Enantioselective Copper-Aminopyridine-catalyzed aza-Henry Reaction with Chelating *N*-(2-Pyridyl)Sulfonyl Imines

GONZALO BLAY,* ANA ESCAMILLA, VÍCTOR HERNÁNDEZ-OLMOS, JOSÉ R. PEDRO,* AND AMPARO SANZ-MARCO
Departament de Química Orgànica, Facultat de Química, Universitat de València, Burjassot, Spain

ABSTRACT This article describes a copper-catalyzed aza-Henry reaction. Copper complexes of camphor-derived aminopyridines catalyze the addition of nitromethane to *N*-(2-pyridyl)sulfonyl aldimines to give the corresponding β-nitrosulfonamides with good yields and variable enantiomeric excesses (up to 83%). An example of transformation of these compounds into *N*-(2-pyridyl)sulfonyl-α-amino acids and deprotection of the sulfonamide with Mg–MeOH is provided. *Chirality 00:000–000, 2012.* © 2012 Wiley Periodicals, Inc.

KEY WORDS: nitro-Mannich reaction; chiral amines; nitro compounds; nucleophilic addition; asymmetric catalysis; copper; chiral ligands

INTRODUCTION

The nucleophilic addition of nitroalkanes to the CN of imines, known as the aza-Henry (or nitro-Mannich) reaction, is a useful carbon–carbon bond-forming reaction of prime importance.[1–3] The resulting β-nitroamines can be readily transformed into valuable structural motifs such as 1,2-diamines by reduction[4–6] or into α-amino carbonyl compounds by oxidation (Nef reaction).[7–9] Most significantly, up to two new stereogenic centers can be formed, both attached to two different nitrogen functional groups. As a result, much attention has been paid to the catalytic asymmetric version of this reaction over the past several years by either using metal-based procedures[10–15,6,17–19] or organocatalysis.[20–39] One of the difficulties that arises when carrying out nucleophilic addition reactions to imines is their lower electrophilicity compared with the carbonyl group. However, this reactivity can be enhanced by attaching strong electron-withdrawing groups to the azomethinic nitrogen atom.[40,41] In the reported aza-Henry reactions, *N*-carbamoyl imines have been the most commonly used electrophiles.[11,12,17,19,20,22–31] However, a common drawback associated with the use of this type of imines is that precautions have to be taken during preparation, handling, and storage because of their substantial hydrolytic lability. *N*-phosphinoyl imines have been seldom used[10,21,32] because of their poor stability and relatively low reactivity, although the phosphinoyl moiety can be easily removed by acidic hydrolysis. Similarly, there are few reports on the enantioselective aza-Henry reaction of *N*-sulfonyl protected imines,[13,6,16] which are usually bench-stable solids and can be easily prepared. A possible explanation for this is the difficult deprotection of the *N*-tosyl amines resulting from the nucleophilic addition to the CN bond.

Our group has developed new iminopyridine and aminopyridine ligands (Fig. 1), which in the presence of copper(II) salts catalyzed the Henry reaction with carbonyl compounds very efficiently and with very high enantioselectivity.[42–49] In this article, we describe the application of these catalysts in the enantioselective aza-Henry reaction with *N*-(2-pyridyl)sulfonyl aldimines.

EXPERIMENTAL

Materials and Methods

Commercial reagents were used as purchased. Reactions were monitored by thin layer chromatography (TLC) analysis using Merck Silica Gel 60 F-254 thin layer plates. Flash column chromatography was performed on Merck silica gel 60, 0.040–0.063 mm (Merck KGaA, Darmstadt, Germany). Specific optical rotations were recorded on a Perkin-Elmer 241 polarimeter using sodium light (D line 589 nm). NMR spectra were recorded on Bruker Avance spectrometers in deuterated solvents as stated, using residual non-deuterated solvent as internal standard. The carbon type was determined by distortionless enhancement by polarization transfer (DEPT) experiments. Mass spectra (EI) were recorded on a Fisons Instruments VG Autospec GC 8000 series at 70 eV. Electrospray ionization mass spectra (ESI) were recorded on a Waters Q-TOF premier mass spectrometer with an electrospray source. The drying gas as well as the nebulizing gas was nitrogen. Chiral high performance liquid chromatography (HPLC) analyses were performed in a Hitachi Elite Lachrom instrument equipped with a Hitachi UV diode-array L-4500 detector using chiral stationary columns from Daicel and are included in the Supporting information. Retention times (t_r) are given in minutes. 2-Pyridylsulfonamide and 2-methoxyphenylsulfonamide were prepared from the corresponding sulfonyl chlorides according to known procedures.[50–52] Pyridine-2-sulfonyl chloride was prepared by oxidation of 2-pyridine-2-thiol (Alfa Aesar, Karlsruhe, Germany) with sodium hypochlorite in sulfuric acid.[50–52] 2-Methoxybenzenesulfonyl chloride was prepared from 2-methoxybenzenethiol (Sigma-Aldrich, St Louis, MO, USA) following the same procedure in concentrated hydrochloric acid instead of sulfuric acid. Ligands **1–5** were prepared according to our reported procedure.[48]

Synthesis of Starting Materials

Synthesis of *N*-sulfonyl imines 6–9. *N*-Sulfonyl imines **6–9** were prepared according to procedures in the literature:[52] A mixture of the corresponding sulfonamides (11.4 mmol), aldehyde (11.4 mmol), activated 5 Å molecular sieves (Sigma-Aldrich, St Louis, MO, USA) (1.70 g), and Amberlyst® (Sigma-Aldrich, St Louis, MO, USA) (225 mg) in toluene (35 mL) contained in a round bottom flask provided with a Dean–Stark system was refluxed under nitrogen for 48–60 h. The reaction mixture was cooled to room temperature (rt) and filtered through a sintered-glass

Additional Supporting Information may be found in the online version of this article.

Contract grant sponsor: Ministerio de Ciencia e Innovación and FEDER; Contract grant number: CTQ2009-13083.
Contract grant sponsor: Generalitat Valenciana; Contract grant number: ACOMP/2011/267.

*Correspondence to: José R. Pedro, Departament de Química Orgànica, Facultat de Química, Universitat de València, C/ Dr. Moliner 50, E-46100-Burjassot, Spain. E-mail: jose.r.pedro@uv.es; Gonzalo Blay, Departament de Química Orgànica, Facultat de Química, Universitat de València, C/ Dr. Moliner 50, E-46100-Burjassot, Spain. E-mail: gonzalo.blay@uv.es

Received for publication 08 September 2011; Accepted 29 December 2011
DOI: 10.1002/chir.22009
Published online in Wiley Online Library (wileyonlinelibrary.com).

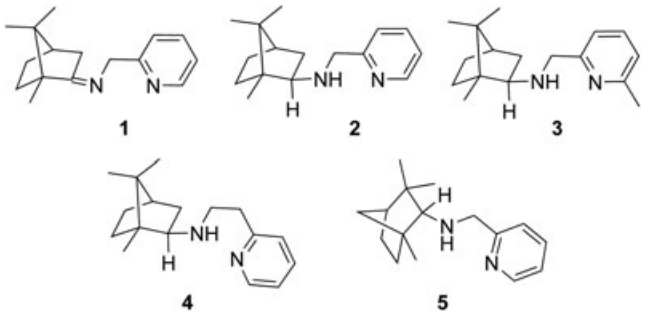


Fig. 1. Iminopyridine and aminopyridine ligands used in this study.

funnel, washing the solid with dichloromethane (40 mL). The filtrates were evaporated under reduced pressure to give a solid that was washed with 1:1 diethyl ether/hexane (3 × 7 mL) to give the imine.

(*E*)-*N*-benzylidene-4-methylbenzenesulfonamide (6)[53]. Obtained in 93% yield: mp 109–111 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.03 (1H, s), 7.97–7.88 (4H, m), 7.62 (1H, tt, *J* = 6.6, 1.2 Hz), 7.49 (2H, t, *J* = 7.8 Hz), 7.35 (2H, d, *J* = 8.1 Hz), 2.44 (3H, s).

(*E*)-*N*-benzylidenethiophene-2-sulfonamide (7)[52]. Obtained in 93% yield: mp 108–109 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.01 (1H, s), 7.97–7.94 (2H, m), 7.80 (1H, dd, *J* = 3.6, 1.2 Hz), 7.71 (1H, dd, *J* = 5.1, 1.2 Hz), 7.64 (1H, tt, *J* = 6.9, 1.2 Hz), 7.51 (2H, t, *J* = 7.2 Hz), 7.15 (1H, dd, *J* = 5.1, 3.9 Hz).

(*E*)-*N*-benzylidene-2-methoxybenzenesulfonamide (8)[54]. Obtained in 63% yield: mp 115–116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.14 (1H, s), 8.12 (1H, dd, *J* = 8.1, 1.7 Hz), 7.97–7.94 (2H, m), 7.66–7.55 (2H, m), 7.50 (2H, t, *J* = 7.2 Hz), 7.13 (1H, td, *J* = 7.8, 0.6 Hz), 6.97 (1H, d, *J* = 8.4 Hz), 3.82 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.0 (CH), 157.1 (C), 135.6 (CH), 134.9 (CH), 132.5 (C), 131.3 (CH), 130.7 (CH), 129.2 (CH), 125.3 (C), 120.7 (CH), 112.3 (CH), 56.2 (CH_3).

(*E*)-*N*-benzylidenepyridine-2-sulfonamide (9a)[50]. Obtained in 87% yield: mp 142–144 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.31 (1H, s), 8.77 (1H, dq, *J* = 4.5, 1.2 Hz), 8.23–8.15 (2H, m), 8.10–8.08 (2H, m), 7.78–7.72 (2H, m), 7.59 (2H, t, *J* = 7.8 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 174.9 (CH), 154.9 (C), 150.5 (CH), 139.1 (CH), 135.6 (CH), 132.0 (C), 131.5 (CH), 129.3 (CH), 128.0 (CH), 122.8 (CH); MS (EI) *m/z* (%): 247 [(M^+ + H), 2.8], 181 (14), 79 (100); HRMS: 247.0547 (M^+ + H), $C_{12}H_{11}N_2O_2S$ required 247.0541.

(*E*)-*N*-(2-methoxybenzylidene)pyridine-2-sulfonamide (9b)[55]. Obtained in 83% yield: mp 116–118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (1H, s), 8.73 (1H, dq, *J* = 4.5, 0.9 Hz), 8.23 (1H, dt, *J* = 7.8, 0.9 Hz), 8.07 (1H, dd, *J* = 7.8, 1.8 Hz), 7.95 (1H, td, *J* = 7.8, 1.8 Hz), 7.59 (1H, td, *J* = 7.8, 1.8 Hz), 7.51 (1H, ddd, *J* = 7.8, 4.8 1.2 Hz), 6.98 (2H, m), 3.93 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.2 (CH), 162.1 (C), 156.1 (C), 150.3 (CH), 138.0 (CH), 137.5 (CH), 129.5 (CH), 127.1 (CH), 123.2 (CH), 120.84 (CH), 120.82 (C), 111.5 (CH), 55.7 (CH_3); MS (EI) *m/z* (%): 277 [(M^+ + H), 20], 181 (12), 79 (100); HRMS: 277.0645 (M^+ + H), $C_{13}H_{13}N_2O_3S$ required 277.0647.

(*E*)-*N*-(2-methylbenzylidene)pyridine-2-sulfonamide (9c). Obtained in 75% yield: mp 109–111 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.55 (1H, s), 8.72 (1H, d, *J* = 4.5 Hz), 8.24 (1H, d, *J* = 7.8 Hz), 8.05 (1H, dd, *J* = 8.4, 1.5 Hz), 7.97 (1H, td, *J* = 7.8, 1.5 Hz), 7.55–7.47 (2H, m), 7.30–7.25 (2H, m), 2.64 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.7 (CH), 162.1 (C), 155.9 (C), 150.3 (CH), 142.8 (C), 138.1 (CH), 135.1 (CH), 131.6 (CH), 130.7 (CH), 130.3 (C), 127.2 (CH), 126.6 (CH), 123.3 (CH), 19.6 (CH_3); MS (EI) *m/z* (%): 261 [(M^+ + H), 0.5], 118 (59), 79 (100); HRMS: 261.0686 (M^+ + H), $C_{13}H_{13}N_2O_2S$ required 261.0698.

(*E*)-*N*-(2-chlorobenzylidene)pyridine-2-sulfonamide (9d). Obtained in 81% yield: mp 152–155 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.71 (1H, s), 8.76 (1H, dq, *J* = 4.5, 0.9 Hz), 8.25 (1H, d, *J* = 8.1 Hz), 8.18 (1H, dd, *J* = 8.1, 1.8 Hz), 7.99 (1H, td, *J* = 7.8, 1.8 Hz), 7.56 (2H, m), 7.49 (1H, m), 7.34 (1H, t, *J* = 7.5 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.7 (CH), 155.5 (C), 150.5 (CH), 139.4 (C), 138.1 (CH), 136.1 (CH), 130.6 (CH), 130.4 (CH), 129.7 (C), 127.38 (CH), 127.35 (CH), 123.5 (CH); MS (EI) *m/z* (%): 281 [(M^+ + H), 0.7], 79 (100); HRMS: 281.0141 (M^+ + H), $C_{12}H_{10}ClN_2O_2S$ required 281.0152.

(*E*)-*N*-(4-methoxybenzylidene)pyridine-2-sulfonamide (9e)[55]. Obtained in 77% yield: mp 110–112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.15 (1H, s), 8.70 (1H, dq, *J* = 4.8, 0.9 Hz), 8.22 (1H, dt, *J* = 8.1, 0.9 Hz), 7.95 (1H, td, *J* = 7.8, 1.8 Hz), 7.93 (1H, d, *J* = 8.7 Hz), 7.51 (1H, ddd, *J* = 7.8, 4.8, 1.2 Hz), 6.79 (2H, d, *J* = 8.7 Hz), 3.88 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.2 (CH), 165.7 (C), 156.2 (C), 150.3 (CH), 138.0 (CH), 134.2 (CH), 127.0 (CH), 125.1 (C), 123.1 (CH), 114.7 (CH), 55.7 (CH_3).

(*E*)-*N*-(4-methylbenzylidene)pyridine-2-sulfonamide (9f)[56]. Obtained in 83% yield: mp 144–145 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.20 (1H, s), 8.71 (1H, dq, *J* = 4.8, 0.9 Hz), 8.23 (1H, dt, *J* = 7.8, 0.9 Hz), 7.96 (1H, td, *J* = 7.8, 1.8 Hz), 7.85 (1H, d, *J* = 8.4 Hz), 7.52 (1H, ddd, *J* = 7.8, 4.8, 0.9 Hz), 7.29 (2H, d, *J* = 8.4 Hz), 2.43 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 174.1 (CH), 155.9 (C), 150.4 (CH), 147.0 (C), 138.1 (CH), 131.8 (CH), 130.0 (CH), 129.7 (C), 127.2 (CH), 123.3 (CH), 22.0 (CH_3).

(*E*)-*N*-(4-chlorobenzylidene)pyridine-2-sulfonamide (9g)[56]. Obtained in 83% yield: mp 163–165 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.22 (1H, s), 8.73 (1H, dq, *J* = 4.8, 0.6 Hz), 8.25 (1H, dt, *J* = 7.8, 0.6 Hz), 7.99 (1H, td, *J* = 7.8, 1.8 Hz), 7.92 (1H, d, *J* = 8.7 Hz), 7.55 (1H, ddd, *J* = 7.8, 4.8, 1.2 Hz), 7.49 (2H, d, *J* = 8.7 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.9 (CH), 155.5 (C), 150.4 (CH), 142.0 (C), 138.2 (CH), 132.7 (CH), 130.6 (C), 129.7 (CH), 127.4 (CH), 123.4 (CH).

***(E)*-*N*-(4-nitrobenzylidene)pyridine-2-sulfonamide (9h)**[57]. Obtained in 82% yield: mp 192–194 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.17 (1H, s), 8.72 (1H, dq, *J* = 4.8, 0.9 Hz), 8.42 (2H, d, *J* = 8.7 Hz), 8.17 (2H, d, *J* = 8.7 Hz), 8.07 (1H, td, *J* = 7.8, 1.8 Hz), 7.93 (1H, dt, *J* = 7.8, 0.9 Hz), 7.64 (1H, ddd, *J* = 7.8, 4.8, 1.2 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 192.3 (CH), 159.7 (C), 150.6 (C), 149.6 (CH), 140.0 (C), 138.5 (CH), 130.6 (CH), 126.6 (CH), 124.2 (CH), 120.4 (CH).

(*E*)-*N*-(3-methoxybenzylidene)pyridine-2-sulfonamide (9i)[58]. Obtained in 75% yield: mp 95–97 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.19 (1H, s), 8.71 (1H, dq, *J* = 4.6, 0.9 Hz), 8.22 (1H, dt, *J* = 7.8, 0.9 Hz), 7.96 (1H, dt, *J* = 6.0, 1.8 H, m), 7.52 (1H, ddd, *J* = 0.9, 4.6, 8.1 Hz), 7.50–7.45 (2H, m), 7.39 (1H, t, *J* = 8.1 Hz), 7.16 (1H, ddd, J = 1.3, 2.6, 8.1 Hz), 3.81 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 174.3 (d), 160.1 (s), 155.8 (s), 150.4 (d), 133.6 (s), 130.1 (d), 127.3 (d), 125.8 (d), 123.4 (d), 122.8 (d), 113.4 (d), 55.5 (q).

(*E*)-*N*-(3-methylbenzylidene)pyridine-2-sulfonamide (9j)[50]. Obtained in 80% yield: mp 141–143 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.22 (1H, s), 8.73 (1H, dq, *J* = 4.6, 0.9 Hz), 8.26 (1H, dt, *J* = 7.8, 0.9 Hz), 7.97 (1H, dt, *J* = 6.0, 1.8 H, m), 7.82 (1H, br s), 7.76 (1H, br d, *J* = 7.5 Hz), 7.53 (1H, ddd, *J* = 0.9, 4.6, 7.8 Hz), 7.46 (1H, br d, *J* = 7.8 Hz), 7.39 (1H, t, *J* = 7.5 Hz), 2.40 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 174.6 (d), 155.9 (s), 150.4 (d), 139.2 (s), 138.1 (d), 136.3 (d), 132.3 (s), 131.6 (d), 129.5 (d), 129.1 (d), 127.2 (d), 123.3 (d), 21.1 (q).

(*E*)-*N*-(3-chlorobenzylidene)pyridine-2-sulfonamide (9k)[57]. Obtained in 75% yield: mp 133–135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.22 (1H, s), 8.73 (1H, dq, *J* = 4.5, 0.9 Hz), 8.26 (1H, dt, *J* = 7.8, 0.9 Hz), 8.02–7.97 (2H, m), 7.83 (1H, dt, *J* = 7.5, 1.2 Hz), 7.61 (1H, dq, *J* = 7.8, 0.9 Hz), 7.55 (1H, ddd, *J* = 7.8, 4.8, 1.2 Hz), 7.46 (1H, t, *J* = 7.8 Hz); ^{13}C

NMR (75.5 MHz, $CDCl_3$) δ 172.9 (CH), 155.5 (C), 150.5 (CH), 138.2 (2xCH), 135.5 (C), 135.1 (CH), 134.4 (C), 130.5 (CH), 130.4 (CH), 123.5 (CH); MS (EI) *m/z* (%): 281 [(M^+ + H), 10], 215 (12), 154 (13), 111 (26), 79 (100); HRMS: 281.0139 (M^+ + H), $C_{12}H_{10}ClN_2O_2S$ required 281.0152.

(*E*)-*N*-(3-nitrobenzylidene)pyridine-2-sulfonamide (9l). Obtained in 52% yield: mp 114–116 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.49 (1H, s), 8.87 (1H, t, *J* = 1.9 Hz), 8.79 (1H, dq, *J* = 4.5, 0.8 Hz), 8.55–8.46 (2H, m), 8.25 (dt, *J* = 6.6, 0.9 Hz), 8.20 (dt, *J* = 7.8, 1.5 Hz), 7.89 (1H, t, *J* = 7.8 Hz), 7.79 (ddd, *J* = 8.7, 3.0, 1.5 Hz); ^{13}C NMR (300 MHz, DMSO-d_6) δ 173.0 (d), 155.7 (s), 150.6 (d), 148.2 (s), 139.2 (d), 136.7 (d), 134.9 (s), 136.7 (d), 134.9 (s), 130.9 (d), 129.2 (d), 128.3 (d), 125.6 (d), 123.1 (d); HRMS (ESI): 314.0228 (M^+ + Na), $C_{12}H_9N_3NaO_4S$ required 314.02115.

(*E*)-*N*-(thiophen-3-ylmethylene)thiophene-2-sulfonamide (9m). Obtained in 64% yield: mp 161–163 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.21 (1H, s), 8.71 (1H, dq, *J* = 4.5, 0.9 Hz), 8.24–8.21 (2H, m), 7.96 (1H, td, *J* = 7.8, 1.5 Hz), 7.61 (1H, dd, *J* = 5.9, 0.9 Hz), 7.52 (1H, ddd, *J* = 7.8, 4.8, 1.2 Hz), 7.39 (1H, ddd, *J* = 5.1, 2.7, 0.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 167.0 (CH), 155.9 (C), 150.4 (CH), 139.3 (CH), 138.1 (CH), 137.0 (C), 127.9 (CH), 127.2 (CH), 126.6 (CH), 123.3 (CH); HRMS (ESI): 274.9925 (M^+ + Na), $C_{10}H_8N_2NaO_2S_2$ required 274.9925.

(*E*)-*N*-(furan-3-ylmethylene)pyridine-2-sulfonamide (9n). Obtained in 70% yield: mp 146–147 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.20 (1H, s), 8.71 (1H, dq, *J* = 4.5, 0.9 Hz), 8.21 (1H, dt, *J* = 7.8, 0.9 Hz), 8.16 (1H, t, *J* = 0.9 Hz), 7.96 (1H, td, *J* = 7.8, 1.5 Hz), 7.54–750 (2H, m), 6.85 (1H, d, *J* = 1.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.9 (CH), 155.8 (C), 152.9 (CH), 150.4 (CH), 145.5 (CH), 138.1 (CH), 127.2 (CH), 123.4 (C), 123.3 (CH), 108.0 (CH); HRMS (ESI): 259.0151 (M^+ + Na), $C_{10}H_8N_2NaO_3S$ required 259.0153.

Asymmetric Reaction

General procedure. A solution of amino pyridine **2** (9.7 mg, 0.04 mmol) in dry diethyl ether (Sigma-Aldrich, St. Louis, MO, USA) (1.2 mL) was added to a suspension of previously dried $Cu(OTf)_2$ (Alfa Aesar, Karlsruhe, Germany) (14.4 mg, 0.04 mmol) and activated 4 Å MS (Sigma-Aldrich, St. Louis, MO, USA) (10 mg) in nitromethane (Sigma-Aldrich, St. Louis, MO, USA) (0.6 mL) contained in a Schlenk tube under nitrogen. The mixture was stirred for 1 h at rt until the formation of a deep blue solution. The imine **9** (0.2 mmol) dissolved in dry diethyl ether: nitromethane (0.24 mL:0.16 mL) was added via syringe, and the reaction flask was introduced in a bath at the reaction temperature. After 10 min, *N*,*N*-diisopropylethylamine (DIPEA) (Sigma-Aldrich, St. Louis, MO, USA) (10 μL, 0.06 mmol) dissolved in diethyl ether (0.2 mL) was added, and the reaction mixture was stirred for the indicated time. The mixture was filtered through a short pad of silica gel eluting with hexane/EtOAc (6:4). The filtrate was concentrated under reduced pressure and chromatographed eluting with hexane/EtOAc mixtures to give the corresponding products.

(−)-(*R*)-4-methyl-*N*-(2-nitro-1-phenylethyl)benzenesulfonamide (10). Obtained according to the conditions in Table 1. Enantiomeric excess (17%) was determined by HPLC (Chiralcel OD-H), hexane–*i*-PrOH 90:10, 1 mL/min, major enantiomer (*R*) t_r = 51.8, minor enantiomer (*S*) t_r = 45.0.

mp 155–157 °C; $[\alpha]_D^{25}$ −14.5 (*c* 0.11, CH_2Cl_2, *ee* 18%), Lit.[6] $[\alpha]_D^{25}$ 73.5 (*c* 0.11, CH_2Cl_2, for the *S*-enantiomer, *ee* 91%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (2H, d, *J* = 8.4 Hz), 7.26–7.20 (5H, m), 7.12–7.08 (2H, m), 5.69 (1H, d, *J* = 7.8 Hz), 5.00 (1H, q, *J* = 6.9 Hz), 4.84 (1H, dd, *J* = 12.9, 6.6 Hz), 4.66 (1H, dd, *J* = 12.9, 6.3 Hz), 2.40 (3H, s).

(−)-*N*-(2-nitro-1-phenylethyl)thiophene-2-sulfonamide (11). Obtained according to the conditions in Table 1. Enantiomeric excess (8%) was determined by HPLC (Chiralcel OD-H), hexane–*i*-PrOH 85:15, 1 mL/min, major enantiomer t_r = 44.5, minor enantiomer t_r = 32.0.

TABLE 1. Addition of nitromethane to *N*-sulfonyl imines according to Scheme 1. Effect of the *N*-sulfonyl group[a]

Entry	R	Imine	*t* (h)	Product	Yield (%)	*ee* (%)[b]
1	*p*-Ts	**6**	24	**10**	99	18
2	2-Thiophenyl	**7**	22	**11**	80	11
3	2-Methoxyphenyl	**8**	16	**12**	75	23
4	2-Pyridyl	**9a**	5	**13a**	80	59

[a]Ligand **2** (20 mol%), $Cu(OTf)_2$ (20 mol%), DIPEA (30 mol%), 4 Å MS (100 mg/mmol imine), THF (1.64 mL), nitromethane (0.76 mL), 0 °C.
[b]Determined by HPLC using chiral stationary phases.

mp 116–118 °C; $[\alpha]_D^{25}$ −0.69 (*c* 0.51, CH_2Cl_2, *ee* 8%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.98 (1H, br s), 7.74 (1H, dd, *J* = 4.8, 1.2 Hz), 7.29–7.20 (6H, m), 6.92 (1H, dd, *J* = 4.8, 3.6 Hz), 5.08 (1H, m), 4.86 (1H, dd, *J* = 13.2, 5.1 Hz), 4.68 (1H, dd, *J* = 13.2, 9.9 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 141.6 (C), 136.0 (C), 132.6 (CH), 131.8 (CH), 128.4 (CH), 128.1 (CH), 127.2 (CH), 126.8 (CH), 78.9 (CH_2), 55.8 (CH); MS (EI) *m/z* (%): 312 (M^+, 0.1), 251 (17), 146 (100), 104 (22); HRMS: 312.0238, $C_{12}H_{12}N_2O_4S$ required 312.0238.

(−)-2-methoxy-*N*-(2-nitro-1-phenylethyl) benzenesulfonamide (12). Obtained according to the conditions in Table 1. Enantiomeric excess (23%) was determined by HPLC (Chiralpak AD-H), hexane–*i*-PrOH 80:20, 1 mL/min, major enantiomer t_r = 19.8, minor enantiomer t_r = 16.5.

$[\alpha]_D^{25}$ −2.5 (*c* 0.90, CH_2Cl_2, *ee* 23%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (1H, dd, *J* = 7.8, 1.8 Hz), 7.46 (1H, td, *J* = 8.4, 1.8 Hz), 7.18 (3H, m), 7.02 (3H, m), 6.73 (1H, d, *J* = 8.4 Hz), 5.98 (1H, t, *J* = 8.4 Hz), 4.88 (2H, m), 4.63 (1H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.8 (C), 135.4 (C), 134.9 (CH), 130.1 (CH), 128.91 (CH), 128.86 (CH), 126.6 (C),126.5 (CH), 120.4 (CH), 111.7 (C), 78.7 (CH_2), 55.9 (CH_3), 55.6 (CH); HRMS (ESI): 359.0676 (M^+ + Na), $C_{15}H_{16}N_2NaO_5S$ required 359.0678.

(−)-*N*-(2-nitro-1-phenylethyl)pyridine-2-sulfonamide (13a). Enantiomeric excess (83%) was determined by HPLC (Chiralpak AD-H), hexane–*i*-PrOH 80:20, 1 mL/min, major enantiomer (*R*) t_r = 23.8, minor enantiomer (*S*) t_r = 29.7.

mp 114–116 °C; $[\alpha]_D^{25}$ −17.1 (*c* 0.52, CH_2Cl_2, *ee* 83%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.96 (1H, d, *J* = 9.0 Hz), 8.49 (1H, dq, *J* = 4.5, 0.9 Hz), 7.86 (1H, td, *J* = 7.8, 1.8 Hz), 7.70 (1H, d, *J* = 7.8 Hz), 7.48 (1H, ddd, *J* = 7.5, 4.5, 0.9 Hz), 7.24–7.14 (5H, s), 5.16 (1H, m), 4.85 (1H, dd, *J* = 13.2, 5.4 Hz), 4.78 (1H, dd, *J* = 13.2, 9.6 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 157.3 (C), 149.6 (CH), 138.1 (CH), 136.4 (C), 128.2 (CH), 127.9 (CH), 126.9 (CH), 126.6 (CH), 121.2 (CH), 78.7 (CH_2), 55.7 (CH); MS (EI) *m/z* (%): 261 [(M^+-NO_2), 0.1], 149 (30), 102 (58), 94 (89), 91 (57), 78 (91), 77 (73), 51 (100); HRMS: 261.0695, $C_{13}H_{13}N_2O_2S$ required 261.0700.

(−)-*N*-(1-(2-methoxyphenyl)-2-nitroethyl)pyridine-2-sulfonamide (13b). Enantiomeric excess (78%) was determined by HPLC (Chiralpak AD-H), hexane–*i*-PrOH 80:20, 1 mL/min, major enantiomer (*R*) t_r = 38.0, minor enantiomer (*S*) t_r = 44.2.

mp 134–135 °C; $[\alpha]_D^{25}$ −23.6 (*c* 0.48, CH_2Cl_2, *ee* 78%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (1H, dq, *J* = 4.5, 0.9 Hz), 7.81 (1H, dt, *J* = 7.8, 0.9 Hz), 7.72 (1H, td, *J* = 7.5, 1.5 Hz), 7.29 (1H, ddd, *J* = 7.5, 4.8, 1.2 Hz), 7.15 (1H, td, *J* = 8.4, 1.8 Hz), 6.93 (1H, dd, *J* = 7.2, 1.5 Hz), 6.71 (2H, m), 6.36 (1H,d, *J* = 9.9 Hz), 5.28 (1H, m), 4.93 (1H, dd, *J* = 12.9, 7.5 Hz), 4.72 (1H, dd, *J* = 12.9, 6.6 Hz), 3.84 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 157.1 (C), 156.5 (C), 149.7 (CH), 137.6 (CH), 130.2 (CH), 129.7 (CH), 126.5 (CH), 122.3 (C), 121.8 (CH), 120.8 (CH), 110.7 (CH), 77.6 (CH_2), 55.4 (CH), 55.1 (CH_3); HRMS (ESI): 360.0631 (M^+ + Na), $C_{14}H_{15}N_3NaO_5S$ required 360.0630.

(−)-*N*-(2-nitro-1-*o*-tolylethyl)pyridine-2-sulfonamide (13c). Enantiomeric excess (58%) was determined by HPLC (Chiralpak AD-H), hexane–*i*-PrOH 80:20, 1 mL/min, major enantiomer (*R*) t_r = 21.1, minor enantiomer (*S*) t_r = 24.8.

mp 109–101 °C; $[\alpha]_D^{25}$ −3.3 (*c* 0.49, CH_2Cl_2, *ee* 58%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (1H, dq, *J* = 5.4, 0.9 Hz), 7.82–7.71 (2H, m), 7.40–7.36 (1H, m), 7.17–7.13 (1H, m), 7.10–6.96 (3H, m), 6.65 (1H, d, *J* = 6.9 Hz), 5.54 (1H, q, *J* = 6.9 Hz), 4.89 (1H, dd, *J* = 13.5, 7.8 Hz), 4.68 (1H, dd, *J* = 13.5, 6.6 Hz), 2.27 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 157.0 (C), 149.8 (CH), 138.0 (CH), 135.6 (C), 133.4 (C), 130.8 (CH), 128.7 (CH), 126.8 (CH), 126.7 (CH), 126.1 (CH), 121.9 (CH), 78.3 (CH_2), 51.8 (CH), 19.0 (CH_3); HRMS (ESI): 344.0683 (M^+ + Na), $C_{14}H_{15}N_3NaO_4S$ required 344.0681.

(−)-*N*-(1-(2-chlorophenyl)-2-nitroethyl)pyridine-2-sulfonamide (13d). Enantiomeric excess (54%) was determined by HPLC (Chiralpak AD-H), hexane–*i*-PrOH 70:30, 1 mL/min, major enantiomer (*R*) t_r = 13.7, minor enantiomer (*S*) t_r = 33.1.

mp 127–128 °C; $[\alpha]_D^{25}$ −13.5 (*c* 0.27, CH_2Cl_2, *ee* 54%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.17 (1H, d, *J* = 9.3 Hz), 8.45 (1H, dq, *J* = 4.8, 0.9 Hz), 7.87 (1H, td, *J* = 7.8, 1.8 Hz), 7.72 (1H, dt, *J* = 7.8, 0.9 Hz), 7.46 (1H, ddd, *J* = 7.8, 4.8, 1.2 Hz), 7.46–7.42 (1H, m), 7.32–7.29 (1H, m), 7.20–7.13 (2H, m), 5.63 (1H, dt, *J* = 9.9, 4.2 Hz), 4.82 (1H, dd, *J* = 13.2, 4.2 Hz), 4.65 (1H, dd, *J* = 13.2, 9.9 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 156.8 (C), 149.6 (CH), 138.1 (CH), 133.8 (C), 131.3 (C), 129.7 (CH), 129.1 (CH), 128.6 (CH), 127.2 (CH), 126.7 (CH), 121.1 (CH), 77.7 (CH_2), 52.3 (CH); HRMS (ESI): 342.0323 (M^+ + Na), $C_{13}H_{12}ClN_3NaO_4S$ required 342.0315.

(−)-*N*-(1-(4-methoxyphenyl)-2-nitroethyl)pyridine-2-sulfonamide (13e). Enantiomeric excess (66%) was determined by HPLC (Chiralpak AD-H), hexane–*i*-PrOH 80:20, 1 mL/min, major enantiomer (*R*) t_r = 31.1, minor enantiomer (*S*) t_r = 36.4.

mp 110–112 °C; $[\alpha]_D^{25}$ −43.4 (*c* 0.47, CH_2Cl_2, *ee* 66%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.82 (1H, d, *J* = 9.0 Hz), 8.51 (1H, dq, *J* = 4.5, 0.9 Hz), 7.87 (1H, td, *J* = 7.8, 1.8 Hz), 7.68 (1H, dt, *J* = 7.8, 0.9 Hz), 7.49 (1H, ddd, *J* = 7.5, 4.5, 0.9 Hz), 7.12 (2H, d, *J* = 8.7 Hz), 6.70 (2H, d, *J* = 8.7 Hz), 5.06 (1H, q, *J* = 8.1 Hz), 4.86–4.77 (2H, m), 3.67 (3H, s); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 158.8 (C), 157.4 (C), 149.6 (CH), 138.1 (CH), 128.3 (C), 128.2 (CH), 126.5 (CH), 121.3 (CH), 113.6 (CH), 78.8 (CH_2), 55.2 (CH), 55.0 (CH_3); HRMS (ESI): 360.0640 (M^+ + Na), $C_{14}H_{15}N_3NaO_5S$ required 360.0630.

(−)-*N*-(2-nitro-1-*p*-tolylethyl)pyridine-2-sulfonamide (13f). Enantiomeric excess (60%) was determined by HPLC (Chiralpak AD-H), hexane–*i*-PrOH 80:20, 1 mL/min, major enantiomer (*R*) t_r = 23.2, minor enantiomer (*S*) t_r = 27.6.

mp 144–145 °C; $[\alpha]_D^{25}$ −29.8 (*c* 0.58, CH_2Cl_2, *ee* 60%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (1H, dq, *J* = 4.8, 0.9 Hz), 7.87 (1H, dt, *J* = 7.5, 0.9 Hz), 7.80 (1H, td, *J* = 7.8, 1.5 Hz), 7.43 (1H, ddd, *J* = 7.2, 4.8, 1.5 Hz), 7.07–7.00 (4H, m) 6.25 (1H, d, *J* = 7.5 Hz), 5.22 (1H, q, *J* = 6.6 Hz), 4.92 (1H, dd, *J* = 13.2, 6.6 Hz), 4.77 (1H, dd, *J* = 13.2, 6.3 Hz), 2.27 (3H, s); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 157.4 (C), 149.6 (CH), 138.1 (CH), 137.2 (C), 133.5 (C), 128.7 (CH), 126.8 (CH), 126.5 (CH), 121.2 (CH), 78.7 (CH_2), 55.4 (CH), 20.5 (CH_3); HRMS (ESI): 344.0675 (M^+ + Na), $C_{14}H_{15}N_3NaO_4S$ required 344.0681.

(−)-*N*-(1-(4-chlorophenyl)-2-nitroethyl)pyridine-2-sulfonamide (13g). Enantiomeric excess (66%) was determined by HPLC (Chiralpak AD-H), hexane–*i*-PrOH 80:20, 1 mL/min, major enantiomer (*R*) t_r = 26.8, minor enantiomer (*S*) t_r = 37.7.

mp 163–165 °C; $[\alpha]_D^{25}$ −35.9 (*c* 0.48, CH_2Cl_2, *ee* 66%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.00 (1H, d, *J* = 9.3 Hz), 8.50 (1H, dq, *J* = 4.8, 0.9 Hz), 7.89 (1H, td, *J* = 7.8, 1.5 Hz), 7.71 (1H, dt, *J* = 7.8, 0.9 Hz), 7.51 (1H, ddd, *J* = 7.8, 4.8, 0.9 Hz), 7.27–7.21 (4H, m), 5.16–5.08 (1H, m), 4.86 (1H, dd, *J* = 13.2, 5.4 Hz), 4.77 (1H, dd, *J* = 13.2, 9.6 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 157.2 (C), 149.7 (CH), 138.2 (CH), 135.5 (C), 132.6 (C), 129.0 (CH), 128.2 (CH), 126.6 (CH), 121.4 (CH), 78.3 (CH_2), 55.0 (CH); HRMS (ESI): 342.0319 (M^+ + Na), $C_{13}H_{12}ClN_3NaO_4S$ required 342.0315.

(−)-*N*-(2-nitro-1-(4-nitrophenyl)ethyl)pyridine-2-sulfonamide (13h). Enantiomeric excess (58%) was determined by HPLC (Chiralpak AD-H), hexane–*i*-PrOH 70:30, 1 mL/min, major enantiomer (*R*) t_r = 30.9, minor enantiomer (*S*) t_r = 45.5.

mp 192–194 °C; $[\alpha]_D^{25}$ −27.2 (*c* 0.14, CH_2Cl_2, *ee* 58%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.17 (1H, d, *J* = 9.3 Hz), 8.48 (1H, dq, *J* = 4.8, 0.9 Hz), 8.06 (2H, d, *J* = 9.0 Hz), 7.89 (1H, td, *J* = 7.8, 1.8 Hz), 7.73 (1H, dt, *J* = 7.8, 0.9 Hz), 7.55 (2H, d, *J* = 9.0 Hz), 7.49 (1H, ddd, *J* = 7.8, 4.8, 1.2 Hz), 5.29 (1H, m), 4.94 (1H, dd, *J* = 13.5, 5.1 Hz), 4.82 (1H, dd, *J* = 13.5, 9.6 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 157.0 (C), 149.7 (CH), 147.0 (C), 144.0 (C), 138.3 (CH), 128.6 (CH), 126.8 (CH), 123.2 (CH), 121.3 (CH), 77.9 (CH_2), 54.9 (CH); HRMS (ESI): 353.0556 (M^+ + Na), $C_{13}H_{12}N_4NaO_6S$ required 353.0556.

(−)-*N*-(1-(3-methoxyphenyl)-2-nitroethyl)pyridine-2-sulfonamide (13i). Enantiomeric excess (69%) was determined by HPLC (Chiralpak IC), hexane–*i*-PrOH 70:30, 1 mL/min, major enantiomer (*R*) t_r = 38.8, minor enantiomer (*S*) t_r = 53.3.

mp 123–124 °C; $[\alpha]_D^{25}$ −32.7 (*c* 0.52, CH_2Cl_2, *ee* 69%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (1H, dq, *J* = 4.5, 0.9 Hz), 7.84–7.80 (1H, m), 7.77 (1H, td, *J* = 7.2, 1.8 Hz), 7.40 (1H, ddd, *J* = 7.2, 4.8, 1.5 Hz), 7.10 (1H, t, *J* = 7.8 Hz), 6.84 (1H, d, *J* = 7.8 Hz), 6.76–6.68 (3H, m), 5.30–5.22 (1H, m), 4.92 (1H, dd, *J* = 13.5, 7.5 Hz), 4.73 (1H, dd, *J* = 13.5, 6 Hz), 3.69 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.8 (C), 157.2 (C), 149.8 (CH), 138.0 (CH), 136.6 (C), 130.0 (CH), 126.8 (CH), 122.2 (CH), 118.9 (CH), 114.6 (CH), 112.2 (CH), 78.6 (CH_2), 55.8 (CH), 55.2 (CH_3); HRMS (ESI): 338.0805 (M^+ + H), $C_{14}H_{16}N_3O_5S$ required 338.0810.

(−)-*N*-(2-nitro-1-*m*-tolylethyl)pyridine-2-sulfonamide (13j). Enantiomeric excess (70%) was determined by HPLC (Chiralcel OD-H), hexane–*i*-PrOH 85:15, 1 mL/min, major enantiomer (*R*) t_r = 29.3, minor enantiomer (*S*) t_r = 27.3.

mp 140–141 °C; $[\alpha]_D^{25}$ −51.9 (*c* 0.47, CH_2Cl_2) (*ee* 70%); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.89 (1H, d, *J* = 8.1 Hz), 8.51 (1H, d, *J* = 3.9 Hz), 7.85 (1H, td, *J* = 7.5, 1.5 Hz), 7.68 (1H, d, *J* = 7.8 Hz), 7.47 (1H, ddd, *J* = 7.5, 4.5, 0.9 Hz), 7.06–6.94 (4H, m), 5.06 (1H, br s), 4.87–4.74 (2H, m), 2.15 (3H, s); ^{13}C NMR (75.5 MHz, DMSO) δ 157.9 (C), 150.0 (CH), 138.5 (CH), 137.9(C), 136.7 (C), 129.0 (CH), 128.7 (CH), 128.1 (CH), 127.1 (CH), 124.5 (CH), 121.8 (CH), 79.2 (CH_2), 56.2 (CH), 21.3 (CH_3); HRMS (ESI): 344.0676 (M^+ + Na), $C_{14}H_{15}N_3NaO_4S$ required 344.0681.

(−)-*N*-(1-(3-chlorophenyl)-2-nitroethyl)pyridine-2-sulfonamide (13k). Enantiomeric excess (60%) was determined by HPLC (Chiralcel OD-H), hexane–*i*-PrOH 75:25, 1 mL/min, major enantiomer (*R*) t_r = 17.4, minor enantiomer (*S*) t_r = 15.4.

mp 147–148 °C; $[\alpha]_D^{25}$ −29.2 (*c* 0.53, CH_2Cl_2, *ee* 60%); ^{1}H NMR (300 MHz, MeOD) δ 8.96 (1H, d, *J* = 9.0 Hz), 8.49 (1H, dq, *J* = 4.5, 0.9 Hz), 7.86 (1H, td, *J* = 7.8, 1.8 Hz), 7.70 (1H, d, *J* = 7.8 Hz), 7.48 (1H, ddd, *J* = 7.5, 4.5, 0.9 Hz), 7.24–7.14 (5H, s), 5.16 (1H, m), 4.85 (1H, dd, *J* = 13.2, 5.4 Hz), 4.78 (1H, dd, *J* = 13.2, 9.6 Hz); ^{13}C NMR (75.5 MHz, MeOD) δ 157.3 (C), 149.6 (CH), 138.1 (CH), 136.4 (C), 128.2 (CH), 127.9 (CH), 126.9 (CH), 126.6 (CH), 121.2 (CH), 78.7 (CH_2), 55.7 (CH); HRMS (ESI): 364.0139 (M^+ + Na), $C_{13}H_{12}ClN_3NaO_4S$ required 364.0135.

(−)-*N*-(2-nitro-1-(3-nitrophenyl)ethyl)pyridine-2-sulfonamide (13l). Enantiomeric excess (66%) was determined by HPLC (Chiralcel AD-H), hexane–*i*-PrOH 70:30, 1 mL/min, major enantiomer (*R*) t_r = 18.6, minor enantiomer (*S*) t_r = 16.7.

mp 166–168 °C; $[\alpha]_D^{25}$ −47.2 (*c* 0.4, CH_2Cl_2, *ee* 66%); ^1H NMR (300 MHz, DMSO-d_6) δ 9.2 (1H, br s), 8.44 (1H, ddd, *J* = 4.5, 1.5, 0.9 Hz), 8.13 (1H, t, *J* = 2.1 Hz), 8.02 (1H, ddd, *J* = 8.4, 2.4, 1.2 Hz), 7.85 (1H, td, *J* = 7.8, 1.8 Hz), 7.74–7.69 (2H, m), 7.50 (1H, t, *J* = 7.8 Hz), 7 (1H, ddd, *J* = 7.8, 4.8, 1.2 Hz), 5.31 (1H, br s), 4.95 (1H, dd, *J* = 13.8, 5.1 Hz), 4.84 (1H, dd, *J* = 13.8, 9.6 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 157.5 (C), 150.2 (CH), 147.9 (C), 139.1 (C), 138.8(CH), 134.6 (CH), 130.4 (CH), 127.2 (CH), 123.4 (CH), 122.6 (CH), 121.9 (CH), 78.5 (CH_2), 55.4 (CH); HRMS (ESI): 375.0370 (M^+ + Na), $C_{13}H_{12}N_4NaO_6S$ required 375.0375.

(−)-*N*-(2-nitro-1-(thiophen-3-yl)ethyl)pyridine-2-sulfonamide (13m). Enantiomeric excess (77%) was determined by HPLC (Chiralpak AD-H), hexane–*i*-PrOH 75:25, 1 mL/min, major enantiomer (*R*) t_r = 18.5, minor enantiomer (*S*) t_r = 20.5.

mp 135–136 °C; $[\alpha]_D^{25}$ −32.8 (*c* 0.24, CH_2Cl_2, *ee* 77%); ^1H NMR (300 MHz, DMSO-d_6) δ 8.84 (1H, d, *J* = 9.3 Hz), 8.53 (1H, dq, *J* = 4.5, 0.9 Hz), 7.91 (1H, td, *J* = 7.8, 1.5 Hz), 7.74 (1H, d, *J* = 7.8 Hz), 7.52 (1H, ddd, *J* = 7.5, 4.5, 0.9 Hz), 7.33–7.28 (2H, m), 6.94 (1H, dd, *J* = 5.1, 1.5 Hz), 5.27–5.19 (1H, m), 4.87 (1H, dd, *J* = 13.2, 5.4 Hz), 4.78 (1H, dd, *J* = 13.2, 9.3 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 157.3 (C), 149.6 (CH), 138.2 (CH), 137.2 (C), 126.6 (CH), 126.5 (CH), 126.2 (CH), 123.4 (CH), 121.2 (CH), 78.5 (CH_2), 51.5 (CH); HRMS (ESI): 336.0095 (M^+ + Na), $C_{11}H_{11}N_3NaO_4S_2$ required 336.0089.

(−)-*N*-(1-(furan-3-yl)-2-nitroethyl)pyridine-2-sulfonamide (13n). Enantiomeric excess (60%) was determined by HPLC (Chiralpak AY-H), hexane–*i*-PrOH 70:30, 1 mL/min, major enantiomer (*R*) t_r = 32.8, minor enantiomer (*S*) t_r = 27.9.

mp 152–154 °C; $[\alpha]_D^{25}$ −15.0 (*c* 0.25, CH_2Cl_2, *ee* 60%); ^1H NMR (300 MHz, DMSO-d_6) δ 8.72 (1H, d, *J* = 9.0 Hz), 8.60 (1H, dq, *J* = 4.8, 0.9 Hz), 7.98 (1H, td, *J* = 7.8, 1.8 Hz), 7.82 (1H, dt, *J* = 7.8, 0.9 Hz), 7.57 (1H, ddd, *J* = 7.5, 4.5, 0.9 Hz), 7.43–7.42 (2H, m), 6.32 (1H, s), 5.16–5.08 (1H, m), 4.83 (1H, dd, *J* = 12.9, 5.7 Hz), 4.76 (1H, dd, *J* = 12.9, 8.7 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 157.4 (C), 149.7 (CH), 143.4 (CH), 140.4 (C), 138.3 (CH), 126.8 (CH), 121.4 (C), 121.3 (CH), 108.9 (CH), 78.4 (CH_2), 48.0 (CH); HRMS (ESI): 320.0316 (M^+ + Na), $C_{11}H_{11}N_3NaO_5S$ required 320.0317.

Determination of the Absolute Stereochemistry of 13a

Synthesis of (−)-(*R*)-methyl 2-phenyl-2-(pyridine-2-sulfonamido) acetate (14) by ozonolysis of compound 13a. To a solution of **13a** (50.0 mg, 0.16 mmol) in MeOH (3 mL) under nitrogen was added a 30% solution of NaOMe in MeOH (46.3 μL, 0.24 mmol), and the resulting solution was stirred at rt for 10 min. This methanolic solution was cooled to −78 °C, and a stream of O_3 was passed through during 60 min. The reaction was purged with N_2 to remove the excess of O_3. The resulting solution was allowed to reach rt, $BF_3{\cdot}Et_2O$ (0.4 mL) was added, and the mixture was heated at reflux temperature for 3.5 h. After cooling to rt, saturated aqueous $NaHCO_3$ (10 mL) was added, the organic solvent was removed under reduced pressure, and the resulting aqueous solution was extracted with dichloromethane (3 × 15 mL), washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The mixture was purified by column chromatography eluting with hexane/EtOAc (7:3) to give 35.7 mg (71%) of (*R*)-**14**. Enantiomeric excess (83%) was determined by HPLC (Chiralcel OD-H), hexane : *i*-PrOH 80:20, 1 mL/min, major enantiomer (*R*) t_r = 13.4, minor enantiomer (*S*) t_r = 12.4.

$[\alpha]_D^{25}$ −50.2 (*c* 0.53, $CHCl_3$, *ee* 83%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.59 (1H, dq, *J* = 4.5, 0.9 Hz), 7.82–7.74 (2H, m), 7.43–7.39 (1H, m), 7.29–7.23 (5H, m), 6.13 (1H, d, *J* = 8.1 Hz), 5.40 (1H, d, *J* = 8.1 Hz), 3.67 (3H, s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.5, (C), 157.8 (C), 149.7 (CH), 137.8 (CH), 135.4 (C), 128.7 (CH), 128.5 (CH), 127.2 (CH), 126.5 (CH), 121.7 (CH), 60.1 (CH), 53.0 (CH_3); HRMS (ESI): 329.0576 (M^+ + Na), $C_{14}H_{14}N_2NaO_4S$ required 329.0572.

Synthesis of (+)-(*S*)-methyl 2-phenyl-2-(pyridine-2-sulfonamido) acetate (14) from (*S*)-(+)-phenylglycine methyl ester hydrochloride. A solution of pyridine-2-sulfonyl chloride (195 mg, 1.1 mmol) in CH_2Cl_2 (10 mL) was added to a solution of (*S*)-(+)-phenylglycine methyl ester hydrochloride (**15**, 208 mg, 1 mmol) and Et_3N (277 μL, 2 mmol) in CH_2Cl_2 (40 mL) cooled to 0 °C. The resulting mixture was allowed to reach rt and was stirred for 2 h. The reaction mixture was washed with saturated aqueous $NaHCO_3$ (2 × 25 mL) water (25 mL). The organic layer was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. Column chromatography eluting with hexane/EtOAc (6:4) gave 281 mg (92%) of (*S*)-**14**. Enantiomeric excess (99%) was determined by HPLC (Chiralcel OD-H), hexane:*i*-PrOH 80:20, 1 mL/min, major enantiomer (*S*) t_r = 12.3, minor enantiomer (*R*) t_r = 13.9. $[\alpha]_D^{25}$ +113.7 (*c* 0.59, $CHCl_3$, *ee* 99%).

(−)-(*R*)-methyl 2-amino-2-phenylacetate (16). To a solution of (*R*)-**14** (30.0 mg, 0.098 mmol, *ee* 83%) in MeOH (2.5 mL) and THF (0.65 mL) under nitrogen at 0 °C was added Mg powder (23.6 mg, 0.98 mmol), and the resulting suspension was stirred at rt for 4 h. Then, diethyl ether (3.8 mL) and a saturated aqueous NH_4Cl (3.8 mL) were added, and the resulting solution was stirred for additional 2 h at rt. The reaction mixture was diluted with water (15 mL) and extracted with diethyl ether (3 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Chromatography on a short pad of silica gel gave 14.5 mg (87%) of compound **16**.

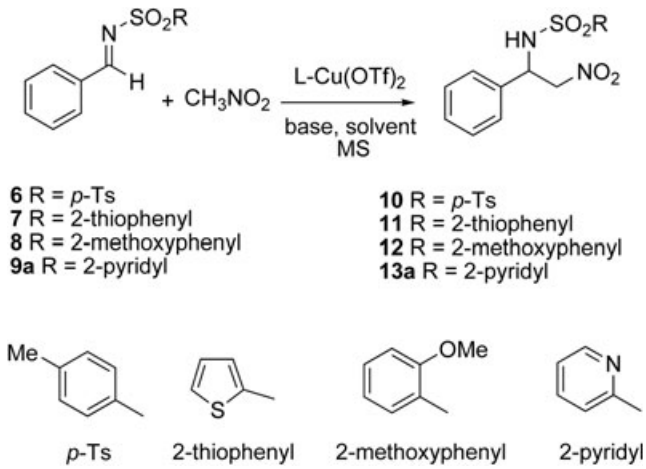
$[\alpha]_D^{25}$ −90.0 (*c* 0.05, MeOH, *ee* 83%), Lit[59] $[\alpha]_D^{25}$ +130 (*c* 0.02, MeOH, for the *S*-enantiomer); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.30 (5H, m), 4.64 (1H, s), 3.70 (3H, m), 2.56 (2H, br s).

RESULTS AND DISCUSSION

In the onset of our research, we tested the effect of different *N*-sulfonyl groups. Thus, *N*-tosyl- (**6**), *N*-(2-thiophenyl)sulfonyl- (**7**), *N*-(2-methoxyphenyl) sulfonyl- (**8**), and *N*-(2-pyridyl)sulfonyl- (**9**) imines derived from benzaldehyde were prepared, and their reaction with nitromethane in the presence of aminopyridine **2** (the best ligand for the enantioselective Henry reaction[44]) and Cu(II) was studied (Scheme 1).

Initially, the reaction was carried out under conditions similar to those described by Feng,[6] using ligand **2**, $Cu(OTf)_2$, catalytic DIPEA in THF-nitromethane, and 4 Å molecular sieves. The results are gathered in Table 1.

The best results were obtained with the *N*-(2-methoxyphenyl) sulfonyl imine **8** and especially with the *N*-(2-pyridyl)



Scheme 1. Copper-catalyzed addition of nitromethane to different N-sulfonyl imines.

TABLE 2. Addition of nitromethane to *N*-sulfonyl imine 9a according to Scheme 1. Effect of ligand, amount of base and solvent[a]

Entry	L	Solvent	Base	Yield (%)	*ee* (%)[b]
1	**2**	THF	DIPEA (30 mol%)	80	59
2	**1**	THF	DIPEA (30 mol%)	65	6
3	**3**	THF	DIPEA (30 mol%)	70	13
4	**4**	THF	DIPEA (30 mol%)	70	6
5	**5**	THF	DIPEA (30 mol%)	50	0
6	**2**	THF	DIPEA (20 mol%)	54	55
7	**2**	THF	DIPEA (10 mol%)	–	–
8	**2**	THF	DIPEA (50 mol%)	85	50
9	**2**	THF	DIPEA (100 mol%)	85	39
10	**2**	EtOH	DIPEA (30 mol%)	60	3
11	**2**	CH_2Cl_2	DIPEA (30 mol%)	65	26
12	**2**	Toluene	DIPEA (30 mol%)	85	57
13	**2**	CH_3NO_2	DIPEA (30 mol%)	95	38
14	**2**	Dioxane	DIPEA (30 mol%)	90	55
15	**2**	*t*-BuOMe	DIPEA (30 mol%)	90	64
16	**2**	*i*-Pr_2O	DIPEA (30 mol%)	90	64
17	**2**	Et_2O	DIPEA (30 mol%)	85	74

[a]Ligand (20 mol%), $Cu(OTf)_2$ (20 mol%), base, 4 Å MS (100 mg/mmol imine), 0 °C.
[b]Determined by HPLC using chiral stationary phases.

TABLE 3. Addition of nitromethane to *N*-sulfonyl imine 9a according to Scheme 1. Effect of base and MS[a]

Entry[b]	Base	MS	*T* (°C)	*t* (h)	Yield (%)	*ee* (%)[c]
1[d]	DIPEA	4 Å MS	0	5	85	74
2[d]	DIPEA	3 Å MS	0	5	80	56
3[d]	DIPEA	5 Å MS	0	5	85	49
4	DIPEA	4 Å MS	0	4	90	82
5	Et_3N	4 Å MS	0	4	90	79
6	Na_2CO_3	4 Å MS	0	3	65	63
7	0BProton Sponge®	4 Å MS	0	24	50	72
8	Bu_3N	4 Å MS	0	22	70	44
9	DIPEA	4 Å MS	−15	3	85	83
10	DIPEA	4 Å MS	−25	3	80	78
11	DIPEA	4 Å MS	−40	3	80	79

[a]**2** (20 mol%), $Cu(OTf)_2$ (20 mol%), base (30 mol%), MS (50 mg/mmol imine), Et_2O.
[b]Experiments in entries 1–5 were not checked before the annotated times.
[c]Determined by HPLC using chiral stationary phases.
[d]100 mg MS/mmol imine was used.

sulfonyl imine **9a**. It is remarkable that both compounds **8** and **9a** have a potential coordinating group at the sulfone substituent, which may indicate that the reaction proceed through a chelated transition state.[1] As a matter of fact, the chelating character of the pyridine nitrogen has been shown to play an essential role in other metal-catalyzed enantioselective reactions with *N*-(2-pyridyl)sulfonyl imines.[50–52]

Further optimization was carried out with *N*-(2-pyridyl)sulfonyl imine **9a**. First, we tested the iminopyridine ligand **1** under the same conditions that allowed obtaining compound **13a** with 65% yield but only 6% *ee* (Table 2, entry 2). Then, we focused our study on aminopyridine ligands **3–5** (entries 3–5), but none of them improved the results obtained with ligand **2**. The optimal amount of base was found to be 30 mol%. Higher base loads had a deleterious effect on the enantioselectivity (entries 8–9), whereas when using a too low amount of base (10 mol%), the reaction did not take place (entry 7). The effect of the different solvents was also tested. Protic solvents (EtOH) provided the expected product almost in racemic form (entry 10). Toluene (entry 12) gave almost the same results as THF, whereas dichloromethane gave lower yield and *ee* (entry 11). Ether-type solvents gave the best performance, the best result being obtained in diethyl ether (entry 17).

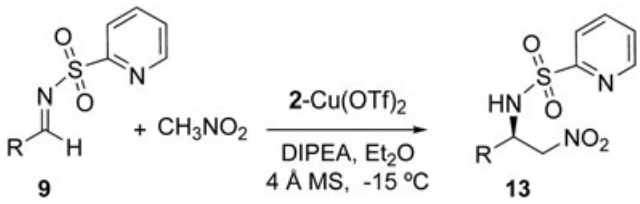
Once the amount of the base (30 mol%) and the solvent (diethyl ether) had been established, we studied the reaction with different bases and with different kinds and amounts of molecular sieves (Table 3). Changing 4 Å MS to 3 or 5 Å MS led to a decrease in the enantiomeric excess of the product (entries 1–3). The amount of 4 Å MS was also adjusted, so when the reaction was carried out with 50 mg MS per mmol of imine, an appreciable increase in enantioselectivity was observed with respect to the reaction in the presence of 100 mg MS per mmol of imine (entry 1 versus entry 4). Although the use of MS as an additive in several enantioselective reactions involving nitrocompounds[6,12,13,22] has been shown to have a beneficial effect on the yield and stereoselectivity, the mechanism of this effect is not clear. It has been suggested that, further to act as scavenger for water and proton contaminants that may have a deleterious effect,[12,60] MS could facilitate the enolization of nitromethane.[61,62] It may also be possible that a heterogeneous catalyst is formed from the copper complex and molecular sieves, which may help to improve the stability of the catalyst and its stereodifferentiation ability.[63,64] Other bases were tested, but none of them performed better than DIPEA. Finally, we tested the reaction at lower temperatures. A slight increase in the enantioselectivity was observed when the temperature was decreased from 0 to −15 °C (entry 9); however, further decrease of the temperature (entries 10–11) did not bring about any noticeable improvement of the reaction.

Once the best reaction conditions have been established, we studied the scope of the reaction with several *N*-(2-pyridyl)sulfonyl aldimines (Scheme 2). The results are gathered in Table 4.

In general, the reactions with aromatic and heteroaromatic[65] sulfonamides **9a–n** were completed in less than 3 h, providing the expected nitro sulfonamides **13a–n** with fair yields and moderate enantiomeric excesses. The highest *ee* values were obtained with the imines derived from benzaldehyde (entry 1), 2-methoxybenzaldehyde (entry 2), and thiophene-3-carbaldehyde (entry 10) with *ee* close to 80%. However, with the rest of imines, the *ee* values were lower, being around 60% in most cases.

Compounds **13** can be easily transformed into *N*-(2-pyridyl)sulfonyl amino acid derivatives. Thus, upon ozonolysis

[1]During the reviewing process, one of the referees suggested that the reaction may not proceed through a chelated transition state, because imine **7**, bearing a thiophene ring with a potentially coordinating sulfur atom, gave poor results. Although the chelating character of *N*-(2-pyridyl)sulfonyl imines has been demonstrated in other enantioselective reactions, it cannot be excluded for the thiophene derivative. However, the size and bite angle of the potential chelate formed with the thiophene derivative may largely differ from those of the pyridine derivative, which may explain the different enantioselectivities obtained in entries 2 and 4 of Table 1.



Scheme 2. Enantioselective addition of nitromethane to N-sulfonyl imines 9.

TABLE 4. Addition of nitromethane to *N*-sulfonyl imines 9[a]

Entry	9	R	*t* (h)	13	Yield (%)	*ee* (%)[b]
1	**9a**	Ph	3	**13a**	77	83
2	**9b**	2-$MeOC_6H_4$	3	**13b**	88	78
3	**9c**	2-MeC_6H_4	3.5	**13c**	70	58
4	**9d**	2-ClC_6H_4	4	**13d**	64	54
5	**9e**	4-$MeOC_6H_4$	3	**13e**	60	64
6	**9f**	4-MeC_6H_4	3	**13f**	71	60
7	**9g**	4-ClC_6H_4	3	**13g**	67	66
8	**9h**	4-$NO_2C_6H_4$	3	**13h**	54	58
9	**9i**	3-$MeOC_6H_4$	3	**13i**	55	69
10	**9j**	3-MeC_6H_4	3	**13j**	63	70
11	**9k**	3-ClC_6H_4	3	**13k**	68	60
12	**9l**	3-$NO_2C_6H_5$	3	**13l**	50	66
13	**9m**	3-Thiophenyl	3	**13m**	70	77
14	**9n**	3-Furanyl	3	**13n**	72	60

[a]**2** (20 mol%), $Cu(OTf)_2$ (20 mol%), DIPEA (30 mol%), 4 Å MS (50 mg/mmol imine), Et_2O, −15 °C.
[b]Determined by HPLC using chiral stationary phases.

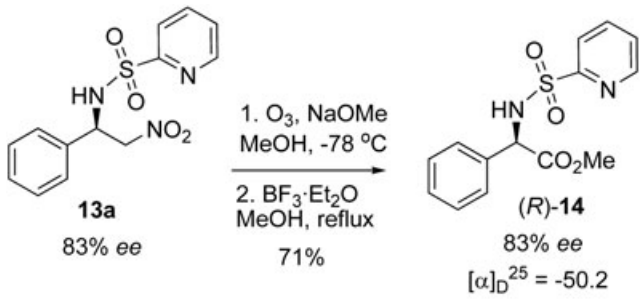
of the nitronate of **13a** followed by esterification with methanol in the presence of $BF_3{\cdot}Et_2O$, we could obtain directly the *N*-sulfonyl amino ester **14** (Scheme 3).

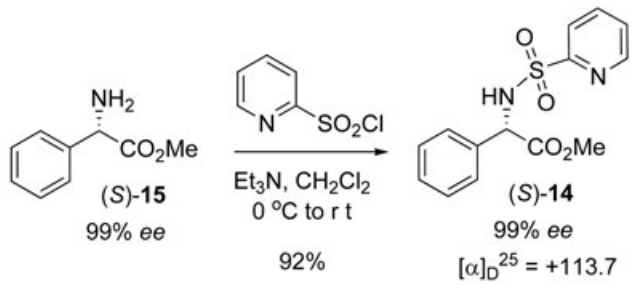
The absolute stereochemistry of compound **14**, and hence that of compound **13a**, was determined by comparison with the same product prepared by sulfonylation of commercially available (*S*)-(+)-methyl phenylglycinate (**15**) with 2-pyridylsulfonyl chloride (Scheme 3). The product prepared in this way showed opposite optical rotation sign to that prepared from **13a**. In this way, the aza-Henry product **13a** was assigned the *R* configuration at the stereogenic center. The rest of compounds **13b–n** were tentatively assigned as *R* on the assumption of a uniform mechanistic pathway.[2]

One of the advantages of the *N*-(2-pyridyl)sulfonyl group is that it can be removed under milder conditions than other *N*-sulfonyl groups. Thus, compound **14** could be transformed into methyl phenylglycinate upon treatment with magnesium in MeOH–THF with good yield and without loss of optical purity (Scheme 4).

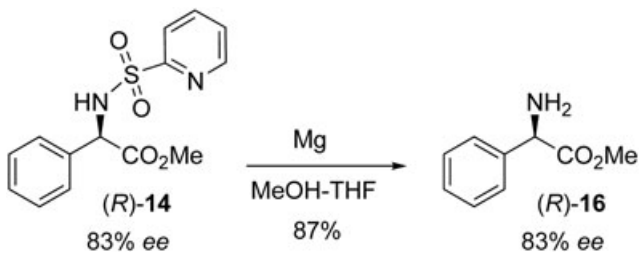
The results obtained with different amounts of base (Table 2, entries 1, 6–9) can be rationalized (Scheme 5) in terms very similar to those described by Jørgensen[66,67] and for us[45] for the Cu(II)-catalyzed addition of nitromethane to α-keto esters. The enantioselective catalytic pathway requires

[2]All compounds **13** showed identical optical rotation signs (−). Compounds **13a–h** and **13n** also showed identical behavior during HPLC analysis with the Chiralpak AD-H column. Compounds **13j** and **13k** showed identical behavior with the Chiralcel OD-H column.





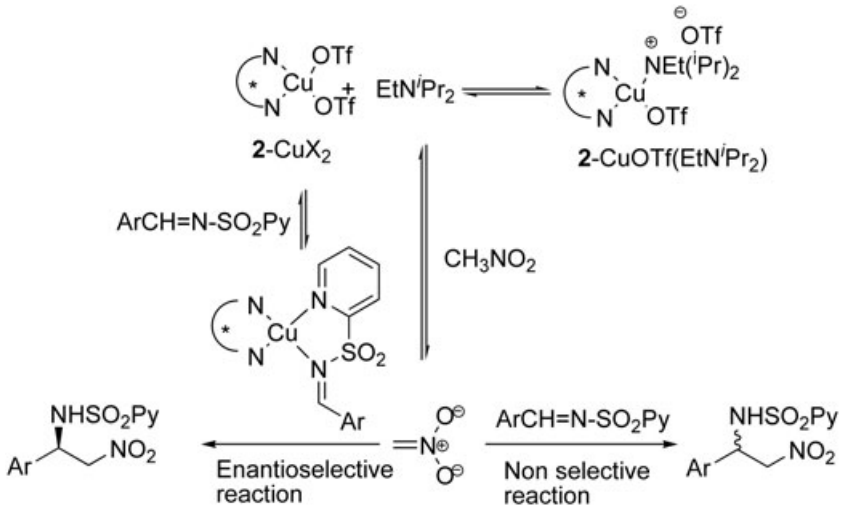
Scheme 3. Determination of the absolute stereochemistry of compound **13a**.



Scheme 4. Deprotection of the amine.

the coordination of the *N*-(2-pyridyl)sulfonyl imine to the copper atom of the **2**-$Cu(OTf)_2$ complex and the presence of a deprotonated molecule of nitromethane (a nitronate). A competitive equilibrium between DIPEA and the initial **2**-$Cu(OTf)_2$ with an inactive **2**-CuOTf(DIPEA) is established. The reaction requires the presence in the solution of enough base to deprotonate the nitromethane. If the base is in excess with respect to the Lewis acid, the equilibrium is shifted toward the inactive complex, hence trapping the chiral Lewis acid. The remaining base induces a nonenantioselective pathway between the nitronate and the uncoordinated imine. If the Lewis acid is in excess with respect to the base, then the low concentration of free amine brings about a slow reaction with low conversion.

With respect to the stereochemical mechanism, the results indicate a preference for the nitronate to attack from the *Si* face of the CN double bond. According to our previous studies on the Henry reaction,[42–49] we propose a plausible stereochemical model that would account for the observed stereochemistry (Fig. 2). This model is similar to that proposed for the Henry reaction with aldehydes catalyzed by **2**-$Cu(OAc)_2$,[44] but with the imine coordinating the two more acidic equatorial positions of the Cu(II) ion by the azomethine and pyridine nitrogen atoms, for a maximum electrophilic activation. The nitronate would occupy the less



Scheme 5. Competitive catalytic and non-catalytic pathways.

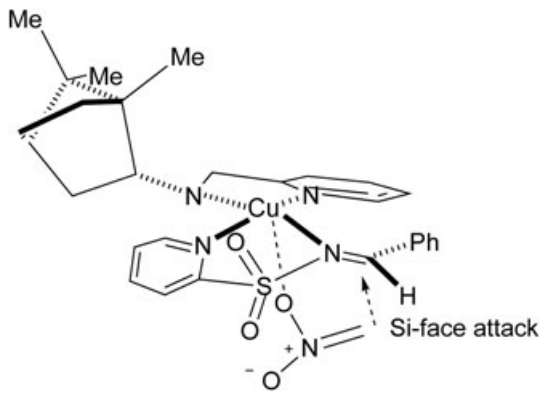


Fig. 2. Proposed transition state model for the copper-catalyzed enantioselective aza-Henry reaction of imines **9** with ligand **2**.

hindered apical position from which it would be transferred to the *Si* face of the imine.

CONCLUSIONS

In conclusion, we have described a new catalytic enantioselective aza-Henry reaction. The reaction expands the application of camphor-derived aminopyridine ligands in asymmetric catalysis. This is the first example of aza-Henry reaction with *N*-(2-pyridyl)sulfonyl imines, which have the advantage of an easy removal of the *N*-protecting group under mild reductive conditions.

ACKNOWLEDGMENTS

Financial support from the Ministerio de Ciencia e Innovación and FEDER (CTQ2009-13083) and from Generalitat Valenciana (ACOMP/2011/267) is acknowledged. V H-O thanks the Universitat de València for a pre-doctoral grant (V Segles program).

LITERATURE CITED

1. For a recent review on this reaction, see: Westermann B. Asymmetric catalytic aza-Henry reactions leading to 1,2-diamines and 1,2-diaminocarboxylic acids. Angew Chem Int Ed 2003;42:151–153.
2. For a recent review on this reaction, see: Ting A, Schaus SE. Organocatalytic asymmetric Mannich reactions. New methodology, catalyst design, and synthetic applications. Eur J Org Chem 2007;5797–5815.
3. For a recent review on this reaction, see: Marqués-López E, Merino P, Tejero P, Herrera RP. Catalytic enantioselective aza-Henry reactions. Eur J Org Chem 2009;2401–2420.
4. Lucet D, Le Gall T, Mioskowski C. The chemistry of vicinal diamines. Angew Chem Int Ed 1998;37:2580–2627.
5. Bernardi L, Bonini BF, Capitò E, Dessole G, Comes-Franchini M, Fochi M, Ricci A. Organocatalyzed solvent-free aza-Henry reaction: a breakthrough in the one-pot synthesis of 1,2-diamines. J Org Chem 2004;69:8168–8171.
6. Zhou H, Peng D, Qin B, Hou Z, Liu X, Feng X. Highly enantioselective aza-Henry reaction of N-tosyl imines catalyzed by N,N-dioxide-Cu(I) complexes. J Org Chem 2007;72:10302–10304.
7. For a review on the Nef reaction, see: Ballini R, Petrini M. Recent synthetic developments in the nitro to carbonyl conversion (Nef reaction). Tetrahedron 2004;60:1017–1047.
8. For a review on the Nef reaction, see: Foresti E, Palmieri G, Petrini M, Profeta R. Highly diastereoselective addition of nitromethane anion to chiral α-amidoalkylphenyl sulfones. Synthesis of optically active α-amino acid derivatives. Org Biomol Chem 2003;1:4275–4281.
9. For a review on the Nef reaction, see: Matt C, Wagner A, Moiskowski C. Novel transformation of primary nitroalkanes and primary alkyl bromides to the corresponding carboxylic acids. J Org Chem 1997;62:234–235
10. For representative work, see: Rare earth catalysts Yamada K, Harwood SJ, Groger H, Shibasaki M. The first catalytic asymmetric nitro-Mannich-type reaction promoted by a new heterobimetallic complex. Angew Chem Int Ed 1999;38:3504–3506.
11. For representative work, see: Zinc catalyst Trost BM, Lupton DW. Dinuclear zinc-catalyzed enantioselective aza-Henry reaction. Org Lett 2007;9:2023–2026.
12. For representative work, see: Zinc catalyst Palomo C, Oiarbide M, Halder R, Laso A, Lopez R. Enantioselective aza-Henry reactions assisted by Zn(II) and *N*-methylephedrine. Angew Chem Int Ed 2005;45:117–120.
13. For representative work, see: Zinc catalyst Gao F, Zhu J, Tang Y, Deng M, Qian C. Asymmetric aza-Henry reaction of *N*-tosyl imine. Chirality 2006;18:741–745.
14. For representative work, see: Copper catalyst Nishiwaki N, Knudsen KR, Gothelf KV, Jørgensen KA. Catalytic enantioselective addition of nitro compounds to imines. A simple approach for the synthesis of optically active β-nitro-α-amino esters. Angew Chem Int Ed 2001;40:2992–2995.
15. For representative work, see: Copper catalyst Anderson JC, Howell GP, Lawrence RM, Wilson CS. An asymmetric nitro-Mannich reaction applicable to alkyl, aryl, and heterocyclic imines. J Org Chem 2005;70:5665–5670.
16. For representative work, see: Copper catalyst Tan C, Liu X, Wang L, Wang J, Feng X. Highly enantioselective aza-Henry reaction of ketoimines

catalyzed by chiral *N*,*N*-dioxide-copper(I) complexes. Org Lett 2008;10: 5305–5308.

17. For representative work, see: PTC Zhang G, Yashima E, Woggon W. Versatile supramolecular copper(II) complexes for Henry and aza-Henry reactions. Adv Synth Catal 2009;351:1255–1262.
18. For representative work, see: Bimetallic complexes Chen Z, Morimoto H, Matsunaga S, Shibasaki M. A bench-stable homodinuclear Ni_2–Schiff base complex for catalytic asymmetric synthesis of α-tetrasubstituted anti-α,β-diamino acid surrogates. J Am Chem Soc 2008;130:2170–2171.
19. For representative work, see: Bimetallic complexes Handa S, Gnanadesikan V, Matsunaga S, Shibasaki M. syn-Selective catalytic asymmetric nitro-Mannich reactions using a heterobimetallic Cu–Sm–Schiff base complex. J Am Chem Soc 2007;129:4900–4901.
20. For representative work, see: Urea and thiourea catalyst Xu X, Furukawa T, Okino T, Miyabe H, Takemoto Y. Bifunctional-thiourea-catalyzed diastereo- and enantioselective aza-Henry reaction. Chem Eur J 2006;12:466–476.
21. For representative work, see: Urea and thiourea catalyst Hu K, Wang C, Ma X, Wang Y, Zhou Z, Tang C. *N*-Thiophosphoryl imines: convenient substrates in the aza-Henry reaction. Tetrahedron: Asymmetry 2009;20: 2178–2184.
22. For representative work, see: Urea and thiourea catalyst Yoon TP, Jacobsen EN. Highly enantioselective thiourea-catalyzed nitro-Mannich reactions. Angew Chem Int Ed 2005;44:466–468.
23. For representative work, see: Urea and thiourea catalyst Robak MT, Trincado M, Ellman JA. Enantioselective aza-Henry reaction with an *N*-sulfinyl urea organocatalyst. J Am Chem Soc 2007;129:15110–15111.
24. For representative work, see: Urea and thiourea catalyst Han B, Liu Q, Li R, Tian X, Xiong X, Deng J, Chen Y. Discovery of bifunctional thiourea/secondary-amine organocatalysts for the highly stereoselective nitro-Mannich reaction of α-substituted nitroacetates. Chem Eur J 2008;14:8094–8097.
25. For representative work, see: Urea and thiourea catalyst Wang C, Dong X, Zhang Z, Xue Z, Teng H. Highly anti-selective asymmetric nitro-Mannich reactions catalyzed by bifunctional amine-thiourea-bearing multiple hydrogen-bonding donors. J Am Chem Soc 2008;130:8606–8607.
26. For representative work, see: Urea and thiourea catalyst Rampalakos C, Wulff WD. A novel bis-thiourea organocatalyst for the asymmetric aza-Henry reaction. Adv Synth Catal 2008;350:1785–1790.
27. For representative work, see: Urea and thiourea catalyst Bode CM, Ting A, Schaus SE. A general organic catalyst for asymmetric addition of stabilized nucleophiles to acyl imines. Tetrahedron 2006;62 11499–11505.
28. For representative work, see: Urea and thiourea catalyst Jiang X, Zhang Y, Wu L, Zhang G, Liu X, Zhang H, Fu D, Wang R. Doubly stereocontrolled asymmetric aza-Henry reaction with in situ generation of *N*-Boc-imines catalyzed by novel rosin-derived amine thiourea catalysts. Adv Synth Catal 2009;351:2096–2100.
29. For representative work, see: Urea and thiourea catalyst Chang Y, Yang J, Dang J, Xue Y. Oxazoline-thiourea as a bifunctional organocatalyst: enantioselective aza-Henry reactions. Synlett 2007;2283–2285.
30. For representative work, see: Urea and thiourea catalyst Wang C, Zhou Z, Tang C. Novel bifunctional chiral thiourea catalyzed highly enantioselective aza-Henry reaction. Org Lett 2008;10:1707–1710.
31. For representative work, see: Urea and thiourea catalyst Takada K, Nagasawa K. Enantioselective aza-Henry reaction with acyclic guanidine-thiourea bifunctional organocatalyst. Adv Synth Catal 2009;351:345–347.
32. For representative work, see: Urea and thiourea catalyst Okino T, Nakamura S, Furukawa T, Takemoto Y. Enantioselective aza-Henry reaction catalyzed by a bifunctional organocatalyst. Org Lett 2004;6:625–627.
33. For representative work, see: Chiral proton catalysis Nugent BM, Yoder RA, Johnston JN. Chiral proton catalysis: a catalytic enantioselective direct aza-Henry reaction. J Am Chem Soc 2004;126:3418–3419.
34. For representative work, see: Chiral proton catalysis Singh A, Johnston JN. A diastereo- and enantioselective synthesis of α-substituted syn-α,β-diamino acids. J Am Chem Soc 2008;130:5866–5867.
35. For representative work, see: Chiral proton catalysis Singh A, Yoder RA, Shen B, Johnston JN. Chiral proton catalysis: enantioselective Brønsted acid catalyzed additions of nitroacetic acid derivatives as glycine equivalents. J Am Chem Soc 2007;129:3466–3467.
36. For representative work, see: Chiral proton catalysis Shen B, Johnston JN. A formal enantioselective acetate Mannich reaction: the nitro functional group as a traceless agent for activation and enantiocontrol in the synthesis of β-amino acids. Org Lett 2008;10:4397–4400.
37. For representative work, see: Chiral proton catalysis Bernardi L, Fini F, Herrera RP, Ricci A, Sgarzani V. Enantioselective aza-Henry reaction using cinchona organocatalysts. Tetrahedron 2005;62:375–380.
38. For representative work, see: PTC Gomez-Bengoa E, Linden A, Lopez R, Mugica-Mendiola I, Oiarbide M, Palomo C. Asymmetric aza-Henry reaction under phase transfer catalysis: an experimental and theoretical study. J Am Chem Soc 2008;130:7955–7966.
39. For representative work, see: Brønsted acid Rueping M, Antonchick AP. Bronsted-acid-catalyzed activation of nitroalkanes: a direct enantioselective aza-Henry reaction. Org Lett 2008;10:1731–1734.
40. Vilaivan T, Bhanthumnavin W, Sritana-Anant Y. Recent advances in catalytic asymmetric addition to imines and related CN systems. Curr Org Chem 2005;9:1315–1392.
41. Ferraris D. Catalytic, asymmetric alkylation of imines Tetrahedron 2007;63:9581–9597.
42. Blay G, Hernández-Olmos V, Pedro JR. Development of new *N*,*N*-ligands for the enantioselective copper(II)-catalyzed Henry reaction. Synlett 2011;1195–2011.
43. Blay G, Hernández-Olmos V, Pedro JR. The construction of quaternary stereocenters by the Henry reaction: circumventing the usual reactivity of substituted glyoxals. Chem Eur J 2011;17:3768–3773.
44. Blay G, Hernández-Olmos V, Pedro JR. Enantioselective Henry addition of methyl 4-nitrobutyrate to aldehydes. Chiral building blocks for 2-pyrrolidinones and other derivatives. Org Lett 2010;12:3058–3061.
45. Blay G, Hernández-Olmos V, Pedro JR. Enantioselective addition of nitromethane to α-keto esters catalyzed by copper(II)-iminopyridine complexes. Org Biomol Chem 2008;6:468–476.
46. Blay G, Domingo LR, Hernández-Olmos V, Pedro JR. New highly asymmetric Henry reaction catalyzed by Cu^{II} and a C_1-symmetric aminopyridine ligand, and its application to the synthesis of miconazole. Chem Eur J 2008;14:4725–4730
47. Blay G, Hernández-Olmos V, Pedro JR. A catalytic highly enantioselective direct synthesis of 2-bromo-2-nitroalkan-1-ols through a Henry reaction. Chem Commun 2008;4840–4842.
48. Blay G, Climent E, Fernández I, Hernández-Olmos V, Pedro JR. Enantioselective Henry reaction catalyzed with copper(II)-iminopyridine complexes. Tetrahedron: Asymmetry 2007;18:1603–1612.
49. Blay G, Climent E, Fernández I, Hernández-Olmos V, Pedro JR. Modular iminopyridine ligands. Application to the enantioselective copper(II)-catalyzed Henry reaction. Tetrahedron: Asymmetry 2006;17:2046–2049.
50. Esquivias J, Gomez-Arrayas R, Carretero JC. A copper(II)-catalyzed aza-Friedel–Crafts reaction of *N*-(2-pyridyl)sulfonyl aldimines: synthesis of unsymmetrical diaryl amines and triaryl methanes. Angew Chem Int Ed 2006;45:629–633.
51. Gomez-Arrayas R, Carretero JC. Catalytic asymmetric direct Mannich reaction: a powerful tool for the synthesis of α,β-diamino acids. Chem Soc Rev 2009;38:1940–1948.
52. Gonzalez AS, Gomez-Arrayas R, Carretero JC. Copper(I)-fesulphos Lewis acid catalysts for enantioselective Mannich-type reaction of *N*-sulfonylimines. Org Lett 2006;8:2977–2980.
53. Trost BM, Marrs C. A convenient synthesis of *N*-tosylimines. J Org Chem 1991;56:6468–6470.
54. Dykhanov NN, Ryzhkova TS. Preparation of azomethine derivatives of arenesulfonamides. Vop Khim Khim Tekhnol 1973;31:23–30.
55. Hussain N, Hussain MM, Ziauddin M, Triyawatanyu P, Walsh PJ. Stereoselective vinylation of aryl *N*-(2-pyridylsulfonyl) aldimines with 1-alkenyl-1,1-heterobimetallic reagents. Org Lett 2011;13:6464–6467.
56. Sugimoto H, Nakamura S, Hattori M, Ozeki S, Shibata N, Toru T. Enantioselective nucleophilic addition to *N*-(2-pyridylsulfonyl)imines by use of dynamically induced chirality. Tetrahedron Lett 2005; 46:8941–8944.
57. Nakamura S, Sakurai Y, Nakashima H, Shibata N, Toru T. Organocatalytic enantioselective aza-Friedel–Crafts alkylation of pyrroles with *N*-(hetero-arenesulfonyl)imines. Synlett 2009;1639–1642.
58. Nakamura S, Nakashima H, Sugimoto H, Sano H, Hattori M, Shibata N, Toru T. Enantioselective C–C bond formation to sulfonylimines through use of the 2-pyridinesulfonyl group as a novel stereocontroller. Chem Eur J 2008;14;2145–2152.
59. Pearson AJ, Bruhn PR, Gouzoules F, Lee SH. Stereoselective synthesis of arylglycine derivatives using arene-manganese tricarbonyl complexes. J Chem Soc Chem Commun 1989;659–661.

60. Abbaraju S, Bhanushali M, Zhao C-G. Quinidine thiourea-catalyzed enantioselective synthesis of beta-nitrophosphonates: beneficial effects of molecular sieves. Tetrahedron 2011;67;7479–7484.
61. Palomo C, Pazos R, Oiarbide M, García JM. Catalytic enantioselective conjugate addition of nitromethane to α-hidroxy enones as surrogates of α,β-unsaturated carboxylic acids and aldehydes. Adv Synth Catal 2006; 348:1161–1164.
62. Hasegawa M, Ono F, Kanemasa S. Molecular sieves 4A work to mediate the catalytic metal enolization of nucleophile precursors: application to catalyzed enantioselective Michael addition reactions. Tetrahedron Lett 2008;49:5220–5223.
63. Kim HY, Kim S, Oh K. Orthogonal enantioselectivity approaches using homogeneous and heterogeneous catalyst systems: Friedel–Crafts alkylation of indole. Angew Chem Int Ed 2010;49:4476–4478.
64. Steinhoff BA, King AE, Stahl SS. Unexpected roles of molecular sieves in palladium-catalyzed aerobic alcohol oxidation. J Org Chem 2006;7:1861–1868.
65. Unfortunately, we were not able to obtain any aliphatic *N*-(2-pyridyl)-sulfonylimine by following the same procedure as for the synthesis of imines **9a–n**, neither following other reported procedures for the synthesis of aliphatic sulfonamides: Chemla F, Hebbe V, Normant JF. An easy synthesis of aliphatic and aromatic *N*-sulfonyl aldimines. Synthesis 2000;75–77.
66. Christensen, C, Juhl K, Jørgensen KA. Catalytic asymmetric Henry reactions: a simple approach to optically active β-nitro α-hydroxy esters. Chem Commun 2001;2222–2223.
67. Christensen C, Juhl K, Hazell RG, Jørgensen KA. Copper-catalyzed enantioselective henry reactions of α-keto esters: An easy entry to optically active β-nitro-α-hydroxy esters and β-amino-α-hydroxy esters. J Org Chem 2002;67:4875–4881.