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First catalytic enantioselective version of a thia hetero-Diels–Alder reaction with dithioesters

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ABSTRACT

The first example of a catalytic asymmetric thia hetero-Diels–Alder reaction, in which a chiral Lewis acid activates the thiocarbonyl dienophile, is described. The reactions catalyzed by copper(II)-bis(oxazolines) complexes of three dithioesters with simple dienes (such as cyclopentadiene or 2,3-dimethyl-1,3-butadiene) afford optically active dihydrothiopyrans with ees up to 82%. Some aspects of the reaction were investigated by computational means.

The asymmetric hetero-Diels–Alder (HDA) reaction represents a powerful and atom-economical synthetic method to obtain optically active six-membered heterocycles.[1] Among the general strategies, the asymmetric catalysis is not only and certainly the most economic, but also the most challenging one. It consists in the use of a chiral catalyst (such as a Lewis acid metal-complex or an organocatalyst), which activates one or both of achiral substrates (diene and dienophile), allowing the direct formation, under mild conditions, of the chiral enantioenriched cycloadduct. Compared to the catalytic asymmetric oxa- and aza-Diels–Alder reactions, the thia-Diels–Alder version has received much less attention, despite its potential utility to afford optically active dihydrothiopyrans. To the best of our knowledge, only two publications by Saito et al. described a catalytic asymmetric thia-Diels–Alder reaction.[2] In these examples, the chiral Lewis acid catalyst activates the oxazolidinone dienophile, but does not activate the thiocarbonyl diene partner.

In the last few years, our research focused on the development of catalyzed thia-Diels–Alder reactions involving dithioesters. A Lewis or a Brønsted acid catalyst affords a more reactive heterodienophile activating the thiocarbonyl group by lowering the LUMO dienophile energy, thereby reducing the activation energy of the process.[3] Our methodology was recently used by other groups in an interesting application involving the thia-HDA reaction as an ultrafast click reaction in the generation of a macromolecular architecture.[4]

In the present work, we describe the first example of a catalytic asymmetric thia-Diels–Alder reaction, in which a dithioester dienophile is activated by a chiral Lewis acid. The cycloadduct is a cyclic dithioacetal, in which the generated quaternary thiodisubstituted carbon stereocenter is interesting to control. For a better understanding, some aspects of the reaction are investigated by computational means.

Three types of dithioesters, phosphonodithioformate **1**,[3a,b] dithiooxalate **2**,[5] and carbonyloxazolidinone dithioester **3**[6] were selected for this first study. The corresponding possible complexes with a Lewis acid are illustrated in Figure 1.

It could be expected in the case of **1** and **2** that the Lewis acid will coordinate both the oxygen and sulfur atoms to form cyclic complexes **A** and **B**, respectively. In the case of dithioester **3** it is more difficult to predict the chelation mode, as the copper atom can coordinate the oxygen and sulfur atoms (complex **C**) or the two oxygen atoms of the carbonyloxazolidinone moiety (complex

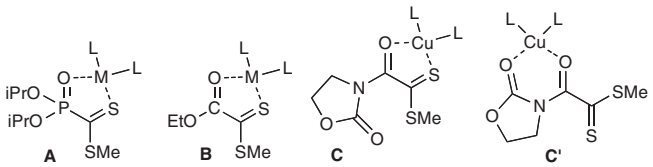

Figure 1. Possible complexes of dithioesters **1**–**3** with the Lewis acid.

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C′) similarly to the known cases of acryloyl and glyoxyl l,3-oxazolidin-2-ones.

Dithioesters **1**, **2**, and **3** were first reacted with two commonly used unfunctionalized dienes, namely cyclopentadiene and 2,3-dimethyl-1,3-butadiene. We decided to start our study by testing $Cu(OTf)_2$-bis(oxazoline) complexes as chiral catalysts,[7] as they are well known for their efficiency in various catalytic asymmetric carbo-, oxa-, and aza-Diels–Alder reactions.[8] Two commercially available bis(oxazolines), (*S*)-*t*Bu-BOX (**L1**) and (4*R*,5*S*)-di-Ph-BOX (**L2**), were selected as the chiral ligands. The first series of experiments was performed with cyclopentadiene (Scheme 1, Table 1).

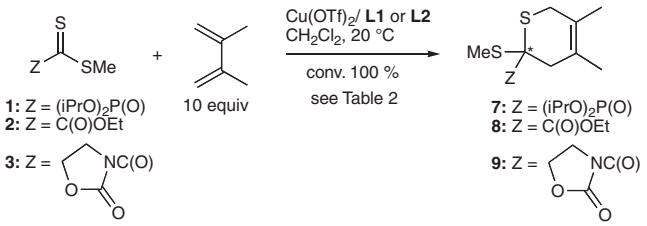
The results obtained in the uncatalyzed reactions (Table 1, entries 1–3) were compared with those obtained in the presence of 5 mol % of catalyst (entries 4–8). All reactions gave full conversion into the expected cycloadducts **4**, **5**, or **6** (visualized by the disappearing of the pink color of the dithioesters and monitored by TLC), The isolated yields were only 40–50% for **4** and **5** (due to the difficult separation of the product from the cyclopentadiene dimer) and 85% for **6**. As expected, the catalyzed cycloadditions get faster than the uncatalyzed ones. The uncatalyzed reactions afforded cycloadducts **4**–**6** with low to moderate *endo*/*exo* selectivities of 62/38,[3a] 57/43, and 70/30, respectively (entries 1–3). In the presence of $Cu(OTf)_2$/**L1** catalyst no significant changes of the *endo*/*exo* selectivities were observed (65/35 for **4** and 59/41 for **5**, entries 4 and 5) and almost no enantioselectivity was obtained in these cases. The use of catalyst $Cu(OTf)_2$/**L2** improved the *endo*/*exo* selectivities leading to a 76/24 ratio for **4** (entry 6) and to very good results for **5** and **6** (93/7 and 92/8 ratio, respectively, entries 7 and 8). Concerning the enantioselectivity using $Cu(OTf)_2$/**L2** catalyst, very low ees (6% and 4%, entry 6) were obtained for both **4**-*endo* and *exo*, however, first some promising results were obtained for cycloadduct **5** (32% ee for **5**-*exo*, entry 7) and for cycloadduct **6** (38% ee for **5**-endo and 15% ee for **5**-exo, entry 8).

Then, the asymmetric catalyzed reactions between dithioesters **1**–**3** and 2,3-dimethyl-1,3-butadiene were performed under the reaction conditions previously used with cyclopentadiene (Scheme 2, Table 2, entries 1–6). Again, all reactions gave full conversion into the HDA cycloadducts, after 24 h for **1** and **3** and after <1 h for **2**. The isolated yields in products **7**–**9** were quantitative. As in the previous series of experiments, no enantioselectivity was obtained in the formation of cycloadducts **7**–**9** with ligand **L1** (entries 1–3). Ligand **L2** also afforded only 8% ee and 4% for cycloadducts **7** and **9**, respectively (entries 4 and 6), but very interestingly, gave a high ee of 82% for the cycloadduct **8** (entry 5). The use of a stoichiometric amount of $Cu(OTf)_2$/**L2** catalyst was then attempted. This considerably increased the ees in the cycloaddition with **1** (from 8% to 62% ee, entry 7) and with **3** (from 4% to 42% ee, entry 9), whereas a similar enantioselectivity was obtained with **2** (82% vs 80%, entry 8). It is possible that the poor enantioselectivity found in the case of dienophile **3** results from its two possible coordination modes with the chiral catalyst (**C** and **C**′ in Fig. 1), the corresponding catalytic chiral intermediates favoring maybe opposite asymmetric induction.[8f]

Table 1
HDA reactions of dithioesters **1**–**3** with cyclopentadiene without and in the presence of a chiral catalyst

Entry	Adduct	Catalyst	Time	*endo*/*exo*[b]	Ee[c] (%) *endo*; *exo*
1	**4**	—[a]	12 h	62/38	—
2	**5**	—[a]	1 h	57/43	—
3	**6**	—[a]	20 h	70/30	—
4	**4**	$Cu(OTf)_2$/**L1**	5 h	65/35	4; 3[d]
5	**5**	$Cu(OTf)_2$/**L1**	40 min	59/41	0; 0[e]
6	**4**	$Cu(OTf)_2$/**L2**	3 h	76/24	6; 4[d]
7	**5**	$Cu(OTf)_2$/**L2**	10 min	93/7	Nd[f], 32[e]
8	**6**	$Cu(OTf)_2$/**L2**	48 h	92/8	38; 15[d]

[a] Uncatalyzed reaction.
[b] Determined by NMR in the crude mixture.
[c] Absolute configuration not assigned.
[d] Determined by HPLC.
[e] Determined by NMR with a chiral shift agent.
[f] Not determinated value of a low ee (see in Supplementary data).

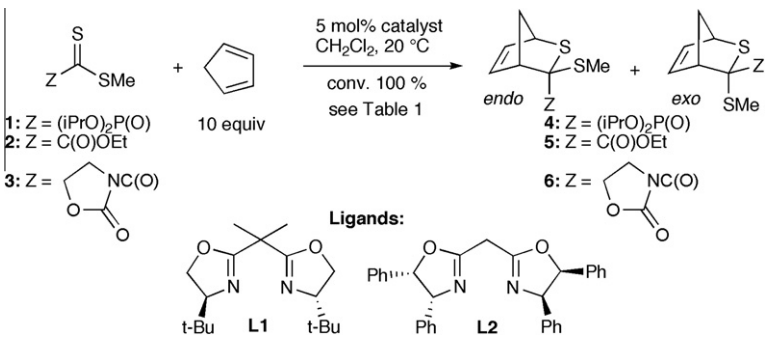


Scheme 2.

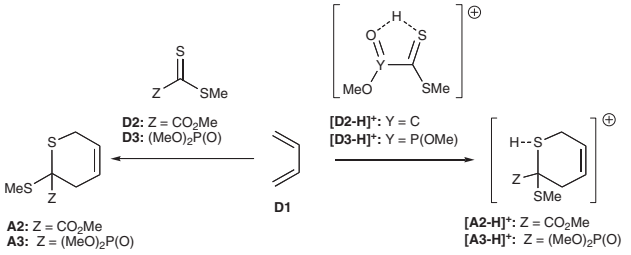
Table 2
Asymmetric catalyzed HDA reactions of dithioesters **1**–**3** with 2,3-dimethyl-1,3-butadiene

Entry	Adduct	$Cu(OTf)_2$ (mol %)	Ligand	Time	Er[a] (ee%)[b,c]
1	**7**	5	**L1**	24 h	51/49 (2)
2	**8**	5	**L1**	40 min	50/50 (0)
3	**9**	5	**L1**	24 h	50/50 (0)
4	**7**	5	**L2**	24 h	54/46 (8)
5	**8**	5	**L2**	10 min	91/9 (82)
6	**9**	5	**L2**	24 h	52/48 (4)
7	**7**	100	**L2**	12 h	81/19 (62)
8	**8**	100	**L2**	10 min	90/10 (80)
9	**9**	100	**L2**	24 h	71/29 (42)

[a] Enantiomeric ratio.
[b] Determined by HPLC.
[c] Absolute configuration not assigned.



Scheme 1.



Scheme 3.

A screening of different parameters (temperature, solvent, and Lewis acid) in the cycloaddition between dithiooxalate **2** and 2,3-dimethylbutadiene was done in order to improve its enantioselectivity. Reducing the temperature from 20 °C to −20 °C led to a significant decrease of the ee from 82% to 52%, while a higher temperature of 40 °C deteriorated almost totally the enantioselectivity giving 4% ee. Whatever the solvent used, more or less polar, enantiomeric excesses did not exceed 14:14% ee in diethylether, 2% ee in acetonitrile, and 0% ee in tetrahydrofuran or toluene. Two other Lewis acids, namely $Zn(OTf)_2$ and $Sn(OTf)_2$, have been tested in combination with ligand **L2**, affording only 8% and 4% ee, respectively. Interestingly, the inversion of the chiral induction was observed with the tin catalyst.

For a better understanding of the heterocycloaddition process, we undertook its examination by using computational means (Gaussian 03 at the B3LYP/6-31+G** level of theory).[9–13] We first examined the model reactions of 1,3-butadiene (**D1**) with dithiooxalate **D2** or phosphonodithioformate **D3**, which represent simplified structures of dithioesters **2** and **1**, respectively (Scheme 3). To compare the non-catalyzed with the acid-catalyzed processes, H^+ was considered as a model of the acidic promoter for calculation cost reasons.[14] Evaluation of the frontier orbitals energies confirmed the preferential interaction between the HOMO of butadiene and the LUMOs of heterodienophiles **D2** and **D3**, respectively, and thus the normal electron demand character of the cycloaddition processes. Optimization of the [**D2**-H]$^+$ [**D3**-H]$^+$ complexes showed a preference for the *s-cis* conformation of the O=C–C=S and O=P–C=S moiety, respectively, the proton lying between the oxygen and sulfur atoms (as supposed for the Lewis acid in complexes **A** and **B** in Fig. 1). The TSs appeared to be nearly synchronic for the uncatalyzed pathway, while asynchronicity (the C–C bond is formed before the C–S bond) was much higher for the catalyzed processes.[14] A small displacement of the nuclear coordinates at the TSs toward the reaction products directly led to cycloadducts and confirmed the concerted nature of both the catalyzed and uncatalyzed HDA processes. The difference $\Delta\Delta G^{\ddagger}$ between the energies of the most favored TSs[15] corresponding to the uncatalyzed process and to the catalyzed one was 14.18 kcal mol^{-1} in the case of dithioester **D2** and 10.35 kcal mol^{-1} for **D3**.[14] This suggests a great preference for the catalyzed pathway in particular for the dithiooxalate dienophile, in line with the experimental results, which showed that the presence of a chiral acid catalyst enables a faster reaction and a chiral induction.

In conclusion, we described the first example of a catalytic asymmetric hetero-Diels–Alder reaction, in which a chiral Lewis acid activates the thiocarbonyl dienophile. The best result in terms of asymmetric induction, remains for instant the 82% ee obtained from reaction between dithiooxalate **2** and 2,3-dimethyl-1,3-butadiene affording cycloadduct **8**, in the presence of 5 mol % of $Cu(OTf)_2$/**L2** as the chiral catalyst.[16] The adducts corresponding to phosphonodithioformate **1** and carbonyloxazolidinone dithioester **3** were obtained, respectively, with 62% and 42% ee, however using a stoichiometric amount of the same catalyst. The absolute configuration for the major enantiomer has not been assigned yet and work addressing this problem is in progress. The theoretical calculations performed for this understudied thia-HDA reaction gave some interesting information: a great preference for the catalyzed pathway, which is important for the development of the asymmetric catalytic version, and a probable O,S-bidentate chelation of the LA by the heterodienophile. The enantioselectivity seems to be difficult to control because its high dependence of the substrates/catalyst combination, however further experimental and theoretical studies are still needed to rationalize the obtained results and to expand the scope of this asymmetric thia-HDA reaction.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.055.

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15. $\Delta G_{298}^{\ddagger}$: gas phase Gibbs energy difference between the optimized transition state and the sum of substrates at 298 K (kcal/mol).
16. *Typical procedure: synthesis of nonracemic* (**8**) *by asymmetric catalyzed cycloaddition*. Into a Schlenk tube, $Cu(OTf)_2$ (0.005 mmol), bis(oxazoline) **L2** (0.0055 mmol), and dried dichloromethane (1 mL) were introduced, and then the obtained green solution was stirred for 1 h at room temperature. Dithioester **2** (0.1 mmol) and 2,3-dimethyl-1,3-dimethylbutadiene (1 mmol, 10 equiv) were added successively and the mixture was stirred at room temperature until completion of the reaction (followed by TLC). The solvent was removed under reduced pressure and the product was purified by flash chromatography (pentane/AcOEt 9:1) to give **8** as pale yellow oil, in quantitative yield.
^{1}H NMR (400.13 MHz, $CDCl_3$) δ 4.31–4.18 (m, 2H, OCH_2), 3.29 and 2.86 (ABX system, J^{AB} = 16.6 Hz, 2H, SCH_2), 2.86 and 2.46 (ABX system, J^{AB} = 17.6 Hz, 2H, CH_2), 2.16 (s, 3H, SCH_3), 1.71 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.29 (t, J = 7.2 Hz, 3H, CH_2CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.2 (C=O), 124.7 (C^5=C^4), 122.3 (C^5=C^4), 62.0 (OCH_2), 57.2 (CSMe), 40.6 (CH_2), 30.6 (SCH_2), 20.1 (CH_3), 19.1 (CH_3), 14.1 (CH_2CH_3), 13.9 (SCH_3). HRMS (ESI−) m/z calcd for $C_{11}H_{18}O_2S_2$: 246.0748; found: 246.0749. IR (neat): 2981, 2916, 1722, 1444, 1366, 1226, 1108, 1024, 965, 937, 861, 793, 748 cm^{-1}.
The enantiomeric excess of **8** was determined by HPLC using a Daicel Chiralpak IC analytical column (*n*-heptane/2-propanol: 95:5, flow rate: 0.5 mL/min, 204.0 nm). Retention time of the corresponding peaks: t_1 = 31.6 min for (+)-**8** and t_2 = 40.5 min for (−)-**8**. 82% ee: $[\alpha]_D^{20}$ −191.0 (*c* 1.0, $CHCl_3$).