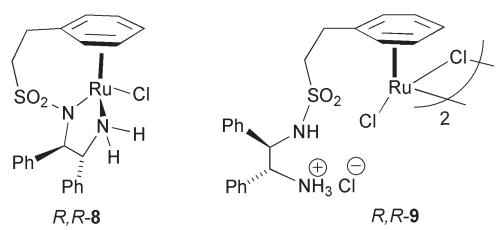
As a part of our own ongoing studies into ATH reactions, we have reported the one-pot conversion of *t*Boc-protected ketoamines into cyclic amines in high enantioselectivity. In our studies we utilised the Ru(II) catalyst **1**.[8] In this paper, we report the extension of our studies of this enantioselective reductive amination process to more complex systems, and demonstrate that two rings can be formed in a single enantioselective process.

In order to establish the scope of the reductive amination, we first wished to investigate the transformation of ketoaldehyde **3** into the tricyclic product **4**. Towards this end, substrate **3** was prepared using the sequence in Scheme 1. The reaction of



Scheme 1 *Reagents and conditions:* (i) CH_2=$CH(CH_2)_3MgBr$ **5**, THF. (ii) OsO_4, $NaIO_4$, dioxane–H_2O. (iii) HCO_2H, then Et_3N and 2 mol% catalyst *R,R*-**1** (formed *in situ*), MeCN, 3 h. (iv) HCO_2H, then Et_3N and 2 mol% catalyst *R,R*-**8** (formed *in situ* from 1 mol% dimer **9**), MeCN, 2 h.

Grignard reagent **5** with the known Boc lactam **6** resulted in formation of the ketone **7** in 71% isolated yield. Oxidative cleavage of the terminal double bond in **7**, using the osmium-catalysed periodate conditions reported by Johnson,[9] then gave the required dicarbonyl compound **3** in 85% yield. When subjected to our conditions for asymmetric one-pot reductive amination, **3** was converted to **4** in 64% isolated yield and 71% enantiomeric excess [determined by chiral HPLC against a racemic standard prepared by TFA-catalysed cyclisation of **3** and reduction with $NaBH(OAc)_3$]. In view of the relative complexity of the process, this was considered a pleasing result. We also took the opportunity to test our tethered catalyst **8**, which we have previously reported and is formed *in situ* by exposure of dimer **9** to the reaction conditions.[10] In the event, **8** gave a very similar result to that obtained with **1**. At present, the configuration of **4** has been assigned by analogy with that of known cyclic substrates, and has not been confirmed.



R,R-**8** *R,R*-**9**

Having obtained a promising result, we wished to establish whether we could extend our one-pot procedure to the conversion of **10** into **11**. Although this is similar to the conversion of **3** to **4** in terms of bond formation, it provides a potential route to a number of berberine natural products with this tetracyclic ring structure.[11]

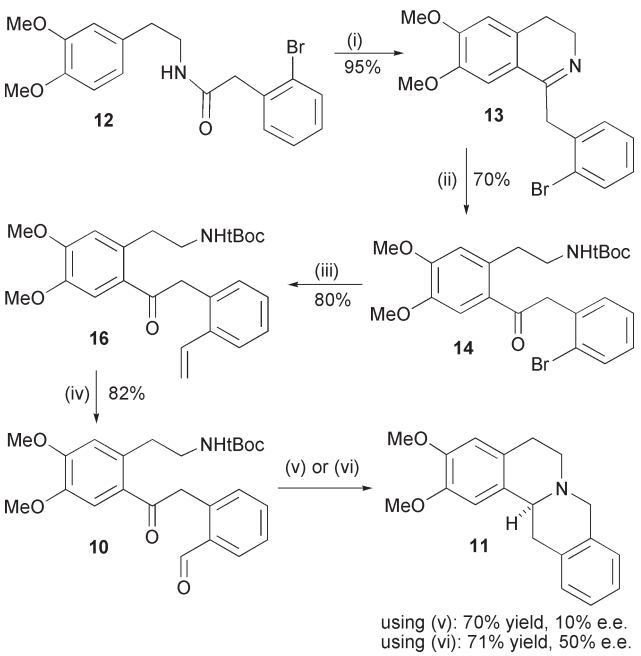
[a]*Department of Chemistry, The University of Warwick, Coventry, UK CV4 7AL. E-mail: m.wills@warwick.ac.uk.; Fax: +44 24 7652 4112; Tel: +44 24 7652 3260*
[b]*GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, UK SG1 2NY*

† Electronic supplementary information (ESI) available: Experimental procedures and characterisation data for intermediates and cyclisation products. See http://dx.doi.org/10.1039/b509231k

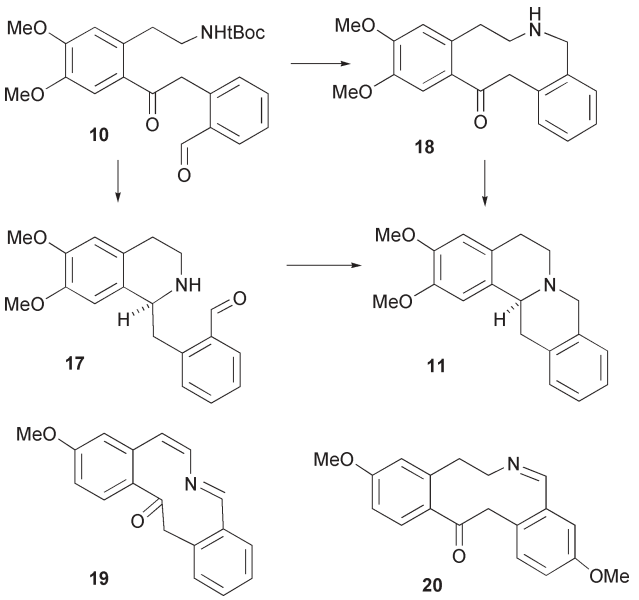
‡ Dedicated to Professor Steven V. Ley on the occasion of his 60th Birthday.

Simple berberine derivatives have been used in medicinal chemistry applications. One example is the synthesis of curare-like agents by GSK, which has been achieved through the use of an ATH step.[6a,b] The synthesis of **10** proved to be challenging, however the successful route to this is shown in Scheme 2. In this sequence, the Bischler–Napieralski cyclisation of amide **12** into cyclic imine **13** was followed by treatment with Boc anhydride and acid-catalysed ring-opening of the resultant acyliminium cation to give **14**. The use of *p*-toluenesulfonic acid was found to be essential; in its absence the formation of water-stable *N*-*t*Boc enamines was observed. A key step was the palladium-catalysed coupling[12] of **14** with potassium vinyltrifluoroborate **15** to furnish **16** in an acceptable 80% yield. Finally, oxidative cleavage of the alkene in **16** resulted in formation of the required ketoaldehyde **10**. The conversion of **10** into the cyclic amine **11** proved to be successful. Using non-tethered catalyst **1**, the product was isolated in an adequate 70% yield, but proved to be of only 10% ee. A better result was obtained using tethered complex **8**; 73% isolated yield and 50% ee. The reaction was also faster; 4 hours with **8** compared to 48 hours for full reaction using the untethered **1**. Enantiomeric excesses were calculated by chiral HPLC against a racemic sample prepared from **10**. The lower ee for the formation of **11** compared to **4** may reflect the similarity of the functional groups flanking the intermediate imine.

The mechanism of the cyclisation–reduction process has not been fully determined. However, two synthetic courses can be envisaged (Scheme 3). In the first of these, a six-membered ring is formed and reduced asymmetrically to give **17**, then a second ring is built upon this. In the second possible route, a ten-membered ring **18** is formed in the first step, then this engages in a transannular cyclisation and reduction to give the product.



Scheme 2 *Reagents and conditions:* (i) $POCl_3$, $PhCH_3$, 110 °C. (ii) Boc_2O, DMF, 90 °C, then *p*-TsOH, DMF, H_2O, 130 °C. (iii) $CH_2{=}CHBF_3{\cdot}K$ **15**, $Pd(PPh_3)_4$, $PhCH_3$, EtOH, K_2CO_3, 85 °C. (iv) OsO_4, $NaIO_4$, dioxane–H_2O. (v) HCO_2H, then Et_3N and 2 mol% catalyst *R*,*R*-**1** (formed *in situ*), MeCN, 48 h. (vi) HCO_2H, then Et_3N and 2 mol% catalyst *R*,*R*-**8** (formed *in situ* from 1 mol% dimer **9**), MeCN, 4 h.

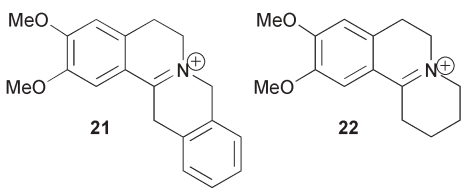


Scheme 3 Possible cyclisation modes.

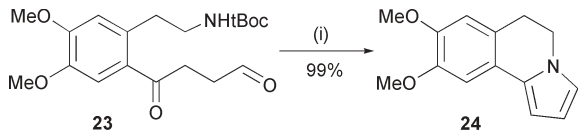
In the cyclisation of **10**, NMR inspection of the reaction mixture at 5, 10 and 24 hours revealed that there was a slow step in the cyclisation process. The first cyclisation–reduction appeared to take place slowly, but then the second reduction was rapid. The crude ^1H NMR spectrum of the intermediate suggested that it was the aldehyde which condensed first with the amine to give the imine which was slowly reduced. This was surprising because normally six-membered ring formation would be expected to outpace that of a ten-membered ring. On the other hand, aldehydes are more electrophilic than ketones and it may be that this reactivity is dominating the selectivity of the reaction.

There is some precedent to support the proposed ten-membered ring formation in the recent literature however. For example the natural products **19** and **20** have both been isolated and speculated to have been formed *via* an imine condensation,[13] even though there is an alternative possibility of formation of a smaller ring with the ketone in the molecule.

If it is indeed the case that **18** is the key intermediate on the way to **11**, then the key asymmetric step will be the reduction of the iminium cation **21**. By analogy, the iminium cation **22** would occupy a corresponding position on the pathway to **4**.



The participation of **21** and **22** in the reduction pathway may account, in part, for the decreasing enantioselectivity upon going from the smaller to the larger substrate, since the steric and electronic difference between each side of the iminium cation in **21** is significantly less than in **22**. What is less clear, however, is the reason for the improved performance of catalyst **8** over **1**. Unlike



Scheme 4 *Reagents and conditions:* (i) HCO_2H, then Et_3N and 2 mol% catalyst *R*,*R*-**1** (formed *in situ*) or TFA.

the reduction of ketones, the mechanism of imine reduction by transfer hydrogenation is not well understood. The proposal of a stereochemical model would be premature at this stage, before further data has been acquired and molecular modelling studies completed. However we believe that the improvement is probably not the result of a steric effect, because the tether is some way from the reaction sphere. It is more likely that a significant stereoelectronic effect may be operating through the ligand, for example involving the SO_2 dipole, as a result of the stereochemically-locked nature of the system.

In order to extend the methodology further, we attempted to prepare the 6,6,5 analogue of **4** through a one-pot cyclisation. However, under the reaction conditions, the pyrrole **24** was formed from the precursor **23** (Scheme 4), presumably through a Pall–Knorr process. Ketoaldehyde **23** was prepared in an analogous manner to **3**. The cyclisation, which may also be effected simply by treating **23** with TFA, may be due to the strong thermodynamic effect of forming a stable heteroaromatic structure. Adjustment of the pH to 12 with aq. NaOH promoted the precipitation of the product in essentially quantitative yield. Although **24** is a known compound,[14] we are not aware of this approach having been taken to its synthesis previously, and we are currently studying the scope of this process.

In conclusion, we have demonstrated that it is possible to form tri- or tetracyclic heterocyclic products in good yields by using a one-pot deprotection–reductive amination process. Using a transfer hydrogenation catalyst to reduce the intermediate iminium cations provides products in ees of 50–70%. Since both enantiomers of the C_2-symmetric diamine precursor of catalysts **1** and **8** are readily available, either enantiomer of imine-reduction product may be prepared using this method. We are currently studying the further applications of this methodology using alternative substrates and catalysts, including some based on Rh. The results of this study will be reported in due course.

EPSRC and GSK are thanked for financial support of this project (to GDW) through an industrial CASE award. The use of the EPSRC Chemical Database Service at Daresbury is acknowledged.[15] Mr J. C. Bickerton of the Warwick MS service and Dr B. Stein of the EPSRC MS service are thanked for their support of this project. We also acknowledge the generous loan of ruthenium salts by Johnson-Matthey Ltd.

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