Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 2407–2415

TETRAHEDRON: *ASYMMETRY*

Asymmetric Diels–Alder reactions of *N*-sulfinyl dienophiles using chiral Ti(IV) Lewis acids

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Received 28 May 2002; revised 14 October 2002; accepted 16 October 2002

Abstract—Enantioselective hetero Diels–Alder (HDA) reactions of 1,3-cyclohexadiene with benzyl *N*-sulfinylcarbamate **1a** and with *N*-sulfinyl-*p*-toluensulfonamide **1b** promoted by chiral Ti(IV)-based Lewis acids are reported. The obtained yields and enantiomeric excesses obtained are heavily dependant on the mode of catalyst preparation. Acceptable reproducibility was obtained with Ti(IV)-catalysts prepared from Me_2TiCl_2 and chiral diols. Testing of various chiral diols gave the *endo* adduct in yields of up to 69% with 76% ee. The absolute configuration of the HDA products were established by chemical correlation and verified by X-ray crystallography.

1. Introduction

The Diels–Alder (DA) and hetero Diels–Alder (HDA) reactions constitute an extremely useful set of reactions, particularly for stereoselective synthesis. Since we are studying reactions for the stereoselective introduction of nitrogen into organic compounds, HDA reactions using *N*-sulfinyl compounds as dienophiles caught our interest.[1–8] This reaction affords 1,2-thiazine 1-oxides, which are precursors for unsaturated, vicinal amino-alcohols and homoallylic amines,[7] and have found application in the total synthesis of natural products[9] and biologically active compounds, e.g. agelastatin A,[10] cylindrospermopsin and 7-epicylindrospermopsin,[11] 5-*epi*-desoamine,[12] *threo*- and *erythro*-sphingosine,[13] benzodiazepines and benzothiadiazepines.[14] Only a few examples of asymmetric HDA reactions using either chiral *N*-sulfinyl dienophiles[15,16] or chiral dienes[17] have been reported to proceed with high diastereoselectivities (>97%). The application of chiral Lewis acid complexes as catalysts for DA and HDA reactions has been demonstrated to give excellent chiral induction for many different reaction systems.[18–20] Recently, we reported briefly on the use of chiral Ti(IV),[21] Cu(II) and Zn(II) complexes[22] as promoters for asymmetric HDA reactions using *N*-sulfinyl dienophiles. Herein, we present a more detailed report on the Ti(IV)-promoted HDA reactions of *N*-sulfinyl compounds **1a**[13a] and **1b**[3] with 1,3-cyclohexadiene (see Fig. 1). In our initial studies, the yields and reproducibilities of the reactions were found to depend strongly on the mode of catalyst preparation. These findings are discussed herein. The relative and absolute configuration of the obtained adducts **2a** and **2b**, respectively, are confirmed by X-ray analysis.

2. Results and discussion

2.1. Preparation of the catalyst

The synthesis and use of chiral titanium complexes has been reviewed by several authors.[23,24] Initially, we prepared [$TiCl_2$(**3b**-ate)] in situ by exchanging the alcohol ligands of $TiCl_2(OiPr)_2$ with diol **3b**, followed by removal of 2-propanol by azeotropic distillation or by absorption onto molecular sieves according to the method of Narasaka et al.[25] The reactions completed with the catalysts prepared by these procedures gave low yields (Table 1, entries 1 and 2). We also experienced great difficulties in obtaining reproducible results. Studies of these catalysts by ^{1}H NMR showed the presence of free 2-propanol. Alcoholysis of the *N*-sulfinyl compound **1a** may explain the low and non-reproducible yields. The insufficient removal of the alcohol may be due to coordination to titanium.[23,26] Unfortunately, attempts to prepare the catalyst by alcohol exchange of $Ti(OiPr)_4$ with **3b**, followed by treatment

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PII: S0957-4166(02)00661-4

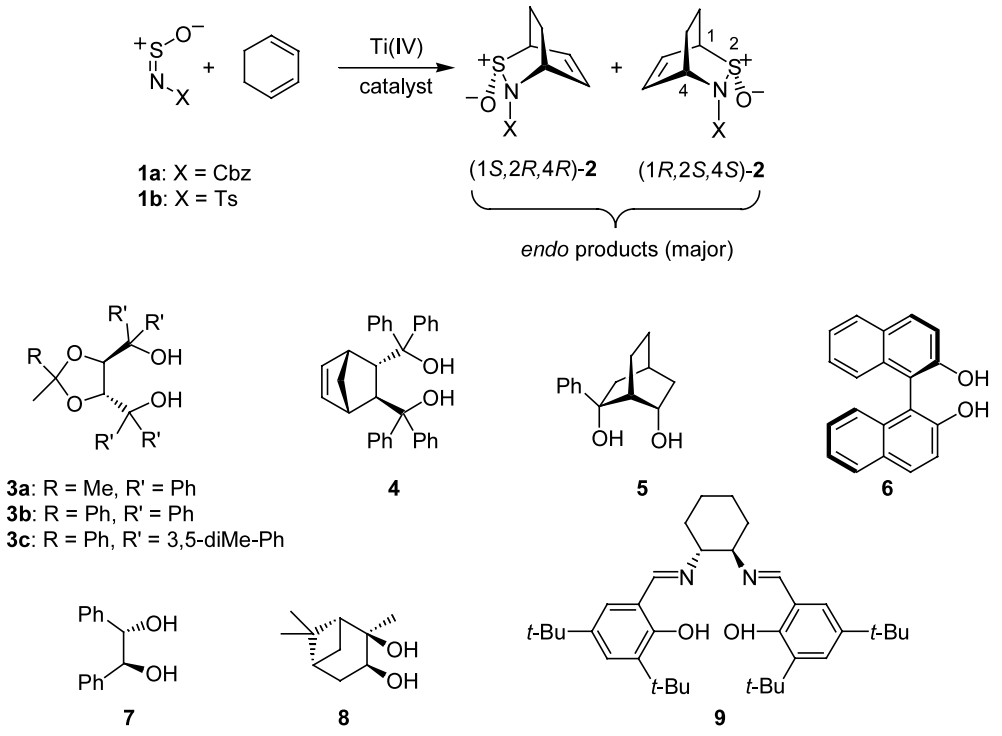


Figure 1. Asymmetric Diels–Alder reactions of *N*-sulfinyl dienophiles **1a** and **1b** with 1,3-cyclohexadiene promoted by chiral Ti(IV) Lewis acids.

Table 1. HDA reactions of **1a** and 1,3-cyclohexadiene at −70°C with [$TiCl_2$(**3b**-ate)] (100 mol%) prepared by different methods

Entry	Method	Solvent (tol.–CH_2Cl_2)	Yield[a] /%	*endo*: *exo*[b] (% ee)[c]	Config. of *endo*-**2a**
1	$TiCl_2(OiPr)_2$ (azeotr.)[25]	6:1	24	>95 (57):5	1*R*,2*S*,4*S*
2	$TiCl_2(OiPr)_2$ (4 Å MS)[25]	6:1	0	–	–
3	1. $Ti(OiPr)_4$; 2. $SiCl_4$[27]	6:1	45	>95 (43):5	1*R*,2*S*,4*S*
4	1. BuLi; 2. $TiCl_4$[28]	6:1	44	>95 (0):5	–
5	Me_2TiCl_2	6:1	70	>95 (58):5	1*R*,2*S*,4*S*

[a] Isolated yield of *endo*- and *exo*-**2a**.
[b] Determined by ^{1}H NMR (400 MHz) on crude product.
[c] Determined by HPLC analysis using DAICEL Chiracel OJ (2-propanol/*n*-hexane, 35:65; 0.5 ml/min).

with $SiCl_4$[27] (entry 3) or by ligand exchange of $TiCl_4$ with deprotonated **3b**[28] (entry 4) did not improve the results sufficiently. Thus, we developed a new method for preparation of the catalyst using the thermally labile Me_2TiCl_2[29] as a titanium precursor. The reactions between Me_2TiCl_2 and the diol were expected to give methane as a by-product, which should not cause problems in the subsequent HDA reactions. Indeed, catalyst solutions prepared in this manner lead to improved and more reproducible results with respect to yield and ee (entry 5). However, minor variations were observed for different catalyst batches (49–58% ee and 60–70% yields).

The complex formed in the reaction of diol **3b** and Me_2TiCl_2 was analyzed by ^{1}H NMR spectroscopy (Fig. 2). The ratio of complexed to uncomplexed diol **3b** in the catalyst solution was determined to be ca. 95:5. The ^{1}H NMR spectrum differs from earlier reports.[30] Some of the differences may be explained by the absence of coordinated isopropanol in complexes prepared from Me_2TiCl_2. The broadening of the signals corresponding to [$TiCl_2$(**3b**-ate)] indicates the formation of aggregates (Fig. 2a). When isopropanol was added (Fig. 2b), these lines sharpened, probably due to coordination of the alcohol to complex [$TiCl_2$(**3b**-ate)], and the spectrum became similar to that reported by Iwasawa et al.[30] (see Fig. 2c). The ^{1}H NMR spectrum also showed that impurities were present in the catalyst solution prepared from Me_2TiCl_2. These impurities were not identified and catalytically active species different from a [$TiCl_2$(**3b**-ate)] complex cannot be excluded.

The relationship between the enantiomeric purity of the chiral ligand and the ee of the product was investigated for the HDA test reaction. Stoichiometric amounts of the catalyst were used in this study. The results are plotted in Fig. 3. A positive nonlinear effect (NLE) was found. The deviation from linearity indicated that diastereomeric species were formed.[31] Moreover, the

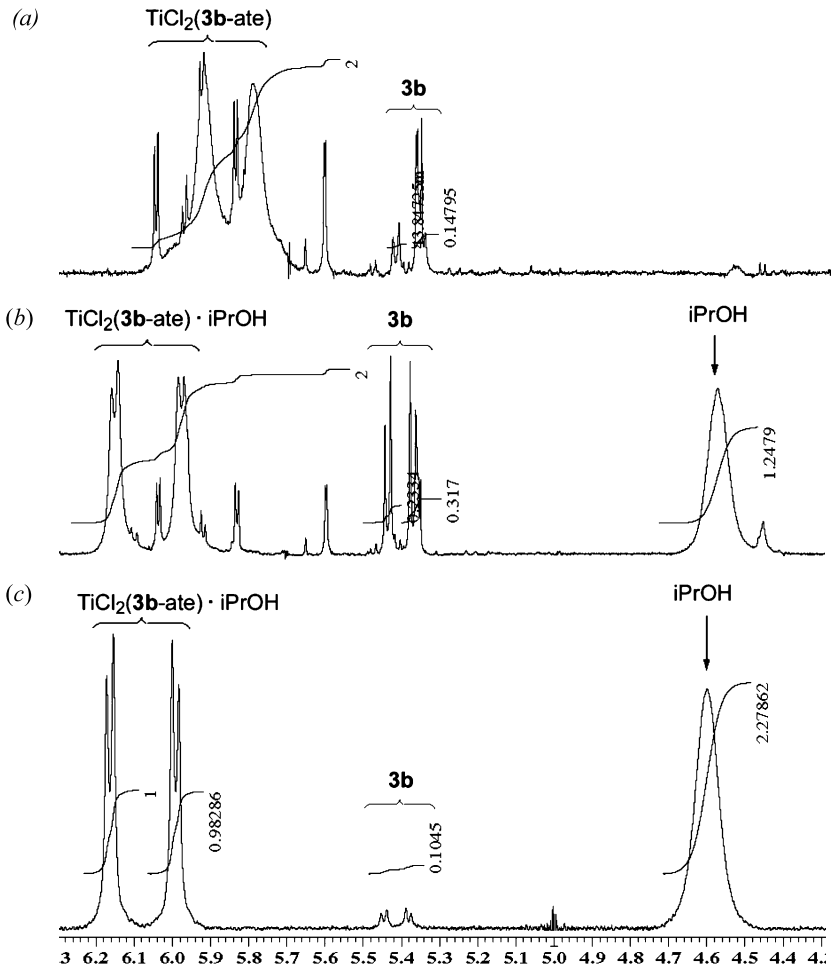


Figure 2. Expansions of ^{1}H NMR spectra of the catalyst prepared from (a) Me_2TiCl_2 (b) Me_2TiCl_2 after addition of 2-PrOH (0.4 equiv.) and (c) $TiCl_2(OiPr)_2$.

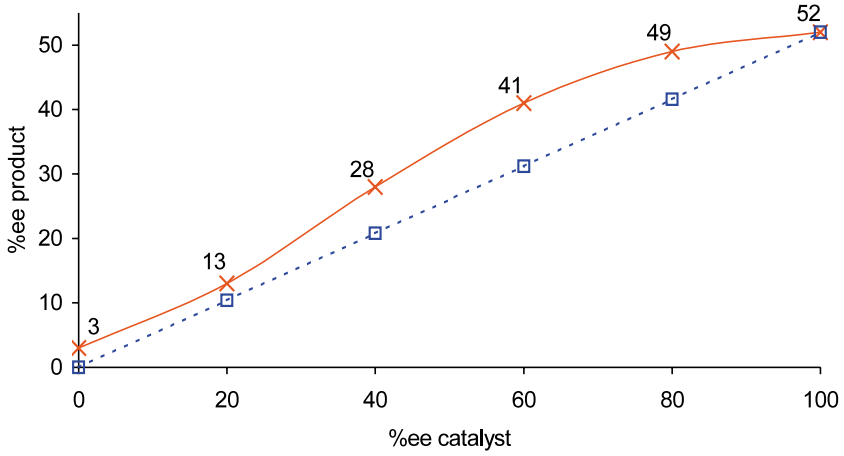


Figure 3. Nonlinear effect in the HDA reaction of **1a** with 1,3-cyclohexadiene promoted by [$TiCl_2$(**3b**-ate)] (100 mol%) of various enantiomeric purities.

homochiral species giving enantiomeric enrichment was more active than the heterochiral species giving racemic products. When scalemic mixtures of the catalyst were prepared a precipitate was formed. This is in agreement with observations reported by Iwasawa et al. who also found positive NLE effects for [$TiCl_2$(**3b**-ate)] mediated DA reactions and precipitation of racemic diol.[30]

2.2. Reaction conditions, ligands and counterions

The chiral diols **3a**,[32] **3b**,[25] **3c**,[33] **4**,[34] **5**,[35] **6**,[36] **7**,[37] **8** and **9**[38] were tested as ligands for the titanium(IV)-promoted HDA reactions of *N*-sufinyl dienophiles **1a** and **1b** with 1,3-cyclohexadiene (Fig. 1). The results are given in Table 2. The minimum amount of catalyst necessary for good results to be obtained was found to be 30 mol%. With catalyst loading of 10 mol%, **1a** a dramatic decrease in the yield was observed, although the ee and de were unaffected. For **1b** the ee and de decreased due to a pronounced background reaction, but the yield was not reduced significantly. The data given in Table 2 were obtained with stoichiometric amounts of catalyst relative to the *N*-sulfinyl compounds. Generally, the HDA reactions were carried out at −70°C (**1a**) or −85°C (**1b**) in toluene with CH_2Cl_2 as cosolvent. The yields were found to increase with the reaction time, 5 h giving around 20% yield and 15–20 h giving up to 86% yield. Prolonging the reaction times beyond 20 h did not lead to further improvement in the yields.

The best results with respect to stereoselectivity were obtained with diol **4** (**2a**: >90% de, 76% ee (entry 4); **2b**: 82% de, 74% ee (entry 13)). The yields were comparable (**2a**: 69%) or somewhat lower (**2b**: 58%) than those seen with the diol **3b** (**2a**: 70%; **2b**: 83%). The ligands **3a**–**c** and **4** induced stereoselectivity in the same sense, (*R*)-ligands giving (1*R*,2*S*,4*S*)-**2a** as the major isomer. Interestingly, a switch of enantioselectivity was observed when changing from *N*-sulfinyl dienophiles **1a** (X = Cbz) to **1b** (X = Ts). For **1b** the (*R*)-ligands gave (1*S*,2*R*,4*R*)-**2b**. In all cases, the major diastereomer resulted from an *endo* approach of the reagents. It seemed that the ligands leading to five-membered titanacycles gave lower stereoselectivities and yields (entries 7, 8, 15 and 16). For these ligands even the diastereoselectivity, which remained high for all six- and seven-membered titanacycles, decreased. In some cases (diols **5**–**7**) a precipitate formed during preparation of the catalyst, which may explain the poor yields obtained with these ligands. The apparent inactivity of the catalyst obtained with ligand **9** may be ascribed to the additional coordination sites of the ligand.

The complexes obtained by exchange of chlorides of [$TiCl_2$(**3b**-ate)] with triflates and tosylates[39] did not promote the HDA reaction.

2.3. Stereochemical proof

The relative configuration (*endo*/*exo*) of the cycloadducts **2a** and **2b** 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.[40] In the *endo* configuration the protons at the 7- and 8-positions are unaffected by the S=O bond (1.76–1.12 ppm), while in the *exo* configuration these protons are significantly less shielded (2.83–1.44 ppm). X-Ray analysis of the major isomers confirmed an *endo* configuration at sulfur. X-Ray crystal structures of *endo*-**2a** and (1*R*,2*S*,4*S*)-**2b** are shown in Figs. 4 and 5, respectively.[41]

For compound **2a** the X-ray structure shown in Fig. 4 gave the relative configuration. For **2b** the absolute configuration was also assigned. In both cases the X-ray showed conglomerate crystals. These observations were also confirmed by chiral HPLC analysis. Absolute configuration of the *endo* isomer of **2a** (X = Cbz) was established by chemical correlation with the known cyclic carbamate (1*R*,2*S*)-**13** following Weinreb's method[16] (Scheme 1).

Table 2. HDA reactions of *N*-sulfinyl compounds **1a** and **1b** with 1,3-cyclohexadiene promoted by the complexes obtained from Me_2TiCl_2 and the chiral ligand (100 mol%)

Entry	*N*-sulf.	Ligand	Solvent (tol.–CH_2Cl_2)	Temp/°C (time/h)	Yield[a]/%	*endo*:*exo*[b] (% ee)[c]	Config. of *endo*-**2**
1	**1a**	**3a**	1:1	−55 (20)	63	>95 (40):5	1*R*,2*S*,4*S*
2	**1a**	**3b**	6:1	−70 (22)	70	>95 (58):5	1*R*,2*S*,4*S*
3	**1a**	**3c**	8:1	−70 (20)	69	92 (37):8	1*R*,2*S*,4*S*
4	**1a**	**4**	6:1	−68 (18)	69	>95 (76):5	1*S*,2*R*,4*R*
5	**1a**	**5**	9:1	−70 (21)	11	>95 (48):5	1*R*,2*S*,4*S*
6	**1a**	**6**	1:6	−68 (18)	0	–	–
7	**1a**	**7**	5:2	−42 (16)	32	75 (13):25 (35)	1*R*,2*S*,4*S*
8	**1a**	**8**	6:1	−42 (16)	35	80 (13):20	1*R*,2*S*,4*S*
9	**1a**	**9**	1:1	−70 (20)	0	–	–
10	**1b**	**3a**	1:1	−85 (16)	63	92 (59):8	1*S*,2*R*,4*R*
11	**1b**	**3b**	6:1	−85 (17)	83	94 (69):6 (22)	1*S*,2*R*,4*R*
12	**1b**	**3c**	6:1	−85 (16)	68	50 (37):50 (25)	1*S*,2*R*,4*R*
13	**1b**	**4**	6:1	−85 (17)	58	91 (74):9 (30)	1*R*,2*S*,4*S*
14	**1b**	**6**	1:6	−85 (17)	38	76 (0):24 (0)	–
15	**1b**	**7**	2:1	−85 (16)	29	82 (15):18 (0)	1*R*,2*S*,4*S*
16	**1b**	**8**	6:1	−85 (16)	42	80 (36):20 (43)	1*R*,2*S*,4*S*

[a] Isolated yield of *endo*- and *exo*-**2**. Generally, the total isolated yield of HDA product and the amine corresponding to the *N*-sulfinyl compound accounted for >80% of the limiting starting material (*N*-sulfinyl compound).

[b] Determined by ^{1}H NMR (400 MHz) on crude product.

[c] Determined by HPLC analysis using DAICEL Chiracel OJ (2-propanol/*n*-hexane, 35:65; 0.5 ml/min) for **2a** (X = Cbz) and DAICEL Chiralpak AD (2-propanol/*n*-hexane, 20:80; 1.0 ml/min) for **2b** (X = Ts).

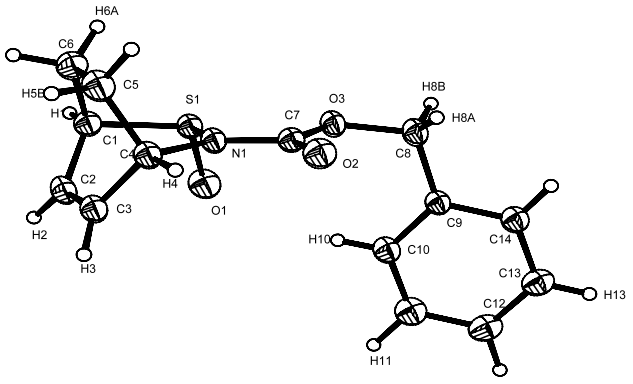


Figure 4. X-Ray crystal structure of *endo*-**2a**.

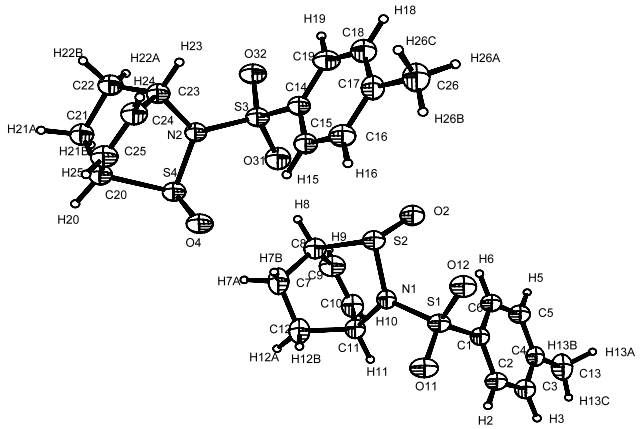


Figure 5. X-Ray crystal structure of (1*R*,2*S*,4*S*)-**2b** (entry 13, Table 2).

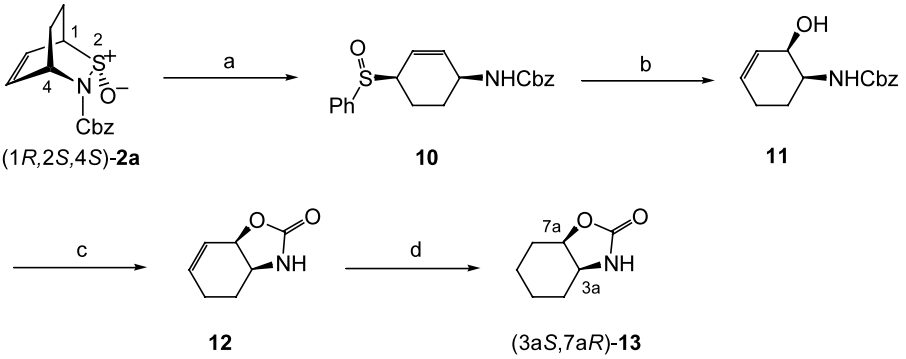
The *endo*-**2a** obtained in entry 2 (Table 2) was rearranged to hydroxy carbamate **11** and then cyclized to carbamate **12**. Catalytic hydrogenation of **12** provided (1*R*,1*S*)-**13**[16] and thus *endo*-**2a** (entry 2, Table 2) had the (1*R*,2*S*,4*S*)-configuration. The absolute configuration of compound *endo*-**2b** (X = Ts) was determined by chemical correlation with *endo*-**2a** (X = Cbz) as depicted in Scheme 2.

The HDA adduct (1*R*,2*S*,4*S*)-**2a** was rearranged to carbamate (*S*)-**14a** followed by deprotection and tosylation to yield tosylate (*S*)-**14b**. Compound *endo*-**2b** (entry 11, Table 2) was rearranged to tosylate (*R*)-**14b**, correspondingly. Comparison of the tosylates **14b** by HPLC showed that *endo*-**2b** had the (1*S*,2*R*,4*R*)-configuration. This result was verified by X-ray crystallography (Fig. 5).[41]

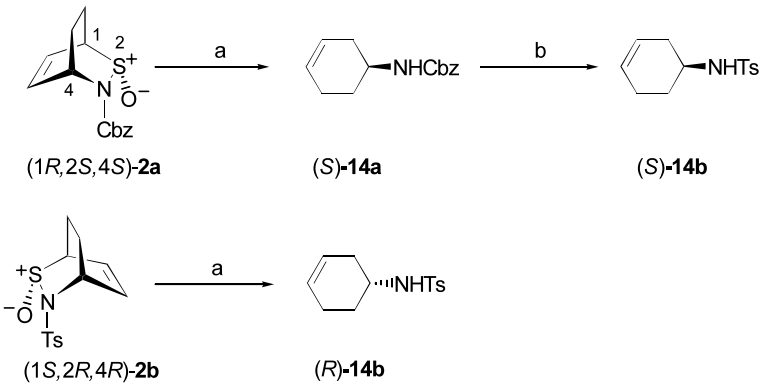
3. Experimental

3.1. General remarks

Melting points were determined on a Buchi 535 apparatus and are uncorrected. TLC was performed on Merck silica gel 60 F_{254} plates, using UV light at 254 nm and a 5% alcoholic molybdophosphoric acid for detection. Silica gel for flash chromatography was purchased from Grace-Amicon. Optical rotations were measured with a Perkin–Elmer 241 Polarimeter. Enantiomeric excesses were determined by HPLC analysis, using Daicels columns Chiracel OD-H and OJ and Chiralpak AD (250×4.6 mm). ^{1}H (400 MHz) and ^{13}C (100 MHz) spectra were obtained on a JEOL JNM-EX 400 FT spectrometer using $CDCl_3$ as solvent and internal standard (reference values 7.25 and 77.1 for ^{1}H and ^{13}C, respectively). IR spectra were run on a Perkin–Elmer 1600 FT-IR instrument, and only the strongest/structurally most important peaks are listed. The mass spectra were recorded on a Finnigan MAT 95XL mass spectrometer, and a VG Quattro quadrupole mass spectrometer connected to a Hewlett Packard 5890 II gas chromatograph, equipped with an unpolar CP-Sil 5CB-MS capillary column (30 m×0.25 mm i.d., film thickness 0.25 μm). The ionization potential was 70 eV and the temperature in the ion source was 180°C. The elemental analysis were performed at the Department of Organic Chemical Technology, Prague, Czech Republic. Compounds **1a**,[13a] **1b**,[3] **3a**,[32] **3b**,[25] **3c**,[33] **4**,[34] **5**,[35] **6**,[36] **7**[37] and **9**[38] were prepared according to literature procedures. The chiral diol **8** was purchased from Fluka. Tetrahydrofuran (THF) was distilled under nitrogen from Na/benzophenone. Acetonitrile and methylene chloride were distilled under nitrogen from calcium hydride and stored over molecular sieves (3 Å).



Scheme 1. *Reagents and conditions*: (a) PhMgBr, THF, –60°C, 0.5 h, 88%; (b) $P(OMe)_3$, MeOH, 80°C, 93%; (c) *t*-BuOK, THF, 0°C, 1 h, 79%; (d) 5% Rh–Al_2O_3, 1 atm H_2, EtOAc:*n*-hexane (1:2), rt, 21 h, 47%.



Scheme 2. *Reagents and conditions*: (a) (i) 1.25 M aq. NaOH, rt, 14 h; (ii) 0.5 M aq HCl, 0°C, 10 min, 75% (Cbz), 34% (Ts); (b) (i) TMSI, MeCN, 0°C, 30 min; MeOH, rt, 10 min; (ii) TsCl, Et_3N, CH_2Cl_2, rt, 21 h, 77%.

3.2. Catalyst preparation

In general, the chiral catalyst was prepared by mixing Me_2TiCl_2[29] (approximately 5.0 mmol) and a solution of the chiral diols **3a**–**c**, **4**, **5** or **8** (5.0 mmol) in dry toluene (15 ml) under argon atm at −75°C. For ligand **6** dry dichloromethane was used as solvent and ligands **7** and **9** were dissolved in toluene/dichloromethane, (4:1) and (3:2), respectively. The resulting solution was then allowed to reach rt and thereafter diluted with toluene or dichloromethane (ca. 0.2 M, quantitative yield was assumed). This solution was stored in the freezer (−20°C) in a sealed flask for up to 1 month without detectable deterioration.

3.3. General method for the HDA reaction (Table 2)

A typical procedure for the asymmetric HDA reaction using stoichiometric amounts of the Ti(IV) complex is given for *N*-sulfinyl **1a**. To a stirred solution of the chiral Ti(IV) complex (0.4 mmol) in toluene (2 ml) a solution of **1a** (0.4 mmol) in dry dichloromethane (0.34 ml) was added at −70°C and argon atm. After 20 min a cold solution of 1,3-cyclohexadiene (1.0 mmol) in toluene (0.4 ml) was added. The reaction mixture was stirred at −70°C for 20 h and then quenched with phosphate buffer (2 ml, pH 7). The resultant mixture was allowed to reach rt, the layers separated, and the aqueous phase extracted with dichloromethane (3×5 ml, p.a. quality). The combined organics were dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was analyzed by ^{1}H NMR to determine the diastereomeric ratio and then purified by flash chromatography (ethyl acetate/*n*-pentane, 1:1). The enantiomeric excess was then determined by chiral HPLC for each of the separated diastereomers. The results and further details are given in Table 2.

3.4. HDA reactions for the investigation of the nonlinear effect

The [$TiCl_2$(**3b**-ate)] catalyst in different enantiomeric compositions were prepared by mixing catalyst solutions of [$TiCl_2$(**3b**-ate)] and [$TiCl_2$(*ent*-**3b**-ate)] (*ent*= enantiomer; 0.15 M in toluene) under Ar-atm. The catalyst mixture (2.7 ml, 0.4 mmol) was stirred for 10 min at rt and then cooled to −70°C. The *N*-sulfinylcarbamate **1a** (1 M in $CHCl_2$, 400 μl, 0.4 mmol) was added and the mixture stirred for 10 min before 1,3-cyclohexadiene (100 μl, 1.0 mmol) was added slowly along the wall of the flask. After stirring at −70°C for 20 h, the reaction mixture was hydrolyzed and worked up as described above. The HDA products **2a** were analyzed by HPLC (Chiracel OJ; 2-propanol/*n*-hexane, 35:65; 0.5 ml min^{-1}; UV detector, 230 nm). The results are shown in Fig. 3.

3.4.1. Benzyl (1*R*,2*S*,4*S*)-2λ^4-thia-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate 2-oxide, (1*R*,2*S*,4*S*)-2a. $[\alpha]_D^{20}$ +134.6 (*c* 1.1, CH_2Cl_2). HPLC analysis (Chiracel OJ; 2-propanol/*n*-hexane, 35:65; 0.5 ml min^{-1}; UV detector, 230 nm): 50% ee; rt 27.6 (1*R*,2*S*,4*S*), 32.5 (1*S*,2*R*,4*R*) min. ^{1}H NMR: 7.40–7.30 (5H, m, Ph), 6.90 (1H, t, *J*=7.5 Hz, H-5), 6.32 (1H, t, *J*=7.3 Hz, H-6), 5.29 (1H, AB, *J*=12.5 Hz, Bn), 5.23 (1H, AB, *J*=12.5 Hz, Bn), 5.17 (1H, br s, H-4), 4.23 (1H, t, *J*=5.2 Hz, H-1), 1.83–1.70 (2H, m, H-1′/H-4′), 1.63–1.55 (1H, m, H-1′), 1.29–1.19 (1H, m, H-4′). ^{13}C NMR: 154.8 (C=O), 136.6 (C-5), 135.5 (1C, Ph), 128.7 (Ph), 128.4 (Ph), 128.0 (Ph), 125.9 (C-6), 68.7 (Bn), 55.7 (C-1), 48.7 (C-4), 24.0 (C-4′), 15.3 (C-1′). IR (KBr): 1717, 1374, 1314, 1297, 1117, 1094. MS: *m*/*z* (% rel. int.) 277 (M^+, 0.2), 233 (2), 107 (3), 91 (100), 80 (35). Anal. calcd for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.73; H, 5.45; N, 5.01%. The relative configuration of (1*R*,2*S*,4*S*)-**2a** was corroborated by X-ray crystallographic analysis (Fig. 4).[41]

3.4.2. Benzyl (1*R,2*R**,4*S**)-2λ^4-thia-3-azabicyclo-[2.2.2]oct-5-ene-3-carboxylate 2-oxide, (1*R**,2*R**,4*S**)-2a**. HPLC analysis (Chiracel OJ; 2-propanol/*n*-hexane, 35:65; 0.5 ml min^{-1}): rt 22.9, 32.6 min. ^{1}H NMR: 7.40–7.30 (5H, m, Ph), 6.80 (1H, t, *J*=7.3 Hz, H-5), 6.29 (1H, t, *J*=7.3 Hz, H-6), 5.30 (1H, AB, *J*=12.5 Hz, Bn), 5.16 (1H, AB, *J*=12.5 Hz, Bn), 5.04 (1H, br s, 4-H), 3.97–3.94 (1H, m, 1-H), 2.86–2.80 (1H, m, H-1′), 2.33–2.27 (1H, m, H-4′), 1.57–1.45 (2H, m, H-1′/H-4′). ^{13}C NMR: 155.2 (C=O), 140.1 (C-5), 135.5, 128.7, 128.4, 128.0, 127.9, 68.6 (Bn), 56.2 (C-1), 48.3 (C-4), 24.9 (C-4′), 11.4 (C-1′). IR: 1712, 1453, 1383,

1294, 1230, 1113, 1051; MS: m/z (% rel. int.) 278 (M^++1, 0.6), 233 (1), 91 (100).

3.4.3. (1*S*,2*R*,4*R*)-3-Tosyl-2λ⁴-thia-3-azabicyclo-[2.2.2]oct-5-ene 2-oxide, (1*S*,2*R*,4*R*)-2b. A colorless oil, which crystallized to a white solid upon standing. $[\alpha]_D^{20}$ −166 (c 1.03, CH_2Cl_2). HPLC analysis (Chiralpak AD; 2-propanol/n-hexane, 1:4; 1.0 ml min^{-1}; 230 nm): 62% ee; rt 29.2 (1*R*,2*S*,4*S*), 46.2 (1*S*,2*R*,4*R*) min. ^{1}H NMR: 7.80 and 7.31 (each 2H, AA′BB′, J_{AB}=8.4 Hz, Ts), 6.70 (1H, dt, J=7.4, 1.5 Hz, H-5), 6.23 (1H, t, J=7.4 Hz, H-6), 4.59–4.54 (1H, m, H-4), 4.35 (1H, dd, J=6.6, 5.2 Hz, H-1), 2.41 (3H, s, Me), 1.80–1.70 (2H, m, H-1′/H-4′), 1.62–1.52 (1H, m, H-1′), 1.16–1.07 (1H, m, H-4′). ^{13}C NMR: 144.5 (Ts), 136.6 (C-5), 136.5 (Ts), 129.9 (Ts), 127.7 (Ts), 125.9 (C-6), 57.4 (C-1), 51.3 (C-4), 24.2 (C-4′), 21.7 (Me), 15.0 (C-1′). IR (KBr): 1348, 1165, 1116. MS m/z (% rel. int.): 298 (0.4), 297 (M^+, 0.7), 266 (0.2), 249 (0.3), 217 (12), 201 (7), 155 (47), 91 (76), 80 (100). Anal. calcd for $C_{13}H_{15}NO_3S_2$: C, 52.51; H, 5.08; N, 4.71. Found: C, 52.26; H, 4.97; N, 4.63%. The structural assignment to (1*S*,2*R*,4*R*)-**2b** was corroborated by X-ray crystallographic analysis of the enantiomer (Fig. 5).[41] A racemic sample, (1*R**,2*S**,4*S**)-**2b**, recrystallized from CH_2Cl_2/n-heptane, melted at mp 109.5–110.5°C

3.4.4. (1*R,2*R**,4*S**)-3-Tosyl-2λ⁴-thia-3-azabicyclo-[2.2.2]oct-5-ene 2-oxide, (1*R**,2*R**,4*S**)-2b**. A colorless oil, which crystallized to a white solid in the refrigerator. Mp 139.0–139.5°C (CH_2Cl_2/heptane). HPLC analysis (Chiralpak AD; 2-propanol/n-hexane, 1:4; 1.0 ml min^{-1}; 230 nm): rt 27.3 (–), 36.3 (+) min. ^{1}H NMR: 7.71 and 7.30 (each 2H, AA′BB′, J_{AB}=8.4 Hz, Tos), 6.37 (1H, dd, J=8.0, 5.9 Hz, H-5), 6.11 (1H, t, J=7.5 Hz, H-6), 4.47 (1H, m, H-4), 4.00 (1H, m, H-1), 2.84–2.79 (1H, m, H-1′), 2.43 (3H, s, Me), 2.28–2.19 (1H, m, H-4′), 1.50–1.38 (2H, m, H-1′/H-4′). ^{13}C NMR: 144.6 (Ts), 139.5 (C-5), 136.6 (Ts), 130.0 (Ts), 128.2 (Ts), 127.1 (C-6), 57.4 (C-1), 50.8 (C-4), 25.4 (C-4′), 21.7 (Me), 10.9 (C-1′). Anal. calcd for $C_{13}H_{15}NO_3S_2$: C, 52.51; H, 5.08; N, 4.71. Found: C, 52.50; H, 4.90; N, 4.62%.

3.5. Benzyl [(1*S*,4*R*)-4-(phenylsulfinyl)cyclohex-2-enyl]-carbamate, 10

A solution of phenylmagnesium bromide in ether (3 M, 1.65 ml, 4.95 mmol) was added to a stirred solution of (1*R*,2*S*,4*S*)-**2a** (50% ee; 1.22 g, 4.4 mmol) in anhydrous THF (30 ml) at −60°C. The resultant mixture was stirred for 30 min and then hydrolyzed with aqueous NH_4Cl (satd, 60 ml). The layers were separated and the aqueous layer extracted with ether (3×20 ml). The combined organics were washed with brine (20 ml), dried ($MgSO_4$) and concentrated in vacuo. Purification of the crude product by flash chromatography (ethyl acetate/n-pentane, 1:1 to 7:3) afforded the allylic sulfoxide **10** (1.38 g, 3.89 mmol, 88%) as a colorless oil which crystallized to white crystals on standing in the refrigerator. $[\alpha]_D^{20}$ +202.3 (c 1.0, $CHCl_3$). HPLC analysis (Chiracel OJ; 2-propanol/n-hexane, 35:65; 0.5 ml min^{-1}): 55% ee; rt 18.6 (1*S*,4*R*), 30.0 (1*R*,4*S*) min. ^{1}H NMR: 7.62–7.54 (2H, m, Ph), 7.54–7.47 (3H, m, Ph), 7.41–7.28 (5H, m, Bn), 6.06 (1H, dd br, J=9.6, 2.2 Hz, H-2), 5.56 (1H, d br, J=9.6 Hz, H-3), 5.09 (1H, AB, J=12.4 Hz, CH$_2$Ph), 5.07 (1H, AB, J=12.4 Hz, CH$_2$Ph), 4.94 (1H, d br, NH), 4.25 (1H, s br, H-1), 3.32 (1H, s br, H-4), 2.13–2.04 (1H, m, H-5), 2.04–1.92 (1H, m, H-5), 1.75–1.63 (2H, m, H-6). ^{13}C NMR: 155.8 (C=O), 141.9, 136.5, 135.9 (C-2), 131.3 (Ph), 129.1 (2×C, Ph), 128.6 (2×C, Bn), 128.2 (Bn), 128.1 (Bn), 124.7 (2×C, Ph), 122.2 (C-3), 66.8 (Bn), 60.2 (C-4), 45.6 (C-1), 26.7 (C-6), 21.1 (C-5). IR (KBr): 3300, 1705, 1525, 1245, 1045. Anal. calcd for $C_{20}H_{21}NO_3S$: C, 67.58; H, 5.95; N, 3.94. Found: C, 67.11; H, 5.76; N, 3.93%. A racemic sample of **10**, recrystallized in CH_2Cl_2/n-heptane, melted at 96.0–96.2°C.

3.6. Benzyl [(1*S*,2*R*)-2-hydroxycyclohex-3-enyl]-carbamate, 11

To a solution of allylic sulfoxide **10** (55% ee; 1.32 g, 3.70 mmol) in methanol (80 ml) was added trimethyl phosphite (525 μl, 4.44 mmol) and the mixture was refluxed at 80°C for 5 h. The mixture was concentrated in vacuo and the residue purified by flash chromatography (ethyl acetate/n-pentane, 1:1) to afford the allylic alcohol **11** as a colorless oil (0.86 g, 3.44 mmol, 93%). $[\alpha]_D^{20}$ −55.8 (c 1.0, CH_2Cl_2). HPLC analysis (Chiracel OD-H; 2-propanol/n-hexane, 1:9; 0.7 ml min^{-1}): 58% ee; rt 13.2 (1*S*,2*R*), 22.0 (1*R*,2*S*) min. ^{1}H NMR: 7.35–7.30 (5H, m, Ph), 5.87 (1H, ABt, J=9.9, 3.5 Hz, H-4), 5.78 (1H, ABdd, J=9.9, 2.2 Hz, H-3), 5.39 (1H, d br, J=7.3 Hz, NH), 5.09 (2H, s, Bn), 4.11 (1H, s br, H-2), 3.81–3.73 (1H, m, H-1), 2.14 (2H, s br, H-5), 2.01 (1H, s br, OH), 1.80–1.72 (1H, m, H-6), 1.68–1.58 (1H, m, H-6). ^{13}C NMR: 156.2 (C=O), 136.6 (Ph), 131.6 (C-4), 128.6 (3×C, Ph), 128.2 (2×C, Ph), 127.3 (C-3), 66.8 (C-2), 65.2 (Bn), 50.7 (C-1), 24.8 (C-5), 23.5 (C-6). IR (KBr): 3400 (m; O-H, N-H), 1700, 1500. MS: m/z (% rel. int.) 248 (M^++1, 0.5), 247 (M^+, 0.3), 178 (27), 117 (30), 91 (100).

3.7. (3a*S*,7a*R*)-3a,4,5,7a-Tetrahydrobenzo[*d*]-[1,3]oxazolidin-2-one, 12

A cooled (0°C) solution of potassium *tert*-butoxide (0.40 g, 3.56 mmol) in anhydrous THF (10 ml) was added to a solution of **11** (58% ee; 0.81 g, 3.28 mmol) in anhydrous THF (110 ml) at 0°C and the mixture was stirred for 1 h. The reaction mixture was diluted with aqueous NH_4Cl (satd, 80 ml) at 0°C, the layers were separated and the aqueous layer was extracted with ether (4×20 ml). The combined organics were washed with brine (20 ml), dried ($MgSO_4$) and concentrated in vacuo. Purification of the crude product by flash chromatography (ethyl acetate/n-pentane, 4:1) afforded the cyclic carbamate **12** as a white solid (0.36 g, 2.58 mmol, 79%). $[\alpha]_D^{20}$ +15.0 (c 1.0, CH_2Cl_2). ^{1}H NMR: 6.58 (1H, s br, NH), 6.16 (1H, dt, J=10.1, 4.0 Hz, H-6), 5.81 (1H, dtt, J=10.1, 3.7, 1.8 Hz, H-7), 4.90 (1H, m, H-7a), 3.97 (1H, sex, J=3.7 Hz, H-3a), 2.28–2.18 (1H, m, H-5), 1.99–1.89 (1H, m, H-5), 1.89–1.82 (1H, m, H-4), 1.72–1.64 (1H, m, H-4). ^{13}C NMR: 160.3 (C=O), 134.3 (C-6), 122.7 (C-7), 72.5 (C-7a), 51.2 (C-3a), 25.7 (C-4),

20.8 (C-5); IR (KBr): 3300, 1740, 1720. GC–MS: m/z (% rel. int.): 139 (M^+, 3), 124 (3), 111 (9), 95 (51), 67 (47), 41 (100). Anal. calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.66; H, 6.54; N, 9.80%. A racemic sample of **12** melted at 83.2–84.5°C.

3.8. (3a*S*,7a*R*)-3a,4,5,6,7,7a-Hexahydrobenzo[*d*]-[1,3]oxazolidin-2-one, (3a*S*,7a*R*)-13

A solution of the carbamate **12** (53 mg, 0.38 mmol) in hexane (5 ml) and ethyl acetate (3 ml) was hydrogenated at 1 atm and 25°C for 21 h using 5% Rh–Al_2O_3 (10 mg) as catalyst. The catalyst was removed by filtration through Celite 545 and the filtrate concentrated in vacuo. Purification of the crude by flash chromatography (ethyl acetate/*n*-pentane, 4:1) afforded the cyclic carbamate (3a*S*,7a*R*)-**13** as a white solid (25 mg, 0.18 mmol, 47%). $[\alpha]_D^{20}$ +17.9 (*c* 1.1, abs. EtOH) lit.[16] +25.0 (*c* 1.0, EtOH). ^{1}H NMR: 5.60 (1H, s br, NH), 4.58 (1H, dt, $J=4.8$, 6.6 Hz, H-7a), 3.73 (1H, qua, $J=6.2$ Hz, H-3a), 2.03–1.96 (1H, m, H-7), 1.86–1.70 (2H, m, H-4/H-7), 1.66–1.40 (4H, m, H-4/H-5/2×H-6), 1.33–1.22 (1H, m, H-5). ^{13}C NMR: 160.5 (C=O), 76.0 (C-7a), 51.8 (C-3a), 28.8 (C-7), 26.8 (C-4), 19.9, 19.6. GC–MS m/z (% rel. int.): 142 (4), 141 (M^+, 53), 98 (100). Anal. calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.92; H, 7.68; N, 9.69%.

3.9. *N*-[(1*R*)-Cyclohex-3-enyl]-*p*-toluenesulfonamide, (*R*)-14b

A suspension of (1*S*,2*R*,4*R*)-**2b** (from entry 11, Table 2; 320 mg, 1.1 mmol) in aqueous NaOH (1.25 M, 5 ml) was stirred for 19 h at 25°C. The mixture was cooled to 0°C and added aqueous HCl (0.5 M, 12 ml) and CH_2Cl_2 (15 ml). The layers were separated and the aqueous layer neutralized by addition of aqueous $NaHCO_3$ (satd), and then extracted with CH_2Cl_2 (3×15 ml). The combined organics were dried ($MgSO_4$) and concentrated in vacuo. Purification of the crude by flash chromatography (ethyl acetate/*n*-pentane, 1:3) afforded the (1*R*)-*N*-tosyl amine (*R*)-**14b** as a white solid (96 mg, 0.38 mmol, 34%, 64% ee). Mp 65.8–67.0°C. $[\alpha]_D^{20}$ +2.0 (*c* 1.0, CH_2Cl_2); HPLC analysis (Chiralpak AD; abs. ethanol/*n*-hexane, 1:9; 1.0 ml min^{-1}, 230 nm): 64% ee; rt 18.8 (1*R*), 21.7 (1*S*) min. ^{1}H NMR: 7.76 and 7.29 (each 2H, AA′BB′, $J_{AB}=8.4$ Hz, Ts), 5.65–5.59 (1H, m AB, 4-H), 5.50–5.44 (1H, m AB, 3-H), 4.62 (1H, d br, $J=7.7$ Hz, NH), 3.50–3.42 (1H, m, 1-H), 2.42 (3H, s, Me), 2.19 (1H, d br, $J=16.9$ Hz, 2-H), 2.08–2.01 (2H, m, 5-H), 1.86–1.76 (1H, m, 2-H), 1.76–1.68 (1H, m, 6-H), 1.56–1.47 (1H, m, 6-H). ^{13}C NMR: 143.3 (C, Ar), 138.3 (C, Ar), 129.8 (2×C, Ar), 127.1 (C-4), 127.0 (2×C, Ar), 123.9 (C-3), 49.0 (C-1), 32.5 (C-2), 28.9 (C-6), 23.4 (C-5), 21.6 (Me). IR (KBr): 3270. MS m/z (% rel. int.) 251 (M^+, 1), 197 (6), 172 (21), 155 (31), 133 (65), 91 (100). Anal. calcd for $C_{13}H_{17}NO_2S$: C, 62.12; H, 6.82; N, 5.57. Found: C, 62.30; H, 6.76; N, 5.46%.

3.10. Benzyl *N*-[(1*S*)-cyclohex-3-enyl]carbamate, (*S*)-14a

Treatment of (1*R*,2*S*,4*S*)-**2a** (52% ee; 284 mg, 1.02 mmol) according to the procedure described above for preparation of (*R*)-**14b** afforded after flash chromatography (ethyl acetate/pentane, 3:7) (*S*)-**14a** as a white solid (205 mg, 87%). Data for (*S*)-**14a**. $[\alpha]_D^{20}$ −13.9 (52% ee, *c* 0.895, CH_2Cl_2). ^{1}H NMR: 7.36–7.32 (5H, m, Ph), 5.67 (1H, ABm, $J=9.9$ Hz, H-4), 5.59 (1H, ABm, $J=9.9$ Hz, H-3), 5.09 (2H, s, Bn), 4.79 (1H, s br, NH), 3.87 (1H, m, H-1), 2.39 (1H, d br, $J=16.8$ Hz, H-2), 2.12 (2H, s br, H-5), 1.92–1.82 (2H, m, H-2/H-6), 1.61–1.53 (1H, m, H-6). ^{13}C NMR: 155.8 (C=O), 136.7 (Ph), 128.6 (2×C, Ph), 128.23 (Ph), 128.17 (2×C, Ph), 127.1 (C-4), 124.4 (C-3), 66.6 (Bn), 46.2 (C-1), 32.0 (C-2), 28.3 (C-6), 23.5 (C-5). IR (KBr): 3300, 1680, 1540. GC–MS m/z (% rel. int.): 231 (M^+, 1.1), 170 (10), 152 (7), 132 (6), 108 (32), 91 (100), 80 (51). Anal. calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.97; H, 7.30; N, 5.97%. A racemic sample of **14a** melted at 63.0–63.5°C.

3.11. *N*-[(1*S*)-Cyclohex-3-enyl]-*p*-toluenesulfonamide, (*S*)-14b

Trimethylsilyl iodide (412 μl, 3.03 mmol) was added to a solution of *N*-benzoyloxyamine (*S*)-**14a** (52% ee; 180 mg, 0.78 mmol) in dry acetonitrile (10 ml) at 0°C. The solution was stirred at 0°C for 30 min before methanol (2.8 ml) was added. After 10 min, the volatiles were evaporated in vacuo and the residue dissolved in dry CH_2Cl_2 (4 ml). The solution was cooled to 0°C before triethylamine (273 μl, 1.96 mmol) and tosyl chloride (187 mg, 0.98 mmol) were added. The reaction mixture was stirred at rt for 24 h. H_2SO_4 (2 M, 2 ml) was added and the aqueous layer neutralized by saturated aqueous $NaHCO_3$ (8 ml). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3×5 ml). The combined organics were dried ($MgSO_4$) and concentrated in vacuo. Purification of the crude by flash chromatography (diethyl ether/*n*-pentane, 3:7) afforded the (1*S*)-*N*-tosylamine, (*S*)-**14b** (73 mg, 0.29 mmol, 37%, 54% ee).

Acknowledgements

This work was supported by a grant from the *Norwegian Research Council* (grant 122792/432 to A.B.) which is gratefully acknowledged. We also thank Mr. Jostein Johansen (University of Tromsø) and Associate Professor Helge Kjøsen (Norwegian University of Science and Technology, Trondheim) for performing the mass spectrometric measurements.

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41. Inquiries concerning the X-ray structures of *endo*-**2a** and (1*R*,2*S*,4*S*)-**2b** should be addressed to L.K.H. Crystallographic data (excluding structure factors) for structures *endo*-**2a** and (1*R*,2*S*,4*S*)-**2b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 181233 and CCDC 178740, respectively. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).