Microwave-Enhanced Asymmetric Transfer Hydrogenation of *N*-(*tert*-Butylsulfinyl)imines

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Abstract: Microwave irradiation considerably enhances the efficiency of the asymmetric transfer hydrogenation of *N*-(*tert*-butylsulfinyl)imines in isopropyl alcohol catalyzed by a ruthenium complex bearing the achiral ligand 2-amino-2-methylpropan-1-ol. Besides shortening reaction times for the transfer hydrogenation processes to only 30 min, the amounts of the ruthenium catalyst and isopropyl alcohol can be considerably reduced in comparison to our previous procedure assisted by conventional heating, which diminishes the environmental impact of this new protocol. This methodology can be applied to aromatic, heteroaromatic and aliphatic *N*-(*tert*-butylsulfinyl)ketimines, leading, after desulfinylation, to the expected primary amines in excellent yields and with enantiomeric excesses up to 96%.

Introduction

The asymmetric transfer hydrogenation (ATH) has proved to be a highly valuable method for the reduction of carbon-heteroatom double bonds, especially in ketones[1] and imines.[1b-d,f,2] There are several features that make this reduction methodology so convenient: (a) it requires a very simple equipment; (b) it is safer than other widely used reduction methods, since it avoids the use of hazardous chemicals such as highly flammable molecular hydrogen or metallic hydrides; (c) it can be performed in environmentally friendly solvents, like isopropyl alcohol, which also acts as the hydrogen source; (d) volatile reaction by-products are formed, which facilitates the isolation of the reduction products in pure form. These advantages have allowed the development of interesting industrial processes.[3] On the other hand, microwave irradiation has shown to be a very efficient technique to accelerate different kinds of reactions,[4] including ATH. Several examples of the use of microwaves to promote the ATH of ketones can be found in the literature.[5] However, the reports of microwave-assisted ATH of the C=N bond are scarce and, to the best of our knowledge, there are only three examples of the reduction of *N*-alkyl- or *N*-arylimines[5g,6] and another one of the reduction of a hydrazone,[7] but none of them are stereoselective processes.

In the last years, one of our main research lines has been focused on the synthesis of highly enantiomerically enriched amines by ATH of *N*-(*tert*-butylsulfinyl)ketimines.[8,9] The ATH process was catalyzed by a ruthenium complex bearing the readily available and inexpensive achiral ligand 2-amino-2-methylpropan-1-ol and isopropyl alcohol was used as the hydrogen source. The reduction of both aromatic and aliphatic sulfinylimines led, after desulfinylation, to the expected α-branched primary amines with excellent enantiomeric excesses. In the search for a procedure with a lower impact to the environment and encouraged by our previous successful applications of microwaves in organic synthesis,[10] we decided to try to use microwave heating to activate the reagents in our ATH protocol and herein we present our results on that matter.

Results and Discussion

We chose imine **1a** as a model substrate and tried to perform its reduction by ATH utilizing the same amounts of reagents that we had used in our previous procedure promoted by conventional heating. The ruthenium catalyst was prepared by refluxing a mixture of $[RuCl_2(p\text{-cymene})]_2$, 2-amino-2-methylpropan-1-ol and 4 Å molecular sieves in isopropyl alcohol, according to our previously described procedure.[8c,d,11] Fortunately, the ATH reaction proceeded very well and was complete in only 30 min (Table 1, entry 1). This time was considerably shorter than the one needed under conventional heating (2 h) and amine **2a** was obtained in 98% yield and with 95% *ee*, which was very similar to the one that we observed in the ATH performed under conventional heating (97% *ee*).[8c,d] After this successful result, we decided to perform an optimization study and the results are collected in Table 1.

First, the irradiation time was reduced to 15, 5 and 1 min, maintaining the rest of the conditions the same. The result with an irradiation time of 15 min was practically equal to the one obtained in 30 min (Table 1, entry 2). With irradiation times shorter than 15 min, reactions did not reach completion and yields decreased as the time was reduced (compare entries 2-4 in Table 1), but no detriment in the *ee* was observed. Next, we tried to reduce the catalyst loading by keeping the same amount of catalyst and base and increasing the amount of imine **1a**. Due to limitations in the size of the reaction vessel used for the microwave-promoted ATH reaction, the final volume of isopropyl alcohol in the reaction mixture was kept to 6 mL in all cases, which implies that the concentration of substrate **1a** in the reaction mixture increased as its amount was increased. Using a common irradiation time of 30 min, the yield slightly decreased when the amount of the imine was varied from 0.9 to 1.5 and to

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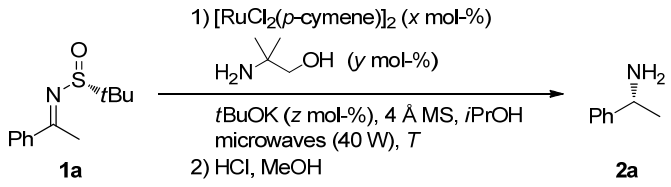
1.8 mmol, the reaction not being complete in the latter case (compare entries 1, 5 and 8 in Table 1), but, interestingly, there was no diminution of the enantiomeric purity of amine **2a**. The same trend was observed when the reactions were irradiated for 15 min (compare entries 2, 6 and 9 in Table 1). When using 1.8 mmol of substrate, an irradiation time of 1 h was needed to reach a 95% yield of the product, but with 94% *ee*. An increase of the reaction temperature to 60 ºC with an irradiation time of 30 min was deleterious for both the yield and the *ee* (compare entries 8 and 10 in Table 1). After having performed all of this study, we chose as the optimum reaction conditions the ones indicated in entry 5.

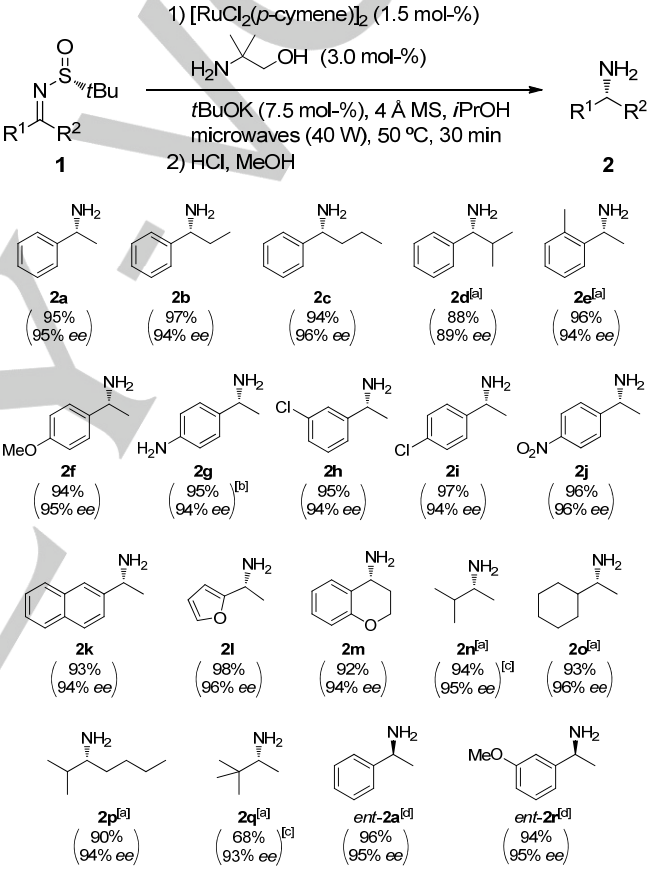
Table 1. Optimization of the reaction conditions.[a]



Ent.	**1a**[b] [mmol]	*x* [mol-%]	*y* [mol-%]	*z* [mol-%]	*T* [ºC]	Time[c] [min]	**2a** Yield[d] [%]	**2a** *ee*[e] [%]
1	0.9	2.5	5	12.5	50	30	98	95
2	0.9	2.5	5	12.5	50	15	96	96
3	0.9	2.5	5	12.5	50	5	84[f]	96
4	0.9	2.5	5	12.5	50	1	74[f]	96
5	1.5	1.5	3	7.5	50	30	95	95
6	1.5	1.5	3	7.5	50	15	83[f]	95
7	1.8	1.25	2.5	6.25	50	60	95	94
8	1.8	1.25	2.5	6.25	50	30	91[f]	95
9	1.8	1.25	2.5	6.25	50	15	82[f]	94
10	1.8	1.25	2.5	6.25	60	30	78[f]	85

[a] The solution of imine **1a** in *i*PrOH was added to a solution of the ruthenium complex [prepared by refluxing a mixture of $[RuCl_2(p\text{-cymene})]_2$ (0.023 mmol), 2-amino-2-methylpropan-1-ol (0.045 mmol) and 4 Å molecular sieves (0.15 g) in *i*PrOH (1.25 mL)] at room temperature. Then, *t*BuOK (1.13 mL of a 0.1 M solution in *i*PrOH, 0.113 mmol) was added and the reaction was irradiated with microwaves (40 W) at the temperature and for the time indicated. [b] The amount of solvent used to prepare the solution of imine **1a** was adjusted in order to have a final volume of *i*PrOH (after the addition of all the reagents) of 6 mL. [c] Time for the microwave-promoted transfer hydrogenation reaction. [d] Yield of isolated 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). [e] Determined for the corresponding benzamide by HPLC using a ChiralCel OD-H column. The (*R*)-enantiomer was the major one in all cases. [f] Some unreacted imine **1a** was detected in the crude reaction mixture.

Once the reaction conditions had been optimized, we decided to investigate the substrate scope. The change of the methyl group in **1a** by other linear or branched aliphatic chains also led to very good results (Scheme 1, compounds **2b**-**d**). The reduction of imines bearing different substituents on the phenyl group gave the expected amines in excellent yields and *ee*'s up to 96%, irrespective of the electronic nature of the substituent or its position on the ring (Scheme 1, compounds **2e**-**j**). Some highly optically enriched amines bearing other aromatic (**2k**) or heteroaromatic (**2l**) substituents and an amine having a heterocyclic bicyclic skeleton (**2m**) could also be obtained in very high yields.



Scheme 1. Microwave-Promoted ATH of *N*-(*tert*-butylsulfinyl)imines **1**. Synthesis of α-Branched Primary Amines **2**: in parentheses, yield of isolated product after acid-base extraction (based on the starting imine **1**) and enantiomeric excess (determined for the corresponding benzamide by HPLC using a ChiralCel OD-H column). All isolated compounds **2** were ≥ 95% pure (300 MHz ^{1}H NMR). [a] $[RuCl_2(p\text{-cymene})]_2$ (3 mol%), 2-amino-2-methylpropan-1-ol (6 mol%) and *t*BuOK (15 mol%) were used in this reaction. [b] In the precursor imine (**1g**) to this compound, R^1 = 4-BocNHC$_6$H$_4$. The Boc group was also removed during the desulfinylation step and diamine **2g** was isolated as its dihydrochloride. [c] The corresponding hydrochloride was isolated. [d] The (S_S)-imine *ent*-**1** was used in this reaction.

Remarkably, our microwave-promoted ATH procedure could also be applied to the more challenging aliphatic imines and the expected aliphatic amines **2n**-**q** were isolated in good yields and

with high enantioselectivities, including the highly sterically congested amine **2q**. It must be pointed out that, as it was the case in our previous ATH of *N*-(*tert*-butylsulfinyl)imines by conventional heating, in the case of the reduction of sterically congested imines bearing aromatic substituents or aliphatic imines, the amounts of catalyst and base had to be doubled in order to get full conversion of the imines in 30 min (Scheme 1, compounds **2d**,**e**,**n**-**q**). Finally, this new ATH protocol was equally efficient for the preparation of (*S*)-configurated amines *ent*-**2a** and *ent*-**2r** from the corresponding imines with a (*S*)-(*tert*-butylsulfinyl) chiral auxiliary. Thus, both enantiomers of an amine (for instance **2a** and *ent*-**2a** in Scheme 1) can be prepared with the same enantiomeric purity using the same catalyst by changing the absolute configuration of the sulfur atom in the sulfinyl moiety of the imine.

This new microwave-assisted ATH of *N*-(*tert*-butylsulfinyl)ketimines represents an interesting improvement in comparison with our previous procedure promoted by conventional heating, for the following reasons: (a) reaction times are much shorter; (b) the amount of catalyst has been reduced to almost half of the one that we had used in our previous procedure; (c) reactions can be carried out at higher concentrations and, therefore, less solvent is needed. All of these features lower the reaction costs, the consumption of electric power and the amount of waste that is generated, thus minimizing the environmental impact of our microwave-promoted protocol. Concerning the rate enhancement observed in this new procedure in comparison with the conventionally heated processes, we assume that it could be due to the fast dielectric heating that is generated by interaction of the microwave irradiation with the polar reaction medium (isopropyl alcohol).[12]

Conclusions

In conclusion, we have developed a very efficient procedure for the asymmetric transfer hydrogenation of *N*-(*tert*-butylsulfinyl)imines promoted by microwave irradiation. Our methodology allows the reduction of a variety of aromatic, heteroaromatic and aliphatic ketimines in very short reaction times, leading, after desulfinylation, to the expected α-branched primary amines in excellent yields and with very high enantiomeric purities. Both enantiomers of an amine are readily accesible using the same ruthenium catalyst by changing the absolute configuration of the sulfinyl group bonded to the nitrogen atom of the imine. This new protocol is more efficient and causes less impact to the environment than our previous ATH procedure assisted by conventional heating.

Experimental Section

General Information: Microwave reactions were performed with a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC) with a continuous focused microwave power delivery system in a pressure glass vessel (10 mL) sealed with a septum under magnetic stirring. The temperature of the reaction mixture was monitored using a calibrated infrared temperature control under the reaction vessel, and control of the pressure was performed with a pressure sensor connected to the septum of the vessel. All glassware was dried in an oven at 100 ºC and cooled to room temperature under argon before use. All reactions were carried out under an argon atmosphere. All starting materials needed for the synthesis of imines **1** and *ent*-**1**, $[RuCl_2(p\text{-cymene})]_2$ and 2-amino-2-methylpropan-1-ol were commercially available and were used as received. *t*BuOK was heated in a Kugel-Rohr distillation apparatus at 170-180 °C under vacuum for 4 h before use. Commercially available 4 Å molecular sieves were dried in a Kugel-Rohr distillation apparatus at 120 ºC under vacuum for 5 h before use. Commercially available anhydrous isopropyl alcohol was used as solvent in all the transfer hydrogenation reactions. Column chromatography was performed with silica gel 60 of 230–400 mesh. Thin layer chromatography (TLC) was performed on precoated silica gel plates; detection was done by UV_{254} light and staining with phosphomolybdic acid (solution of 1 g of phosphomolybdic acid in 24 mL of absolute ethanol). Unless otherwise stated, NMR samples were prepared using $CDCl_3$ as solvent. The internal references used for NMR spectra were tetramethylsilane (TMS) for ^{1}H NMR and $CDCl_3$ for ^{13}C NMR. ^{13}C NMR assignments were made on the basis of DEPT experiments. Infrared (FT-IR) spectra were obtained on a spectrophotometer equipped with an attenuated total reflectance (ATR) accessory. Mass spectra (EI) were obtained at 70 eV. Optical rotation measurements and HPLC analyses were performed at 20 ºC.

Synthesis of Imines 1 and *ent*-1. General Procedure: *N*-(*tert*-Butylsulfinyl)ketimines were prepared by condensation of the corresponding ketones with (*R*)-2-methylpropane-2-sulfinamide (for **1**) or (*S*)-2-methylpropane-2-sulfinamide (for *ent*-**1**) following our reported procedure.[10b] Imines **1a**,[13] **1b**,[13] **1c**,[14] **1d**,[15] **1e**,[8d] **1f**,[13] **1g** (R^1 = 4-$BocNHC_6H_4$),[8b] **1h**,[8b] **1i**,[16] **1j**,[15] **1k**,[17] **1l**,[18] **1m**,[19] **1n**,[8d] **1o**,[8b] **1p**,[8d] **1q**,[8d] *ent*-**1a**[15] and *ent*-**1r**[8b] were identified by comparison of their physical and spectroscopic data with the ones reported in the literature.

Microwave-Promoted Asymmetric Transfer Hydrogenation of *N*-(*tert*-Butylsulfinyl)imines 1 and *ent*-1. General Procedure: A mixture of $[RuCl_2(p\text{-cymene})]_2$ (14 mg, 0.023 mmol), 2-amino-2-methylpropan-1-ol (4 mg, 0.045 mmol), 4 Å molecular sieves (0.15 g) and anhydrous *i*PrOH (1.25 mL) under argon was heated up to 90 ºC (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 room temperature and a solution of the imine **1** or *ent*-**1** (1.5 mmol) in *i*PrOH (3.60 mL) and *t*BuOK (1.13 mL of a 0.1 M solution in *i*PrOH, 0.113 mmol) were successively added. Immediately, the reaction mixture was heated at 50 ºC with microwave irradiation (40 W power) for 30 min. After completion of the reaction, the mixture was cooled down to room temperature and 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.

For aromatic imines **1d**-**e** and the aliphatic imines **1n**-**q**, $[RuCl_2(p\text{-cymene})]_2$ (28 mg, 0.045 mmol), 2-amino-2-methylpropan-1-ol (8 mg, 0.090 mmol) and *t*BuOK (2.25 mL of a 0.1 M solution in *i*PrOH, 0.225 mmol) were used.

Removal of the Sulfinyl Group. Isolation of Amines 2a-f, 2h-m, 2o-p and *ent*-2. General Procedure: The crude mixture of the transfer hydrogenation reaction was dissolved in a 2 M solution of HCl in methanol (7 mL; prepared by dropwise addition of $SOCl_2$ to methanol at 0 ºC) and stirred overnight at room temperature. Then, the solvent was evaporated, a 2 M aqueous HCl solution (10 mL) was added and the

mixture was extracted with ethyl acetate (3 × 10 mL). The organic layers were discarded. The aqueous layer was basified with a buffer solution of NH_3 (2 M) / NH_4Cl (2 M) (10 mL) and a 2 M aqueous NaOH solution to ensure pH > 11. The mixture was 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 **2a**-**f**, **2h**-**m**, **2o**-**p** and *ent*-**2** were obtained with the *ee*'s indicated in Scheme 1 and in the following yields: **2a** (173 mg, 95%), **2b** (197 mg, 97%), **2c** (210 mg, 94%), **2d** (197 mg, 88%), **2e** (195 mg, 96%), **2f** (213 mg, 94%), **2h** (222 mg, 95%), **2i** (226 mg, 97%), **2j** (239 mg, 96%), **2k** (239 mg, 93%), **2l** (163 mg, 98%), **2m** (206 mg, 92%), **2o** (177 mg, 93%), **2p** (174 mg, 90%), *ent*-**2a** (174 mg, 96%) and *ent*-**2r** (213 mg, 94%). Amines **2a**, *ent*-**2a** and **2b**, which are commercially available, were identified by comparison of their physical and spectroscopic data with the ones of authentic samples. Amines **2c**,[8b] **2d**,[20] **2e**,[8d] **2f**,[8b] **2h**,[8b] **2i**,[8b] **2j**,[8b] **2k**,[8b] **2l**,[8b] **2m**,[8b] **2o**,[8b] **2p**,[8d] and *ent*-**2r**[8b] were identified by comparison of their physical and spectroscopic data with the ones reported in the literature.

Synthesis of amines 2g·2HCl, 2n·HCl and 2q·HCl: A 2 M solution of HCl in Et_2O (10 mL, 20 mmol) was added to the crude residue of the asymmetric transfer hydrogenation of imine **1g** (R^1 = 4-BocNHC$_6$H$_4$), **1n** or **1q** and the mixture was stirred overnight. After filtration, the solid was washed with Et_2O (3 × 10 mL) and dried, affording the corresponding hydrochlorides with the *ee*'s indicated in Scheme 1 and in the following yields: **2g**·2HCl (298 mg, 95%), **2n**·HCl (174 mg, 94%) and **2q**·HCl (140 mg, 68%). Compounds **2g**·2HCl,[8b] **2n**·HCl[8d] and **2q**·HCl[8d] were identified by comparison of their physical and spectroscopic data with the ones previously reported by us.

Determination of the enantiomeric excesses of amines 2 and *ent*-2: Amine **2** or *ent*-**2** (0.4 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled to 0 ºC. A 2 M aqueous NaOH solution (5 mL) was added and the mixture was stirred for 5 min. Benzoyl chloride (93 µL, 0.8 mmol; for the benzoylation of diamine **2g**, 186 µL, 1.6 mmol were used) was added dropwise, the cold bath was removed and the reaction mixture was stirred at room temperature for 3 h. Then, layers were separated, the organic phase was washed with a 2 M aqueous NaOH solution (3 × 5 mL) and the aqueous layers were discarded. The organic phase was washed with brine (2 × 5 mL) and then dried (Na_2SO_4). After filtration and evaporation of the solvent, the expected benzamides were obtained, which were analyzed by HPLC on a ChiralCel OD-H column using a 254 nm UV detector, 10% *i*PrOH in hexane as eluent and a flow rate of 0.5 mL/min. The major enantiomer was the one with lower retention time in all cases, except for amines *ent*-**2a** and *ent*-**2r**. The racemic amines were prepared by reaction of the corresponding ketones with a solution of NH_3 in EtOH following a literature procedure,[21] and were benzoylated as described above. The retention times of the two enantiomers of all the benzamides are collected in the Supporting Information (Table S1).

Supporting Information: HPLC retention times of benzamides derived from amines **2** and *ent*-**2**; copies of ^{1}H NMR and ^{13}C NMR spectra for all imines **1** and *ent*-**1** and all amines **2** and *ent*-**2**.

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Keywords: amines • asymmetric synthesis • asymmetric transfer hydrogenation • reduction • sulfinylimine

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Entry for the Table of Contents

Key topic: ATH, *N*-(*tert*-butylsulfinyl)imine, microwaves

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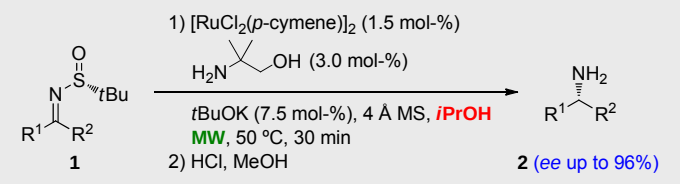

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Page No. – Page No.

Microwave-Enhanced Asymmetric Transfer Hydrogenation of *N*-(*tert*-Butylsulfinyl)imines

The application of microwaves to promote the asymmetric transfer hydrogenation of *N*-(*tert*-butylsulfinyl)imines in 2-propanol catalyzed by a ruthenium complex bearing an achiral β-aminoalcohol as a ligand is reported. After desulfinylation, α-branched primary amines containing aromatic, heteroaromatic and aliphatic substituents are obtained in excellent yields and enantiomeric excesses up to 96%.