Discussion Addendum for:
Synthesis of Highly Enantiomerically Enriched Amines by Asymmetric Transfer Hydrogenation of \( N\)-(tert-Butylsulfinyl) Imines

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It is believed that more than 75% of all drugs and drug candidates contain the amine functionality.\(^2\) In many cases, especially natural products, aminated compounds possess at least one stereogenic center, so asymmetric methodologies that provide chiral amines enantioselectively are of great synthetic importance. For chiral \(\alpha\)-substituted amines, the most useful procedure involves the reduction of chiral ketimines or the addition of organometallic reagents to chiral aldimes.\(^3\) Among different possible starting imines, those possessing a sulfanyl moiety attached to the nitrogen atom are of especial interest because this group plays two important roles: (a) activation of the \(\text{C=N}\) group in the reaction with nucleophiles, and (b) introduction of asymmetric information, which makes it possible to perform asymmetric reactions. Two families of chiral sulfanyl imines have been reported in the literature, one containing a \(p\)-tolyl group\(^4\) and the other a \(\text{tert}\)-butyl group\(^5\) attached to the sulfanyl moiety, the latter being more efficient concerning diastereoselectivity.\(^6\) The asymmetric reduction of sulfanyl ketimines has been performed using boranes,\(^3c,7,8\) sodium or lithium borohydrides,\(^3,7,9\) or diethylzinc in the presence of nickel acetylacetate.\(^10\) Some years ago\(^11\) we found that the transfer hydrogenation\(^12,13\) is a very useful reduction protocol because, on one hand, it avoids the use of dangerous molecular hydrogen and, on the other hand, it uses an inexpensive and easy-to-handle hydrogen source such as isopropanol or formic acid derivatives.\(^14\)

The starting enantiomerically pure \(N\text{-}\text{tert}\)-butylsulfanyl imines\(^15\) are easily prepared by mixing the corresponding carbonyl compounds with enantiomerically pure commercially available \(\text{tert}\)-butanesulfimides in the presence of a Lewis acid, titanium tetaethoxide being the most commonly used, under thermal\(^16\) or microwave\(^17\) activation. Other procedures involving epoxides\(^18\) or allylic alcohols and aryl iodides\(^19\) are complementary but are not as general.

**Ruthenium-catalyzed transfer hydrogenation of \(N\text{-}\text{tert}\)-butylsulfanyl imines\(^12\)**

Due to the versatility of \(\beta\)-amino alcohols as ligands for asymmetric catalysis in transfer hydrogenation to ketones,\(^20\) and after screening different compounds,\(^11\) the corresponding indanol derivative was found to be the most effective.\(^21\) The match combination is shown in Scheme 1, where use of \([\text{RuCl}_2(p\text{-cymene})]_2\) as catalyst provided the expected \(N\)-sulfanyl amines, which were deprotected in situ with hydrochloric acid in methanol to afford...
the corresponding chiral primary amines with enantioselectivities up to >99% ee (Figure 1).\textsuperscript{11,22}

Scheme 1. Preparation of enantioenriched primary amines by transfer hydrogenation of \(N\)-tert-butylsulfinyl imines

Using the starting imine and the amino alcohol with opposite configuration, two representative \textit{ent}-amines were prepared (Figure 2).\textsuperscript{22}
An interesting simplification of the procedure shown in Scheme 1 has been the use of an achiral amino alcohol as ligand for the same ruthenium catalyst. After screening several commercially available compounds, 2-amino-1,1-dimethylethanol was determined to be the most efficient both in terms of yield and enantioselectivity for the obtained amines (Scheme 2).23

![Figure 2. ent-Primary amines prepared](image)

Scheme 2. Preparation of enantioenriched primary amines using an achiral amino alcohol

From the reaction depicted in Scheme 2 it is remarkable that the mentioned improvement gives excellent enantioselectivities for aliphatic amines (Figure 3)24, comparable to the procedure shown in Scheme 1. A mechanistic proposal based on both experimental results and DFT calculations indicates that the reaction pathway involves two transition states and three intermediates, with the reaction being a stepwise process and not a concerted one.24
Figure 3. Enantioenriched primary amines prepared according to Scheme 2

When starting materials with the opposite configuration were used, the corresponding enantiomeric primary amines were isolated (Figure 4).

Figure 4. Enantiomeric primary amines from ent-imines

A further improvement of the procedure depicted in Scheme 2 was the use of microwaves (40 W) instead of heating: yields and enantioselectivities
are similar to those given in Figures 3 and 4, but reaction times are significantly reduced (from 1-4 hours to less than 30 minutes).25

**Synthetic applications of the asymmetric transfer hydrogenation to N-tert-butylsulfinyl imines**

When the starting imine bears an ester group at one of the ω-positions the asymmetric transfer hydrogenation gives a chiral amino ester that after deprotection spontaneously cyclizes to provide enantioenriched substituted lactams.26 The starting enantiopure imino esters were prepared from the corresponding keto esters following literature procedures16,17 in 59-85% yields. After performing the transfer hydrogenation, deprotection with hydrochloric acid in methanol gives direct access to the expected enantioenriched lactams (Scheme 3): in this case both series of enantiomers were prepared (Figure 5).26

![Scheme 3. Preparation of enantioenriched lactams from imino esters](image)

R = Ph, 4-MeOC₆H₄, 4-ClC₆H₄, c-C₆H₉, Cy, i-Pr, 2-naphthyl, 2-thienyl
n = 1-3
The use of \( \omega \)-chloro imines allows the preparation of \( N \)-sulfinylnitrogen-containing saturated heterocycles.\(^{27}\) In this case, it was not possible to prepare the corresponding imine with \( n = 1 \) because a \( \beta \)-elimination occurred in the starting chloro imine under the reaction conditions used for the synthesis of the imine. For \( n = 0 \) and for \( n = 2 \)-4 the expected chloro imines were isolated\(^{16,17}\) with yields ranging from 64 to 92%. Reaction conditions for the second step of the process (cyclization) depend on the size of the ring formed: whereas for aziridines and pyrrolidines, the basic reaction medium is sufficient to provoke the cyclization (Scheme 4 and Figure 6), for the 6- and 7-membered heterocycles an additional treatment with KHMDS was necessary to promote the desired cyclization (Scheme 5). In the latter case, the cyclization reaction failed, which made it necessary to start from the corresponding bromo derivative in order to obtain the expected azepine. In all cases the corresponding \( N \)-sulfinoylated products were isolated (hydrolysis was performed with \( \text{NH}_4\text{Cl} \) instead of \( \text{HCl} \)) in order to facilitate their isolation and purification. Desulfinylation can be easily carried out with \( \text{HCl} \).
in methanol to give the expected free amines. Figure 7 shows two examples of enantiomeric pyrrolidines.

Scheme 4. Preparation of enantioenriched protected aziridines and pyrrolidines

Figure 6. Enantioenriched protected aziridines and pyrrolidines prepared
Figure 7. Two examples of enantiomeric deprotected pyrrolidines

Scheme 5. Preparation of protected enantioenriched piperidines and azepines

The same reaction conditions have been applied to \(\alpha, \beta\)-unsaturated \(N\)-tert-butylsulfinyl imines in order to prepare enantioenriched allylic amines.\(^{28}\) Once the transfer hydrogenation took place, the corresponding desulfinylation under standard conditions afforded a series of enantioenriched primary allylic amines with high enantioselectivity (Scheme 6 and Figure 8).
Scheme 6. Preparation of enantioenriched primary allylic amines

Figure 8. Enantioenriched allylic amines prepared
Other synthetic methodologies from our research group starting from N-tert-butylsulfinyl imines involve In-promoted allylation,\(^1^5\) homoallylic oxidation,\(^2^9\) addition of organomagnesium,\(^3^0\) organolithium compounds\(^3^1\) or enolates,\(^3^2\) and reaction with nitrocompounds.\(^3^3\) These methods are useful in the synthesis of enantioenriched natural and unnatural nitrogen-containing compounds, including heterocyclic derivatives.

In summary, transfer hydrogenation to chiral imines, followed by desulfinylation under acidic conditions, is a versatile and useful methodology for the preparation of a wide range of enantioenriched primary \(\alpha,\alpha\)-disubstituted amines. In addition, the chiral auxiliary can be recycled by application of simple reported procedures.\(^3^4\)

References

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Miguel Yus received his Ph.D. in Chemistry at the University of Saragossa in 1973. After postdoctoral studies at the Max Planck Institute für Kohlenforshung (Mülheim Ruhr), he joined the University of Oviedo and was appointed Professor in 1987. In 1988 Miguel moved to a Chair in Organic Chemistry at the University of Alicante, where he has developed his academic career ever since. He has published more than 600 papers in international journals, with his h factor being 74 as of June 2019.