Preparation and Evaluation of *N*-Sulfinyl Dienophiles for Asymmetric Hetero-Diels-Alder Reactions

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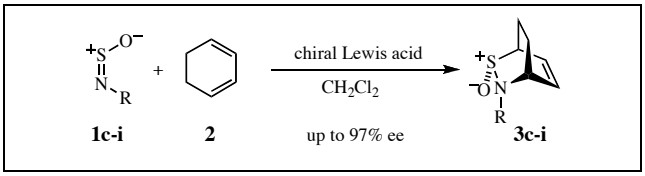

A series of *N*-sulfinyl dienophiles **1c-i** has been screened in asymmetric hetero-Diels-Alder reactions using chiral bis(oxazoline)copper(II) and –zinc(II) triflates. The survey pointed out *N*-sulfine **1c** (R = P(=O)(OPh)$_2$) as the most promising *N*-sulfine regarding yield and stereoselectivity (up to 97% ee). The relative configurations, and in one case the absolute configuration, of the HDA adducts were established by X-ray analysis.

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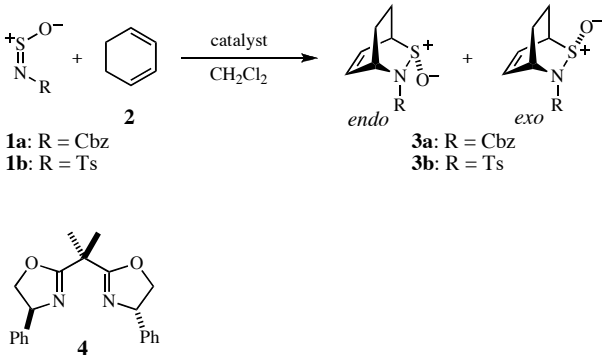
INTRODUCTION

The Diels-Alder (DA) and hetero-Diels-Alder (HDA) reactions constitute an extremely useful set of reactions, particularly for stereoselective synthesis. We are currently studying the asymmetric HDA reaction using *N*-sulfinyl dienophiles **1** as reagents for stereoselective introduction of nitrogen into organic compounds [1]. This reaction affords 1,2-thiazine 1-oxides, which can be further transformed into synthetically useful derivatives, *e.g.* homoallylic amines and vicinal amino alcohols, by well established techniques [2].

A series of chiral Lewis acids have previously been tested as promoters for the stereoselective HDA reactions of *N*-sulfinyl dienophiles **1a** and **1b** with 1,3-cyclohexadiene (**2**) (Scheme 1) [1].

Scheme 1



HDA test reactions

The catalyst survey pointed out **4**-Cu(OTf)$_2$ and **4**-Zn(OTf)$_2$ as the most suitable catalysts regarding yields and stereoselectivities (63 – 85% yield, 92 – 98% ee) [1a,1b]. Unfortunately, reactions run with 10 mol % of the chiral Lewis acid gave poor yields and selectivities. However, in combination with trimethylsilyl trifluoromethanesulfonate (TMSOTf, 100 mol %), high yields (68 – 86%) and enantioselectivities (97 – 98% ee) were obtained.

HDA reactions with acyclic dienes were in general less successful under the catalytic conditions [1a]. For Ts sulfine **1b**, a pronounced competitive uncatalyzed HDA reaction reduced the impact of the catalyst. For Cbz sulfine **1a** the modest results (30 – 60% ee) were comparable to the results of reactions promoted by stoichiometric amounts of **4**-Cu(OTf)$_2$. The disturbing uncatalyzed HDA reaction of Ts sulfine **1b**, the low selectivity observed for **1a** in the reactions with acyclic dienes, and the general need of TMSOTf as an additive in the catalytic system prompted us to seek more suitable *N*-sulfines. Thus, a survey of the *N*-sulfines **1c** – **1i** was undertaken (Scheme 2).

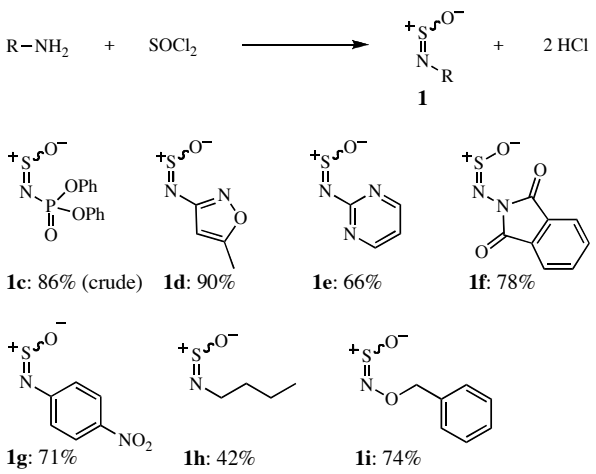
The optimum *N*-sulfinyl dienophile for the asymmetric HDA reaction should (i) be moderately reactive in the uncatalysed reaction, (ii) engage in a bidentate coordination to the chiral Lewis acid, restricting the conformational freedom of the complex and thereby induce high enantiomeric excess in the HDA adduct, and (iii) release from the Lewis acid immediately after the HDA product is formed. In addition, the R group at N (Scheme 2) should be easily cleaved. *N*-Sulfines **1c** – **1f** were chosen since they were assumed to form a bidentate coordination to the tested Lewis acids. The *p*-nitrophenyl sulfine **1g** was expected to be less reactive compared to **1c** – **1f**, and was therefore included. *N*-Sulfines **1h** and **1i** with the electron donating R groups *n*-Bu and BnO were

selected to elucidate the scope and limitations of the asymmetric HDA reaction.

RESULTS AND DISCUSSION

The *N*-sulfinyl compounds **1c** – **1i** were in general prepared by treating the respective amino precursor with thionyl chloride, using ether or benzene as solvent. Occasionally pyridine or triethyl amine was added as base in accordance with literature procedures (Scheme 2) [3-6].

Scheme 2



Preparation of *N*-sulfinyl dienophiles **1c-i**

Since *N*-sulfines **1** in general, are known to be highly reactive towards nucleophilic attack on the electropositive sulfur atom and moisture sensitive (returning back to the amino precursor), purification of the crude product was either performed by distillation (high vacuum) or crystallization. The products were either stored neat or as 1.0 – 2.5 *M* solutions in dry dichloromethane in sealed flasks in the freezer (-20 ºC). Since we were unable to purify *N*-sulfinyl **1c** the crude product was used as a stock solution in dry dichloromethane.

The *N*-sulfinyl compounds may adopt *E* and *Z* configurations. Structure analyses in the solid or gaseous state have revealed that *N*–sulfines generally have a *Z*-configuration, while the configuration in solution is more uncertain [6,7]. The X-ray of the new *N*-sulfine **1f** with *Z*-configuration (shown in Figure 1) fits with the general trend [8].

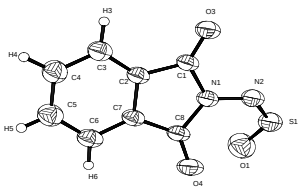


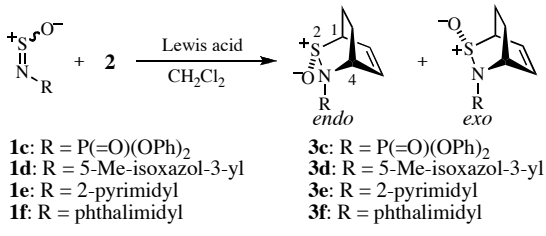
Figure 1. X-ray crystal structure of *N*-sulfinyl **1f** [8].

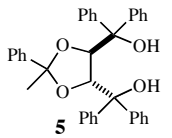
The results of the asymmetric HDA reaction of *N*-sulfines **1c** – **1f** with 1,3-cyclohexadiene (**2**) promoted either by **4**-$Cu(OTf)_2$, **4**-$Zn(OTf)_2$) or **5**-$TiCl_2$ (Scheme 3) are presented in Table 1. The survey pointed out **1c** as the most promising *N*-sulfine regarding yield, diastereomeric and enantiomeric excess in the **4**-$Zn(OTf)_2$ promoted reaction at -75 ºC (entry 4: 73% yield, *endo*/*exo* > 90%, 95% ee). Unfortunately, a distinct drop in ee (45% ee, entry 5) was observed when the reaction was run with 10 mol % of the catalyst. In combination with TMSOTf (100 mol %), the enantiomeric excess was only slightly improved (60% ee, entry 6). However, **4**-$Cu(OTf)_2$ (10 mol %) and TMSOTf (100 mol %) appeared to be the optimum combination and gave *endo*-**3c** in 51% yield and 97% ee (entry 7).

Attempts to apply *N*-sulfinyl dienophiles **1e** and **1f** with either **4**-$Cu(OTf)_2$ or **4**-$Zn(OTf)_2$ failed to give any HDA adduct at all. For **1e**, the HDA reaction mediated by the Lewis acid **5**-$TiCl_2$ gave *endo*-**3e** in 45% yield and 24% ee (entry 13). *N*-Sulfine **1f** failed also with **5**-$TiCl_2$ as promoter (entry 15).

Several attempts have been made at the HDA reactions of *N*-sulfines **1g**, **1h** and **1i** with 1,3-cyclohexadiene (**2**) under various reaction conditions, in the presence or absence of the chiral Lewis acids mentioned above. No HDA adducts were observed in any of the reactions. For the *N*-sulfines **1h** and **1i** with electron donating groups (R = *n*-Bu and OBn, respectively) this result was expected. Attempts to react **1h** and **1i** in an "inverse electron demand" HDA reaction with the electron-deficient diene crotonaldehyde, with and without Lewis acid (BF_3 x OEt_2, **4**-$Cu(OTf)_2$ and **4**-$Zn(OTf)_2$), also failed.

Scheme 3





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Screening of *N*-sulfinyl dienophiles **1** in asymmetric HDA reactions with **2**

The different reactivity observed for **1c** – **1f** and **1g** – **1i** in the HDA reaction may be ascribed to their different ability in forming a chelate ring with the Lewis acid catalyst. The former dienophiles have in common two

Table 1

Screening of *N*-Sulfinyl Dienophiles **1** in the HDA Test Reaction with 1,3-cyclohexadiene (**2**) [a].

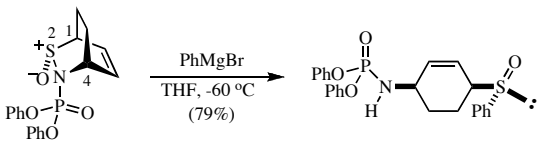
Entry	*N*-Sulfine	Lewis acid (mol %)	Temp/°C (time/h)	Yield % [b]	*Endo* (% ee) : *Exo* [c]	Configuration of *endo*-**3**
1	**1c**	-	rt (22)	63	>95 : <5	-
2	**1c**	**4**-$Zn(OTf)_2$ (100)	rt (22)	60	>95 (46) : <5	(1*S*,2*R*,4*R*)
3	**1c**	**4**-$Zn(OTf)_2$ (100)	-40 (22)	61	>95 (74) : <5	(1*S*,2*R*,4*R*)
4	**1c**	**4**-$Zn(OTf)_2$ (100)	-75 (22)	73	>95 (95) : <5	(1*S*,2*R*,4*R*)
5	**1c**	**4**-$Zn(OTf)_2$ (10)	-75 (22)	67	>95 (45) : <5	(1*S*,2*R*,4*R*)
6	**1c**	**4**-$Zn(OTf)_2$ (10) [d]	-75 (22)	40	>95 (60) : <5	(1*S*,2*R*,4*R*)
7	**1c**	**4**-$Cu(OTf)_2$ (10) [d]	-75 (22)	51	>95 (97) : <5	(1*S*,2*R*,4*R*)
8	**1d**	-	rt (22)	82	67 : 33	-
9	**1d**	**4**-$Zn(OTf)_2$ (100)	-75 (22)	57	>95 (68) : <5	[e]
10	**1d**	**4**-$Cu(OTf)_2$ (100)	-75 (22)	51	>95 (25) : <5	[e]
11	**1d**	**5**-$TiCl_2$ (100)	-75 (20)	33	>95 (47) : <5	[e]
12	**1e**	-	rt (22)	65	20 : 80	-
13	**1e**	**5**-$TiCl_2$ (100)	-75 (20)	45	>95 (24) : <5	[e]
14	**1f**	-	rt (22)	30	60 : 40	-
15	**1f**	**5**-$TiCl_2$ (100)	-75 (20)	0	-	-

[a] All reactions except for the **5**-$TiCl_2$ promoted ones were carried out in CH_2Cl_2. The **5**-$TiCl_2$ promoted reactions were carried out in a mixture of toluene and CH_2Cl_2 (8:1). [b] Isolated yield of *endo*- and *exo*-**3**. [c] The endo/exo ratio was determined by ^{1}H NMR (400 MHz). [d] Reaction with 100 mol% TMSOTf. [e] The absolute configuration was not determined.

basic coordination sites that may form either a 6-membered ring (**1c** – **1e**) or a 7-membered ring (**1f**) with the metal. On the contrary, compounds **1g** – **1i** have only one basic coordination site (at sulfoxide O) and will therefore be less activated for the HDA reaction.

The absolute configuration of *endo*-**3c**, from the **4**-$Zn(OTf)_2$ and **4**-$Cu(OTf)_2$ catalysed reactions (Table 1, entries 2 – 7), was determined by X-ray analysis of the ring opened allylic phenyl sulfoxide [1*R*,4*S*,S(*S*)]-**6**, shown in Scheme 4 and Figure 2 [8]. The ring opening reaction of *endo*-**3c** with phenyl magnesium bromide was expected to proceed with inversion at the sulfoxide group and thus *endo*-**3c** had the (1*S*,2*R*,4*R*)-configuration.

Scheme 4



(1*S*,2*R*,4*R*)-**3c** [1*R*,4*S*,S(*S*)]-**6**

Ring opening of *endo*-**3c** to [1*R*,4*S*,S(*S*)]-**6**

The relative configurations of HDA adducts *endo*-**3d** and *exo*-**3e** were determined by X-ray analysis (Fig. 3 and 4) [8]. For *endo*-**3f**, the relative configuration was determined by considering the shielding effect of the "S=O" group in the ^{1}H NMR spectra, similar to the work described by Zhang and Flann [9]. In the *endo* configuration the protons at the 7- and 8-positions are unaffected by the S=O bond (2.26 - 1.24 ppm), while in the *exo* configuration these protons are less shielded (3.0 – 1.5 ppm). ^{1}H NMR data of other *endo*/*exo*-**3** adducts with known configurations supported this assignment [1d].

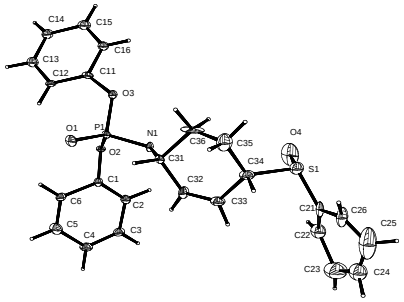


Figure 2. X-ray structure of [1*R*,4*S*,S(*S*)]-**6** [8].

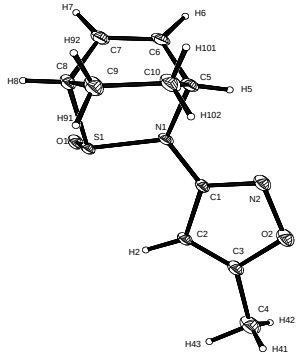


Figure 3. X-ray structure of *endo*-**3d** [8].

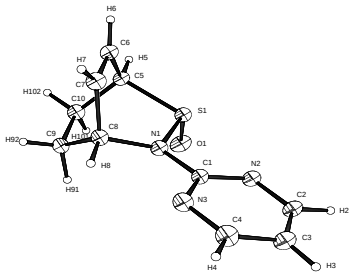


Figure 4. X-ray structure of *exo*-**3e** [8].

In conclusion, a screening of *N*-sulfinyl dienophiles for asymmetric hetero-Diels-Alder reactions using chiral bis(oxazoline)copper(II) and –zinc(II) triflates has been presented. The survey pointed out P(O)(OPh)$_2$ sulfine **1c** as the most promising *N*-sulfine regarding yield and stereoselectivity (up to 97% ee). The result is comparable with results reported earlier for Cbz sulfine **1a** and Ts sulfine **1b** [1].

EXPERIMENTAL

General Remarks. *N*-Sulfines 5-methyl-*N*-sulfinyl-3-isoxazolamine (**1d**) [10], *N*-sulfinyl-2-pyrimidinamine (**1e**) [11], *p*-nitro-*N*-sulfinylaniline (**1g**) [10], *N*-sulfinyl-1-butanamine (**1h**) [12], and *O*-(phenylmethoxy)-*N*-sulfinylhydroxylamine (**1i**) [13,14] were prepared according to the literature. Ligands **4** [15] and **5** [16] were prepared as described in the literature. Solvents were dried according to standard procedures [17]. Tlc was performed on Merck silica gel 60 F_{254} plates and visualized with UV light (254 nm) and phosphomolybdic acid in ethanol solution. Silica gel for flash chromatography was purchased from Grace-Amicon (35-70 micron). Optical rotations were measured with a Perkin Elmer 241 Polarimeter. Enantiomeric excesses were determined by hplc analysis, using Daicels columns Chiralpak AD and Chiralcel OJ (250 × 4.6 mm). ^{1}H and ^{13}C nmr spectra (Bruker Advance DPX instruments 300/75 MHz, 400/100 MHz and 600/150 MHz) were obtained from solutions of $CDCl_3$, and chemical shifts are in ppm and referenced to TMS *via* the lock signal of the solvent. ^{1}H and ^{13}C nmr signals were assigned by 2D correlation techniques. Ir spectra were run on a Thermo Nicolet FT-IR NEXUS instrument, and only the strongest/structurally most important peaks are listed. The mass spectra were recorded on a Finnigan MAT 95XL mass spectrometer. The electron-impact mass spectra were recorded at 70 eV with a direct inlet and the chemical ionization mass spectra were obtained using methane (ionized at 200 eV) as carrier gas. The high resolution mass spectra (hrms) were obtained by using perfluorokerosene (PFK) as standard to provide the reference masses. X-rays were recorded on Enraf-Nonius CAD-4 diffractometer. Elemental analysis was determined by the Laboratory of Organic Elemental analysis, Prague Institute of Chemical Technology, Czech Republic. Melting points are reported uncorrected.

***N*-Sulfinylphosphoramidic acid diphenyl ester (1c)** [18]**.** The title compound was prepared according to a general literature procedure [19]. Since **1c** is highly moisture sensitive and was difficult to purify by vacuum distillation, the crude product (86% yield) was stored and used as a stock solution in dry dichloromethane. Analytical data for **1c**: Ir (neat): 3056 (w), 1592 (s), 1545 (s), 1490 (s), 1264 (s), 1160 (s) cm^{-1}; ^{1}H nmr: δ 7.41-7.15 (10H, m, Ph); ^{13}C nmr: δ 150.1, 150.0, 130.2 (d, J_{PC} = 3 Hz), 126.2 (d, J_{PC} = 5.7 Hz), 120.6, 120.5; ms: (chemical ionization) m/z 296 (0.4, M+1), 295 (0.4, M$^+$), 264 (2), 250 (17), 249 (23), 248 (13), 170 (12), 94 (4), 77 (7), 29 (100).

(*Z*)-*N*-Sulfinyl-*N*-aminophthalimide (1f). A solution of *N*-aminophthalimide (3.3 g, 20.4 mmol) in dry benzene (40 ml) was heated to 40 °C and stirred for 10 min. Thionylchloride (4.6 ml, 63.2 mmol) was then added to the solution *via* a syringe and the mixture was refluxed overnight. The product (3.29 g, 77%), a yellow solid, precipitated from the reaction mixture at room temperature. Analytical data for **1f**: Mp 157-158 °C (from benzene); ir (potassium bromide): 1709 (s, C=O), 1596 (s), 1463 (s), 1370 (m), 1351 (m) cm^{-1}; ^{1}H nmr: δ 7.98 (2H, dd, *J* = 5.6, 2.8 Hz, Ar), 7.85 (2H, dd, *J* = 5.6, 2.8 Hz, Ar); ^{13}C nmr: δ 160.5 (C=O), 135.6, 130.4, 125.0; ms: (70 eV, electron impact) m/z 208 (46, M$^+$), 180 (18), 132 (89), 104 (100), 76 (5); hrms calcd for $C_8H_4N_2O_3S$ 207.9943, found 207.9943. *Anal*. Calcd for $C_8H_4N_2O_3S$: C, 46.15; H, 1.94; N, 13.46. Found: 46.21; H, 1.98; N, 13.41. The (*Z*)-configuration of **1f** was determined by X-ray crystallographic analysis (Figure 1) [8].

General Procedure for the Uncatalysed HDA Reaction. To a solution of the *N*-sulfinyl compound **1** (1.8 mmol) in dry CH_2Cl_2 (3 ml) was added 1,3-cyclohexadiene (**2**) (0.43 ml, 4.5 mmol). The reaction mixture was then stirred at room temperature for 24 h under N_2-atmosphere. The solvent was evaporated *in vacuo*, and the crude product analysed by ^{1}H nmr to determine the *endo*/*exo* ratio. The crude product was purified by flash chromatography.

Preparation of the Copper(II)-bis(oxazoline) Catalyst, 4-Cu(OTf)$_2$, and the Zinc(II)-bis(oxazoline) Catalyst, 4-Zn(OTf)$_2$. An oven dried round bottom flask was charged with copper(II) triflate or zinc triflate (0.025 mmol) in an argon atmosphere. Dry CH_2Cl_2 (2 ml) and a solution of the phenyl box ligand **4** [15] in CH_2Cl_2 (0.5 *M*, 52 µl, 0.026 mmol) were added and the resulting suspension was stirred for 2 h. At this time most of the solids had dissolved. A light green solution was observed in generation of the copper(II) catalyst. No colour was observed with zinc.

General Procedure A: Asymmetric HDA Reaction with 10 mol % of 4-Cu(OTf)$_2$ or 4-Zn(OTf)$_2$. A solution of the *N*-sulfinyl dienophile **1** (620 µl, 0.4 *M* in CH_2Cl_2, 0.248 mmol) was added into the precooled solution of the catalyst (0.025 mmol) at -75 °C. A precooled solution of 1,3-cyclohexadiene (**2**) (0.5 mmol) in CH_2Cl_2 (0.3 ml) and TMSOTf (0.248 mmol) was added into the reaction mixture, respectively. The diene solution was added slowly along the wall of the round bottom flask. The reaction mixture was stirred for 22 h and quenched by addition of a phosphate buffer (pH 7, 3 ml), allowed to warm to room temperature and extracted with CH_2Cl_2 (3 x 3 ml). The combined organics were dried ($MgSO_4$), filtered through a short silica plug and concentrated. The crude product was analysed by ^{1}H nmr to determine the *endo*/*exo* ratio and, thereafter purified by flash chromatography. The enantiomeric composition was determined by chiral hplc.

General Procedure B: Asymmetric HDA Reaction with 100 mol % of 4-Cu(OTf)$_2$ or 4-Zn(OTf)$_2$. A solution of the catalyst (0.40 mmol) was cooled to -75 °C before a solution of *N*-sulfinyl compound **1** in dry CH_2Cl_2 (0.5 -1.0 *M*, 0.40 mmol)

was added. The resulting mixture was stirred for 10 min before a precooled solution of 1,3-cyclohexadiene (**2**) (0.80 mmol) in dry CH_2Cl_2 (0.5 ml) was added slowly along the wall of the flask. After 22 hours reaction time, the reaction mixture was quenched by addition of a phosphate buffer (pH 7, 3 ml), allowed to warm to room temperature, and worked up as described in general procedure A.

Asymmetric HDA Reaction with 100 mol % of 5-$TiCl_2$.

The **5**-$TiCl_2$ promoted HDA reactions were performed as described in the literature [1d].

(1*S*,2*R*,4*R*)-(2-Oxo-2λ^4-thia-3-azabicyclo[2.2.2]oct-5-en-3-yl)phosphonic acid diphenyl ester ((1*S*,2*R*,4*R*)-3c). Asymmetric HDA reaction between **1c** and **2**, catalysed by **4**-$Cu(OTf)_2$ or **4**-$Zn(OTf)_2$ according to the general procedures A and B, afforded only the *endo* adduct (1*S*,2*R*,4*R*)-**3c** in 46 – 97% ee and in 51 – 73% yields (Table 1, entries 2 - 7) as a white solid. The crude product was in general purified by flash chromatography (EtOAc/pentane 1/1). Analytical data for (1*S*,2*R*,4*R*)-**3c**: Tlc R_f 0.16 (EtOAc/pentane 1/1); mp 101-103 °C; $[\alpha]_D^{20}$ -163.5 (c = 1.0, CH_2Cl_2); hplc: (Chiralpak AD, 2-propanol/*n*-hexane 20/80, 1 ml min^{-1}, 230 nm) 88% ee, t_R 22.84 (1*R*,2*S*,4*S*) and 27.77 (1*S*,2*R*,4*R*) min; ir (potassium bromide): 3241 (w), 3058 (w), 2967 (w), 1586 (s), 1487 (s), 1373 (s), 1283 (m), 1234 (m) cm^{-1}; ^{1}H nmr: δ 7.38-7.23 (10H, m, Ph), 6.86 (1H, app t, *J* = 7.55, 7.45 Hz, H-5), 6.28 (1H, app t, *J* = 7.4 Hz, H-6), 4.88-4.82 (1H, m, H-4), 4.38-4.32 (1H, m, H-1), 1.80-1.60 (2H, m, H-7/H-8), 1.48-1.35 (1H, m, H-8), 1.20-1.07 (1H, m, H-7); ^{13}C nmr: δ 150.6 (d, J_{PC} = 4.02 Hz), 150.5 (d, J_{PC} = 4.02 Hz), 137.2 (d, J_{PC} = 5.01 Hz, C-5), 130.0, 129.9, 125.7, 125.6 (d, J_{PC} = 3.02 Hz, C-6), 120.6 (d, J_{PC} = 5.03 Hz), 120.5 (d, J_{PC} = 5.03 Hz), 56.1 (d, J_{PC} = 5.03 Hz, C-1), 50.9 (d, J_{PC} = 2.01 Hz, C-4), 24.6 (C-7), 14.9 (C-8); ms: (70 eV, electron impact) m/z 375 (0.1, M^+), 329 (3), 295 (47), 247 (67), 246 (63), 201 (8), 170 (50), 156 (19), 94 (44), 77 (96), 65 (29), 51 (29). *Anal*. Calcd for $C_{18}H_{18}NO_4PS$: C, 57.59; H, 4.83; N, 3.73. Found: C, 57.66; H, 4.81; N, 3.81.

[1*R*,4*S*,S(*S*)]-(4-Benzenesulfinylcyclohex-2-enyl)phosphoramidic acid diphenyl ester, [1*R*,4*S*,S(*S*)]-6. A solution of phenyl magnesium bromide in THF (1 *M*, 604 μl, 0.604 mmol) was added to a stirred solution of (1*S*,2*R*,4*R*)-**3c** (88% ee, 201 mg, 0.537 mmol) in dry THF (4 ml) at -60 °C and the mixture was stirred for 30 min and then hydrolyzed with aqueous NH_4Cl (satd. 8 ml). The layers were separated and the aqueous layer extracted with Et_2O (3 x 4 ml). The combined organics were washed with brine (5 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude was purified by flash chromatography (EtOAc/pentane, gradient 1/1 to 7/3) yielded the allylic sulfoxide [1*R*,4*S*,S(*S*)]-**6** (192.4 mg, 79%) as a white solid. Analytical data for [1*R*,4*S*,S(*S*)]-**6**: Mp 140-141 °C (from CH_2Cl_2/heptane); $[\alpha]_D^{20}$ -222 (c = 1.0, CH_2Cl_2); hplc: (Chiralpak AD, 2-propanol/*n*-hexane 40/60, 1 ml min^{-1}, 230 nm) 77% ee, t_R 13.47 [1*S*,4*R*,S(*R*)] and 21.06 [1*R*,4*S*,S(*S*)] min.); ir (potassium bromide): 3193 (w), 2918 (w), 1589 (m), 1483 (s), 1251 (m), 1194 (s) cm^{-1}; ^{1}H nmr: δ 7.60-7.54 (2H, m, Ph) 7.46-7.43 (3H, m, Ph), 7.40-7.30 (4H, m, Ph), 7.28-7.21 (4H, m, Ph), 7.20-7.13 (2H, m, Ph), 6.07 (1H, ddd, *J* = 10.1, 3.4, 1.7 Hz, H-2), 5.50 (1H, ddd, *J* = 10.1, 3.4, 1.5 Hz, H-3), 3.95 (1H, m, H-1), 3.30 (1H, m, H-4), 3.20 (1H, t, *J* = 11.6 Hz, NH), 2.12-2.0 (1H, m, H-5), 1.95-1.84 (1H, m, H-5), 1.83-1.70 (1H, m, H-6), 1.68-1.55 (1H, m, H-6); ^{13}C nmr: δ 151.0 (d, J_{PC} = 4.5 Hz), 150.91 (d, J_{PC} = 4.5 Hz), 141.9, 137.5 (d, J_{PC} = 6.64 Hz, C-2), 131.4, 129.9, 129.2, 125.2 (app. d, J_{PC} = 2.9 Hz), 124.8, 121.9, 120.5 (d, J_{PC} = 5.3 Hz), 120.4(d, J_{PC} = 5.4 Hz), 60.1 (C-4), 46.9 (C-1), 28.6 (d, J_{PC} = 3.9 Hz, C-6), 21.1 (C-5); ms: (70 eV, electron impact) m/z 326 (33), 275 (4.6), 250 (57.9), 249 (100), 248 (66.1), 232 (13.9), 218 (10.4), 170 (65.6), 156 (23.3), 126 (14.7), 110 (25.1), 94 (93.6), 78 (89.1), 77 (97.7), 65 (24.5), 51 (24.3). *Anal*. Calcd for $C_{24}H_{24}NO_4PS$; C, 63.56; H, 5.33; N, 3.09. Found: C, 63.25; H, 5.36; N, 2.97. The absolute configuration of [1*R*,4*S*,S(*S*)]-**6** was determined by X-ray crystallographic analysis (Figure 2) [8].

3-(5-Methylisoxazol-3-yl)-2λ^4-thia-3-azabicyclo[2.2.2]oct-5-ene 2-oxide (3d). The uncatalysed reaction between *N*-sulfine **1d** and **2** according to the general procedure afforded a mixture of *endo*-**3d** and *exo*-**3d** (2:1). Flash chromatography (EtOAc/hexane 4/1) of the crude product yielded 259 mg (64% yield) of *endo*-**3d** as a white solid and second fraction containing a mixture of 5-methyl-3-isoxazolamine and *exo*-**3d**. All attempts to separate 5-methyl-3-isoxazolamine and *exo*-**3d** failed. Analytical data for *endo*-**3d**: Tlc R_f 0.15 (EtOAc/hexane 4/1); mp 126-127 °C; ir (potassium bromide): 3130 (w), 2963 (w), 1616 (s), 1485 (s), 1455 (s), 1433 (s), 1367 (s), 1273 (s), 1163 (s), 1102 (s), 1045 (s), 1009 (s) cm^{-1}; ^{1}H nmr: δ 7.00 (1H, ddd, *J* = 7.9, 7.1, 1.5 Hz, H-5), 6.35 (1H, app t, *J* = 7.49, 7.27 Hz, H-6), 6.02 (1H, s, 4-isoxozol), 5.12-5.09 (1H, m, H-4), 4.35-4.31(1H, m, H-1), 2.36 (3H, s, CH_3), 2.05-1.94 (1H, m, H-8), 1.87-1.79 (1H, m, H-7), 1.58-1.51 (1H, m, H-8), 1.31-1.23 (1H, m, H-7); ^{13}C nmr: δ 170.3 (5-isoxazol), 162.5 (3-isoxazol), 137.6 (C-5), 125.2 (C-6), 94.4 (4-isoxazol), 55.4 (C-1), 50.8 (C-4), 22.4 (C-8), 15.9 (C-7), 12.8 (CH_3); ms: (70 eV, electron impact) m/z 224 (M^+, 0.1), 163 (2), 146 (9), 144 (134), 109 (18), 80 (82), 79 (100). *Anal*. Calcd for $C_{10}H_{12}N_2O_2S$: C, 53.55; H, 5.39; N, 12.49; S, 14.30. Found: C, 53.31; H, 5.43; N, 12.43; S, 14.45. The relative configuration of (1*R**,2*S**,4*S**)-**3d** was determined by X-ray crystallographic analysis (Figure 3) [8]. Data for *exo*-**3d**: Tlc R_f 0.31 (EtOAc/hexane 4/1); ^{1}H nmr: δ (selected signals) 6.98 (1H, ddd, *J* = 8.2, 5.8, 1.0 Hz, H-5), 6.30 (1H, app t, *J* = 7.6 Hz, H-6), 5.95 (1H, s, 4-isoxazol), 5.00-4.97 (1H, m, H-4), 4.13-4.07 (1H, m, H-1), 2.91-2.85 (1H, m, H-7), 2.34 (3H, s, CH_3), 2.44-2.38 (1H, m, H-8), 1.64-1.51 (2H, m, H-7/8); ^{13}C nmr: 170.6 (5-isoxazol), 162.4 (3-isoxazol), 141.4 (C-5), 127.5 (C-6), 94.4 (4-isoxazol), 56.0 (C-1), 50.5 (C-4), 24.7 (C-7), 12.7 (CH_3), 11.4 (C-8).

The asymmetric HDA reaction between **1d** and **2**, promoted by **4**-$Zn(OTf)_2$ according to the general procedure B, afforded exclusively *endo*-**3d** as product (Table 1, entry 9). Analytical data: $[\alpha]_D^{20}$ -230.2 (c = 1.0, CH_2Cl_2); hplc: (Chiralcel OJ, 2-propanol/*n*-hexane 35/65, 0.5 ml min^{-1}, 230 nm) 68% ee, t_R 23.69 and 30.59 (major) min. The absolute configuration was not determined.

3-(2-Pyrimidinyl)-2λ^4-thia-3-azabicyclo[2.2.2]oct-5-ene 2-oxide (3e). The uncatalysed reaction between *N*-sulfine **1e** and **2** according to the general procedure afforded a mixture of *endo*-**3e** and *exo*-**3e** (1:4). Flash chromatography (EtOAc/hexane 4/1) of the crude product yielded 155 mg (51% yield) of *exo*-**3e** as a white solid and a second fraction containing a mixture of *endo*-**3e** and 2-pyrimidinamine. Flash chromatography (acetone /CH_2Cl_2 1/9) of the latter fraction afforded 43 mg (14% yield) of *endo*-**3e** as a white solid. Analytical data of *endo*-**3e**: Tlc R_f 0.13 (EtOAc/hexane 4/1); mp 126-127 °C; ir (potassium bromide): 3074 (w), 2939 (w), 1578 (s), 1556 (s), 1416 (s), 1370 (m), 1349 (m), 1109 (m) cm^{-1}; ^{1}H nmr: δ 8.48 (2H, d, *J* = 4.8 Hz, 4-pyr/6-pyr), 7.00 (1H, ddd, *J* = 8.1, 7.2, 1.6 Hz, H-5), 6.84 (1H, t, *J* = 4.8 Hz, 5-pyr), 6.44 (1H, app t, *J* = 7.2 Hz, H-6), 5.75-5.72 (1H,

m, H-4), 4.34-4.30 (1H, m, H-1), 1.90-1.77 (2H, m, H-7/8), 1.71-1.63 (1H, m, H-8), 1.38-1.29 (1H, m, H-7); ^{13}C nmr: δ 161.0 (2-pyr), 158.3 (4-pyr/6-pyr), 137.1 (C-5), 126.6 (C-6), 114.2 (5-pyr), 55.3 (C-1), 47.3 (C-4), 23.6 (C-8), 15.9 (C-7); ms: (70 eV, electron impact) m/z 221 (M^+, 5), 173 (49), 172 (96), 143 (46), 142 (14), 125 (27), 95 (20), 80 (100), 79 (93), 77 (18). *Anal.* Calcd for $C_{10}H_{11}N_3OS$: C, 54.28; H, 5.01; N, 18.99. Found: C, 54.01; H, 4.93; N, 18.76. Analytical data of *exo*-**3e**: Tlc R_f 0.27 (EtOAc/hexane 4/1); mp 124-125 °C (from CH_2Cl_2/pentane); hplc: (Chiralpak AD, 2-propanol/*n*-hexane 10/90, 1 ml min^{-1}, 241 nm) t_R 18.88 and 23.06 min; ir (potassium bromide): 3074 (w), 2937 (w), 1578 (s), 1560 (s), 1417 (s), 1366 (m), 1351 (m), 1289 (m), 1233 (m), 1183 (m), 1087 (s), 1055 (m), 1026 (m) cm^{-1}; ^{1}H nmr: δ 8.47 (2H, d, J = 4.8 Hz, 4-pyr/6-pyr), 6.90 (1H, ddd, J = 7.9, 6.2, 0.7 Hz, H-5), 6.84 (1H, t, J = 4.7 Hz, 5-pyr), 6.36 (1H, app t, J = 7.6 Hz, H-6), 5.69-5.66 (1H, m, H-4), 4.09-4.05 (1H, m, H-1), 3.02-2.92 (1H, m, H-7), 2.41-2.31 (1H, m, H-8), 1.69-1.54 (2H, m, H-7/8); ^{13}C nmr: δ 161.2 (2-pyr), 158.3 (4-pyr/6-pyr), 140.5 (C-5), 128.2 (C-6), 114.4 (5-pyr), 56.1 (C-1), 47.2 (C-4), 25.1 (C-7), 12.2 (C-8); ms: (70 eV, electron impact) m/z 221 (M^+, 4), 173 (28), 172 (68), 143 (28), 141 (47), 125 (18), 95 (18), 80 (96), 79 (100), 77 (25). *Anal.* Calcd for $C_{10}H_{11}N_3OS$: C, 54.28; H, 5.01; N, 18.99, S, 14.49. Found: C, 53.97; H, 5.00; N, 18.92; S, 14.45. The relative configuration of (1*R**,2*R**,4*S**)-**3e** was corroborated by X-ray crystallographic analysis (Figure 4) [8].

The asymmetric HDA reaction between **1e** and **2**, promoted by **5**-$TiCl_2$ according to literature [1d], afforded exclusively *endo*-**3e** as product (Table 1, entry 13). Analytical data: $[\alpha]_D^{20}$ -55.7 (c = 1.0, CH_2Cl_2); hplc: (Chiralcel OJ, 2-propanol/*n*-hexane 35/65, 0.7 ml min^{-1}, 241 nm) 24% ee t_R 19.4 (major) and 23.3 min. The absolute configuration was not determined.

2-(2-Oxo-2λ^4-thia-3-azabicyclo[2.2.2]oct-5-en-3-yl)isoindole-1,3-dione (3f). The uncatalysed reaction between *N*-sulfine **1f** and **2** according to the general procedure afforded a mixture of *endo*-**3f** and *exo*-**3f** (3:2). Flash chromatography (EtOAc/hexane 4/1) of the crude product yielded 100.3 mg (17% yield) of *endo*-**3f** as a white solid and a second fraction, tlc R_f 0.28 (EtOAc/hexane 4/1), containing an inseparable mixture assumed to be *exo*-**3f** and *N*-aminophthalimide. Overlap in the ^{1}H nmr spectrum of the latter fraction made it difficult to report the *exo*-**3f** data. Analytical data for *endo*-**3f**: Tlc R_f 0.15 (EtOAc/hexane 4/1); mp 169-171 °C (Charred at this temperature); ir (potassium bromide): 3090 (w), 2935 (w), 1727 (s), 1467 (m), 1371 (s), 1199 (s), 1109 (s) cm^{-1}; ^{1}H nmr: δ 7.90 (2H, dd, J = 5.5, 3.1 Hz, Isoindole), 7.79 (2H, dd, J = 5.5, 3.1 Hz, Isoindole), 7.10 (1H, ddd, J = 8.1, 7.2, 1.7 Hz, H-5), 6.32 (1H, app t, J = 7.4, 7.2 Hz, H-6), 4.39-4.35 (1H, m, H-1), 4.19-4.16 (1H, m, H-4), 2.26-2.21 (1H, m, H-7), 2.12-2.06 (1H, m, H-8), 1.95-1.85 (1H, m, H-7), 1.32-1.24 (1H, m, H-8); ^{13}C nmr: δ 166.2 (C=O), 138.3 (C-5), 135.0, 129.9, 124.4, 124.1, 59.1, 57.3, 23.6, 16.7; ms: (chemical ionization) m/z 289 (M+1, 3), 208 (8), 192 (11), 162 (20), 132 (18), 104 (33), 80 (100), 79 (39). *Anal.* Calcd for $C_{14}H_{12}N_2O_3S$: C, 58.32; H, 4.20; N, 9.72. Found: C, 58.14; H, 4.28; N, 9.98.

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