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Preparation of α-amino ketones, β-amino hydroxylamines using asymmetric aza-Henry reactions of *N*-*p*-tolylsulfinylimines with nitroethane

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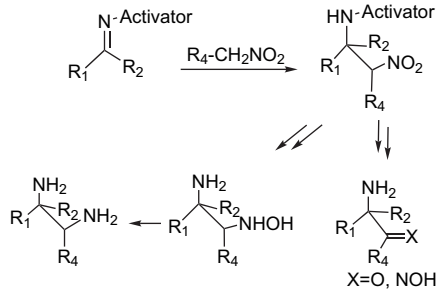
Abstract—*N*-Sulfinylimines derived from aromatic and aliphatic aldehydes react with nitroethane and NaOH, yielding mainly two diastereoisomeric β-nitroamines as the result of a highly diastereoselective reaction and further epimerization of the carbon linked to the nitro group. The resulting β-nitroamines are used as precursors of *N*-sulfonyl α-amino methyl ketones and β-amino hydroxylamines.

1. Introduction

Diastereoselective and enantioselective versions of the aza-Henry (or nitro-Mannich) reaction are recently attracting a great deal of attention.[1–3] This interest is due to the formation of optically pure β-nitroamines, which are attractive targets in asymmetric synthesis mainly due to their possible but not always easy conversion to diamines.[4] Additionally, the nitro moiety can be transformed into other interesting functional groups like carbonyl groups,[5] hydroxylamines,[6] and oximes or nitriles[7] (Scheme 1).



Scheme 1. Aza-Henry reaction and some interesting transformations.

We have recently reported the asymmetric diastereoselective aza-Henry reaction of nitromethane with a wide variety of *N*-*p*-tolylsulfinylimines from aliphatic and aromatic aldehydes as well as from ketones, even when they have enolizable protons.[8] Depending on the reaction conditions employed (NaOH or TBAF) we were able to obtain as the major product one of the two possible diastereoisomers.

As a part of our ongoing investigations on the asymmetric aza-Henry reaction, we present herein the results obtained when these *N*-*p*-tolylsulfinylimines are treated with nitroethane under the conditions previously optimized with nitromethane, and the transformation of the resulting β-nitro sulfinylamines into other compounds of interest such as α-amino methyl ketones and β-amino hydroxylamines.

2. Results and discussion

N-Sulfinylimines **1a–i** have been obtained by condensation of the corresponding aldehydes and ketones with (*S*)-*N*-*p*-tolylsulfinylamide following the $Ti(OEt)_4$ Davis' protocol[9] with slight modifications in the work-up.[10]

Aza-Henry reactions of *N*-sulfinylimines **1** with $EtNO_2$, under the same reaction conditions optimized when $MeNO_2$ was used as nucleophile,[8] led to a mixture of diastereoisomers (Table 1). The four possible ones were obtained with very low diastereoselectivity with the aromatic *N*-sulfinylaldimine **1a** using TBAF as the base (entry 1) with no improvement by lowering the reaction temperature. Nevertheless, when this reaction was carried out in the presence of NaOH, diastereoisomers **2a** and **3a** were clearly predominant and can be easily separated from **4a** and **5a** by simple crystallization in ether (entry 2). A similar result was

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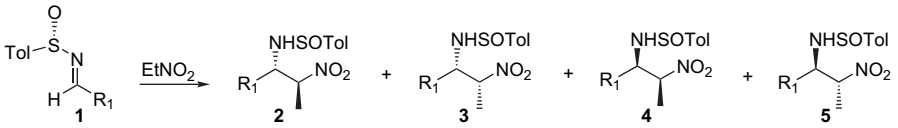
Table 1. Aza-Henry reaction of nitroethane with *N*-sulfinylaldimines (*Ss*)-**1a–g**



Entry	Substrate's R_1	s.m./prod	Conditions	Conv [%][a]	*t* [h]	Ratio of products **2/3/4/5**[a]	Yield[b] (**2/3**) [%]
1	C_6H_5	**a**	Method B	95	0.5	28:13:38:21	92 (**2–5**)
2	C_6H_5	**a**	Method A	81	36	50:44:3:3	75 [43 (**2a**)/32 (**3a**)] 70[d] (58:42)
3	*p*-CNC_6H_4	**b**	Method A	100	26	51:41:3:5	82 [45 (**2b**)/37 (**3b**)]
4	*p*-$MeOC_6H_4$	**c**	Method A	74	66	55:41:2:2	68 [40 (**2c**)/28 (**3c**)]
5	PhCH=CH	**d**	Method A	93	72	51:40:6:3[c]	70 [36 (**2d**)/34 (**3d**)]
6	Me	**e**	Method A	94	17	91 (**2+3**):5:4	80[e]
7	Me	**e**	Method A, Yb(O*i*-Pr)$_3$ (1 equiv)	93	24	42:40:9:9	Not determined
8	*i*-Pr	**f**	Method A	62	138	83:17	48[f] (83:17) 42[d] (93:7)
9	*i*-Pr	**f**	NaOH (5 equiv), 40 °C	73	168	81:19	34[g]

Method A: $EtNO_2$ (solvent), NaOH (5 equiv), 4 Å MS, 40 °C. Method B: $EtNO_2$ (solvent), TBAF.
[a] Determined by ^1H NMR.
[b] After flash chromatography.
[c] Determined after isolation of products by flash chromatography.
[d] After crystallization in ether.
[e] After chromatography the ratio **2e/3e** was 55.2:44.8 (determined by HPLC).
[f] Recovered starting material: 17%.
[g] Recovered starting material: 15%.

obtained with other aromatic imines **1b**,**c**, α,β-unsaturated **1d**, and the aliphatic *N*-sulfinylimine **1e**, derived from acetaldehyde (entries 3–6). In the later case, the addition of Yb(O*i*-Pr)$_3$ produced a deleterious effect on the stereoselectivity of the reaction (entry 7).[11] The bulkier aliphatic *i*-Pr substituent required longer reaction times to afford the β-nitroamines with higher stereoselectivity (entry 8). The results in entries 8 and 9 clearly illustrate that the isolated yields decreased when the reactions were carried out in the absence of molecular sieves, which could suggest that they have some role in preventing the hydrolysis of the *N*-sulfinylimine, by absorbing the water generated by the HO^-.

The bulky *tert*-butyl *N*-sulfinylimine reacts with nitroethane under both catalyzed (Yb(O*i*-Pr)$_3$) and uncatalyzed conditions affording the corresponding β-nitroamines in very low yields.[12] Finally, *N*-sulfinylketimines failed to undergo aza-Henry reaction with nitroethane under the same reaction conditions.

The absolute configurations of compounds **2f** and **3a** were respectively established as (*Ss*, 1*S*,2*S*) and (*Ss*, 1*S*,2*R*) by X-ray crystallography (Fig. 1). The major diastereoisomers **2** obtained in the reactions carried out in the presence of NaOH have been assigned the same configurations as **2f** by assuming that all imines should evolve through the same stereochemical course.[13]

When compounds **2a** and **3a** were treated independently with nitromethane using NaOH as well as TBAF, a mixture

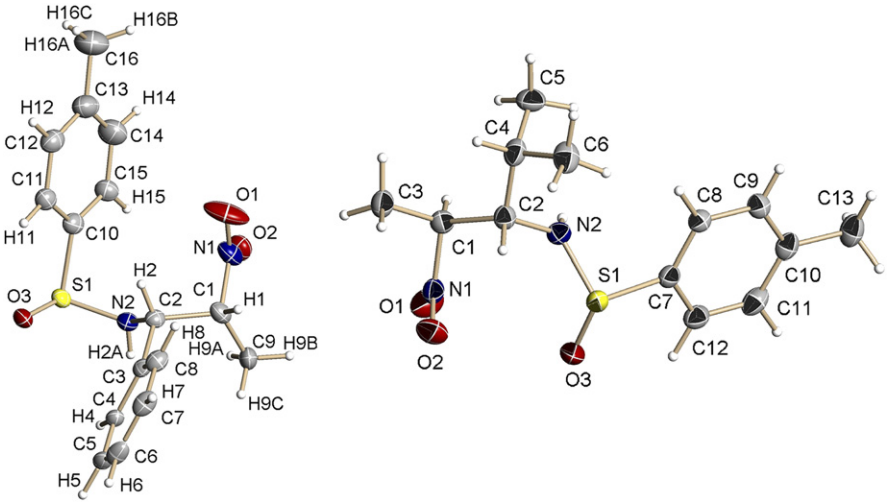
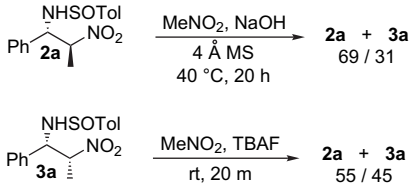


Figure 1. X-ray structure of **2f** and **3a**.

of **2a** and **3a** was obtained in both cases (Scheme 2). It indicates that the carbon bearing the nitro group is easily epimerizable under both reaction conditions. The fact that no traces of the compounds resulting from the aza-Henry reaction with nitromethane were detected in the latter experience, despite the presence of nitromethane as solvent, also indicates that retro aza-Henry reaction is not taking place under these conditions. The above results suggest that the lack of stereoselectivity observed in these reactions could be due to the epimerization under the reaction conditions, and therefore it is not easily avoidable. The use of only 1 equiv of NaOH after 40 h affords the same mixture of diastereoisomers, but the conversion decreases to 64%.



Scheme 2. Isomerization of **2a** into **3a**.

The high selectivity observed at the new chiral center bearing the sulfinamide moiety when NaOH was used as the base is in agreement with the proposed model for the reactions with nitromethane[8] and could be attributed to a rigid transition state in which both reacting partners were coordinated to the metal, as outlined in Figure 2. The *S* configuration of the sulfoxide favors the TS leading the (*S*s, *S*) diastereoisomer (**I** in Fig. 2), since the TS affording the (*S*s, *R*) diastereoisomer (**II** in Fig. 2) would be destabilized by the steric interactions of the bulky *p*-tolyl group.

Several synthetic manipulations of the β-nitroamines **2** and **3** can be envisioned (Schemes 3 and 4). All the attempts carried out to transform the nitro group in the sulfinyl β-nitroamines **2** and **3** into a carbonyl one were unsuccessful. However, this transformation could be easily achieved from the corresponding sulfonyl β-nitroamines **6** and **7** (easily prepared from **2** and **3** by oxidation with *m*-CPBA). Thus, the reaction of a mixture of **6a** and **7a** with *t*-BuOK/*t*-BuOH and subsequent addition of $KMnO_4$ afforded the corresponding ketone **8a** in 73% yield and 80% ee.[14] This loss of optical purity can be explained through epimerization of the stereogenic center once the ketone is formed, due to the acidity at the α position.[15] This acidity is lower when R is an aliphatic chain and thus ketone **8e** is obtained optically pure (ee>99%) from β-nitroamines **2e** and **3e** following the same procedure.[16] Therefore, ketones **8a** and **8e** are obtained in 51 and 63% yields, respectively, from the corresponding sulfinylimines **1a** and **1e** employing only one final chromatographic purification.[17]

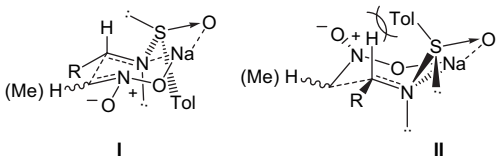
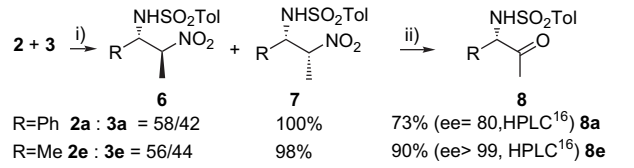
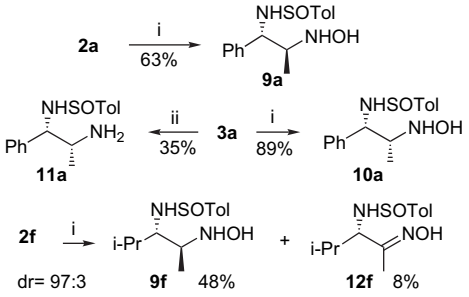


Figure 2. Transition states involved in aza-Henry reactions of nitromethane and nitroethane with *N*-sulfinylaldimines in the presence of NaOH.



Scheme 3. Preparation of α-amino ketones **8a** and **8e**. (i) *m*-CPBA, CH_2Cl_2, rt–0 °C, 30 min, 90%; (ii) (a) *t*-BuOK/*t*-BuOH, rt, 10 min; (b) EtOAc, $KMnO_4$, 0 °C, 2 h 30 min.



Scheme 4. Preparation of β-amino hydroxylamines. (i) Al/Hg (3 equiv), 40 min; (ii) Al/Hg (10 equiv), 65 h.

When compounds **2a** and **3a**, which can be obtained by flash chromatography in 43 and 32% yields, respectively, were independently treated for 40 min with aluminum amalgam[18] (3 equiv) in THF/H_2O at rt, the corresponding hydroxylamines **9a** and **10a** could be isolated in 63 and 89% yields, respectively, after flash chromatography. Prolonging the reaction times of **3a** and using 10 equiv of aluminum amalgam the 1,2-diamine **11a** was obtained in 35% yield. When the β-nitroamine **2f**, with aliphatic substituents, was submitted to the same reaction conditions hydroxylamine **9f** could be isolated in 48% yield along with 8% of the oxime **12f**.

3. Conclusions

In summary, the aza-Henry reaction of *N*-sulfinylimines derived from aromatic and aliphatic aldehydes with nitroethane and NaOH takes place to afford the corresponding β-nitroamines as a mixture of two major diastereoisomers (**2** and **3**) as a consequence of the easy epimerization at the carbon linked to the nitro group. The synthetic interest of these compounds is illustrated with several transformations. After separation of the minor isomers (**4** and **5**) by crystallization of the crude, β-nitroamines **2** and **3** are transformed into *N*-sulfonyl α-amino methyl ketones **8** in good yields. Reduction of the nitro group using aluminum amalgam provides β-amino hydroxylamines in moderate to good yields.

4. Experimental

4.1. General

^1H NMR and ^{13}C NMR spectra were acquired in a Bruker spectrometer at 200 or 300 MHz and 75 MHz, respectively. THF and CH_2Cl_2 were distilled from sodium-benzophenone and P_2O_5, respectively. Melting points were measured using a *Gallemkamp* apparatus in open capillary tubes. Optical

rotations were recorded in cells with 10 cm path length on a Perkin–Elmer 241 MC polarimeter. Flash column chromatography was performed using silica gel Merk-60 (230–400 mesh) or Redisep™ normal phase columns in an Isco CombiFlash instrument. All reagents were purchased from Aldrich. All the *N*-sulfinylimines and ketimines were synthesized using Davis' methodology[9] with slight modifications in the work-up.[10]

4.2. General procedure for the aza-Henry reaction of (*S*)-*N*-sulfinylimines by using NaOH. (Method A)

Powdered NaOH (2 mmol) was added to a slurry of the corresponding *N*-sulfinylimine (0.4 mmol) and the same weight of 4 Å MS in $EtNO_2$ (5.7 mL) at rt. The reaction mixture was stirred at the indicated temperature and reaction time specified in each case (Table 1). All reactions were monitored by TLC (hex/EtOAc 2:1), the mixture was filtrated through a short pad of silica gel, and the crude purified by flash chromatography.

4.2.1. (1*S*,2*S*,(S)*S*)-*N*-(*p*-Tolylsulfinyl)-2-nitro-1-phenyl-propylamine (2a) and (1*S*,2*R*,(S)*S*)-*N*-(*p*-tolylsulfinyl)-2-nitro-1-phenyl-propylamine (3a). These compounds were obtained following the general method A and method B. *Method A*: at 40 °C after 36 h as a mixture **2a/3a/others**=50:44:3:3. After flash chromatography **2a** and **3a** were obtained in 43 and 32% yields, respectively. Crystallization from ether of the crude provides a mixture of **2a** and **3a** in 70% combined yield (**2a/3a**=58:42). *Method B*: a 1 M solution of TBAF (66 μL) was added to a solution of the corresponding *N*-sulfinylimine (0.328 mmol) in $EtNO_2$ (4.7 mL) at rt. The reaction mixture was stirred for 0.5 h. The reaction was monitored by TLC (hex/EtOAc 2:1), the mixture (**2a/3a/4a/5a**=28:13:38:21) was filtrated through a short pad of silica gel, the solvent evaporated, and the crude purified by flash chromatography. Data of the major diastereoisomer **2a**: white solid; mp: 123–125 °C; $[\alpha]_D^{20}$ +153 (*c* 0.2, $CHCl_3$); IR: 3184, 1554, 1455, 1389, 1360, 1089, 1057 cm^{-1}; ^1H NMR (300 MHz): δ 7.53 (d, *J*=8.3 Hz, 2H), 7.42–7.30 (m, 7H), 4.94 (br d, *J*=6.4 Hz, 1H), 4.80 (dq, *J*=8.1, 6.6 Hz, 1H), 4.69 (dd, *J*=8.1, 6.6 Hz, 1H), 2.43 (s, 3H), 1.33 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (75 MHz): δ 141.8, 140.9, 136.6, 129.7, 129.2, 129.0, 127.7, 125.4, 87.3, 60.6, 21.4, 17.0; MS (FAB) *m/z* 319.1 (M+1, 81), 154 (32), 139 (100); HRMS [M+1]: calcd for $C_{16}H_{19}N_2O_3S$: 319.1116; found: 319.1124. Anal. Calcd for $C_{16}H_{18}N_2O_3S$: C, 60.36; H, 5.70; N, 8.80; S, 10.07. Found: C, 60.56; H, 5.84; N, 8.40; S, 9.62. Data of the minor diastereoisomer **3a**: mp: 120 °C; $[\alpha]_D^{20}$ +160 (*c* 0.2, $CHCl_3$); IR: 3196, 2924, 1554, 1389, 1361, 1088, 1051 cm^{-1}; ^1H NMR (300 MHz): δ 7.57 (d, *J*=8.1 Hz, 2H), 7.40–7.31 (m, 7H), 4.95–4.86 (m, 2H), 4.79 (dq, *J*=6.8, 5.0 Hz, 1H), 2.43 (s, 3H), 1.46 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (75 MHz): δ 142.0, 141.3, 136.3, 129.8, 129.0, 128.9, 127.6, 125.4, 86.6, 60.0, 21.4, 14.9; MS (FAB) *m/z* 319.1 (M+1, 45), 154 (28), 139 (100); HRMS [M+1]: calcd for $C_{16}H_{19}N_2O_3S$: 319.1116; found: 319.1115.

4.2.2. (1*S*,2*S*,(S)*S*)-*N*-(*p*-Tolylsulfinyl)-2-nitro-1-(4-nitrilephenyl)-propylamine (2b) and (1*S*,2*R*,(S)*S*)-*N*-(*p*-tolylsulfinyl)-2-nitro-1-(4-nitrilephenyl)-propylamine (3b). These compounds were obtained following the general method A at 40 °C after 26 h in 45 and 37% yields, respectively, after flash chromatography (hex/EtOAc 2:1). Data of **2b** as a mixture **2b/3b**=85:15; white solid, mp: 78 °C; $[\alpha]_D^{20}$ +236 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz): δ 7.70 (d, *J*=7.7 Hz, 2H), 7.52–7.34 (m, 6H), 5.13 (d, *J*=7.67 Hz, 1H), 4.80–4.78 (m, 1H), 4.66–4.61 (m, 1H), 2.45 (s, 3H), 1.37 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (75 MHz): δ 142.1, 141.9, 139.5, 132.4, 129.7, 127.8, 125.2, 117.8, 112.1, 86.2, 59.6, 21.2, 17.2. Data of **3b**: ^1H NMR (300 MHz): δ 7.70 (d, *J*=8.3 Hz, 2H), 7.56–7.34 (m, 6H), 4.94–4.75 (m, 3H), 2.45 (s, 3H), 1.49 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (75 MHz): δ 142.8, 142.3, 132.7, 129.4, 127.7, 125.5, 125.4, 117.0, 113.0, 87.0, 59.5, 21.4, 14.2.

4.2.3. (1*S*,2*S*,(S)*S*)-*N*-(*p*-Tolylsulfinyl)-2-nitro-1-(4-methoxyphenyl)-propylamine (2c) and (1*S*,2*R*,(S)*S*)-*N*-(*p*-tolylsulfinyl)-2-nitro-1-(4-methoxyphenyl)-propylamine (3c). These compounds were obtained following the general method A at 40 °C after 66 h in 40 and 28% yields, respectively, after flash chromatography (hex/EtOAc 2:1). Data of **2c**: yellow oil; $[\alpha]_D^{20}$ +89 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz): δ 7.52 (d, *J*=8.2 Hz, 2H), 7.32–7.25 (m, 4H), 6.94 (d, *J*=8.8 Hz, 2H), 4.80–4.65 (m, 3H), 3.82 (s, 3H), 2.43 (s, 3H), 1.33 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (75 MHz): δ 160.0, 142.0, 141.5, 129.8, 129.0, 128.0, 125.4, 114.3, 86.7, 59.6, 55.3, 21.4, 15.0. Data of **3c**: colorless oil; $[\alpha]_D^{20}$ +135 (mixture **3c/2c/4c** or **5c**=86:10:4, *c* 2, $CHCl_3$); ^1H NMR (300 MHz): δ 7.57 (d, *J*=8.5 Hz, 2H), 7.34–7.24 (m, 4H), 6.92 (d, *J*=8.7 Hz, 2H), 4.84–4.75 (m, 3H), 3.65 (s, 3H), 2.43 (s, 3H), 1.46 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (75 MHz): δ 160.0, 141.8, 141.1, 129.4, 129.0, 128.2, 125.4, 114.6, 87.5, 60.2, 55.3, 21.4, 16.9.

4.2.4. (1*S*,2*S*,(S)*S*)-*N*-(*p*-Tolylsulfinyl)-1-nitro-2-methyl-4-phenylbut-3-en-2-amine (2d) and (1*S*,2*R*,(S)*S*)-*N*-(*p*-tolylsulfinyl)-1-nitro-2-methyl-4-phenylbut-3-en-2-amine (3d). These compounds were obtained following the general method A at 40 °C after 72 h in 36 and 34% yields, respectively, after flash chromatography (hex/EtOAc 2:1). Data of **2d**: yellow oil; $[\alpha]_D^{20}$ +134 (*c* 0.8, $CHCl_3$); IR (film): 3196, 2924, 1545, 1088, 1056 cm^{-1}; ^1H NMR (300 MHz): δ 7.60 (d, *J*=8.2 Hz, 2H), 7.42–7.20 (m, 7H), 6.73 (d, *J*=15.8 Hz, 1H), 6.13 (dd, *J*=15.8, 7.8 Hz, 1H), 4.77–4.58 (m, 2H), 4.46–4.32 (qd, *J*=6.8, 1.0 Hz, 1H), 2.42 (s, 3H), 1.51 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (75 MHz): δ 142.0, 141.1, 135.8, 135.5, 129.7, 128.7, 128.6, 126.8, 125.5, 123.9, 85.9, 58.8, 21.4, 16.2; MS (FAB) *m/z* 345 (M+1, 55), 139 (100), 154 (10); [M+1]: calcd for $C_{18}H_{21}N_2O_3S$: 345.1272; found: 345.1282. Data of **3d**: colorless oil; $[\alpha]_D^{20}$ +143 (*c* 0.81, $CHCl_3$); ^1H NMR (300 MHz): δ 7.61 (d, *J*=8.3 Hz, 2H), 7.43–7.29 (m, 7H), 6.75 (d, *J*=15.8 Hz, 1H), 6.16 (dd, *J*=15.8, 8.1 Hz, 1H), 4.69–4.57 (m, 2H), 4.43–4.34 (ddd, *J*=6.5, 4.1, 1.1 Hz, 1H), 2.43 (s, 3H), 1.51 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (75 MHz): δ 142.0, 141.3, 136.4, 135.6, 129.8, 128.7, 128.6, 126.9, 125.5, 122.6, 86.0, 58.2, 21.4, 15.4; MS (FAB) *m/z* 345 (M+1, 9), 139 (100), 154 (24); [M+1]: calcd for $C_{18}H_{21}N_2O_3S$: 345.1272; found: 345.1279.

4.2.5. (2*S*,3*S*,(S)*S*)-*N*-(*p*-Tolylsulfinyl)-3-nitrobutan-2-amine (2e) and (2*S*,3*R*,(S)*S*)-*N*-(*p*-tolylsulfinyl)-3-nitrobutan-2-amine (3e). These compounds were obtained

following the general method A at 40 °C after 17 h as a **2e/3e/others**=91:5:4 mixture in an 80% combined yield of **2e** and **3e** after flash chromatography (CombiFlash) as a **2e/3e**=55.2:44.8 mixture (determined by HPLC with a Chiralpak® AD, hex/*i*-PrOH=93:7, 0.7 mL/min, *T*=25 °C, major diastereomer t_R=27.3 min, minor diastereomer t_R=32.9 min). Data of the mixture: IR (film): 3196, 1550, 1389, 1452, 1391, 1363, 1088, 1058 cm^{-1}; ^1H NMR (300 MHz): δ 7.55 (d, *J*=7.9 Hz, 2H **2e**), 7.51 (d, *J*=7.9 Hz, 2H **3e**), 7.28 (br d, 2H **2e** and 2H **3e**), 4.73 (br d, *J*=8.9 Hz, 1H **2e** and 1H **3e**), 4.45–4.36 (m, 1H **2e** and 1H **3e**), 3.77–3.58 (m, 1H **2e** and 1H **3e**), 2.40 (s, 3H **2e** and 3H **3e**), 1.37–1.31 (4d, 6H **2e** and 6H **3e**); MS (FAB) *m/z* 257.1 (M+1, 59), 139 (100), 55 (16); HRMS [M+1]: calcd for $C_{11}H_{17}N_2O_3S$: 257.0960; found: 257.0973. Anal. Calcd for $C_{11}H_{16}N_2O_3S$: C, 51.54; H, 6.29; N, 10.93; S, 12.51. Found: C, 51.76; H, 6.32; N, 10.65; S, 12.27. Data of the major diastereoisomer **2e**: ^{13}C NMR (75 MHz): δ 141.8, 140.7, 129.7, 125.7, 86.7, 51.3, 21.4, 18.4, 14.9. Data of the minor diastereoisomer **3e**: ^{13}C NMR (75 MHz): δ 141.7, 140.3, 129.6, 125.8, 87.0, 51.1, 20.0, 15.6, 14.2.

4.2.6. (3*S*,4*S*,(S)*S*)-*N*-(*p*-Tolylsulfinyl)-2-methyl-4-nitropentan-3-amine (2f). This compound was obtained following the general method A at 40 °C after 138 h as a **2f/3f**=83:17 mixture in 48% yield after flash chromatography (CombiFlash) recovering 17% of starting material **1f**. Compound **2f** was obtained as a 93:7 mixture after crystallization in ether. Data of the diastereoisomer **2f**: white solid; mp: 115–116 °C; $[\alpha]_D^{20}$ +33 (*c* 1, $CHCl_3$); IR (film): 3197, 1549, 1454, 1389, 1362, 1089, 1061 cm^{-1}; ^1H NMR (300 MHz): δ 7.62 (d, *J*=8.1 Hz, 2H), 7.31 (d, *J*=7.9 Hz, 2H), 4.90–4.80 (m, 1H), 4.72 (d, *J*=9.4 Hz, 1H), 3.27 (ddd, *J*=9.3, 7.3, 4.5 Hz, 1H), 2.41 (s, 3H), 1.83 (sept, *J*=6.9 Hz, 1H), 1.61 (d, *J*=6.9 Hz, 3H), 1.06 (d, *J*=6.9 Hz, 3H), 1.03 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (75 MHz): δ 142.5, 141.9, 129.7, 125.3, 83.7, 64.4, 31.8, 21.4, 20.1, 19.2, 17.9; MS (FAB) *m/z* 285 (M+1, 55), 139 (100), 55 (21); HRMS [M+1]: calcd for $C_{13}H_{21}N_2O_3S$: 285.1273; found: 285.1281. Anal. Calcd for $C_{13}H_{20}N_2O_3S$: C, 54.91; H, 7.09; N, 9.85; S, 11.28. Found: C, 55.0; H, 6.94; N, 9.56; S, 11.00.

4.3. Typical procedure for the oxidation of *p*-tolylsulfinylamines to *p*-tolylsulfonylamines

m-CPBA (0.12 mmol) was added to a solution of the corresponding sulfinylamine (0.1 mmol) in CH_2Cl_2 (0.5 mL) at rt. The reaction mixture was stirred at 0 °C for 30–50 min. The reactions were monitored by TLC (hex/EtOAc 3:1) and when the reaction was completed, CH_2Cl_2 (1 mL) was added, the organic phase was washed with $NaHSO_3$ (2×1 mL) and the aqueous phase was extracted with CH_2Cl_2 (2×1 mL). The organic extracts were washed with a saturated solution of $NaHCO_3$ (2×1 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent evaporated, obtaining the corresponding pure sulfonylamines without further purification.

4.3.1. (1*S*,2*S*)-*N*-(*p*-Tolylsulfonyl)-2-nitro-1-phenylpropylamine (6a). This compound was obtained following the general method for oxidation starting from **2a** at 0 °C after 30 min in 100% yield. Data of **6a**: white solid; mp: 171 °C; $[\alpha]_D^{20}$ +68 (*c* 0.375, $CHCl_3$); IR (film): 3255, 1598, 1458, 1388, 1359, 1165, 1092, 1068 cm^{-1}; ^1H NMR (300 MHz): δ 7.54 (d, *J*=8.4 Hz, 2H), 7.22–7.01 (m, 7H), 5.8 (br d, *J*=9.3 Hz, 1H), 4.89–4.75 (m, 2H), 2.35 (s, 3H), 1.51 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (75 MHz): δ 143.7, 136.7, 135.1, 128.7, 128.8, 127.1, 127.2, 86.2, 60.3, 21.4, 15.56.

4.3.2. (1*S*,2*R*)-*N*-(*p*-Tolylsulfonyl)-2-nitro-1-phenylpropylamine (7a). This compound was obtained following the general method for oxidation starting from **3a** at 0 °C after 30 min in 100% yield. Data of **7a**: white solid; mp: 156–157 °C; $[\alpha]_D^{20}$ +55 (*c* 0.10, $CHCl_3$); IR (film): 3419, 1551, 1458, 1389, 1321, 1162, 1089 cm^{-1}; ^1H NMR (300 MHz): δ 7.54 (d, *J*=8.2 Hz, 2H), 7.30–6.95 (m, 7H), 5.50 (br d, *J*=9 Hz, 1H), 4.78 (m, 2H), 2.38 (s, 3H), 1.62 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (75 MHz): δ 143.7, 136.7, 134.9, 129.5, 128.8, 128.7, 127.41, 126.8, 86.0, 60.2, 21.4, 15.7.

4.3.3. (1*S*,2*S*)-*N*-(*p*-Tolylsulfonyl)-2-nitrobutylamine (6e) and (1*S*,2*R*)-*N*-(*p*-tolylsulfonyl)-2-nitrobutylamine (7e). These compounds were obtained following the general method at 0 °C after 45 min in 98% yield. Data of the mixture **6e** and **7e**: IR (film): 3277, 1552, 1439, 1394, 1334, 1093, 1034 cm^{-1}; ^1H NMR (300 MHz): δ 7.76–7.73 (m, 4H), 7.31 (br d, *J*=8.1 Hz, 4H), 5.42–5.37 (m, 2H), 4.59 (qd, *J*=6.8, 1.7 Hz, 1H), 4.49 (qd, *J*=1.9, 1.6 Hz, 1H), 3.80–3.69 (m, 2H), 2.42 (s, 6H), 1.50 (d, *J*=6.8 Hz, 3H), 1.49 (d, *J*=6.9 Hz, 3H), 1.04 (d, *J*=6.9 Hz, 3H), 1.02 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (75 MHz): δ 150.0, 143.9, 137.4, 130.0, 127.0, 127.0, 86.2, 86.2, 53.5, 52.1, 51.6, 21.5, 17.5, 16.7, 15.4, 15.3.

4.4. Procedure for preparing *N*-sulfonyl α-amino methyl ketones (8)

The corresponding nitro sulfone (0.075 mmol), obtained by oxidation of *p*-tolylsulfinylnitroamines with *m*-CPBA (1.2 equiv) in CH_2Cl_2 (0.5 mL) at 0 °C, was dissolved in 3 mL of *t*-BuOH at 60 °C and added to a solution of *t*-BuOK (0.26 mmol) in 1 mL of *t*-BuOH at rt. The mixture was stirred under argon atmosphere for 10 min while cooling to rt and then 18 mL of ethyl acetate was added and the reaction mixture was cooled to 0 °C. Immediately, a solution of $KMnO_4$ (0.11 mmol) in 5.4 mL of water at 0 °C was added to the mixture and stirred vigorously for 2 h 30 min at 0 °C, whereupon 0.3 mL of 1 M solution of H_2SO_4 was added at once and stirred for 5 min, then 0.15 mL of 1 M solution of sodium bisulfite ($NaHSO_3$) was added until the solution turns colorless. The two layers were separated and the aqueous layer was extracted with ethyl acetate (2× 4 mL). The combined organic layers were washed with ice-cold water (2×4 mL) and brine and then dried over $MgSO_4$ anhydride. The crude was purified by flash chromatography (hex/EtOAc=90:10–70:30).

4.4.1. (*S*)-(+)-*N*-(*p*-Tolylsulfonyl)-3-amino-3-phenyl-2-propanone (8a).[15] Yield: 73%; mp: 157 °C (Ref. 15 136–137 ° C); ee=80%; $[\alpha]_D^{20}$ +202 (*c* 0.8, $CHCl_3$) [Ref. 15 $[\alpha]_D^{20}$ +287 (*c* 0.8, $CHCl_3$)]. The enantiomeric excess of ketone **8a** has been determined by HPLC with a Chiralpak®

AD column (hex/*i*-PrOH=90:10, 1 mL/min, T=25 °C), minor enantiomer t_R=37.1 min (10%), major enantiomer t_R=41.8 min (90%).

4.4.2. (*S*)-(+)-*N*-(*p*-Tolylsulfonyl)-amino-2-butanone (8e). Yield: 90%; mp: 93–94 °C; $[\alpha]_D^{20}$ +57 (*c* 0.6, $CHCl_3$); IR (film): 3269, 1721, 1428, 1420, 1050, 1088, 1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, J=8.0 Hz, 2H), 7.30 (d, J=8.0 Hz, 2H), 5.6 (br d, J=6.3 Hz, 1H), 3.93 (quin, J=7.2 Hz, 1H), 2.43 (s, 3H), 2.11 (s, 3H), 1.35 (d, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.6, 143.6, 136.9, 129.7, 127.1, 57.7, 26.2, 21.5, 18.8; MS (FAB^+) *m*/*z*: 242.0 (M+1, 100), 198.0 (42), 155.0 (38), 136.0 (37), 91.0 (47); HRMS [M+1]: calcd for $C_{11}H_{15}NO_3S$: 242.0851; found: 242.0852. The enantiomeric excess of ketone **8e** (>99%) has been determined by HPLC with a Chiralpak® AD column (hex/*i*-PrOH=90:10, 1 mL/min, T=25 °C), t_R=21.8 min.

4.5. Procedure for preparing β-amino hydroxylamines

Aluminum amalgam (48 mg) was added to a solution of the corresponding sulfinylnitroamine (0.12 mmol) in THF/H_2O (9:1) (11.7 mL). The reaction mixture was stirred at rt for 40 min whereupon it was filtrated through a short pad of Celite and the crude purified by flash chromatography (hex/EtOAc=1:2).

4.5.1. (1*S*,2*S*,(S)*S*)-*N*-(*p*-Tolylsulfinyl)-2-hydroxylamine-1-phenylpropylamine (9a). Yield: 63%; $[\alpha]_D^{20}$ +74 (*c* 1.7, $CHCl_3$); IR (film): 3251, 2100, 1650, 1492, 1455, 1087, 1042 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, J=8.2 Hz, 2H), 7.42–7.32 (m, 7H), 5.49 (br d, J=2.8 Hz, 1H), 4.44 (dd, J=9.4 and 2.8 Hz, 1H), 2.97 (dq, J=9.4 and 6.5 Hz, 1H), 2.40 (s, 3H), 1.05 (d, J=6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.1, 141.4, 140.3, 129.5, 128.6, 128.2, 128.0, 125.5, 61.5, 61.4, 21.3, 15.4; MS (FAB^+) *m*/*z*: 305.0 (M+1, 33), 106 (100), 57 (49); HRMS [M+1]: calcd for $C_{16}H_{20}N_2O_2S$: 305.1327; found: 305.1330.

4.5.2. (1*S*,2*R*,(S)*S*)-*N*-(*p*-Tolylsulfinyl)-2-hydroxylamine-1-phenylpropylamine (10a). Yield: 89%; $[\alpha]_D^{20}$ +78 (*c* 0.2, $CHCl_3$); IR (film): 3251, 1632, 1492, 1453, 1089, 1054 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, J=8.2 Hz, 2H), 7.42–7.32 (m, 7H), 5.07 (br t, J=3.5 Hz, 1H), 4.95 (br d, J=3.1 Hz, 1H), 3.40 (dq, J=6.7 and 4.0 Hz, 1H), 2.43 (s, 3H), 0.69 (d, J=6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.0, 141.7, 139.3, 129.7, 128.5, 127.6, 127.5, 125.4, 61.2, 57.4, 21.4, 10.8; MS (FAB^+) *m*/*z*: 305.0 (M+1, 39), 289 (55), 219 (26); HRMS [M+1]: calcd for $C_{16}H_{20}N_2O_2S$: 305.1323; found: 305.1322.

4.5.3. (3*S*,4*S*,(S)*S*)-*N*-(*p*-Tolylsulfinyl)-2-methyl-4-hydroxylamine-pentan-3-amine (9f). Yield: 48%; $[\alpha]_D^{20}$ +83 (*c* 0.9, $CHCl_3$); IR (film): 3352, 2089, 1645, 1492, 1464, 1087, 1045, 1015 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, J=8.2 Hz, 2H), 7.30 (d, J=8.2 Hz, 2H), 4.30 (br d, J=6.9 Hz, 1H), 3.32–3.26 (m, 1H), 2.79 (dq, J=9.7 and 6.4 Hz, 1H), 2.41 (s, 3H), 1.89 (quind, J=6.8 and 2.5 Hz, 1H), 1.24 (d, J=6.4 Hz, 3H), 1.11 (d, J=6.81 Hz, 3H), 0.79 (d, J=6.7 Hz, 3H); MS (FAB^+) *m*/*z*: 271.2 (M+1, 46), 194 (100), 109 (17), 139 (21), 83 (43); HRMS [M+1]: calcd for $C_{13}H_{22}N_2O_2S$: 271.1486; found: 271.1495.

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