Tetrahedron: *Asymmetry* 19 (2008) 1744–1750

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Screening of amino sulfur ferrocenes as catalysts for the enantioselective addition of diethylzinc to benzaldehyde

Guillaume Grach, Vincent Reboul *, Patrick Metzner *

Laboratoire de Chimie Moléculaire et Thio-organique, ENSICAEN, Université de Caen-Basse Normandie, CNRS, 6, Boulevard du Maréchal Juin, 14050 Caen, France

ARTICLE INFO

Article history:
Received 6 June 2008
Accepted 25 June 2008
Available online 22 July 2008

ABSTRACT

Seventeen amino-sulfoxides and sulfides incorporating a ferrocene backbone were prepared in enantiopure form and tested as ligands for the asymmetric addition of diethylzinc to benzaldehyde. They all exhibited catalytic activity. Fine tuning of substituents, the nature of the sulfur functionality, and configurations with a synergy of planar and central chiralities allowed us to reach an enantiomeric excess of 90%.

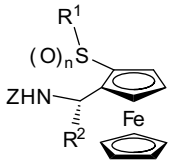
1. Introduction

Searching for a range of ligands aimed at asymmetric catalysis led us to screen 17 ferrocenes bearing *amino* and *sulfur* functionalities *ortho* to each other. These proved efficient for the addition of diethylzinc to benzaldehyde.[1,2] Herein, we report on the effect of various substituents on enantioselectivity, leading to ee's of up to 90%.

Sulfur compounds are emerging as ligands for a variety of asymmetric reactions.[3–7] The prospect of non-phosphorous molecules[8] for the coordination of transition metals, or non-oxygen substrates for diethylzinc additions, has started to bring about breakthroughs. As a result, we wished to explore N,S-ligands[3–5] of structures **2**–**11** (Figs. 1 and 3).

They exhibit

- A ferrocenyl backbone,[9–14]
- an *ortho* relationship between the two substituents,
- an affinity of the sulfur and nitrogen atoms toward zinc,
- a potential limitation of the conformational flexibility in metal complexes of **2**–**11**,
- planar chirality,
- a complementary central chirality, α to the nitrogen substituent,
- the possibility of fine tuning of the conformation and steric bulk by variation of the R^2 group,
- a choice of the Z group, to modify the acidity of the proton linked to the nitrogen atom,
- variation of the sulfur group (sulfide, sulfoxide) and substitution of R^1 at the sulfur atom.



n = 0, 1
R^1 = *t*-Bu, *p*-Tol, Ph, Me
R^2 = Me, *i*-Pr, Cy, *t*-Bu, Ph
Z = H, Ts, Boc

Figure 1. Structure of ligands **2**–**11**.

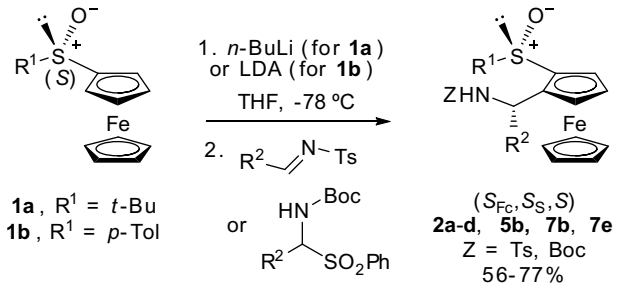
2. Synthesis of ligands

Six amino *t*-butylsulfoxides [(S_{Fc},S_S,*S*) **2a**–**d**, **5b**, and **4b** (S_{Fc},S_S,*R*), diastereomer of **2b** at carbon] were prepared in only two steps from ferrocene.[15] The sequence involves the synthesis of (*S*)-*t*-butylsulfinylferrocene **1a** by the reaction[16] of ferrocenelithium with Ellman's (*S*)-*t*-butylthio-*t*-butanethiosulfinate,[17] followed by *ortho*-lithiation[18,19] and addition to imines.[15] This was successfully applied to two *p*-tolylsulfoxides, **7b**, **7e**, starting from **1b**. Deprotection of Boc-amine **5b** with TFA provided the free amino sulfoxide **6b** in 95% yield (Scheme 1).

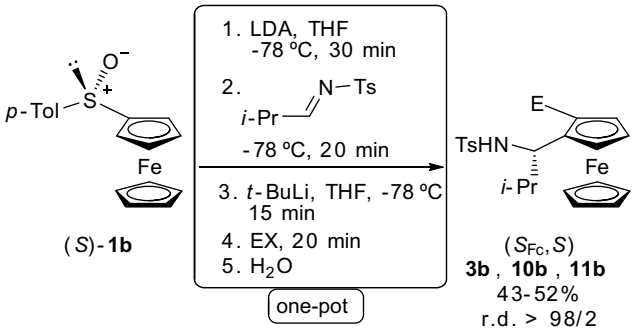
Sulfoxide **3b** (S_{Fc},R_S,*S*), diastereomer of **2b** (S_{Fc},S_S,*S*) at sulfur, was obtained[20] via a one-pot sequence: deprotonation of **1b**, the addition of the imine, displacement of the *p*-tolylsulfinyl group by *t*-butyllithium, and subsequent reaction with (R_S)-*t*-butyl-*t*-butanethiosulfinate. Substituting the latter reagent by phenyl disulfide or methyl disulfide, respectively, provided sulfides **10b** and **11b** (Scheme 2).

* Corresponding authors. Tel.: +33 2 31 45 28 84; fax: +33 02 31 45 28 77 (V.R.).
E-mail address: vincent.reboul@ensicaen.fr (V. Reboul).

0957-4166/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2008.06.031

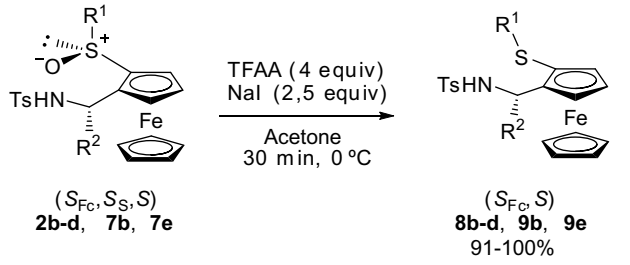


Scheme 1. Synthesis of sulfoxides **2a–d**, **5b**, **7b**, and **7e**.



Scheme 2. Synthesis of sulfoxide **3b**, and sulfides **10b** and **11b**.

Sulfides **8b–d**, **9b**, and **9e** were prepared by the reduction of the corresponding sulfoxides **2b–d**, **7b**, and **7e** by trifluoroacetic anhydride and sodium iodide (Scheme 3).[21]



Scheme 3. Synthesis of sulfides **8b–d**, **9b**, and **9e**.

We determined the structure of **8b** by X-ray crystallographic analysis thus confirming its (S_{Fc},*S*) configuration (Fig. 2).[22] We observed that both the bulky alkyl groups, *t*-butyl and isopropyl, are on the *exo* side of the ferrocene, analogous to the corresponding sulfoxide **2b**.[15]

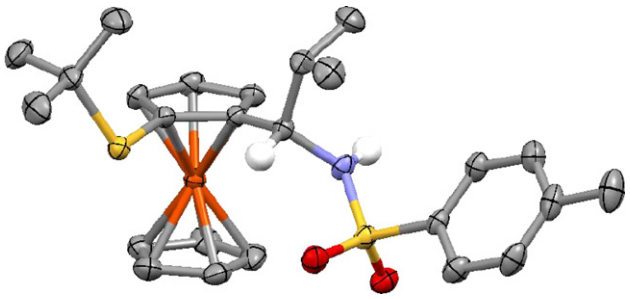
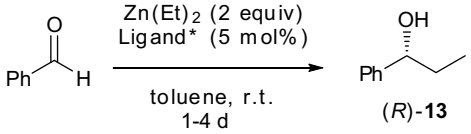


Figure 2. X-ray crystal structure of aminosulfide **8b** (one of the two subunits of the dimer). Hydrogen atoms are omitted for clarity except for C*H and NH. Selected bond lengths (Å) and torsion angles (°): C*–C_{Cp}: 1.503; C_{Cp}–S: 1.751; C*–N: 1.479; S–C_{Cp}–C_{Cp}–C*: −12.98.

The structures of the ligands are represented in Figure 3.

3. Results of diethylzinc addition

Ligands **2–12** were screened under standard conditions: reaction of benzaldehyde with 2 equiv of diethylzinc and 5 mol % ligand in anhydrous toluene at room temperature (Scheme 4). The results are summarized in Figure 4 and Table 1.



Scheme 4. Asymmetric catalysis of the diethylzinc addition to benzaldehyde.

3.1. Catalytic activity

After a reaction time of 1–3 days, we observed the complete conversion of benzaldehyde into 1-phenyl-1-propanol **13** for 10 ligands (Table 1). For sulfoxides **2d** and **7e**, and sulfides **8d** and **9e**, having R^2 = *t*-Bu or Ph, conversion ranged from 53% to 87%, demonstrating moderate activity. Therefore, all tested amino-sulfoxides and -sulfides exhibited catalytic activity, while the kinetic rate decreased with an excess of steric hindrance, critical at the R^2 position.

3.2. Asymmetric induction

Enantiomeric excesses of **13** were measured by enantioselective HPLC (Daicel AD-H column), usually on the crude product. The ee's vary to a great extent: from 1% to 90% (Table 1).

3.2.1. Effects of the R^2 group on the carbon atom and R^1 on the sulfur atom of sulfoxides

For sulfoxides of type **2**, bearing an *N*-tosyl group and a *t*-butyl on the sulfur atom, we have compared the effect of the R^2 substituent (line 1 of Fig. 4, or entries 1–4 of Table 1). With a methyl group, the ee was 57%, which increased with steric hindrance: 65% for *i*-Pr and 70% for Cy. However, with a *t*-butyl group we observed a dramatic drop to 1%.

Replacing the *t*-butyl group on the sulfinyl moiety of **2b** by a *p*-tolyl **7b** provided (entries 5 and 6 of Table 1) the same level of enantioselectivity (65%) and conversion (100%).

3.2.2. Behavior of sulfides

We then studied four sulfides, bearing an *N*-tosyl group. For R^2 = Ph **9e** or *t*-Bu **8d**, the ee's were very poor, 4% and 5%, respectively (entries 11 and 13 of Table 1). With an isopropyl group as R^2, better results were observed: starting at 27% for SPh (**10b**, entry 8 of Table 1), the ee increased to 50% with S-*p*-Tol (entry 12 of Table 1), and more significantly to 77 and 80% with S-Me and S-*t*-Bu (**11b** and **8b**, entries 7 and 9 of Table 1). The best selectivity was obtained with **8c** (entry 10 of Table 1) with the synergy of S-*t*-Bu and R^2 = Cy: 90%. The reaction time was not increased: 1 day was sufficient enough for a full conversion. In the series with a *t*-butyl on sulfur, there is a general trend toward higher ees with sulfides, relative to sulfoxides. It should be noted that the absolute sense of induction is the same.

3.2.3. Effect of the group on the nitrogen atom

We tested three ligands, **2b**, **5b**, **6b**, bearing a *t*-butylsulfinyl group, an *i*-Pr as R^2 and differing by the group on the nitrogen atom: the previous *N*-tosyl, an *N*-Boc and a free NH_2 (Fig. 5). The two last substituents afforded the same very poor induction, 12%

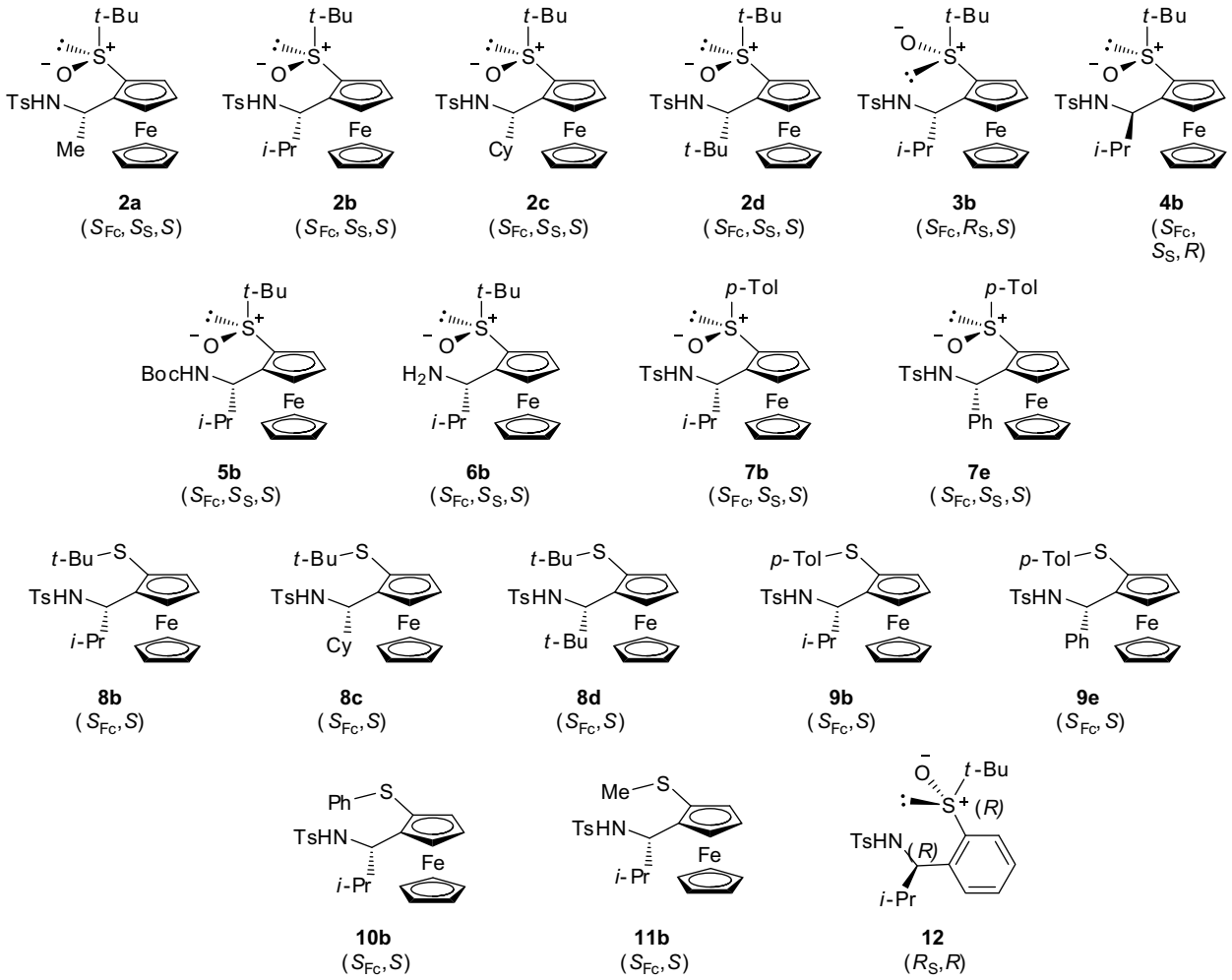


Figure 3. List of ligands **2**–**12**.

(entries 14 and 15 of Table 1), as compared to the tosyl group, which exhibited 65% ee (entry 5 of Table 1).

3.2.4. Effect of central chirality

Sulfoxides **2** and **5** bear 3 stereogenic elements and exhibit both planar and central chiralities. We have tested the influence of the central chirality with diastereomers of **2b**: (i) **3b** with an inverted configuration of the sulfinyl moiety and (ii) **4b** with inversion of the carbon stereogenic center, *alpha* to the nitrogen group (Fig. 6). In Comparison to **2b**, which afforded 65% ee, both diastereomers **3b** and **4b** lead to largely reduced selectivities: respectively, 36% ee for the configuration change at carbon and 4% at sulfur. It is amazing that the first configuration to be tested (S_{Fc},S_S,S) is the best of the three.

We also tested substrate (R_S,R) **12**, which is devoid of planar chirality. The ferrocene backbone was replaced by a benzene ring. Its preparation is very easy, as reported earlier.[23] It catalyzed the addition of diethylzinc, to give 1-phenyl-1-propanol with the opposite (*S*)-configuration, albeit in a low enantiomeric excess of 15%.

4. Mechanism and induction model

The mechanism of the reaction of benzaldehyde in the presence of aminoalcohols is largely considered[1] to involve the deprotonation of the aminoalcohol by 1 equiv of Et_2Zn, providing a cyclic chelate, which then coordinates through its zinc and oxygen atoms to the second equivalent of Et_2Zn and the aldehyde.

With our amino-sulfoxides and sulfides, analogous deprotonation provides complex **14** (Scheme 5). Complex **14** is both a chiral Lewis acid, prone to coordinate with benzaldehyde, and a Lewis base, which activates the second molecule of Et_2Zn. This can be further enhanced by the affinity of the sulfur atom toward zinc to furnish **15**, illustrated here for the most efficient ligand **8c**. Two types of stereochemical arrangements are possible. For the bicyclic type, *syn* and *anti* attacks are possible. The *syn* **15** provides the alcohol with the experimentally observed (*R*) configuration. A pseudo-cyclic chair, such as **16**, is also a plausible transition state.

5. Discussion

Screening 18 amino-sulfoxides and sulfides has demonstrated that they all exhibit catalytic activity for the addition of diethylzinc to benzaldehyde. In many cases the reaction was efficient at rt with full conversion.

The structural study has revealed that tuning the nature and size of substituents in amino sulfur ferrocenes could lead to optimization:

– For complete conversion, a variety of alkyl groups can be used as R^2, with the exception of the highly encumbered *t*-butyl

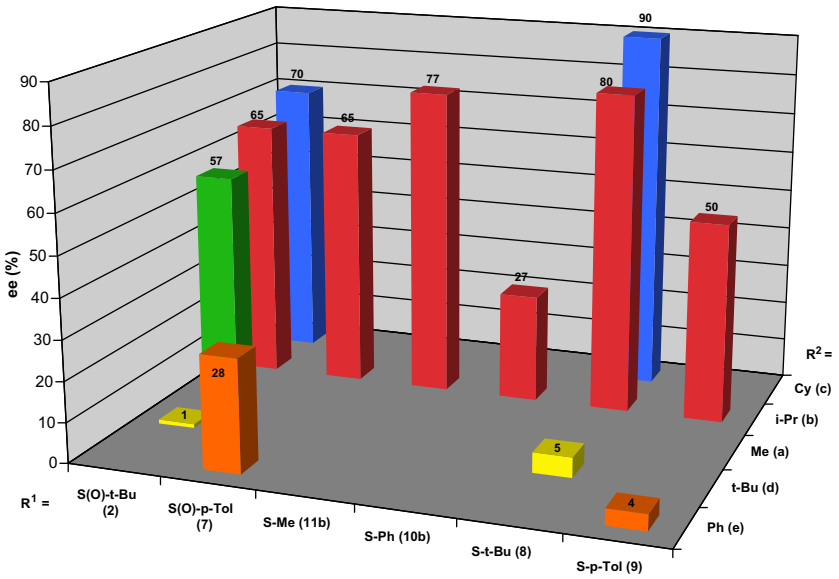


Figure 4. Enantiomeric excess of the diethylzinc addition to benzaldehyde catalyzed by *N*-tosylamino-sulfoxides **2**, **7**, and sulfides **8**–**11**.

Table 1
Diethylzinc addition to benzaldehyde catalyzed by aminosulfoxides **2**–**7**, **12**, and sulfides **8**–**11**

Entry	Ligand (5%)	Configuration	Sulfoxide or sulfide	R^1	Z	R^2	Reaction time (d)	% Conversion (yield)	ee[a] (*R*) (%)
1	**2a**	(S_{Fc},S_S,*S*)	Sulfoxide	*t*-Bu	Ts	Me	3	100	57
2	**2b**	(S_{Fc},S_S,*S*)	Sulfoxide	*t*-Bu	Ts	*i*-Pr	1	100 (82)	65
3	**2c**	(S_{Fc},S_S,*S*)	Sulfoxide	*t*-Bu	Ts	Cy	1	100	70
4	**2d**	(S_{Fc},S_S,*S*)	Sulfoxide	*t*-Bu	Ts	*t*-Bu	4	53	1
5	**7b**	(S_{Fc},S_S,*S*)	Sulfoxide	*p*-Tol	Ts	*i*-Pr	1	100	65
6	**7e**	(S_{Fc},S_S,*S*)	Sulfoxide	*p*-Tol	Ts	Ph	4	89	28
7	**11b**	(S_{Fc},*S*)	Sulfide	Me	Ts	*i*-Pr	1	100	77
8	**10b**	(S_{Fc},*S*)	Sulfide	Ph	Ts	*i*-Pr	2.5	86	27
9	**8b**	(S_{Fc},*S*)	Sulfide	*t*-Bu	Ts	*i*-Pr	1	100 (84)	80
10	**8c**	(S_{Fc},*S*)	Sulfide	*t*-Bu	Ts	Cy	1	100 (79)	90
11	**8d**	(S_{Fc},*S*)	Sulfide	*t*-Bu	Ts	*t*-Bu	4	61	5
12	**9b**	(S_{Fc},*S*)	Sulfide	*p*-Tol	Ts	*i*-Pr	1.5	100	50
13	**9e**	(S_{Fc},*S*)	Sulfide	*p*-Tol	Ts	Ph	3	87	4
14	**5b**	(S_{Fc},S_S,*S*)	Sulfoxide	*t*-Bu	Boc	*i*-Pr	6	70	12
15	**5b**	(S_{Fc},S_S,*S*)	Sulfoxide	*t*-Bu	H	*i*-Pr	4	90	12
16	**8c** (0.5 mol %)	(S_{Fc},*S*)	Sulfide	*t*-Bu	Ts	Cy	2	95	69
17	**8c** (10 mol %)	(S_{Fc},*S*)	Sulfide	*t*-Bu	Ts	Cy	1	100	88
18	**3b**	(S_{Fc},R_S,*S*)	Sulfoxide	*t*-Bu	Ts	*i*-Pr	3.5	61	4
19	**4b**	(S_{Fc},S_S,*R*)	Sulfoxide	*t*-Bu	Ts	*i*-Pr	4	88	36
20	**12**	(R_S,*R*)	Sulfoxide	*t*-Bu	Ts	*i*-Pr	1.5	100	15 (*S*)

[a] Determined by HPLC on a chiral stationary phase (Daicel AD-H column).

group, or a phenyl group. The *N*-tosyl group is preferable to *N*-Boc[24] and NH_2.

– The enantiomeric excess increases with the size of R^2 with a maximum reached with cyclohexyl (racemic reaction with *t*-Bu. We suppose, in this case, a switch of conformation with the *t*-butyl group of the sulfoxide being directed toward the iron atom, as observed[15] in the X-ray analysis of **2d**). The best stereoselectivity is achieved with an *N*-tosyl group and drops dramatically with *N*-Boc and NH_2. Hydrogen bonding could also explain this result.

– Central and planar chiralities can provide synergy. The best configuration combination is (S_{Fc},S_S,*S*).

– Another piece of information comes from the comparison between amino-sulfoxides and sulfides. In the *N*-tosyl series, sulfides provide higher selectivities.

– For the group on the sulfur atom, the *t*-butyl series lead to better results than the *p*-tolyl one.

Finally, this study has shown that an ee of 90% could be reached with sulfide **8c**, bearing R^1 = *t*-Bu, Z = Ts, and R^2 = Cy. It is at its best with a 5 mol % loading (entries 1, 16, and 17).

These sulfur–nitrogen ligands can be compared with literature precedents. In terms of the sulfur group, studies[3–5] have mainly dealt with thiols, disulfides, thiolates, sulfides,[1] and more rarely sulfoxides.[6] The ferrocene nucleus has been advantageously used in the sulfur series.[7,13,19] In terms of asymmetric reaction types, N,S-ligands have been used to catalyze mainly palladium allylation, hydrogenation, 1,4-addition, and cycloaddition. A few reports have dealt with the catalysis of diethylzinc to an aldehyde[16,25–29]

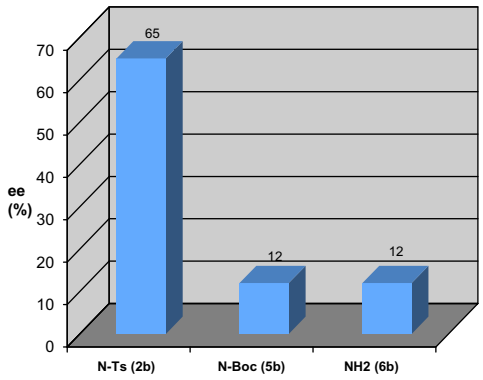


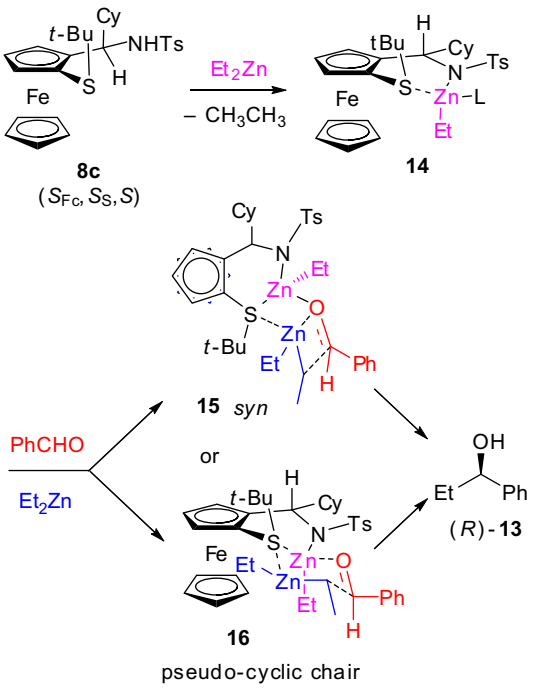
Figure 5. Enantiomeric excesses with various substituents on *the nitrogen atom*.

Precedents with aminosulfoxides are limited to a single report by Carretero et al.[16,28] These authors observed a small difference in behavior between sulfoxides and sulfides, which led them to speculate on the absence of coordination of the metal to sulfur and intervention of a monocoordinated amino species. With our ligands, there is a significant difference in favor of the sulfide moiety.

In terms of structure, we were able to confirm that the ferrocene moiety is a convenient scaffold for asymmetric synthesis, using efficient *ortho*-substituted structures, with the addition of complementary stereogenic carbon and variation of several substituents.

6. Conclusion

All 18 aminosulfur compounds catalyzed the addition of diethylzinc to benzaldehyde. Screening various structural parameters allowed us to identify an aminosulfide with suitable substitution and configuration leading to 90% ee. The ferrocene scaffold plays a significant role in terms of rigidity and chirality. The use of an amine bearing an electron withdrawing substituent for the formation of a complex with the first equivalent of Et_2Zn, and of a sulfide moiety as the Lewis base for coordination to the second Et_2Zn are key factors for the success of this reaction. Further applications of ferrocene aminosulfides and sulfoxides are anticipated in the near future.



Scheme 5. Proposed models for the attack of Et_2Zn onto benzaldehyde catalyzed by aminosulfide **8c**.

7. Experimental

7.1. General methods

All non-aqueous reactions were carried out under an atmosphere of dry nitrogen or argon in flame- or oven-dried glassware with magnetic stirring. All liquid reagents were transferred via oven-dried syringes. All reagents and solvents are commercially available and used without further purification, unless otherwise

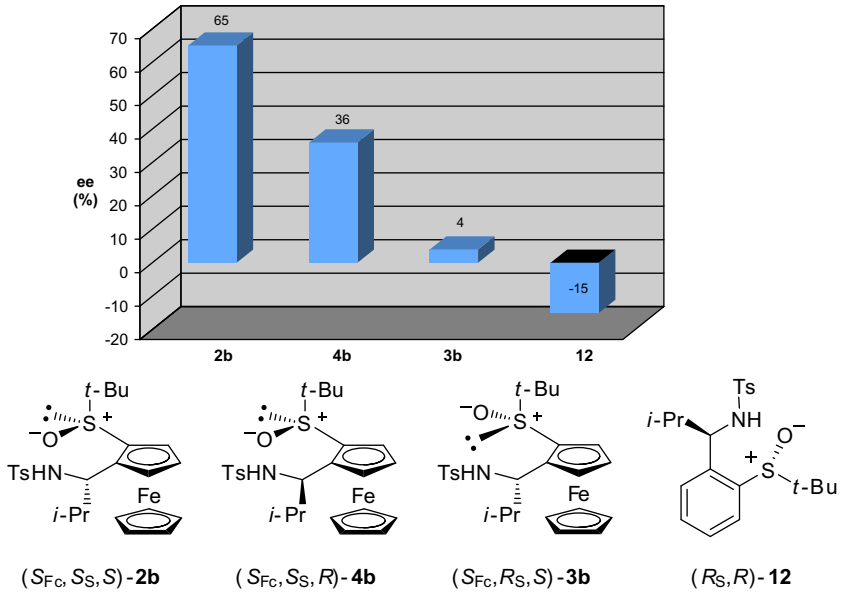


Figure 6. Effect of configurations and chiralities on selectivity.

noted. Dry solvents were obtained with a PURESOLV™ apparatus developed by Innovative Technology Inc. THF, Toluene, CH_2Cl_2, MeCN, and ether were passed through activated alumina columns under nitrogen pressure. Toluene was also passed through a copper column to remove traces of water. This system provided a solvent with 5–15 ppm of water measured with a Coulometer (Karl Fisher method). Lithium bases were purchased from Aldrich, and concentrations were checked before experiments by titration with benzylbenzamide. The end point was noted by the characteristic dianion blue color.

Thin layer chromatography (TLC) was performed on Silica Gel 60 F_{254} (Merck), and the plates were visualized with UV light (254 nm) or a potassium permanganate solution (1 g with 2 g of K_2CO_3 in 200 mL of water). Chromatographic purification of compounds was achieved with Merck Si 60 Silica Gel (40–63 μm). High pressure liquid chromatography (HPLC) was performed on a Waters apparatus with a diode array M996 detector. *t*-Butylbenzene was used as t_0. UV absorption maxima were reported in nanometers (nm).

Known compound structures were assigned by comparison with the literature spectroscopic data. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker DPX 250 or on a Bruker DRX 400. Data appear in the following order: chemical shift in ppm, multiplicity (s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet), number of protons, coupling constant *J*, and assignment. TMS was the internal standard for the $CDCl_3$ solutions. Exact mass spectra were obtained with a Waters Q-Tof Micro apparatus (LC/MS) with Xterra MS column. Melting points are determined using an Electrothermal IA9000 capillary apparatus.

Amino *t*-butylsulfoxides and amino *p*-tolylsulfoxides were prepared according to the literature.[15,20] Benzene aminosulfoxide **12** was reported previously.[23]

7.2. (S_{Fc},S_S,*S*)-1-[2-(*t*-Butylsulfinyl)ferrocenyl]-2-methylpropylamine 6b

To a solution of **5b** (50 mg, 0.11 mmol) in CH_2Cl_2 (1 mL) under nitrogen, TFA (250 μL, 3.37 mmol) was added and the mixture was stirred for 1 h at room temperature. Excess TFA and CH_2Cl_2 were removed under vacuum. The resulting yellow brown oil was neutralized by sat. $NaHCO_3$. The product was extracted with CH_2Cl_2 (3 × 2 mL), dried over $MgSO_4$, and evaporated. Compound **6b** was obtained as a yellow brown solid (35 mg, 95%). Mp 123 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.49–4.50 (m, 1H, Cp), 4.41 (s, 5H, Cp), 4.32–4.35 (m, 2H, Cp), 4.10 (d, J = 8.0 Hz, CH–N), 2.10 (br, 2H, NH_2), 1.88–1.94 (m, 1H, CH of *i*-Pr), 1.21 (s, 9H, *t*-Bu-SO), 0.97 (d, 3H, J = 8.0 Hz, Me of *i*-Pr), 0.92 (d, 3H, J = 8.0 Hz, Me of *i*-Pr). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 82.6, 71.1, 69.3, 68.8, 56.9 (C_{quat} *t*-Bu), 52.0 (CH–N), 33.7 (CH of *i*-Pr), 24.1 (3C, C *t*-Bu), 21.8 (Me of *i*-Pr), 16.8 (Me of *i*-Pr). HRMS (ESI) calcd for $C_{18}H_{28}FeNOS$ (MH^+): 362.1242, found: 362.1248.

7.3. (S_{Fc},*S*)-*N*-*p*-Tosyl-1-[2-(methylsulfanyl)ferrocenyl]-2-methylpropylamine 11b

According to the typical procedure of Ref. 20 the reaction was performed on 100 mg (0.308 mmol) of (S_S)-*p*-tolylsulfinylferrocene, 84 mg (0.370 mmol) of 4-methyl-*N*-(isopropylmethylene)benzenesulfonamide, and 61 μL (65 mg, 0.678 mmol) of methyl disulfide. The mixture was stirred for 20 min at −78 °C. The crude product was purified by column chromatography, using pentane/ethyl acetate (9/1) as eluent, to afford **11b** as an orange oil (45%, 63 mg). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89 (d, 2H, J = 8.0 Hz, Ar), 7.35 (d, 2H, J = 8.0 Hz, Ar), 5.11 (d, 1H, J = 4.8 Hz, C–NH), 4.44 (t, 1H, J = 4.8 Hz, CH–N), 4.38–4.40 (m, 1H, Cp), 4.18–4.20 (m, 1H, Cp), 4.14 (s, 5H, Cp), 4.08–4.10 (m, 1H, Cp), 2.45 (s, 3H, Me of Ts), 2.21 (s, 3H, Me-S), 2.04–2.09 (m, 1H, CH of *i*-Pr), 0.65 (d, 3H, J = 6.8 Hz, Me of *i*-Pr), 0.60 (d, 3H, J = 6.8 Hz, Me of *i*-Pr). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 143.3 (Ar), 138.5 (Ar), 129.6 (2C, Ar), 127.1 (2C, Ar), 90.2 (Cp), 83.9 (Cp), 71.5 (Cp), 70.5 (5C, Cp), 67.6 (Cp), 65.7 (Cp), 56.6 (CH–N), 32.5 (CH of *i*-Pr), 21.6 (Me of Ts), 20.4 (Me-S), 18.4 (Me of *i*-Pr), 17.1 (Me of *i*-Pr). HRMS (ESI) calcd for $C_{22}H_{28}FeNO_2S_2$ (MH^+): 458.0911, found: 458.0899.

7.4. General procedure for the reduction of sulfoxides 2 into sulfides 8

To a cold solution (0 °C) of sulfoxide (1 equiv) and sodium iodide (2.5 equiv) in dry acetone (1 mL for 0.25 mmol of sulfoxide) under nitrogen, a solution of TFAA (4 equiv) in dry acetone (1 mL for 0.25 mmol of sulfoxide) was slowly added. After stirring for 30 min at 0 °C, the reaction mixture was concentrated under reduced pressure. Water (4 mL for 0.25 mmol of sulfoxide) was added and the mixture was extracted with $CHCl_3$ (3 × 5 mL for 0.25 mmol of sulfoxide). The combined organic layers were washed with a 10% aqueous solution of $Na_2S_2O_3$, dried over $MgSO_4$, and then evaporated to dryness.

7.5. (S_{Fc},*S*)-*N*-Tosyl-1-[2-(*t*-butylsulfanyl)ferrocenyl]-2-methylpropylamine 8b

The reaction was performed on 200 mg (0.39 mmol) of (S_{Fc},S_S,*S*)-**2b**, 146 mg (0.98 mmol) of NaI, and 328 mg (1.56 mmol) of TFAA. Compound **8b** was obtained as a yellow solid (94%, 183 mg) without further purification. Mp 140–142 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (d, 2H, J = 8.4 Hz, Ar), 7.32 (d, 2H, J = 8.4 Hz, Ar), 5.02 (d, 1H, J = 5.6 Hz, NH), 4.59 (m, 1H, Cp), 4.35 (m, 1H, CH–N), 4.23–4.33 (m, 7H, Cp), 2.43 (s, 3H, Me), 1.98–2.03 (m, 1H, CH of *i*-Pr), 1.19 (s, 9H, *t*-Bu), 0.71 (t, 6H, J = 6.4 Hz, Me of *i*-Pr). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 143.3 (Ar), 139.5 (Ar), 129.9 (2C, Ar), 127.7 (2C, Ar), 94.9 (Cp), 78.4 (Cp), 75.7 (Cp), 71.3 (5C, Cp), 68.4 (Cp), 66.5 (Cp), 56.7 (C_{quat} *t*-Bu), 46.5 (CH–N), 33.9 (CH of *i*-Pr), 31.9 (3C, C *t*-Bu), 21.9 (Me of Ts), 20.4 (Me of *i*-Pr), 17.3 (Me of *i*-Pr). HRMS (ESI) calcd for $C_{25}H_{33}FeNO_2S_2Na$ (MNa^+): 522,1200, found: 522.1176.

7.6. (S_{Fc},*S*)-*N*-Tosyl-1-[2-(*t*-butylsulfanyl)ferrocenyl]-1-cyclohexylmethylamine 8c

The reaction was performed on 150 mg (0.27 mmol) of (S_{Fc},S_S,*S*)-**2c**, 102 mg (0.67 mmol) of NaI, and 227 mg (1.08 mmol) of TFAA. The crude product was purified by column chromatography, using *n*-dichloromethane/pentane (7/3) as eluent, to afford **8c** as a yellow solid (100%, 146 mg). Mp 168 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.88 (d, 2H, J = 8.0 Hz, Ar), 7.33 (d, 2H, J = 8.0 Hz, Ar), 5.01 (d, 1H, J = 6.4 Hz, NH), 4.53 (m, 1H, Cp), 4.35 (dd, 1H, J = 6.4, J = 3.3 Hz, CH–N), 4.24 (m, 1H, Cp), 4.15 (s, 5H, Cp), 4.14–4.16 (m, 1H, Cp), 2.42 (s, 3H, Me), 1.49–1.59 (m, 5H, Cy), 1.21 (s, 9H, *t*-Bu), 0.75–1 (m, 6H, Cy). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 143.3 (Ar), 139.6 (Ar), 129.8 (2C, Ar), 127.7 (2C, Ar), 95.0 (Cp), 78.1 (Cp), 75.6 (Cp), 71.1 (5C, Cp), 68.2 (Cp), 66.4 (Cp), 56.5 (CH–N), 46.4 (C_{quat} *t*-Bu), 44.5 (Cy), 31.9 (3C, C *t*-Bu), 31.0 (Cy), 27.8 (Cy), 26.9 (Cy), 26.6 (Cy), 26.5 (Cy), 21.9 (Me of Ts). HRMS (ESI) calcd for $C_{28}H_{37}FeNO_2S_2Na$ (MNa^+): 562.1513, found: 562.1508.

7.7. (S_{Fc},*S*)-*N*-Tosyl-1-[2-(*t*-butylsulfanyl)ferrocenyl]-2,2-dimethylpropylamine 8d

The reaction was performed on 50 mg (0.10 mmol) of (S_{Fc},S_S,*S*)-**2d**, 36 mg (0.24 mmol) of NaI, and 80 mg (0.38 mmol) of TFAA. Compound **8d** was obtained as a yellow solid (91%, 45 mg) without

further purification. Mp 115–118 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.88 (d, 2H, J = 8.4 Hz, Ar), 7.31 (d, 2H, J = 8.3 Hz, Ar), 5.23 (d, 1H, J = 6.0 Hz, NH), 4.77 (br, 1H, Cp), 4.27–4.30 (m, 8H, Cp and CH–N), 2.43 (s, 3H, Me), 1.29 (s, 9H, *t*-Bu-S), 0.72 (s, 9H, *t*-Bu-C). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 143.2 (Ar), 139.9 (Ar), 129.8 (2C, Ar), 127.8 (2C, Ar), 95.2 (Cp), 73.6 (Cp), 71.7 (5C, Cp), 71.4 (Cp), 67.9 (Cp), 65.4 (Cp), 59.6 (C_{quat} *t*-Bu-S), 46.6 (CH–N), 36.8 (C_{quat} *t*-Bu-CH), 32.3 (3C, *t*-Bu-CH), 28.2 (3C, *t*-Bu-SO), 21.9 (Me of Ts). HRMS (ESI) calcd for $C_{26}H_{35}FeNO_2S_2Na$ (MNa^+): 536.1356, found: 536.1363.

7.8. (S_{Fc},S)-*N*-Tosyl-1-[2-(*p*-tolylsulfanyl)ferrocenyl-2-methylpropylamine 9b

The reaction was performed on 150 mg (0.27 mmol) of (S_{Fc},S_S,S)-**7b**, 102 mg (0.68 mmol) of NaI, and 229 mg (1.09 mmol) of TFAA. The crude product was purified by column chromatography, using *n*-dichloromethane/pentane (7/3) as eluent, to afford **9b** as a yellow solid (90%, 132 mg). Mp 155 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (d, 2H, J = 8.4 Hz, Ar), 7.34 (d, 2H, J = 7.6 Hz, Ar), 6.91–6.95 (m, 4H, Ar), 4.90 (d, 1H, J = 5.6 Hz, C–NH), 4.55–4.56 (m, 1H, Cp), 4.52 (dd, 1H, J = 6.0 Hz, J = 3.6 Hz, CH–N), 4.35–4.36 (m, 1H, Cp), 4.25 (s, 6H, Cp), 2.45 (s, 3H, Me), 2.24 (s, 3H, Me), 1.75–1.81 (m, 1H, CH of *i*-Pr), 0.51 (d, 3H, J = 6.8 Hz, Me of *i*-Pr), 0.31 (d, 3H, J = 6.8 Hz, Me of *i*-Pr). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 143.6 (Ar), 139.2 (Ar), 136.4 (Ar), 135.2 (Ar), 130.0 (2C, Ar), 129.7 (2C, Ar), 127.5 (2C, Ar), 126.6 (2C, Ar), 93.1 (Cp), 76.1 (Cp), 73.6 (Cp), 71.3 (5C, Cp), 68.8 (Cp), 57.5 (CH–N), 33.1 (CH of *i*-Pr), 22.0 (Me), 21.3 (Me), 18.5 (Me of *i*-Pr), 17.6 (Me of *i*-Pr). HRMS (ESI) calcd for $C_{28}H_{31}FeNO_2S_2Na$ (MNa^+): 556.1043, found: 556.1036.

7.9. (S_{Fc},S)-*N*-Tosyl-1-[2-(*p*-tolylsulfanyl)ferrocenyl]-1-phenylmethylamine 9e

The reaction was performed on 40 mg (0.069 mmol) of (S_{Fc},S_S,S)-**7e**, 26 mg (0.173 mmol) of NaI, and 58 mg (0.276 mmol) of TFAA. The crude product was purified by column chromatography, using *n*-dichloromethane/pentane (7/3) as eluent, to afford **9e** as a yellow solid (90%, 35 mg). Mp decomposition over 100 °C. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.46 (d, 2H, J = 8.3 Hz, Ar of Ts), 7.04 (d, 2H, J = 8.1 Hz, Ar of Ts), 6.74–6.89 (m, 5H, Ar), 6.69 (d, 2H, J = 8.1 Hz, Ar of Ts), 6.43 (d, 2H, J = 8.2 Hz, Ar of Ts), 5.55 (d, 1H, J = 3.9 Hz, NH), 4.77 (d, 1H, J = 3.9 Hz, CH–N), 4.40–4.42 (m, 1H, Cp), 4.36–4.38 (m, 1H, Cp), 4.334 (s, 5H, Cp), 4.29–4.31 (m, 1H, Cp), 2.32 (s, 3H, Me), 2.16 (s, 3H, Me). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 143.1 (Ar), 139.9 (Ar), 137.2 (Ar), 135.5 (Ar), 134.5 (Ar), 129.3 (2C, Ar), 129.1 (2C, Ar), 127.5 (2C, Ar), 127.8 (2C, Ar), 127.4 (2C, Ar), 127.4 (2C, Ar), 126.9 (Ar), 125.8 (2C, Ar), 95.2(Cp), 77.4 (Cp), 75.9 (Cp), 70.8 (5C, Cp), 69.1 (Cp), 66.8 (Cp), 56.1 (CH–N), 21.6 (Me), 20.9 (Me). HRMS (ESI) calcd for $C_{31}H_{29}FeNO_2S_2Na$ (MNa^+): 590.0887, found: 590.0874.

7.10. General procedure for the enantioselective addition of diethylzinc to benzaldehyde

To a solution of the chosen ligands **2**–**12** (5 mol %, 0.02 mmol) in dry toluene (1 mL) at room temperature under nitrogen was added diethylzinc (0.8 mL, 1 M in hexane, 0.8 mmol). After stirring for 30 min, benzaldehyde (43 mg, 0.4 mmol) was added and the reaction mixture was stirred at room temperature for 1 to 4 days (the disappearance of the aldehyde was monitored by TLC). The reaction mixture was quenched with a solution of HCl (3 M, 2 mL), and extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$. Solvents were removed, and the crude alcohol **13** was analyzed by HPLC. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.19–7.51 (m, 5H, Ar), 4,60 (t, 1H, J = 6.9 Hz, CH–O), 2.90 (s, 1H, OH), 1.78–1.91 (m, 2H, CH_2), 1.00 (t, J = 7.0 Hz, Me). HPLC (Daicel OD-H column) 250 × 4.6 (L × I.D.) 5 μm, 98% *n*-heptane: 2% porpoan-2-ol at 1 mL min^{-1}, 207 nm, 15 °C. t_R = 9.98 min (*R*), t_R = 12.68 min (*S*).

Acknowledgments

We thank the 'PunchOrga' Network, now 'Crunch' ('Centre de Recherche Universitaire Normand de Chimie'), the 'Région Basse-Normandie', the 'Ministère de la Recherche', CNRS (Centre National de la Recherche Scientifique), and the European Union (FEDER funding) for financial support, and Jean-François Lohier (LCMT) for the X-ray diffraction analysis.

References

1. Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757–824.
2. Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49–69.
3. Mellah, M.; Voituriez, A.; Schulz, E. *Chem. Rev.* **2007**, *107*, 5133–5209.
4. Pellissier, H. *Tetrahedron* **2006**, *63*, 1297–1330.
5. Masdeu-Bultó, A. M.; Diégueza, M.; Martin, E.; Gómez, M. *Coordin. Chem. Rev.* **2003**, *242*, 159–201.
6. Fernández, I.; Khiar, N. *Chem. Rev.* **2003**, *103*, 3651–3706.
7. Bonini, B. F.; Fochi, M.; Ricci, A. *Synlett* **2007**, 360–373.
8. de Vries, J. G.; de Vries, A. H. M. *Eur. J. Org. Chem.* **2003**, 799–811.
9. Atkinson, R. C. J.; Gibson, V. C.; Long, N. J. *Chem. Soc. Rev.* **2004**, *33*, 313–328.
10. Dai, L. X.; Tu, T.; You, S. L.; Deng, W. P.; Hou, X. L. *Acc. Chem. Res.* **2003**, *36*, 659–667.
11. Colacot, T. J. *Chem. Rev.* **2003**, *103*, 3101–3118.
12. Richards, C. J.; Locke, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2377–2407.
13. Arrayás, R. G.; Adrio, J.; Carretero, J. C. *Angew. Chem., Int. Ed.* **1998**, *45*, 7674–7715.
14. Togni, A. *Angew. Chem., Int. Ed.* **1996**, *35*, 1475–1477.
15. Grach, G.; Sopkova-de Oliveira Santos, J.; Lohier, J.-F.; Mojovic, L.; Plé, N.; Turck, A.; Reboul, V.; Metzner, P. *J. Org. Chem.* **2006**, *71*, 9572–9579.
16. Priego, J.; Mancheño, O. G.; Cabrera, S.; Carretero, J. C. *J. Org. Chem.* **2002**, *67*, 1346–1353.
17. Weix, D. J.; Ellman, J. A. *Org. Lett.* **2003**, *5*, 1317–1320.
18. Rebière, F.; Riant, O.; Ricard, L.; Kagan, H. B. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 568–570.
19. Ferber, B.; Kagan, H. B. *Adv. Synth. Catal.* **2007**, *349*, 493–507.
20. Grach, G.; Lohier, J.-F.; Sopkova-de Oliveira Santos, J.; Reboul, V.; Metzner, P. *Chem. Commun.* **2007**, 4875–4877.
21. Drabowicz, J.; Oae, S. *Synthesis* **1977**, 404–405.
22. Crystallographic data for the structural analysis of **8b** have been deposited with the Cambridge Crystallographic Data Centre (CCDC 690393).
23. Le Fur, N.; Mojovic, L.; Plé, N.; Turck, A.; Reboul, V.; Metzner, P. *J. Org. Chem.* **2006**, *71*, 2609–2616.
24. Boaz, N. W.; Ponasik, J. A.; Large, S. E.; Debenham, S. D. *Tetrahedron: Asymmetry* **2004**, *15*, 2151–2154.
25. Hof, R. P.; Poelert, M. A.; Peper, N. C. M. W.; Kellogg, R. M. *Tetrahedron: Asymmetry* **1994**, *5*, 31–34.
26. Anderson, J. C.; Harding, M. *Chem. Commun.* **1998**, 393–394.
27. Braga, A. L.; Appelt, H. R.; Schneider, P. H.; Silveira, C. C.; Wessjohann, L. A. *Tetrahedron: Asymmetry* **1999**, *10*, 1733–1738.
28. Priego, J.; Mancheño, O. G.; Cabrera, S.; Carretero, J. C. *Chem. Commun.* **2001**, 2026–2027.
29. Bonini, B. F.; Fochi, M.; Comes-Franchini, M.; Ricci, A.; Thijs, L.; Zwanenburg, B. *Tetrahedron: Asymmetry* **2003**, *14*, 3321–3327.