Thermal and Lewis Acid-promoted Asymmetric Hetero Diels–Alder Reaction of a 1-Thiabuta-1,3-diene System (Thiochalcone) with Chiral Acrylic Esters and *N*-Acryloyl- and *N*-Crotonyl-carboximides

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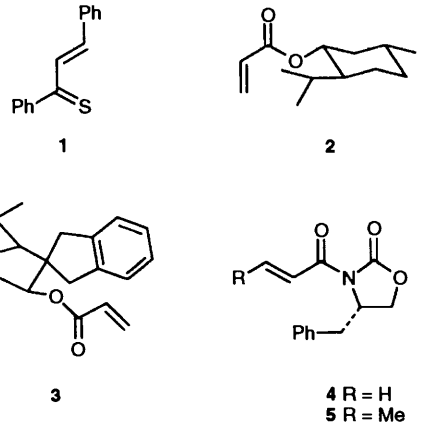
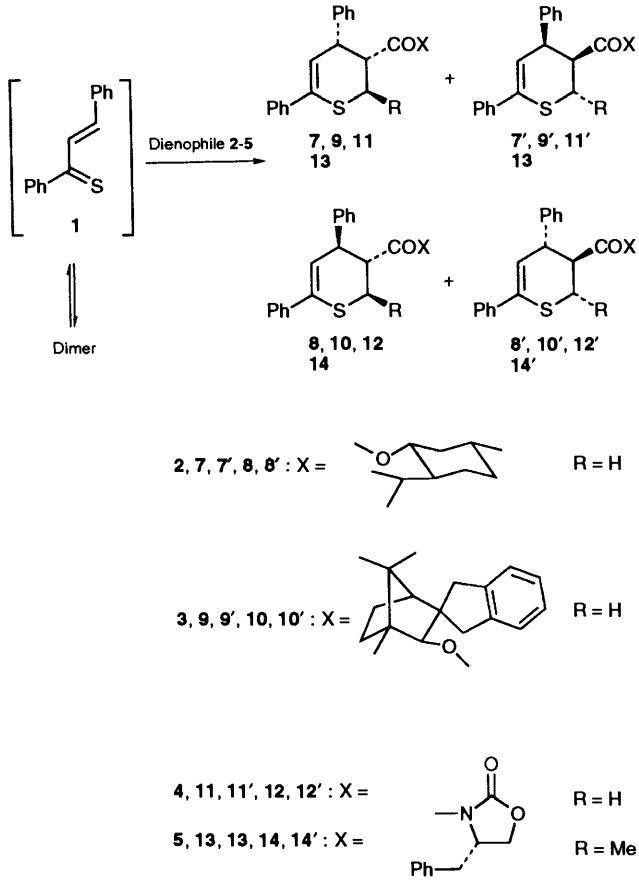
Thermal and Lewis acid-promoted asymmetric hetero Diels–Alder reactions of the thiabutadiene **1** with the chiral dienophiles **2–5** derived from (−)-menthol, (+)-borneol and (−)-4-benzyloxazolidinone affords the optically active dihydrothiopyran derivatives. The chiral induction is in the range 13–92% d.e. depending mainly upon the auxiliary chiral groups. The absolute configuration of the *endo* cycloadducts is confirmed by the derivatization based on X-ray crystallographic analysis.

We recently reported the first example of an asymmetric hetero-Diels–Alder (AHDA) reaction of the thiabutadiene (thiochalcone **1**) with chiral (−)-dimethyl fumarate to give an optically active dihydrothiopyran derivative.[1] With this di-substituted, C_2 symmetric dienophile, asymmetric induction as high as 71% d.e. was attained by the use of a suitable Lewis acid catalyst. Generally, diastereoselectivities in Diels–Alder reactions can be dramatically influenced by the substitution pattern and as well as the arrangement within both dienes and dienophiles, and upon the nature of the chiral auxiliaries attached and the reaction conditions employed.[2] In order to evaluate this thiabutadiene–AHDA reaction in this respect, we have now investigated the reaction with other well-documented acryloyl or crotonyl dienophiles **2–5**. These bear chiral auxiliary groups



that serve as chiral templates of both morphologically and topographically typical models for asymmetric induction, *i.e.*, the convex, concave and Lewis acid chelation models[2,3] derived from (−)-menthol,[4] (+)-borneol[5] and (*S*)-(−)-4-benzyloxazolidinone,[6] respectively. Here, we report results on the uncatalysed (thermal) and Lewis acid-catalysed AHDA reactions of the diene **1** with these chiral dienophiles (Scheme 1).

These results are summarized in Table 1. In all cases, the reaction proceeded smoothly at low temperatures† within a reasonable reaction time to give a good chemical yield of the



Scheme 1

cycloadduct. With (−)-menthyl acrylate **2** the uncatalysed reaction afforded a mixture of the cycloadducts of four diastereoisomers, **7**, **7'**, **8** and **8'**, in 98% yield with an *endo* (3,4-*cis*, **7** + **7'**):*exo* (3,4-*trans*, **8** + **8'**) ratio of 89:11 (Run 1). The diastereo π-face selectivities of the *endo* and *exo* adducts were rather low (24% and 11% d.e., respectively). After screening various Lewis acids and varying the reaction conditions,[1,7] the Lewis acid-promoted reaction at 0 °C (run 4) was found to give the highest d.e. (48%) of the *endo* adducts of compound **2**, whilst maintaining a moderate selectivity. It is noteworthy that the

† The uncatalysed reactions below *ca.* 40 °C and the catalysed reactions at lower temperatures (≪0 °C) were impractical owing to the low rate of the reactions.[1,7]

Table 1 The uncatalysed (thermal) and Lewis acid-catalysed reactions of **1**[a] with dienophiles **2–5**[b]

Run	Dienophile	Lewis acid (equiv.)	Solvent	Temp. (°C)	Time (*t*/h)	Yield[c] (%)	Ratio *endo*:*exo*	π-Facial d.e. *endo*	(%)[d,e] *exo*
1	**2**	—	$CHCl_3$	40	26	98	89:11	24	11
2	**2**	$AlCl_3$ (0.5)	Et_2O	25	2	91	94:6	38	31
3	**2**	$EtAlCl_2$ (1.0)	CH_2Cl_2	25	0.2	97	95:5	44	16
4	**2**	$EtAlCl_2$ (2.0)	CH_2Cl_2	0	3.5	93	93:7	48	8
5	**3**	—	$CHCl_3$	40	53	99	27:73	13	72
6	**3**	$AlCl_3$ (1.0)	Et_2O	25	3.5	75	37:63	48	80
7	**4**	—	PhH	80	1	99	72:28	−50	*f*
8	**4**	Me_2AlCl (0.5)	CH_2Cl_2	−78–0	1.7	99	77:23	73	*f*
9	**5**	—	Ph-H	80	24	99	93:7	−42	−37
10	**5**	$EtAlCl_2$ (1.0)	CH_2Cl_2	25	0.7	96	87:13	92	>98

[a] Thiopyran type dimer and dithiin type dimer were used as precursors of compound **1** in the uncatalysed and catalysed reactions, respectively.[1,7] [b] Molar ratio of **1**:dienophile:Lewis acid = 1.0:3.0:0–2.0 for compounds **2** and **3**; 1.2:1.0:0–1.0 for **4** and **5**. [c] Isolated yield of a mixture of diastereoisomers. [d] Ratio was determined by ^1H NMR (270 or 500 MHz) spectra and/or HPLC. [e] A plus sign denotes that the isomers **7–14** with a 3*R*-configuration was the major product, whilst a minus sign denotes that **7′–14′** was the major product. [f] Ratio was unclear.

Lewis acid (0.5 equiv. $AlCl_3$ in Et_2O) catalyses this thiabutadiene Diels–Alder reaction.

The reaction with the concave dienophile **3** exhibited preferred formation of the *exo* adduct with good π-facial selectivity over the *endo* adduct, using both uncatalysed and catalysed conditions. The preference may be attributable to steric congestion around the highly protected bornyl skeleton encountered in the *endo* transition structures.

With the *N*-acryloyl- and *N*-crotonyl-oxazolidinone dienophiles **4** and **5**, of which the stereochemical behaviour in carbon Diels–Alder reactions have been well-defined by Evans *et al.*,[6] the reactions of compound **1** (runs 7–10) resulted in excellent yields and good stereoselectivities though with some loss of *endo–exo* selectivities compared to those in the reactions with the dienophile **2**. With the more reactive dienophile **4**, the reaction was effectively catalysed by < 1 equiv. of the Lewis acid, whilst the use of 2 equiv. of Lewis acid caused a severe decrease (< 60%) of the chemical yield.[6] The best diastereofacial selectivity (92% d.e.) of the *endo* adducts was observed in the reaction with the dienophile **5** (run 10). The thermal and catalysed reactions with both **4** and **5** showed the opposite diastereofacial selectivity in each case.

The diastereoisomers of the *endo* major cycloadducts **7**, **11** and **13** obtained from the Lewis acid-induced reactions could easily be separated using silica gel chromatography and recrystallisation (except for compound **7**, which was obtained as an oil). Non-destructive removal of the chiral auxiliaries from these diastereoisomerically pure cycloadducts with lithium aluminium hydride (LAH) in tetrahydrofuran at 0 °C afforded the alcohols **15** and **16** (Scheme 2). Mesylation of compound **16** followed by reduction of compound **17** gave the enantiomerically pure dihydrothiopyran **18** with $[\alpha]_D^{26}$ +132.2. On the other hand, the dihydrothiopyran **18** with the same configuration was obtained *via* the procedures i–iii from the cycloadduct **19**, which was formed by the reaction of compound **1** with (−)-dimenthyl fumarate,[1] whose structure was unequivocally established by X-ray crystallographic analysis (Fig. 1).* These facts suggest that the Lewis acid-induced cycloaddition occurs selectively from the C_α-*Si* face of the dienophiles **2**, **4** and **5**. The sense of asymmetric induction in these AHDA reactions is consistent with the topographically well-recognized models.[2–6] The homochiral alcohol **15′**, which could be obtained from the pure minor isomer **9′** by the LAH-reduction, showed the antipodal optical rotation to that of compound **15** ($[\alpha]_D^{26}$ +176), suggesting that the selective cycloadditions occur also from the C_α-*Si* face of **3** under both catalysed and uncatalysed conditions.

Thus, the enantiomerically pure cycloadducts **7**, **11** and **13** could be easily obtained by virtue of both their high chromatographic separability and crystallinity. A promising advantage of this ADHA process is that they can be converted into useful chiral compounds, such as acyclic alcohols with contiguous homochiral stereogenic centres, by further manipulation *via* desulfurization ring-opening.[1]

Experimental†

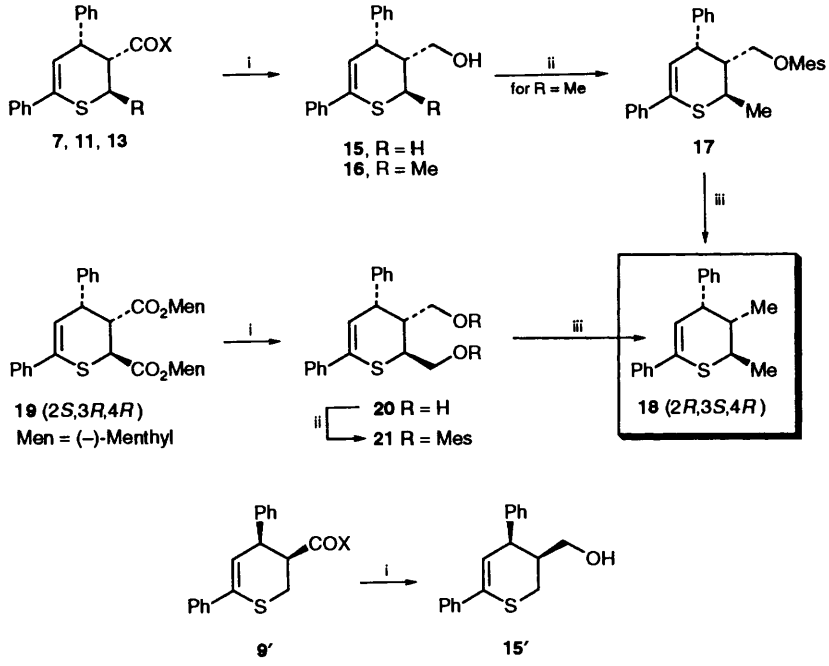
AHDA Reaction of **1** *with* (4S)-3-*Acryloyl*-4-*benzyl*-1,3-*oxazolidin*-2-*one* **4**.—*Typical procedure* (run 8). To a solution of compound **4** (23 mg, 0.1 mmol) in CH_2Cl_2 (2 cm^3) was added a 1.01 mol dm^{-3} hexane solution of Me_2AlCl (0.5 equiv., 0.05 cm^3) at −78 °C under an argon atmosphere and the mixture was stirred for a few min at the same temperature. After the dimer‡ of **1** (27 mg, 1.2 mmol as a monomer) in CH_2Cl_2 (1.5 cm^3) had been added, the reaction mixture was warmed to 0 °C and stirred for a further 1.7 h. The reaction was quenched with 1 mol dm^{-3} HCl or sat. aq. NH_4Cl (3 cm^3) and extracted with CH_2Cl_2 (150 cm^3). The extract was washed with sat. aq. $NaHCO_3$ (30 cm^3), water (2 × 50 cm^3) and sat. brine (2 × 50 cm^3), dried ($MgSO_4$) and filtered (HPLC check). Evaporation of the solvent followed by column chromatography of the residue [silica gel, CH_2Cl_2–hexane (1:1)] gave a mixture of the cycloadducts **11**, **11′**, **12** and **12′** (HPLC, ^1H NMR measurements) in a quantitative yield. Recrystallization of the mixture from ethyl acetate–hexane gave diastereoisomerically pure compound **11**. The *exo* cycloadduct **12** was obtained from the mother liquor *via* chromatography [silica gel, ethyl acetate–hexane (1:2)] followed by recrystallization [ethyl acetate–hexane (1:1)].

(4S)-4-*Benzyl*-3-[(3R,4R)-4,6-*diphenyl*-3,4-*dihydrothiopyran*-3(2H)-*ylcarbonyl*]-1,3-*oxazolidin*-2-*one* **11**: colourless needles, m.p. 258.8–266.4 °C (Found: C, 73.6; H, 5.8; N, 3.1. $C_{28}H_{25}NO_3S$ requires C, 73.8; H, 5.5; N, 3.1%) $[\alpha]_D^{26}$ +362.4 (*c* 0.17 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1782 and 1698; *m*/*z* 455 (M^+, 13%); δ_H(500 MHz, $CDCl_3$) 2.53 (1 H, dd, *J* 11.17 and 13.19), 2.89 (1 H, dd, *J* 2.56 and 13.37), 3.14 (1 H, dd, *J* 3.29 and 13.19), 3.45 (1 H, dd, *J* 11.72 and 13.37), 4.16–4.20 (2 H, m), 4.26 (1 H, ddd, *J* 2.56, 5.68 and 11.72), 4.50 (1 H, t, *J* 5.68), 4.58 (1 H, dddd, *J* 3.29, 4.76, 6.59 and 11.17), 6.20 (1 H, d, *J* 5.68), 7.15–7.17 (2 H, m), 7.22–7.38 (11 H, m) and 7.56–7.59 (2 H, m); δ_C(67.5 MHz, $CDCl_3$) 24.10 (CH_2), 38.24 (CH_2), 41.98 (CH), 43.94 (CH), 55.65 (CH), 66.56 (CH_2O), 120.75 (CH), 126.54 (CH),

* Details will be published in a full paper.

† *J* Values are measured in Hz; $[\alpha]_D$ values are reported in units of 10^{-1} deg cm^2 g^{-1}.

‡ See footnote *a* in Table 1.



Scheme 2 *Reagents and conditions:* i, $LiAlH_4$, THF, 0 °C; ii, $MeSO_2Cl$, Et_3N, 0 °C–room temp., CH_2Cl_2; iii, $NaBH_4$, DMSO, 85 °C

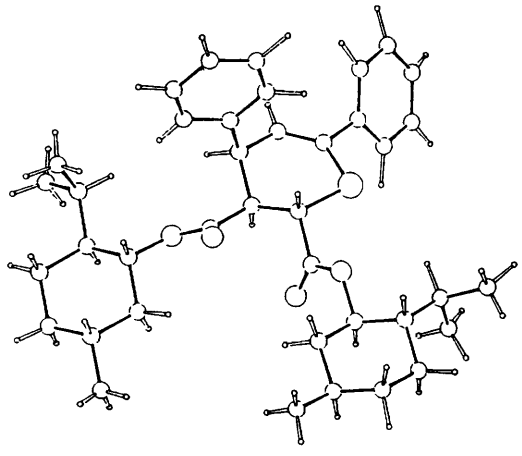


Fig. 1 Molecular structure of **19**

127.37 (CH), 127.69 (CH), 128.30 (CH), 128.43 (CH), 129.04 (CH), 129.25 (CH), 129.59 (CH), 133.83 (C), 135.49 (C), 139.47 (C), 140.30 (C), (*ca.* 153, CO, undetected) and 172.76 (CO).

Conversion of (4S)-4-*Benzyl*-3[(2R,3R,4R)-2-*methyl*-4,6-*diphenyl*-3,4-*dihydrothiopyran*-3-*ylcarbonyl*]-1,3-*oxazolidin*-2-*one* **13** *to* (2R,3S,4R)-2,3-*Dimethyl*-4,6-*diphenyl*-3,4-*dihydro*-2H-*thiopyran* **18**.—To lithium aluminium hydride (81 mg, 2.13 mmol) in tetrahydrofuran (THF, 15 cm^3) was added a solution of the diastereoisomerically pure compound **13** (200 mg, 0.426 mmol) in THF (4 cm^3) at 0 °C under an atmosphere of argon. The reaction mixture was stirred for a while at 0 °C and then diluted with a mixture of THF (5 cm^3) and CH_2Cl_2 (5 cm^3). The reaction was quenched with water (0.1 cm^3), 15% aq. NaOH (0.1 cm^3) and again with water (0.3 cm^3). The mixture was dried ($MgSO_4$) and then filtered through Celite. Concentration of the filtrate and column chromatography of the residue [silica gel, ethyl acetate–benzene–hexane (0.005:1:1)] gave the alcohol **16** as a colourless oil (35 mg, 28%): $[\alpha]_D^{26}$ +13.2 (*c* 0.73 in $CHCl_3$); δ_H(270 MHz, $CDCl_3$) 1.25 (1 H, br s), 1.49 (3 H, d, *J* 6.60), 2.05–2.14 (1 H, m), 3.30 (1 H, dd, *J* 5.93 and 10.89), 3.46 (1 H, dq, *J* 6.60 and 6.60), 3.67 (1 H, dd, *J* 7.59 and 10.89), 3.93 (1 H, dd, *J* 3.96 and 4.29), 6.14 (1 H, d, *J* 3.96), 7.22–7.36 (8 H, m) and 7.53–7.56 (2 H, m); δ_C(67.5 MHz, $CDCl_3$) 21.04 (Me), 35.45 (CH), 40.11 (CH), 44.35 (CH), 61.85 (CH_2), 120.02 (CH), 126.25 (CH), 126.84 (CH), 128.08 (CH), 128.39 (CH), 128.55 (CH), 128.91 (CH), 134.12 (C), 139.94 (C) and 142.01 (C).

To a solution of the alcohol **16** (35 mg, 0.12 mmol) and triethylamine (18 mg, 0.18 mmol) in CH_2Cl_2 (15 cm^3) was added a solution of mesyl chloride (20 mg, 0.18 mmol) in CH_2Cl_2 (3 cm^3) at room temp. After being stirred overnight at room temp., the mixture was extracted with diethyl ether, and the extract dried ($MgSO_4$) and concentrated to give compound **17**, which was immediately subjected to the following reduction.

To a solution of the mesylate **17** in dimethyl sulfoxide (5 cm^3) was added sodium borohydride (28 mg, 0.72 mmol) and the resultant mixture was heated to 85 °C for 2.5 h. After cooling of the mixture the reaction was quenched with water and the organic layer was extracted with diethyl ether and the extract dried ($MgSO_4$). Evaporation of the solvent and column chromatography of the residue [silica gel, benzene–hexane (1:40)] afforded compound **18** (20 mg, 59% from **16**): oil (Found: M^+, 280.1278. $C_{19}H_{20}S$ requires *M*, 280.1287): $[\alpha]_D^{26}$ +132.2 (*c* 1.20 in $CHCl_3$); δ_H(270 MHz, $CDCl_3$) 0.82 (3 H, d, *J* 6.93), 1.41 (3 H, d, *J* 6.93), 2.02 (1 H, ddq, *J* 4.62, 6.93 and 6.93), 3.12 (1 H, dq, *J* 6.93 and 6.93), 3.70 (1 H, dd, *J* 4.62 and 4.62), 6.13 (1 H, d, *J* 4.62), 7.20–7.36 (8 H, m) and 7.52–7.57 (2 H, m); δ_C(67.5 MHz, $CDCl_3$) 16.17 (Me), 21.04 (Me), 37.25 (CH), 39.37 (CH), 44.08 (CH), 120.59 (CH), 126.29 (CH), 126.49 (CH), 127.92 (CH), 128.03 (CH), 128.34 (CH), 129.50 (CH), 133.74 (C), 140.12 (C) and 142.15 (C)

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