Copper(II)-Bisoxazoline-Catalysed Asymmetric Diels–Alder Reactions of α-Thioacrylates

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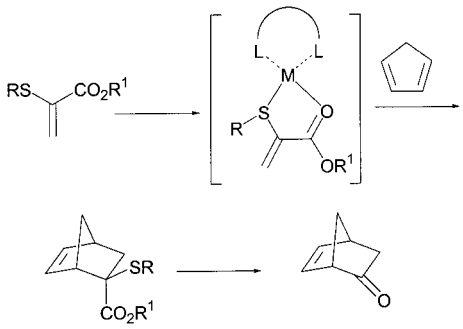
A range of C_2-symmetric, chiral Cu^{II}·bisoxazoline complexes were tested as catalysts for the asymmetric Diels–Alder cycloaddition between cyclopentadiene and a range of α-sulfenylacrylates. The optimum acrylate was ethyl α-phenylthioacrylate and the optimum catalyst was the bisoxazoline derived from phenylalanine which, upon complexation with $Cu(SbF_6)_2$, gave the cycloadducts in 92% yield, 88% *de* and >95% *ee* for the *endo* product. The α-phenylthio ester moiety was easily converted into a carbonyl group furnishing (1*S*,4*S*)-norbornenone with high enantioselectivity. Attempts to improve the diastereoselectivity by changing the bite angle of the ligand were unsuccessful. An attempt is made to rationalise our findings in terms of the transition-state structure of the ligand–metal–dienophile complex.

Introduction

The asymmetric Diels–Alder reaction using catalytic amounts of chiral Lewis acids has emerged as a powerful strategy in asymmetric synthesis.[1–4] A vast array of metals, ligands and dienophiles have been studied in this reaction and, generally, the most successful systems involve chiral ligands capable of bidentate chelation to a metal centre, together with dienophiles capable of two-point binding to the metal–ligand complex. Such systems result in a reduction of the number of accessible conformations of the dienophile–metal–ligand complex thereby enhancing the enantioselectivity.[5–7]

We have been interested in developing ketene equivalents for Diels–Alder reactions and have therefore sought dienophiles that could be easily converted into carbonyl compounds. Initially, we utilised bis-sulfoxides of ketene thioacetals as chiral ketene equivalents,[8] but this auxiliary-based approach is limited compared to catalytic methods. We therefore considered the possibility of using chiral Lewis acids with dienophiles in which the activating groups could be readily converted into a carbonyl functionality.

α-Thioacrylates seemed an ideal choice as ketene equivalents since it is known that such dienophiles undergo Diels–Alder reactions with cyclopentadiene and that the cycloadducts can be readily converted into norbornenones.[9–11] Such dienophiles may also act as two point binders to appropriate metals through carbonyl and sulfenyl coordination (Scheme 1). Copper bisoxazolines were chosen as the metal–ligand system due to the known ability of copper to bind to both sulfur and oxygen and due to the success of such complexes in a range of transformations including Diels–Alder reactions.[12–14] In this paper we describe our complete studies in this area.[15]



Scheme 1. Proposed strategy for asymmetric Diels–Alder reaction

Results and Discussion

We screened a range of bisoxazolines at various temperatures and found that the phenyl-substituted ligand was optimum (Scheme 2).[16]

We therefore concentrated our studies on the Ph substituted ligand **7**. The results of our studies into the effect of the acrylate structure,[17] reaction temperature and counterion are presented in Table 1 and Scheme 3.

It was found that the selectivity of the Diels–Alder reaction was highly dependent on the nature of the ester and sulfenyl substituents. Higher selectivity was obtained with phenylthio- rather than methylthioacrylates (entries 1, 3), and higher selectivity was also obtained with small or moderately sized ester substituents [Me, Et, *i*Pr >> *t*Bu (entries 2, 3, 6, 8, 9)]. The *t*Bu ester was much less reactive than the other esters and the reaction had to be conducted at 0 °C (entry 8). This, presumably, was the cause of the reduction in enantioselectivity. Higher selectivity was obtained at lower temperature (see entries 3 and 4) and the use of cationic complexes[13] led to high reactivity even at −78 °C (entries 5, 7) as well as high *exo*/*endo* selectivity and high enantioselectivity. The optimum reagents and conditions required ethyl α-phenylthioacrylate as dienophile, the cationic

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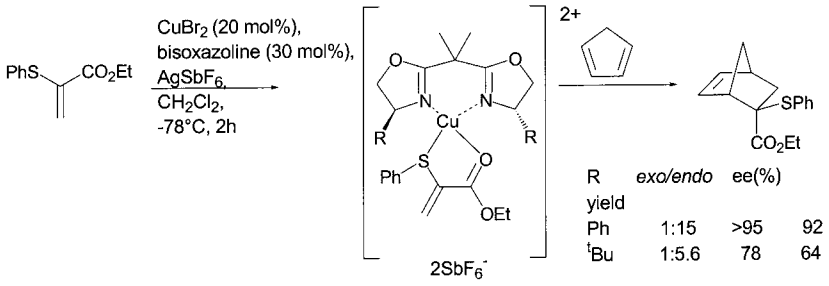
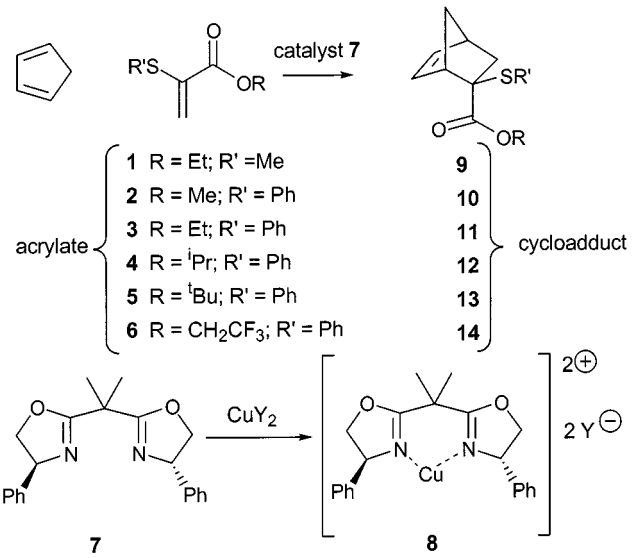


Scheme 2. Variation of bisoxazoline in Diels–Alder reactions

Table 1. Diels–Alder reactions of α-sulfenylacrylates with cyclopentadiene catalysed by Cu-bisoxazoline complex **8** (Scheme 3)

Entry	Dienophile	R	R′	Metal catalyst[a]	Time	Temp (°C)	Yield	*exo:endo*[b]	*ee*[c]
1	**1**	Et	Me	$Cu(OTf)_2$	6h	−40	53	1:2.4	40
2	**2**	Me	Ph	$Cu(OTf)_2$	6h	−40	44	1:3.7	84
3	**3**	Et	Ph	$Cu(OTf)_2$	6h	−40	50	1:4	80
4	**3**	Et	Ph	$Cu(OTf)_2$	9h	−78	76	1:7	>95
5	**3**	Et	Ph	$CuBr_2/AgSbF_6$[d]	1h	−78	92	1:15	>95
6	**4**	*i*Pr	Ph	$Cu(OTf)_2$	4h	−40	70	1:2.3	85
7	**4**	*i*Pr	Ph	$CuBr_2/AgSbF_6$[d]	2.5h	−78	90	1:5	81
8	**5**	*t*Bu	Ph	$Cu(OTf)_2$	5.5h	0	91	1:2.5	26
9	**6**	CH_2CF_3	Ph	$CuBr_2/AgSbF_6$[d]	2h	−78	92	1:13	>95

[a] 20 mol-% $Cu(OTf)_2$, 30 mol-% bisoxazoline **7**, 1 equiv. of dienophile and 4 equiv. of cylopentadiene. – [b] Determined by NMR integration of crude reaction mixtures. – [c] Determined by NMR integration in presence of Pirkle's reagent, (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol. – [d] 10 mol-% of $CuBr_2/AgSbF_6$, 10 mol-% bisoxazoline **7**, 1 equiv. dienophile and 4 equiv. cylopentadiene.



Scheme 3. Variation of acrylate in Diels–Alder reactions

phenyl-substituted bisoxazoline-copper complex, and a reaction temperature of −78 °C in CH_2Cl_2 (entry 5); under these conditions good diastereo- and essentially complete enantioselectivity was observed.

The ethyl acrylate **3** reacted rapidly at −78 C with cyclopentadiene and so we considered the possibility of using less-reactive dienes, in particular furan. As we recognised that furan is an especially unreactive diene we also prepared the more reactive dienophile, trifluoroethyl acrylate **6**. Interestingly, the trifluoroethyl acrylate **6** is substantially more stable than the ethyl acrylate **3**, which has to be used immediately after preparation to avoid polymerisation. In the event, neither **3** nor **6** proved to be reactive enough with furan under our optimum conditions, even at higher temperatures (up to 0 C): whilst **3** polymerised, **6** could be reisolated.

A transition state involving bidentate binding of the dienophile through sulfur and the carbonyl oxygen to a square planar or distorted square planar Cu^{II} complex[13,14,18–21] may be proposed to rationalise the enantio- and diastereoselectivities. However, the high enantioselectivity observed is perhaps surprising as the alkene of the dienophile lies close to the C_2 axis of the metal catalyst where it encounters the minimum steric influence from the phenyl groups of the oxazoline moiety. The fact that high enantioselectivity is achieved in this situation is highly unusual as such selectivities are only usually observed when the prochiral carbon or group is placed directly above one of the oxazoline substituents. Indeed, very few examples exist where the prochiral carbon is positioned on or close to the C_2 axis of the ligand.[22,23] In our case we believe that the substituent on sulfur plays a major role in controlling enantioselectivity. We believe there is very high diastereoselectivity in formation of the dieneophile–metal–oxazoline complex (only one of the two enantiotopic lone pairs of the sulfur atom binds to the copper) and it is the orientation of the sulfur substituent which controls the facial attack on the dienophile (Figure 1). This substituent is forced below the plane of the complex, and when this group is large it effectively

blocks the *Si* face of the dienophile and therefore forces the diene onto the *Re* face. Increasing the size of the sulfur substituent may not only increase the diastereoselectivity of the complexation but also the subsequent facial selectivity of the dienophile. From analysis of molecular models, the opposite enantiomer would be expected if the dienophile was bound to Cu in a tetrahedral arrangement. This provides further circumstantial evidence for a square planar complex. It is also possible that *endo*/*exo* selectivity is influenced not only by secondary orbital interactions but also by steric interaction of the cyclopentadiene with the Ph substituent on the oxazoline ring which disfavours the *exo* approach.

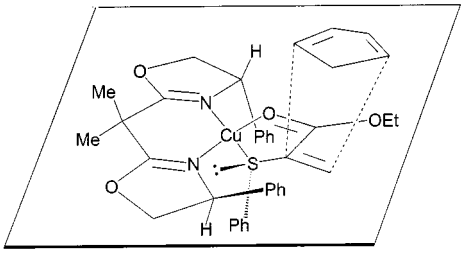


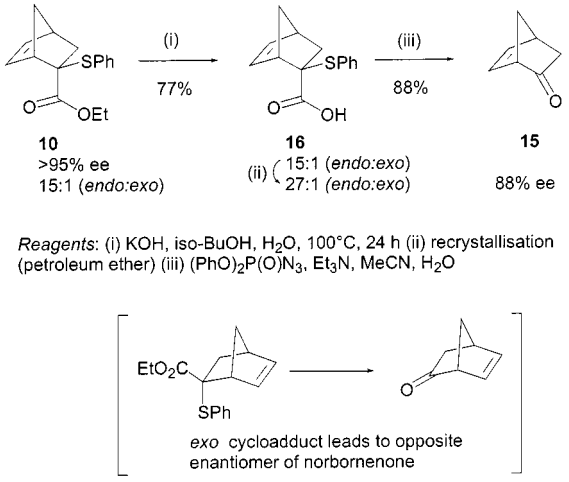
Figure 1. Proposed transition state for Diels–Alder reaction

The size of the ester group of the dienophile is critical. An excessively bulky group may inhibit two-point binding of the dienophiles, as seems to be the case with the *tert*-butylester such that no reaction occurs at low temperatures. At higher temperatures, low selectivity is observed perhaps because of a more loosely bound complex.

Conversion of the α-phenylthioester to a carbonyl group was initially problematic. Hydrolysis of the ester into the acid occurred efficiently but required high temperatures and an appropriate solvent to ensure that both the ester and base had dissolved (Scheme 4). Interestingly, the trifluoroethyl ester **14** was hydrolysed under the same conditions in less than five minutes. Whilst ester hydrolysis proceeded smoothly, all attempts to convert the α-phenylthioacid **16** to the carbonyl group using NCS was unsuccessful (Scheme 4). This reagent has previously been used to convert an α-methylthioacid to a carbonyl group, but we believe that the lower nucleophilicity of the phenylthio group is the problem.[9]

We were eventually successful using a different strategy: instead of activating the sulfide we activated the acid. Thus reacting the α-phenylthioacid with diphenylphosphoryl azide[24] we obtained the corresponding ketone **15** directly in high yield and with 88% *ee* (Scheme 4). The lower enantioselectivity observed for **15** is due to the presence of the *exo* isomer in **16**. As only a small amount of the *exo* isomer was present in **16**, it indicates that this isomer must have been formed with high, but opposite, enantioselectivity with respect to the major *endo* isomer.

Whilst we were satisfied with the enantioselectivity of the *endo* cycloadduct, the *endo*/*exo* selectivity was somewhat disappointing, especially as this led to a lowering of the attainable enantiomeric excess of norbornenone de-



Scheme 4. Conversion of Diels–Alder adduct into norbornenone

rived from the cycloadduct. In order to increase the *endo*/*exo* selectivity, we considered varying the bisoxazoline ligand under our "optimised" conditions. Part of our inspiration came from the work of Davies et al. at Merck.[18,19,25] They noted a marked improvement in *endo* enantioselectivity and *endo*/*exo* selectivity in Diels–Alder reactions of cyclopentadiene with acrylimides catalysed by $Cu(OTf)_2$-bisoxazoline when the "bite angle" of the ligands was increased. The bite angle was varied by changing the substituents on the bridging methylene group of the bisoxazoline (e.g. **17**–**19**; largest bite angle was observed with the spirocyclopropyl ligand **17**). A similar effect was observed by Ghosh[26] in a related series of reactions in which the methylene bridged ligand **20** gave much improved selectivity compared with its dimethyl-substituted counterpart **7**. The bite angle of ligand **20** is larger than that of **7** due to a reduced steric compression[27] effect which, in the latter case, causes an angular contraction. Increasing the bite angle of the ligand should result in the metal being forced closer to the ligand centre and any dienophile bound to the metal will then also be brought closer to the substituents of the chiral ligand and will experience increased influence from the ligand. This accounts for the improvements in stereoselectivity observed.

The results of our studies with different bisoxazoline ligands (Figure 2) are presented in Table 2.

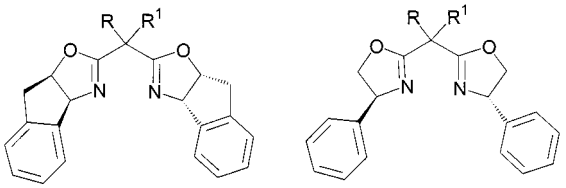


Figure 2. Other bisoxazolines tested

Table 2. Effect of varying ligand on selectivity of Diels−Alder reaction between cyclopentadiene and ethyl α-phenylthioacrylate

Entry[a]	Ligand	Yield (%)	*exo:endo*[b]	*endo ee* (%)[c]
1	**7**	92	1:15	>95
2	**17**	75	1:2.3	0
3	**18**	52	1:3	68[d]
4	**19**	87	1:2	0
5	**20**	76	1:3.8	56
6	**21**	81	1:11	>95

[a] 10 mol-% of $CuBr_2/AgSbF_6$, 10 mol-% bisoxazoline, 1 equiv. ethyl α-phenylthioacrylate and 4 equiv. cylopentadiene. − [b] Determined by NMR integration of crude reaction mixtures. − [c] Determined by NMR integration in the presence of Pirkle′s reagent, (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol. − [d] The *endo* cycloadduct shows the opposite absolute configuration to the other examples.

Entry 1 is our usual conditions with ligand **7**. Changing from a dimethyl- to a spirocyclopentyl substituent on the methylene bridge (ligand **21**) should increase the ligand bite angle slightly.[25] This resulted in a small decrease in *endo*/*exo* selectivity whilst the *endo* enantioselectivity remained excellent (entry 6). A larger increase in bite angle should occur with ligand **20** (entry 5). However, contrary to what we had expected, this resulted in a greatly diminished stereoselectivity both in terms of *endo*/*exo* selectivity and enantioselectivity.

No clear trend between the diastereoselectivity and/or enantioselectivity with the bite angle was observed with the indanol-derived ligands **17**−**19** (entries 2−4). Indeed, the ligands having largest and smallest bite angles (**17** and **19,** respectively) both gave racemic products with low diastereoselectivity (entries 2 and 4), whilst the ligand with intermediate bite angle (**18**) gave moderate selectivity, but now in favour of the opposite enantiomer. The lack of selectivity observed with the indanol-derived bisoxazolines was surprising.

Reversal of the sense of induction in certain reactions catalysed by metal-bisoxazoline complexes, wherein the only variable that changes is the pendant substituent on the oxazoline ring, is well documented.[20,28−33] This has been attributed either to a change in the metal geometry from square planar to tetrahedral[20,29−33] or to the extent of distortion away from planarity of the square planar complexes.[28] However, because of the low selectivity observed with the indanol series of bisoxazolines, it is not possible to comment on which of these is occurring.

In conclusion, we have developed a catalytic asymmetric Diels−Alder cycloaddition reaction of α-thioacrylates with cyclopentadiene, achieving good levels of *endo* selectivity and excellent enantioselectivity, and converted the cycloadducts into norbornenone in good yields and high enantioselectivity. Attempts to increase the *endo*/*exo* selectivity by changing the bite angle of the bisoxazolines were ultimately unsuccessful.

Experimental Section

All reactions were performed in oven dried glassware under dry argon unless otherwise stated. THF was distilled from potassium/benzophenone; dichloromethane, triethylamine and DMF were distilled from calcium hydride; cyclopentadiene was cracked and distilled immediately prior to use. Other commercially available reagents were used as received from the supplier. Acrylates (**1**−**5**) were prepared as described in the literature.[17,34] NMR spectra were recorded on a Bruker AM250 instrument in $CDCl_3$ unless otherwise stated and are referenced to the appropriate solvent signal. Mass spectra were obtained on KRATOS MS25, MS80 and VG Prospec instruments. Infra red spectra were obtained on a Perkin−Elmer PE684 instrument. GC analysis of norbornenone was achieved on a Perkin−Elmer PE Autosystem XL instrument using an α-cyclodextrin capillary column (Supelco Alphadex 120 fused silica capillary column column, length 30 m, 0.25 mm id., 0.25 μm film thickness) at 70 °C isothermal, hydrogen carrier gas (20psi); retention times 8.8 min and 9.1 min. The bisoxazolines were purchased from Aldrich and were used without further purification.

2′2′2′-Trifluoroethyl 2-Bromopropionate:[36] To an ice-cooled stirred solution of 2-bromopropionyl chloride (5.10 g, 29.7 mmol) in dichloromethane (30 mL) was added dropwise 2,2,2-trifluoroethanol (3.13 g, 31.3 mmol) and freshly distilled triethylamine (4.56 mL). The mixture was stirred at room temperature for 16 h. Then it was washed with water and the two layers were separated. The aqueous phase was extracted with dichloromethane (2 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. The resulting solid was purified by flash chromatography (dichloromethane) giving 5.83 g of the title compound (83% yield). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.87 (d, *J* = 7.0 Hz, 3 H), 4.44 (q, *J* = 7.0 Hz, 1 H), 4.55 (dq, *J* = 8.2, 0.9 Hz, 2 H).

2′2′2′-Trifluoroethyl 2-Phenylthiopropionate: KOH pellets (0.99 g, 16.0 mmol) were added to a solution of thiophenol (1.79 g, 16.2 mmol) in tetrahydrofuran (15 mL). The mixture was stirred under argon at room temperature until all the pellets had dissolved (ca. 2 h). A solution of 2-bromo-2′2′2′-trifluoroethylpropionate (3.53 g, 15.0 mmol) in tetrahydrofuran (10 mL) was added dropwise to the ice-cooled white reaction mixture, with continuous stirring. Upon completion of the addition the ice bath was removed and the mixture was stirred at room temperature for 18 h. Then water (20 mL) was added and the two layers were separated. The aqueous layer was extracted with dichloromethane (4 × 50 mL), the combined organic extracts were dried (Na_2SO_4), and the solvent was evaporated to give the title compound as a colourless oil (3.01 g, 76% yield); − IR (thin film): ν_{max} = 1755 cm^{-1}. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.52 (d, *J* = 7.0 Hz, 3 H), 3.85 (q, *J* = 7.0 Hz, 1 H), 4.42 (dq, *J* = 8.2, 1.8 Hz, 2 H), 7.28−7.35 (m, 3 H), 7.41−7.53 (m, 2 H). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 16.9, 44.6, 60.7 (q, *J* = 36.9 Hz), 122.8 (q, *J* = 277.5 Hz), 128.4, 128.9, 132.2, 133.3, 171.0. − MS: *m/z* (%) = 264 (71) [M^+], 218 (100), 185 (9), 154 (11), 137 (73), 109 (76), 65 (24). − HR-MS ($C_{11}H_{11}F_3O_2S$): calcd. 264.0432; found 264.0438.

2′2′2′-Trifluoroethyl 2-(Phenylsulfinyl)propionate: To an ice-cooled stirred solution of 2′2′2′-trifluoroethyl 2-phenylthiopropionate (1.06 g, 4.03 mmol) in diethyl ether (10 mL) was added dropwise a solution of *m*-chloroperoxybenzoic acid (1.23 g; 56−86%) in diethyl ether (10 mL) over 10 minutes. The resulting solution was stirred at room temperature for 5 h. The solvent was evaporated giving a white solid. This solid was dissolved in dichloromethane (50 mL) and the organic solution was washed with sodium thiosulfate (aq. ca. 50%, 20 mL) and saturated aqueous $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4) and evaporated. The resulting solid was purified by flash chromatography (petroleum ether 40−60 fraction/ethyl acetate 1:2) giving 125 mg of sulfoxide

A (R_f = 0.41), 89 mg of sulfoxide **B** (R_f = 0.36) and 469 mg of **A** + **B** mixture (61% overall yield). − IR (thin film): ν_{max} = 1756 cm^{-1}. − ^1H NMR (250 MHz, $CDCl_3$) isomer **A**: δ = 1.50 (d, *J* = 7.0 Hz, 3 H), 3.63 (q, *J* = 7.0 Hz, 1 H), 4.41 (m, 2 H), 7.51−7.59 (m, 3 H), 7.59−7.66 (m, 2 H); isomer **B**: δ = 1.42 (d, *J* = 7.3 Hz, 3 H), 3.89 (q, *J* = 7.3 Hz, 1 H), 4.41 (m, 2 H), 7.49−7.65 (m, 5 H). − ^{13}C NMR (62.9 MHz, $CDCl_3$) isomer **A**: δ = 9.0, 61.1 (q, *J* = 37.2 Hz), 64.7, 124.5, 124.7 (q, *J* = 277.5 Hz), 129.6, 133.0, 141.0, 167.0; isomer **B**: δ = 9.3, 60.8 (q, *J* = 37.2 Hz), 63.2, 124.7 (q, *J* = 277.5 Hz), 124.8, 129.1, 132.0, 139.8, 166.5. − MS: *m*/*z* (%) = (isomer **A**) 280 (39) [M^+], 156 (7), 139 (6), 125 (100), 83 (10), 77 (22); (isomer **B**) 280 (30) [M^+], 156 (16), 139 (14), 125 (100), 83 (11), 77 (26). − HR-MS ($C_{11}H_{11}F_3O_3S$): calcd. 280.0381; found (isomer **A**) 280.0390; (isomer **B**) 280.0390. − $C_{11}H_{11}F_3O_3S$: calcd. C 47.14, H 3.96; found C 46.99, H 3.93.

2′2′2′-Trifluoroethyl 2-Phenylthioacrylate (6): To a solution of 2′2′2′-trifluoroethyl (2-phenylsulfinyl)propionate (1:1 mixture of diastereomers; 411 mg, 1.47 mmol) in anhydrous dichloromethane (10 mL) under argon, was added a solution of trifluoroacetic anhydride (434 mg, 2.07 mmol) in dichloromethane (0.5 mL). The mixture was stirred at room temperature for 2 h. The solvent was evaporated and the crude material was purified by flash chromatography (petroleum ether 40−60 fraction/dichloromethane 3:2) to afford the title compound as a very pale yellow oil (262 mg, 68%). − IR (thin film): ν_{max} = 1749 cm^{-1}. − ^1H NMR (250 MHz, $CDCl_3$): δ = 4.55 (q, *J* = 8.2 Hz, 2 H), 5.43 (d, *J* = 0.6 Hz, 1 H), 6.43 (d, *J* = 0.6 Hz, 1 H), 7.36−7.2 (m, 3 H), 7.43−7.50 (m, 2 H). It was not possible to obtain further data as the acrylate decomposed.

General Procedure for the Preparation of the Catalyst. − Cu(OTf)$_2$/(*S*)-(−)-2,2′-Isopropylidene-bis(4-phenyl)-2-oxazoline: A solution of the bisoxazoline (65 mg, 0.19 mmol) in dichloromethane (3.0 mL) was added to a flask containing copper(II) triflate (62 mg, 0.17 mmol) and the resulting blue-green solution stirred at room temperature for 3 h.

$CuBr_2$/$AgSbF_6$/(*S*)-(−)-2,2′-Isopropylidene-bis(4-phenyl)-2-oxazoline: A solution of the bisoxazoline (66 mg, 0.20 mmol) in dichloromethane (5.0 mL) was added to $CuBr_2$ with a cannula and the mixture stirred at room temperature for 3 h. Silver hexafluoroantimonate was weighed into a dry, round-bottomed flask fitted with a magnetic stir bar. The flask was evacuated (0.01 Torr), gently heated and then flushed with argon and this procedure was repeated three times. The orange brown solution of copper(II) bromide/bisoxazoline was transferred to this flask with a cannula and the mixture stirred at room temperature for 1 h with exclusion of light giving a green solution of the desired complex plus precipitated AgBr.

General Procedure for the Diels−Alder Cycloaddition of Thioacrylates with Cyclopentadiene. − Preparation of Ethyl 2-(Phenylthio)-bicyclo[2.2.1]hept-5-ene-2-carboxylate (11): A solution of freshly prepared **3** (1.49 g, 7.15 mmol) in dichloromethane (12.0 mL) was cooled to −78 °C, then added with a cannula to a solution of freshly cracked and distilled cyclopentadiene (0.70 g, 10.61 mmol) in dichloromethane (8.0 mL), also cooled to −78 °C, and this solution stirred with cooling at −78 °C for 5 min. A solution of the Cu^{II} catalyst prepared as above [20 mol-% Cu with $Cu(OTf)_2$, 10mol-% with $Cu(SbF_6)_2$], was cooled to −78 °C and the solution of cyclopentadiene and dienophile added with a cannula. The green reaction mixture was stirred at −78 °C for 2 h or until the reaction had gone to completion. It was then allowed to warm to room temperature and filtered through a small plug of silica gel washing thoroughly with dichloromethane. The solvent was evaporated and the crude material purified by flash column chromatography on silica gel (petroleum ether 40−60 fraction/dichloromethane 1:1) giving the title product as a very pale yellow oil (1.81 g, 92%). − IR (thin film): ν_{max} = 1720cm^{-1}. − ^1H NMR (250 MHz, $CDCl_3$): δ = (*endo*) 1.10 (t, *J* = 7.5 Hz, 3 H), 1.55−1.67 (m, 1 H), 1.89 (dd, *J* = 12.5, 3.1 Hz, 1 H), 2.13−2.22 (m, 1 H), 2.88−2.96 (m, 1 H), 3.03−3.10 (m, 1 H), 3.84−4.10 (m, 2 H), 5.91 (dd, *J* = 5.6, 2.5 Hz, 1 H), 6.21 (dd, *J* = 5.6, 2.5 Hz, 1 H), 7.25−7.39 (m, 3 H), 7.41−7.53 (m, 2 H); (*exo*) 1.19 (t, *J* = 7.5 Hz, 3 H), 1.24−1.30 (m, 1 H), 1.34 (dd, *J* = 12.5, 3.1 Hz, 1 H), 1.60−1.68 (m, 1 H), 2.88−2.95 (m, 1 H), 3.38−3.44 (m, 1 H), 3.84−4.10 (m, 2 H), 6.25−6.38 (m, 2 H), 7.25−7.39 (m, 3 H), 7.42−7.53 (m, 2 H). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = (*endo*) 14.0, 38.9, 42.7, 47.2, 49.7, 60.7, 60.9, 128.6, 128.9, 132.5, 134.1, 135.7, 139.8, 172.9. − HR-MS ($C_{15}H_{18}O_2S$): calcd. 262.0871; found 262.0876.

Ethyl 2-(Methylthio)bicyclo[2.2.1]hept-5-ene-2-carboxylate (9): IR (thin film): ν_{max} = 1720cm^{-1}. − ^1H NMR (250 MHz, $CDCl_3$): δ = (*endo*) 1.26 (t, *J* = 6.0 Hz, 3 H), 1.49−1.68 (m, 2 H), 1.77 (dd, *J* = 12.5, 3.0 Hz, 1 H), 2.04 (dd, *J* = 12.5, 3.0 Hz, 1 H), 2.09 (s, 3 H), 2.84−2.90 (m, 1 H), 3.09−3.13 (m, 1 H), 3.52 (s, 3 H), 4.12 (q, *J* = 6.0 Hz, 2 H), 6.00 (dd, *J* = 8.0, 3.5 Hz, 1 H), 6.21 (dd, *J* = 8.0, 3.5 Hz, 1 H); (*exo*) 1.13 (dd, *J* = 12.5, 3.0 Hz, 1 H), 1.31 (t, *J* = 6.0 Hz, 3 H), 1.49−1.68 (m, 2 H), 2.17 (s, 3 H), 2.58 (dd, *J* = 12.5, 3.0 Hz, 1 H), 2.90−2.95 (m, 1 H), 3.09−3.13 (m, 1 H), 4.22 (q, *J* = 6.0 Hz, 2 H), 6.11 (dd, *J* = 8.0, 3.5 Hz, 1 H), 6.29 (dd, *J* = 8.0, 3.5 Hz, 1 H). − MS: *m*/*z* (%) = 212 (72) [M^+], 146 (100), 139 (17), 100 (56), 91 (48) 73 (44), 66 (67). − HR-MS ($C_{11}H_{16}O_2S$): calcd. 212.0871; found 212.0876.

Methyl 2-(Phenylthio)bicyclo[2.2.1]hept-5-ene-2-carboxylate (10): IR (thin film): ν_{max} = 1730cm^{-1}. − ^1H NMR (250 MHz, $CDCl_3$): δ = (*endo*) 1.54−1.66 (m, 2 H), 1.88 (dd, *J* = 12.5, 2.0 Hz, 1 H), 2.06 (dd, *J* = 12.5, 2.0 Hz, 1 H), 2.88−2.95 (m, 1 H), 3.00−3.05 (m, 1 H), 3.52 (s, 3 H), 5.90 (dd, *J* = 5.0, 2.0 Hz, 1 H), 6.22 (dd, *J* = 5.0, 2.0 Hz, 1 H), 7.26−7.36 (m, 5 H); (*exo*) 1.35 (dd, *J* = 12.5, 2.0 Hz, 1 H), 1.54−1.66 (m, 1 H), 2.61 (dd, *J* = 12.5, 2.0 Hz, 1 H), 2.88−2.95 (m, 1 H), 3.35−3.39 (m, 1 H), 3.56 (s, 3 H), 6.28 (dd, *J* = 5.0, 2.0 Hz, 1 H), 6.35 (dd, *J* = 5.0, 2.0 Hz, 1 H), 7.39−7.52 (m, 5 H). − MS: *m*/*z* (%) = 260 (22) [M^+], 218 (11), 194 (100), 135 (98), 109 (26), 91 (38), 65 (19). − HR-MS ($C_{15}H_{18}O_2S$): calcd. 260.0871; found 260.0876.

Isopropyl 2-(Phenylthio)bicyclo[2.2.1]hept-5-ene-2-carboxylate (12): ^1H NMR (250 MHz, $CDCl_3$): δ = (*endo*) 1.00 (d, *J* = 7.5 Hz, 3 H), 1.10 (d, *J* = 7.5 Hz, 3 H),1.48−1.54 (m, 1 H), 1.83 (dd, *J* = 12.5, 5.6 Hz, 1 H), 2.00 (dd, *J* = 12.5, 5.6 Hz, 1 H), 2.06−2.13 (m, 1 H), 2.80−2.88 (m, 1 H), 2.97−3.02 (m, 1 H), 4.77 (septet, *J* = 7.5 Hz, 1 H), 5.84 (dd, *J* = 6.3, 3.1 Hz, 1 H), 6.14 (dd, *J* = 6.3, 3.1 Hz, 1 H), 7.17−7.26 (m, 3 H), 7.32−7.44 (m, 2 H); (*exo*) 0.96 (d, *J* = 7.5 Hz, 3 H), 1.08 (d, *J* = 7.5 Hz, 3 H), 1.14−1.27 (m, 1 H), 1.29 (dd, *J* = 12.5, 5.0 Hz, 1 H), 1.54−1.61 (m, 1 H), 2.57 (dd, *J* = 12.5, 5.0 Hz, 1 H), 2.80−2.88 (m, 1 H), 3.32−3.37 (m, 1 H), 4.82 (septet, *J* = 7.5 Hz, 1 H), 6.20 (dd, *J* = 6.3, 3.1 Hz, 1 H), 6.26 (dd, *J* = 6.3, 3.1 Hz, 1 H), 7.17−7.26 (m, 3 H), 7.32−7.44 (m, 2 H).

***tert*-Butyl 2-(Phenylthio)bicyclo[2.2.1]hept-5-ene-2-carboxylate (13):** ^1H NMR (250 MHz, $CDCl_3$): δ = (*endo*) 1.30 (s, 9 H), 1.63−1.67 (m, 1 H), 1.76 (dd, *J* = 12.5, 3.1 Hz, 1 H), 2.15−2.20 (m, 1 H), 2.65 (dd, *J* = 12.5, 3.1 Hz, 1 H), 2.89−2.95 (m, 1 H), 3.35−3.42 (s, 1 H), 6.28 (dd, *J* = 12.5, 3.1 Hz, 1 H), 6.35 (dd, *J* = 12.5, 3.1 Hz, 1 H), 7.15−7.23 (m, 3 H), 7.28−7.39 (m, 2 H); (*exo*) 1.32 (s, 9 H), 1.55−1.60 (m, 1 H), 1.83 (dd, *J* = 12.5, 3.1 Hz, 1 H), 2.05 (dd, *J* 12.5, 3.1 Hz, 1 H), 2.13−2.16 (m, 1 H), 2.89−2.95 (m, 1 H), 3.01−3.05 (s, 1 H), 5.92 (dd, *J* = 12.5, 3.0 Hz, 1 H), 6.24 (dd, *J* = 12.5, 3.0 Hz, 1 H), 7.15−7.23 (m, 3 H), 7.28−7.39 (m, 2 H).

2′2′2′-Trifluoroethyl 2-(Phenylthio)bicyclo[2.2.1]hept-5-ene-2-carboxylate (14): IR (thin film): ν_{max} = 1747cm^{-1}. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.63 (m, 1 H), 2.00 (m, 2 H), 2.17 (m, 1 H), 2.96 (m, 1 H), 3.09 (m, 1 H), 4.08 (dq, *J* = 12.6, 8.5 Hz, 1 H), 4.46 (dq, *J* = 12.6, 8.5 Hz, 1 H), 5.92 (dd, *J* = 5.8, 3.1 Hz, 1 H), 6.25 (dd, *J* = 5.8, 3.1 Hz, 1 H), 7.29−7.51 (m, 5 H). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 39.0, 42.6, 47.1, 49.6, 60.4 (q, *J* = 36.5 Hz), 122.8 (q, *J* = 277.5 Hz), 128.8, 129.3, 133.7, 135.8, 136.6, 140.3, 171.3. − MS: *m*/*z* (%) = 328 (11) [M$^+$], 262 (100), 135 (95), 109 (14), 91 (42), 77 (7), 65 (18). − HR-MS ($C_{16}H_{15}F_3O_2S$): calcd. 328.0745; found 328.0729.

Preparation of 2-(Phenylthio)bicyclo[2.2.1]hept-5-ene-2-carboxylic Acid (16): A solution of KOH in isobutyl alcohol (10% w/w, 30 mL) was added to **11** (1.80 g, 6.57 mmol). The cloudy solution was stirred at 100 °C for 28 h and then cooled to room temperature. The resulting mixture was dissolved in water (100 mL) and the solution extracted with dichloromethane (100 mL). The aqueous phase was then acidified (conc. HCl) and extracted with dichloromethane (3 × 100 mL). These extracts were combined and dried over magnesium sulfate, and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petroleum ether 40−60/acetone 2:1) giving the title compound as a pale yellow crystalline solid (1.24 g, 77%). − m.p. 75−83 °C. − $[\alpha]_D^{22}$ = −51.7 (*c* = 0.1 in $CHCl_3$) [ref. for the opposite enantiomer:[37] $[\alpha]_D^{22}$ = +21 (*c* = 0.67)]. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = (*endo*) 1.49−1.59 (m, 1 H), 1.79−1.99 (m, 2 H), 2.07−2.14 (m, 1 H), 2.84−2.89 (m, 2 H), 2.89−2.96 (m, 1 H), 5.90 (dd, *J* = 5.0, 1.9 Hz, 1 H), 6.16 (dd, *J* = 5.0, 1.9 Hz, 1 H), 7.15−7.34 (m, 3 H), 7.34−7.45 (m, 2 H); (*exo*) 1.59−1.63 (m, 1 H), 1.79−1.99 (m, 2 H), 2.46−2.56 (m, 1 H), 2.89−2.96 (m, 2 H), 3.23−3.28 (m, 1 H), 6.13−6.20 (m, 1 H), 6.23−6.28 (m, 1 H), 7.15−7.35 (m, 3 H), 7.35−7.45 (m, 2 H). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = (*endo*) 38.6, 42.8, 47.2, 49.3, 60.7, 128.8, 129.3, 132.2, 134.7, 140.1, 178.5. − MS: *m*/*z* (%) = 246 (25) [M$^+$], 180 (98), 135 (100), 109 (12), 91 (45), 77 (15), 66 (20). − HR-MS ($C_{14}H_{14}O_2S$): calcd. 246.0715; found 246.0707.

(1*S*,4*S*)-Bicyclo-[2.2.1]-hept-5-ene-2-one (norbornenone) (15): A solution of **4** (240 mg, 0.96 mmol) in acetonitrile (0.5 mL) was added to a solution of diphenylphosphorylazide (272 mg, 0.96 mmol) and triethylamine (97 mg, 0.96 mmol) in acetonitrile (4.0 mL) and water (0.8 mL) and the solution refluxed for 23 h. Upon cooling to room temperature, the reaction mixture was poured into aqueous $NaHCO_3$ (satd. 15 mL) and extracted with dichloromethane (4 × 20 mL). The combined organic extracts were washed with aqueous NH_4Cl (3 × 15 mL) and water (3 × 15 mL), then dried over $MgSO_4$ and solvent removed under reduced pressure. Flash column chromatography (pentane/diethyl ether 9:1) gave the title compound as a sweet smelling, pale-yellow liquid (91 mg, 88%). − ^{1}H NMR (250 MHz, $CDCl_3$) δ = (*endo* + *exo*) 1.72−1.96 (m, 3 H), 2.06−2.17 (m, 1 H), 2.90−2.97 (m, 1 H), 3.07−3.14 (m, 1 H), 5.97−6.06 (m, 1 H), 6.47 (dd, *J* = 5.0, 2.5 Hz, 1 H). − $[\alpha]_D^{22}$ = −711 (*c* = 0.15 in $CHCl_3$) [ref.(1*R*,4*R*),[35] = +980 (*c* = 0.3 in $CHCl_3$).

The enantiomeric excess was determined by chiral GC analysis which was carried out on a chiral cyclodextrin-α column (30 m, 0.25 mm i.d.), using hydrogen as the carrier gas at a flow rate of 16Psi, 70 °C isothermal, flame ionisation detection. (1*R*,4*R*)-(+)-**15** had a retention time of 10.50 min while (1*S*,4*S*)-(−)-**15** had a retention time of 10.04. From GC analysis, (1*S*,4*S*)-(−)-**15** was obtained with 88% *ee*.

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