Catalytic asymmetric Diels–Alder reactions of α-thioacrylates for the preparation of norbornenone

Varinder K. Aggarwal,*[a]† Emma S. Anderson,[a] D. Elfyn Jones,[a] Kerstin B. Obierey[a] and Robert Giles[b]

[a] *Department of Chemistry, University of Sheffield, Sheffield, UK S3 7HF*
[b] *SmithKline Beecham, Old Powder Mills, Tonbridge, Kent, UK TN11 9AN*

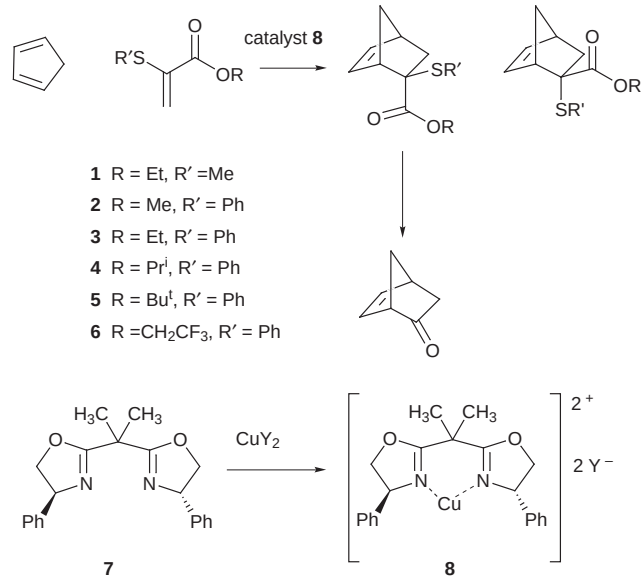
Cu^{II}–bisoxazoline complexes catalyse the asymmetric Diels–Alder cycloaddition of α-thioacrylates with cyclopentadiene to give the cycloadducts in up to 92% yield, 88% de and >95% ee for the *endo* product; deprotection gives good yields of (1*S*,4*S*)-norbornenone with high enantioselectivity.

The catalytic asymmetric Diels–Alder reaction has been an area of considerable interest over the last two decades and a large number of metals, ligands and dienophiles have been studied.[1–4] The most successful systems have common features associated with them: a bidentate ligand which complexes to the metal and a dienophile which acts as a two point binder to the ligand–metal complex.[5–7] Two point binding of both the ligand to the metal and dienophile to the complex results in limiting the number of accessible conformations of the dienophile bound to the Lewis acid and can result in high enantioselectivity.

We have been interested in developing ketene equivalents for Diels–Alder reactions[8] and have therefore sought dienophiles that could be easily converted to carbonyl compounds. To achieve good levels of enantioselectivity we also needed dienophiles that could act as two point binders to appropriate metals. α-Thioacrylates seemed ideal for our purpose as it was known that α-methylthioacrylates underwent Diels–Alder reactions with cyclopentadiene, for example, and that the adducts could be readily converted into norbornenones.[9–11] Such dienophiles may also act as two point binders to appropriate metals through carbonyl and sulfur coordination. We therefore prepared a range of α-thioacrylates.[12] We chose copper as the metal due to its known propensity to bind to both the sulfide and ester moieties and as ligands we chose bisoxazolines[13,14] due to the success of copper–bisoxazoline complexes in Diels–Alder reactions.[15–25]

Diels–Alder reactions were conducted between cyclopentadiene and the various acrylates[26] using the copper bisoxazoline complex **8**[27] (Scheme 1) and the results are shown in Table 1.

It was found that the selectivity of the Diels–Alder reaction was highly dependent on the nature of the ester and thio substituent. Higher selectivity was obtained with phenylthio- compared to methylthio-acrylates (entries 1 and 3) and higher selectivity was obtained with small or moderately sized ester substituents [Me, Et, Pr^i >> Bu^t (entries 2, 3, 6, 8 and 9)]. The Bu^t 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 (compare entries 3 and 4) and the use of cationic complexes[16] led to high reactivity even at −78 °C (entries 5 and 7) and high *exo*/*endo* selectivity as well as high enantioselectivity. The optimum reagents and conditions required ethyl α-phenylthioacrylate as dienophile, the cationic phenyl-substituted bisoxazoline–cop-



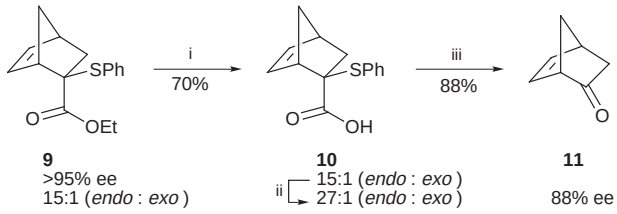
7 **8**

Scheme 1

Table 1 Diels–Alder reactions of α-thioacrylates with cyclopentadiene catalysed by Cu–bisoxazoline complexes

	Dienophile								
Entry		R	R′	Catalyst[a]	*t*/h	*T*/°C	Yield (%)	*exo*:*endo*[b]	Ee[c] (%)
1	**1**	Et	Me	$Cu(OTf)_2$	6	−40	53	1:2.4	40
2	**2**	Me	Ph	$Cu(OTf)_2$	6	−40	44	1:3.7	84
3	**3**	Et	Ph	$Cu(OTf)_2$	6	−40	50	1:4	80
4	**3**	Et	Ph	$Cu(OTf)_2$	9	−78	76	1:7	>95
5	**3**	Et	Ph	$CuBr_2/AgSbF_6$[d]	1	−78	92	1:15	>95
6	**4**	Pr^i	Ph	$Cu(OTf)_2$	4	−40	70	1:2.3	85
7	**4**	Pr^i	Ph	$CuBr_2/AgSbF_6$[d]	2.5	−78	90	1:5	81
8	**5**	Bu^t	Ph	$Cu(OTf)_2$	5.5	0	91	1:2.5	26
9	**6**	CF_3CH_2	Ph	$CuBr_2/AgSbF_6$[d]	1.5	−78	92	1:13	>95

[a] 20 mol% $Cu(OTf)_2$, 30 mol% bisoxazoline **7**, 1 equiv. dienophile 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] 10 mol% of $CuBr_2/AgSbF_6$, 10 mol% bisoxazoline **7**, 1 equiv. dienophile and 4 equiv. cylopentadiene.



Scheme 2 *Reagents and conditions*: i, KOH, Bu^{i}OH, H_2O; ii, recrystallisation (light petroleum); iii, $(PhO)_2P(O)N_3$, Et_3N, MeCN, H_2O

per complex, and reaction at −78 °C in CH_2Cl_2 (entry 5); under these conditions good diastereoselectivity and essentially complete enantioselectivity was observed.

Conversion of the α-phenylthio ester to a carbonyl group was initially problematic. Hydrolysis of the ester to the acid occurred efficiently but attempts to convert the α-phenylthio acid **10** to the carbonyl group using NCS was unsuccessful. This reagent had previously been used to convert an α-methylthio acid to a carbonyl group.[9] We were eventually successful using a different strategy: instead of activating the sulfide we activated the acid and reacted the α-phenylthio acid with diphenylphosphoryl azide[28] and obtained the corresponding ketone **11** directly in high yield and with 88% ee[29] (Scheme 2). The lower enantioselectivity observed for **11** is due to the presence of the *exo* isomer in **10**.

A transition state involving bidentate binding of the dienophile *via* sulfur and the carbonyl oxygen to a square planar Cu^{II} complex[15,16,21,23,24,30,31] may be used to rationalise the enantio- and diastereo-selectivities. 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. Indeed, all successful dienophile–metal–oxazoline combinations place the alkene moiety directly over one of the oxazoline substituents where it has maximum influence on the enantioselectivity of the reaction.[32] 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 binds to the copper) and it is the orientation of the sulfur substituent which controls the facial attack on the dienophile (Fig. 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. 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.

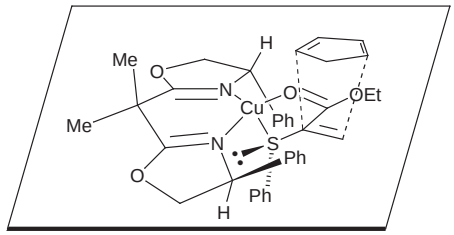


Fig. 1 The dienophile–metal–oxazoline complex

The size of the ester group of the dienophile is critical; an excessively bulky group may prevent the essential two-point binding, as seems to be the case with *tert*-butyl. Equally, the substituent on sulfur of the dienophile is also critical. Although the same discrimination between the lone pairs on sulfur may be observed with the *S*-methyl substituted dienophile, the methyl group is not sufficiently sterically hindering to effectively block the *Si* face to approach of the diene component, resulting in significantly reduced enantioselectivity in this case.

We thank the EPSRC and SB for a CASE award (E. A.), the European Union and Sheffield University for additional support. We thank Ian Davies (Merck) for valuable discussions.

Notes and References

† E-mail: v.aggarwal@sheffield.ac.uk

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Received in Liverpool, UK, 10th July 1998; 8/05366I