A Lewis acid dependent asymmetric Diels–Alder process in the cyclization of new chiral acrylamides with dienes

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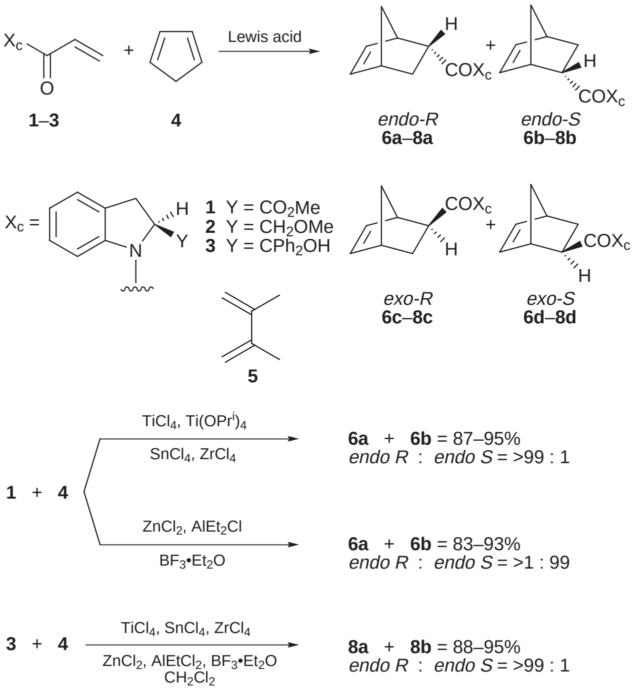
Received (in Cambridge, UK) 30th March 1999, Accepted 20th April 1999

Diels–Alder cycloadditions of chiral acrylamides with cyclopentadiene proceed with high diastereofacial selectivity, giving either *endo-R* to *endo-S* products depending of the Lewis acid used.

Lewis acid catalyzed addition of dienes to chiral acrylamides is a useful reaction because it provides one of the most effective methods for creating new chiral centers during the formation of six-membered rings.[1] Various types of chiral dienophiles such as chiral esters,[1] *N*-acyloxazole derivatives,[2] *N*-acylsultams,[3] acrylates[4] and acrylamides[5] have been developed. Metal coordination is important for diastereofacial selectivity in the asymmetric synthesis. Lewis acids have been used for chelate formation in Diels–Alder cyclizations to obtain high diastereofacial selectivities.[1–5] In general, the *S* form of the chiral dienophile (auxiliary) exclusively afford the *endo-R* adduct over the *endo-S* one, and the *R* form exclusively gives the *S* adduct over the *endo-R* one. Issues associated with this absolute stereochemical control depending upon Lewis acids and the structures of dienophiles provide an important challenge in the area of practical Diels–Alder reaction designs.[4a,5b]

In the hope of obtaining the opposite configuration of the *endo* adduct and understanding the mechanism, three different dienophiles **1**, **2** and **3** were prepared and reacted with dienes in the presence of various Lewis acids. Here we describe the intriguing results obtained during development of Lewis acid dependent stereocontrol toward both *endo-R* and *endo-S* configuration with high diastereofacial selectivity. In order to generalize the results, the requisite dienophiles **1**–**3** were synthesized from (*S*)-indoline-2-carboxylic acid.[6] They were purified and their optical purities (> 99.8% ee) were determined by HPLC (Daicel chiral OD column, Pr^{i}OH–n-hexane, 5 : 95). The preliminary studies involved reaction of **1**–**3** with **4** and **5**, as shown in Scheme 1.

Extremely high levels of asymmetric induction can be achieved in Diels–Alder cycloadditions of **1** or **3** with **4**; in contrast to other general dienophiles, **1** containing a carboxylate moiety reacts with **4** to give differently configured adducts depending on the Lewis acids employed; in the presence of $TiCl_4$, $Ti(OPr^i)_4$ or $SnCl_4$, **6a** was obtained as the major diastereomer (**6a** : **6b** = *endo-R* : *endo-S* = > 99 : 1; entries 4–6 in Table 1), but with $AlEt_2Cl$, $ZnCl_3$ or $BF_3{\cdot}Et_2O$ the opposite configuration of **6b** was obtained (**6a** : **6b** = 1 : > 99; entries



Scheme 1

Table 1 Assymetric Diels–Alder cycloaddition with **1** and **3**

Entry	Dienophile	Lewis acid	*T*/°C	*t*/h	Yield (%)[a]	*endo* : *exo*[b]	*endo*[b] ds	Config.[c]
1	**1**	Et_2AlCl	−78	10	95	90 : 10	> 99 : 1	*S*
2	**1**	$BF_3{\cdot}Et_2O$	−78	5	90	94 : 6	> 99 : 1	*S*
3	**1**	$ZnCl_2$	25	12	90	83 : 17	99 : 1	*S*
4	**1**	$TiCl_4$	0	10	92	65 : 5	99 : 1	*R*
5	**1**	$Ti(OPr^i)_4$	25	12	87	72 : 28	94 : 6	*R*
6	**1**	$SnCl_4$	−78	5	92	95 : 5	91 : 1	*R*
7	**3**	—	25	48	92	> 99 : 1	> 99 : 1	*R*
8	**3**	Et_2AlCl	−40	10	95	> 99 : 1	> 99 : 1	*R*
9	**3**	$AlCl_3$	−40	8	88	> 99 : 1	> 99 : 1	*R*
10	**3**	$BF_3{\cdot}Et_2O$	−78	5	91	> 99 : 1	> 99 : 1	*R*
11	**3**	$ZnCl_2$	25	12	90	> 99 : 1	> 99 : 1	*R*
12	**3**	$TiCl_4$	25	7	90	> 99 : 1	> 99 : 1	*R*
13	**3**	$Ti(OPr^i)_4$	25	15	89	> 99 : 1	> 99 : 1	*R*
14	**3**	$SnCl_4$	−78	10	91	98 : 2	98 : 2	*R*
15	**3**	$ZrCl_4$	−40	5	93	> 99 : 1	> 99 : 1	*R*
16	**2**	$EtAlCl_2$	−78	7	83	88 : 12	86 : 14	*S*
17	**2**	$TiCl_4$	−78	12	75	85 : 15	97 : 3	*R*

[a] Isolated yield. [b] Determined by HPLC analysis. (Chiral Column: Daicel OD). [c] Confirmed by $[\alpha]_D$ of iodolactone or norbonene-2-methanol.

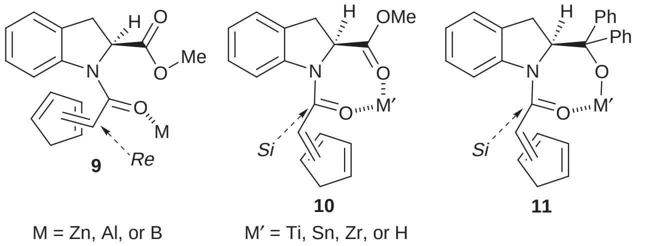


Fig 1 Possible intermediates in Diels–Alder reactions.

1–3 in Table 1). In the case of **2**, the same trend of **7b** was observed, but in a less diastereoselective manner than for **1** (entries 16 and 17). In particular, **3** containing a diphenyl-substituted tertiary alcohol moiety affords exceptionally high diastereofacial selectivities (**8a** : **8b** = > 99 : 1, yield = > 90%; entries 7–15) regardless of the natures of the Lewis acid. The *endo* configurations were readily ascertained by iodolactonization of **6a**–**8a** with I_2 in DMF.[5b] The *exo* compound cannot be lactonized under the same reaction conditions. The ratio of *endo-R* and *endo-S* was determined by HPLC with the crude **6a**–**8a** and **6b**–**8b** without purification.[7] The absolute configuration of **6a**, **7b** or **8a** was determined by reductive cleavage of **6a** to the known norbornene-2-methanol and subsequent comparison of $[\alpha]_D$ values.[8]

The differently configured adducts produced can be rationalized by the different intermediates formed between **1–3** and the metals of the Lewis acids. Compounds **1–3** react with **4** to favor formation of *endo-R* species **6a** or **8a** with $TiCl_4$, $Ti(OPr^i)_4$, $SnCl_4$ or $ZrCl_4$ probably *via* formation of seven-membered ring chelates with the acryloyl moiety of **10** or **11** having a *cisoid* conformation.[4a,5b] Helmechen and co-workers reported the first evidence of formation of a seven-membered ring chelate complex.[4a] It is noteworthy that even in the absence of any Lewis acid, **3** reacts with **4** to give an excellent chemical yield (92%) and high stereofacial selectivity (*endo* : *exo* = > 99 : 1, *endo-R* : *endo-S* = > 99 : 1; entry 9 in Table 1) at 25 °C after a long reaction time (24 h). The results can be attributed to the hydrogen-bond *cisoid* conformation intermediate **11** where the hydrogen acts as a Lewis acid. On the other hand, **1** or **2** prefer *endo-S* formation **6b** or **7b** with $ZnCl_2$, $AlEtCl_2$ or $BF_3 \cdot Et_2O$, with high diastereofacial selectivity probably resulting from intermediate **9**, as shown in Fig. 1 In contrast to Ti or Sn Lewis acids, relatively weaker Lewis acids such as Zn, Al, or B may not form a seven-membered ring complex, instead forming a weak coordination with the amide carbonyl group (**9**).[4a,5b] In the case of Evans' model dienophile, an α,β-unsaturated *S*-oxazolidinone, the *endo-R* form was obtained[2a] and explained by formation of a six-membered ring intermediate with Et_2AlCl, which was clarified by a ^{13}C NMR study.[2c] However, in contrast to a significant chemical shift change[9a] in the **1**–$SnCl_4$ chelation complex **11**, ^{13}C NMR measurement of the **1**-Et_2AlCl mixture did not show significant changes in the chemical shifts for either of the amide or ester carbonyl peaks,[9b] *which can be explained by a weak coordination* (**9**) between **1** and Et_2AlCl. Species **1** and **3** also reacted with less reactive acrylic diene **5** at 25 °C to result in the same trend: for **1** with $TiCl_4$ the ratio of *endo R* : *endo S* was 97 : 3, while with $EtAlCl_2$ the ratio was reversed to 3 : 97, which is comparable to entry 1; for **3** with both $TiCl_4$ and Et_2AlCl, *endo R* : *endo S* = 97 : 3 and 94 : 6 respectively, which is comparable to entries 8 and 12.

In summary, asymmetric Diels–Alder cycloadditions of **1**, or **3** with **4** proceed with absolutely stereocontrolled diastereofacial selectivities in both *endo-S* and *endo-R* (up to > 99% de) depending upon Lewis acids used and the structures of chiral dienophiles.

This work was supported by the Center for Biological Molecules, Korea Science and Engineering Foundation.

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7 In a typical experimental, a Lewis acid (1 mmol) was added to a solution of **1** (0.5 mmol) in CH_2Cl_2 (5 ml) under N_2. After stirring 10 min, **4** (5 mmol) was added. The reaction mixture was stirred while following the reaction by TLC, quenched with 1 M HCl solution, and then extracted with CH_2Cl_2 three times. The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The *endo* configurations were determined by the known iodolactonizations of **6a**–**8a** with I_2 in DMF [**8a** lactone: $[\alpha]_D$ −110.6 (*c* 1.0, $CHCl_3$)] [ref. 5(*b*)]. The ratio of *endo-R* and *endo-S* was determined by HPLC analysis using a chiral column (Daicel OD, Pr^iOH–n-hexane 1 : 9).

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9 (*a*) The ^{13}C NMR spectrum of the mixture of **6a** and $SnCl_4$ (1 : 1) was taken to show the significant chemical shift changes of the acrylamide carbonyl carbon (δ 163.8) and ester carbonyl carbon (δ 171.7) to δ 169.6 and 175.0, respectively, which support formation of a seven-membered ring complex between **6a** and $SnCl_4$. (*b*) In the case of **6a**–Et_2AlCl (1 : 2) no significant chemical shift changes for the two carbonyl carbons could be observed.

Communication 9/02535I