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Ruthenium-catalysed asymmetric transfer hydrogenation of *N*-(*tert*-butanesulfinyl)imines

David Guijarro *, Óscar Pablo, Miguel Yus *

Departamento de Química Orgánica, Facultad de Ciencias and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apdo. 99, 03080 Alicante, Spain

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This Letter is dedicated to the memory of Professor Octavio A. C. Antunez, who tragically died in the airplane crash of June 1, 2009

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ABSTRACT

The ruthenium complex prepared from $[RuCl_2(p\text{-cymene})]_2$ and (1*S*,2*R*)-1-amino-2-indanol is a very efficient catalyst for the asymmetric transfer hydrogenation of (*R*)-*N*-(*tert*-butanesulfinyl)ketimines in isopropanol. By carefully removing all possible moisture from the reaction medium, chiral primary amines with very high optical purities (up to >99% ee) can be easily prepared in excellent yields by the diastereoselective reduction of the imines followed by removal of the sulfinyl group under mild acidic conditions. Reaction times of 1–4 h were needed to complete the reduction reactions when they were performed at 40 °C.

The asymmetric transfer hydrogenation has shown to be an excellent method to achieve the enantioselective reduction of ketones.[1] This approach to chiral secondary alcohols presents several advantages over other reduction methods: the reactions are carried out under very mild conditions with generally low catalyst loadings and using relatively non-hazardous chemicals as hydrogen sources, avoiding the handling of metallic hydrides or molecular hydrogen. In spite of the success achieved in the reduction of ketones, the application of the transfer hydrogenation protocol to the enantioselective reduction of imines is much less developed.[1b,1c,2] Ruthenium complexes bearing monotosylated diamines as chiral ligands have shown to be effective catalysts to carry out the asymmetric reduction of *N*-alkyl- and *N*-benzylimines, as well as endocyclic imines.[1] Among the iminic substrates, *N*-(*tert*-butanesulfinyl)imines have emerged as very useful starting materials for the preparation of chiral primary amines.[3] The diastereoselective reduction of *N*-(*tert*-butanesulfinyl)ketimines leads to the expected branched sulfinamides, which can be easily transformed into the corresponding chiral primary amines by desulfinylation under mild acidic conditions.[4] The reduction process has been achieved using several boranes,[3c,5] sodium or lithium borohydrides,[3c,5,6] lithium aluminium hydrides[3c] and diethylzinc in the presence of $Ni(acac)_2$.[7] However, to the best of our knowledge, no reports on the asymmetric transfer hydrogenation of sulfinylimines have appeared up to date. As part of our studies on the use of this kind of imines in asymmetric synthesis,[8] herein we present our preliminary results on the application of a ruthenium-catalysed transfer hydrogenation methodology to the asymmetric synthesis of primary amines with very high optical purities starting from *N*-(*tert*-butanesulfinyl)ketimines.

During the last years, our research group has been studying the utility of β-aminoalcohols as ligands for asymmetric catalysis, especially for the synthesis of chiral amines.[9] Since those ligands have shown to be very effective in the ruthenium-catalysed transfer hydrogenation of ketones in isopropanol,[1] we decided to investigate if they could also be applied to the reduction of imines by the same methodology. We chose the acetophenone-derived *N*-(*tert*-butanesulfinyl)imine **1a** (Scheme 1) as a model substrate and β-aminoalcohols **L1**–**L5** as potential ligands for ruthenium complexes which would be tested as catalysts for the transfer hydrogenation processes. The catalysts were prepared by refluxing a mixture of $[RuCl_2(p\text{-cymene})]_2$ (5 mol %) and the ligand **L1**–**L5** (20 mol %) in isopropanol. The results obtained in the attempted reductions of imine **1a** are collected in Table 1. With the proportion of reagents specified above, ligand **L1** did not give any reduction product. Instead, acetophenone and *tert*-butanesulfinamide were found in the crude mixture (Table 1, entry 1), which are the result of the hydrolysis of

* Corresponding authors. Fax: +34 965903549.
E-mail addresses: dguijarro@ua.es (D. Guijarro), yus@ua.es (M. Yus).

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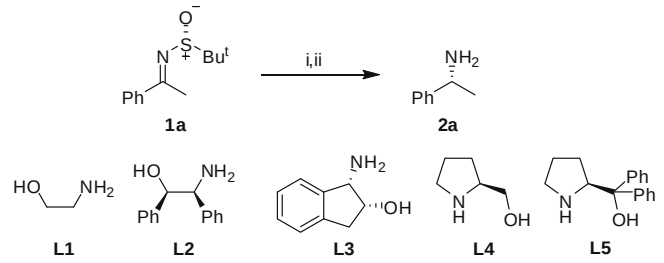


Scheme 1. Reagents and conditions: (i) $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), Ligand (20 mol %), KOH (50 mol %), Pr^iOH, 25 °C; (ii) HCl, MeOH.

Table 1
Test of different amino alcohols as chiral ligands for the ruthenium-catalysed transfer hydrogenation of imine **1a**[a]

Entry	Ligand	t[b] (h)	Yield[c] (%)	ee[d] (%)
1	**L1**	6	—[e]	—[f]
2[g]	**L1**	15	11[h]	84
3	**L2**	24	41[h]	95
4	**L3**	15	31[h]	98
5	**L4**	24	—[h,i]	—[f]
6	**L5**	21	—[e]	—[f]

[a] The solution of imine **1a** (0.9 mmol) in Pr^iOH (9 mL) was added to a solution of the ruthenium complex [prepared by refluxing a mixture of $[RuCl_2(p\text{-cymene})]_2$ (5 mol %) and the ligand (20 mol %) in Pr^iOH (2 mL)] at room temperature. Then, KOH (2.25 mL of a 0.1 M solution in Pr^iOH) was added and the reaction mixture was stirred at the same temperature for the time indicated.
[b] Time for the transfer hydrogenation reaction.
[c] Isolated yield of amine **2a** after acid–base extraction based on the starting imine **1a**. The isolated compound **2a** was always ≥95% pure (GC and/or 300 MHz ^{1}H NMR).
[d] Determined for the corresponding benzamide by HPLC using a ChiralCel OD-H column. The (*R*)-enantiomer was the major one in all cases.
[e] No reduction product **2a** was formed. Acetophenone and Bu^tSONH_2 were found in the crude reduction mixture.
[f] Not determined.
[g] The reaction was performed with 3 equiv of the ligand instead of 20 mol %.
[h] Acetophenone, Bu^tSONH_2 and 1-phenylethanol were also formed in the reduction reaction.
[i] A very small amount of the reduction product **2a** was detected in the crude reduction mixture.

the starting imine. When the amount of ligand **L1** was increased to 3 equiv (with respect to the imine), the reduction product **2a** was obtained in a poor 11% yield, together with the hydrolysis products and 1-phenylethanol (which results from the reduction of acetophenone). However, a promising ee of 84% was measured in amine **2a**, which seems to indicate that the chirality of the imine plays a crucial role in determining the stereochemical outcome of the reaction. We were pleased to see that the enantioselectivity improved considerably with the chiral ligands **L2** and **L3**, reaching the excellent values of 95% and 98% ee, respectively (Table 1, entries 3 and 4). It is interesting to note that the *erythro* configuration of the aminoalcohols **L2** and **L3** seems to match very well with the (*R*)-configuration of the sulfur atom of the imine, giving very high enantioselectivities. The need of having a primary amino group in the ligand became evident when ligands **L4** and **L5** were tested. In these cases, either no reduction product or only traces of it could be detected after work-up (Table 1, entries 5 and 6). Although the yield of amine **2a** was higher with ligand **L2** than with **L3** (the ee's being quite similar), we selected (1*S*,2*R*)-1-amino-2-indanol[10] **L3** as the ligand to do a screening of the reaction conditions because it is cheaper than aminoalcohol **L2**.

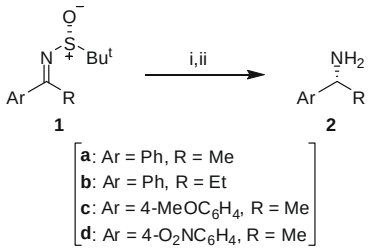
The observation that acetophenone, Bu^tSONH_2, and 1-phenylethanol were always formed as by-products (or main products) in all the reactions led us to think that the hydrolysis of the imine was taking place by reaction with the water that was forming after the deprotonation was carried out by KOH, since no water was used in the work-up procedure which consisted in filtration through a small column of silica gel and evaporation of the solvent. We were delighted to see that the use of Bu^tOK instead of KOH gave better results, affording amine **2a** in 76% yield and 99% ee (Table 2, entry 2). Since the removal of all traces of water seemed to be crucial to avoid the hydrolysis of the imine, the reaction was repeated in the presence of 0.5 g of 4 Å molecular sieves, giving the reduction product in 95% yield and >99% ee (Table 2, entry 4).

Next, the effect of the proportion of the reagents on the enantioselectivity was evaluated. No detriment in the enantioselectivity was observed when the proportion Ru-dimer:**L3** was reduced to 1:2 (Table 2, compare entries 2, 4, and 6 with entries 3, 5, and 7, respectively). Practically the same results were obtained when the Ru-dimer:Bu^tOK ratio was either 1:10 or 1:5 (Table 2, compare entries 4 with 6 and 5 with 7). We decided to keep the proportion

Table 2
Ruthenium-catalysed asymmetric transfer hydrogenation of *N*-(*tert*-butanesulfinyl)imines **1**. Preparation of amines **2**[a]

Entry	Imine	Ru-dimer(mol %)	**L3**(mol %)	Base		T (°C)	t[b] (h)	Product		
				Base	(mol %)			No.	Yield[c] (%)	ee[d] (%)
1[e]	**1a**	5	20	KOH	50	25	15	**2a**	31[f]	98
2[e]	**1a**	5	20	Bu^tOK	50	25	6	**2a**	76	99
3[e]	**1a**	5	10	Bu^tOK	50	25	20	**2a**	63	>99
4	**1a**	5	20	Bu^tOK	50	25	20	**2a**	95	>99
5	**1a**	5	10	Bu^tOK	50	25	22	**2a**	97	>99
6	**1a**	5	20	Bu^tOK	25	25	24	**2a**	97	>99
7	**1a**	5	10	Bu^tOK	25	25	20	**2a**	98	>99
8	**1a**	8	16	Bu^tOK	40	25	5	**2a**	99	99
9	**1a**	3	6	Bu^tOK	15	25	30	**2a**	84	99
10	**1a**	5	10	Bu^tOK	25	40	2	**2a**	99	97
11	**1a**	3	6	Bu^tOK	15	40	4	**2a**	67	96
12	**1b**	5	10	Bu^tOK	25	40	4	**2b**	98	97
13	**1c**	5	10	Bu^tOK	25	40	3	**2c**	85	95
14	**1d**	5	10	Bu^tOK	25	40	1	**2d**	86	98

[a] The solution of imine **1** (0.9 mmol) in Pr^iOH (9 mL) was added to a solution of the ruthenium complex [prepared by refluxing a mixture of $[RuCl_2(p\text{-cymene})]_2$, ligand **L3** and 4 Å molecular sieves (0.5 g) in Pr^iOH (2 mL)] at the temperature indicated. Then, the base (2.25 mL of a 0.1 M solution in Pr^iOH) was added and the reaction mixture was stirred at the same temperature for the time indicated.
[b] Time for the transfer hydrogenation reaction.
[c] Isolated yield of amine **2** after acid-base extraction based on the starting imine **1**. All isolated compounds **2** were ≥95% pure (GC and/or 300 MHz ^{1}H NMR).
[d] Determined for the corresponding benzamide by HPLC using a ChiralCel OD-H column. The (*R*)-enantiomer was the major one in all cases.
[e] The reaction was performed in the absence of molecular sieves.
[f] Acetophenone, Bu^tSONH_2 and 1-phenylethanol were also formed in the reduction reaction.



Scheme 2. Reagents and conditions: (i) $[RuCl_2(p\text{-cymene})]_2$ (cat.), (1*S*,2*R*)-1-amino-2-indanol (cat.), base (cat.), 4 Å molecular sieves (0.5 g), Pr^iOH, T; (ii) HCl, MeOH.

Ru-dimer:**L3**:Bu^tOK = 1:2:5 in further experiments. The amount of the ruthenium complex was also varied to 8 and 3 mol %. The use of 8 mol % of the catalyst reduced the reaction time to 5 h keeping the excellent yield and enantioselectivity (Table 2, entry 8). With 3 mol % of the catalyst, the reaction time was much longer than with 5 mol % of it, which was accompanied by a reduction of the yield to 84% (Table 2, entry 9).

The influence of the temperature was also studied. Increasing the temperature of the reduction process to 40 °C led to a considerable reduction in the reaction time to only 2 h, giving a quantitative yield of amine **2a** with a very slight decrease in the ee (Table 2, entry 10). Another attempt to reduce the amount of catalyst to 3 mol % was done in a reaction at 40 °C. The reaction time was quite short (4 h), but again a reduced yield was obtained (Table 2, entry 11).

After performing the optimisation of the reaction conditions, some other imines **1b–d**[11] were used as substrates (Scheme 2, Table 2, entries 12–14). All the reactions were carried out at 40 °C in order to have short reduction times.[12] Imine **1b**, derived from propiophenone, gave an excellent yield and enantioselectivity in a reaction time of 4 h (Table 2, entry 12). The methodology is equally efficient for the reduction of phenone-derived imines bearing either an electron-withdrawing or an electron-releasing group on the aromatic ring. Very high yields and ee's were obtained irrespective of the electronic nature of the aromatic ring of the imine (Table 2, entries 13 and 14).

It is worth noting that, in our previous studies, we could not prepare amine **2a** in good yields by addition of a trimethylzincate to *N*-(*tert*-butanesulfinyl)benzaldimine due to the slow transfer rate of the methyl group.[8] Therefore, this transfer hydrogenation process can be considered as complementary to the addition of triorganozincates to the sulfinylimines.

In conclusion, we have presented here a new and very efficient procedure to prepare optically pure primary amines through the highly diastereoselective reduction of *N*-(*tert*-butanesulfinyl)imines by a ruthenium-catalysed transfer hydrogenation process. The careful removal of all possible moisture allows the reduction of the imine to proceed very efficiently in short reaction times. To the best of our knowledge, this is the first time that the asymmetric transfer hydrogenation of an acyclic imine in isopropanol using a β-aminoalcohol as chiral ligand has been reported.[13,14] Further efforts to extend the substrate scope and to find more synthetic applications of this reduction methodology are currently underway in our laboratories.

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