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Asymmetric *N*-sulfinyl dienophile Diels–Alder cycloadditions using chiral Ti(IV)-based Lewis acids

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Abstract

Enantioselective Diels–Alder reactions of 1,3-cyclohexadiene with *N*-sulfinylbenzyl carbamate (**1a**) or *N*-sulfinyl-*p*-toluenesulfonamide (**1b**) promoted by chiral Ti(IV)-based Lewis acids are reported. The *endo*-adducts were obtained in 15–76% ee.

Keywords: asymmetric inductions; Diels–Alder reactions; *N*-sulfinyl compounds; titanium and compounds.

Hetero [4+2]-cycloadditions of *N*-sulfinylaniline to conjugated dienes were first described by Wichterle and Rocek in 1953.[1] Since then a number of Diels–Alder reactions for various types of *N*-sulfinyl compounds have been reported.[2–8] The resulting heterocyclic products can be further transformed into synthetically useful derivatives, e.g. homoallyl amines and vicinal aminoalcohols, by well-established techniques.[7] Stereoselective Diels–Alder reactions with chiral *N*-sulfinyl dienophiles[9,10] or chiral dienes[11] have given optically active adducts with high diastereoselectivity (>97%). However, no reports of Diels–Alder reactions with *N*-sulfinyl dienophiles utilising chiral Lewis acid catalysts to induce enantioselectivity have been found. Herein, we present enantio- and diastereoselective Diels–Alder reactions of 1,3-cyclohexadiene and *N*-sulfinyl compounds **1a**[12] or **1b**[3] promoted by chiral Ti(IV)-based Lewis acids (Table 1).

Initial studies using titanium catalysts prepared in situ from titanium sources such as $TiCl_2(O\text{-}i\text{-}Pr)_2$,[13] $TiCl_4$ or $Ti(O\text{-}i\text{-}Pr)_4$ and the bidentate ligands **3a**,[14] **3c**,[15] and **3d**[16] following established methods,[14,16,17] afforded low and/or not reproducible yields of the Diels–Alder products **2**. However, by turning to the thermally labile precursor Me_2TiCl_2,[18] more reliable results were obtained.

In general, the chiral catalyst was prepared by mixing Me_2TiCl_2[18] (approximately 5.0 mmol) and a solution of the chiral diols **3a**–**c** (5.0 mmol) in dry toluene (15 ml) under argon atm at −75°C. For the ligands **3d**–**e**, dichloromethane was used as solvent. The resulting solution was then allowed to reach room temperature 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.

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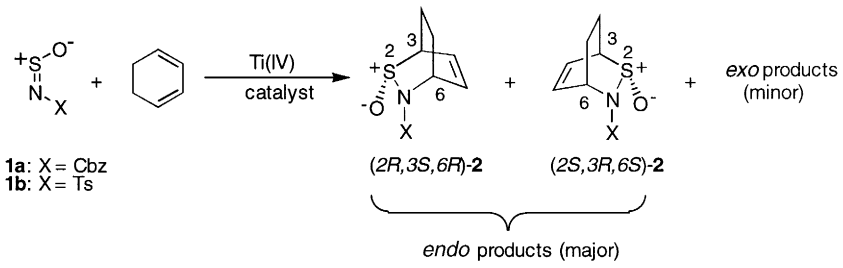
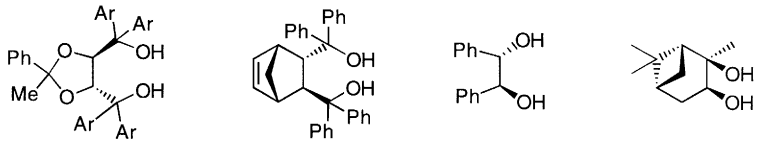
Table 1
Asymmetric Diels–Alder reactions of *N*-sulfinyl dienophiles **1a** and **1b** with 1,3-cyclohexadiene promoted by chiral Ti(IV) Lewis acids





Entry	Dienophile	Ligand	Solvent Tol.-CH_2Cl_2	Temp, °C (time, h)	% Yield[a]	*endo*/*exo*[b]	% ee[c] (config. *endo*-**2**)
1	**1a**	**3a**	8 : 1	-55 (20)	71	>95 : <5	53 (*2S,3R,6S*)
2	**1b**	**3a**	6 : 1	-90 (17)	83	94 : 6	69 (*2R,3S,6R*)
3	**1a**	**3b**	8 : 1	-70 (20)	69	92 : 8	37 (*2S,3R,6S*)
4	**1b**	**3b**	6 : 1	-86 (16)	68	50 : 50	37 (*2R,3S,6R*)
5	**1a**	**3c**	6 : 1	-68 (18)	69	>95 : <5	76 (*2R,3S,6R*)
6	**1b**	**3c**	6 : 1	-86 (17)	58	91 : 9	74 (*2S,3R,6S*)
7	**1a**	**3d**	5 : 2	-42 (16)	32	75 : 25	13 (*2S,3R,6S*)
8	**1b**	**3d**	2 : 1	-90 (16)	29	82 : 18	15 (*2S,3R,6S*)
9	**1a**	**3e**	6 : 1	-42 (16)	35	80 : 20	13 (*2S,3R,6S*)
10	**1b**	**3e**	6 : 1	-90 (16)	42	80 : 20	36 (*2S,3R,6S*)

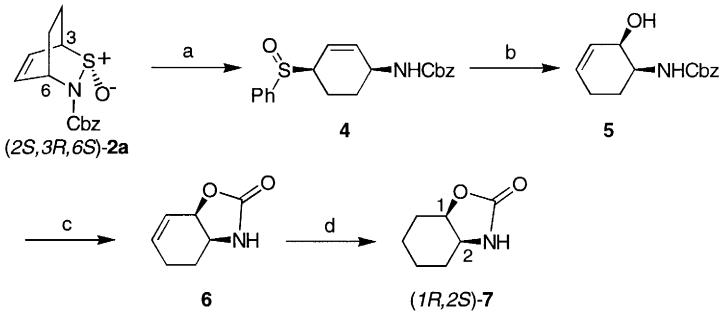
[a] Isolated yield of *endo*- and *exo*-**2**.
[b] Determined by ^{1}H NMR (400 MHz) on crude product.
[c] Determined by HPLC analysis using DAICEL Chiracel OJ (2-propanol/*n*-hexane, 35:65; 0.5 ml/min) for **2** (X = Cbz) and DAICEL Chiralpak AD (2-propanol/*n*-hexane, 20:80; 1.0 ml/min) for **2** (X = Ts).

A typical experiment for the asymmetric Diels–Alder reaction using stoichiometric amounts of the Ti(IV) complex was as follows: 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 precooled solution of 1,3-cyclohexadiene (1.0 mmol) in toluene was added. The reaction mixture was stirred for 20 h and then quenched with phosphate buffer (2 ml, pH=7). The resultant mixture was heated to room temperature, 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 analysed by ^{1}H NMR (400 MHz) to determine the diastereomeric ratio and then purified by flash chromatography (ethyl acetate:*n*-pentane, 50:50). The diastereomers were separated and the enantiomeric excess determined by chiral HPLC (Chiracel OJ; 2-PrOH:*n*-hexane, 35:65; 0.5 ml/min; UV detector, 230 nm).

The results of the enantioselective Diels–Alder reactions of the dienophiles **1a** or **1b** with 1,3-

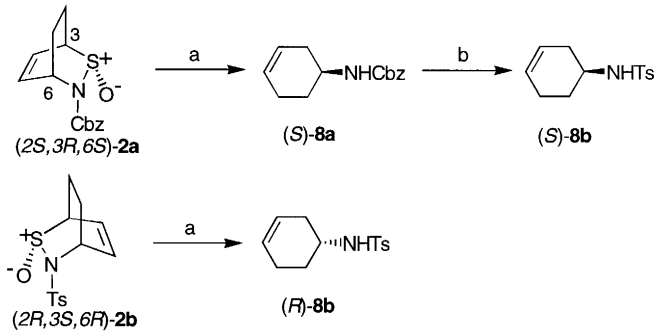
cyclohexadiene in the presence of the Ti(IV) complexes (1 equiv.) are shown in Table 1. The overall yields of *endo*- and *exo*-isomers were 29–83% with the *endo*-isomer as the major product. The *endo*-adduct **2** was formed with 15–76% ee. Interestingly, reactions promoted by the Ti(IV)–TADDOL-based ligands **3a**–**c** gave *endo*-**2a** (X=Cbz) and **2b** (X=Ts) of opposite configuration. In addition, ligands **3a** and **3c** behaved like 'enantiomers' in the way that they gave enantiomers of *endo*-**2** as the predominant product (compare entry 1 with 5, and entry 2 with 6). The best enantioselectivities, 76% ee for **1a** (entry 5) and 74% ee for **1b** (entry 6), were obtained with ligand **3c**. In general, the 1,4-diol ligands **3a**–**c** were superior to the 1,2-diols **3d**–**e** with respect to yield and selectivity. While 1,4-diols constitute the optimal ligands for chelated titanium complexes, 1,2-diols most likely form aggregates to reduce ring strain.[19]

The relative configuration of the cycloadducts **2** were determined by considering the shielding effect of the 'S=O' group similar to the work described by Zhang and Flann.[20] The absolute configuration of **2a** (X=Cbz) at C-3 and C-6 was established by chemical correlation with the known cyclic carbamate **7**[21] using Weinreb's methodology[10] (see Scheme 1). The *endo*-**2a** obtained in entry 1 (Table 1) was rearranged to hydroxy carbamate **5** and then cyclized to carbamate **6**. Catalytic hydrogenation of **6** provided (1*R*,2*S*)-**7**[21] ($[\alpha]_D^{20}$ +17.9 (*c* 1.1, abs. EtOH)) and thus *endo*-**2** (entry 1, Table 1) had the (2*S*,3*R*,6*S*)-configuration.



Scheme 1. (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%

The absolute configuration of *endo*-**2b** (X=Ts) was determined by chemical correlation with *endo*-**2a** (Scheme 2). The *endo*-**2a** obtained in entry 1 (Table 1) was rearranged to carbamate **8a** followed by deprotection and tosylation to yield tosylate (*S*)-**8b**. Compound *endo*-**2b** (entry 2) was rearranged to tosylate (*R*)-**8b**, correspondingly. Comparison of the tosylates **8b** by HPLC (Chiralpak AD column; abs. EtOH:*n*-hexane, 1:9; 1.0 ml/min; UV detector, 230 nm) showed that *endo*-**2b** obtained in entry 2 had the (2*R*,3*S*,6*R*) configuration.



Scheme 2. (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; (ii) MeOH, rt, 10 min; (iii) TsCl, Et_3N, CH_2Cl_2, rt, 21 h, 77%

In summary, the first enantioselective hetero [4+2]-cycloaddition of *N*-sulfinyl dienophiles with 1,3-cyclohexadiene have been achieved by using stoichiometric amounts of chiral titanium catalysts. Efforts to develop new catalysts with the aim to increase the turnover and the enantioselectivities for these reactions are now in progress.

Acknowledgements

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