DOI: 10.1002/ejoc.200800576

Synthesis of Novel Amino-Acid-Derived Sulfinamides and Their Evaluation as Ligands for the Enantioselective Transfer Hydrogenation of Ketones

Lorenzo Zani,[a] Lars Eriksson,[b] and Hans Adolfsson*[a]

Keywords: Amino acids / Sulfinamides / N-Ligands / Homogeneous catalysis / Transfer hydrogenation

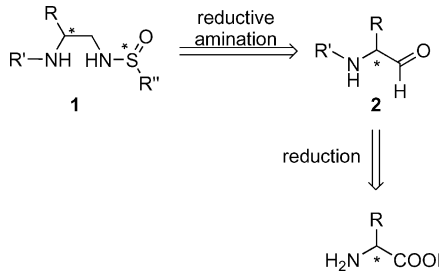
Novel chiral mono-sulfinyl diamines bearing a stereogenic sulfur atom were prepared in moderate to good yields starting from amino acids by means of a reductive amination of the corresponding amino aldehydes. Their potential as ligands for asymmetric catalysis was evaluated in the metal-catalyzed enantioselective transfer hydrogenation of alkyl-aryl ketones. The catalysts were generated in situ from sulfinamides **1a–i** and arene complexes of rhodium and ruthenium, and the catalytic reductions led to the formation of chiral alcohols with up to 91 % *ee*.

Introduction

The sulfinyl group, bearing a stereogenic center on sulfur, has since long time been established as a reliable chiral auxiliary in asymmetric synthesis.[1] In particular, enantiopure *N*-sulfinyl imines have been extensively applied to the synthesis of chiral amines, due to the high diastereoselectivity usually displayed in their reactions with various nucleophiles.[2]

On the other hand, use of compounds incorporating a stereogenic tricoordinate sulfur atom as chiral ligands for enantioselective catalysis has remained underdeveloped for a long time, and only recently significant progress has been achieved in this field. For example, chiral sulfoxides have found application in such processes as (transfer) hydrogenations of olefins or ketones,[3] Lewis acid catalyzed Diels–Alder cycloadditions,[4] diethylzinc addition to aldehydes[5] and Pd-catalyzed allylic alkylations.[6] In addition, Ellman and co-workers introduced ligands containing the *N*-sulfinyl imine moiety, and employed them in various asymmetric transformations, including the hydrogenation of prochiral olefins.[7] In contrast, very few reports dealt with the use of chiral sulfinamides as ligands or catalysts; Riera, Verdaguer and co-workers described the application of *N*-phosphanyl sulfinamides as stoichiometric ligands for a cobalt-mediated Pauson–Khand reaction,[8] while three different groups employed sulfinamide-containing organocatalysts to carry out such transformations as the hydrosilylation of imines,[9] the aza-Henry reaction[10] and the indium-mediated allylation of *N*-acylhydrazones.[11]

In recent years, we reported on the use of various amino acid derived compounds as efficient stereocontrollers in enantioselective catalysis. They included ligands for the metal-catalyzed transfer hydrogenation of ketones[12] and titanium-catalyzed diethylzinc addition to aldehydes,[13] as well as organocatalysts for the α-oxidation or α-amination of carbonyl groups.[14] Some of these catalysts contained sulfur atoms within thioamide or sulfonamide functionalities.[12e,14a–14b] Given our experience in this field, we became interested in preparing novel amino acid derivatives **1** incorporating a chiral sulfinamide unit, and subsequently in evaluating them as ligands for metal-catalyzed asymmetric transformations. We envisaged that compounds **1** could be easily accessed from the corresponding amino acids through reduction to form the amino aldehydes **2** and subsequent reductive amination of the latter. Our retrosynthetic approach is detailed in Scheme 1.



Scheme 1. Retrosynthetic approach to the amino-acid-derived sulfinamides **1**.

Compounds **1** are obtained by the combination of various amino acids and sulfinamides, which made possible to vary substituents in three different positions (R, R′ and R′′ in Scheme 1). Moreover, the possibility of preparing both diastereomers of a certain ligand allowed us to evaluate possible match/mismatch effects to be displayed in catalysis.

[a] Department of Organic Chemistry, Stockholm University, The Arrhenius Laboratory,
10691 Stockholm, Sweden
Fax: +46-8-154908
E-mail: hansa@organ.su.se
[b] Department of Physical Chemistry, Inorganic Chemistry and Structural Chemistry, University, The Arrhenius Laboratory,
10691 Stockholm, Sweden

Herein, we report the synthesis of the sulfinamides **1a**–**i** through the aforementioned synthetic route and their evaluation as ligands for the metal-catalyzed enantioselective transfer hydrogenation of prochiral ketones.[15] In addition, comparison of the catalytic performance of sulfinamide **1h** with its analogue **16**, bearing a sulfonamide group, will also be discussed, with the aim of highlighting the importance of the stereogenic center on sulfur for the selectivity of the transfer hydrogenation reaction.

Results and Discussion

In agreement with our retrosynthetic proposal (Scheme 1), the sulfinamides **1a**–**i** were prepared starting from the corresponding protected amino acids through the intermediacy of the known amino aldehydes **2a**–**g** (Scheme 2).

The structural characteristics of compounds **1a**–**i** are summarized in Table 1, along with the yield of their two-step preparation sequence from the aldehydes **2a**–**g**.

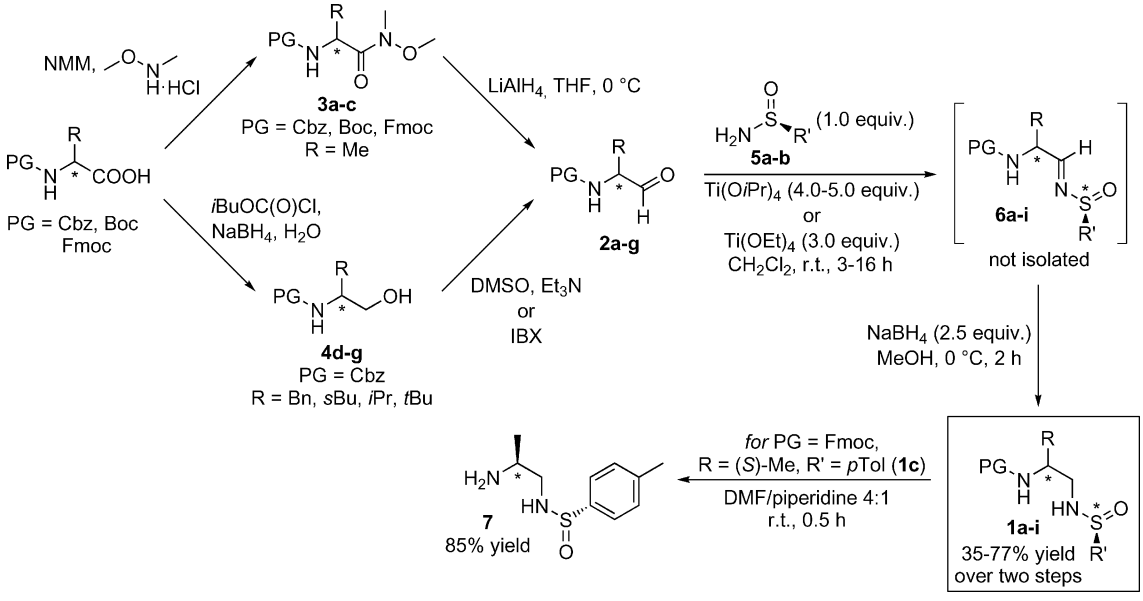
Table 1. Sulfinamides **1a**–**i** prepared in this study.

	Prepared from		PG	R	R′	% Yield[a]
	Aldehyde	Sulfinamide				
1a	**2a**	**5a**	Cbz	(*S*)-Me	*p*Tol	36
1b	**2b**	**5a**	Boc	(*S*)-Me	*p*Tol	55
1c	**2c**	**5a**	Fmoc	(*S*)-Me	*p*Tol	68
1d	*ent*-**2a**	**5a**	Cbz	(*R*)-Me	*p*Tol	35
1e	**2a**	**5b**	Cbz	(*S*)-Me	*t*Bu	58
1f	**2d**	**5a**	Cbz	(*S*)-Bn	*p*Tol	47
1 g	**2e**	**5a**	Cbz	(*S*)-*s*Bu	*p*Tol	51
1h	**2f**	**5a**	Cbz	(*S*)-*i*Pr	*p*Tol	77
1i	**2g**	**5a**	Cbz	(*S*)-*t*Bu	*p*Tol	50

[a] Yield of pure product over two steps starting from the aldehydes **2a**–**g**.

Initially, we set to prepare compounds **1a**–**c**, all derived from L-alanine but carrying different protecting group on the *N*-terminus (Table 1). Our aim at this stage was to access compound **7**, bearing a free, basic nitrogen atom. To this end, we wanted to determine which one of the chosen protecting groups (Cbz, Boc, Fmoc) would be most easily cleaved in the last step. The aldehydes **2a**–**c** were first prepared by means of a known reaction sequence, comprising the conversion of the *N*-protected carboxylic acids into the corresponding Weinreb amides **3a**–**c**,[16] and the subsequent chemoselective reduction of the latter with $LiAlH_4$ in THF at 0 °C.[17] Although we were able to prepare all three aldehydes **2a**–**c**, we noticed that the last reductive step afforded the Fmoc-protected species **2c** in only 31% yield, as opposed to 55–63% for the other two aldehydes, alongside with a more polar by-product.[18] Moreover, we found that the crude aldehydes obtained by this route were in general not pure enough to be used as such in the following imination step (Scheme 2), and therefore chromatographic purification was needed. Because it is known that chiral α-amino aldehydes tend to give partial racemization when subjected to column chromatography,[19] we later employed a different sequence to access compounds **2** (vide infra).

With the aldehydes **2a**–**c** in hand, we turned our attention to the reductive amination step. The formation of the imine **6a** was initially carried out according to the procedure reported by Davis, employing an equimolar amount of (*S*)-*p*-toluenesulfinamide (**5a**) and 5.0 equiv. of a Ti^{IV} alkoxide in refluxing CH_2Cl_2.[20] The expected imine was formed smoothly, but the crude was of low purity, and when a chromatographic purification was attempted, partial hydrolysis to yield the aldehyde **2a** was observed (approx. 10%). Given the corresponding loss in yield and the fact that the aldehyde **2a** and the imine **6a** were difficult to separate, we seeked alternative conditions to carry out the desired transformation.



Scheme 2. Synthesis of the sulfinamides **1a**–**i** starting from *N*-protected amino acids.

We found that performing the reaction at room temperature[21] in the presence of 4.0 equiv. of $Ti(OiPr)_4$ gave full conversion of the starting material within 4 h. A simplified work-up (see Exp. Section for details) afforded the crude imine **6a**, which was cleaner than that obtained under the previous conditions. To avoid decomposition, the crude was directly used in the next step. Reduction with 2.5 equiv. of $NaBH_4$ in MeOH at 0 °C afforded the desired sulfonamide **1a**, although as a 6:1 mixture of diastereomers: this was likely to be due to partial racemization occurring during the chromatographic purification of the aldehyde **2a**, as mentioned earlier. Fortunately, (*S*,*S*)-**1a** could finally be isolated in 36% yield over two steps by means of flash column chromatography followed by crystallization (see Exp. Section for details).

The same procedure was subsequently applied also for the synthesis of the compounds (*S*,*S*)-**1b**–**c**, which were obtained in 55% and 68% yield over two steps, respectively. The same protocol was then used for the synthesis of all the other sulfinamides prepared in this study (**1d**–**i**).

At this stage, deprotection to afford the mono-sulfinyldiamine **7** was attempted. Disappointingly, we found that removal of neither the Boc- nor the Cbz-group could be effected under a variety of conditions.[22] Fortunately, however, the Fmoc group was cleaved smoothly upon treatment of **1c** with a mixture of DMF and piperidine at room temp., and the desired product could thus be isolated in good yield. Compound **7** was also later evaluated as a ligand for the enantioselective metal-catalyzed transfer hydrogenation of ketones (vide infra).

As mentioned earlier, the sequence chosen to prepare the α-amino aldehydes **2** suffered from some notable drawbacks, such as low yields and partial racemization of the products. For this reason, we looked for an alternative route to access the compounds **2**. After a brief survey of the literature,[18,23] we found that the latter could be prepared by formation of the mixed anhydrides of the corresponding amino acids with isobutyl chloroformate, followed by reduction with aqueous $NaBH_4$,[24] and by subsequent chemoselective oxidation of the resulting amino alcohols **4** (Scheme 2). Generally, we converted the alcohols **4** into the corresponding aldehydes by means of a Swern oxidation;[25] this protocol was found to work well for almost all the substrates, giving aldehydes in 82–93% yield, but when the amino alcohol **4g**, derived from L-*tert*-leucine, was subjected to the same conditions, the desired product was not obtained. Fortunately, we found that the oxidation of **4g** could be carried out in good yield (75%) according to a procedure reported by Finney,[26] employing 3.0 equiv. of IBX (*o*-iodoxybenzoic acid) in EtOAc at reflux.

In general, we found this second route to α-amino aldehydes **2** to be more convenient than the first one, which is in agreement with previous observations reported in the literature.[23,27] The aldehydes **2** were usually obtained in good yields and in some instances the crude products were pure enough to be carried onto the next step without need for further purification; unfortunately, however, this was not always the case, and isolation by column chromatography, accompanied by the aforementioned partial racemization of the aldehydes **2**, could not be avoided in some cases.

The α-amino aldehydes **2d**–**g** were then subjected to the same reductive amination protocol already used for the compounds **2a**–**c**. In the first step either 3.0 equiv. of $Ti(OEt)_4$ or 4.0 equiv. of $Ti(iPrO)_4$ were employed in CH_2Cl_2 at room temp. for 3–4 h, giving in general full conversion to the corresponding imines **6**. Once again, only for the aldehyde **2g**, bearing a *tert*-butyl group, a change in the reaction conditions was required: full conversion to **6i** was obtained with 5.0 equiv. of $Ti(iPrO)_4$ after 16 h stirring at room temp. Subsequent reduction with $NaBH_4$ afforded smoothly sulfinamides **1f**–**i**, which were purified by flash column chromatography, in some cases followed by crystallization (see Exp. Section for details).

The compounds **1a**–**i** were generally isolated as solids. Gratifingly we were able to grow crystals of sulfinamide **1h** suitable for X-ray diffraction. The solid-state structure of **1h** is shown in Figure 1.[28] As expected, the configuration of the two stereogenic centers was confirmed to be (*S*).

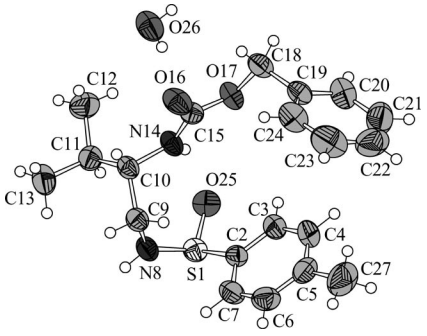
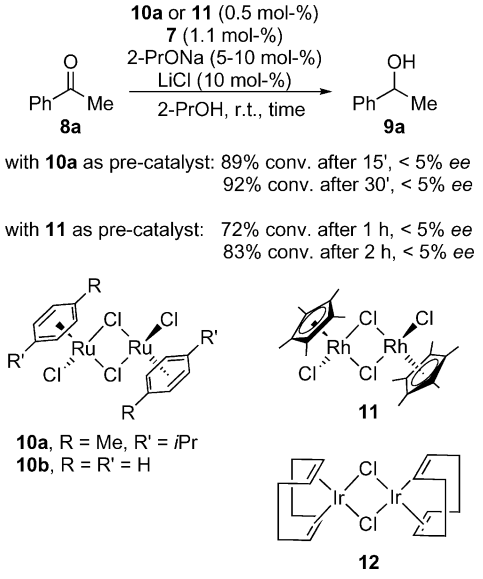


Figure 1. ORTEP plot (50% probability) of compound **1h**, obtained by X-ray diffraction.

Having managed to prepare the compounds **1a**–**i** and **7**, we proceeded to evaluate their ability to serve as ligands for metal-catalyzed enantioselective reactions. We selected the asymmetric transfer hydrogenation of ketones,[15] given our considerable experience in the field[12] and the possibility to readily compare the performance of the new catalysts with well-established promoters, such as, for example, chiral monotosylated diamines.[29]

Initially, we applied the mono-sulfinyldiamine **7** in the enantioselective reduction of acetophenone (**8a**) to 1-phenylethanol (**9a**), employing 2-propanol as the hydrogen donor. The catalyst was generated in situ by mixing compound **7** with typical pre-catalysts such as $[Ru(p\text{-cymene})Cl_2]_2$ (**10a**) or $[(Cp^*RhCl_2)_2]$ (**11**) (Scheme 3), in the presence of sodium 2-propoxide as a base. Having found previously that the addition of lithium salts as additives can be beneficial to the outcome of the catalytic transfer hydrogenation reaction,[12f] lithium chloride was added also in this case.

Interestingly, sulfinamide **7** in combination with Ru complex **10a** generated a very efficient catalyst, able to give 89% conversion of the starting material within 15 min (TOF = 356 mol h^{-1}); disappointingly, however, the catalyst showed



Scheme 3. Asymmetric transfer hydrogenation of acetophenone (**8a**) using compound **7** as the chiral ligand.

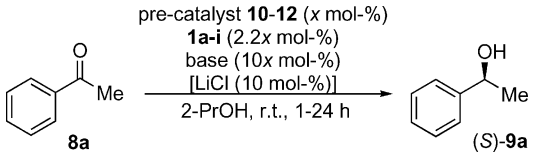
no selectivity, and the product was formed as a racemic mixture. When Rh complex **11** was employed the reaction was slower, albeit alcohol **9a** could still be formed in good conversion after 2 h, but still no selectivity was displayed by the catalytic system.

After these disappointing results, we turned our attention to the use in catalysis of compounds **1a**–**i**, featuring two substituted nitrogen atoms. It is worth pointing out that these species do not bear any intrinsically basic nitrogen center, in contrast to the ligands traditionally used for the catalytic transfer hydrogenation reaction, such as monosulfonated diamines or amino alcohols. The results obtained are summarized in Table 2.

As can be seen from Table 2, compound **1a**, bearing a Cbz group, in combination with complex **11** was able to yield the alcohol **9a** in 87% conversion after 2 h, but this time the *ee* was 43% (Entry 1). In comparison with ligand **7**, the introduction of a substituent on one side of the molecule remarkably increased the selectivity of the resulting catalyst.

Prompted by this encouraging result, we then examined compounds **1b**–**c**, which differ from **1a** only for the protecting group on one nitrogen atom; we found that more sterically demanding groups such as Boc or Fmoc greatly reduced both the efficiency and selectivity of the reaction (Entries 2–3). In order to evaluate possible match/mismatch effects, we subsequently tested the sulfinamide **1d**, the (*R*,*S*)-diastereomer of **1a**. To our surprise, we found that also in this case both the efficiency and the selectivity of the process were largely diminished (Entry 4). This observation suggests that the relative configuration of the ligand is crucial in determining the performance of the present catalytic system. Interestingly, the configuration of the product was found to be also in this case (*S*); thus, the sense of enantioselection seems to be influenced by the absolute configuration of the stereogenic center on sulfur, rather than that of the amino acid part, as found in previous systems.[12a–12d]

Table 2. Transfer hydrogenation of acetophenone (**8a**) employing compounds **1a**–**i** as the chiral ligands.



Entry	Ligand	Pre-cat.	*x*	Time	% Conv.[a]	% *ee* [a]
1	**1a**	**11**	0.5	2	87	43 (*S*)
2	**1b**	**11**	0.5	1	54	19 (*S*)
3	**1c**	**11**	0.5	2	30	< 5
4	**1d**	**11**	0.5	2	33	29 (*S*)
5	**1e**	**11**	0.5	2	18	34 (*S*)
6	**1f**	**11**	0.5	2	87	39 (*S*)
7	**1g**	**11**	0.5	2	81	46 (*S*)
8	**1h**	**11**	0.5	4	83	58 (*S*)
9	**1i**	**11**	0.5	24	< 10	67 (*S*)
10	**1h**	**12**	0.5	18	0	–
11	**1h**	**10a**	0.5	18	39	76 (*S*)
12	**1h**	**10a**	1.0	2	60	74 (*S*)
13	**1i**	**10a**	1.0	5	**42**	**86 (*S*)**
				22	**61**	**84 (*S*)**
14[b]	**1i**	**10a**	1.0	5	< 15	65 (*S*)
15[c]	**1i**	**10a**	1.0	5	15	**87 (*S*)**
16[d]	**1i**	**10a**	1.0	5	29	**87 (*S*)**
17	**1i**	**10b**	1.0	2	24	50 (*S*)

[a] Determined by chiral GC-analysis (CP-Chirasil-Dex CB). [b] Lithium chloride was absent. [c] KOH (10 mol-%) was used as the base. [d] *t*BuONa (10 mol-%) was used as the base.

When compound **1e**, bearing a *tert*-butylsulfinamido group, was used, once again a poor conversion of ketone **8a** and an enantiomeric excess of the product lower than that obtained with **1a** were observed (Entry 5). Therefore, the introduction of a bulkier substituent on the sulfur atom seems to be detrimental to the catalytic results.

Use of the compounds **1f**–**g**, featuring substituted methyl groups on the amino acid side chain, provided results similar to that obtained with **1a** (Entries 6–7), but when sulfinamide **1h**, derived from L-valine, was employed, an increase in enantioselectivity was observed, although the reaction was slower (Entry 8). This tendency was confirmed when the L-*tert*-leucine derivative **1i** was tested: the enantioselectivity increased to 67% *ee*, but the reaction was extremely slow, and poor conversion was observed even after one day (Entry 9). Thus, it seems that the introduction of bulkier substituents on the amino acid side chain, while being beneficial for the enantioselectivity of the process, at the same time reduced the efficiency of the catalyst.

Looking for improvements, we next examined the possibility of using metals other than rhodium to effect the transformation. While employment of Ir in the form of the complex $[(COD)_2IrCl_2]$ (**12**) was unsuccessful (Entry 10), use of **1h** in combination with Ru pre-catalyst **10a** afforded the product in low conversion and 76% *ee* after one night (Entry 11). An increase in the catalyst loading allowed to obtain a moderate conversion of the starting material

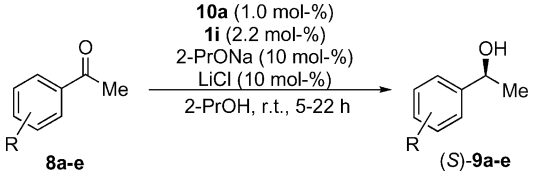
within 2 h, with alcohol **9a** formed with 74% *ee* (Entry 12). In agreement with the observation made for the Rh-based pre-catalyst, the sulfinamide **1i** in combination with the complex **10a** generated also in this case a slower, but more selective catalyst (Entry 13); after 22 h at room temperature a moderate conversion of the ketone **8a** was achieved, and the product of reduction was formed with 84% *ee*.

It should be pointed out that the highest enantioselectivity observed so far for a transfer hydrogenation of a prochiral ketone employing ligands containing a stereogenic sulfur atom was 80%, as reported by van Leeuwen and coworkers (who also employed a different metal and a different hydrogen donor, namely iridium in combination with the triethylamine/formic acid azeotrope).[3c]

Some further tests were conducted at this stage: first, we found that in the absence of lithium chloride the reaction proceeded to a much lesser extent and also the enantioselectivity was greatly reduced (Entry 14); while this is in agreement with our previous findings about the positive effect of lithium salts on the outcome of transfer hydrogenation reacions,[12f] the magnitude of such effect was surprising. Second, a change in the base to KOH or *t*BuONa was found to be detrimental, since lower conversions were recorded after 5 h, although the change had no effect on the enantioselectivity (Entries 15–16). Lastly, variation of the Ru pre-catalyst to $[Ru(benzene)Cl_2]_2$ (**10b**) was also unproductive, as both activity and selectivity of the resulting catalyst were low (Entry 17).

Having found a catalyst able to promote the reduction of acetophenone (**8a**) with good enantioselectivity, we next decided to apply it to the reduction of some other prochiral ketones. Our aim was to determine if the same level of selectivity would be retained also in the presence of substituents on the aromatic ring (Table 3).

Table 3. Ru-catalyzed transfer hydrogenation of prochiral ketones using sulfinamide **1i** as the chiral ligand.



8a-e (*S*)-**9a-e**

Entry	Product	R	Time	% Conv.[a]	% *ee*[a]
1	**9a**	H	5	42	86 (*S*)
			22	61	84 (*S*)
2	**9b**	4-Br	5	43	84 (*S*)
			21	58	83 (*S*)
3	**9c**	3-CF_3	5	58	88 (*S*)
			22	77	87 (*S*)
4	**9d**	4-Me	21	30	86 (*S*)
5	**9e**	3-MeO	22	32	91 (*S*)

[a] Determined by chiral GC-analysis (CP-Chirasil-Dex CB).

As can be seen from Table 3, 4′-Br-acetophenone (**8b**) furnished a result similar to that obtained with acetophenone (**8a**), although the product of the reduction was formed with slightly lower enantiomeric excess (Entry 2). The more electron-poor substrate **8c**, bearing a trifluoromethyl group, was converted smoothly with good enantioselectivity (Entry 3). Unfortunately, the reduction of more electron-rich ketones such as **8d**–**e** was much slower, and low conversions were observed even after 21–22 h at room temp. (Entries 4–5); alcohols **9d**–**e** were nevertheless formed in good to high enantiomeric excess (86–91% *ee*).

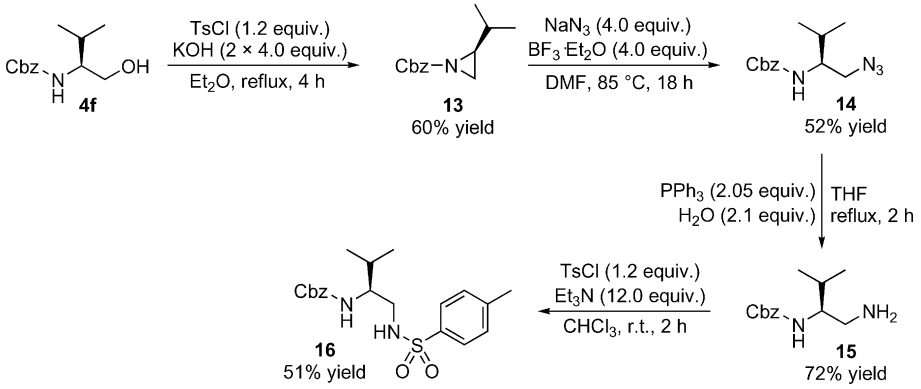
It should be mentioned that a color change was observed during the course of the reaction, usually occurring after several hours (i.e. overnight): the reaction mixture, which was initially deep purple, slowly turned red-brown. We suspect this to be associated with catalyst decomposition, because no further progress in conversion was recorded after the color change had occurred. We found that the presence of moisture in the reaction mixture greatly accelerated this process, which led to color change within minutes. We therefore found it necessary to operate under strictly anhydrous conditions, using dry solvents and a freshly prepared solution of the base, in order to replicate the results reported above.

After having obtained such promising results, we were interested in evaluating the importance of the stereogenic center on sulfur for the selectivity of the reduction. For this purpose, we decided to synthesize compound **16**, structurally similar to **1h** but bearing a non-chiral sulfonamide moiety, and to employ it as a ligand in the transfer hydrogenation under the conditions used in Table 2, Entry 12. A comparison of the results would allow us to assess the role of the chiral sulfinamide unit in imparting significant enantioselectivity to the process. The preparation of sulfonamide **16** is detailed in Scheme 4.

Initially, the amino alcohol **4f** was converted into the aziridine **13** following a known protocol.[30] The latter compound was subjected to nucleophilic ring-opening with sodium azide promoted by $BF_3{\cdot}Et_2O$ as Lewis acid, to yield azide **14** in 52% yield (unoptimized). Subsequent reduction of the azide by means of a Staudinger reaction followed by tosylation under standard conditions[14a] provided the desired compound **16**.

To our surprise, when the sulfonamide **16** was used as a ligand for the Ru-catalyzed transfer hydrogenation of acetophenone (**8a**), only 55% conversion was measured after 18 h at room temp., and the resulting alcohol **9a** was produced in nearly racemic form (< 5% *ee*). Thus, the catalyst stemming from compound **16** was neither more active nor more selective than that derived from its sulfinamide analogue **1h** (which, as mentioned earlier, promoted the formation of **9a** with 74% *ee*, Table 2, Entry 12). Interestingly, this observation is in agreement with previous findings by Hiroi[31] and Ellman,[10] who, in the context of different catalytic enantioselective reactions, found that ligands or catalysts in which a sulfinamide group had been replaced by a sulfonamide were much less selective than their counterparts.

From all these results it appears that a stereogenic center on sulfur can often play a decisive role in the generation of selective catalysts for metal-mediated or organocatalytic reactions; in particular, the chiral S-center is a very impor-



Scheme 4. Synthesis of L-valine-derived sulfonamide **16**.

tant structural feature of the ligands prepared in this study, and in its absence no enantioselectivity was observed in the Ru-catalyzed asymmetric transfer hydrogenation.

Conclusions

In summary, we prepared novel chiral sulfinamides **1a**–**i**, derived from protected amino acids, through the intermediacy of protected α-amino aldehydes **2a**–**g**. The latter were accessed either by preparation of the corresponding Weinreb amides and subsequent reduction with $LiAlH_4$, or by initial reduction of the amino acids to the protected amino alcohols **4** followed by chemoselective reoxidation. The second route was found to be operationally simpler and afforded in general higher yields of the desired intermediates. The aldehydes **2a**–**g** were then subjected to reductive amination in combination with the enantiopure sulfinamides **5a**–**b** to provide the compounds **1a**–**i** in moderate to good yields. In addition, removal of the Fmoc group from sulfinamide **1c** afforded monosulfinylated diamine **7**.

The compounds **1a**–**i** and **7** were tested as ligands for the metal-catalyzed transfer hydrogenation of ketones. The catalyst generated from **7** in combination with the Ru complex **10b** exhibited high activity (TOF = 356 mol h^{-1}), unfortunately accompanied by no selectivity. Catalysts stemming from compounds **1a**–**i** and Rh- or Ru-based pre-catalysts showed variable levels of efficiency and selectivity; the catalyst resulting from the combination of the sulfinamide **1i** and the pre-catalyst **10a** was found to be the most selective one, promoting the formation of chiral secondary alcohols from various ketones with 83–91% *ee*. Finally, the importance of the stereogenic center on sulfur for the enantioselectivity of the process was confirmed by the observation that compound **16**, structurally similar to **1h** but bearing a non-chiral sulfonamide unit, produced the alcohol **9a** in nearly racemic form, as opposed to 74% *ee* with sulfinamide **1h** under otherwise identical conditions. Further refinement of the ligand design as well as application of the compounds **1a**–**i** to other enantioselective processes are currently underway in our laboratory.

Experimental Section

General Remarks: Air- and moisture-sensitive manipulations were carried out under nitrogen using either standard Schlenk tubes or flasks (ligand preparation) or a Radleys Carousel® 12 reaction station (transfer hydrogenation). The glassware employed for those manipulations was either oven- or flame-dried and then cooled under a stream of nitrogen. THF and Et_2O were distilled from sodium-benzophenone ketyl radical, *i*PrOH and CH_2Cl_2 from calcium hydride prior to use. DMF was dried on molecular sieves before use. Ethyl acetate, pentane, methanol and 1,2-dimethoxyethane were reagent- or HPLC-grade and were used as received. Acetophenone (**8a**) and 4′-Me-acetophenone (**8d**) were distilled prior to use, whereas the other ketones were used as received from commercial sources. ^1H and ^{13}C NMR spectra were recorded with a Bruker BioSpin 400 spectrometer (400 and 100 MHz, respectively). IR spectra were recorded with a Perkin–Elmer SpectrumOne instrument; absorptions are given in wavenumbers (cm^{-1}). High-resolution mass spectra with electrospray ionization (MS-ESI) were recorded with a Bruker Daltonics MicroTOF instrument. Optical rotation measurements were conducted at room temperature with a Perkin–Elmer PE-241 polarimeter at a wavelength of 589 nm (D-line of a Na-vapour lamp). Chiral GC measurements were conducted with a Varian 3800 gas chromatograph with a CP-Chirasil-Dex CB Chrompack 7503 column. The aldehydes **2a**–**g** were prepared from the corresponding amino acids following literature methods,[16–17,24–26] and their analytical data were in agreement with those previously reported.[32] IBX was prepared following the procedure described by Frigerio and co-workers.[33] Melting points of solid compounds were measured in open capillaries with an Electrothermal 9200 instrumet and are uncorrected.

General Procedure for the Synthesis of Sulfinamides 1a-i: A round-bottom Schlenk flask under nitrogen was charged with the appropriate protected amino aldehyde **2a**–**g**. The latter was dissolved in dry CH_2Cl_2 (8 mL/mmol), and either (*S*)-*p*-toluenesulfinamide (**5a**) or (*S*)-1,1-dimethylethanesulfinamide (**5b**) (1.0 equiv.) were added at room temperature, followed by $Ti(OiPr)_4$ (4.0–5.0 equiv.). The reaction mixture was stirred at room temperature for 3–16 h (TLC control). The reaction was quenched by careful addition of H_2O (8 mL/mmol) under vigorous stirring. The resulting heterogeneous mixture was filtered through a short pad of Celite®, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (8 mL/mmol). The combined organic layers were dried with $MgSO_4$. Removal of the solvent under reduced pressure afforded crude sulfinyl imines **6a**–**i** (^1H NMR: δ = 8.00–8.30 ppm) typically

as colorless or light yellow oils. The crude imines were placed in a round-bottom Schlenk flask under nitrogen, and were dissolved in methanol (10 mL/mmol). The solution was cooled to 0 °C, and sodium borohydride (2.5 equiv.) was carefully added. After stirring for 2–3 h (TLC control) at 0 °C, the reaction was quenched with a diluted aqueous NH_4Cl solution (20 mL/mmol), and CH_2Cl_2 (20 mL/mmol) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL/mmol). The combined organic layers were washed with brine (40 mL/mmol) and dried with Na_2SO_4. Removal of the solvent in vacuo gave crude sulfinamides **1a**–**i**, sometimes as a mixture of diastereomers, which were purified by flash column chromatography sometimes followed by crystallization.

(*S*,*S*)-*N*-Cbz-*N*′-*p*-Tolylsulfinyl-1,2-diaminopropane (1a): Prepared according to general procedure from aldehyde **2a** (0.300 g, 1.45 mmol) and (*S*)-*p*-toluenesulfinamide (**5a**, 0.225 g, 1.45 mmol, 1.0 equiv.). The crude was obtained as a 6:1 mixture of the title compound and its (*R*,*S*)-diastereomer, as determined by NMR specroscopy. Purification by flash column chromatography (EtOAc/pentane, 3:2) followed by crystallization from EtOAc/*c*Hex afforded pure (*S*,*S*)-**1a** as a colorless solid (0.180 g, 0.52 mmol, 36% yield over two steps), m.p. 98.9–99.1 °C. $[\alpha]_D^{20}$ = +93.9 (*c* = 0.38, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.12 (d, *J* = 6.8 Hz, 3 H), 2.39 (s, 3 H), 2.74–2.81 (m, 1 H), 3.10 (ddd, *J* = 13.6, 6.8, 3.7 Hz, 1 H), 3.75–3.85 (m, 1 H), 4.62 (br. s, 1 H), 5.02–5.13 (AB system, 2 H), 5.41 (br. s, 1 H), 7.24 (d, *J* = 8.2 Hz, 2 H), 7.31–7.37 (m, 5 H), 7.52 (d, *J* = 8.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.3, 21.3, 46.4, 47.1, 66.5, 126.1, 128.1, 128.5, 129.6, 136.6, 140.0, 141.4, 156.1 ppm. IR (KBr): $\tilde{\nu}$ = 3263, 2922, 1699, 1533, 1452, 1337, 1249, 1054 cm^{-1}. HRMS-ESI: *m*/*z* calcd. for $C_{18}H_{23}N_2O_3S$ [M + 1]: 347.1424; found 347.1430.

(*S*,*S*)-*N*-Boc-*N*′-*p*-Tolylsulfinyl-1,2-diaminopropane (1b): Prepared according to general procedure from aldehyde **2b** (0.260 g, 1.5 mmol) and (*S*)-*p*-toluenesulfinamide (**5a**, 0.233 g, 1.5 mmol, 1.0 equiv.). The crude was obtained as a 4.5:1 mixture of the title compound and its (*R*,*S*)-diastereomer, as determined by NMR specroscopy. Purification by flash column chromatography (EtOAc/pentane, 1:1) afforded pure (*S*,*S*)-**1b** as a colorless solid (0.258 g, 0.83 mmol, 55% yield over two steps), m.p. 117.2–117.4 °C. $[\alpha]_D^{20}$ = +72.3 (*c* = 0.47, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.08 (d, *J* = 6.8 Hz), 1.42 (s, 9 H), 2.39 (s, 3 H), 2.72 (dt, *J* = 13.2, 6.6 Hz), 3.10 (ddd, *J* = 13.3, 6.5, 3.9 Hz, 1 H), 3.69–3.78 (m, 1 H), 4.74 (s, 1 H), 4.96 (s, 1 H), 7.27 (d, *J* = 8.2 Hz, 2 H), 7.55 (d, *J* = 8.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.5, 21.3, 28.4, 46.0, 47.0, 79.3 126.0, 129.5, 140.4, 141.2, 155.7 ppm. IR (KBr): $\tilde{\nu}$ = 3262, 2976, 1705, 1693, 1526, 1454, 1365, 1248, 1171, 1053 cm^{-1}. HRMS-ESI: *m*/*z* calcd. for $C_{15}H_{24}N_2NaO_3S$ [M + Na]: 335.1400; found 335.1376.

(*S*,*S*)-*N*-Fmoc-*N*′-*p*-Tolylsulfinyl-1,2-diaminopropane (1c): Prepared according to general procedure from aldehyde **2c** (0.384 g, 1.3 mmol) and (*S*)-*p*-toluenesulfinamide (**5a**, 0.201 g, 1.3 mmol, 1.0 equiv.). The crude was obtained as a 3:1 mixture of the title compound and its (*R*,*S*)-diastereomer, as determined by NMR specroscopy. Purification by flash column chromatography (EtOAc/pentane, 3:2) afforded pure (*S*,*S*)-**1c** as a colorless solid (0.391 g, 0.9 mmol, 68% yield over two steps), m.p. 117.7–117.9 °C. $[\alpha]_D^{20}$ = +71.1 (*c* = 0.85, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.13 (d, *J* = 6.5 Hz, 3 H), 2.39 (s, 3 H), 2.75–2.80 (m, 1 H), 3.08–3.13 (m, 1 H), 3.75–3.85 (m, 1 H), 4.22 (t, *J* = 6.5 Hz, 1 H), 4.40 (d, *J* = 6.6 Hz, 2 H), 4.57 (br. s, 1 H), 5.50 (br. s, 1 H), 7.25 (d, *J* = 8.1 Hz, 2 H), 7.29–7.35 (m, 2 H), 7.37–7.43 (m, 2 H), 7.53 (d, *J* = 8.1 Hz, 2 H), 7.55–7.63 (m, 2 H), 7.76–7.84 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.4, 21.3, 46.2, 47.1, 47.3, 66.5, 119.9, 125.1, 126.1, 127.1, 127.66, 127.70, 129.6, 141.3, 141.4, 143.9, 156.1 ppm. IR (KBr): $\tilde{\nu}$ = 3330, 3142, 3051, 2932, 1694, 1532, 1450, 1251, 1055, 1045 cm^{-1}. HRMS-ESI: *m*/*z* calcd. for $C_{25}H_{26}N_2O_3SNa$ [M + Na]: 457.1556; found 457.1542.

(*R*,*S*)-*N*-Cbz-*N*′-*p*-Tolylsulfinyl-1,2-diaminopropane (1d): Prepared according to general procedure from aldehyde *ent*-**2a** (0.207 g, 1.0 mmol) and (*S*)-*p*-toluenesulfinamide (**5a**, 0.155 g, 1.0 mmol, 1.0 equiv.). The crude was obtained as a 6:1 mixture of the title compound and its (*S*,*S*)-diastereomer, as determined by NMR specroscopy. Purification by flash column chromatography (EtOAc/pentane, 3:2) followed by crystallization from EtOAc/*c*Hex afforded pure (*R*,*S*)-**1d** as a colorless solid (0.121 g, 0.35 mmol, 35% yield over two steps), m.p. 121.7–121.9 °C. $[\alpha]_D^{20}$ = +130.7 (*c* = 0.30, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.09 (d, *J* = 6.7 Hz, 3 H), 2.40 (s, 3 H), 2.87 (ddd, *J* = 13.2, 6.8, 4.2 Hz, 1 H), 2.98–3.05 (m, 1 H), 3.71–3.82 (m, 1 H), 4.60 (br. s, 1 H), 5.09 (AB system, 2 H), 5.32 (br. s, 1 H), 7.27 (d, *J* = 8.1 Hz, 2 H), 7.29–7.35 (m, 5 H), 7.55 (d, *J* = 8.1 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.7, 21.3, 46.3, 46.8, 66.7, 126.0, 127.98, 128.03, 128.5, 129.6, 136.5, 140.7, 141.3, 156.3 ppm. IR (KBr): $\tilde{\nu}$ = 3265, 2925, 1699, 1537, 1454, 1339, 1262, 1240, 1087, 1054 cm^{-1}. HRMS-ESI: *m*/*z* calcd. for $C_{18}H_{22}N_2NaO_3S$ [M + Na]: 369.1243; found 369.1230.

(*S*,*S*)-*N*-Cbz-*N*′-(1,1-Dimethyl)ethylsulfinyl-1,2-diaminopropane (1e): Prepared according to general procedure from aldehyde **2a** (0.300 g, 1.45 mmol) and (*S*)-1,1-dimethylethanesulfinamide (**5b**, 0.176 g, 1.45 mmol, 1.0 equiv.). Purification by flash column chromatography (EtOAc/pentane, 3:1) afforded pure (*S*,*S*)-**1e** as a light yellow oil (0.261 g, 0.83 mmol, 58% yield over two steps). $[\alpha]_D^{20}$ = +36.5 (*c* = 0.72, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.17 (d, *J* = 5.9 Hz, 3 H), 1.18 (s, 9 H), 3.13–3.19 (m, 1 H), 3.64 (br. s, 1 H), 3.83–3.88 (m, 1 H), 5.05 (br. s, 1 H), 5.08 (s, 2 H), 7.31–7.37 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.7, 22.6, 47.7, 50.9, 55.9, 66.7, 128.08, 128.10, 128.5, 136.4, 156.1 ppm. IR (KBr): $\tilde{\nu}$ = 3261, 2958, 2926 1701, 1536, 1455, 1264, 1239, 1054 cm^{-1}. HRMS-ESI: *m*/*z* calcd. for $C_{15}H_{24}N_2NaO_3S$ [M + Na]: 335.1400; found 335.1382.

(*S*,*S*)-*N*-Cbz-*N*′-*p*-Tolylsulfinyl-1,2-diamino-3-phenylpropane (1f): Prepared according to general procedure from aldehyde **2d** (0.397 g, 1.40 mmol) and (*S*)-*p*-toluenesulfinamide **5a** (0.217 g, 1.40 mmol, 1.0 equiv.). The crude was obtained as a 5.5:1 mixture of the title compound and its (*R*,*S*)-diastereomer, as determined by NMR specroscopy. Purification by flash column chromatography (EtOAc/pentane, 2:3) followed by crystallization from EtOAc/*c*Hex afforded pure (*S*,*S*)-**1f** as a colorless solid (0.280 g, 0.66 mmol, 47% yield over two steps), m.p. 139.4–139.6 °C. $[\alpha]_D^{20}$ = +86.0 (*c* = 0.58, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3 H), 2.71 (dd, *J* = 13.8, 7.7 Hz, 1 H), 2.81–2.88 (m, 2 H), 3.04–3.11 (m, 1 H), 3.88–3.98 (m, 1 H), 4.52 (br. s, 1 H), 5.03–5.12 (AB system, 2 H), 5.64 (br. s, 1 H), 7.13–7.17 (m, 2 H), 7.20–7.34 (m, 10 H), 7.50 (d, *J* = 8.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 38.4, 44.9, 51.6, 66.5, 126.0, 126.7, 127.97, 128.02, 128.5, 128.7, 129.0, 129.6, 137.3, 139.6, 141.4, 156.1 ppm. IR (KBr): $\tilde{\nu}$ = 3259, 3029, 2924, 1701, 1538, 1454, 1252, 1086, 1049 cm^{-1}. HRMS-ESI: *m*/*z* calcd. for $C_{24}H_{26}N_2NaO_3S$ [M + Na]: 445.1556; found 445.1535.

(*S*,*S*)-*N*-Cbz-*N*′-*p*-Tolylsulfinyl-1,2-diamino-4-methylpentane (1g): Prepared according to general procedure from aldehyde **2e** (0.490 g, 1.97 mmol) and (*S*)-*p*-toluenesulfinamide **5a** (0.305 g, 1.97 mmol, 1.0 equiv.). The crude was obtained as a 7.5:1 mixture of the title compound and its (*R*,*S*)-diastereomer, as determined by NMR

specroscopy. Purification by flash column chromatography (EtOAc/pentane, 1:2) followed by crystallization from EtOAc/*c*Hex afforded pure (*S*,*S*)-**1g** as a colorless solid (0.375 g, 1.0 mmol, 51% yield over two steps), m.p. 93.3–93.5 °C. $[\alpha]_D^{20}$ = +79.1 (*c* = 0.71, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.5 Hz, 3 H), 0.89 (d, *J* = 6.4 Hz, 3 H), 1.14–1.21 (m, 1 H), 1.25–1.33 (m, 1 H), 1.53–1.63 (m, 1 H), 2.38 (s, 3 H), 2.71–2.80 (m, 1 H), 3.09 (ddd, *J* = 13.6, 6.9, 3.4 Hz, 1 H), 3.72–3.81 (m, 1 H), 4.53 (br. s, 1 H), 5.03–5.17 (AB system, 2 H), 5.64 (br. d, *J* = 8.3 Hz, 1 H), 7.21 (d, *J* = 8.1 Hz, 2 H), 7.29–7.39 (m, 5 H), 7.50 (d, *J* = 8.1 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 22.1, 22.9, 24.7, 41.6, 46.2, 48.7, 66.5, 126.1, 128.0, 128.1, 128.5, 129.6, 136.7, 139.8, 141.3, 156.4 ppm. IR (KBr): $\tilde{\nu}$ = 3260, 3033, 2955, 1701, 1536, 1454, 1240, 1087, 1052 cm^{-1}. HRMS-ESI: *m*/*z* calcd. for $C_{21}H_{28}N_2NaO_3S$ [M + Na]: 411.1713; found 411.1707.

(*S*,*S*)-*N*-Cbz-*N*′-*p*-Tolylsulfinyl-1,2-diamino-3-methylbutane (1h): Prepared according to general procedure from aldehyde **2f** (0.460 g, 1.96 mmol) and (*S*)-*p*-toluenesulfinamide (**5a**, 0.304 g, 1.96 mmol, 1.0 equiv.). Purification by flash column chromatography (EtOAc/pentane, 3:2) afforded pure (*S*,*S*)-**1h** as a colorless solid (0.567 g, 1.51 mmol, 77% yield over two steps), m.p. 97.5–97.7 °C. $[\alpha]_D^{20}$ = +58.6 (*c* = 0.58, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.7 Hz, 3 H), 1.69–1.75 (m, 1 H), 2.38 (s, 3 H), 2.83 (qu, *J* = 6.9 Hz, 1 H), 3.13 (ddd, *J* = 13.5, 6.6, 3.4 Hz, 1 H), 3.47–3.55 (m, 1 H), 4.49 (br. s, 1 H), 5.04–5.17 (AB system, 2 H), 5.20 (br. d, *J* = 8.1 Hz, 1 H), 7.21 (d, *J* = 8.0 Hz, 2 H), 7.29–7.39 (m, 5 H), 7.50 (d, *J* = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.4, 19.4, 21.3, 30.1, 43.9, 56.1, 66.7, 126.0, 128.0, 128.1, 128.5, 129.6, 136.6, 140.0, 141.3, 156.7 ppm. IR (KBr): $\tilde{\nu}$ = 3259, 2961, 1702, 1536, 1454, 1242, 1087, 1047 cm^{-1}. HRMS-ESI: *m*/*z* calcd. for $C_{20}H_{26}N_2O_3SNa$ [M + Na]: 390.1556; found 390.1535.

(*S*,*S*)-*N*-Cbz-*N*′-*p*-Tolylsulfinyl-1,2-diamino-3,3-dimethylbutane (1i): Prepared according to general procedure from aldehyde **2g** (0.495 g, 1.98 mmol) and (*S*)-*p*-toluenesulfinamide **5a** (0.307 g, 1.98 mmol, 1.0 equiv.). Purification by flash column chromatography (EtOAc/pentane, 1:1) afforded pure (*S*,*S*)-**1i** as a colorless solid (0.389 g, 1.0 mmol, 50% yield over two steps), m.p. 136.0–136.2 °C. $[\alpha]_D^{20}$ = –6.7 (*c* = 0.62, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.86 (s, 9 H), 2.38 (s, 3 H), 2.61 (ddd, *J* = 12.8, 10.8, 7.6 Hz, 1 H), 3.38 (ddd, *J* = 12.8, 5.3, 3.1 Hz, 1 H), 3.58 (dt, *J* = 10.5, 3.0 Hz, 1 H), 4.36–4.41 (m, 1 H), 4.52 (br. d, *J* = 10.3 Hz, 1 H), 5.04–5.21 (AB system, 2 H), 7.21 (d, *J* = 8.0 Hz, 2 H), 7.29–7.39 (m, 5 H), 7.49 (d, *J* = 8.0 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 26.5, 34.1, 41.6, 59.6, 66.9, 126.0, 128.1, 128.2, 128.6, 129.5, 136.5, 140.7, 141.2, 157.1 ppm. IR (KBr): $\tilde{\nu}$ = 3261, 2962, 1705, 1539, 1455, 1342, 1240, 1087, 1055 cm^{-1}. HRMS-ESI: *m*/*z* calcd. for $C_{21}H_{28}N_2O_3SNa$ [M + Na]: 411.1713; found 411.1699.

(*S*,*S*)-*N*-*p*-Tolylsulfinyl-1,2-diaminopropane (7): The sulfinamide **1c** (0.135 mg, 0.31 mmol) was placed in a round-bottom flask under an air atmosphere. Piperidine (0.085 mg, 1.0 mmol, 0.1 mL, 3.2 equiv.) and dry DMF (0.4 mL) were added, and the resulting homogeneous mixture was stirred at room temp. After 30′ a thick colorless precipitate was formed. The latter was dissolved by addition of EtOAc, and the resulting mixture was directly loaded onto a column and purified by flash chromatography (MeOH/EtOAc/Et_3N, 1:3:0.1), to furnish pure (*S*,*S*)-**7** as a colorless oil (0.056 mg, 0.26 mmol, 85% yield). $[\alpha]_D^{20}$ = +161.2 (*c* = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.03 (d, *J* = 6.3 Hz, 3 H), 2.03 (br. s, 2 H), 2.40 (s, 3 H), 2.51–2.60 (m, 1 H), 3.02–3.07 (m, 2 H), 4.84 (br. s, 1 H), 7.29 (d, *J* = 8.3 Hz, 2 H), 7.56 (d, *J* = 8.3 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.29, 21.32, 47.1, 48.5, 125.9, 129.5, 141.0, 141.2 ppm. IR (neat): $\tilde{\nu}$ = 3193, 2963, 2923, 2870, 1596, 1491, 1455, 1394, 1087, 1057 cm^{-1}. HRMS-ESI: *m*/*z* calcd. for $C_{10}H_{16}N_2OSNa$ [M + Na]: 235.0876; found 235.0879.

(*S*)-*N*-Cbz-2-Isopropylaziridine (13): In a round-bottom flask under air, the protected amino alcohol **4f** (1.54 g, 6.49 mmol) was dissolved in dry diethyl ether (130 mL). Tosyl chloride (1.49 g, 7.79 mmol, 1.2 equiv.) was added, followed by freshly powdered KOH (1.46 g, 26.0 mmol, 4.0 equiv.). The reaction mixture was heated at reflux and stirred for 3 h. A TLC check (EtOAc/pentane, 1:2) showed the presence of residual starting material; a further 4.0 equiv. of KOH were added, and stirring was continued for 1 h, after which a second TLC control showed no more starting material. The reaction mixture was poured in a separatory funnel containing 150 mL of a ice/water mixture. The layers were separated, and the aqueous layer was extracted with diethyl ether (75 mL). The combined organic layers were washed with brine (120 mL), and dried with $MgSO_4$. Removal of the solvent under vacuum gave crude aziridine **13**. Purification by flash column chromatography (EtOAc/pentane, 1:4) afforded pure (*S*)-**13** (0.860 g, 3.92 mmol, 60% yield) as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.97 (d, *J* = 6.8 Hz, 3 H), 1.07 (d, *J* = 6.8 Hz, 3 H), 1.46 (se, *J* = 6.8 Hz, 1 H), 2.03 (d, *J* = 3.8 Hz, 1 H), 2.25 (ddd, *J* = 7.3, 6.2, 3.9 Hz, 1 H), 2.31 (d, *J* = 6.2 Hz, 1 H), 5.13 (s, 2 H), 7.29–7.39 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.9, 19.7, 30.69, 30.74, 44.4, 67.9, 127.9, 128.1, 128.5, 136.0, 163.6 ppm. The analytical data are in agreement with those reported in the literature.[34]

(*S*)-*N*-Cbz-2-Amino-1-azido-3-methylbutane (14): Aziridine **13** (0.274 g, 1.25 mmol) was placed in a round-bottom Schlenk flask under nitrogen, and was dissolved in dry DMF (12.5 mL). Sodium azide (0.325 g, 5.0 mmol, 4.0 equiv.) and boron trifluoride–diethyl ether (0.710 g, 5.0 mmol, 0.63 mL, 4.0 equiv.) were added in sequence at room temperature, and the reaction mixture was heated to 85 °C and stirred overnight. The reaction mixture was then cooled to room temperature and was diluted with EtOAc (20 mL). Water (20 mL) was added, and the layers were separated. The organic layer was washed with water (5 × 20 mL). The combined aqueous layers were extracted with EtOAc (20 mL). The combined organic layers were washed with with brine (40 mL) and dried with $MgSO_4$. Removal of the volatiles furnished crude azide **14**, which was purified by flash column chromatography (EtOAc/pentane, 1:11) to give pure (*S*)-**14** (0.170 g, 0.64 mmol, 52% yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.8 Hz, 3 H), 0.96 (d, *J* = 6.8 Hz, 3 H), 1.83 (se, *J* = 6.8 Hz, 1 H), 3.45 (d, *J* = 4.8 Hz, 2 H), 3.57–3.63 (m, 1 H), 4.80 (br. d, *J* = 8.9 Hz, 1 H), 5.12 (s, 2 H), 7.28–7.38 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.4, 19.4, 29.7, 53.0, 56.1, 66.9, 128.1, 128.2, 128.5, 136.3, 156.1 ppm. The analytical data are in agreement with those reported in the literature.[35]

(*S*)-1-Amino-2-(Cbz-amino)-3-methylbutane (15):[36] In a round-bottom flask under air, the azide **14** (0.170 g, 0.65 mmol) was dissolved in THF (8 mL). Triphenylphosphane (0.340 g, 1.33 mmol, 2.05 equiv.) and water (0.025 g, 1.37 mmol, 25 μL, 2.1 equiv.) were added in sequence, and the resulting mixture was heated to reflux and stirred for 2 h. The reaction mixture was then cooled to room temperature and the solvent was evaporated. The oily residue was taken up with Et_2O (12 mL). The mixture was vigorously stirred and acidified with aq. HCl 1 M until pH 2. The layers were separated and the aqueous layer was washed with Et_2O (2 × 7 mL). The pH was then adjusted to 12 with aq. NaOH 1 M, and the aqueous layer was extracted with CH_2Cl_2 (6 × 8 mL), and the combined organic layers were dried with Na_2SO_4. Removal of the volatiles afforded the crude, which was purified by flash column chromatog-

raphy (MeOH/EtOAc/Et_3N, 3:5:0.05) to afford pure monoprotected diamine (*S*)-**15** (0.110 g, 0.465 mmol, 72% yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (d, J = 6.8 Hz, 3 H), 0.92 (d, J = 6.8 Hz, 3 H), 1.77 (se, J = 6.7 Hz, 1 H), 2.68–2.75 (m, 1 H), 2.81–2.86 (m, 1 H), 3.40–3.51 (m, 1 H), 3.90 (br. s, 2 H), 5.03–5.13 (AB system, 2 H), 5.31 (br. s, 1 H), 7.28–7.38 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.2, 19.3, 30.2, 42.9, 58.1, 66.7, 127.96, 128.02, 128.5, 136.5, 156.9 ppm.

(*S*)-*N*-Cbz-*N*′-*p*-Tolylsulfonyl-1,2-diamino-3-methylbutane (16): Monoprotected diamine (*S*)-**15** (0.110 g, 0.47 mmol) was placed in a round-bottom flask under air, and was dissolved in $CHCl_3$ (1.0 mL). Triethylamine (0.581 g, 5.7 mmol, 0.8 mL, 12.0 equiv.) was added. The reaction mixture was cooled to 0 °C and tosyl chloride (0.106 g, 0.56 mmol, 1.2 equiv.) was added. The mixture was stirred at 0 °C for 2 h. The reaction mixture was subsequently diluted with diethyl ether (20 mL). The organic layer was washed with aq. HCl 1 M (10 mL), satd. aq. $NaHCO_3$ (2 × 10 mL) and brine (2 × 10 mL), and dried with Na_2SO_4. Removal of the solvent in vacuo afforded crude **16**. Purification by flash column chromatography (EtOAc/pentane, 2:5) afforded pure (*S*)-**16** (0.092 g, 0.24 mmol, 51% yield) as a colorless oil which slowly solidified upon standing, m.p. 99.1–99.3 °C. $[\alpha]_D^{20}$ = –6.3 (c = 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.86 (d, J = 6.9 Hz, 3 H), 0.88 (d, J = 6.9 Hz, 3 H), 1.77 (se, J = 6.8 Hz, 1 H), 2.40 (s, 3 H), 2.94–3.01 (m, 1 H), 3.03–3.10 (m, 1 H), 3.45–3.51 (m, 1 H), 4.85 (br. s, 1 H), 5.07 (s, 2 H), 5.25 (br. s, 1 H), 7.26 (d, J = 8.1 Hz, 2 H), 7.29–7.38 (m, 5 H), 7.71 (d, J = 8.1 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.1, 19.2, 21.5, 29.9, 45.5, 56.1, 67.0, 127.0, 128.0, 128.2, 128.5, 129.7, 136.2, 136.8, 143.4, 156.9 ppm. IR (KBr): $\tilde{\nu}$ = 3305, 2962, 1697, 1529, 1454, 1329, 1234, 1160, 1093 cm^{-1}. HRMS-ESI: m/z calcd. for $C_{20}H_{26}N_2O_4S$ [M]: 390.1608; found 390.1628.

General Procedure for the Transfer Hydrogenation of Ketones 8a-e: A Radleys Carousel® reaction tube was charged with the metal precatalyst **10**–**12** (0.005–0.01 mmol, 0.5–1.0 mol-%), sulfinamide **1a**–**i**, **7** or the sulfonamide **16** (0.011–0.022 mmol, 1.1–2.2 mol-%) and litihium chloride (4.2 mg, 0.1 mmol, 10 mol-%) under nitrogen. The solid compounds were dried under vacuum for 10–15 min, and the nitrogen atmosphere was restored. 2-Propanol (4.0–4.5 mL, final concentration 0.2 M) was added, followed by a 0.1 M solution of the appropriate base in 2-propanol (0.5–1.0 mL, 0.05–0.1 mmol, 5–10 mol-%). After 5 min stirring at room temperature, the appropriate ketone **8** was added (1.0 mmol), and the reaction mixture was stirred at room temperature. Samples of the reaction mixture (approx 0.2 mL) were taken at regular intervals and filtered through silica gel using EtOAc as a solvent before being analyzed by means of chiral gas chromatography (CP-Chirasil-Dex CB Chrompack 7503) to determine conversion of the starting materials and enantiomeric excess of the products. The absolute configuration was assigned by comparison with previously reported data.[12c]

Acknowledgments

We thank the Swedish Research Council and the Wenner-Gren Foundation (post-doctoral fellowship to L. Z.). Dr. J.-B. Sortais is acknowledged for a generous donation of complex **10b**.

[1] I. Fernández, N. Khiar, *Chem. Rev.* **2003**, *103*, 3651.
[2] Reviews: a) J. A. Ellman, T. D. Owens, T. P. Tang, *Acc. Chem. Res.* **2002**, *35*, 984; b) J. A. Ellman, *Pure Appl. Chem.* **2003**, *75*, 39; c) P. Zhou, B.-C. Chen, F. A. Davis, *Tetrahedron* **2004**, *60*, 8003; d) C. H. Senanayake, D. Krishnamurthy, Z.-H. Lu, Z. Han, I. Gallou, *Aldrichimica Acta* **2005**, *38*, 93; e) F. A. Davis, B. Yang, J. Deng, J. Zhang, *ARKIVOC* **2006**, *##VII*, 120; f) D. Morton, R. A. Stockman, *Tetrahedron* **2006**, *62*, 8869.
[3] a) B. R. James, R. S. McMillan, *Can. J. Chem.* **1977**, *55*, 3927; b) P. Kvintovics, B. R. James, B. Heil, *J. Chem. Soc., Chem. Commun.* **1986**, 1810; c) D. G. I. Petra, P. C. J. Kamer, A. L. Spek, H. E. Schoemaker, P. W. N. M. van Leeuwen, *J. Org. Chem.* **2000**, *65*, 3010.
[4] a) N. Khiar, I. Fernández, F. Alcudia, *Tetrahedron Lett.* **1993**, *34*, 123; b) M. Ordoñez, V. Guerrero de la Rosa, V. Labastida, J. M. Llera, *Tetrahedron: Asymmetry* **1996**, *7*, 2675; c) K. Hiroi, K. Watanabe, I. Abe, M. Koseki, *Tetrahedron Lett.* **2001**, *42*, 7617.
[5] a) M. Carreño, J. L. Garcia-Ruano, M. C. Maestro, M. L. Cabreras, *Tetrahedron: Asymmetry* **1993**, *4*, 727; b) G. Chelucci, D. Berta, A. Saba, *Tetrahedron: Asymmetry* **1997**, *8*, 3843; c) J. Priego, O. G. Mancheño, S. Cabrera, J. C. Carretero, *J. Org. Chem.* **2002**, *67*, 1346.
[6] Selected references: a) J. V. Allen, J. F. Bower, J. M. J. Williams, *Tetrahedron: Asymmetry* **1994**, *5*, 1895; b) R. Tokunoh, M. Sodeoka, M. Shibasaki, *Tetrahedron Lett.* **1995**, *36*, 8035; c) K. Hiroi, Y. Suzuki, *Tetrahedron Lett.* **1999**, *40*, 715; d) K. Hiroi, Y. Suzuki, I. Abe, R. Kawagishi, *Tetrahedron* **2000**, *56*, 4701; e) K. Hiroi, I. Izawa, T. Takizawa, K.-i. Kawai, *Tetrahedron* **2004**, *60*, 2155.
[7] a) T. D. Owens, F. J. Hollander, A. G. Oliver, J. A. Ellman, *J. Am. Chem. Soc.* **2001**, *123*, 1539; b) T. D. Owens, A. J. Souers, J. A. Ellman, *J. Org. Chem.* **2003**, *68*, 3; c) L. B. Schenkel, J. A. Ellman, *Org. Lett.* **2003**, *5*, 545; d) L. B. Schenkel, J. A. Ellman, *J. Org. Chem.* **2004**, *69*, 1800.
[8] J. Solà, M. Revés, A. Riera, X. Verdaguer, *Angew. Chem. Int. Ed.* **2007**, *46*, 5020.
[9] a) D. Pei, Z. Wang, Y. Zhang, S. Wei, J. Sun, *Org. Lett.* **2006**, *8*, 5913; b) D. Pei, Y. Zhang, S. Wei, M. Wang, J. Sun, *Adv. Synth. Catal.* **2008**, *350*, 619.
[10] M. T. Robak, M. Trincado, J. A. Ellman, *J. Am. Chem. Soc.* **2007**, *129*, 15110.
[11] K. L. Tan, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2007**, *46*, 1315.
[12] Selected references: a) I. M. Pastor, P. Västilä, H. Adolfsson, *Chem. Commun.* **2002**, 2046; b) I. M. Pastor, P. Västilä, H. Adolfsson, *Chem. Eur. J.* **2003**, *9*, 4031; c) A. Bøgevig, I. M. Pastor, H. Adolfsson, *Chem. Eur. J.* **2004**, *10*, 294; d) P. Västilä, J. Wettergren, H. Adolfsson, *Chem. Commun.* **2005**, 4039; e) A. B. Zaitsev, H. Adolfsson, *Org. Lett.* **2006**, *8*, 5129; f) P. Västilä, A. B. Zaitsev, J. Wettergren, T. Privalov, H. Adolfsson, *Chem. Eur. J.* **2006**, *12*, 3218; g) K. Ahlford, A. B. Zaitsev, J. Ekström, H. Adolfsson, *Synlett* **2007**, 2541.
[13] a) I. M. Pastor, H. Adolfsson, *Tetrahedron Lett.* **2002**, *43*, 1743; b) P. Västilä, I. M. Pastor, H. Adolfsson, *J. Org. Chem.* **2005**, *70*, 2921.
[14] a) N. Dahlin, A. Bøgevig, H. Adolfsson, *Adv. Synth. Catal.* **2004**, *346*, 1101; b) H. Sundén, N. Dahlin, I. Ibrahem, H. Adolfsson, A. Córdova, *Tetrahedron Lett.* **2005**, *46*, 3385.
[15] a) R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97; b) S. Gladiali, E. Alberico, *Chem. Soc. Rev.* **2006**, *35*, 226.
[16] A. K. Ghosh, K. Xi, K. Ratia, B. D. Santarsiero, W. Fu, B. H. Harcourt, P. A. Rota, S. C. Baker, M. E. Johnson, A. D. Mesecar, *J. Med. Chem.* **2005**, *48*, 6767.
[17] D. A. Nugiel, K. Jacobs, T. Worley, M. Patel, R. F. Kaltenbach III, D. T. Meyer, P. K. Jadhav, G. V. De Lucca, T. E. Smyser, R. M. Klabe, L. T. Bacheler, M. M. Rayner, S. P. Seitz, *J. Med. Chem.* **1996**, *39*, 2156.
[18] This is likely to be due to partial cleavage of the Fmoc protecting group. For an extensive discussion on the synthesis of Fmoc-protected amino aldehydes, see: J. J. Wen, C. M. Crews, *Tetrahedron: Asymmetry* **1998**, *9*, 1855.
[19] a) J. A. Fehrentz, M. Paris, A. Heitz, J. Velek, C.-F. Liu, F. Winternitz, J. Martinez, *Tetrahedron Lett.* **1995**, *36*, 7871; b)

J. N. Ede, S. N. Eagle, G. Wickham, A. M. Bray, B. Warne, K. Shoemaker, S. Rosenberg, *J. Pept. Sci.* **2000**, *6*, 11.
[20] F. A. Davis, Y. Zhang, Y. Andemichael, T. Fang, D. L. Fanelli, H. Zhang, *J. Org. Chem.* **1999**, *64*, 1403.
[21] G. K. S. Prakash, M. Mandal, *J. Am. Chem. Soc.* **2002**, *124*, 6538.
[22] These included treatment with HCl in EtOAc/H_2O, TMS-Cl in MeOH or TMSOTf + Et_3N for *N*-Boc-protected substrate **1b**, or employment of H_2 over Pd/C, BBr_3 in CH_2Cl_2, or KOH 40% in MeOH for *N*-Cbz-protected substrate **1a**. For details, see: T. W. Greene, P. G. M. Wuts, *Protecting Groups in Organic Chemistry*, Wiley, New York, **1999**, and references therein.
[23] F. Guillaumie, J. C. Kappel, N. M. Kelly, G. Barany, K. J. Jensen, *Tetrahedron Lett.* **2000**, *41*, 6131.
[24] M. Rodriguez, M. Llinares, S. Doulut, A. Heitz, J. Martinez, *Tetrahedron Lett.* **1991**, *32*, 923.
[25] A. W. Konradi, S. F. Pedersen, *J. Org. Chem.* **1992**, *57*, 28.
[26] J. D. More, N. S. Finney, *Org. Lett.* **2002**, *4*, 3001.
[27] It should be pointed out that the preparation of the α-amino aldehyde derived from *N*-Cbz-phenylglycine was impossible through either of the routes presented in this work. This is probably due to the instability of such compound, possessing a highly acidic proton in the α-position. For a similar observation, see ref. [26].
[28] CCDC-691608 contains the supplementary crystallographic data for compound **1h**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[29] T. Ikariya, A. J. Blacker, *Acc. Chem. Res.* **2007**, *40*, 1300.
[30] P. Wessig, J. Schwarz, *Synlett* **1997**, 893.
[31] K. Hiroi, K. Watanabe, I. Abe, M. Koseki, *Tetrahedron Lett.* **2001**, *42*, 7617.
[32] a) **2a, 2c, 2d**: F. Debaene, J. A. Da Silva, Z. Pianowski, F. J. Duran, N. Winssinger, *Tetrahedron* **2007**, *63*, 6577; b) **2b**: A. Alexakis, N. Lensen, J.-P. Tranchier, P. Mangeney, J. Feneau-Dupont, J. P. Declercq, *Synthesis* **1995**, 1038; c) *ent*-**2a**: L. Espelt, T. Parella, J. Bujons, C. Solans, J. Joglar, A. Delgado, P. Clapés, *Chem. Eur. J.* **2003**, *9*, 4887; d) **2e**: T. Schmidlin, P. E. Burckhardt, N. Waespe-Šarčević, C. Tamm, *Helv. Chim. Acta* **1983**, *66*, 450; e) **2f**: D. Schirlin, S. Baltzer, J. M. Altenburger, C. Tarnus, J. M. Remy, *Tetrahedron* **1996**, *52*, 305; f) **2g**: S. Steurer, J. Podlech, *Eur. J. Org. Chem.* **1999**, 1551.
[33] M. Frigerio, M. Santagostino, S. Sputore, *J. Org. Chem.* **1999**, *64*, 4537.
[34] J. L. Garcia-Ruano, A. Lorente, J. H. Rodríguez Ramos, *Tetrahedron Lett.* **1998**, *39*, 9765.
[35] C. Betschart, L. S. Hegedus, *J. Am. Chem. Soc.* **1992**, *114*, 5010.
[36] G. V. Reddy, G. V. Rao, D. S. Iyengar, *Tetrahedron Lett.* **1999**, *40*, 3937.

Received: June 13, 2008
Published Online: August 14, 2008

