JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

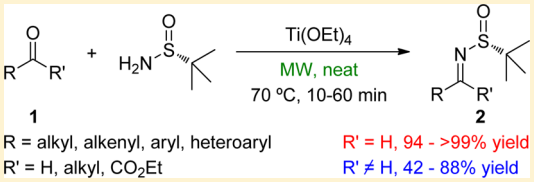
Microwave-Assisted Solvent-Free Synthesis of Enantiomerically Pure *N*-(*tert*-Butylsulfinyl)imines†

Juan F. Collados, Estefanía Toledano, David Guijarro,* and Miguel Yus

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

Supporting Information

ABSTRACT: A simple, environmentally friendly, and very efficient procedure for the synthesis of optically pure *N*-(*tert*-butylsulfinyl)imines has been developed with microwave-promoted condensation of aldehydes and ketones using (*R*)-2-methylpropane-2-sulfinamide in the presence of $Ti(OEt)_4$, under solvent-free conditions. This procedure allows for the preparation of a variety of sulfinyl aldimines with excellent yields and purities in only 10 min, making any further purification of the imines unnecessary. Several sulfinyl ketimines have also been prepared in good yields by extension of the reaction times to 1 h. This methodology has proved to be equally efficient for the synthesis of aromatic, heteroaromatic, and aliphatic *N*-(*tert*-butylsulfinyl)imines. Conventional heating has also been shown to be useful to promote these reactions, especially for the synthesis of aldimines.



INTRODUCTION

Enantiomerically pure *N*-(*tert*-butylsulfinyl)imines have shown to be very versatile substrates for the asymmetric synthesis of chiral primary amines,[1] which are a very interesting class of compounds because they are present in many natural and biologically active products and also form part of pharmaceuticals, agrochemicals, and compounds with industrial interest.[1j] The chiral and electron-withdrawing sulfinyl group plays a dual role as an activating and a stereodirecting group and has an advantage in that it can be easily removed from the reaction products leading to the free primary amines.[2] There are several methods available to prepare these kind of aldimines, which are mainly based on the direct condensation of aldehydes with optically pure 2-methylpropane-2-sulfinamide in the presence of an activating and dehydrating agent such as copper(II) sulfate,[3] magnesium sulfate/pyridinium *p*-toluenesulfonate,[3] titanium(IV) alkoxides,[3,4] cesium carbonate,[5] ytterbium(III) triflate,[6] or potassium hydrogensulfate.[7] Another method based on the activation of the sulfinamide, instead of the aldehyde, has also been reported.[8] Less reactive ketones usually require more drastic conditions to transform them into the corresponding *N*-(*tert*-butylsulfinyl)ketimines [$Ti(OEt)_4$[3,9] or $Ti(OPr^i)_4$[10] being the activating agents of choice in these cases]. However, most of the reported methods for the synthesis of *N*-(*tert*-butylsulfinyl)imines require an excess of the carbonyl precursor or the sulfinamide and give moderate yields with sterically hindered or electronically deactivated aldehydes or with ketones.

On the other hand, microwave irradiation has proved to be an efficient technique to accelerate different types of reactions.[11] However, it has rarely been used in the synthesis of imines. *N*-Alkyl or *N*-aryl imines have been prepared by microwave irradiation in the absence of a catalyst[12] or in the presence of calcium oxide,[13] silica gel,[14] or the solid acid montmorillonite K-10.[15] *N*-Sulfonylimines have been synthesized using calcium carbonate/montmorillonite K-10 clay[16] or a $ZrO_2/S_2O_8^{2-}$ solid superacid[17] as a catalyst. With regard to *N*-(*tert*-butylsulfinyl)imines, to the best of our knowledge, only one procedure for the synthesis of aldimines by condensation of aldehydes with 2-methylpropane-2-sulfinamide in CH_2Cl_2 has been reported using microwave irradiation,[4a,18] but the iminic products were not obtained in pure form due to the excess of the aldehydes used. With the aim of finding a fast and efficient procedure for the synthesis of these interesting imines, we decided to study the possibility of preparing them under solvent-free conditions. Herein, we present a straightforward synthesis of *N*-(*tert*-butylsulfinyl)imines assisted by microwave irradiation under solvent-free conditions with an unprecedented substrate scope.

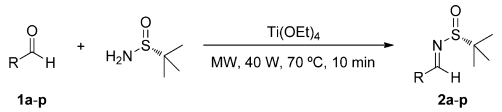
RESULTS AND DISCUSSION

During the past few years, one of our main research lines has focused on the use of *N*-(*tert*-butylsulfinyl)imines in asymmetric synthesis.[19] As a result of our need to prepare a variety of those imines, we were willing to find a practical and general method for their synthesis in high yields and purities. Because the development of efficient and environmentally friendly synthetic procedures is always desirable, we decided to investigate whether those imines could be prepared by condensation of carbonylic compounds with 2-methylpropane-2-sulfinamide in the absence of any solvent, which would reduce the amount of waste material. According to our previous experience with the use of microwaves in asymmetric

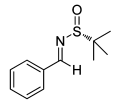
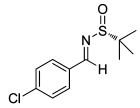
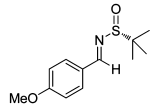
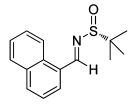
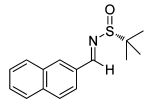
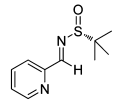
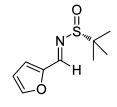
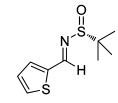
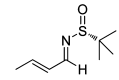
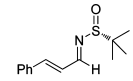
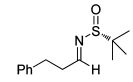
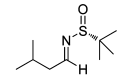
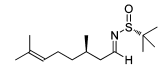
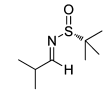
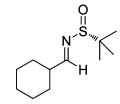
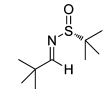
Received: May 7, 2012
Published: June 13, 2012

   dx.doi.org/10.1021/jo300919x | J. Org. Chem. 2012, 77, 5744−5750

Table 1. Solvent-Free Microwave-Promoted Synthesis of *N*-(*tert*-Butylsulfinyl)aldimines 2a–p[a]



1a-p 2a-p

Entry	Aldehyde No.	Aldehyde R	Product No.	Product Structure	Yield[b] (%)
1	**1a**	Ph	**2a**		> 99
2	**1b**	4-ClC_6H_4	**2b**		> 99
3	**1c**	4-$MeOC_6H_4$	**2c**		98
4	**1d**	1-naphthyl	**2d**		97
5	**1e**	2-naphthyl	**2e**		> 99
6	**1f**	2-pyridyl	**2f**		> 99
7	**1g**	2-furyl	**2g**		99
8	**1h**	2-thienyl	**2h**		97
9	**1i**	(*E*)-MeCH=CH	**2i**		95[c]
10	**1j**	(*E*)-PhCH=CH	**2j**		94[c]
11	**1k**	$PhCH_2CH_2$	**2k**		> 99
12	**1l**	*i*-$PrCH_2$	**2l**		85
13	**1m**	(*R*)-$Me_2C{=}CH(CH_2)_2CH(Me)CH_2$	**2m**		> 99
14	**1n**	*i*-Pr	**2n**		53
15	**1o**	Cy	**2o**		86
16	**1p**	*t*-Bu	**2p**		87

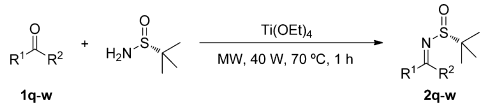
[a]The mixture of aldehyde **1** (2 mmol), (*R*)-*t*-$BuSONH_2$ (2 mmol), and $Ti(OEt)_4$ (4 mmol) was stirred under microwave irradiation (40 W, 70 °C) for 10 min. [b]Yield of isolated product after workup. Compounds **2a–p** were always ≥95% pure (300 MHz ^1H NMR). [c]The reaction was scaled up to 7 mmol of aldehyde.

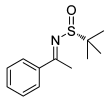
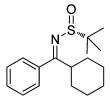
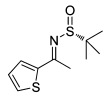
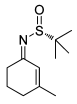
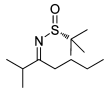
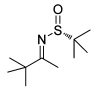
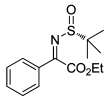
synthesis,[20] we thought that microwave irradiation could be an interesting way of promoting the condensation reaction since the reaction times would probably be short, which would reduce the reaction costs. We chose benzaldehyde **1a** as a model substrate and tried its condensation with (*R*)-2-methylpropane-2-sulfinamide in the presence of $Ti(OEt)_4$, which has proved to be a very efficient activator and water scavenger for the synthesis of sulfinylimines.[3,4,9] Equimolar amounts of **1a** and the sulfinamide were mixed with $Ti(OEt)_4$ (2 equiv), and the mixture was stirred and heated in a microwave reactor at various powers, temperatures, and times, in order to find the conditions with the minimum energy cost and the maximum yield and purity of the sulfinylimine. After this study, we found that an irradiation time of 10 min at a power of 40 W and a temperature of 70 °C was enough to get full conversion to the expected imine **2a**. The workup procedure was very simple: the reaction mixture was diluted with ethyl acetate and poured into a small volume of brine while being stirred, and the resulting suspension was filtered through a plug of Celite. We were delighted to see that, after evaporation of the solvent, the crude reaction mixture showed benzaldimine **2a** as the only product, without significant amounts of either benzaldehyde or the sulfinamide. Sulfinylimine **2a** was obtained in quantitative yield and was practically pure according to the ^1H NMR spectrum (Table 1, entry 1). Our procedure is very convenient, since it makes any further purification of the imine by column chromatography unnecessary, avoiding the use of solvents and silica gel. This fact represents an improvement compared with the microwave-assisted synthesis of *N*-(*tert*-butylsulfinyl)aldimines previously reported.[4a] Furthermore, the only byproduct of the reaction is a small amount of environmentally friendly titanium dioxide,[21] which was separated from the desired imine in the filtration process. In order to evaluate whether the obtained imine was contaminated with sodium chloride, we performed an elemental analysis of the crude reaction product, which showed that no significant amounts of sodium chloride were present in the imine (see Experimental Section).[22]

Once we had established the optimal reaction conditions, we decided to investigate the substrate scope (Tables 1 and 2). First, we tried to prepare several aldimines from the corresponding aldehydes (Table 1). Substituted benzaldehydes **1b** and **1c** produced excellent yields of the expected imines, irrespective of the electronic nature of the substituent on the

dx.doi.org/10.1021/jo300919x | J. Org. Chem. 2012, 77, 5744–5750

Table 2. Solvent-Free Microwave-Promoted Synthesis of *N*-(*tert*-Butylsulfinyl)ketimines 2q−w[a]



	Ketone			Product			
Entry	No.	R^1	R^2	No.	Structure	Conv.[b]	Yield[c] (%)
1	**1q**	Ph	Me	**2q**		92	88
2	**1r**	Ph	Cy	**2r**		68	54
3	**1s**	2-thienyl	Me	**2s**		83	77
4	**1t**	---[d]	---[d]	**2t**		80	65[e]
5	**1u**	*i*-Pr	*n*-Bu	**2u**		65	58
6	**1v**	*t*-Bu	Me	**2v**		58	42
7	**1w**	Ph	CO_2Et	**2w**		92	88

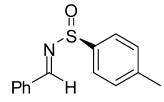
[a]The mixture of ketone **1q−w** (2 mmol), (*R*)-*t*-BuSONH$_2$ (2 mmol), and Ti(OEt)$_4$ (4 mmol) was stirred under microwave irradiation (40 W, 70 °C) for 1 h. [b]Conversion estimated by 300 MHz ^{1}H NMR based on the signal of the remaining sulfinamide protons. [c]Yield of isolated product after workup. Compounds **2q−w** were always ≥95% pure (300 MHz ^{1}H NMR). [d]The starting ketone was 3-methylcyclohex-2-enone. [e]The imine was obtained as a 1.2:1 *Z*/*E* mixture.

aromatic ring (Table 1, entries 2 and 3). Some other aromatic substituents, such as 1- and 2-naphthyl, and heterocycles, such as pyridine, furan, and thiophene, could also be introduced in the iminic carbon atom with the corresponding imines isolated in yields ranging from 97 to >99% (Table 1, entries 4−8). α,β-Unsaturated sulfinylimines **2i** and **2j** could also easily be prepared. In order to test the scalability of our methodology, the latter two reactions were performed at a higher scale, namely 7 mmol of aldehyde, under the same conditions as the synthesis of benzaldimine **2a**, giving the expected imines **2i** and **2j** in yields of 95 and 94%, respectively (Table 1, entries 9 and 10). The fact that no solvent was employed allowed for the setup of those reactions in the same small tubes of the microwave reactor that we had used in the reactions scaled to a 2 mmol level.

This procedure could be extended to enolizable aliphatic aldehydes **1k−m** bearing primary alkyl chains (Table 1, entries 11−13) and to sterically demanding aliphatic aldehydes, such as methylpropanal **1n**, cyclohexanecarbaldehyde **1o**, or pivalaldehyde **1p** (Table 1, entries 14−16). In the synthesis of the aliphatic imines, yields were always higher than 85% and were quantitative in the case of the imines derived from 3-phenylpropanal and (*R*)-citronellal (Table 1, entries 11 and 13). The exception was the imine **1n** prepared from methylpropanal, which was obtained with a yield of only 53%. Loss probably occurred when the solvent was evaporated after workup, due to the volatility of the product.

It is worth noting that in all the preparations of aldimines **2b−p**, the crude reaction products were pure enough not to require any purification step, as in the case of benzaldimine **2a**.

N-(*p*-Tolylsulfinyl)imines have also proved to be very good substrates for asymmetric synthesis.[1c−f] We decided to study whether our synthetic protocol could also be extended to the preparation of those interesting imines. Thus, we attempted the synthesis of *N*-(*p*-tolylsulfinyl)benzaldimine **3** (Figure 1) by



3

Figure 1. Structure of the *N*-(*p*-tolylsulfinyl)imine **3**.

condensation of benzaldehyde and the commercially available (*S*)-4-methylbenzenesulfinamide in the presence of Ti(OEt)$_4$ under our microwave-promoted conditions. After an irradiation time of 10 min, the expected imine **3** was obtained in practically pure form with a yield of 98%. Therefore, it seems that other substituents different from the *tert*-butyl group are also tolerated on the sulfur atom of the starting sulfinamide in our synthetic methodology.

The excellent results obtained for the synthesis of aldimines encouraged us to try to extend this methodology to the preparation of *N*-(*tert*-butylsulfinyl)ketimines (Table 2). The synthesis of the ketimine derived from acetophenone was selected as a model reaction. The mixture of ketone **1q** (2 mmol), (*R*)-2-methylpropane-2-sulfinamide (2 mmol), and Ti(OEt)$_4$ (4 mmol) was stirred under microwave irradiation for 10 min using the optimal conditions found for the condensation of the aldehydes. However, after that irradiation time, only a 67% conversion into ketimine **2q** was observed. Fortunately, an extension of the reaction time to 1 h led to a 92% conversion with the corresponding imine isolated with a yield of 88% (Table 2, entry 1). An irradiation time longer than 1 h did not improve the conversion of acetophenone to imine **2q**.

Varied results were obtained with other ketones when they were subjected to the condensation reaction under the optimal conditions found for acetophenone imine **2q**. Imine **2r**, derived from cyclohexyl phenyl ketone, was obtained in moderate yield (Table 2, entry 2). 2-Acetylthiophene led to the expected heterocyclic imine **2s** with a yield of 77% (Table 2, entry 3). Our procedure was also applicable to the synthesis of aliphatic ketimines **1t−v**. A gradual decrease in conversion and isolated yield was observed when the steric hindrance around the carbonyl group of the starting ketone was increased (Table 2, entries 4−6). The same trend was also observed in the syntheses of aromatic ketimines (compare entries 1 and 2 in Table 2). In general, only the *E* isomer of the sulfinylketimine was detected by ^{1}H and ^{13}C NMR, except for ketones with similar steric demands in both substituents such as 3-methylcyclohex-2-enone (Table 2, entry 4). Imine **2t**, derived

dx.doi.org/10.1021/jo300919x | J. Org. Chem. 2012, 77, 5744−5750

from the latter, was obtained as a 1.2:1 mixture of geometrical isomers.

The preparation of α-imino esters from the corresponding keto esters was also attempted. When ethyl 2-oxo-2-phenylacetate **1w** was used as a substrate, an 88% yield of imino ester **2w** was obtained (Table 2, entry 7). However, when the aliphatic keto ester **1x** (Figure 2) was subjected to the

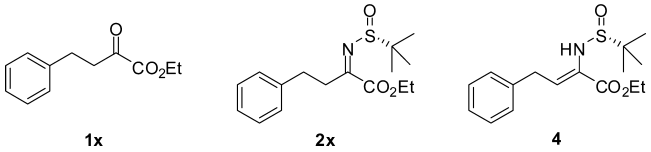


Figure 2. Structures of compounds **1x**, **2x**, and **4**.

condensation reaction with the chiral sulfinamide, the expected sulfinylimine **2x** was not formed; the corresponding enamine **4** was isolated instead with a yield of 40%.

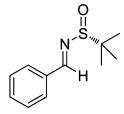
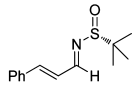
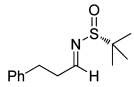
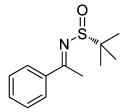
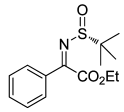
In all the attempted syntheses of ketimines, the crude reaction mixtures showed the expected imines together with unreacted 2-methylpropane-2-sulfinamide and starting ketones. Therefore, a purification step was necessary, which was carried out by column chromatography, giving the pure ketimines **2q**–**w** in the yields indicated in Table 2. Although these yields vary from moderate to good, our procedure is very convenient from an economic point of view because it produces *N*-(*tert*-butylsulfinyl)ketimines in only 1 h. Similar yields have been reported in the literature for some of the ketimines that we have prepared, but the reaction times were much longer; for instance, it has been reported that 15 h in a refluxing THF solution was necessary to get an 89% yield of imine **2q**[3] versus a reaction time of only 1 h in our case without the need to use a solvent (see entry 1 in Table 2). Thus, the expense in electric power is much lower with our procedure. To the best of our knowledge, this is the first time that the microwave-promoted synthesis of *N*-(*tert*-butylsulfinyl)ketimines has been reported.

Since it has been described in the literature that some racemization occurred in some sulfinylketimines after they had been heated at elevated temperatures for a prolonged time,[9] we investigated to determine whether or not there was any loss of optical purity in the imines that we had prepared by our microwave-assisted procedure. We chose imines **2a**, **2q**, and **2v** as test compounds for this study. The corresponding racemic imines were prepared by condensation of the precursor carbonylic compounds and racemic 2-methylpropane-2-sulfinamide. The optical purities of imines **2a**, **2q**, and **2v** were evaluated by HPLC analyses on a chiral column by comparison with the corresponding racemic samples, and an enantiomeric excess of >99% was determined in all three cases. Thus, there was no racemization of the iminic products under our reaction conditions.

Although microwaves had previously been used to promote the synthesis of *N*-(*tert*-butylsulfinyl)imines,[4a] our procedure presents several advantages: (a) the previously reported methodology is useful only for the preparation of aldimines, while our procedure is more general, being applicable to the synthesis of both aldimines and ketimines; (b) our reaction temperature (70 °C) is lower than the one used in the literature (90–110 °C), which is convenient because a low temperature diminishes the risk of thermal decomposition that has been observed in several cases at higher temperatures;[4] (c) we perform the synthesis under solvent-free conditions; (d) our procedure does not require a purification step for the synthesis of aldimines, whereas separation of the imine from the excess aldehyde is necessary in the reported methodology. These last two features make our protocol more economically viable and reduce the impact of our process on the environment since less waste is produced.

To evaluate whether or not there was any beneficial effect in the use of microwave irradiation, the synthesis of imine **2a** was carried out by conventional heating in an oil bath at 70 °C, and a complete conversion of the starting materials was observed after a reaction time of 10 min (Table 3, entry 1). This seemed

Table 3. Solvent-Free Synthesis of *N*-(*tert*-Butylsulfinyl)imines by Conventional Heating at Room Temperature

Entry	Imine No.	Imine Structure	t (min)	Conv. at 70 °C[a,b]	Conv. at rt[a,c]
1	**2a**		10	> 99	91
2	**2j**		10	> 99	90
3	**2k**		10	> 99	89
4	**2q**		60	72	7
5	**2w**		60	81	12

[a]Conversion estimated by 300 MHz ^{1}H NMR based on the signal of the remaining aldehydic proton (for compounds **2a**, **2j**, and **2k**) or the remaining sulfinamide protons (for compounds **2q** and **2w**). [b]The mixture of the precursor carbonylic compound (2 mmol), (*R*)-*t*-BuSONH$_2$ (2 mmol), and Ti(OEt)$_4$ (4 mmol) was stirred in an oil bath at 70 °C for the time indicated. [c]The mixture of the precursor carbonylic compound (2 mmol), (*R*)-*t*-BuSONH$_2$ (2 mmol), and Ti(OEt)$_4$ (4 mmol) was stirred at 20 °C for the time indicated.

to indicate that there is no special impact of the microwave irradiation, and the solvent-free conditions employed are the main factor responsible for the success of our synthetic procedure. This result is interesting because it indicates that the sulfinyl aldimines can be prepared quickly using a conventional heating method when a microwave reactor is not available. However, the use of microwave irradiation is still convenient because the reaction mixture reaches the temperature of 70 °C more quickly than it does with conventional heating, which reduces the expense in electric power because the oil bath must be preheated to 70 °C before introducing the reaction flask. After these observations, we decided to try to carry out the same reaction at room temperature, and a 91% conversion was obtained after stirring for 10 min (Table 3, entry 1). Full conversion to imine **2a** was observed after the mixture had been stirred for 1 h at room temperature. This result supports our

dx.doi.org/10.1021/jo300919x | J. Org. Chem. 2012, 77, 5744–5750

assumption that the concentrated reaction conditions facilitate the preparation of the aldimines.

We extended this study to some other aldimines and ketimines. In the case of aldimines **2j** and **2k**, we observed the same trend as for benzaldimine **2a**: full conversions to the imines were obtained by conventional heating at 70 °C, and conversions around 90% were reached after stirring for 10 min at room temperature (Table 3, entries 2 and 3). However, the advantage of using microwave irradiation to promote these reactions was clearer when the preparation of ketimines was attempted. When the syntheses of imines **2q** and **2w** were performed by conventional heating at 70 °C for 1 h, the conversions were 72 and 81%, respectively, which are lower than the ones observed when the same reactions were assisted by microwave irradiation (compare entries 4 and 5 in Table 3 with entries 1 and 7 in Table 2). The decrease in conversion was much more dramatic when the preparations of those ketimines were carried out at room temperature: only 7 and 12% conversions were reached after stirring for 1 h at 20 °C (Table 3, entries 4 and 5).

After having established that the synthesis of the aldimines could be effectively performed by heating the reaction mixture in an oil bath, we decided to study the possibility of scaling up our protocol and tried to prepare benzaldimine **2a** under conventional heating at a 20 mmol level. We were pleased to see that imine **2a** was obtained in only 10 min in a practically pure form with a yield of 95%, as was the case in the reaction at the 2 mmol level. This reaction could not be performed under microwave irradiation due to volume limitations of the tubes of the microwave reactor used.

■ CONCLUSION

In conclusion, we have developed a very efficient and environmentally friendly procedure for the solvent-free synthesis of *N*-(*tert*-butylsulfinyl)imines promoted by microwave irradiation, by condensation of the corresponding carbonylic precursors with (*R*)-2-methylpropane-2-sulfinamide in the presence of titanium tetraethoxide. Our methodology allows for the preparation of a variety of aldimines in pure form in only 10 min, without the need for a purification step. The procedure is applicable to the synthesis of sulfinylketimines with good yields, in a reaction time of only 1 h. Aromatic, heteroaromatic, and aliphatic sulfinylimines can be prepared with similar efficiencies. Alternatively, the imines can be synthesized using conventional heating methods instead of microwave irradiation, leading to the same results for aldimines and lower reaction rates for ketimines.

■ 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 the pressure was controlled with a pressure sensor connected to the septum of the vessel. All glassware was dried in an oven at 100 °C and cooled to room temperature under argon prior to use. All reactions were carried out under an argon atmosphere. All the starting aldehydes and ketones, (*R*)-*t*-BuSONH$_2$, (*S*)-4-MeC$_6$H$_4$SONH$_2$, and Ti(OEt)$_4$ (Alfa Aesar, 33% TiO$_2$ min) are commercially available and were used as received, except for benzaldehyde, which was distilled before use. Column chromatography was performed with silica gel 60 of 230−400 mesh. Thin layer chromatography (TLC) was performed on precoated silica gel plates (Merck 60, F254, 0.25 mm); detection was accomplished using a UV254 light and staining with phosphomolybdic acid (solution of 1 g of phosphomolybdic acid in 24 mL of absolute ethanol); R_f values are given under these conditions. NMR spectra were recorded using $CDCl_3$ as the solvent and internal references, tetramethylsilane (TMS) for ^{1}H NMR and $CDCl_3$, for ^{13}C NMR; chemical shifts are given in δ parts per million and coupling constants (J) in hertz. ^{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; fragment ions in m/z with relative intensities (%) in parentheses are given. HRMS spectra were measured with electron impact (EI) ionization at 70 eV and a double focusing mass analyzer (magnetic and electric fields). Optical rotation measurements and HPLC analyses were performed at 20 °C.

Microwave-Promoted Synthesis of *N*-(*tert*-Butylsulfinyl)-imines. *General Procedure.* The corresponding aldehyde or ketone **1** (2.0 mmol), (*R*)-*t*-BuSONH$_2$ (242 mg, 2.0 mmol), and Ti(OEt)$_4$ (0.84 mL, 4.0 mmol) were mixed and stirred under argon at room temperature. The reaction vessel was placed into the microwave reactor and heated to 70 °C (constant microwave irradiation at 40 W with air stream cooling) for 10 min (for the synthesis of aldimines **2a**−**p**) or 60 min (for the synthesis of ketimines **2q**−**w**) while the contents were stirred.[23] After cooling to room temperature, the mixture was diluted with ethyl acetate (10 mL) and poured into 0.5 mL of brine while being rapidly stirred. The resulting suspension was filtered through a plug of Celite (diatomaceous earth), and the filter cake was washed with ethyl acetate. After evaporation of the solvent, pure sulfinyl aldimines **2a**−**p** were obtained with the yields indicated in Table 1. In order to evaluate a possible contamination of the obtained aldimines with sodium chloride, an elemental analysis of benzaldimine **2a** was carried out, which gave C = 62.8% and H = 7.3%. These values are in good agreement with the theoretical ones (C = 63.1% and H = 7.2%), which indicates that no significant amounts of sodium chloride are present in the imine **2a**.[22] Sulfinyl ketimines **2q**−**w** were purified by column chromatography (silica gel, hexane/ethyl acetate), to give the expected imines in the yields indicated in Table 2. Imines **2a**,[4] **2b**,[24] **2c**,[4] **2d**,[25] **2e**,[26] **2f**,[4] **2g**,[4] **2i**,[27] **2j**,[28] **2k**,[29] **2l**,[30] **2n**,[4] **2o**,[27] **2p**,[4] **2q**,[4] **2r**,[19i] **2s**,[31] **2u**,[4] **2v**,[4] and **2w**[19b] were characterized by comparison of their physical and spectroscopic data with those reported in the literature. The optical rotation values for imines **2d**, **2e**, and **2l** have not been described in the literature and are given below. The corresponding physical, spectroscopic, and analytical data for imines **2h**, **2m**, and **2t** and enamine **4** follow.

*(R)-2-Methyl-N-(1-naphthylmethylidene)propane-2-sulfinamide (**2d**):*[25] $[\alpha]_D^{20}$ −4.5 (c 1.0, $CHCl_3$).

*(R)-2-Methyl-N-(2-naphthylmethylidene)propane-2-sulfinamide (**2e**):*[26] $[\alpha]_D^{20}$ −146.0 (c 1.0, $CHCl_3$).

*(R)-2-Methyl-N-(3-methylbutylidene)propane-2-sulfinamide (**2l**):*[30] $[\alpha]_D^{20}$ −312.0 (c 1.0, $CHCl_3$).

*(R)-2-Methyl-N-(2-thienylmethylidene)propane-2-sulfinamide (**2h**):* yellow oil; R_f 0.50 (hexane/ethyl acetate 3:1); $[\alpha]_D^{20}$ +27.7 (c 1.0, $CHCl_3$); IR (ATR) 1580 (C═N), 1069 cm^{-1} (S═O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (1H, s), 7.59 (1H, dd, J = 5.0, 0.7 Hz), 7.54 (1H, dd, J = 3.7, 0.7 Hz), 7.15 (1H, dd, J = 5.0, 3.7 Hz), 1.25 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 140.5, 133.7, 133.2, 128.1, 57.9, 22.5; m/z 215 (M$^+$, <1%), 159 (100), 111 (59), 57 (61); HRMS calcd for $C_9H_{13}NOS_2$ M$^+$ m/z 215.0439, found m/z 215.0459.

*(R_S,R)-N-(3,7-Dimethyloct-6-en-1-ylidene)-2-methylpropane-2-sulfinamide (**2m**):* yellow oil; R_f 0.64 (hexane/ethyl acetate 3:1); $[\alpha]_D^{20}$ −194.2 (c 0.7, $CHCl_3$); IR (ATR) 1620 (C═N), 1083 cm^{-1} (S═O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (1H, dd, J = 5.7, 4.8 Hz), 5.08 (1H, t, J = 7.1 Hz), 2.53 (1H, ddd, J = 15.0, 5.8, 4.8 Hz), 2.37 (1H, ddd, J = 15.0, 7.7, 5.7 Hz), 2.11−1.85 (3H, m), 1.68, 1.60 (3H each, 2 s), 1.47−1.22 (2H, m), 1.21 (9H, s), 0.98 (3H, d, J = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 131.7, 124.1, 56.6, 43.3, 36.8, 30.4, 25.7, 25.4, 22.4, 19.8, 17.7; m/z 257 (M$^+$, <1%), 201 (13), 137 (48), 69 (29), 57 (100), 41 (39); HRMS calcd for $C_{14}H_{27}NOS$ M$^+$ m/z 257.1813, found m/z 257.1800.

dx.doi.org/10.1021/jo300919x | J. Org. Chem. 2012, 77, 5744−5750

*(R)-2-Methyl-N-(3-methylcyclohex-2-en-1-ylidene)propane-2-sulfinamide (**2t**):* yellow oil; R_f 0.24 (hexane/ethyl acetate 3:1); $[\alpha]_D^{20}$ −127.8 (*c* 1.0, $CHCl_3$); IR (ATR) 1562 (C═N), 1069 cm^{-1} (S═O); ^1H NMR (300 MHz, $CDCl_3$) δ major 6.07 (1H, s), 2.96 (1H, ddd, *J* = 17.0, 8.8, 5.1 Hz), 2.73 (1H, ddd, *J* = 17.0, 7.5, 4.9 Hz), 2.57−2.42, 2.28−2.17, 1.96−1.83 (1H, 2H, and 1H, respectively, 3 m), 1.93 (3H, s), 1.23 (9H, s); δ minor 6.89 (1H, s), 2.57−2.42, 2.28−2.17, 1.96−1.83 (1H, 2H, and 3H, respectively, 3 m), 1.94 (3H, s), 1.23 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ^{32} 178.65 (176.61), 156.4 (158.0), 126.6 (119.6), 56.2 (56.4), 35.4 (31.2), 30.2 (30.4), 24.5 (24.9), 22.1 (22.2), 22.08 (22.35); *m*/*z* 213 (M^+, <1%), 157 (100), 109 (29), 81 (32), 57 (33); HRMS calcd for $C_{11}H_{19}NOS$ M^+ *m*/*z* 213.1187, found *m*/*z* 213.1178.

*(R)-Ethyl 2-(1,1-dimethylethylsulfinamido)-4-phenylbut-2-enoate (**4**):* yellow oil; R_f 0.31 (hexane/ethyl acetate 3:1); $[\alpha]_D^{20}$ −66.8 (*c* 1.0, $CHCl_3$); IR (ATR) 1706 (C═O), 1252 (C−N), 1074 cm^{-1} (S═O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.36−7.19 (5H, m), 6.55 (1H, dd, *J* = 8.2, 6.6 Hz), 5.83 (1H, s), 4.25, 4.23 (1H each, 2 dq, *J* = 10.8, 7.1 Hz each), 3.76 (1H, dd, *J* = 16.6, 8.2 Hz), 3.68 (1H, dd, *J* = 16.6, 6.6 Hz), 1.35 (9H, s), 1.30 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 138.8, 129.3, 128.7, 128.6, 127.7, 126.6, 62.0, 57.1, 34.2, 22.5, 14.1; *m*/*z* 309 (M^+, <1%), 253 (36), 205 (97), 176 (69), 159 (100), 131 (69), 130 (51), 91 (61), 57 (71); HRMS calcd for $C_{16}H_{23}NO_3S$ M^+ *m*/*z* 309.1399, found *m*/*z* 309.1371.

Microwave-Promoted Synthesis of *N*-(*p*-Tolylsulfinyl)imine 3. *N*-(*p*-Tolylsulfinyl)benzaldimine **3** was prepared from benzaldehyde (0.10 mL, 1.0 mmol) and (*S*)-4-methylbenzenesulfinamide (156 mg, 1.0 mmol) in the presence of $Ti(OEt)_4$ (0.42 mL, 2.0 mmol) as described above in the general procedure for the synthesis of *N*-(*tert*-butylsulfinyl)aldimines. After filtration through Celite and evaporation of the solvent, practically pure imine **3** was obtained in 98% yield. Imine **3** was characterized by comparison of its physical and spectroscopic data with those reported in the literature.[33]

Synthesis of Imines 2a, 2j, 2k, 2q, and 2w by Conventional Heating at 70 °C. General Procedure. The mixture of the corresponding aldehyde or ketone **1a**, **1j**, **1k**, **1q**, or **1w** (2.0 mmol), (*R*)-*t*-$BuSONH_2$ (242 mg, 2.0 mmol), and $Ti(OEt)_4$ (0.84 mL, 4.0 mmol) was stirred under argon at 70 °C (oil bath temperature) for 10 min (for the synthesis of aldimines **2a**, **2j**, and **2k**) or 60 min (for the synthesis of ketimines **2q** and **2w**). Then, workup was performed in the same way as the microwave-promoted reactions.

Synthesis of Imines 2a, 2j, 2k, 2q, and 2w at Room Temperature. General Procedure. The mixture of the corresponding aldehyde or ketone **1a**, **1j**, **1k**, **1q**, or **1w** (2.0 mmol), (*R*)-*t*-$BuSONH_2$ (242 mg, 2.0 mmol), and $Ti(OEt)_4$ (0.84 mL, 4.0 mmol) was stirred under argon at 20 °C for 10 min (for the synthesis of aldimines **2a**, **2j**, and **2k**) or 60 min (for the synthesis of ketimines **2q** and **2w**). Then, workup was performed in the same way as the microwave-promoted reactions.

Determination of the Optical Purity of Imines 2a, 2q, and 2v. Racemic imines *rac*-**2a**, *rac*-**2q**, and *rac*-**2v** were prepared by condensation of the corresponding aldehyde (**1a**) or ketone (**1q** or **1v**) and racemic *t*-$BuSONH_2$ in the presence of $Ti(OEt)_4$, following the general procedure for the microwave-promoted synthesis. The optical purities of imines **2a**, **2q**, and **2v** were evaluated by HPLC analyses on a chiral column by comparison with the corresponding racemic samples, and an enantiomeric excess of >99% was determined in all three cases. Unless otherwise stated, the HPLC analyses were performed using a UV detector, with 10% *i*-PrOH in hexane as the eluent and a flow rate of 0.5 mL/min. The retention times were 11.0 (*S*) and 13.2 (*R*) min for **2a** (OD-H column, 333 nm detector wavelength), 15.1 (*R*) and 19.4 (*S*) min for **2q** (AS-H column, 289 nm detector wavelength), and 11.7 (*S*) and 16.5 (*R*) min for **2v** (AS-H column, 2% *i*-PrOH in hexane as the eluent, 236 nm detector wavelength).

Synthesis of Imine 2a by Conventional Heating at 70 °C at a 20 mmol Scale. The mixture of benzaldehyde (2.0 mL, 20.0 mmol), (*R*)-*t*-$BuSONH_2$ (2.42 g, 20.0 mmol), and $Ti(OEt)_4$ (8.5 mL, 40.0 mmol) was stirred under argon at 70 °C (oil bath temperature) for 10 min. After cooling to room temperature, the mixture was diluted with ethyl acetate (40 mL) and poured into 2.0 mL of brine while being rapidly stirred. The resulting suspension was filtered through a plug of Celite (diatomaceous earth) and the filter cake was washed with ethyl acetate. After evaporation of the solvent, practically pure imine **2a** was obtained in 95% yield.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H NMR spectra for all known imines and copies of ^1H NMR and ^{13}C NMR spectra for products **2h**, **2m**, **2t**, and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*dguijarro@ua.es.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was generously supported by the Spanish Ministerio de Ciencia e Innovación (MICINN; grant CONSOLIDER INGENIO 2010, CSD2007-00006, CTQ2007-65218, and CTQ11-24151) and the Generalitat Valenciana (PROMETEO/2009/039 and FEDER). J.F.C. and E.T. thank the Instituto de Síntesis Orgánica for their fellowships. We also thank MEDALCHEMY S.L. for a gift of chemicals.

■ DEDICATION

†Dedicated to Prof. Carlos Álvarez Ibarra and Dr. María Luz Quiroga Feijóo on occasion of their retirements.

■ REFERENCES

(1) (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984−995. (b) Ellman, J. A. *Pure Appl. Chem.* **2003**, *75*, 39−46. (c) Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003−8030. (d) Davis, F. A. *J. Org. Chem.* **2006**, *71*, 8993−9003. (e) Davis, F. A. In *Asymmetric Synthesis*; Christmann, M., Braese, S., Eds.; Wiley-VCH: Weinheim, Germany, 2007; pp 16−20. (f) Davis, F. A. In *Asymmetric Synthesis*, 2nd ed.; Christmann, M., Braese, S., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2008; pp 17−22. (g) Lin, G.-Q.; Xu, M.-H.; Zhong, Y.-W.; Sun, X.-W. *Acc. Chem. Res.* **2008**, *41*, 831−840. (h) Ferreira, F.; Botuha, C.; Chemla, F.; Pérez-Luna, A. *Chem. Soc. Rev.* **2009**, *38*, 1162−1186. (i) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600−3740. (j) *Chiral amine synthesis. Methods, developments and applications*; Nugent, T. C., Ed.; Wiley-VCH: Weinheim, Germany, 2010.

(2) See, for instance: (a) Sun, X.; Wang, S.; Sun, S.; Zhu, J.; Deng, J. *Synlett* **2005**, 2776−2780. (b) Kosciolowicz, A.; Rozwadowska, M. D. *Tetrahedron: Asymmetry* **2006**, *17*, 1444−1448. (c) Denolf, B.; Mangelinckx, S.; Toernroos, K. W.; De Kimpe, N. *Org. Lett.* **2006**, *8*, 3129−3132.

(3) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278−1284.

(4) (a) Mukade, T.; Dragoli, D. R.; Ellman, J. A. *J. Comb. Chem.* **2003**, *5*, 590−596. (b) Tanuwidjaja, J.; Peltier, H. M.; Lewis, J. C.; Schenkel, L. B.; Ellman, J. A. *Synthesis* **2007**, 3385−3389.

(5) Higashibayashi, S.; Tohmiya, H.; Mori, T.; Hashimoto, K.; Nakata, M. *Synlett* **2004**, 457−460.

(6) Jiang, Z.-Y.; Chan, W. H.; Lee, A. W. M. *J. Org. Chem.* **2005**, *70*, 1081−1083.

(7) Huang, Z.; Zhang, M.; Wang, Y.; Qin, Y. *Synlett* **2005**, 1334−1336.

(8) Ardej-Jakubisiak, M.; Kawecki, R.; Swietlinska, A. *Tetrahedron: Asymmetry* **2007**, *18*, 2507−2509.

(9) (a) Borg, G.; Cogan, D. A.; Ellman, J. A. *Tetrahedron Lett.* **1999**, *40*, 6709−6712. (b) Tanuwidjaja, J.; Peltier, H. M.; Ellman, J. A. *J. Org. Chem.* **2007**, *72*, 626−629. (c) Datta, G. K.; Ellman, J. A. *J. Org. Chem.* **2010**, *75*, 6283−6285.
(10) Xu, J.; Liu, Z.-J.; Yang, X.-J.; Wang, L.-M.; Chen, G.-L.; Liu, J.-T. *Tetrahedron* **2010**, *66*, 8933−8937.
(11) (a) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199−9223. (b) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225−9283. (c) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717−727. (d) Loupy, A. *Microwaves in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2002. (e) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250−6284. (f) Roberts, B. A.; Strauss, C. R. *Acc. Chem. Res.* **2005**, *38*, 653−661. (g) Polshettiwar, V.; Varma, R. S. *Acc. Chem. Res.* **2008**, *41*, 629−639.
(12) Paquin, L.; Hamelin, J.; Texier-Boullet, F. *Synthesis* **2006**, 1652−1656.
(13) Gopalakrishnan, M.; Sureshkumar, P.; Kanagarajan, V.; Thanusu, J. *Res. Chem. Intermed.* **2007**, *33*, 541−548.
(14) Keypour, H.; Rezaeivala, M.; Fall, Y.; Dehghani-Firouzabadi, A. A. *ARKIVOC* **2009**, *x*, 292−301.
(15) (a) Varma, R. S.; Dahiya, R.; Kumar, S. *Tetrahedron Lett.* **1997**, *38*, 2039−2042. (b) Abid, M.; Savolainen, M.; Landge, S.; Hu, J.; Prakash, G. K. S.; Olah, G. A.; Török, B. *J. Fluorine Chem.* **2007**, *128*, 587−594.
(16) Vass, A.; Dudás, J.; Varma, R. S. *Tetrahedron Lett.* **1999**, *40*, 4951−4954.
(17) Jin, T.; Feng, G.; Yang, M.; Li, T. *Synth. Commun.* **2004**, *34*, 1277−1283.
(18) *N*-(*tert*-Butylsulfinyl)imines have also been proposed as intermediates in a microwave-promoted synthesis of nitriles from aldehydes in acetonitrile solution. See ref 4b.
(19) (a) Almansa, R.; Guijarro, D.; Yus, M. *Tetrahedron: Asymmetry* **2008**, *19*, 603−606. (b) Almansa, R.; Guijarro, D.; Yus, M. *Tetrahedron: Asymmetry* **2008**, *19*, 2484−2491. (c) Almansa, R.; Guijarro, D.; Yus, M. *Tetrahedron Lett.* **2009**, *50*, 3198−3201. (d) Almansa, R.; Guijarro, D.; Yus, M. *Tetrahedron Lett.* **2009**, *50*, 4188−4190. (e) Guijarro, D.; Pablo, O.; Yus, M. *Tetrahedron Lett.* **2009**, *50*, 5386−5388. (f) Almansa, R.; Collados, J. F.; Guijarro, D.; Yus, M. *Tetrahedron: Asymmetry* **2010**, *21*, 1421−1431. (g) Guijarro, D.; Pablo, O.; Yus, M. *J. Org. Chem.* **2010**, *75*, 5265−5270. (h) Guijarro, D.; Pablo, O.; Yus, M. *Tetrahedron Lett.* **2011**, *52*, 789−791. (i) Pablo, O.; Guijarro, D.; Kovács, G.; Lledós, A.; Ujaque, G.; Yus, M. *Chem.−Eur. J.* **2012**, *18*, 1969−1983.
(20) Almansa, R.; Guijarro, D.; Yus, M. *Tetrahedron: Asymmetry* **2008**, *19*, 1376−1380.
(21) Titanium dioxide has been approved as a food coloring additive (E-171). See the list of "Current EU approved additives and their E Numbers", available via the Internet from the Food Standards Agency.
(22) We are very grateful to a reviewer for suggesting that we carry out this study.
(23) For a critical review comparing the efficiency of conventional and microwave heating, see: Moseley, J. D.; Kappe, C. O. *Green Chem.* **2011**, *13*, 794−806 . We thank a reviewer for calling our attention to this paper.
(24) Kells, K. W.; Chong, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 15666−15667.
(25) Plobeck, N.; Powell, D. *Tetrahedron: Asymmetry* **2002**, *13*, 303−310.
(26) The spectroscopic data for the enantiomer of imine **2e** have been described. See: Bolshan, Y.; Batey, R. A. *Org. Lett.* **2005**, *7*, 1481−1484.
(27) Chemla, F.; Ferreira, F. *J. Org. Chem.* **2004**, *69*, 8244−8250.
(28) The physical and spectroscopic data for the enantiomer of imine **2j** have been described. See: Maji, M. S.; Fröhlich, R.; Studer, A. *Org. Lett.* **2008**, *10*, 1847−1850.
(29) Schenkel, L. B.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 3621−3624.
(30) Nielsen, L.; Lindsay, K. B.; Faber, J.; Nielsen, N. C.; Skrydstrup, T. *J. Org. Chem.* **2007**, *72*, 10035−10044.
(31) The physical and spectroscopic data for the enantiomer of imine **2s** have been described. See: Zhang, D.; Yuan, C. *Chem.−Eur. J.* **2008**, *14*, 6049−6052.
(32) The δ values for the minor isomer are given in parentheses.
(33) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M. *J. Org. Chem.* **1995**, *60*, 7037−7039.