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Achiral β-amino alcohols as efficient ligands for the ruthenium-catalysed asymmetric transfer hydrogenation of sulfinylimines

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This Letter is dedicated to Professor Antonio García Martínez on occasion of his 70th anniversary

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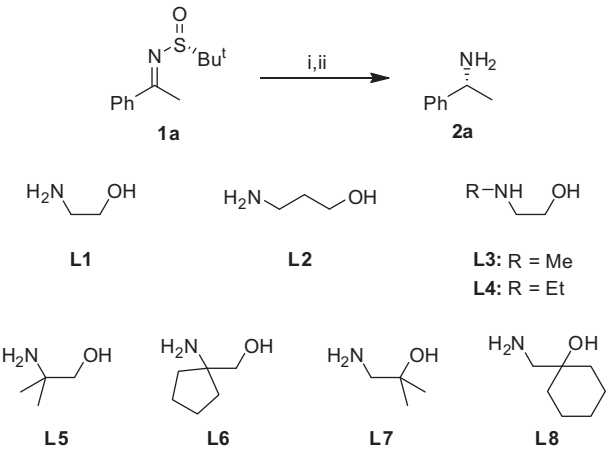
ABSTRACT

Some achiral β-amino alcohols have been shown as efficient ligands for the ruthenium-catalysed asymmetric transfer hydrogenation of *N*-(*tert*-butylsulfinyl)imines in isopropanol. The ruthenium complex prepared from $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %) and 2-amino-2-methyl-1-propanol (5 mol %) leads to α-branched chiral primary amines with very high optical purities (up to 98% ee) by the diastereoselective reduction of the imines followed by removal of the sulfinyl group under mild acidic conditions. Short reaction times (2–3 h) were needed to complete the reduction reactions when they were performed at 50 °C.

The asymmetric transfer hydrogenation has been widely applied to the reduction of ketones to give the corresponding enantiomerically enriched secondary alcohols.[1] However, the number of examples of the application of this methodology to the stereoselective synthesis of amines from imines is much more limited. Some ruthenium, rhodium or iridium complexes bearing chiral ligands, such as monotosylated diamines, β-aminoalcohols, diphosphines and *N*-heterocyclic carbenes, have been used as catalysts for the asymmetric transfer hydrogenation of *N*-alkyl,[1d] *N*-aryl,[1c,d] *N*-benzyl,[1c,d,2] *N*-phosphinyl,[1d,3] or *N*-sulfonyl[1b,d,4] imines and endocyclic imines.[1b–d,2] We have recently reported the first highly diastereoselective reduction of *N*-(*tert*-butylsulfinyl)ketimines using a hydrogen transfer protocol catalysed by a ruthenium complex bearing (1*S*,2*R*)-1-amino-2-indanol as a chiral ligand.[5] These sulfinylimines are very interesting substrates for the preparation of chiral primary amines,[6] since the *tert*-butylsulfinyl group can be easily removed from the reduction products under mild acidic conditions.[7] During our research on the asymmetric transfer hydrogenation of sulfinylimines, we found some evidences that the diastereoselectivity of the process was mainly controlled by the *tert*-butylsulfinyl group on the nitrogen atom of the imine,[5b] which suggested to us the possibility of using an achiral ligand in the ruthenium catalyst. This would be very convenient since it would probably reduce the reaction costs. Continuing with our studies on the use of sulfinylimines in asymmetric synthesis,[8] herein we present our preliminary results on that matter.

In our first studies on the asymmetric transfer hydrogenation of sulfinylimines, we found that imine **1a** (Scheme 1) could be



Scheme 1. Reagents and conditions: (i) $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), ligand (50 mol %), Bu^{t}OK (25 mol %), 4 Å MS, Pr^{i}OH, T; (ii) HCl, MeOH.

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transformed into amine **2a** at room temperature with an 84% ee using simple 2-aminoethanol as a ligand in the ruthenium catalyst, but an excess (3 equiv) of the ligand had to be used and the yield was very low (11%, Table 1, entry 1).[5a] Later on, we determined the optimum reaction conditions for the reductions in isopropanol with the ruthenium complex prepared with (1*S*,2*R*)-1-amino-2-indanol as a chiral ligand, which involved the use of 4 Å molecular sieves, Bu^{t}OK as a base and a reaction temperature of 40 °C.[5] We decided to try these new conditions in the reaction catalysed by the complex bearing 2-aminoethanol using 50 mol % of the ligand and we were pleased to see that the reaction time was reduced to 6 h and the yield of **2a** improved to 89%, maintaining the enantioselectivity of 84% (Table 1, entry 2). This result encouraged us to test some other achiral β-amino alcohols **L2**–**L8** as ligands for this process. All of these ligands were either commercially available (**L1**–**L6** and **L8**) or prepared in one step (**L7**).[9] The obtained results are collected in Table 1. From these results, it was clear that a β-amino alcohol structure with a primary amino group in the ligand was needed for the reductions to give good yields and diastereoselectivities. The extension of the carbon chain separating the amino and the hydroxy groups of the ligand (**L2**) or the methylation of the nitrogen atom (**L3**) led to incomplete reactions after 22 h with diminished ee's of around 70% in both cases (Table 1, entries 3 and 4). The introduction of a bulkier group on the nitrogen atom had an even more detrimental effect, the yield of the amine **2a** being only 15% (Table 1, entry 5). Having established that a 2-aminoethanol skeleton was necessary in the ligand, we next introduced substituents in both carbon atoms. Ligand **L5**, bearing two methyl groups on C2, gave, after desulfinylation, a 94% yield of amine **2a** with a very high enantiomeric excess (97%, Table 1, entry 6). Ligand **L6**, in which the carbon bearing the amino group belongs to a cyclopentane ring, gave a 97% yield of the reduction product with an ee slightly lower than the one obtained with the dimethyl-substituted ligand **L5** (compare entries 6 and 7 in Table 1). The effect of the substituents on the carbinol carbon was studied with ligands **L7** and **L8**, which gave amine **2a** in very good yields (Table 1, entries 8 and 9), but the stereoselectivities were lower than the one obtained with the ligand **L5**. As it was the case with ligands **L5** and **L6**, the ee slightly decreased with the cyclic ligand **L8** in comparison with the dimethyl-substituted amino alcohol **L7**. From these results, it seems clear that the increase of the steric hindrance close to the carbon of the ligand bearing the amino group contributes more to the improvement of the ee than the introduction of substituents at the carbinol site. We arrived at the conclusion that the ligand of choice was **L5**, not only because of the very high yield and ee obtained with it, but also due to its low price.

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

Entry	Ligand	*T* (°C)	*t*[b] (h)	Yield[c] (%)	ee[d] (%)
1[e]	**L1**	25	15	11[f]	84
2	**L1**	40	6	89	84
3	**L2**	40	22	44[g]	70
4	**L3**	40	22	31[g]	71
5	**L4**	40	22	15[g]	–[h]
6	**L5**	40	4	94	97
7	**L6**	40	4	97	94
8	**L7**	40	3	96	89
9	**L8**	40	3	96	80

[a] The solution of imine **1a** [0.9 mmol in Pr^{i}OH (9 mL)] and Bu^{t}OK (2.25 mL of a 0.1 M solution in Pr^{i}OH) were successively added to a solution of the ruthenium complex [prepared by refluxing a mixture of $[RuCl_2(p\text{-cymene})]_2$ (0.045 mmol), the ligand (0.45 mmol) and 4 Å molecular sieves (0.5 g) in Pr^{i}OH (2 mL)] at the temperature indicated and the reaction 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 (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 with 3 equiv of the ligand **L1**, in the absence of 4 Å molecular sieves and using KOH (50 mol %) as a base instead of Bu^{t}OK (see Ref. 5a).

[f] Acetophenone, Bu^{t}SONH$_2$ and 1-phenylethanol were also formed in the reduction reaction.

[g] Some unaltered imine was also observed in the crude reaction mixture.

[h] Not determined.

With this ligand in hand, we tried to optimize the reaction conditions using imine **1a** as a model substrate. First, the amount of the ligand **L5** was reduced keeping the loading of the ruthenium source $[RuCl_2(p\text{-cymene})]_2$ and Bu^{t}OK constant at values of 5 and 25 mol %, respectively. Fortunately, no detriment in either the yield or the enantioselectivity was observed when the amount of the ligand was gradually reduced up to 10 mol % (Table 2, entries 1–3). The proportion Ru-dimer: **L5**:Bu^{t}OK was then 1:2:5, which is the same that we found as the optimum one in our first report on the asymmetric transfer hydrogenation of sulfinylimines.[5] A minimum ratio **L5**:Bu^{t}OK of 2:5 seems to be crucial for the reaction to work, since the change of this ratio to 2:2.5 completely prevented the reduction process, the unaltered imine being recovered (Table 2, entry 4). Maintaining the proportion Ru-dimer:**L5**:Bu^{t}OK = 1:2:5, we tried to reduce the catalyst loading and we were pleased to see that 2.5 mol % of the Ru-dimer was enough to achieve the preparation of amine **2a** in 90% yield without loss of enantiomeric purity (Table 2, entry 5). In this case, the reaction time had to be extended to 5 h in order to get full conversion of the imine. However, this reaction time could be reduced to 2 h by performing the transfer hydrogenation reaction at 50 °C, which afforded the expected amine in 97% yield and 97% ee (Table 2, entry 6). Encouraged by this result, we tried to further reduce the catalyst loading to 1 mol % of the Ru-dimer: the ee was slightly lower but the yield drastically fell to 50% (Table 2, entry 7). With the idea of trying to improve the yield, we repeated the reaction at 60 °C but this led to an even more pronounced reduction of the yield with some loss of optical purity (Table 2, entry 8). After all of these experiments, we chose the conditions of entry 6 as the optimum one. It is worth noting that these conditions represent the reduction of the catalyst loading to half of the one used in our previous report on the asymmetric transfer hydrogenation of *N*-(*tert*-butylsulfinyl)imines.[5]

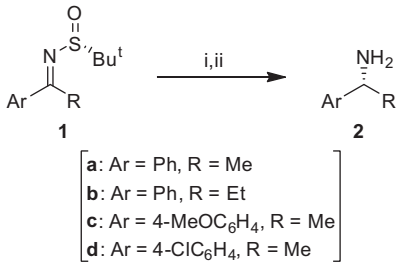
After performing the optimization of the reaction conditions, some other imines **1b**–**d**[10] were used as substrates (Scheme 2, Table 2, entries 9–11).[11] Imine **1b**, derived from propiophenone, gave an excellent yield and enantioselectivity in a reaction time of only 2 h (Table 2, entry 9). Our methodology is equally efficient for the reduction of imines derived from phenones bearing either an electron-releasing or an electron-withdrawing group on the aromatic ring. Very high yields and ee's were obtained irrespective of the electronic nature of the substituent on the aromatic ring of the imine (Table 2, entries 10 and 11). We also performed the reduction of the (*S*)-*N*-(*tert*-butylsulfinyl)benzaldimine *ent*-**1a** and the expected enantiomeric amine *ent*-**2a** was obtained, after desulfinylation, in very good yield with the same enantiomeric purity as for the preparation of the (*R*)-amine **2a** (compare entries 6 and 12). This result confirms our assumption that the diastereoselectivity of the reduction process is mainly controlled by the *tert*-butylsulfinyl group.

In conclusion, we have presented here a very efficient procedure to prepare highly optically enriched primary amines through the asymmetric transfer hydrogenation of *N*-(*tert*-butylsulfinyl)imines in isopropanol catalysed by a ruthenium complex bearing a commercially available and inexpensive achiral β-amino alcohol as a ligand. Simple 2-amino-2-methyl-1-propanol as a ligand for the ruthenium catalyst presents some advantages over (1*S*,2*R*)-1-amino-2-indanol that we previously used:[5] the first

Table 2
Ruthenium-catalysed asymmetric transfer hydrogenation of *N*-(*tert*-butylsulfinyl)imines **1** using 2-amino-2-methyl-1-propanol as a ligand. Preparation of amines **2**.[a]

Entry	Imine	Ru-dimer (mol %)	**L5** (mol %)	Bu^{t}OK (mol %)	*T* (°C)	*t*[b] (h)	Product		
							No.	Yield[c] (%)	ee[d] (%)
1	**1a**	5	50	25	40	4	**2a**	94	97
2	**1a**	5	25	25	40	2	**2a**	94	96
3	**1a**	5	10	25	40	2	**2a**	96	96
4	**1a**	5	10	12.5	40	22	**2a**	–[e]	–[f]
5	**1a**	2.5	5	12.5	40	5	**2a**	90	96
6	**1a**	2.5	5	12.5	50	2	**2a**	97	97
7	**1a**	1	2	5	50	5	**2a**	50	93
8	**1a**	1	2	5	60	3	**2a**	24	88
9	**1b**	2.5	5	12.5	50	2	**2b**	98	98
10	**1c**	2.5	5	12.5	50	3	**2c**	94	96
11	**1d**	2.5	5	12.5	50	2.5	**2d**	95	97
12	*ent*-**1a**	2.5	5	12.5	50	2	*ent*-**2a**	96	98

[a] The solution of imine **1** (0.9 mmol) in Pr^{i}OH (6.3 mL) was added to a solution of the ruthenium complex [prepared by refluxing a mixture of $[RuCl_2(p\text{-cymene})]_2$, ligand **L5** and 4 Å molecular sieves (0.4 g) in Pr^{i}OH (1.3 mL)] at the temperature indicated. Then, Bu^{t}OK (1.13 mL of a 0.1 M solution in Pr^{i}OH) was added and the reaction 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 (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.
[f] Not determined.



Scheme 2. Reagents and conditions: (i) $[RuCl_2(p\text{-cymene})]_2$ (cat.), 2-amino-2-methyl-1-propanol (cat.), Bu^{t}OK (cat.), 4 Å molecular sieves (0.4 g), Pr^{i}OH, T; (ii) HCl, MeOH.

ligand is much cheaper and the catalyst loading that we used in this report is much lower. Further efforts to extend the substrate scope and to study a possible mechanism that could explain the diastereoselectivity of this reduction process are currently underway in our laboratories.

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11. *Typical experimental procedure* (Table 2, entry 6): a mixture of the ligand **L5** (4 mg, 0.045 mmol), $[RuCl_2(p\text{-cymene})]_2$ (14 mg, 0.0225 mmol), 4 Å molecular sieves (0.4 g) and anhydrous Pr^{i}OH (1.3 mL) was heated up to 90 °C (oil bath temperature) for 20 min. During this heating period, the initially orange reaction mixture turned into a dark red colour. The reaction was then cooled to 50 °C and the imine **1a** [0.9 mmol, dissolved in Pr^{i}OH (6.3 mL)] and Bu^{t}OK (1.13 mL of a 0.1 M solution in Pr^{i}OH, 0.113 mmol) were successively added. After completion of the reaction (monitored by TLC), the reaction mixture was passed through a small column of silica gel, the column was washed with ethyl acetate and the combined organic phases were evaporated to give a residue that was directly submitted to the desulfinylation step, which was carried out following the procedure previously described by us (see Ref. 8b). The absolute configuration of the asymmetric carbon atom of the major enantiomer was determined by comparison of the sign of the specific rotation of the free amine **2a** with the reported data. The enantiomeric excess was determined for the corresponding benzamide by HPLC as previously described by us (see Ref. 8b).