HETEROCYCLES, Vol. 68, No. 5, 2006, pp. 1025 - 1030. © The Japan Institute of Heterocyclic Chemistry
Received, 8th February, 2006, Accepted, 20th March, 2006, Published online, 24th March, 2006. COM-06-10695

ASYMMETRIC DIELS–ALDER REACTION OF 2-(*p*-TOLYLSULFINYL)-1-INDOLYL α,β-UNSATURATED ENONES

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Abstract–The asymmetric Diels–Alder reaction of chiral 1-[2-(*p*-tolylsulfinyl)-indolyl enones was examined. The cycloaddition of cinnamyl and crotonyl α,β-unsaturated enones with cyclopentadiene in the presence of a lanthanoid triflate as a Lewis acid proceeds smoothly to give the corresponding *endo* cycloadducts with high diastereoselectivity.

INTRODUCTION

As an extension of our studies on asymmetric cycloaddition using a chiral sulfoxide whose sulfinyl group is remote from the reactive site, we recently reported that the 1-[2-(*p*-tolylsulfinyl)]pyrrolyl enone (**1**) serves as a good dienophile in the Diels–Alder reaction and an acceptor in the Michael reaction.[1] Moreover, 1-[2-(*p*-tolylsulfinyl)]indolyl enones (**2**) give high diastereoselectivity in the conjugate addition[2] as well as in the tandem conjugate addition[3] by the use of an arylcopper reagent, whereas the 3-sulfinyl derivative (**3**) showed poor diastereoselectivity in the conjugate addition reaction.

In contrast to the pyrrolyl sulfinyl enones (**1**), with the indolyl system of **2**, the unfavorable steric interaction with the H-7 of the indole ring and the carbonyl substituent is counter-balanced by the steric interaction due to the *p*-tolylsulfinyl moiety. The H-7 in the indole nucleus should thus affect the diastereoselectivity in cycloadditions. Judging from the results of the conjugate addition of **2** and **3**, it is likely that the enone **3** also gives lower diastereoselectivities in the Diels–Alder reaction. We thus carried out the Diels–Alder reaction of 1-indolyl enone (**2**). The preparation of the dienophile (**2**) starting from the auxiliary (**4**) was previously reported.[1]

RESULTS AND DISCUSSION

At first, we examined the cycloaddition of **2a** with cyclopentadiene in the absence or presence of a Lewis acid (Table 1). Without a Lewis acid, the reaction was sluggish and no substantial yield of the cycloadduct was obtained under mild conditions (Entry 1). On the other hand, Lewis acid-promoted Diels–Alder reaction using **2a** proceeded smoothly to give the cycloadducts (**5a**)–(**8a**) under mild conditions. Since we showed that lanthanoid triflates are more effective than other Lewis acids such as $AlCl_3$, BF_3•Et_2O or ZnX_2 for the Diels–Alder reaction using chiral sulfoxides,[4] we employed a variety of lanthanoid trflates as a reaction promoter.[5] Of the lanthanoid triflates examined, good results were obtained by using an equal amount of $Nd(OTf)_3$ as a Lewis acid, although lower diastereoselectivities were observed with a smaller amount of the Lewis acid. At lower reaction temperature (Entry 15), high diastereoselectivity was observed, accompanied by a certain amount of the starting material (**2a**). With the crotonyl derivative (**2b**), the diastereoselectivity and the yield are comparable with those of the cinnamoyl derivative (**2a**).

Table 1. Diels–Alder Reaction of **2** with Cyclopentadiene[a]

Entry	Dienophile	Lewis acid	(equivalent)	Solvent	Time /h	Isolated total yield/%	De/% of **5** and **6** [b]	Ratio of (**5**+**6**):(**7**+**8**)
1	**2a**	none	—	CH_2Cl_2	48	9	42	70:30
2	**2a**	$AlCl_3$	1.0	CH_2Cl_2	48	9	55	—[c]
3	**2a**	$Zn(OTf)_3$	1.0	CH_2Cl_2	48	53	64	89:11
4	**2a**	$Sc(OTf)_3$	1.0	CH_2Cl_2	48	60	87	90:10
5	**2a**	$Yb(OTf)_3$	1.0	CH_2Cl_2	48	67	61	92:8
6	**2a**	$Sm(OTf)_3$	1.0	CH_2Cl_2	48	75	73	96:4
7	**2a**	$La(OTf)_3$	1.0	CH_2Cl_2	48	47	88	89:11
8	**2a**	$Nd(OTf)_3$	1.0	CH_2Cl_2	48	85	76	99:1
9	**2a**	$Nd(OTf)_3$	1.0	THF	48	27	72	88:12
10	**2a**	$Nd(OTf)_3$	1.0	PhH	48	35	96	99:1
11	**2a**	$Nd(OTf)_3$	0.1	CH_2Cl_2	48	25	54	88:12
12	**2a**	$Nd(OTf)_3$	0.5	CH_2Cl_2	48	78	77	97:3
13[d]	**2a**	$Nd(OTf)_3$	1.0	CH_2Cl_2	72	83	83	>99:1
14	**2a**	$Nd(OTf)_3$	1.0	PhH	144	68	89	>99:1
15	**2a**	$Nd(OTf)_3$	1.0	CH_2Cl_2	91	39	87	99:1
16	**2a**	$Nd(OTf)_3$	1.0	CH_2Cl_2	142	91	78	96:4
17	**2b**	$Nd(OTf)_3$	0.5	CH_2Cl_2	142	63	82	90:10
18	**2b**	$Nd(OTf)_3$	1.0	CH_2Cl_2	168	87	85	91:9

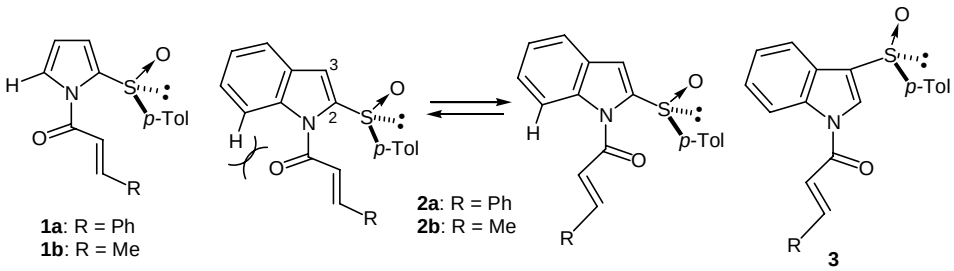
[a] Reaction was conducted with a large excess of cyclopentadiene (25 equiv.) at room temperature.

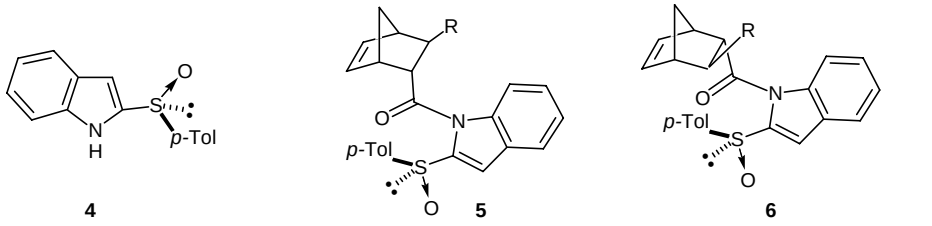
[b] De's (diastereoisomeric excesses) were calculated by chiral HPLC analysis and/or ^{1}H-NMR analysis.

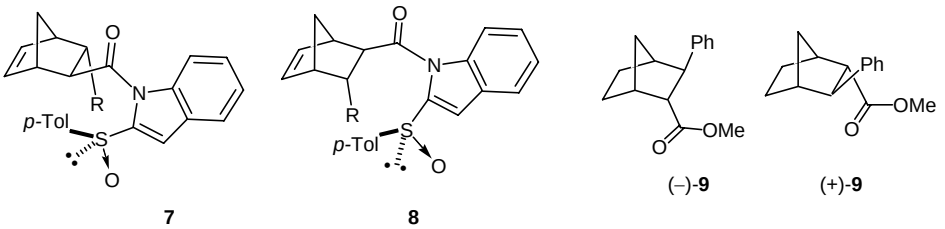
[c] Not determined.

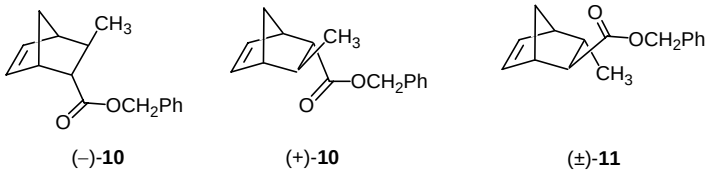
[d] The reaction was carried out at 0 °C.

The absolute stereochemistry of the major *endo* adduct (**5a**) was determined by transformation of **5** and **6** into **9** by methanolysis followed by hydrogenation of the resulting methyl ester.[1] Treatment of the original product mixture with MeONa thus produced essentially a mixture of the known methyl esters (**9**) and **4** without any loss of optical purity, although no substantial yield of the *exo* ester, derived from the adducts (**7a** and **8a**), was obtained. HPLC analysis of **9** by using a chiral column resolved two peaks in the ratio indicated in Table 1. The *endo* product ratios were also confirmed by ^{1}H NMR analysis (*see* EXPERIMENTAL).









The reaction mechanism of the diastereoselective Diels–Alder reaction of **2** induced by the sulfinyl auxiliary (**4**) is consistent with previous proposals.[4]

In summary, we have shown that asymmetric Diels–Alder reaction using the sulfinylindole as a chiral auxiliary proceeds to give the *endo* adducts in high yield under conventional conditions. Mechanistic analysis of the conformations of the sulfoxides and their Lewis acid complexes by theoretical calculation[6] is now in progress.

EXPERIMENTAL

The symbol S_s expresses that the absolute configuration of the sulfinyl center is *S*. Melting points were determined with a Yanaco micro melting point apparatus and are uncorrected. IR spectra were recorded as KBr disk on a Perkin-Elmer Spectrum One FT-IR spectrometer. NMR spectra were measured in $CDCl_3$ solution with tetramethylsilane as internal standard, on a JEOL AL-400 or EX-400 spectrometer. The following abbreviations are used: singlet (s), doublet (d), doublet of doublets (dd), multiplet (m), and

broad (br). *J*-Values are given in Hz. MS were taken with a JEOL JMS-D300 or JMS-SX102A spectrometer. Optical rotations were recorded on a JASCO DIP-360 digital polarimeter. Extracts were dried over anhydrous $MgSO_4$ before evaporation of solvents on a rotary evaporator under reduced pressure. Dry dichloromethane was freshly distilled with CaH_2 prior to use. TLC analyses were performed using Merck precoated silica $60F_{254}$ plates (0.2 mm). Column chromatography was carried out on Merck silica gel (70–230 mesh) or Merck silica gel (230–400 mesh). Chiral HPLC analyses were performed using a chiral column (4.6×250 mm). Peak ratios by HPLC were determined with an integrator (Shimadzu Chromatopac C-R6A).

Typical procedure for the Diels–Alder reaction of 2 with cyclopentadiene (Entry 16 in Table 1).

To a solution of **2a**[2] (200 mg, 0.52 mmol, 94% ee) in dry dichloromethane (10 mL) was added $Nd(OTf)_3$ (305 mg, 0.52 mmol) in a pressure bottle and the suspension was stirred at room temperature for 0.5 h. Cyclopentadiene (1.1 mL, 13 mmol) was added to the suspension via a syringe. After being stirred for 142 h, the mixture was treated with saturated aq. NH_4Cl (10 mL). The aqueous layer was extracted with $CHCl_3$ (10 mL×3) and the combined organic phase was washed with saturated brine, dried, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane–AcOEt) to afford a mixture of **5a**–**8a** (212 mg, 91%). Although the other diastereoisomeric adducts were not obtained in isomerically pure form, crystallization afforded almost diastereomerically pure **5a.**

(1*S*,2*S*,3*R*,4*R*,*S*$_s$)-2-[2-(*p*-Tolylsufinyl)indolyl-1-carbonyl]-3-phenylbicyclo[2.2.1]hept-5-ene (5a): mp 112–124 °C (hexane–Et_2O); $[\alpha]_D^{24}$ –111.8 (*c* 0.51, $CHCl_3$)[95% ee (*S*$_s$,1*S*,2*S*,3*R*,4*R* *vs* *R*$_s$,1*R*,2*R*,3*S*,4*S*), 90% de (*S*$_s$,1*S*,2*S*,3*R*,4*R*) *vs* (*S*$_s$,1*R*,2*R*,3*S*,4*S*)]; ν_{max}/cm^{-1} 1686, 1042; δ_H (400 MHz) 7.75–7.70 (2H, m, ArH), 7.59 (2H, d, *J* 8.2, *p*-Tol), 7.4–7.1 (7H, m, ArH), 6.22 (1H, dd, *J* 5.4, 3.1, CH=), 4.56 (1H, dd, *J* 5.4, 2.7, CH=), 3.74 (1H, dd, *J* 4.6, 3.5, H-2), 3.49 (1H, dd, *J* 4.6, 1.7, H-3), 3.26 (1H, br s, H-1), 3.11 (1H, br s, H-4), 2.36 (3H, s, Me), 1.98 (1H, d, *J* 8.8, H-7), 1.57 (1H, dd, *J* 8.8, 1.7, H-7); δ_C (100 MHz) 171.9, 145.8, 143.4, 142.7, 141.8, 140.0, 136.6, 131.1, 130.1, 129.4 (2C), 128.7 (2C), 127.5 (2C), 127.3 (2C), 126.3, 125.9, 123.7, 122.7, 114.2, 113.4, 53.7, 48.1, 47.8, 46.8, 46.5, 21.4. Anal. Calcd for $C_{29}H_{25}NO_2S$: C, 77.14; H, 5.58; N, 3.10. Found: C, 77.21; H, 5.27; N, 2.91; HRMS Calcd for $C_{29}H_{25}NO_2S$: 451.16060. Found: 451.16228; EI-MS 451 (M^+), 435, 385, 239, 207, 131, 103.

Minor adduct (**6a**): δ_H (400 MHz) 7.75–7.05 (11H, m, ArH), 6.48 (1H, dd, *J* 5.4, 3.1, CH=), 6.25 (1H, dd, *J* 5.4, 3.9, CH=), 4.19 (1H, dd, *J* 4.3, 3.9, H-3), 3.34 (1H, d, *J* 4.3, H-2), 3.18 (1H, br s, H-1 or H-4), 2.84 (1H, br s, H-4 or H-1), 2.34 (3H, s, Me), 2.02 (1H, d, *J* 8.7, H-7), 1.57 (1H, dq, *J* 8.7, 1,9, H-7).

The *endo* diastereoselectivity (**5a** *vs* **6a**) was determined by the integral value of each of the apparent olefinic signals (δ 6.22, 4.56 for **5a**, and δ 6.48, 6.26 for **6a**). The *endo*/*exo* selectivity (96:4) was also estimated by the integral value of each of the olefinic signals (δ 6.48, 6.22 for **5a** and **6a,** respectively, δ 6.61, 6.52 for **7a** and **8a**). The absolute stereochemistry of the major *endo* adduct (**5a**) was finally established by transformation of **5a** into the known methyl ester (**9**).

A mixture of the **5a**-enriched adducts (51 mg, 0.11 mmol), purified by recrystallization, was thus treated with MeONa (0.34 mL, 0.5 M in MeOH) followed by hydrogenation by the usual method to give (–)-**9** (13 mg, 52%) whose chiral HPLC shows 90% ee. Chiral HPLC analysis [Chiralcel OD-H, 254 nm, hexane–propan-2-ol (400:1), flow rate 1.0 mL min^{-1}, retention time (–)-**9**: t_R 7.7 min; (+)-**9**: t_R 10.7 min]. The auxiliary (**4**) was also recovered without a loss of optical purity.

(1*S*,2*S*,3*R*,4*R*,*S*$_s$)-2-[2-(*p*-Tolylsufinyl)indolyl-1-carbonyl]-3-methylbicyclo[2.2.1]hept-5-ene (2b). Starting from **2b** (96% ee) the adducts (**5b**–**8b**) were obtained in a similar manner to the procedure for **5a**–**8a**. The major *endo* adduct (**5b**) was isolated as a crystalline material by recrystallization from hexane–AcOEt and characterized by ^{1}H NMR analysis.

The *endo* diastereoselectivity (**5b** *vs* **6b**) was determined by the integral value of each of the olefinic signals (δ 6.09, 4.44 for **5b**, and δ 6.38, 6.29 for **6b**). The *endo*/*exo* selectivity (96:4) and the absolute stereochemistry of **5b** were deduced by the chiral HPLC analysis of the benzyl esters (**10** and **11**). Thus, alcoholysis of the original product mixture (12.2 mg) with BnOLi (6 equiv.) in dry THF (2 mL) produced a mixture of **10**[1] and **11**[7], (5.6 mg, 76%) with efficient recovery of **4** (6.9 mg, 86%, 95% ee). Chiral HPLC analysis [Chiralcel OJ-H, 245 nm, hexane–propan-2-ol (200:1), flow rate 0.5 mL min^{-1}, retention time (–)-**10**: t_R 30.8 min; (+)-**10**: t_R 34.4 min]. The *exo* benzyl ester (**11**) was not adequately resolved on the chiral HPLC under these conditions (retention time (±)-**11**: t_R 25.2 min). (–)-**10**:(+)-**10**:(±)-**11** = 83:8:9.

5b: mp 174–177 °C (hexane–AcOEt); $[\alpha]_D^{17}$ –183.2 (*c* 0.41, $CHCl_3$)[95% ee (*S*$_s$,1*S*,2*S*,3*R*,4*R*) *vs* (*R*$_s$,1*R*,2*R*,3*S*,4*S*), 86% de (*S*$_s$,1*S*,2*S*,3*R*,4*R*) *vs* (*S*$_s$,1*R*,2*R*,3*S*,4*S*)]; ν_{max}/cm^{-1} 1688, 1049; δ_H (400 MHz) 7.75 (2H, br d, *J* 7.7, ArH), 7.69 (1H, s, ArH), 7.67 (1H, br d, *J* 8.4, ArH), 7.56 (2H, d, *J* 8.1, ArH), 7.45–7.32 (2H, m, ArH), 7.18 (2H, d, *J* 8.1, ArH), 6.09 (1H, dd, *J* 5.6, 3.1, CH=), 4.44 (1H, dd, *J* 5.6, 2.7, CH=), 3.18 (1H, t, *J* 3.7, H-2), 3.13 (1H, br s, H-1 or H-4), 2.54 (1H, br s, H-4 or H-1), 2.34 (3H, s, Me), 2.25 (1H, m, H-3), 1.73 (1H, d, *J* 8.8, H-7), 1.42 (1H, dd, *J* 8.8, 1,6, H-7), 1.18 (3H, d, *J* 7.1, Me); δ_C (100 MHz) 172.3, 142.8, 141.7, 130.1, 129.6 (2C), 129.4 (2C), 127.4 (2C), 125.9, 123.6, 122.7 (2C), 114.3, 113.1 (2C), 53.5, 49.2, 46.8, 46.6, 36.4, 21.4, 20.5. Anal. Calcd for $C_{24}H_{23}NO_2S$: C, 74.02; H, 5.95; N, 3.60. Found: C, 73.92; H, 6.04; N, 3.64; EI-MS 389 (M^+), 373, 239, 207, 132, 69.

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