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Asymmetric Synthesis of Chiral Primary Amines by Transfer Hydrogenation of *N*-(*tert*-Butanesulfinyl)ketimines[§]

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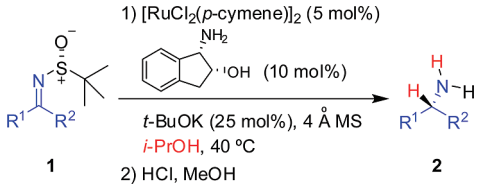

The diastereoselective reduction of (*R*)-*N*-(*tert*-butanesulfinyl)ketimines by a ruthenium-catalyzed asymmetric transfer hydrogenation process in isopropyl alcohol, followed by desulfinylation of the nitrogen atom, is an excellent method to prepare highly enantiomerically enriched α-branched primary amines (up to >99% ee) in short reaction times (1−4 h). (1*S*,2*R*)-1-Amino-2-indanol has been shown to be a very efficient ligand to perform this transformation. Ketimines bearing either an aryl or a heteroaryl group and an alkyl group as substituents of the iminic carbon atom are very good substrates for this process. The reduction of a dialkyl ketimine could also be achieved, affording the expected amine with moderate optical purity (69% ee). Some amines which are precursors of very interesting biologically and pharmacologically active compounds have been prepared in excellent yields and enantiomeric excesses.

Introduction

Chiral amines are present in many natural products and biologically active compounds.[1] α-Branched amines are constituents of pharmaceutical compounds, and several therapeutic applications have been found for them.[2] Optically active amines have also extensively been used as chiral auxiliaries[3] and resolving agents[4] in asymmetric synthesis. Due to all of these features, considerable efforts have been made by chemists in order to design efficient procedures for their stereoselective preparation. Among the reported methodologies to produce enantiomerically enriched primary amines, we can find (a) resolution of racemic amines by crystallization of their diastereomeric salts with carboxylic acids,[2] (b) addition of organometallic reagents to imines,[5] (c) asymmetric reduction of ketimines,[2,5e,6] and (d) enzyme-mediated methods like transamination between carbonyl compounds and amines[2] and kinetic resolution of racemic amines.[2,7] In recent years, the reduction of compounds containing C=N bonds has emerged as a powerful way of synthesizing chiral amines. Due to the low electrophilic character of the C=N bond, the nitrogen atom of these precursors is normally bonded to an activating group, such as aryl, alkoxy, amino, phosphinyl, sulfonyl, or sulfinyl. The latter is especially interesting because its inherent chirality makes it act as a chiral auxiliary apart from being an activating group for the

[§] Dedicated to Professor Carmen Nájera on the occasion of her 60th birthday.

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imine functionality and a protecting group for the nitrogen atom of the reduction product. Furthermore, the sulfinyl group can easily be removed under mild acidic conditions[8] for further transformations. The *tert*-butanesulfinyl group is particularly interesting because it has shown high levels of asymmetric induction in a variety of processes. Since the initial studies carried out by Ellman, *N*-(*tert*-butanesulfinyl)-imines have consolidated as excellent substrates for the preparation of chiral primary amines.[9] The diastereoselective reduction of *N*-(*tert*-butanesulfinyl)ketimines has been achieved using several boranes,[9b,c,10] sodium or lithium borohydrides,[9b,c,e,10,11] aluminum hydrides,[9c,10,11] and diethylzinc in the presence of $Ni(acac)_2$.[12]

Among the different approaches to perform the reduction of a carbon−heteroatom double bond, the transfer hydrogenation protocol presents several advantages because it is operationally simple, normally uses low catalyst loadings, and avoids the handling of hazardous chemicals such as metallic hydrides or molecular hydrogen. Moreover, volatile reaction side products, such as acetone or carbon dioxide, are formed, which facilitates the isolation of the reduction products. The asymmetric transfer hydrogenation has widely been applied to the synthesis of chiral secondary alcohols by reduction of ketones.[13] However, there are only a limited number of examples of stereoselective preparation of amines by this methodology. The asymmetric reduction of imines bearing alkyl,[13d] aryl,[13c,d] benzyl,[5c,13c,d] phosphinyl,[2,13d] or sulfonyl[13b,d] groups on the nitrogen atom and endocyclic imines[5c,13b−d] by transfer hydrogenation has been published, with the catalysts being ruthenium,[14] rhodium, or iridium complexes with chiral ligands such as monotosylated diamines, β-aminoalcohols, diphosphines, and N-heterocyclic carbenes. Some organocatalysts have also been employed in the reduction of *N*-aryl- and endocyclic imines.[13c,d] However, to the best of our knowledge, the asymmetric transfer hydrogenation has never been applied to the reduction of sulfinylimines. As part of our research on the use of these useful imines in asymmetric synthesis,[15] herein we report our results on the preparation of highly enantiomerically enriched amines by a ruthenium-catalyzed transfer hydrogenation of *N*-(*tert*-butanesulfinyl)imines.[16]

Results and Discussion

The use of β-aminoalcohols as ligands for asymmetric catalysis has been one of the subjects of our research activities during the last several years.[17] Since one of the most successful applications of these compounds has been as ligands for ruthenium complexes used as catalysts for the transfer hydrogenation of ketones,[13] we decided to explore the possibility of extending this reduction methodology to *N*-(*tert*-butanesulfinyl)imines. After screening several aminoalcohols,[16] we found that (1*S*,2*R*)-1-amino-2-indanol[18,19] **3** (20 mol %) gave a complex by reaction with $[RuCl_2(p\text{-cymene})]_2$ (5 mol %) that was able to catalyze the reduction of the imine derived from acetophenone **1a** (Table 1) in isopropyl alcohol at room temperature and in the presence of KOH (50 mol %). The yield of the reduction product **2a** was quite low (31%), but we were pleased to see that the ee was excellent (98%, Table 1, entry 1). The high enantioselectivity obtained encouraged us to do an optimization study of the reaction conditions since, to the best of our knowledge, this was the first time that the asymmetric transfer hydrogenation of an acyclic imine using a β-aminoalcohol as a chiral ligand and isopropyl alcohol as a hydrogen source had been achieved.[20,21] Moreover, the possibility of performing the reductions in isopropyl alcohol was very attractive because it has been proven to be a convenient solvent for industrial scale processes.[22,23]

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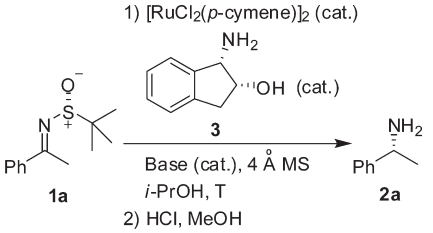
(21) Andersson has reported the synthesis of chiral aziridines by a ruthenium-catalyzed asymmetric transfer hydrogenation of strained 2*H*-azirines in isopropyl alcohol using a β-aminoalcohol as a chiral ligand: Roth, P.; Andersson, P. G.; Somfai, P. *Chem. Commun.* **2002**, 1752–1753.

TABLE 1. Optimization of the Reaction Conditions[a]



			base					product	
entry	Ru dimer (mol %)	**3** (mol %)	base	(mol %)	4 Å MS (g)	T (°C)	t[b] (h)	yield[c] (%)	ee[d] (%)
1	5	20	KOH	50		25	15	31[e]	98
2	5	20	*t*-BuOK	50		25	16	76	99
3	5	20	*t*-BuOK	50	0.2	25	19	74	99
4	5	20	*t*-BuOK	50	0.5	25	20	95	>99
5	5	10	*t*-BuOK	50	0.5	25	22	97	>99
6	5	20	*t*-BuOK	25	0.5	25	24	97	>99
7	5	10	*t*-BuOK	25	0.5	25	20	98	>99
8	3	6	*t*-BuOK	15	0.5	25	30	84	99
9	8	16	*t*-BuOK	40	0.5	25	5	99	99
10	5	10	*t*-BuOK	25	0.5	40	2	99	98
11	3	6	*t*-BuOK	15	0.5	40	4	67	96
12[f]	5	10	*t*-BuOK	25	0.5	40	3	83	98
13[g]	5	10	*t*-BuOK	25	0.5	40	2	96	97

[a]The solution of imine **1a** (0.9 mmol) in *i*-PrOH (9 mL) was added to a solution of the ruthenium catalyst [prepared by refluxing a mixture of $[RuCl_2(p\text{-cymene})]_2$, aminoalcohol **3**, and 4 Å molecular sieves in *i*-PrOH (2 mL)] at the temperature indicated. Then, the base (as a 0.1 M solution in *i*-PrOH) 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 **2a** after acid−base extraction based on the starting imine **1a**. Compound **2a** was ≥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]Acetophenone, *t*-BuSONH$_2$ and 1-phenylethanol were also obtained in the crude reaction mixture. [f]A solution of the imine **1a** (0.9 mmol) in *i*-PrOH (5 mL) was used. [g]A solution of the imine **1a** (0.9 mmol) in *i*-PrOH (18 mL) was used.

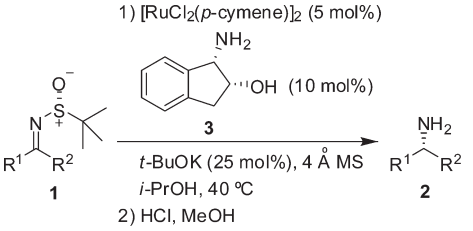
The detection of acetophenone, *t*-BuSONH$_2$ and 1-phenylethanol (the latter resulting from the reduction of acetophenone) in the crude reaction mixture suggested to us that a hydrolysis of the sulfinylimine was occurring, which was certainly the reason for the low yield obtained. Since we had used anhydrous isopropyl alcohol and a non-aqueous workup procedure was carried out (simply filtration through silica gel to remove the ruthenium complex and evaporation of the solvent), we suspected that the water that was forming after the deprotonation with KOH was responsible for the decomposition of the imine. Therefore, we decided to change the base to *t*-BuOK, and we were glad to see that the yield of the reduction product improved to 76%, keeping the excellent ee value (Table 1, entry 2). To be sure that all traces of water had been removed, we repeated the reaction in the presence of 0.2 g of activated 4 Å molecular sieves, but this additive did not seem to cause any improvement (Table 1, entry 3). However, when 0.5 g of 4 Å molecular sieves was used, a much higher yield of **2a** (95%) was obtained (Table 1, entry 4).

We next tried to find the optimum proportion between the reagents. The reduction of the Ru dimer/**3** ratio to 1:2 did not cause any detriment to the ee (compare entries 4 and 5 in Table 1). When the amount of *t*-BuOK was reduced to 25 mol %, keeping the amounts of Ru complex and ligand constant, the result did not vary (compare entry 4 with 6 and 5 with 7 in Table 1). After these observations, we decided to use the ratio Ru dimer/**3**/*t*-BuOK = 1:2:5 in further tests. The reduction of the amount of the Ru dimer to 3 mol % slowed the transfer hydrogenation reaction and led to a lower yield of **2a**, although the stereoselectivity was still excellent (compare entries 7 and 8 in Table 1). When 8 mol % of the Ru complex was used, the reaction was much faster than the one with 5 mol % of it, with the yield and ee of the amine **2a** being almost the same in both cases (compare entries 7 and 9 in Table 1). For this reason, we did not consider it necessary to use more than 5 mol % of the Ru dimer as the catalyst precursor. The effect of an increase of the reaction temperature was also studied, and we found that a quantitative yield of the amine **2a** was obtained in only 2 h with a very slight decrease in the ee when the transfer hydrogenation was performed at 40 °C (Table 1, entry 10). This fast reaction encouraged us to try to reduce the amount of the ruthenium precatalyst to 3 mol %, but an important reduction in yield and a lower enantioselectivity were obtained (Table 1, entry 11). Finally, the influence of the reaction concentration was investigated, and it was observed that neither a higher (entry 12) nor a lower (entry 13) concentration improved the results in comparison with the ones obtained under the conditions of entry 10. After all of these tests, we chose conditions of entry 10 as the optimum ones because they gave a good combination of short reaction time and excellent yield and enantioselectivity.

(22) See, for instance: (a) Reference 18e. (b) Blacker, J.; Martin, J. In *Asymmetric Catalysis on Industrial Scale*; Blaser, H. U., Schmidt, E., Eds.; Wiley-VCH: Weinheim, Germany, 2004; pp 201−216.

(23) The use of *tert*-butanesulfinamide as a precursor of the sulfinylimines might appear as an economical drawback for possible industrial scale applications of our methodology. However, the cost of the process could be diminished taking into account that an efficient procedure for the recycling of the sulfinyl chiral auxiliary has been recently reported: Wakayama, M.; Ellman, J. A. *J. Org. Chem.* **2009**, *74*, 2646–2650.

TABLE 2. Ruthenium-Catalyzed Asymmetric Transfer Hydrogenation of Imines 1[a]



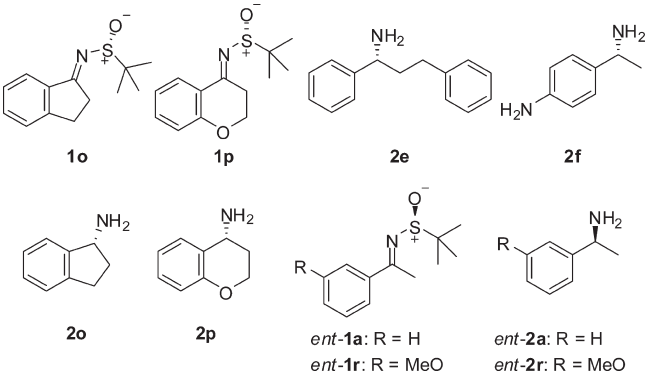
					product		
entry	imine	R^1	R^2	t[b] (h)	no.	yield[c] (%)	ee[d] (%)
1	**1a**	Ph	Me	2	**2a**	99	98
2	**1b**	Ph	Et	4	**2b**	98	98
3	**1c**	Ph	Pr	3	**2c**	94	99
4	**1d**	Ph	CH_2Cl	5	**2d**	95	99[e]
5	**1e**[f]	Ph	(*E*)-CH=CHPh	0.5	**2e**[g]	97	98
6	**1f**	4-BocNHC$_6$H$_4$	Me	2.5	**2f**[g]	97[h]	98
7	**1g**	4-MeOC$_6$H$_4$	Me	3	**2g**	99	95
8	**1h**	3-ClC$_6$H$_4$	Me	2	**2h**	98	>99
9	**1i**	4-ClC$_6$H$_4$	Me	2.5	**2i**	97	>99
10	**1j**	4-CF$_3$C$_6$H$_4$	Me	1.5	**2j**	97	99
11	**1k**	4-NO$_2$C$_6$H$_4$	Me	1	**2k**	99	97
12	**1l**	2-naphthyl	Me	2	**2l**	96	98
13	**1m**	2-furyl	Me	3	**2m**	95	99
14	**1n**	2-thienyl	Me	8	**2n**	81	97
15	**1o**[g]	---	---	3.5	**2o**[g]	92	93
16	**1p**[g]	---	---	5	**2p**[g]	91	98
17	**1q**[i]	Cy	Me	24	**2q**	82	69
18	*ent*-**1a**[g]	Ph	Me	3	*ent*-**2a**[g]	97	84[j]
19	*ent*-**1a**[g,k]	Ph	Me	2.5	*ent*-**2a**[g]	98	98[j]
20	*ent*-**1r**[g,k]	3-MeOC$_6$H$_4$	Me	3	*ent*-**2r**[g]	97	>99[j]

[a]The solution of imine **1** (0.9 mmol) in *i*-PrOH (9 mL) was added to a solution of the ruthenium catalyst [prepared by refluxing a mixture of [$RuCl_2$(*p*-cymene)]$_2$ (0.045 mmol), aminoalcohol **3** (0.09 mmol), and 4 Å molecular sieves (0.5 g) in *i*-PrOH (2 mL)] at 40 °C. Then, *t*-BuOK (0.225 mmol, as a 0.1 M solution in *i*-PrOH) 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 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]The absolute configuration of this product was *S* due to the priority order of the groups according to the CIP rules. [f]This reaction was performed at 20 °C. [g]For the structure of this compound, see Chart 1. [h]Compound **2f** was isolated as its dihydrochloride. [i]This reaction was performed at 80 °C using 10 mol % of Ru dimer, 20 mol % of ligand **3**, and 50 mol % of *t*-BuOK. [j]The *S*-enantiomer was the major one in this case. [k]The (S_S)-imine *ent*-**1** and (1*R*,2*S*)-1-amino-2-indanol (the enantiomer of ligand **3**) were used in this reaction.

The transfer hydrogenation of ketones in isopropyl alcohol is a reversible process, and an unnecessarily long reaction time can cause a reduction of the enantiomeric excess of the desired secondary alcohol, as it has been observed by several research groups.[13a,18a,d,f,i,22b] Concerned about this problem, we investigated whether a prolonged reaction time could cause any decrease in the diastereoselectivity of our transfer hydrogenation procedure under the optimum reaction conditions. Two aliquots were taken from a reduction of **1a** at reaction times of 4.5 and 24 h. No detriment in the ee (98%) of the final amine **2a** was observed in any of them, which seems to indicate that the transfer hydrogenation of the sulfinylimines in isopropyl alcohol is not a reversible process.

Once the optimum reaction conditions had been established, we explored the substrate scope, and all of the obtained results are summarized in Table 2. Imines **1a**−**c**, bearing different straight chain alkyl substituents, led to the expected primary amines **2a**−**c** in very good yields and enantioselectivities (Table 2, entries 1−3). The chloro-substituted imine **1d** also gave an excellent ee in the reduction product **2d** (Table 2, entry 4). The transfer hydrogenation of imine **1e**, derived from chalcone, was very fast. It was not necessary to raise the temperature to 40 °C since the reaction at room temperature was finished in 30 min, affording product **2e** (Chart 1), resulting from reduction of both the imine and the C=C bond (Table 2, entry 5). This reaction was repeated at −40 °C in an attempt to get a selective reduction of one of the unsaturated bonds. The reaction was monitored by ^{1}H NMR, and it seemed that the reduction of the C=C bond was taking place faster than the reduction of the C=N bond. After a reaction time of 10 min, a sample was withdrawn and worked up, and its ^{1}H NMR spectrum showed that the main

CHART 1



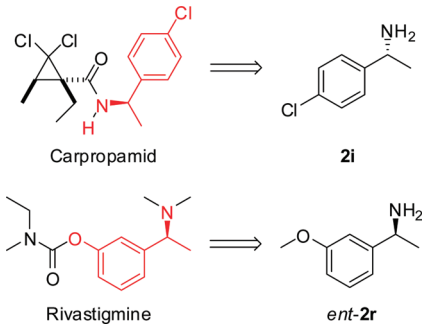
product was the one resulting from reduction of the olefin (ratio of **1e**/monoreduction product ≅ 3:1). However, the signals corresponding to the double reduction product could be detected, too, which suggested that the selective reduction of the C=C bond would not be possible. Further evolution of the reaction confirmed our suspicion: after 2 h, the ratio of **1e**/monoreduction product/double reduction product was 1.1:0.9:0.14.

Next, we studied the effect of several substituents on the aromatic ring bonded to the iminic carbon atom. Almost quantitative yields and excellent enantiomeric excesses were obtained in the transfer hydrogenation of acetophenones bearing either electron-releasing (Table 2, entries 6 and 7) or electron-withdrawing groups (Table 2, entries 8−11). The same good results were found when isomeric imines **1h** and **1i** were reduced: very high yields and enantioselectivities were obtained when the chloro substituent was either in *meta* or *para* position to the imine functionality. However, the reduction of the imine derived from *o*-chloroacetophenone was much slower: after the reaction was stirred at 40 °C for 8 h, a conversion of less than 20% was observed. In the case of the imine **1f**, the Boc protecting group was also removed during the desulfinylation process, affording the diamine **2f** (Chart 1), which was isolated as its dihydrochloride due to problems in the purification of the free diamine.

Some other aromatic systems different from benzene were introduced in the iminic substrate. The 2-naphthyl-substituted imine **1l** was reduced with the same efficiency as the acetophenone-derived imines (Table 2, entry 12). Our methodology was shown to be equally effective for the preparation of heterocyclic amines **2m** and **2n** (Table 2, entries 13 and 14) by reduction of imines bearing a 2-furyl or a 2-thienyl substituent, respectively. Benzo-condensed cyclic imines **1o** and **1p** (Chart 1), derived from 1-indanone and 4-chromanone, respectively, also yielded the expected amines **2o** and **2p** (Chart 1) with very high optical purity (Table 2, entries 15 and 16). We also tried the reduction of the aliphatic imine **1q**. As expected, it was much less reactive than the aromatic imines: the reaction had to be set up at 80 °C in order to get full conversion of the imine after 24 h. However, the isolated yield of amine **2q** was good, and the 69% ee that was obtained is comparable to the enantioselectivities reported for other transfer hydrogenation processes with aliphatic imines.[24] Moreover, to the best of our knowledge, this is the first time that the asymmetric transfer hydrogenation of an aliphatic imine using isopropyl alcohol as hydrogen source has been reported.

Finally, we also explored the possibility of preparing the enantiomeric amines *ent*-**2** by application of our transfer hydrogenation protocol to (S_S)-sulfinimines. The reduction of imine *ent*-**1a** (Chart 1) catalyzed by the same ruthenium complex and ligand as before gave the (*S*)-amine *ent*-**2a** (Chart 1) in very high yield and with an 84% ee (Table 2, entry 18). The comparison of this result with the one obtained with the (R_S)-imine **1a** (Table 2, entry 1) leads to the conclusion that the configuration of the imine plays a leading role in determining the stereochemical outcome of the reaction, but the structure of the ligand also has an influence on the stereoselectivity. The use of ligand **3** for the reduction of the (R_S)-imines turned out to be a matched combination: the transfer hydrogenation of imine **1a** using ligand **3** gave the (*R*)-amine **2a** with a 98% ee (Table 2, entry 1), which is higher than the one obtained for the reduction of the same imine with the enantiomer of the ligand (1*R*,2*S*)-1-amino-2-indanol (*ent*-**3**) that was 84% ee (data not shown in Table 2). The latter ee value is equal to the one that we had obtained using simple 2-aminoethanol as a ligand (see ref 16). This suggests that maybe it is not necessary to use a chiral ligand to achieve high stereoselectivity levels.[25] The search for a ligand with the appropriate substituents, even if achiral, would probably improve the diastereoselectivity of the transfer hydrogenation process. This possibility is currently being explored in our laboratory, and the results will be reported in due course. A theoretical study is also in progress in order to ascertain the role of the sulfinyl group and a possible mechanism for the asymmetric transfer hydrogenation process. The enantiomeric purity of the (*S*)-amine *ent*-**2a** could be improved by preparing the ruthenium catalyst with the ligand *ent*-**3** (Table 2, entry 19), reproducing the 98% ee that had been obtained in the reduction of the (R_S)-imine **1a** using ligand **3**. Another (S_S)-imine substituted with a methoxy group, *ent*-**1r** (Chart 1), was submitted to the transfer hydrogenation process using the enantiomer of ligand **3**, and the expected (*S*)-amine *ent*-**2r** (Chart 1) was obtained in optically pure form in 97% yield (Table 2, entry 20).

SCHEME 1



The usefulness of this reduction procedure becomes clear if we think about possible applications of the obtained primary amines. Some of these amines are potential precursors of pharmaceuticals or biologically active compounds. For instance, the *p*-chloro-substituted amine **2i** is a key intermediate in the synthesis of the agricultural fungicide Carpropamid[26] (Scheme 1), which is useful for the control of rice blast. The synthesis of amine **2i** in 90% ee by crystallization of the racemic amine with a chiral carboxylic acid has been described,[2] with the consequent loss of 50% of the yield. With our methodology, this amine was obtained in 97% yield in optically pure form (Table 2, entry 9). On the other hand, the (*S*)-amine *ent*-**2r** is a suitable substrate for the synthesis of Rivastigmine (Scheme 1), which is a cholinesterase inhibitor that is used to treat moderate dementia in people with Alzheimer's or Parkinson's diseases[27] and is on

(24) See, for instance: Renat, K.; Thomas, H. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 5472–5474.

(25) We thank the reviewers for suggesting that we comment on the possibility of using an achiral ligand.

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the market as its tartrate salt under the brand name Exelon. Recently, a total synthesis of (*S*)-Rivastigmine in three steps from amine *ent*-**2r** has been reported.[28] In that article, the required amine *ent*-**2r** was prepared from 3-methoxyacetophenone in five synthetic steps, including an enzyme-mediated dynamic kinetic resolution, with an overall yield of 55% and an ee of 99%. Another reported procedure for the synthesis of amine *ent*-**2r** involves the copper-catalyzed addition of dimethylzinc to 3-methoxy-*N*-(diphenylphosphinoyl)benzaldimine and gives the expected amine in 88% yield and 92% ee.[29] Our methodology is a very good alternative to these two approaches since we obtained amine *ent*-**2r** from 3-methoxyacetophenone in only three steps in an overall yield of 82% and with an optical purity of >99%.

During our assays to reduce different substrates, we found some difficulties with certain imines derived from ketones with substituents close to the carbonyl group. For instance, when the transfer hydrogenation procedure was attempted with the imines derived from methyl 1-naphthyl ketone, isobutyrophenone, cyclohexyl phenyl ketone, or 2-methylbenzophenone, only traces of the expected amines were detected in the ^{1}H NMR spectra of the crude reaction mixtures, the major component of these mixtures being the corresponding unaltered imines. Some attempts to reduce imines bearing nitrogen-containing heterocyclic substituents, such as 2- or 4-pyridyl, were unsuccessful, too. In these cases, a possible coordination of the imine to the ruthenium complex through those nitrogen atoms could compete with the coordination of the iminic nitrogen, which would prevent the transfer hydrogenation process.

Conclusion

We have presented here a ruthenium-catalyzed asymmetric transfer hydrogenation procedure that reduces *N*-(*tert*-butanesulfinyl)imines in isopropyl alcohol in short reaction times and with very high diastereoselectivities. The methodology is very efficient for the reduction of imines bearing one aromatic substituent on the iminic carbon atom. The reduction of one aliphatic imine has been also achieved, although the stereoselectivity was lower in this case. The diastereoselectivity seems to be controlled mainly by the absolute configuration of the starting imine. An important feature of this process is that, contrary to the decrease of ee that has been observed in the transfer hydrogenation of ketones, there is no detriment in the de of the reduction products with extended reaction times. Since the sulfinyl group can be easily removed from the reduction products, this protocol represents a very efficient way to prepare α-branched primary amines with very high optical purities. Both enantiomers of *tert*-butanesulfinamide, needed to prepare the starting imines, and of the ligand used are commercially available, which allows the preparation of both enantiomers of the final amines in highly enantiomerically enriched form. To the best of our knowledge, this is the first time that the asymmetric transfer hydrogenation of an acyclic imine and using a β-aminoalcohol as chiral ligand has been achieved in isopropyl alcohol, which is a very interesting solvent for designing procedures applicable to the chemical industry.

Experimental Section

General Procedure for the Asymmetric Transfer Hydrogenation of Imines 1. A mixture of $[RuCl_2(p\text{-cymene})]_2$ (28 mg, 0.045 mmol), the ligand **3** (14 mg, 0.09 mmol), 4 Å molecular sieves (0.5 g), and anhydrous *i*-PrOH (2 mL) was heated to 90 °C (oil bath temperature) for 20 min. During this heating period, the initially orange reaction mixture turned into a dark red color. The reaction was then cooled to 40 °C, and a solution of the imine **1** (0.9 mmol) in *i*-PrOH (9 mL) and *t*-BuOK (2.25 mL of a 0.1 M solution in *i*-PrOH, 0.225 mmol) was 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.

General Procedure for the Removal of the Sulfinyl Group. Isolation of Amines 2. The crude mixture of the transfer hydrogenation reaction was dissolved in a 1.5 M solution of HCl in methanol (4 mL; prepared by dropwise addition of $SOCl_2$ to methanol at 0 °C) and stirred overnight at room temperature. Then, the solvent was evaporated, a 2 M aqueous HCl solution (5 mL) was added, and the mixture was extracted with ethyl acetate (3 × 5 mL). The organic layers were discarded. The aqueous layer was basified with a buffer solution of NH_3 (1 M)/NH_4Cl (1 M) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried (Na_2SO_4). After filtration and evaporation of the solvent, pure amines **2** were obtained in the yields indicated in Table 2. The corresponding physical and spectroscopic data for the representative compound **2i** follow:

(*R*)-1-(4-Chlorophenyl)ethanamine (2i):[30] Colorless oil; R_f 0.33 (ethyl acetate, deactivated silica gel); $[\alpha]^{20}_D$ +31.0 (*c* 1.2, $CHCl_3$, >99% ee) {literature[30] $[\alpha]^{20}_D$ +18.9 (*c* 1.0, $CHCl_3$, 92% ee)}; IR (neat) 3365, 3285, 3046, 1590, 1491, 1093 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (3H, d, J = 6.7 Hz), 1.56 (2H, br s), 4.10 (1H, q, J = 6.7 Hz), 7.24−7.31 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.7, 50.6, 127.1, 128.5, 132.2, 146.1; *m*/*z* 155 (M^+, 3%), 142 (25), 140 (100), 139 (14), 138 (31), 137 (11), 77 (23), 75 (18), 51 (10).

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Supporting Information Available: Complete experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for imines **1** and amines **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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