HETEROCYCLES, Vol. 60, No. 9, 2003, pp. 2141 - 2145
Received, 23rd June, 2003, Accepted, 4th August, 2003, Published online, 18th August, 2003

METAL CHELATIONS IN ASYMMETRIC DIELS-ALDER REACTION

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Abstract – In the presence of chiral catalysts, Diels-Alder reaction of a *N*-acryloyl chiral dienophile with cyclopentadiene gave the corresponding *endo* norbornenecarboxamide with high diastereoselectivity. In the reaction, 8-membered chelation was effective enough to distinguish *transoid* and *cisoid* conformation in the presence of divalent Lewis acid catalysts, such as $TiCl_4$.

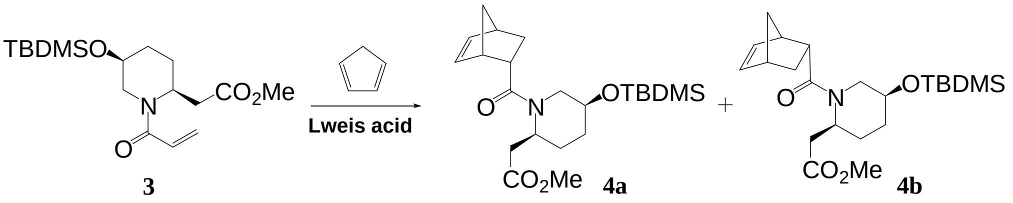
Diels-Alder reaction has been a well-known process to construct complex organic molecules.[1] The reaction provides up to four stereogenic centers in one step. The asymmetric Diels-Alder reaction was usually carried out using chiral catalysts or chiral auxiliaries.[2] Recently, an enantioselective Diels-Alder reaction was intensively studied in the presence of a chiral catalyst.[3]

The chiral auxiliaries are mainly employed to prepare chiral dienophiles and consisted of many functional groups such as alcohols, amines, oxazolidinones, and sultams.[4~7] In the reaction of dienes with chiral dienophiles, Lewis acids often increase *endo*-selectivity and diastereoselectivity. Depending on metals in Lewis acids, different diastereoselectivities were observed in some cases.

The reaction of the acrylate of (*S*)-ethyl lactate with cyclopentadiene proceeded with 86% *endo*-*S* selectivity in the presence of $TiCl_4$, divalent Lewis acid, whereas did with 32% *endo*-*R* selectivity in the presence of $BF_3 \cdot Et_2O$, monovalent Lewis acid.[5] When a chiral dienophile which was prepared from benzyl ester of (*S*)-proline or methyl ester of (*S*)-indoline-2-carboxylic acid was employed in the reaction, a similar diastereofacial selectivity was also observed.

(*S*)-3-Hydroxypiperidine was a good chiral auxiliary to prepare chiral α-hydroxy carbonyl compounds.[8] Herein, we want to report the diastereoselectivity in the reaction of derivatives of (*S*)-3-hydroxypiperidine with cyclopentadiene in the presence of various Lewis acids.

Treatment of *N*-acryl-(*S*)-3-*t*-butyldimethylsilyloxypiperidine (**1**) with cyclopentadiene gave norbornenecarboxamide (**2**) in good yield. But we failed to separate two diastereomers. Meanwhile, the reaction with methyl *N*-acryl-[(2*S*,5*S*)-5-(*t*-butyldimethylsilyloxy)piperidin-2-yl]acetate (**3**)[9] proceeded with different diastereo-selectivity depending on the Lewis acids. $TiCl_4$ induced **4a** as the major diastereomer, while **4b** was major in the presence of $BF_3{\cdot}Et_2O$.



Scheme 1. Diels-Alder reaction of **3** with cyclopentadiene

The different diastereoselectivity in Diels-Alder reaction was often rationalized by the chelation between dienophiles and Lewis acids.[5,6,7] The coordination between a metal and a substrate was proven by X-Ray analysis; 5-membered ring complex was formed between $TiCl_4$ and ethyl lactate.[10] In the case of α,β–unsaturated *N*-acyloxazolidinones, 6-membered chelation was proposed by a NMR spectral analysis.[11] According to Waldmann's[6] and Kim's reports,[7] 7-membered ring complex was formed between $TiCl_4$ and dienophiles. In Diels-Alder reactions, the configuration of the adducts could be explained by the different chelation of monovalent metals from divalent ones in the Lewis acids.

$TiCl_4$, a divalent metal compound, forms chelation with amide and ester carbonyl moieties resulting that a *cisoid* conformation was preferred to the *transoid* one. However $BF_3{\cdot}Et_2O$, a monovalent one, coordinated only by amide carbonyl group and the *cisoid* conformation was sterically hindered, resulting that the *transoid* one was favored.[6,7]

A spectroscopic analysis indicated that a *transoid* conformer was favored by 0.32kcal/mol in solution, although *cisoid* one was predominant in the crystal.[5] We attempted to examine energy difference between **5a** and **5b** by a MNDO calculation as a model study. The difference was not significant; energy of **5a** is –29.674 kcal/mol, and **5b** is –29.620 kcal/mol.

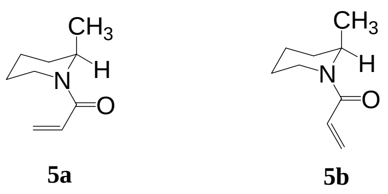


Figure 1. *Transoid* (**5a)** and *cisoid* (**5b)**

As expected, the amount of **4a** and **4b** was almost same, when the reaction was taken place without a catalyst (Entry 1). In the presence of $BF_3{\cdot}Et_2O$, the equilibrium shifted to the *transoid* conformer **(6a)** and *endo*-*S* **(4a)** was given as a major compound (Entry 3). However, $TiCl_4$ was employed in the reaction, *endo-R* (**4b)** was major (Entry 5). In this experiment, a best diastereoselectivity was obtained with $Ti(OPr^i)_4$ (entry 6).

Table 1. Asymmetric Diels-Alder Reaction of **3** with cyclopentadiene

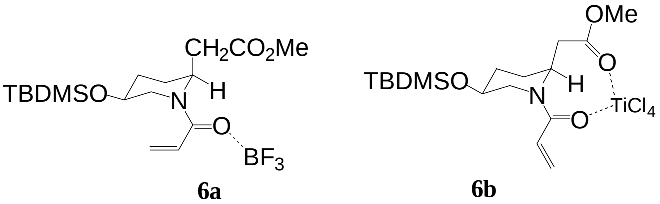
Entry	Lewis acid	Temp.(°C)	Time(h)	Yield(%)	*Endo*:*exo*[a]	*Endo* ds[b]	Config.[c]
1	none	5	96	33	81:19	4	S
2	$AlCl_3$	0	5	87	92:8	85	S
3	$BF_3{\cdot}Et_2O$	-78	24	65	82:18	95	S
4	$SnCl_4$	-78	12	70	93:7	75	R
5	$TiCl_4$	0	19	89	80:20	82	R
6	$Ti(OPr^i)_4$	RT	3	90	90:10	99	R
7	$ZnCl_4$	RT	5	86	80:20	85	S
8	$ZrCl_4$	-40	48	68	83:17	92	R
9	Et_2AlCl	-78	48	77	72:28	65	S

[a] The ratio of **4** to their corresponding *exo* isomer· [b] Calculated by the ratio of **4a** to **4b.**

[c] **4a** was prepared from *endo*-(2*R*)-5-norbonene-2-carboxylic acid.[6]

The role of $TiCl_4$ is not clear, but the Lewis acid apparently affected the diastereofacial selectivity. If $TiCl_4$ formed a chelation between the catalyst and the dienophile, the size of the chelation was presumably 8-membered. The 8-membered complex has not been reported in Diels-Alder reaction, but 8 or larger membered ring was often considered in the other reactions, such as asymmetric hydrogenation,[12] allylic alkylation,[13] and so on.[14] In those reactions, rare earth metals were participated in the chelation.

As mentioned before, the energy of **6a** and **6b** might be very similar, resulting that the amount of **4a** was almost same as that of **4b** (Entry 1). However, $TiCl_4$ would make **6b** more stable than **6a** through the chelation with two carbonyl groups in the amide and ester functionalities.



6a **6b**

Figure 2. *Transoid* (**6a)** and *cisoid* (**6b)**

In summary, a divalent Lewis acid might be involved in the formation of 8-menbered chelation which was effective enough to distinguish *transoid* and *cisoid* comformation of a *N*-acryloyl chiral dienophile in Diels-Alder reaction with cyclopentadiene.

EXPERIMENTAL

All chemicals were reagent grade (Aldrich Chemical Co.) and were used as purchased without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 2000 (200 MHz) spectrometer in $CDCl_3$, otherwise noted. Column chromatographic purifications were performed using 70-230 mesh silica gel.

Methyl *N*-acryl-[(2*S*,5*S*)-5-(*t*-butyldimethylsilyloxy)piperidin-2-yl]ethanoate (**3**). To a mixture of methyl (2*S*,5*S*)-(5-*t*-butyldimethylsilyloxypiperidin-2-yl)ethanoate (0.20 g, 0.70 mmol), dichloromethane (5 mL), and triethylamine (0.80 g, 0.79 mmol) was added dropwise acryloyl chloride (0.90 g, 0.99 mmol) at 0 ^{o}C. After stirring for 2 h at rt, the mixture was quenched with 0.1N HCl. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The oily residue was purified by column chromatography on silica gel (EtOAc/ methylene chloride, 1:19) to give a colorless oil (0.23 g, 98%).

^{1}H NMR δ 0.07 (s, 6H), 0.88 (s, 9H), 1.49-1.87 (m, 4H), 2.41-2.91 (m, 3H), 3.45-3.85 (m, 2H), 3.64 (s, 3H), 4.43-4.64 (m, 1H), 5.70 (dd, *J*=10.5, 2.0 Hz, 1H), 6.20-6.35 (m, 1H), 6.60-6.75 (m, 1H); ^{13}C NMR δ -5.05, 17.7, 25.4, 27.7, 28.1, 35.0, 43.3, 48.6, 52.0, 67.0, 127.3, 127.8, 165.5, 170.8. HRMS found *m/z* 342.2087(MH$^+$), $C_{17}H_{32}NO_4Si$ requires 342.2100.

General Procedure for Diels-Alder Reaction. To a stirred solution of **3** (0.050 g, 0.146 mmol) in dichloromethane (1.5 mL) was added a solution of 2 equiv. Lewis acid in dichloromethane (5 mL) at 0 ^{o}C. After stirring for 30 min, a solution of cyclopentadiene (0.048 g, 0.73 nmol) in dichloromethane (5 mL) was added during 10 h with a syringe pump at the respective temperature. The mixture was stirred for additional 5 h and then quenched with 0.1N HCl. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The oily residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:4), and the yield and the diastereomeric ratio was determined by HPLC analysis.[7]

^{1}H NMR δ 0.08 (m, 6H), 0.90 (m, 9H), 1.25-1.44 (m, 4H), 1.57-2.00 (m, 4H), 2.45-2.64 (m, 2H), 2.81-3.13 (m, 4H), 3.44 (m, 1H), 3.58, 3.71 (s, 3H), 3.80, 4.53 (m, 1H), 4.62, 5.07 (m, 1H), 6.07-6.09 (m, 2H)[15]; ^{13}C NMR δ -4.4, 18, 26.0, 27.6, 29.6, 31.4, 35.7, 42.6, 44.6, 46.0, 47.9, 49.6, 52, 53.6, 68.6, 133.7, 136.4, 171.7, 173.7. HRMS found *m/z* 408.2565 (MH$^+$), $C_{22}H_{38}NO_4Si$ requires 408.2570.

ACKNOWLEDGEMENTS

We are grateful for the support of this work through a grant from National Research Laboratory program.

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15. The ester methyl group in **4a** consisted of two peaks, separated by 0.131ppm at 10 ^{o}C, 0.127 ppm at 30 ^{o}C, and 0.120 ppm at 50 ^{o}C. Therefore **4a** existed in two conformers.