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Diastereoselective [4+2]Cycloaddition of Cyclopentadiene to N-Tosyliminoacetyl Derivatives of Chiral Secondary Alcohols

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Syntheses of five *N*-tosylimines of chiral glyoxylates are described. The *N*-tosylimines obtained were used as dienophiles in the Lewis acid-catalyzed asymmetric hetero--Diels-Alder reaction with cyclopentadiene to afford cycloadducts with moderate diastereoisomeric excess.

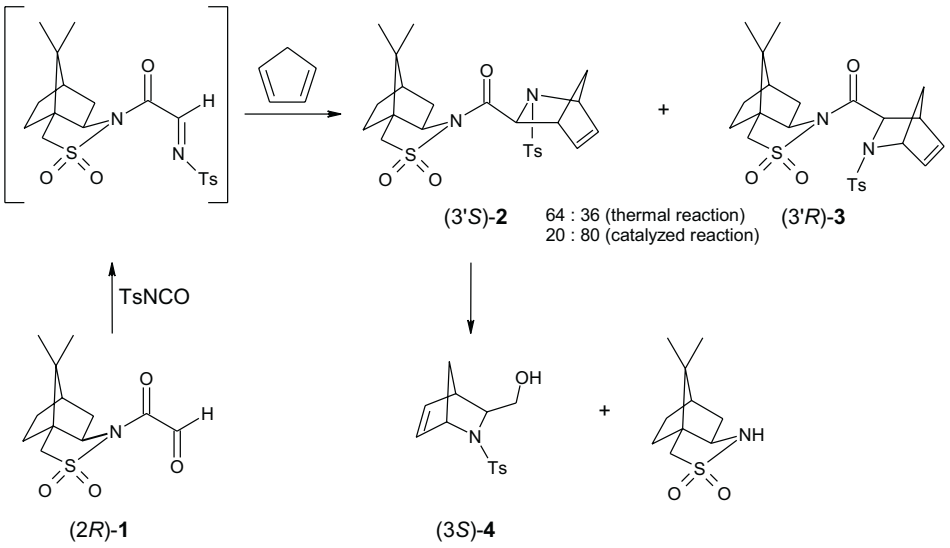
Key words: [4+2]cycloaddition, *N*-tosylimines, cyclopentadiene, Lewis acids, diastereoselectivity

The [4+2]cycloaddition reaction of reactive imines with 1,3-dienes is a promising tool for the synthesis of many interesting natural compounds, such as alkaloids, antivirial agents, ribofuranosylamines, *etc*., possessing six-membered heterocyclic units [1–4]. This methodology has been further extended to the asymmetric version [5] by means of chiral dienes [6], chiral imines [7] or chiral catalysts [8,9].

In the case of the asymmetric imine-Diels-Alder reaction using chiral heterodienophiles, the chiral auxiliary is usually connected either directly to the nitrogen atom [10–12] or by connection to the acyl moiety [13]. When the chiral auxiliary is connected directly to the nitrogen atom, its removal is often performed by hydrogenation with sacrifice of the inducting stereogenic center and concomitant reduction of unprotected unsaturated linkages. Recently, we have shown the alternative acyl substitution and its consequence for the stereochemical course of the imine-Diels-Alder reaction (Scheme 1) [14].

When the *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam (**1**) was treated with tosyl isocyanate, followed by cyclopentadiene, a selectivity of 28% d.e. was observed for the uncatalyzed [4+2]cycloaddition, performed in toluene at room temperature (20°C). The diastereoselectivity increased to 60% d.e. of the opposite (3′*R*)-diastereoisomer, when the reaction was conducted in the presence of $TiCl_4$ at –78°C. More recently, we have found that the reduction of the cycloadduct (3′*S*)-**2** with $LiAlH_4$ leads to the optically pure amino alcohol (3*S*)-**4**, and the (2*R*)-bornane-10,2-sultam is regenerated in 95% yield [15]. Similar results have also been obtained when *N*-benzyliminoacetyl derivatives of (2*R*)-bornane-10,2-sultam and other chiral secondary alcohols were used as dienophiles [15].

Scheme 1

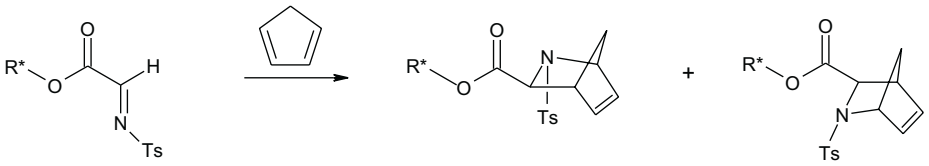


Now we report the extension of our studies on the asymmetric Lewis acid-catalyzed [4+2]cycloaddition of cyclopentadiene to *N*-tosylimines of glyoxylates of five various chiral secondary alcohols (**5a**–**5e**).

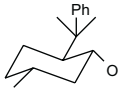
RESULTS AND DISCUSSION

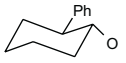
The known (1*R*)-menthyl glyoxylate (**5a**) [16] was treated with *p*-toluenesulfonyl isocyanate in refluxing toluene for 32 hours. Subsequent addition of cyclopentadiene (1.0 mol. equiv.) to the crude *N*-tosylimine afforded, after 48 hours at 20°C, a 55:45 diastereoisomeric mixture of (3′*S*)-*exo*-**6a**/(3′*R*)-*exo*-**7a** (10% d.e.), unseparable by chromatography. This mixture was then subjected to reduction with $LiAlH_4$ to give an enantiomeric mixture of (3*S*)/(3*R*)-*exo*-**4** with predominance of laevorotatory (3*S*)-enantiomer, which has been previously obtained in optically pure form (Scheme 1) [15]. Scheme 2 and Table 1 show the results of our studies of asymmetric induction in thermal as well as Lewis acid-catalyzed [4+2]cycloadditions using chiral *N*-tosylimines obtained from the known glyoxylates of chiral secondary alcohols **5a** [16], **5b** [17], **5c** [18], **5d** [19], and **5e** [20]. In all instances we obtained unseparable mixtures of diastereoisomers (3′*S*)-*exo*-**6**/(3′*R*)-*exo*-**7** with predominance of the former one of (3′*S*) absolute configuration.

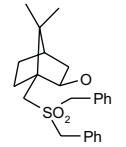
Scheme 2

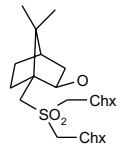


5a R*=  (3'*S*) - **6a** (3'*R*) - **7a**

5b R*=  (3'*S*) - **6b** (3'*R*) - **7b**

5c R*=  (3'*S*) - **6c** (3'*R*) - **7c**

5d R*=  (3'*S*) - **6d** (3'*R*) - **7d**

5e R*=  (3'*S*) - **6e** (3'*R*) - **7e**

Chx = cyclohexyl

Table 1. Results of asymmetric [4+2]cycloaddition of cyclopentadiene to chiral dienophiles **5a**–**5e**.

Dienophile	Lewis Acid (equiv.)	Temp. [°C]	Time [h]	Yield [%]	Diastereoisomeric Ratio (3′*S*)-**6** : (3′*R*)-**7**	Diastereoisomeric Excess (d.e.) [%]
5a	–	20	48	51	55 : 45	10
	$Eu(fod)_3$ (0.02)	20	48	45	54 : 46	8
	$SnCl_4$ (0.1)	–78	3	17	55 : 45	10
	$SnCl_4$ (0.5)	–78	3	15	55 : 45	10
	$SnCl_4$ (1.0)	–78	3	15	54 : 46	8
	$TiCl_4$ (0.2)	–78	3	16	53 : 47	6
5b	–	20	48	45	66 : 34	32
	$Eu(fod)_3$ (0.02)	20	48	48	63 : 37	26
	$SnCl_4$ (0.1)	–78	3	15	60 : 40	20
	$SnCl_4$ (0.5)	–78	3	19	58 : 42	16
	$SnCl_4$ (1.0)	–78	3	16	55 : 45	10
	$TiCl_4$ (0.2)	–78	3	13	62 : 38	24
	$TiCl_2(OPr^i)_2$ (0.2)	–78	3	22	58 : 42	16
	$TiCl(OPr^i)_3$ (0.2)	–78	3	12	66: 34	32

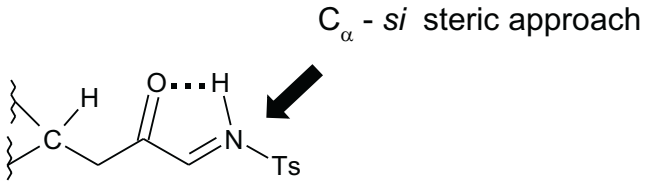
Table 1 (continuation)

	–		20	48	49	61 : 39	22
	$Eu(fod)_3$	(0.02)	20	48	53	60 : 40	20
	$SnCl_4$	(0.1)	–78	3	20	58 : 42	16
5c	$SnCl_4$	(0.5)	–78	3	19	57 : 43	14
	$SnCl_4$	(1.0)	–78	3	15	55 : 45	10
	$TiCl_4$	(0.2)	–78	3	17	56 : 44	12
	$TiCl_4$	(0.5)	–78	3	16	55 : 45	10
	–		20	48	62	61 : 39	22
	$Eu(fod)_3$	(0.02)	20	48	60	58 :42	16
	$SnCl_4$	(0.1)	–78	3	18	59 : 41	18
5d	$SnCl_4$	(0.5)	–78	3	17	57 : 43	14
	$SnCl_4$	(1.0)	–78	3	13	55 : 45	10
	$TiCl_4$	(0.2)	–78	3	14	56 : 44	12
	$TiCl_4$	(0.5)	–78	3	15	55 : 45	10
	–		20	48	60	60 : 40	20
	$Eu(fod)_3$	(0.02)	20	48	65	59 : 41	18
	$SnCl_4$	(0.1)	–78	3	19	60 : 40	20
5e	$SnCl_4$	(0.5)	–78	3	13	56 : 44	12
	$SnCl_4$	(1.0)	–78	3	14	55 : 45	10
	$TiCl_4$	(0.2)	–78	3	16	57 : 43	14
	$TiCl_4$	(0.5)	–78	3	13	54 : 46	8

Surprisingly, the best asymmetric induction as well as chemical yields were obtained for thermal, uncatalyzed reactions. Application of a weak Lewis acid ($Eu(fod)_3$) as a catalyst resulted in a slight decrease in the diastereoselectivity for all five chiral dienophiles used. Stronger Lewis acids, such as $SnCl_4$ and $TiCl_4$, caused more pronounced decrease in the diastereoselectivity as well as in the chemical yield. Among chiral dienophiles, *N*-tosylimine derived from (–)-phenylmenthyl glyoxylate (**5b**) gave the best asymmetric inductions in both thermal and Lewis acid-catalyzed [4+2]cycloadditions.

Rationalization of our results may be based on earlier well established concepts. The very high *exo*-selectivity (*endo*-cycloadducts were not detected) resulting from this type of aza-Diels-Alder reaction can be explained on the basis of minimized hydrophobic interactions in water or wet organic solvents [10,21] or greater second-order orbital electronic requirements of the *N*-withdrawing group [2]. The predominance of (3′*S*) absolute configuration of cycloadducts formed under both thermal and catalytic conditions, according to earlier Oppolzer's proposals [22], may be explained by the assumption that the most favorable conformation is reached when the alkoxy C–H bond is *syn*-periplanar with the C=O moiety of the ester. As a consequence, all these prosthetic groups possess identical sterically induced C_α-*si* topicity, when the (*E*) C=N bond is *s-cis* with that of the C=O (Scheme 3). Despite the fact that the N–H and C=O bonds are parallel, an intramolecular weak hydrogen bond with the carbonyl moiety is not excluded and could partially account for this conformational stability.

Scheme 3



More precise rationalization of the decrease in the diastereoselectivity, when strong Lewis acids ($SnCl_4$ and $TiCl_4$) are applied, is difficult, and some additional experiments are needed for clarification of this problem.

The [4+2]cycloadditions of 1,3-dienes to *N*-substituted imines derived from glyoxylates of chiral alcohols seem to be an interesting preparative route to the six-membered heterocycles containing nitrogen atom. Since this type of cycloadducts are of substantial interest in medicinal chemistry, as valuable starting materials for the straightforward synthesis of many antibiotics and antivirial agents, more work oriented on improvement of asymmetric induction as well as isolation procedures is necessary.

EXPERIMENTAL

General. Optical rotations were recorded using a JASCO DIP-360 polarimeter with a thermally jacketed 10 cm cell. ^{1}H NMR spectra were measured with a Varian Unity Plus 200 (200 MHz) spectrometer, and ^{13}C NMR spectra were recorded using a Varian Unity Plus 200 (50 MHz) spectrometer. All chemical shifts are quoted in parts per million relative to tetramethylsilane (δ, 0.00 ppm). IR spectra were obtained on a Perkin-Elmer 1640 FTIR spectrophotometer in films or KBr pellets. Mass spectra were recorded on an AMD-604 Intectra instrument using the electron impact (EI) technique. Flash-column chromatography was performed according to Still *et al*. [23] on silica gel (Kieselgel-60, Merck, 200–400 mesh). TLC was performed on Merck DC Alufolien Kieselgel 60F-254. Cyclopentadiene was prepared prior to use by distillation of a commercially available cyclopentadiene dimer. Glyoxylates of chiral alcohols were prepared according to the known literature procedures: **5a** [16], **5b** [17], **5c** [18], **5d** [19], **5e** [20]. Optically pure reference alcohol (3*S*)-**4** was prepared according to our own procedure [15].

General procedure for the cyclization reactions.

Thermal reaction. A glyoxylate (**5a**–**5e**, 1 mmol) was dissolved in 10 mL of freshly distilled toluene, then tosyl isocyanate (0.15 mL, 1 mmol) was added, and the solution was heated under reflux for 32 hours. After cooling, 0.5 mL of freshly distilled cyclopentadiene was added, the reaction mixture was stirred at 20°C for 48 hours, then evaporated, and the residue was subjected to flash chromatography on silica gel (hexane-ethyl acetate, 8:2 v/v) yielding an unseparable mixture of diastereoisomers. The same procedure was applied for the $Eu(fod)_3$-catalyzed reaction.

Lewis acid-catalyzed reaction. To cold –78°C toluene, a toluene solution of *N*-tosylimine (1 mmol), prepared as in the previous procedure, was added under argon, followed by an appropriate portion of a Lewis acid and cyclopentadiene (0.5 mL). The reaction mixture was stirred under these conditions for 3 hours, and then it was worked up as in the previous procedure.

A mixture of cycloadducts (3′*S*)-6a and (3′*R*)-7a. IR (film): 3487, 3058, 2963, 2919, 2884, 1728, 1603, 1492, 1476, 1386, 1369, 1223, 1179, 1093, 986, 908, 824, 732 cm^{-1}; ^1H NMR: 0.65 (d, 2H), 0.75 (d, 2H), 0.8–1.15 (m, 9H), 1.32–1.54 (m, 2H), 1.66 (s, 1H), 1.71 (s, 1H), 1.86 (m, 2H), 2.03 (t, 1H), 2.41 (s, 3H), 3.28 (s, 1H), 3.46 (d, 1H), 4.59 (d, 1H), 4.72 (m, 1H), 6.21 (m, 2H), 7.48 (dd, 4H); ^{13}C NMR: 15.8, 16.0, 20.5, 20.7, 21.4, 21.8, 22.9, 23.1, 25.8, 26.0, 31.2, 34.0, 40.3, 40.4, 45.9, 46.6, 49.5, 49.6, 53.3, 59.7, 59.8, 64.3, 64.5, 75.2, 127.5, 127.7, 129.2, 135.7, 136.0, 136.1, 136.4, 136.5, 143.3, 170.1; EIMS HR calculated for $C_{24}H_{33}NO_4S$: 431.21303, found: 431.21307; Elemental analysis, calculated: C, 66.8%, H, 7.7%, N, 3.3%, obtained: C, 66.0%, H, 8.0%, N, 2.9%; $[\alpha]_D^{22}$ –0.5 for the sample of the alcohol **4** obtained from reduction of the mixture of cycloadducts **6a** and **7a**.

A mixture of cycloadducts (3′*S*)-6b and (3′*R*)-7b. IR(film): 3462, 3058, 2955, 2869, 1734, 1599, 1496, 1444, 1342, 1160, 1092, 1032, 909, 814, 766, 732 cm^{-1}; ^1H NMR: 0.82 (d, 6H), 0.93 (m, 1H), 1.14 (d, 4H), 1.16–2.2 (m, 9H), 2.35 (s, 3H), 2.82 (s, 0.34H), 2.94 (s, 0.66H), 4.41 (d, 0.66H), 4.48 (d, 0.34H), 4.69 (dt, 1H), 5.58 (m, 1H), 6.15 (m, 1H), 7.03–7.26 (m, 7H), 7.57 (d, 0.68H), 7.75 (d, 1.36H); ^{13}C NMR: 21.0, 21.6, 21.7, 23.4, 26.3, 28.7, 31.2, 34.5, 35.2, 39.2, 40.6, 48.9, 50.0, 50.4, 58.0, 125.0, 125.3, 127.0, 127.4, 128.2, 129.2, 129.6, 131.1, 135.8, 137.0, 137.2, 142.6, 143.4, 152.0, 170.2; LSIMS HR calculated for $C_{30}H_{37}NO_4SNa^+$: 530.2362, found: 530.2357; Elemental analysis, calculated: C, 70.7%, H, 7.6%, N, 2.7%, obtained: C, 70.9%, H, 7.5%, N, 2.6%; $[\alpha]_D^{22}$ –1.7 for the sample of the alcohol **4** obtained from reduction of the mixture of cycloadducts **6b** and **7b**.

A mixture of cycloadducts (3′*S*)-6c and (3′*R*)-7c. IR (film): 3470, 3028, 2935, 2859, 1747, 1599, 1495, 1449, 1348, 1327, 1250, 1191, 1094, 1017, 911, 816, 757, 701 cm^{-1}; ^1H NMR: 0.99 (m, 2H), 1.17–1.62 (m, 6H), 1.75–2.18 (m, 5H), 2.39 (s, 3H), 2.70 (m, 1H), 3.17 (s, 0.4H), 3.29 (s, 0.6H), 4.35 (d, 0.6H), 4.46 (d, 0.4H), 5.05 (m, 1H), 6.08 (m, 2H), 7.12–7.28 (m, 5H), 7.59 (d, 0.8H), 7.73 (d, 1.2H); ^{13}C NMR: 21.7, 24.9, 25.9, 32.0, 32.5, 34.3, 45.9, 46.0, 49.4, 49.9, 50.1, 50.5, 59.9, 60.3, 64.4, 65.0, 76.8, 77.5, 126.7, 127.7, 127.8, 128.0, 128.5, 129.5, 135.5, 136.2, 136.5, 137.0, 143.2, 143.6, 169.9, 170.3; LSIMS HR calculated for $C_{26}H_{29}NO_4SNa^+$: 474.1705, found: 474.1715; Elemental analysis, calculated: C, 67.2%, H, 6.4%, N, 3.1%, obtained: C, 66.9%, H, 6.6%, N, 2.8%; $[\alpha]_D^{22}$ –1.4 for the sample of the alcohol **4** obtained from reduction of the mixture of cycloadducts **6c** and **7c**.

A mixture of cycloadducts (3′*S*)-6d and (3′*R*)-7d. IR (KBr): 3434, 3048, 2968, 2866, 1757, 1666, 1583, 1568, 1323, 1297, 1147, 1099, 1055, 936, 917, 803, 795, 754, 741 cm^{-1}; ^1H NMR: 0.75 (s, 3H), 0.95 (s, 3H), 0.84–1.39 (m, 3H), 1.58–2.17 (m, 6H), 2.37 (s, 1.26H), 2.39 (s, 1.74H), 2.55 (d, 0.58H), 2.57 (d, 0.42H), 3.43 (m, 3H), 4.2–4.58 (m, 5H), 5.04 (m, 1H), 5.76–6.11 (m, 2H), 7.17-7.33 (m, 12H), 7.59 (d, 0.84H), 7.69 (d, 1.16H); ^{13}C NMR: 20.2, 20.6, 21.7, 27.3, 30.6, 39.6, 44.6, 46.5, 47.0, 49.4, 49.7, 50.3, 51.7, 59.6, 60.8, 64.6, 64.9, 77.4, 79.7, 80.0, 128.1, 128.2, 128.3, 128.9, 129.7, 135.3, 136.0, 136.1, 136.2, 136.4, 136.6, 170.0; LSIMS HR calculated for $C_{36}H_{44}N_2O_6S_2Na^+$: 711.2569, found: 711.2533; Elemental analysis, calculated: C, 66.3%, H, 6.4%, N, 4.1%, obtained: C, 64.6%, H, 6.5%, N, 3.8%, $[\alpha]_D^{22}$ –1.4 for the sample of the alcohol **4** obtained from the reduction of the mixture of cycloadducts **6d** and **7d**.

A mixture of cycloadducts (3′*S*)-6e and (3′*R*)-7e. IR (KBr): 3441, 2935, 2856, 1747, 1634, 1599, 1454, 1394, 1326, 1258, 1161, 1093, 1049, 982, 894, 854, 821, 775 cm^{-1}; ^1H NMR: 0.87 (s, 1.23H), 0.89 (s, 1.77H), 1.01–1.51 (m, 13H), 1.54–2.08 (m, 20H), 2.40 (s, 3H), 2.64 (d, 0.59H), 2.69 (d, 041H), 3.21–3.51 (m, 5H), 4.57 (s, 0.59H), 4.64 (s, 0.41H), 4.88 (dd, 0.59H), 5.01 (dd, 0.41H), 6.18 (m, 1H), 7.11–7.77 (m, 4H); ^{13}C NMR: 20.3, 20.7, 21.7, 25.4, 26.7, 27.3, 31.0, 32.7, 32.9, 33.2, 33.4, 39.7, 44.6, 46.4, 46.9, 49.6, 54.3, 57.7, 57.8, 59.3, 60.8, 64.4, 64.9, 79.9, 125.5, 128.0, 128.3, 129.7, 136.0, 136.2, 136.5, 136.8, 143.8, 170.0; LSIMS HR calculated for $C_{36}H_{52}N_2O_6S_2Na^+$: 695.3164, found: 695.3186; Elemental analysis, calculated: C, 62.1%, H, 7.7%, N, 4.0%, obtained: C, 60.9%, H, 8.2%, N, 3.7%; $[\alpha]_D^{22}$ –1.3 for the sample of the alcohol **4** obtained from the reduction of the mixture of cycloadducts **6e** and **7e**.

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