Stereochemistry of the Catalysed Diels–Alder Reaction between Cyclopentadiene and Dimethyl Monothionofumarate; Soft *versus* Hard Lewis Acids

D. Christopher Braddock, John M. Brown and Patrick J. Guiry

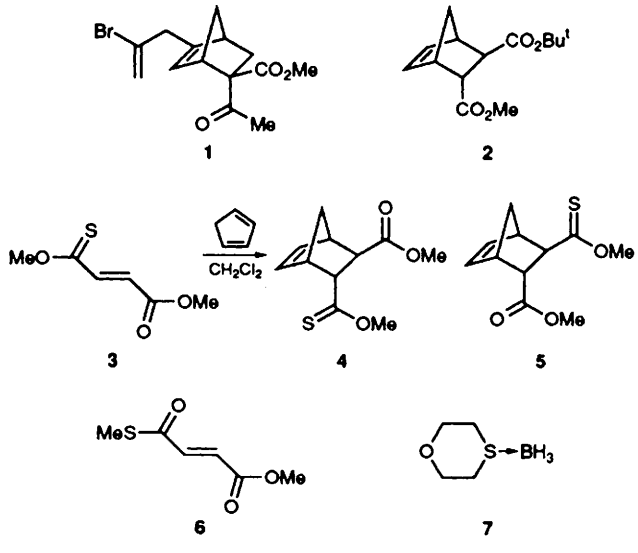
The Dyson Perrins Laboratory, South Parks Road Oxford, UK OX1 3QY

In the title reaction, hard Lewis acids promote the formation of the *endo*-ester diastereoisomer with up to 96% selectivity whereas soft Lewis acids give the *endo*-thionoester with up to 89% selectivity. $BF_3{\cdot}OEt_2$ behaves as if it were in the latter category, giving 94% *endo*-thionoester.

Much current work is directed towards controlling the stereospecificity of Diels–Alder and related cycloadditions, and impressive results have been obtained by the application of Lewis acid catalysts that bind to the carbonyl group of the dienophile.[1] This has stimulated the synthesis of many novel types of Lewis acids, particularly compounds of B, Al and Ti, and the structural and mechanistic chemistry of C=O complexation.[2] A parallel, but much more limited literature has developed around the complexation of C=S in thiones and thionoesters to Lewis acids (mostly in organometallic complexes),[3] demonstrating that both π or n-bonding to a metal centre is possible. Thiocarbonyl complexation appears not to have been exploited in catalysis, however.

The reaction of cyclopentadiene with 1,1- or (*E*)-1,2-disubstituted ethenes where both substituents are electron-withdrawing gives two diastereoisomeric bicyclo[2.2.1]heptenes. In an uncatalysed reaction, discrimination between the two is generally quite small.[4] In the presence of $BF_3{\cdot}Et_2O$ the acetyl group of methyl α-(carbomethoxy)vinyl ketone is 95 : 5 *endo* : *exo* in the adduct **1**.[5] For unsymmetrically substituted dialkyl fumurates, it is possible to control the stereochemistry of addition; with bulky alane Lewis acids the *tert*-butyl ester group in **2** is *exo* and the methyl ester group *endo* although the stereoselectivity is minimal with unhindered catalysts.[6] These precedents, and particularly Yamamoto's work, indicate that it is possible to identify the site of complexation in a catalysed cycloaddition since the enhanced acceptor properties conferred by Lewis acid complexation augment *endo*-positioning of that group.

Following literature precedent,[7] dimethyl monothionomaleate was prepared by the reaction of 2,5-dimethoxythiophene with 4-phenyl-1,2,4-triazoline-3,5-dione in MeOH. It was isomerised to the more stable fumarate **3** (m.p. 31–32 °C, ν_{max} 1739, 1314 cm^{-1}, analytically pure bright-orange crystals) either by treatment with a catalytic quantity of DABCO (1, 4-diazabicyclo[2.2.2.]octane) or by slow silica gel chromatography. In the ^1H NMR spectrum ($CDCl_3$), the methyl resonance of the thionoester group at δ 4.18 was essentially unchanged on addition of successive amounts of the shift reagent tris-(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium, whilst the methyl resonance of the ester



group shifted from δ 3.81 to an asymptotic value 2.95 ppm downfield. This demonstrates specific complexation of the hard europium centre to the hard C=O group.

The ambient Diels–Alder reaction of **3** with cyclopentadiene gave rise to two cycloadducts in a 7:3 ratio which were separated by preparative TLC (hexane–CH_2Cl_2).† Europium shift experiments proved crucial in assigning their stereochemistry showing that the favoured isomer **4** was the *endo*-thionoester, and the less favoured one **5** was the *endo*-ester. The ratio was rather independent of solvent. This indicates that the ester and thionoester groups have a comparable *endo*-directing ability with the latter slightly superior; the thioester **6**[8] reacts with cyclopentadiene to produce a diastereoisomeric mixture in which *endo*-COSMe is likewise preferred by 2:1.

Although the europium shift reagent $Eu(fod)_3$ binds exclusively to the ester, it has only a small effect on the stereoselectivity of the Diels–Alder reaction, and in the expected sense of increasing the extent of *endo*-ester. Stronger hard Lewis acids have a more marked effect in favouring the *endo*-ester **5**, the most clear-cut being BCl_3, which gave this

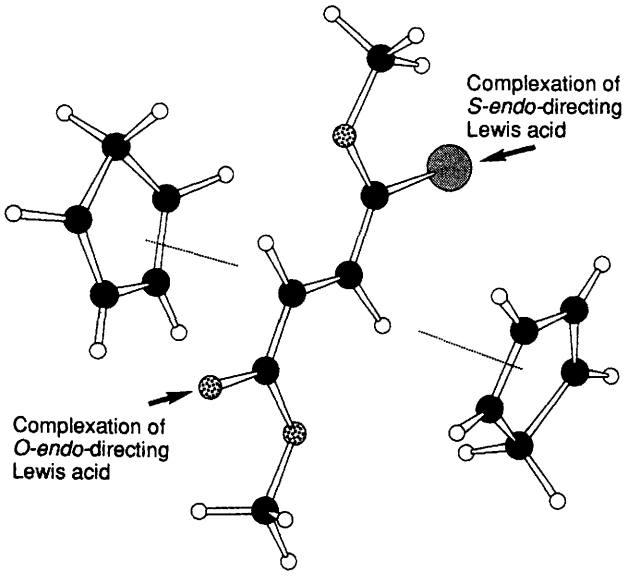


Fig. 1 Lewis acid control of the stereoselectivity of cycloadditions to thionofumarate **3**

† The product from reaction on 0.5 mmol scale (satisfactory elemental analysis) was separated by prep. TLC (5% Et_2O in hexane) to give first *O,O*-dimethyl *endo,exo*-bicyclo[2.2.1]hept-5-ene-2-thionocarboxylate-3-carboxylate **4** (70 mg, 62%); ν_{max} (liquid film)/cm^{-1} 1749 (C=O), 1320 (C=S); δ_H (200 MHz; $CDCl_3$) 1.47 (1 H, br dd, $J_{3,7}$ 1.6, $J_{7,7'}$ 8.8 Hz, 7-H), 1.68 (1 H, br d, 7'-H), 3.00 (1 H, br dd, $J_{2,3}$ 4.8, $J_{3,7}$ 1.6 Hz, 3-H), 3.12 (1 H, br s, 4-H), 3.38 (1 H, br s, 1-H), 3.69 (1 H, br dd, $J_{1,2}$ 4.1 Hz, 2-H), 3.73 (3 H, s, CO_2CH_3), 4.05 (3 H, s, $CSOCH_3$), 6.03 (1 H, dd, $J_{5,6}$ 5.6, $J_{1,6}$ 2.8 Hz, 6-H), 6.27 (1 H, dd, $J_{4,5}$ 3.2 Hz, 5-H); δ_C (50.3 MHz; $CDCl_3$) 224.2 (C=S), 175.4 (C=O), 137.3, 134.9 (C=C), 59.1 ($CSOCH_3$), 58.2 (C2) 52.1 (CO_2CH_3), 49.7 (C3), 47.9 (C1, C4) and 47.4 (C7); *m/z* (CI^+, NH_3) 227 (MH^+, 100%), 194 (83), 167 (30) and 66 (35); and then *O,O*-dimethyl *exo,endo*-bicyclo[2.2.1]hept-5-ene-2-thiocarboxylate-3-carboxylate **5** (22 mg, 19%); ν_{max} (liquid film)/cm^{-1} 1750 (C=O), 1324 (C=S); δ_H(200 MHz; $CDCl_3$) 1.46 (1 H, br dd, $J_{7,7'}$ 8.8, $J_{2,7}$ 1.7 Hz, 7-H), 1.86 (1 H, br d, 7'-H), 3.03 (1 H, dd, $J_{2,3}$ 4.8 Hz, 2-H), 3.14 (1 H, br s, 1-H), 3.26 (1 H, br s, 4-H), 3.65 (3 H, s, CO_2CH_3), 3.74 (1 H, dd, $J_{3,4}$ 3.7 Hz, 3-H), 4.12 (3 H, s, $CSOCH_3$), 6.11 (1 H, dd, $J_{5,6}$ 5.6, $J_{4,5}$ 2.8 Hz, 5-H) and 6.33 (1 H, dd, $J_{1,6}$ 3.2 Hz, 6-H); δ_C (50.3 MHz; $CDCl_3$) 224.9 (C=S), 175.0 (C=O), 137.4, 135.0 (C=C), 59.3 ($CSOCH_3$), 57.7 (C2), 51.8 (CO_2CH_3), 50.7, 50.2 (C1, C3), 46.7, 45.7 (C4, C7); *m/z* (CI^+, NH_3) 227 (MH^+, 100%), 167 (30), 66 (35).

product effectively exclusively, and at the same time caused a substantial rate acceleration. There appears to be a direct correlation between the strength of the Lewis acid[9] and the extent of *endo*-ester product formation (Table 1). Soft Lewis acids show the reverse trend, however. With the trifluoromethanesulfonate of Cu^{II}, a ratio of 9:1 in favour of the *endo*-thionoester is observed, indicating that the reaction is now controlled by complexation of the Lewis acid to the thiocarbonyl group. The product ratio is identical in the presence and absence of HgI_2, and no increase in reaction rate is observed. This suggests that the model described by Fig. 1 does operate; it should be treated with some caution as MMX calculations on coplanar forms of **3** suggest that the *syn,syn* conformer of the S=C–C=C–C=O moiety of **3** is preferred, and rotation of either the carbonyl or the thiocarbonyl group into the *anti*-conformation preferred for Lewis acid complexation[10] is disfavoured by *ca.* 4 kJ mol^{-1}.

The least expected result was obtained with BF_3·Et_2O as catalyst, since boron halides are generally considered to be hard Lewis acids.[11] Under optimum conditions, the *endo*-thionoester **4** was obtained with 16:1 selectivity at −26 °C, indicating that the sulfur atom may be the preferred site of BF_3 complexation during the cycloaddition. The effect persists at substoichiometric concentrations of BF_3·Et_2O although the enhancement of reactivity is substantially less than with BCl_3. The same results were obtained using BF_3 in toluene or CH_2Cl_2, or with BF_3·SMe_2 in $CHCl_3$.

The literature offers contradictory evidence on the preferences for boron complexation with carbonyl *versus* thiocarbonyl bases. Evidence to support a favourable B–S interaction comes from the structure **7** of the 1,4-oxathiane borane adduct,[12] which is exclusively sulfur bound. In contrast,[13] BF_3 prefers to coordinate to Et_2O rather than Et_2S in C_6H_6. ^1H and ^{13}C NMR chemical shifts in the vicinity of the carbonyl oxygen of **3**, but not of the thiocarbonyl sulfur, shift downfield substantially on addition of BCl_3 or Et_2AlCl. On BF_3·Et_2O addition the chemical shifts are unchanged, indicating much weaker complexation. Nevertheless, the substantial difference between apparently similar Lewis acids is quite unexpected and not easily explained in terms of current theory, and the preference may be sensitive to the *O*- or *S*-bearing functional groups involved.

In summary, we have demonstrated the promotion of Diels–Alder cycloaddition, which is most simply interpreted as due to Lewis acid binding to the sulfur of a thionoester albeit other explanations are permissible at this stage. Given the range of potential complexing agents for thiocarbonyl compounds, this preliminary observation holds promise for asymmetric catalysis which is currently being explored.

We thank the European Community for a grant under the Science Plan (SCI-0319-C) (to P. J. G.) and Nottingham City

Table 1 Ratio of adducts in the cycloaddition reaction

Lewis acid	Conditions[a]	Ratio of adducts[b] **4**:**5**
None	Room temp.[c], $CDCl_3$	70:30
None	Room temp., DMSO	71:29
BF_3·Et_2O	−26 °C, $CDCl_3$	**94**:**6**[d]
$Cu(OTf)_2$	Room temp., $CDCl_3$	89:11
$TiCl_4$	0 °C, CH_2Cl_2	52:48
$Eu(fod)_3$	−26 °C, CH_2Cl_2	50:50
Et_2AlCl	−20 °C, CH_2Cl_2	21:79
BCl_3	0 °C, $CDCl_3$	**4**:**96**

[a] All the reactions were carried out under argon, with 1 equiv. of the Lewis acid, and with 10 equiv. of cyclopentadiene to ≥ 95% conversion unless otherwise stated. [b] Ratio determined from integration of ^1H NMR spectrum. [c] The stereoselectivity of the uncatalysed reaction increases slightly on cooling, being 79:21 at 0 °C. [d] 92:8 at 0 °C.

Council for maintenance (to D. C. B.). Dr Mark Pearson made helpful suggestions.

Received, 9th March 1993; 3/01366I

References

1 E. J. Corey and T-P. Loh, *J. Am. Chem. Soc.*, 1991, **113**, 8966; Q. Gao, T. Maruyama, M. Mouri and H. Yamamoto, *J. Org. Chem.*, 1992, **57**, 1951; E. J. Corey, T-P. Loh, T. D. Roper, M. D. Azimioara and M. C. Noe, *J. Am. Chem. Soc.*, 1992, **114**, 8290.

2 R. C. Corcoran and J. Ma, *J. Am. Chem. Soc.*, 1992, **114**, 4536; S. Shambayati, W. E. Crowe and S. L. Schrieber, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 256, and references therein.

3 *E.g.* J. Campora, E. Carmona, E. Gutlerrez-Puebla, M. L. Poveda and C. Ruiz, *Organometallics*, 1988, **7**, 2577; K. Seitz and U. Behrens, *J. Organomet. Chem.*, 1985, **288**, C47; H. Alper, N. D. Silavwe, G. I. Birnbaum and F. R. Ahmed, *J. Am. Chem. Soc.*, 1979, **91**, 6582.

4 In (*E*)-1,2-disubstituted dienophiles-CHO *vs.* SO_2Ar: A. Riahi, J. Muzart and J. P. Pete, *Recl. Trav. Chim. Pays-Bas.*, 1992, **111**, 345; MeCO *vs.* SO_2Ar: F. M. Leon and J. C. Carretero, *Tetrahedron Lett.*, 1991, **32**, 5405; CO_2R *vs.* SOAr: S. M. Proust and D. D. Ridley, *Aust. J. Chem.*, 1984, **37**, 1677; M. A. Brimble and B. R. Davis, *Tetrahedron*, 1985, **41**, 4965; A. Guessous, F. Rouessac and C. Maignan, *Bull. Soc. Chim. Fr.*, 1986, 837; SOR *vs.* CO_2H: H. Johnsson and S. Allenmark, *Chem. Scr.*, 1988, **8**, 216; SOR *vs.* SO_2R: O. de Lucchi, V. Lucchini, C. Marchioro, G. Valle and G. Modena, *J. Org. Chem.*, 1986, **51**, 1457. For COMe *vs.* CO_2H, a single diastereoisomer (CO_2H *exo*?) is observed: L. A. Badovskaya, O. B. Kravchenko, V. G. Kul'nevich and I. A. Kuzovnikova, *J. Org. Chem., USSR* (*Engl. Trans*)., 1979, **15**, 43.

5 E. J. Corey and J. E. Munroe, *J. Am. Chem. Soc.*, 1982, **104**, 6129.

6 K. Maruoka, S. Saito and H. Yamamoto, *J. Am. Chem. Soc.*, 1992, **114**, 1089.

7 D. del Mazza, *J. Chem. Soc., Chem. Commun.*, 1982, 1033; 2,5-dimethoxythiophene was prepared in 30% yield from the diiodide with NaOMe and CuBr: H. L. Aalten, G. van Koten, D. M. Grove, T. Kuilman, O. G. Piekstra, L. A. Hulshof and R. A. Sheldon, *Tetrahedron*, 1989, **45**, 5565.

8 B. Wladislaw, L. Marzorati and J. Gruber, *Phosphorus Sulfur and Silicon*, 1991, **59**, 185.

9 For quantification of Lewis acidity see: J. W. Faller and Y. Ma, *J. Am. Chem. Soc.*, 1991, **113**, 1579; R. F. Childs, D. L. Mulholland and A. Nixon, *Can. J. Chem.*, 1982, **60**, 801; M. K. Kroeger and R. S. Drago, *J. Am. Chem. Soc.*, 1981, **103**, 3250; P. Kollman and J. Douglas, *J. Phys. Chem.*, 1981, **85**, 2717.

10 S. E. Denmark and N. G. Almstead, *J. Am. Chem. Soc.*, 1993, **115**, 3133, and references therein.

11 R. S. Drago, *Struct. Bond.*, 1973, **15**, 73.

12 H. C. Brown and A. K. Mandal, *J. Org. Chem.*, 1992, **57**, 4970.

13 P. C. Maria and J. F. Gal, *J. Phys. Chem.*, 1985, **89**, 1296; D. P. N. Satchell and R. S. Satchell, *Chem. Rev.*, 1969, **69**, 251; N. N. Kharabaev, *Koord. Khim.*, 1991, **17**, 435.