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Enantioselective synthesis of β-hydroxy amines and aziridines using asymmetric transfer hydrogenation of α-amido ketones

Aparecida Kawamoto† and Martin Wills*

Department of Chemistry, University of Warwick, Coventry, CV4 7AL, UK

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Abstract

A rapid, expedient and enantioselective method for the synthesis of β-hydroxy amines and monosubstituted aziridines in up to 99% e.e., via asymmetric transfer hydrogenation of α-amido ketones, is described.

Aziridines are valuable synthetic reagents and intermediates. In particular they benefit from a high reactivity due to the small strained nitrogen-containing ring, thus permitting their rapid conversion into a range of derivatives. The synthesis of enantiomerically pure derivatives is a desirable objective since the physiological properties of both the aziridines themselves and the products formed from them are likely to be dependant on the absolute configuration.[1]

Enantiomerically enriched aziridines may be formed by the asymmetric catalysis of the addition of a nitrene onto one face of a prochiral alkene.[2] However, the most conceptually simple approach to these targets is probably through the cyclisation of an appropriate enantiomerically pure β-amino alcohol precursor.[1] Whilst a number of homochiral β-amino alcohols are available from natural sources such as amino acids, the range of materials is limited. In this paper we describe a simple and expedient route for the asymmetric synthesis of aziridines through a sequence of α-amido ketone reduction followed by cyclisation.

We have previously described the use of asymmetric transfer hydrogenation for the reduction of ketones containing α-amido groups (Scheme 1).[3] In the example shown we first employed a catalyst formed by the combination of (1*R*,2S)-*cis*-aminoindanol **1** with $[Ru(cymene)Cl_2]_2$ and isopropanol/KOH as the hydrogen source, which gave a product of 79% e.e. In subsequent studies we found that the combination of (*R*,*R*)-TsDPEN **2** with the same ruthenium complex, a system first reported by Noyori, gave marginally superior results (Scheme 1) when used with the formic acid/triethylamine hydrogen source.[3e] Since the enantioselectivities of the reductions were high, we considered that this might be a suitable method for the asymmetric synthesis of aziridines.

* Corresponding author.

† On leave from the Brazilian Space Aeronautical Institute-Praca Mal. Eduardo Gomes 50, Vila das Acacias, SJ Campos, SP Brazil.

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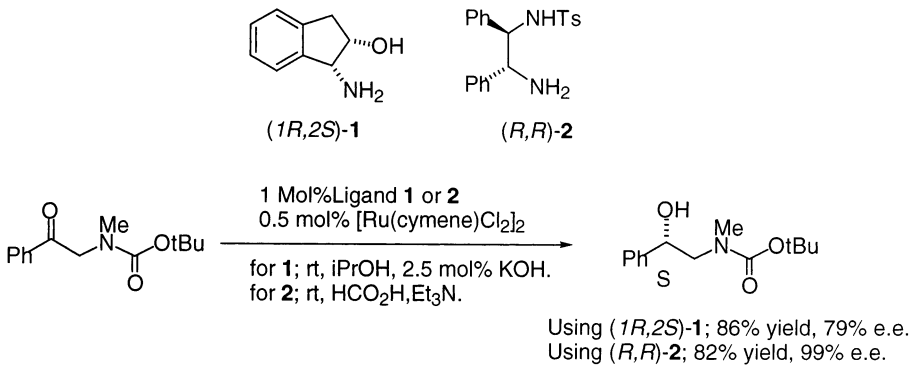
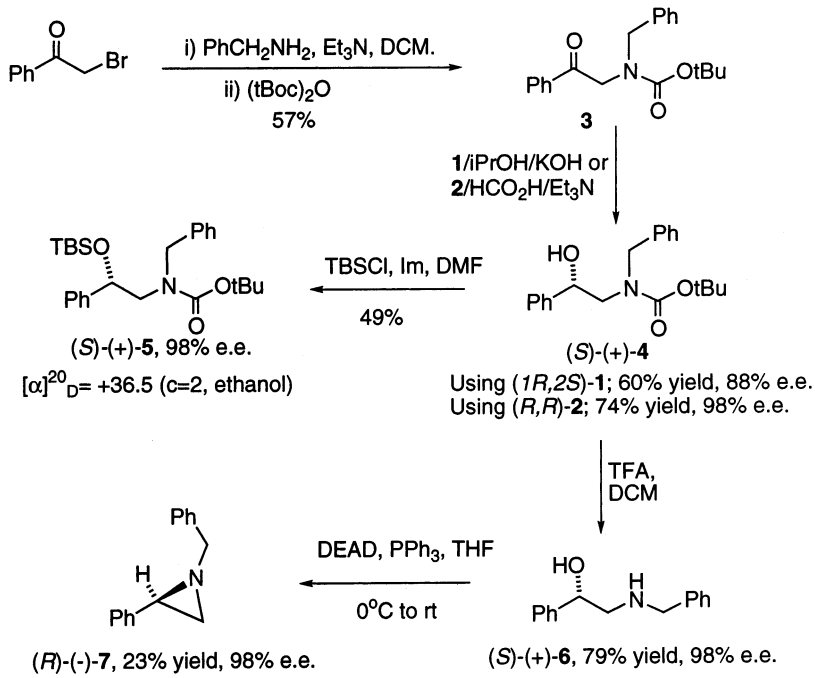


Scheme 1.

Indeed this proved to be the case. A sample of the (*N*-benzyl)(*N*-*t*Boc)-α-amino ketone **3** was prepared by the route shown in Scheme 2. A one-pot procedure was favoured for this synthesis as the intermediate *N*-benzyl-α-amino ketone appeared to be unstable under the conditions used for working up the reaction. Enantioselective reduction of **3** to the alcohol **4** was successfully achieved using both the (1*R*,2*S*)-**1**/isopropanol and (*R*,*R*)-**2**/formic acid systems. In both cases the enantiomeric excesses were measured by chiral HPLC, whilst the absolute configuration in each case was shown to be (*S*)-(+) by conversion to the *O*-*tert*-butyldimethylsilyl ether **5**.[4] The independent synthesis of (*S*)-(+)-**5** is described in a later discussion.

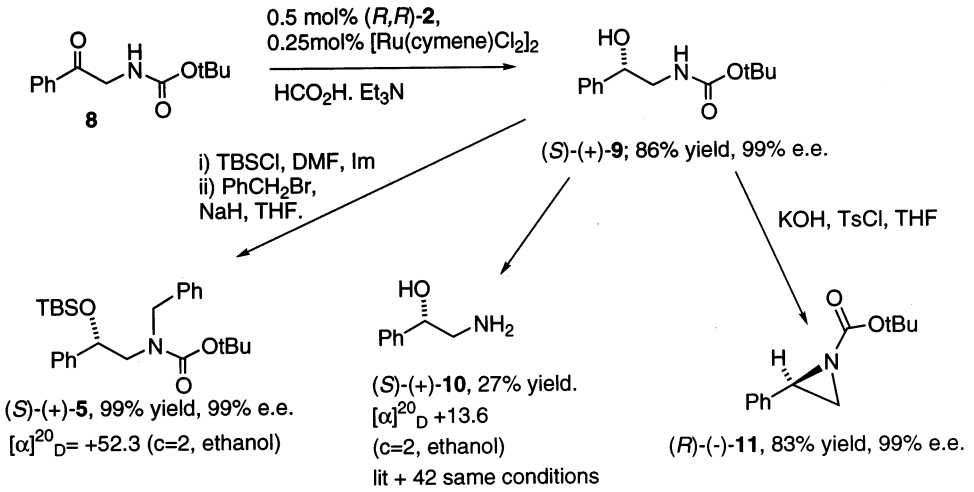


Scheme 2.

Deprotection of the nitrogen atom in (*S*)-(+)-**4** gave the amino alcohol (*S*)-(+)-**6,** which was the subject of cyclisation studies. Attempts to achieve this by *O*-tosylation followed by base treatment failed;[5] however, the use of Mitsunobu conditions resulted in cyclisation in low yield but high enantiomeric excess to the aziridine (*R*)-(−)-**7**.[6] Cyclisation of the racemic analogue of

6 was achieved in similar yield (27%), whilst *N*-benzyl-2-aminoethanol could be converted to the corresponding aziridine in only 17% yield.

In an attempt to identify an improved route, we studied the asymmetric reduction of the *N*-*t*Boc–α-aminoketone **8**. Our studies revealed that the monotosylated diamine system was highly efficient at this reduction, furnishing alcohol (*S*)-(+)-**9** in 99% e.e. as measured by chiral HPLC. In contrast the *cis*-**1**/Ru(II)/isopropanol system totally failed in this application (Scheme 3). The reasons for this dramatic difference are not fully clear, however we have previously speculated that chelating reduction products (as might be obtained from the reduction of **8**) may inhibit, and lead to subsequent decomposition of, the amino alcohol/Ru(II) complex.[3] In contrast the monotosylated diamine may well form much stronger complexes with the same metal, and be resistant to such chelation-initiated decomposition.

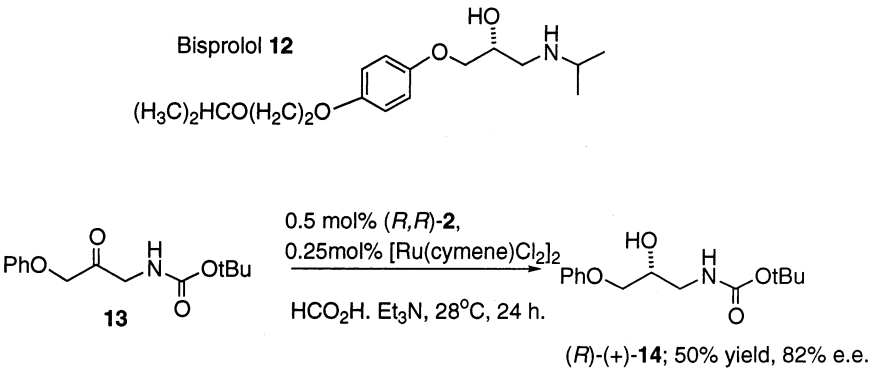


Scheme 3.

The configuration of (*S*)-(+)-**9** was confirmed by deprotection of the nitrogen atom with TFA to give the known amino alcohol (*S*)-(+)-**10**.[7] Conversion of the same sample of (*S*)-(+)-**9** to (*S*)-(+)-**5** served to confirm the absolute sense of the product of reduction of **3** as described previously (Scheme 2).

The alcohol (*S*)-(+)-**9** was cyclised to the *N*-*t*Boc aziridine (*R*)-(−)-**11** in 83% yield and 99% e.e. through treatment with tosyl chloride and base,[5] thus delivering an efficient synthesis of aziridines in high yield and enantioselectivity.[8]

In view of the importance of 2-hydroxy-3-phenoxy-propylamine derivatives, such as bisprolol **12**,[9] as β-selective adrenoceptor blocking agents (β-blockers), we chose to examine the synthetic approach to such targets through the asymmetric transfer hydrogenation of the corresponding ketone precursor **13**.[10] In the event, the use of the (*R*,*R*)-**1**/formic acid system gave alcohol **14** in 82% e.e. and 50% yield, although the configuration remains to be determined (we have assumed that it follows the pattern of other reductions). We believe that this reduction represents a competitive, and highly practical, new approach for the reduction of this class of ketones, which are normally regarded as 'difficult' substrates due to the lack of steric differentiation between the groups flanking the C=O group. The results of our ongoing studies in this area will be reported in due course (Scheme 4).



Scheme 4.

In conclusion, we have demonstrated that the use of a monotosylated diamine/formic acid/triethylamine system is highly effective at the enantioselective reduction of α-amido ketones and that this process provides an efficient method for the asymmetric synthesis of β-amino alcohol and azidiridines.

Acknowledgements

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4. All compounds gave appropriate physical and spectroscopic data. The optical rotations and chiral HPLC retention data (OD column 250×4 mm, 0.5 mL/min, retention times in minutes unless otherwise indicated) are as follows; (*S*)-(+)-**4** (reduction using **2**); $[\alpha]_D^{20}=+3.3$ ($c=2$, EtOH), HPLC (hexane:ethanol:diethylamine 95:4.9:0.1) 13.93 (R), 15.27 (S). (*S*)-(+)-**5**; (product from **9**) $[\alpha]_D^{20}=+52.3$ ($c=2$, EtOH), HPLC (hexane:ethanol:diethylamine 97:2.9:0.1) 9.45 (*R*), 8.63 (*S*). (*S*)-(+)-**6**; $[\alpha]_D^{20}=+33.8$ ($c=2$, EtOH), HPLC (hexane:ethanol:diethylamine 95:4.9:0.1) 33.19 (*R*), 31.97 (*S*). (*R*)-(−)-**7**; $[\alpha]_D^{20}=-49.4$ ($c=2$, EtOH), e.e. determined using NMR shift reagent Eu(hfc)$_3$. (*S*)-(+)-**9**; $[\alpha]_D^{20}=+3.5$ ($c=1$, EtOH), HPLC (hexane:ethanol:diethylamine 95:4.9:0.1) 19.49 (*R*), 17.86 (*S*). (*R*)-(−)-**11**; $[\alpha]_D^{20}=-137.3$ ($c=2$, EtOH), e.e. determined using NMR shift reagent Eu(hfc)$_3$. (*R*)-(+)-**14**; $[\alpha]_D^{20}=+3.5$ ($c=1$, EtOH), HPLC (hexane:ethanol:diethylamine 95:4.9:0.1) 41.62 (*R*), 22.48 (*S*).

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7. There appears to be a discrepancy in the signs of optical rotation for compound **11**. Previous work, and the conversion of **9** to (*S*)-(+)-**10**, suggests that **11** should be of (*R*) configuration (i.e. through inversion). However, our specific rotation for **11** ($[\alpha]_D^{20}=-137.3$ ($c=1$, EtOH)) suggests that it is in fact (*S*) when compared to literature results ($[\alpha]_D^{20}=-163.5$ ($c=1$, CH_2Cl_2) for the (*S*) compound; Ref. 6a). A sample of (*R*)-(−)-**11** was also prepared from a commercial sample of (*S*)-(+)-**10** via *t*-Boc protection of the N atom followed by cyclisation with TsCl/KOH. This material exhibited $[\alpha]_D^{20}=-132.8$ ($c=1$, EtOH), $[\alpha]_D^{20}=-142.6$ ($c=1$, CH_2Cl_2).
8. The reduction appears to be quite versatile in terms of substrate scope. In a preliminary investigation the asymmetric reduction of the challenging substrate 3-*tert*-butyloxycarbonylaminoacetone worked smoothly with the (*R*,*R*)-**2** system to give an alcohol in 87% yield ($[\alpha]_D^{20}=+27.5$ ($c=1$, DCM)). Although the e.e. of the product remains to be determined, cyclisation to the *N*-Boc aziridine using the conditions given in Scheme 3 gave a product of $[\alpha]_D^{20}=-54.5$ ($c=1$, EtOH) and $[\alpha]_D^{20}=-42.2$ ($c=1$, DCM), which compares favourably to the literature value for this material, i.e. $[\alpha]_D^{20}=+39.2$ ($c=1$, DCM) for the (*S*) enantiomer (Ref. 6a). In this case, the expected aziridine configuration, (*R*), matches that found by comparison with the literature.
9. Kitaori, K.; Furukawa, Y.; Yoshimoto, H.; Otera, J. *Tetrahedron Lett*. **1998**, *39*, 3173.
10. Ketone **13** was conveniently prepared by the epoxidation of *N*-*t*Boc-allylamine, followed by ring-opening with sodium phenoxide and oxidation of the alcohol (80% overall yield). An alternative method, avoiding an alcohol oxidation step but resulting in a slightly lower yield, involves sequential reaction of 2-bromomethylallylbromide with phenol and sodium azide, reduction of azide and amine protection, followed by ozonolysis of the alkene.