COMMUNICATION

A novel, chiral Lewis acid-induced enantioselective hetero Diels–Alder reaction of a thiabutadiene

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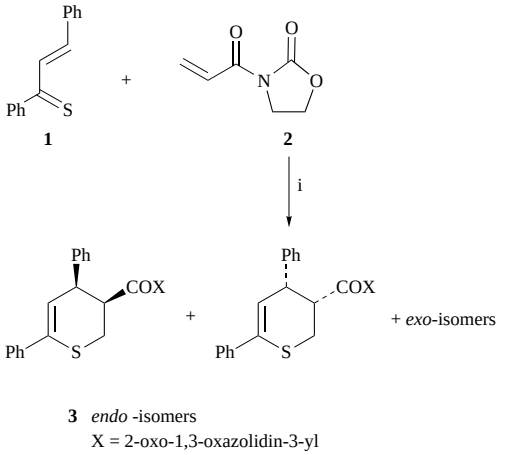
The chiral Lewis acid-induced, enantioselective thia Diels–Alder reaction is described for the first time.

Asymmetric hetero Diels–Alder reactions have occupied an important position in organic chemistry because of their synthetic versatility and usefulness for highly efficient and straightforward construction of a wide range of optically active six-membered heterocycles.[1] This utility is unambiguously enhanced by its high regio- and stereo-selectivities, and widespread application. In spite of the great synthetic potential of this asymmetric hetero Diels–Alder methodology, efforts have been restricted to those involving only oxa-, aza- and several other particular[2] heterodienes or heterodienophiles;[1] much less attention has been paid to the use of thiabutadienes taking part as heterodienes in asymmetric hetero Diels–Alder reactions.[3–8] There are only a few reports on the thiabutadiene-asymmetric hetero Diels–Alder reaction that have been devoted toward the diastereo-π-face-differentiating processes utilizing chiral thiadienes[8] or dienophiles.[3–7] † In this communication we report the first, homochiral Lewis acid-induced, enantioselective thia Diels–Alder cycloaddition, which provides a highly efficient access to optically active dihydrothiopyrans with very high enantioselectivity (up to 95% ee).

The reports by Evans *et al.*[10] and Li *et al.*[11] on the chiral bis(benzylideneamino)cyclohexane–copper complex-catalyzed enantioselective cyclopentadiene (carbo) Diels–Alder reaction and aziridination, respectively, prompted us to choose this promising, readily available bis(imine)–Lewis acid complex system in the hope that this type of chiral catalyst could be successfully applicable to the thiabutadiene-asymmetric hetero Diels–Alder reaction (Scheme 1).‡ Initial efforts were directed to



Scheme 1 *Reagent and conditions*: i, Lewis acid–bis(imine) **4**, CH_2Cl_2

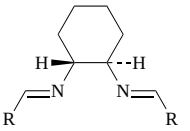
† We have found that the sense and degree of the diastereo π-facial selectivity in the thiabutadiene-asymmetric hetero Diels–Alder reaction varies as a function of stoichiometry of the added Lewis acid,[6] the features of which are apparently distinct from those of the carbo Diels–Alder reaction with the same combination of dienophile and Lewis acid.[9]

Table 1 Asymmetric hetero Diels–Alder reaction of thiabutadiene **1** with **2** in the presence of a Lewis acid–bis(imine) **4a** complex [a]

Run	Lewis acid	*T*/°C	Yield[b] (%)	*endo*:*exo*[c]	*endo* ee[d] (%)
1	$Cu(OTf)_2$	RT[e]	99	93:7	54
2	$Cu(OTf)_2$	0	99	98:2	73
3	$Cu(OTf)_2$	−78	95	72:18	27
4	$Mg(OTf)_2$	RT[e]	91	76:24	−8
5	$Mg(OTf)_2$	0	62	69:31	−5
6	$Yb(OTf)_3$;	RT[e]	27	65:35	13

[a] Reaction was performed in CH_2Cl_2 for 3 h in a ratio of **1**:**2**:catalyst (Lewis acid:**4a** = 1.0:1.1) = 1.2:1.0:1.0. [b] Isolated yield. [c] Determined by ^1H NMR spectroscopy and HPLC analysis. [d] Determined by HPLC analysis. [e] 22 ± 2 °C, RT = room temperature.

finding a suitable Lewis acid to use in combination with ligand **4** as a chiral catalyst in the reaction. The results are summarized



4a R = phenyl
4b R = 2,6-Cl_2phenyl
4c R = 4-Pr^{i}phenyl

in Table 1. The best results in yield, *endo*:*exo* ratio, and *endo* ee were obtained by employing $Cu(OTf)_2$ (copper trifluoromethanesulfonate) at 0 °C (run 2).§ Somewhat surprisingly, the reaction at low temperature (−78 °C, run 3) furnished lower enantioselectivity. In order to enhance the enantioselectivity and to assess the feasibility of the catalytic process of this reaction, we investigated the reaction using $Cu(OTf)_2$ by varying the substituent R in ligand **4** in the presence of catalytic or stoichiometric amounts of the complex. The results are listed in Table 2. The data in Table 2 reveal that a stoichiometric amount (100 mol%) of the chiral $Cu(OTf)_2$-**4** complex catalyst (promoter) is needed to obtain the highest *endo* ees together with the best *endo*:*exo* ratios and yields of **3**¶ in the reaction with ligands **4a** (run 6) and **4b** (run 12) at 0 °C, and with ligand **4c** (run 15) at room temp.

‡ We applied some other chiral Lewis acid catalysts such as tartrate-derived TADDOLate–$TiCl_2$ (dichlorotitanium α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanolate)[12] permitting the highly enantioselective carbo Diels–Alder reaction in this thiabutadiene-asymmetric Diels–Alder reaction, only to find disappointing results with the enantioselectivity.

§ Some other Lewis acids such as $ZnCl_2$, $MgCl_2$, $TiCl_4$ and $TiCl_2(OPr^i)_2$ for the complex with **4** were screened in this Diels–Alder reaction and found to be inferior to $Cu(OTf)_2$.

¶ The absolute configuration of the major *endo* isomer of **3** was determined to be (3*R*, 4*R*) by transformation of scalemic **3** (*endo*) to alcohol **5** (Scheme 2) and by comparison of its specific rotation with that of the authentic sample **5** ($[\alpha]_D^{25}$ + 176, *c* = 1.87, $CHCl_3$).[4]

Table 2 Asymmetric hetero Diels–Alder reaction of thiabutadiene **1** with **2** in the presence of a $Cu(OTf)_2$–bis(imine) **4a–c** complex[a]

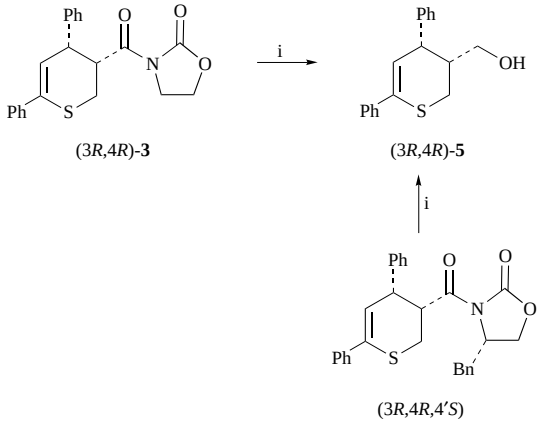
Run	R in **4**	$Cu(OTf)_2$ mol%	*T*/°C	Yield[b] (%)	*endo*:*exo*[c]	*endo* ee[d] (%)
1	Phenyl **4a**	10	RT[e]	99	82:18	64
2		50	RT[e]	99	81:19	63
3		100	RT[e]	99	93:7	54
4		10	0	74	85:15	54
5		50	0	60	83:17	56
6		100	0	99	98:2	73
7	2,6-Cl_2Ph **4b**	10	RT[e]	62	82:18	45
8		50	RT[e]	82	82:18	45
9		100	RT[e]	94	84:16	62
10		10	0	83	69:31	40
11		50	0	99	79:21	64
12		100	0	99	82:18	76
13	4-Pr^iPh **4c**	10	RT[e]	69	78:22	59
14		50	RT[e]	99	84:16	60
15		100	RT[e]	99	88:12	74
16		10	0	73	91:9	48
17		50	0	74	85:15	42
18		100	0	94	90:10	68

[a–e] See footnotes in Table 1.

Table 3 $Cu(OTf)_2$–bis(imine) **4**-induced hetero Diels–Alder reaction of thiabutadiene **1** with **2** in the presence of 4 Å molecular sieves at 0 °C[a]

Run	Ligand	Yield[b] (%)	*endo*:*exo*[c]	*endo* ee[d] (%)
1	**4a**	91	96:4	94
2	**4b**	90	95:5	95
3	**4c**	90	88:12	90

[a–d] See footnotes in Table 1.



Scheme 2 *Reagent and conditions*: i, $LiAlH_4$, THF, 0 °C

We finally performed the reaction in the presence of 4 Å molecular sieves under the optimized conditions to obtain satisfactorily higher enantioselectivity. As shown in Table 3, the best enantioselectivity of 90–95% ees was achieved. A further study to extend the scope of this asymmetric hetero Diels–Alder reaction to a catalytic process is underway.

Experimental

Typical procedure

A mixture of bis(benzylideneamino)cyclohexane **4** (12–120 mol%) and $Cu(OTf)_2$ (10–100 mol%) in dry dichloromethane (10 cm^3) was stirred for 1 h at room temp. under an argon atmosphere. The dienophile **2** (20.0 mg, 0.142 mmol, 1.00 equiv.) was then added to the catalyst mixture with stirring for 1 h at room temp. After maintaining the temperature (0 °C, −78 °C or room temp.) of the mixture, thiabutadiene **1** (38.0 mg, 0.170 mmol, 1.20 equiv.) was added in one portion and the reaction mixture was stirred for 3 h at the same temperature, and then quenched with water. The reaction mixture was diluted with dichloromethane (15 cm^3), washed with water and brine, and dried ($MgSO_4$). The solution was evaporated and the resulting crude product (HPLC analysis) was purified by column chromatography on silica gel (70 cm^3) using EtOAc–hexane (1:10)–(1:1) as eluent to give the cycloadduct **3**, of which the *endo*:*exo* ratio and optical purity were determined by ^1H NMR spectroscopy [$Pr(hfc)_3$ as a shift reagent] and HPLC analysis (DAICEL CHIRALCEL OD column, 1.0 ml min^{-1} flow rate, 10% ethanol in hexane as eluent). The *endo*-**3** and *exo*-**3** isomers could be separated diastereoisomerically pure but not enantiomerically pure by repeated recrystallisation and silica gel chromatography.

3-(*c*-4,6-Diphenyl-3,4-dihydro-2*H*-thiopyran-*r*-3-ylcarbonyl)-1,3-oxazolidin-2-one *endo*-3

Obtained as colourless crystals, mp 240.9–242.6 °C (Found: M^+, 365.1099. $C_{21}H_{19}NO_3S$ requires *M*, 365.1087); *m*/*z* 365 (M^+, 28%) and 223 ($\mathbf{1}^+$, 100%); ν_{max}(KBr)/cm^{-1} 1788 and 1690; δ_H(500 MHz, $CDCl_3$) 2.85 (1H, dd, *J* 2.56 and 13.37), 3.36 (1H, dd, *J* 11.90 and 13.37), 3.80 (1H, ddd, *J* 6.59, 9.16 and 10.99), 4.00 (1H, ddd, *J* 7.51, 9.16 and 10.99), 4.32 (1H, dd, *J* 5.13 and 5.68), 4.34 (1H, ddd, *J* 2.56, 5.13 and 11.90), 4.45 (1H, ddd, *J*, 6.59, 9.16 and 9.16), 4.49 (1H, ddd, *J* 7.51, 9.16 and 9.16), 6.16 (1H, d, *J* 5.68), 7.10–7.13 (2H, m, Ar-H) and 7.23–7.37 (8H, m, Ar-H); δ_C(125 MHz, $CDCl_3$, DEPT) 22.57 (SCH_2), 41.14 (NCH_2), 42.57 (CH), 42.61 (CH), 62.59 (OCH_2), 120.52 (CH), 125.90 (2CH), 127.12 (CH), 128.14 (2CH), 128.43 (CH), 128.66 (2CH), 129.27 (2CH), 133.08 (C), 138.80 (C), 140.00 (C), 153.57 (CO) and 172.06 (CO).

3-(*t*-4,6-Diphenyl-3,4-dihydro-2*H*-thiopyran-*r*-3-ylcarbonyl)-1,3-oxazolidin-2-one *exo*-3

δ_H(500 MHz, $CDCl_3$) 3.12 (1 H, dd, *J* 2.64 and 12.86), 3.31 (1H, dd, *J* 9.57 and 12.86), 3.76 (1H, ddd, *J* 6.27, 9.57 and 10.89), 3.90 (1H, ddd, *J* 7.26, 9.57 and 10.89), 4.06 (1H, dd, *J* 2.97 and 9.57), 4.09 (1H, ddd, *J* 7.26, 9.57 and 9.57), 4.28 (1H, ddd, *J* 6.27, 9.57 and 9.57), 4.37 (1H, ddd, *J* 2.64, 9.57 and 9.57), 6.06 (1H, d, *J* 2.97), 7.20–7.36 (8H, m, Ar-H) and 7.46–7.52 (2H, m, Ar-H); δ_C(125 MHz, $CDCl_3$, DEPT) 28.89 (SCH_2), 42.67 (NCH_2), 44.26 (CH), 44.68 (CH), 61.89 (OCH_2), 122.30 (CH), 126.45 (2CH), 127.32 (CH), 128.26 (2CH), 128.52 (CH), 128.59 (2CH), 129.39 (2CH), 133.55 (C), 139.28 (C), 142.71 (C), 152.81 (CO) and 173.78 (CO).

References and notes

1 H. Waldmann, *Synthesis*, 1994, 535; J. Streith and A. Defoin, *Synthesis*, 1994, 1107; C. Kibayashi and S. Aoyagi, *Synlett*, 1995, 873; H. B. Kagan and O. Riant, *Chem. Rev.*, 1992, **92**, 1007; T. Oh and M. Reilly, *Org. Prep. Proced. Int.*, 1994, **26**, 129; U. Pindur, G. Lutz and C. Otto, *Chem. Rev.*, 1993, **93**, 741; T. Kametani and S. Hibino, *Adv. Heterocycl. Chem.*, 1987, **42**, 245; L. F. Tietze and U. Beifuss, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 131; R. R. Schmidt, *Acc. Chem. Res.*, 1986, **19**, 250; M. D. Bednarski and J. P. Lyssikatos, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, I. Fleming and L. A. Paquette, Pergamon, Oxford, 1991, vol. 2, p. 661; S. M. Weinreb, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, I. Fleming and L. A. Paquette, Pergamon, Oxford, 1991, vol. 5, p. 401; D. L. Boger, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, I. Fleming and L. A. Paquette, Pergamon, Oxford, 1991, vol. 5, p. 451. For recent reports on asymmetric hetero Diels–Alder reactions: J. Mulzer and F. Meyer, *Tetrahedron Lett.*, 1995, **36**, 3503; K. Mikami, O. Kotera, Y. Motoyama and H. Sakaguchi, *Synlett*, 1995, 975; A. Graven, M. Johannsen and K. A. Jørgensen, *Chem. Commun.*, 1996, 2373; R. Lock and H. Waldmann, *Tetrahedron Lett.*, 1996, **37**, 2753; H. Ishitani and S. Kobayashi, *Tetrahedron Lett.*, 1996, **37**, 7359; R. Badorrey, C. Cativiela, M. D. Díaz-de-Villegas and J. A. Gálvez, *Tetrahedron Lett.*, 1997, **38**, 2547; S. E. Denmark, A. R. Hurd and H. J. Sacha, *J. Org. Chem.*, 1997, **62**, 1668; S. E. Denmark and A. Thorarensen, *J. Am. Chem. Soc.*, 1997, **119**, 125; S. E. Denmark and L. R. Marcin, *J. Org. Chem.*, 1997, **62**, 1675.

2 For asymmetric hetero Diels–Alder reaction with nitroso dienophiles: M. Naruse, S. Aoyagi and C. Kibayashi, *J. Org. Chem.*, 1994, **59**, 1358; J.-B. Behr, A. Defoin, J. Pires, J. Streith, L. Macko and M. Zehnder, *Tetrahedron*, 1996, **52**, 3283; A. R. Ritter and M. J. Miller, *J. Org. Chem.*, 1994, **59**, 4602. For asymmetric hetero Diels–Alder reaction with nitroso dienes: T. Arnold, B. Orschel and H.-V. Reissig, *Angew. Chem.*, *Int. Ed. Engl.*, 1992, **31**, 1033. For asymmetric hetero Diels–Alder reaction with nitro dienes: S. E. Denmark and M. E. Schnute, *J. Org. Chem.*, 1994, **59**, 4576. For asymmetric hetero Diels–Alder reaction with *N*-sulfinylamine dienophiles: S. M. Weinreb, *Acc. Chem. Res.*, 1988, **21**, 313. For asymmetric hetero Diels–Alder reaction with thiocarbonyl dienophiles: E. Vedjes, J. S. Stults and R. G. Wilde, *J. Am. Chem. Soc.*, 1988, **110**, 5452; G. W. Kirby and A. D. Sclare, *J. Chem. Soc.*, *Perkin Trans. 1*, 1991, 2329; B. F. Bonini, G. Mazzanti, P. Zani and G. Maccagnani, *J. Chem. Soc.*, *Chem. Commun.*, 1988, 365; P. A. T. W. Porskamp, R. C. Haltiwanger and B. Zwanenburg, *Tetrahedron Lett.*, 1983, **24**, 2035; L. A. G. M. van den Broek, P. A. T. W. Porskamp, R. C. Haltiwanger and B. Zwanenburg, *J. Org. Chem.*, 1984, **49**, 1691; T. Takahashi, N. Kurose and T. Koizumi, *Heterocycles*, 1993, **36**, 1601.
3 S. Motoki, T. Saito, T. Karakasa, H. Kato, T. Matsushita and S. Hayashibe, *J. Chem. Soc.*, *Perkin Trans. 1*, 1991, 2281; T. Saito, H. Fujii, S. Hayashibe, T. Matsushita, H. Kato and K. Kobayashi, *J. Chem. Soc.*, *Perkin Trans. 1*, 1996, 1897.
4 T. Saito, T. Karakasa, H. Fujii, E. Furuno, H. Suda and K. Kobayashi, *J. Chem. Soc.*, *Perkin Trans. 1*, 1994, 1359.
5 T. Saito, M. Kawamura and J. Nishimura, *Tetrahedron Lett.*, 1997, **38**, 3231.
6 T. Saito, H. Suda, M. Kawamura, J. Nishimura and A. Yamaya, *Tetrahedron Lett.*, 1997, **38**, 6035.
7 A. Marchand, D. Mauger, A. Guingant and J.-P. Pradère, *Tetrahedron*: *Asymmetry*, 1995, **6**, 853.
8 A. S. Bell, C. W. G. Fishwick and J. E. Reed, *Tetrahedron Lett.*, 1996, **37**, 123.
9 D. A. Evans, K. T. Chapman and J. Bisaha, *J. Am. Chem. Soc.*, 1988, **110**, 1238.
10 D. A. Evans, T. Lectka and S. J. Miller, *Tetrahedron Lett.*, 1993, **34**, 7027.
11 Z. Li, K. R. Conser and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1993, **115**, 5326.
12 K. Narasaka, N. Iwasawa, M. Inoue, T. Yamada, M. Nakashima and J. Sugimori, *J. Am. Chem. Soc.*, 1989, **111**, 5340; K. Narasaka, *Synthesis*, 1991, 1; D. Seebach, R. Dahinden, R. E. Marti, A. K. Beck, D. A. Plattner and N. M. Kühnle, *J. Org. Chem.*, 1995, **60**, 1788; K. V. Gothelf and K. A. Jørgensen, *J. Org. Chem.*, 1995, **60**, 6847; C. Haase, C. R. Sarko and M. DiMare, *J. Org. Chem.*, 1995, **60**, 1777.

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