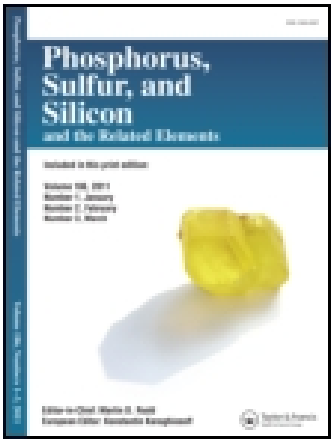

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Recent Developments in Asymmetric Hetero-Diels-Alder Reactions of Dithioesters

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RECENT DEVELOPMENTS IN ASYMMETRIC HETERO-DIELS-ALDER REACTIONS OF DITHIOESTERS

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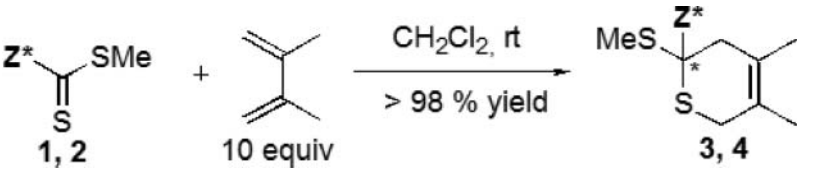
GRAPHICAL ABSTRACT



Abstract *Recent studies dealing with asymmetric thia-Diels-Alder reactions of dithioesters as heterodienophiles are described. A diastereoselective version involving new chiral dithioesters and the first example of a catalytic enantioselective version are described. The absolute stereochemistry of the cycloadducts was assigned based on an X-ray structure and chemical correlation. In order to rationalize the sense of the chiral induction observed experimentally, stereochemical models for Cu(II)/BOX/dithioester complexes are proposed.*

Keywords Asymmetric hetero-Diels-Alder reaction; thia-Diels-Alder reaction; chiral dithioester; Cu(II)/bis(oxazoline) complex; stereochemical models

INTRODUCTION

The asymmetric carbo- and hetero-Diels−Alder (DA and HDA) reactions represent a powerful and atom-economical synthetic method to obtain optically active six-membered carbocycles and heterocycles.[1] Compared to the carbo-, oxa-, and aza-DA reactions, the asymmetric thia-DA version has received much less attention, despite its potential utility to afford chiral enantioenriched dihydrothiopyrans. Due to their easy access in a large variety of structures, dithioesters represents convenient partners in cycloadditions.[2] Moreover, when the thiocarbonyl group is activated *via* an electronwithdrawing substituent[3] or by addition of a catalyst (Lewis or Brønsted acid),[4] dithioesters represents highly reactive

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Table 1 The HDA reactions of chiral dithioesters 1 and 2 with 2,3-dimethylbutadiene

Entry	Dithioester	Cycloadduct	dr[a]	de (%)[b]
1	**1a**	**3a**	59/41	18
2	**1b**	**3b**	50/50	0
3	**2a**	**4a**	53/47	6
4	**2b**	**4b**	57/43	14
5	**2c**	**4c**	89/11	78

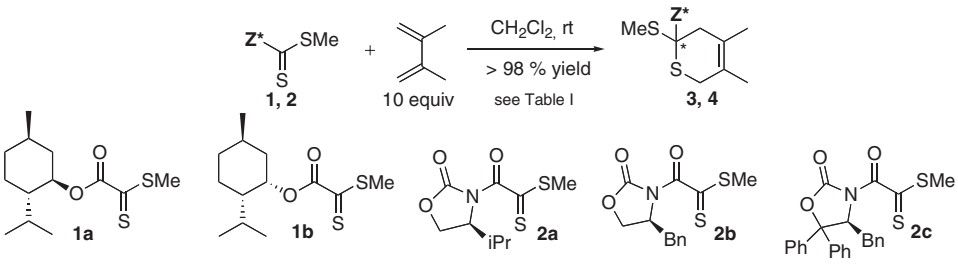
[a]Diastereomeric ratio determined by ^{1}H NMR spectroscopy in the crude mixture. [b]Diastereomeric excess.

heterodienophiles for various applications.[5] Before our study, only a few asymmetric HDA reactions involving dithioesters as dienophiles[6] had been described and the enantioselective catalyzed version was unprecedented. Herein are summarized the most significant results that we obtained in asymmetric Diels-Alder reactions with dithiooxalates and carbonyloxazolidinone dithioesters, which were chosen as sulfur analogues of well studied acrylate and glyoxalate derivatives.[7]

RESULTS AND DISCUSSION

Diastereoselective Version

Commercially available enantiopure menthol stereoisomers and oxazolidinones, commonly used in asymmetric synthesis, were chosen as chiral auxiliaries to prepare dithiooxalates **1** and carbonyloxazolidinone dithioesters **2**, respectively. The chiral dithioesters **1** and **2** were reacted with dimethyl-1,3-butadiene (Scheme 1, Tables 1). All cycloadditions were carried out in dichloromethane, at room temperature, using 10 equivalents of diene. Full conversions that translated into quantitative yields have been obtained for the expected cycloadducts **3** and **4**. (−)-Menthol induced a low diastereoselectivity affording cycloadduct **3a** with 18% de (entry 1), while no selectivity was obtained with its epimer (+)-neomenthol having opposite configuration at C-1 (entry 2). Dithioesters **2a** and **2b**, derived from chiral 4-isopropyl and 4-benzyl oxazolidinones, led to the corresponding cycloadducts with diastereoselectivities of 6% and 14%, respectively (entries 3 and 4). A much higher diastereomeric excess of 78% was obtained with dithioester **2c** derived from a more hindered oxazolidinone (entry 5). An X-ray structure has been obtained for **2a** and showed that the stereodifferentiation of the *Re* and *Si* faces is small since the chiral



Scheme 1

Table 2 Enantioselective HDA reactions of dithioesters **1x** and **2x** with 2,3-dimethylbutadiene, catalyzed by a $Cu(OTf)_2$/bis(oxazoline) complex

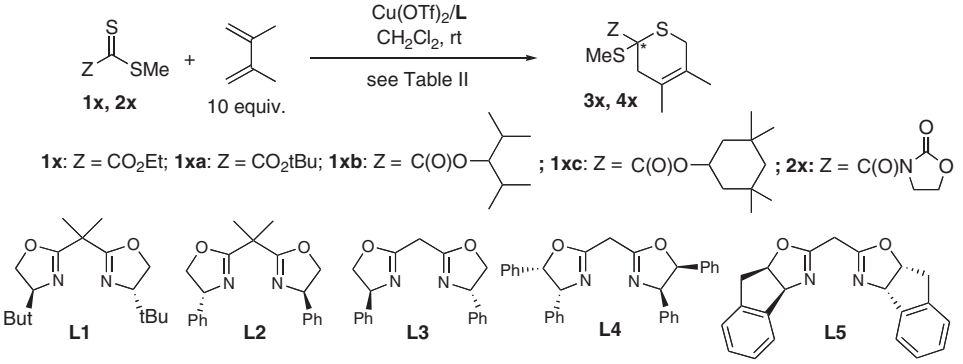
Entry	Dithioester	Cycloadduct	Ligand	mol% catalyst	ee (%)[a]
1	**1x**	**3x**	**L1**	5	2
2	**1x**	**3x**	**L2**	5	54
3	**1x**	**3x**	**L3**	5	0
4	**1x**	**3x**	**L4**	5	82
5	**1x**	**3x**	**L5**	5	0
6	**1xa**	**3xa**	**L4**	5	10
7	**1xb**	**3xb**	**L4**	5	78
8	**1xc**	**3xc**	**L4**	5	10
9	**2x**	**4x**	**L4**	5	4
10	**1x**	**3x**	**L4**	100	82
11	**2x**	**4x**	**L4**	100	42

[a]Enantiomeric excess determined by chiral HPLC.

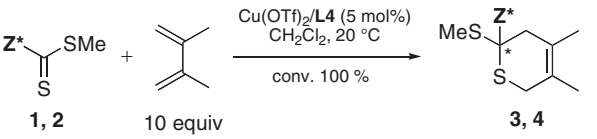
center is placed too far from the reacting site. This is in line with the experimental poor stereoselectivity observed in this case.

Enantioselective Version

Le dithiooxalate **1x** and 2,3-dimethyl-1,3-butadiene was chosen as the cycloaddition partners for the first series of experiments (Scheme 2, Table 2, entries 1–5). We decided to start our study by testing $Cu(OTf)_2$-bis(oxazoline) complexes as chiral catalysts, as they are well known for their efficiency in various catalytic asymmetric carbo, oxa, and aza-Diels-Alder reactions.[8] Five commercially available bis(oxazolines) **L1–L5** were tested as chiral ligands. All reactions gave full conversion into the HDA cycloadducts, after less than 1 h. No enantioselectivity was obtained with ligands **L1**, **L3**, and **L5**, but very promising results were obtained with **L2** (54% ee) and in particular with **L4** (82% ee). Kipping the best ligand **L4**, a screening of different parameters, temperature (−20 °C, 20 °C, 40 °C), solvent (dietylether, acetonitrile, tetrahydrofurane, toluene, dichloroethane), Lewis acid [$Zn(OTf)_2$, $Sn(OTf)_2$, $CuCl_2$, $Cu(ClO_4)_2$] was done in order to improve the enantioselectivity of this cycloaddition. Whatever the modifications performed, the enantiomeric excess did not



Scheme 2



Scheme 3

exceed the previous result of 82% ee. Also in order to increase the enantioselectivity, three more hindered dithiooxalates have been prepared and reacted in the same conditions (Scheme 3, Table 2, entries 6–8). *Tert*-butyl and 3,3,4,4-tetramethyl-cyclohexyl derivatives **1xa** and **1xc** led to low ees of 10%. A better ee of 78% was obtained with 2,4-dimethylpentyl dithiooxalate **1xb**, however, still lower than with the ethyl derivative **1x**. Placed in the same reaction conditions, carbonyloxazolidinone **2x** led to a very poor enantioselectivity of 4% ee (Scheme 2, Table 2, entry 9). The use of a stoichiometric amount of catalyst was then attempted (Table 2, entries 10–11). Similar enantioselectivity was obtained with **1x** (Table 2, entry 4 vs. entry 10), while with **2x** the ee was considerably increased, from 4% to 42% (Table 2, entry 9 vs. entry 11).

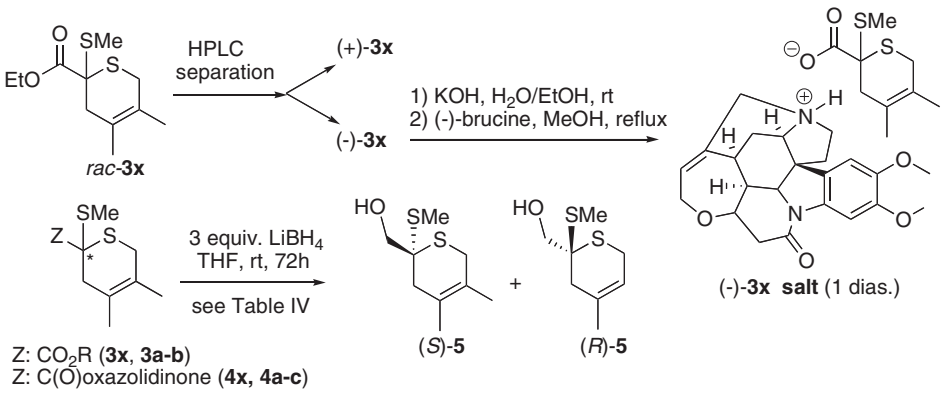
Double-Stereodifferentiating Experiments

Experiments combining the chiral induction of both auxiliary and catalyst were then considered. This could bring additional information about the stereochemical outcome of the cycloadditions and the metal center geometry of the reactive catalyst-dithioester complexes. Chiral dithioesters **1** and **2** were reacted with 2,3-dimethylbutadiene in the presence of 5 mol% of $Cu(OTf)_2$/**L4** (Scheme 3, Table 3). In these conditions, (−)-menthyl dithiooxalate **1a** led to a higher diastereomeric excess of 28% (vs. 18% in the uncatalyzed version), but with an opposite chiral induction (Table 3, entry 1), representing the mismatched case. The (+)-menthol derivative **1a'** gave matched reaction with a diastereoselectivity of 66% (Table 3, entry 2). While no selectivity was observed with **1b** in the uncatalyzed reaction, the catalyzed version led to a high diastereomeric excess of 90% (Table 3, entry 3). The results indicate that in this case the asymmetric induction comes mainly from the chiral catalyst. The presence of the chiral catalyst in the cycloaddition of (*S*)-oxazolidinone derivative **2c** did not really change the diastereoselectivity compared to the uncatalyzed reaction (80% vs. 78% de, Table 3, entry 4). The combination of the opposite enantiomer **2c'** with the chiral catalyst represents the mismatched pair, leading to 56% de (Table 3, entry 5).

Table 3 HDA reactions of chiral dithioesters **1** and **2** catalyzed by $Cu(OTf)_2$/**L4**

Entry	Dithioester	Cycloadduct	dr[(a)]	de (%)[(b)]
1	**1a**	**3a**	31/69	38
2	**1a′**	**3a′**	83/17	66
3	**1b**	**3b**	95/5	90
4	**2c**	**4c**	90/10	80
5	**2c′**	**4c′**	78/22	56

[a]Diastereomeric ratio determined by ^{1}H NMR spectroscopy in the crude mixture. [b]Diastereomeric excess.



Scheme 4

Assignment of Absolute Stereochemistry of Cycloadducts 3 and 4

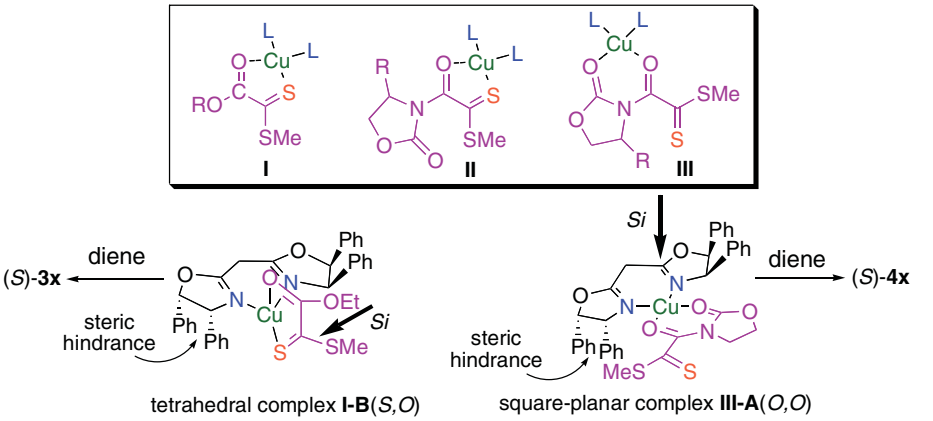
We next tried to assign the absolute configuration of the quaternary stereogenic center (C-2) formed during the cycloaddition in order to rationalize the stereochemical outcome of this asymmetric HDA reaction. Starting from the racemic **3x**, enantiomers (+)-**3x**, and (−)-**3x** were separated by preparative chiral HPLC, then each one was hydrolyzed into the carboxylic acid, and reacted with (−)-brucine (Scheme 4). The carboxylic acid derived from the levorotatory ester formed a diastereomerically pure crystalline ammonium salt, of which X-ray analysis allowed us to assign the (*S*) absolute stereochemistry to (-)-**3x**.

Then, cycloadducts **1** and **2** resulted from the different asymmetric cycloadditions were reduced into the corresponding enantioenriched alcohol **5** (Scheme 4). The most significant results are given in Table 4. After analysis by chiral HPLC we could correlate the major alcohol (*S*)-**5** to the major cycloadduct (*S*)-**3x** or (*S*)-**4x** (Table 4, entries 1, 2). Cycloadducts **3a**, **3a'**, **3b**, and **4c** led to the major alcohol of (*S*)-configuration (Table 4, entries 3–6). As expected, major alcohol (*R*)-**5** was obtained from cycloadduct **3c'** (Table 4, entry 7).

Table 4 Absolute stereochemical assignments of cycloadducts **3** and **4**

Entry	Cycloadduct[a]	Uncatalyzed HDA ee%[b] (config. at C-2)	Catalyzed HDA ee%[b] (config. at C-2)
1	**3x**	—	82 (*S*)
2	**4x**	—	42 (*S*)[(c)]
3	**3a**	18 (*R*)	28 (*S*)
4	**3′**	18 (*S*)	66 (*S*)
5	**3b**	0 (*rac*)	90 (*S*)
6	**4c**	78 (*S*)	80 (*S*)
7	**4c′**	78 (*R*)	56 (*R*)

[a]Cycloadducts obtained from the different asymmetric HDA reactions (see Schemes 1–3, Tables 1–3). [b]Enantiomeric excess of **5**, determined by chiral HPLC. [c]With 100 mol% chiral catalyst.



Stereochemical Models

A bidentate chelation catalyst-dithioester was considered (Scheme 5). Both of dithiooxalate and carbonyloxazolidinone dithioester were supposed to coordinate the copper *via* an oxygen and a sulfur atom (Scheme 5, complexes **I** and **II**). In the case of dithioesters **2**, the copper atom can also coordinate the two oxygen atoms of the carbonyloxazolidinone moiety (Scheme 5, complex **III**) similarly to the known cases of acryloyl and glyoxyl l,3-oxazolidin-2-ones. In order to rationalize the sense of the chiral induction observed experimentally, we used by analogy models already proposed in the literature for carbo- and oxa-dienophiles,[9] Thus, for each of these complexes, two geometries of the catalyst-dienophile[10] complex were considered: a square-planar (**A**) and a tetrahedral (**B**).

Dithiooxalate case. In the asymmetric cycloaddition of dithiooxalate **1x** catalyzed by 5 mol% of $Cu(OTf)_2$/**L4** the major cycloadduct was of *S*-configuration (82% ee). Two catalyst-dienophile complexes were considered: a square-planar **I-A** and a tetrahedral **I-B**, both of them having Cu(*S*,*O*) coordination (Scheme 5). In the case of **I-A**, the *Re*-face would be more accessible to the diene attack, leading preferentially to the cycloadduct with *R*-configuration at C-2, while in the case of **I-B**, the *Si*-face should be the most accessible, leading to the opposite isomer (*S*)-**3x**, which is in accordance with the experimental result. It is however difficult to explain reasonably the influence of the steric hindrance of the ester moiety, especially in the case of the matched/mismatched effect observed with the menthol derivatives.

Carbonyloxazolidinone dithioester case. In the asymmetric catalyzed reaction of dienophile **2x**, the major (*S*)-cycloadduct was obtained with 42% ee, however, in the presence of a stoichiometric amount of $Cu(OTf)_2$/**L4**. Two stereochemical models predict the major (*S*)-cyloadduct (*via* a *Si*-face attack) in accordance with the experimental results: the square-planar complex **III-A** with *O*,*O*-chelation mode[10] and a tetrahedral complex of type **II-B** with *S*,*O*-chelation mode (Scheme 5). When these two stereochemical models were applied to the enantiomeric substrates **2c** and **2c'**, only the asymmetric induction predicted by the square-planar complex of type **III-A** (*O*,*O*) fitted with the experimental results of the double-differentiation study. These results suggesting a metal bidentate chelation between the two oxygen atoms (similar to the acryloyl-oxazolidinones series) can explain the low selectivities obtained in the asymmetric catalyzed HDA reaction involving carbonyloxazolidinone dithioesters, as the chiral auxiliary is placed too far from the C=S reacting site.

CONCLUSION

New aspects of asymmetric thia-HDA reactions with dithioesters as heterodienophiles were studied. In the diastereoselective version, the best result (78% de) was obtained with a hindered oxazolidinone as the chiral auxiliary. In the enantioselective version, which represent the first example in this topic, the best result remains 82% ee, which was obtained in the cycloaddition of dithiooxalate with 2,3-dimethylbutadiene, catalyzed by a Cu(II)/bis(oxazoline) chiral complex. The enantioselectivity of this type of cycloaddition seems to be difficult to control because highly dependent of the substrate. The double-differentiating experiments showed that in dithiooxalates series, the sense of the chiral induction is mainly controlled by the chiral catalyst, whereas for the carbonyloxazolidinone dithioesters the chiral auxiliary dominates the stereochemical control. Stereochemical models for catalyst/dithioester complexes were proposed in order to rationalize the sense of the chiral induction obtained experimentally: a tetrahedral complex with a (*S*,*O*) metal chelation for dithiooxalates and a square-planar complex with a (*O*,*O*) metal chelation for the carbonyloxazolidinone dithioesters. Further studies are needed to expand the scope of this asymmetric thia-HDA reaction.

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