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Asymmetric Synthesis of β-Amino Alcohols and 1,2-Diamines Through DuPHOS-Rh Catalysed Hydrogenation

Mark J. Burk,*[a] Nicholas B. Johnson[a] and Jeffrey R. Lee[b]

[a]*Chirotech Technology Limited, Cambridge Science Park, Milton Road, Cambridge CB4 0WG, UK*

[b]*Department of Chemistry, Duke University, P. M. Gross Chemical Laboratory, Durham, North Carolina 27706*

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Abstract: A novel enantioselective synthesis of β-amino alcohols and 1,2-diamines is reported which incorporates the first description of the asymmetric hydrogenation of dehydro-β-amino alcohols and dehydro-α-amino aldoximes.

Chiral β-amino alcohols and 1,2-diamines are important components of myriad biologically active compounds and also have been applied extensively as chiral auxiliaries and ligands for asymmetric catalysis. Consequently, development of efficient asymmetric syntheses of these classes of chiral compounds is of great interest.

β-Amino alcohols generally are accessed by reduction of the corresponding α-amino esters typically using $LiAlH_4$[1] or $NaBH_4$,[2] or related reactions involving the reduction of α-amino acids.[3] These approaches are limited by the availability of the precursor α-amino acid. Moreover, product yields are often limited due to problematic isolation procedures. The preparation of chiral 1,2-diamines generally is restricted to classical resolution of a racemic mixture of the amine, which entails all the limitations of such processes: identification of resolving agents; availability of each enantiomer of resolving agent; 50% maximum yield of desired enantiomer, etc.[4]

The broad scope of the DuPHOS and BPE ligand systems for asymmetric catalytic transformations has been amply demonstrated.[5] For example, recently we have shown the use of cationic DuPHOS-Rh and BPE-Rh catalysts for the asymmetric synthesis of amino acid,[6] amine,[7] and succinate[8] derivatives. Herein, we describe application of these catalyst systems to the direct synthesis of β-amino alcohols through efficient asymmetric hydrogenation of prochiral dehydro-β-amino alcohol derivatives **3** and **4**. Furthermore, the dehydro-β-amino alcohols **3** are readily transformed into dehydro-α-amino aldoximes **8** which, following asymmetric hydrogenation and oxime reduction, afford selectively protected chiral 1,2-diamines **10** with high enantiomeric excesses. An alternative approach to β-amino alcohol derivatives, *via* asymmetric hydrogenation using DuPHOS-Rh and related catalyst systems recently has been reported.[9]

The requisite dehydro-β-amino alcohols **3** were obtained by $LiAlH_4$ reduction of dehydro-α-amino esters,[10] which were prepared using the Horner-Emmons method of Schmidt *et al.*[11] Initially, the procedure was examined with *N*-Boc and *N*-acetyl dehydro-α-amino esters. However, in the case of *N*-acetyl protected substrates, there was a propensity for reduction of the *N*-protecting group and so efforts were concentrated on

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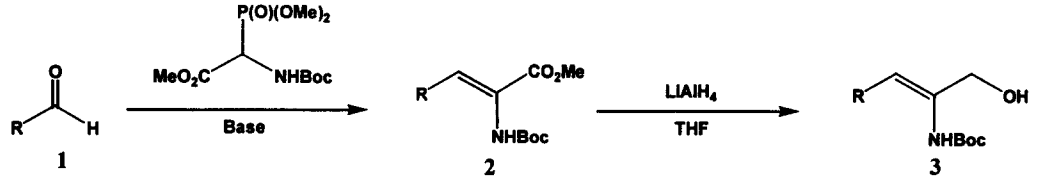
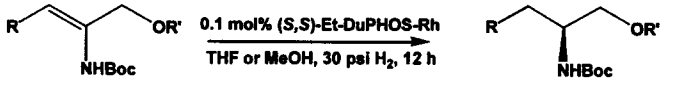
the *N*-Boc derivatives. The *N*-Boc protected enamides **2** proved highly amenable to the reduction procedure and the corresponding alcohols **3** were obtained in good yield after either chromatography and/or crystallisation (75 – 85%). In all cases the spectroscopic data for the products **2** and **3** were consistent with them being single geometric isomers (Scheme 1).[10,11]



Scheme 1. Synthesis of dehydro-β-amino alcohols **3**.

Dehydro-β-amino alcohols **3** thus obtained were subjected to asymmetric hydrogenation using cationic Et-DuPHOS-Rh[12] complexes. A range of β-amino alcohols **5** was produced using this method and the results are depicted in Scheme 2.[13] Substrates **3**, containing various R-substituents, were examined and the selectivities achieved using the Et-DuPHOS-Rh catalyst generally were excellent. However, certain heterocyclic substrates **3** were reduced with anomalously low selectivities. It was postulated that for these substrates there might be competitive coordination of the free OH to the metal centre of the catalyst, thus reducing enantioselectivity. In order to mitigate any such interaction, the free OH of these substrates **3** was acetylated to provide substrates **4**. Subsequent hydrogenation of dehydro-β-amino acetates **4** proceeded with excellent enantioselectivities, to give the products **6** (Table in Scheme 2). It was determined that the (*S,S*)-Et-DuPHOS-Rh catalyst provided β-amino alcohols with (*S*)-absolute configuration.[14] These reactions proceeded smoothly to completion over 12 h using S/C ratios of 1000.



3; R' = H
4; R' = Ac

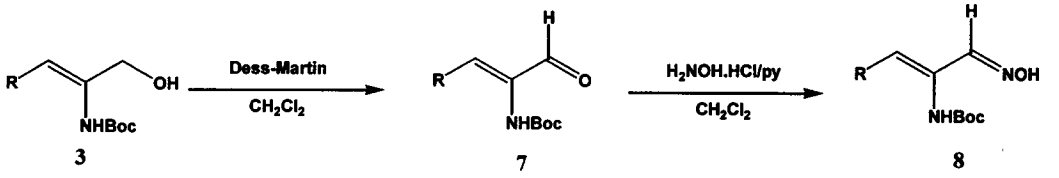
5; R' = H
6; R' = Ac

R	Methyl	Phenyl	Cyclohexyl	2-MeO-Phenyl	Benzyl	2-Naphthyl	2-Furanyl	2-Thienyl
3, % ee	95	93	96	93	>99	87	21	28
4, % ee	-	-	-	-	-	98	98	96

Scheme 2. Asymmetric hydrogenation of substrates **3** and **4**.

We next examined the use of the dehydro-β-amino alcohols **3** for the preparation of enantiomerically enriched 1,2-diamines **10**. A synthetic sequence was devised to avoid extensive chemical manipulation of molecules bearing a sensitive stereogenic centre. To achieve this, the achiral dehydro-β-amino alcohols **3**,

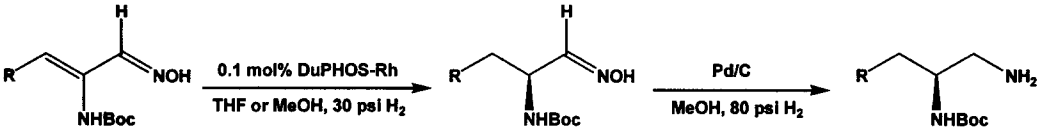
were subjected directly to Dess-Martin oxidation to form the dehydro-α-amino aldehydes **7** in good yield (>70%, following chromatographic purification). These aldehydes **7** were then reacted with hydroxylamine hydrochloride/pyridine to afford the corresponding oximes **8**, also in good yield (>85%).[15] Spectroscopic data indicated products **8** were formed as mixtures of oxime geometric isomers (Scheme 3).



3 **7** **8**

Scheme 3. Synthesis of dehydro-α-amino aldoximes **8**.

Dehydro-α-amino aldoximes **8** were examined as substrates for asymmetric hydrogenation, ultimately to afford chiral 1,2-diamines. Preliminary studies of the asymmetric hydrogenation of the substrates **8** showed that the cationic DuPHOS-Rh catalyst systems were again extremely efficient for the required asymmetric hydrogenation and provided the enantiomerically-enriched oxime products **9**. These reactions also proceeded smoothly to completion over 12 h again using S/C ratio of 1000.[13] The homogeneous asymmetric catalysts displayed high chemoselectivity in the hydrogenation and in no case was reduction of the oxime unit observed. The oximes **9** were, however, readily reduced with hydrogen and Pd/C to afford the interesting 1,2-diamines **10**, which are selectively protected at the secondary amine centre (Scheme 4). In order to effectively assess enantioselectivity in the asymmetric hydrogenation step, the products **9** were reduced with hydrogen and Pd/C in the presence of $(Boc)_2O$ to afford 1,2-di-*N*-Boc-1,2-diamines, which were readily analysed using standard chiral GC or chiral HPLC methods.[16]



8 **9** **10**

R	Methyl	Phenyl	Cyclohexyl	2-MeO-Phenyl	Benzyl	2-Naphthyl
Me-DuPHOS-Rh % ee	93	96	98	91	97	90
Et-DuPHOS-Rh % ee	94	90	99	88	98	81

Scheme 4. Asymmetric hydrogenation of dehydro-α-amino aldoximes **8**.

Initially, Et-DuPHOS-Rh was examined and although it provided excellent selectivity with several of the substrates, others were reduced with somewhat lower enantioselectivity (e.g. **8**, R = 2-naphthyl: 81% ee). This prompted further screening with the Me-DuPHOS-Rh[12] catalyst system, which for specific substrates, was found to furnish superior enantioselectivity (Scheme 4). Here the advantages of the modular design of

the DuPHOS ligand system is clearly demonstrated, as it allows 'tailoring' of the catalyst to each substrate individually, and in each case the products **10** could be obtained with ≥90% ee.[17] Overall, this synthetic route provides access to enantiomerically enriched 1,2-diamines without proceeding through α-amino aldehydes, which are known to be configurationally unstable.[18]

In summary, we have described the development of concise methods to prepare valuable enantiomerically-enriched β-amino alcohols and selectively protected chiral 1,2-diamines. The approach encompasses a common intermediate (**3**) that is readily obtained with a variety of substituents. In each case, the synthesis involves the efficient and highly stereoselective DuPHOS-Rh-catalysed asymmetric hydrogenation of appropriate prochiral precursors. The ready availability of a variety of substituted DuPHOS ligands should facilitate employment of this method for the synthesis of useful single enantiomer intermediates such as **5**, **9** and **10**.

References and Notes

1. P. Karrer, P. Portmann, M. Suter, *Helv. Chim. Acta* **1948**, *31*, 1617.
2. H. Seki, K. Koga, H. Matsuo, S. Ohki, I. Matsuo, S. Yamada, *Chem. Pharm. Bull.* **1965**, *13*, 995.
3. See for example: M.J. McKennon and A.I. Meyers, *J. Org. Chem.* **1993**, *58*, 3568 and references therein.
4. P. Newman, *Optical Resolution Procedures for Chemical Compounds, Volume 1, Amines and Related Compounds*, Optical Resolution Information Center, New York, 1981.
5. M.J. Burk in *Chiral Chemicals*, D.J. Ager (Ed), Marcel Dekker, New York, 1999, Chapter 18.
6. M.J. Burk, J.G. Allen and W.F. Kiesman, *J. Am. Chem. Soc.* **1998**, *120*, 657.
7. M.J. Burk, G. Casy and N.B. Johnson, *J. Org. Chem*, **1998**, *63*, 6084.
8. M.J. Burk, F. Bienewald, M. Harris and A. Zanotti-Gerosa, *Angew. Chem., Int. Ed.* **1998**, *37*, 1931.
9. G. Zhu, A.L. Casalnuovo and X. Zhang, *J. Org. Chem.* **1998**, *63*, 8100.
10. Y. Nakamura and C. Shin, *Synthesis*, **1993**, 1158.
11. U. Schmidt, H. Griesser, V. Leitenberger, A. Lieberknecht, R. Mangold, R. Meyer, B. Riedl, *Synthesis* **1992**, 487.
12. The catalysts used for the study have the general formulae: [(Et-DuPHOS)Rh(COD)]OTf and [(Me-DuPHOS)Rh(COD)]OTf.
13. General Procedure for Asymmetric Hydrogenation: A Fisher-Porter bottle was charged with substrate and catalyst (S/C = 1000) under argon, followed by addition of degassed solvent. The vessel was purged with hydrogen by five vacuum/H_2 cycles, charged to 30 psi H_2 and stirred at 20-25 °C for 12 h or until no further hydrogen uptake was observed. The reactions were then evaporated and the residue passed through a short silica plug in EtOAc:hexane (1:1) to remove catalyst residues. The products obtained were analysed directly, without further purification, for conversion and/or enantiomeric excess.
14. The absolute configuration was assigned either by direct comparison to β-amino alcohols prepared by an alternative route or by reference to literature values for optical rotation.
15. General Procedure: To a 0.25 M solution of the dehydro-β-amino alcohol **3** in CH_2Cl_2 was added 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (1.5 eq). After 30 minutes the reaction was evaporated and purified by flash chromatography. The resultant aldehyde **7** was then added to a premixed solution of hydroxylamine hydrochloride/pyridine (2:1) in CH_2Cl_2. After 1 h , the reaction was added to 1M $KHSO_4$ and the mixture extracted with CH_2Cl_2. The combined extracts were washed with 1M $KHSO_4$, dried (Na_2SO_4) and evaporated. The resultant residue was purified by flash chromatography to afford the dehydro-α-amino aldoximes **8**.
16. Due to the geometric isomers of the oxime function, the two diastereomers of the products **9** could not be resolved using our standard GC and HPLC analytical techniques.
17. M.J. Burk, *Synlett*, Accounts Article, 1999, in preparation.
18. M.T. Reetz, M.W. Drews and A. Schmitz, *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141; J. Jurczak and A. Golebiowski, *Chem. Rev.* **1989**, *89*, 149.