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Lewis Acid-Catalyzed Asymmetric Hetero Diels-Alder Cycloaddition of a 1-Thiabuta-1,3-diene with Chiral *N*-Acryloyl- and *N*-Crotonoyl-oxazolidinone Dienophiles

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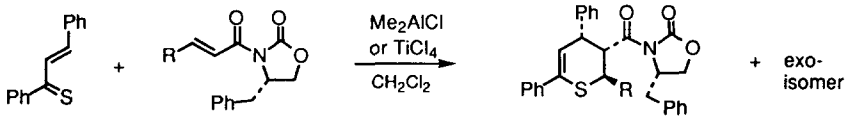
Abstract: Me_2AlCl- and $TiCl_4$-catalyzed asymmetric hetero Diels-Alder cycloaddition reactions of 2,4-diphenyl-1-thiabuta-1,3-diene with (*S*)-*N*-acryloyl- and (*S*)-*N*-crotonoyl-4-benzyl-1,3-oxazolidin-2-one dienophiles are described in which not only the sense of the π-facial selectivity but also the degree dramatically varied as a function of stoichiometry of the added Lewis acids.

The asymmetric Diels-Alder and hetero Diels-Alder (AHDA) reactions are among the most powerful and versatile synthetic procedures for a variety of optical active compounds, because of the straightforward and potential construction of a wide range of six-membered carbo- and hetero-cycles with predictable, high regio- and stereo-selectivities and their widespread applications as a consequence thereof.[1] Despite their high synthetic potential, AHDA reactions utilizing a 1-thiabuta-1,3-diene as a heterodiene have received much less attention: only a very few reports have appeared so far.[2-5] In the previous reports we described the AHDA reactions of 2,4-diaryl-1-thiabuta-1,3-dienes with some homochiral dienophiles derived from (-)-menthol, (+)-borneol and (*S*)-4-benzyl-1,3-oxazolidin-2-one,[2,3] in which the Lewis acid-promoted AHDA reaction with the oxazolidinone-derived, two-points binding dienophiles **2** and **3** using Me_2AlCl or $EtAlCl_2$ as a monodentate catalyst showed an opposite diastereo π-facial selectivity to that of the corresponding thermal (uncatalyzed) reaction. These results led us to further study to gain more insight into the AHDA reaction and we have now found that not only the sense of the π-facial selectivity but also the degree dramatically vary as functions of stoichiometry of the added Lewis acid. We report herein our preliminary results in this regard.



1

2 R = H
3 R = Me

endo (3,4-cis)

4 R = H, **5** R = Me

First, we chose to use Me_2AlCl as a representative monodentate Lewis acid catalyst in the AHDA reaction of **1** with **2**. The results are summarized in Table 1 and Fig. 1. For comparisons, the thermal reaction in refluxing benzene (80°C) for 1 h was examined to give a quantitative yield of the cycloadduct in an *endo:exo* ratio of 72:28 with -50% d.e. of the (3*S*,4*S*)-*endo* isomer **4'** predominating,[3] while the uncatalyzed reaction at 0°C for 2 h showed the highest *endo-exo* selectivity (99:1) and good diastereo π-facial selectivity (-78% d.e.) of the *endo* addition but poor yield (8%). Me_2AlCl efficiently accelerated the reaction under the conditions to give good yields of the cycloadduct even when catalytic amounts of the Lewis acid were used. The *endo:exo* d.e.s are decreased as mol % (based on a single equivalent of the dienophile) of the added Me_2AlCl increases

Table 1. Me_2AlCl-Catalyzed AHDA Reaction[a]

R	Lewis acid mol %	Yield / %	Ratio [b] *endo:exo*	π-Facial d.e. [b] (*endo*) / %	Configuration[10]
H	none[c]	99	72:28	-50	[3*S*,4*S*]
H	none	8	99:1	-78	[3*S*,4*S*]
H	10	81	96:4	-73	[3*S*,4*S*]
H	15	83	93:7	-59	[3*S*,4*S*]
H	20	82	88:12	-34	[3*S*,4*S*]
H	22	84	82:18	-10	[3*S*,4*S*]
H	25	90	80:20	76	[3*R*,4*R*]
H	30	94	78:22	78	[3*R*,4*R*]
H	50	98	77:23	78	[3*R*,4*R*]
H	80	90	72:23	88	[3*R*,4*R*]
H	100	88	68:32	82	[3*R*,4*R*]
H	150	88	61:39	83	[3*R*,4*R*]
Me	none[c]	16	98:2	-52	[2*S*,3*S*,4*S*]
Me	10	10	95:5	-43	[2*S*,3*S*,4*S*]
Me	20	14	94:6	-22	[2*S*,3*S*,4*S*]
Me	30	32	93:7	4	[2*R*,3*R*,4*R*]
Me	40	37	91:9	34	[2*R*,3*R*,4*R*]
Me	50	41	90:10	65	[2*R*,3*R*,4*R*]
Me	60	43	89:11	75	[2*R*,3*R*,4*R*]
Me	70	46	86:14	85	[2*R*,3*R*,4*R*]
Me	100	78	85:15	88	[2*R*,3*R*,4*R*]
Me	150	99	84:16	94	[2*R*,3*R*,4*R*]
Me	none[d,e]	45	97:3	-55	[2*S*,3*S*,4*S*]
Me	5[d]	9	96:4	-44	[2*S*,3*S*,4*S*]
Me	10[d]	19	90:10	7	[2*R*,3*R*,4*R*]
Me	20[d]	31	86:14	45	[2*R*,3*R*,4*R*]
Me	30[d]	80	86:14	68	[2*R*,3*R*,4*R*]
Me	50[d]	95	84:16	89	[2*R*,3*R*,4*R*]
Me	100[d]	94	84:16	94	[2*R*,3*R*,4*R*]

[a] Reactions were carried out at 0 °C for 2 h in CH_2Cl_2 in a molar ratio of **1**: **2(3)** : L.A. = 1.20 : 1.00 : 0-1.50 unless otherwise noted. [b] Determined by ^1H NMR spectroscopy and HPLC analysis. *Exo* d.e.s could not be determined due to overlapping of indicator peaks. [c] At 80 °C in benzene for 1 h. [d] At 25 °C. [e] Reaction time for 3 days.

(Fig. 1). In contrast, the π-facial selectivity of the *endo* isomer dramatically changes increasingly as molar amounts of the added Me_2AlCl increase (10 → 30 mol %). Also, the sense of the π-facial selectivity reverses in the region. Evans et al. also reported interesting observations on both *endo:exo*- and *endo*-diastereoface selectivities as a function of Me_2AlCl stoichiometry in the AHDA reaction of (*S*)-*N*-crotonoyl-4-isopropyloxazolidinone dienophile with cyclopentadiene.[6] However, in contrast to our cases, the reaction requires stoichiometric amounts (> 1.0 equiv.) of the added Lewis acid to attain the high levels of selectivitiy. Moreover, the sense of the π-facial selectivity is uniformly the same (*Cα-Si*) in the reaction. In the AHDA reaction of **1** with *N*-crotonoyloxazolidinone dienophile **3** (Table 1, Fig. 2), essentially analogous phenomena to those with **2** for both the selectivities were observed, though the slopes showing the selectivities in the reaction at either temperature (0 °C or 25 °C) are somewhat gentle compared to those corresponding in Fig. 1.

We next examined $TiCl_4$ as a bidentate Lewis acid catalyst in the AHDA reaction of **1** with **2**. The results are summarized in Table 2 and Fig. 3. Surprisingly, both the Lewis acid catalysts, Me_2AlCl and $TiCl_4$, were revealed to show essentially the same behavior in terms of the π-facial selection in spite of our expectation that the difference in their coordination numbers would produce different results.[7] By employing more than 25 mol

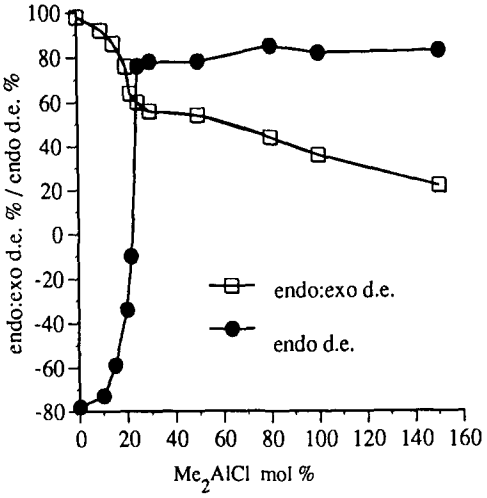


Fig. 1. Variation of diastereoselectivities in Me_2AlCl-catalyzed AHDA reaction of **1** with **2**: endo:exo d.e. (□) as a function of Me_2AlCl stoichiometry; endo d.e. (●) as a function of Me_2AlCl stoichiometry.

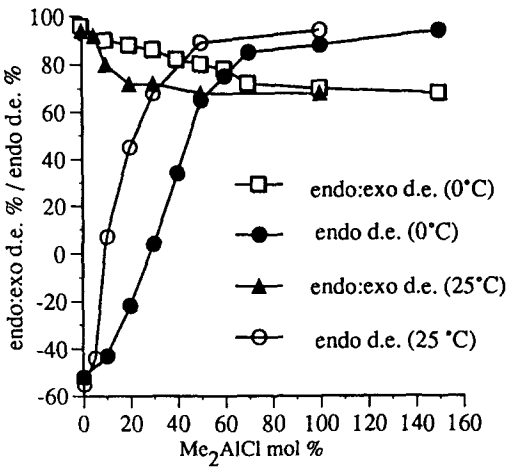


Fig. 2. Variation of diastereoselectivities in Me_2AlCl- catalyzed AHDA reaction of **1** with **3**: endo:exo d.e. (□, ▲) as a function of Me_2AlCl stoichiometry; endo d.e. (●, O) as a function of Me_2AlCl stoichiometry.

Table 2. $TiCl_4$-Catalyzed AHDA Reaction of **1** with **2** [a]

$TiCl_4$ mol %	Yield / %	Ratio [b] *endo:exo*	π-Facial d.e.[b] (*endo*) / %	Config.[10]
none	8	99:1	-78	[3*S*,4*S*]
5	90	78:22	-69	[3*S*,4*S*]
8	90	78:22	-65	[3*S*,4*S*]
10	98	78:22	-32	[3*S*,4*S*]
12	99	79:21	-1	[3*S*,4*S*]
15	99	81:19	40	[3R,4R]
17	96	82:18	59	[3R,4R]
20	94	83:17	>98	[3R,4R]
25	97	85:15	>99[c]	[3R,4R]
50	99	86:14	>99[c]	[3R,4R]
70	99	89:11	>99[c]	[3R,4R]
100	94	90:10	>99[c]	[3R,4R]

[a] Reactions were carried out at 0 °C for 0.5-3.5 h in CH_2Cl_2 in a molar ratio of **1**: **2** : L.A. = 1.20 : 1.00 : 0-1.00 unless otherwise noted. [b] Determined by ^1H NMR spectroscopy. *Exo* d.e.s could not be determined due to overlapping of indicator peaks. [c] A minor isomer of the *endo* adduct was not detected.

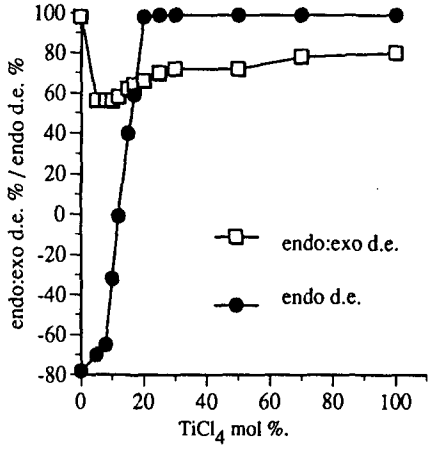
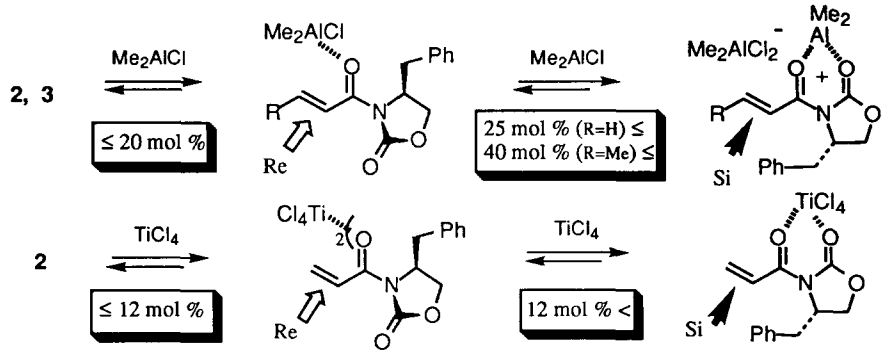


Fig. 3. Variation of diastereoselectivities in the $TiCl_4$-catalyzed AHDA reaction of **1** with **2**: endo:exo d.e.(□) as a function of $TiCl_4$ stoichiometry; endo d.e.(●) as a function of $TiCl_4$ stoichiometry.

% of $TiCl_4$ under the conditions, the almost complete π-facial selectivity (>99% endo d.e.s) was attained. It is noteworthy that in this case the *endo:exo* selectivity increases as mol % of the added $TiCl_4$ increases in contrast to the decreasing selectivity in the above Me_2AlCl-catalyzed reaction.

A rational interpretation of these observations is illustrated in the Scheme.[8] The mono-complexed species formed in the presence of less than 20 mol % (or 12 mol % for $TiCl_4$ catalysis) of the Lewis acid is sufficiently

reactive under the conditions (0 °C) to allow for the attack by the diene from the *Cα-Re* face of the dienophile, while the chelated species formed with more than 25 mol % (or 40 mol % for R = Me, 12 mol % for $TiCl_4$ catalysis) of the Lewis acid is much more reactive for the attack from the *Cα-Si* face. A pertinent question then arises as to what else controls the equilibrium between these complexed species to result in such asymmetric induction in contrast to Evans' observations.[6] We presume that the thiabutadiene itself or its derived species may be involved in the equilibrium and the catalytic cycle.[9]



Thus, both diastereoisomers of *endo* cycloadducts can selectively be prepared by simply choosing the quantity of the added Lewis acid without altering the auxiliary chirality for asymmetric induction.

Studies are in progress to gain further insight into, particularly, a transition state picture involving a diene and dienophile-Lewis acid complex for rationale of the stereoselectivities.

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