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The first catalytic, highly enantioselective hetero-Diels–Alder reaction of thiabutadienes

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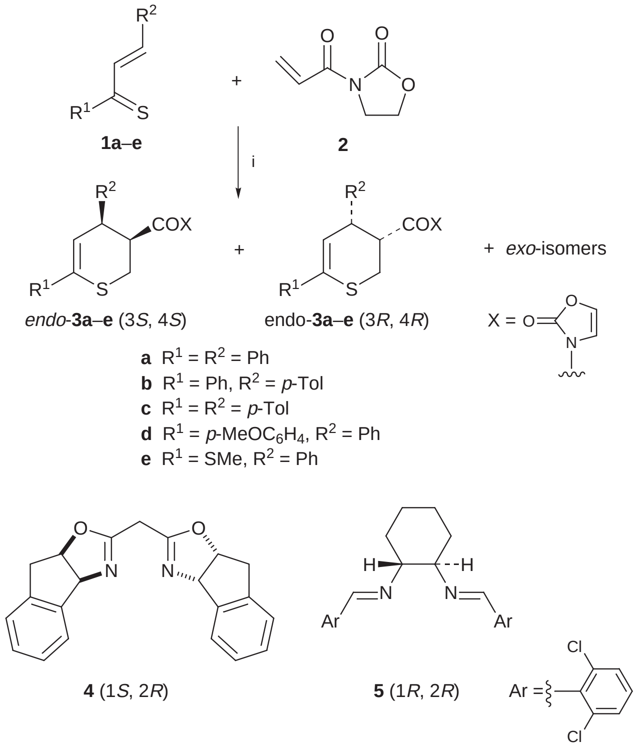
The catalytic, highly enantioselective hetero-Diels–Alder reactions of thiabutadienes using homochiral copper and nickel triflate and perchlorate bis(oxazoline) and bis(imine) complex catalysts to afford optically active dihydrothiopyrans are described for the first time.

The asymmetric hetero-Diels–Alder reaction is a powerful and versatile synthetic method and has a wide range of applications for the synthesis of not only optically active heterocycles as targets themselves but also useful compounds derived from them *via* further synthetic manipulation.[1] Despite its promising utility, however, the asymmetric hetero-Diels–Alder reaction of thiocarbonyl compounds has received much less attention and very few reports on the reaction have appeared so far.[2–4] Amongst the hitherto reported examples of asymmetric hetero-Diels–Alder reactions with thiabutadienes taking part as 4π-components, are diastereoselective methods that utilize chiral auxiliaries attached to either thiadienes or dienophiles for asymmetric induction.[3] To the best of our knowledge, the only report of an enantioselective thiadiene Diels–Alder reaction has been that recently presented by us.[4] Unfortunately, however, it required stoichiometric amounts of chiral Lewis acid to attain a high level of asymmetric induction (up to 95% ee). Therefore, our research has been focused on the development of chiral Lewis acid-induced catalytic thiadiene Diels–Alder cycloadditions giving dihydrothiopyrans with high enantiomeric excess. Here, we present for the first time the *catalytic*, highly enantioselective hetero-Diels–Alder reaction of thiabutadienes.

Prompted by the report by Ghosh and co-workers on the highly enantioselective carbo- and oxa-Diels–Alder reactions using bis(oxazoline) **4**–Lewis acid complexes as chiral catalysts,[5] we selected bis(oxazoline) **4** as the chiral catalyst ligand from among a variety of chiral bis(oxazoline) derivatives with a great deal of structural diversity employed in numerous asymmetric reactions.[6]

Initially, screening of Lewis acids used in combination with chiral ligand **4** was performed in the hetero-Diels–Alder reaction of thiabutadiene **1a** with dienophile **2** (Scheme 1) under various conditions,† and it was found that $Cu(OTf)_2$, $Cu(ClO_4)_2$, and $Ni(ClO_4)_2$ were the Lewis acids of choice in this reaction.‡ Some selected results are summarized in Table 1.

When the reaction was carried out at room temperature using 50 mol% $Ni(ClO_4)_2$–bis(oxazoline) **4** complex (run 3), cycloadduct **3a** was obtained in good yield (99%) with high enantiomeric excess (96%) of the *endo* adduct (3*S*, 4*S*),§ albeit with moderate *endo*:*exo* selectivity (76:24). It was found that at lower temperatures (−78 to 0 °C), the enantioselectivity was markedly decreased in the $Ni(ClO_4)_2$- and $Cu(OTf)_2$-catalyzed reactions (runs 1, 2, 5 and 6). The amount of the Ni^{II} catalyst could be reduced to 10 mol% while maintaining a good enantiomeric excess of 80% (run 4). The reaction using 100 mol% $Cu(OTf)_2$–**4** catalyst at room temperature (run 7) also afforded the cycloadduct **3a** in good yield (92%) with excellent enantioselectivity (98% ee). The high enantioselectivity (98% ee) was maintained in the presence of even catalytic amounts (10 mol%) of the catalyst (run 8). $Cu(ClO_4)_2$–**4** catalyst also induced good enantioselectivity (93 and 89% ee) with the use of only 5 mol% of the catalyst (runs 9 and 10).



Scheme 1 *Reagent and conditions*: i, Lewis acid–bis(oxazoline) **4** or –bis(imine) **5**.

Table 1 Asymmetric hetero-Diels–Alder reaction of thiabutadiene **1a** (using precursor dimer D) with **2** in the presence of a chiral catalyst [Lewis acid-bis(oxazoline) **4** complex] to afford cycloadduct **3a**[a]

Run	Lewis acid (mol%)	*T*/°C[b]	Yield[c] (%)	*endo*:*exo*[d]	Ee (%) (*endo*)[e]
1	$Ni(ClO_4)_2$ (50)	−65	49[f]	79:21	1
2	$Ni(ClO_4)_2$ (50)	0	90	78:22	85
3	$Ni(ClO_4)_2$ (50)	rt	99	76:24	96
4	$Ni(ClO_4)_2$ (10)	rt	80	78:22	80
5	$Cu(OTf)_2$ (100)	−78	23[f]	77:23	1
6	$Cu(OTf)_2$ (100)	0	90	79:21	78
7	$Cu(OTf)_2$ (100)	rt	92	71:29	98
8	$Cu(OTf)_2$ (10)	rt	92	70:30	98
9	$Cu(ClO_4)_2$ (5)	rt	91	77:23	93
10	$Cu(ClO_4)_2$ (5)	0	92	78:22	89

[a] Reaction was carried out in CH_2Cl_2 for 1.5–7 h with a ratio of **1a**:**2**:catalyst (Lewis acid:**4** = 1.0:1.1) = 1.2:1.0:0.05–1.0. A dithiine-type dimer (D) of **1a** was used as the precursor. Concerning the dithiine-type (D) and thiopyran-type (T) dimers used in asymmetric hetero-Diels–Alder reactions, see our earlier report [ref. 3(*b*)]. [b] rt = room temperature. [c] Isolated yield. [d] Determined by ^1H NMR spectroscopy and HPLC analysis. [e] Determined by HPLC analysis. [f] Reaction was incomplete after 3 h.

Table 2 Asymmetric hetero-Diels–Alder reaction of thiabutadienes **1a**–**d** (using precursor dimer T) with **2** in the presence of a chiral catalyst [Lewis acid–bis(oxazoline) **4** complex] to afford cycloadducts **3a**–**d**[a]

Run	**1**, **3**	Lewis acid (mol %)	Yield[b] (%)	*endo* : *exo*[c]	Ee (%) (*endo*)[d]
1	**a**	$Ni(ClO_4)_2$ (50)	84	78 : 22	91
2	**a**	$Cu(OTf)_2$ (50)	62	60 : 40	80
3	**a**	$Cu(ClO_4)_2$ (10)	89	77 : 23	90
4	**a**	$Cu(ClO_4)_2$ (5)	84	78 : 22	86
5	**b**	$Cu(OTf)_2$ (50)	65	74 : 26	85
6	**b**	$Cu(ClO_4)_2$ (10)	88	64 : 36	81
7	**c**	$Cu(OTf)_2$ (50)	60	64 : 36	83
8	**d**	$Cu(OTf)_2$ (20)	66	71 : 29	96
9	**d**	$Cu(ClO_4)_2$ (10)	86	82 : 18	86

[a] Reaction was carried out in CH_2Cl_2 at room temperature for 3 h in a ratio of **1** : **2** : catalyst (Lewis acid : **4** = 1.0 : 1.1) = 1.2 : 1.0 : 0.05–0.5. A thiopyran-type dimer (T) of **1** was used as the precursor. [b] Isolated yield. Reaction was incomplete after 3 h. [c] Determined by ^1H NMR spectroscopy and HPLC analysis. [d] Determined by HPLC analysis.

The Cu^{II}– and Ni^{II}–**4** catalyzed reactions between thiabutadienes **1a**–**d** and **2** using the corresponding thiopyran-type dimers as the precursors of **1** were examined (Table 2). It was found that the reactions also proceeded efficiently at room temperature to show satisfactory enantioselectivities (96–80% ee). In the cases of **1a–c** using either $Ni(ClO_4)_2$ or $Cu(OTf)_2$, at least 50 mol% of the catalyst was needed to preserve the high enantioselectivities (> 80% ee) (runs 1, 2, 5 and 7), while 5–10 mol% $Cu(ClO_4)_2$–**4** catalyst efficiently catalyzed the reactions to give the high ees of the *endo* adducts (runs 3, 4, 6 and 9). It is noteworthy that the reaction with the *p*-methoxyphenyl-substituted thiabutadiene **1d** showed excellent enantioselectivity (96% ee) even with the use of 20 mol% $Cu(OTf)_2$–**4** catalyst (run 8).

Finally, α,β-unsaturated dithiocarboxylic ester **1e**, which can exist as a monomer, was subjected to a chiral Lewis acid-catalyzed hetero-Diels–Alder reaction and the results are summarized in Table 3. The observed enantioselectivity was found to be largely dependent on reaction temperature, the combination of the Lewis acid and the ligand (**4**/**5**), the amount used (stoichiometric or catalytic), and the presence or absence of an additive (molecular sieves). Namely, when the reactions were performed at room temperature in the presence of 100 or 20 mol% of the catalyst [$Ni(ClO_4)_2$–**4**] (runs 1 and 2), a cycloadduct **3e** was obtained in good to fair enantiomeric excess (89–82% ee). It is noteworthy that the use of a small amount (5 mol%) of $Cu(OTf)_2$–**4** catalyst in the reaction at room temperature gave cycloadduct **3e** in 74% yield with fair enantiomeric induction (74% ee) (run 3), whereas the reactions using 100 mol% of the catalyst at either room temperature, 0 or −78 °C) afforded none of the cycloadduct; only a decomposition reaction took place. By use of ligand **5** instead of **4** complexed with 100 mol% $Cu(OTf)_2$ at low temperature (−78 °C), almost complete enantioselectivity (> 99% ee) was obtained (run 4). Disappointingly, however, the enantioselectivity was reduced to only 10% ee in the presence of 20 mol% of the catalyst (run 5). It was exciting to eventually find that in the presence of 4 Å molecular sieves as an additive,¶ the catalytic process was completely restored without any reduction of the high enantiomeric excess (> 99%) when performed at −78 °C (runs 7 and 8) rather than at room temperature (run 6).‖

Table 3 Asymmetric hetero-Diels–Alder reaction of thiabutadiene **1e** with **2** in the presence of a chiral catalyst [Lewis acid–ligand **4**/**5** complex] to afford cycloadduct **3e**[a]

Run	Lewis acid (mol%)	Ligand	*T*/°C[b]	Yield[c] (%)	*endo* : *exo*[d]	Ee (%) (*endo*)[e]
1	$Ni(ClO_4)_2$ (100)	**4**	rt	53	78 : 22	89
2	$Ni(ClO_4)_2$ (20)	**4**	rt	55	70 : 30	82
3	$Cu(OTf)_2$ (5)	**4**	rt	74	65 : 35	74
4	$Cu(OTf)_2$ (100)	**5**	−78	95	89 : 11	> 99
5	$Cu(OTf)_2$ (20)	**5**	−78	78	85 : 15	10
6	$Cu(OTf)_2$ (10)[f]	**5**	rt	78	82 : 18	86
7	$Cu(OTf)_2$ (10)[f]	**5**	−78	70	86 : 14	> 99
8	$Cu(OTf)_2$ (5)[f]	**5**	−78	74	88 : 12	> 99

[a] Reaction was carried out in CH_2Cl_2 for 3–16 h in a ratio of **1e** : **2** : catalyst (Lewis acid : **4**/**5** = 1.0 : 1.1) = 1.2 : 1.0 : 0.05–1.0. [b] rt = room temperature. [c] Isolated yield. [d] Determined by ^1H NMR spectroscopy and HPLC analysis. [e] Determined by HPLC analysis. [f] In the presence of powdered 4 Å molecular sieves.

Notes and references

† For example, solvent effects on enantioselectivity were observed to a greater or lesser extent, and the presence of an additive such as powdered molecular sieves (4 Å) was found to effect almost no improvement in either ee or catalytic turnover in this cycloaddition.

‡ Some other Lewis acids used were found to be inferior to $Cu(OTf)_2$, $Cu(ClO_4)_2$ and $Ni(ClO_4)_2$: *e.g.* $Co(ClO_4)_2$ (50 mol%) 50% ee, $NiCl_2$–$6H_2O$ (100 mol%) 0% ee, $Mg(OTf)_2$ (100 mol%) 1% ee, $Mg(ClO_4)_2$ (100 mol%) 64% ee, and $Zn(OTf)_2$ (100 mol%) 5% ee.

§ The absolute configuration of the major *endo* isomer of **3a** was determined by comparison of its retention time by chiral HPLC analysis and specific rotation of its derived alcohol with those of authentic samples. (ref. 3, 4).

¶ In the presence of a dehydrating agent such as $Mg(SO_4)_2$ instead of 4 Å molecular sieves, only 40% ee was observed.

‖ Recently, a new aspect of the role of molecular sieves in metal-catalyzed asymmetric 1,3-dipolar cycloaddition reactions was reported by Jørgensen *et al.* (ref. 7). See also our earlier report (ref. 4).

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