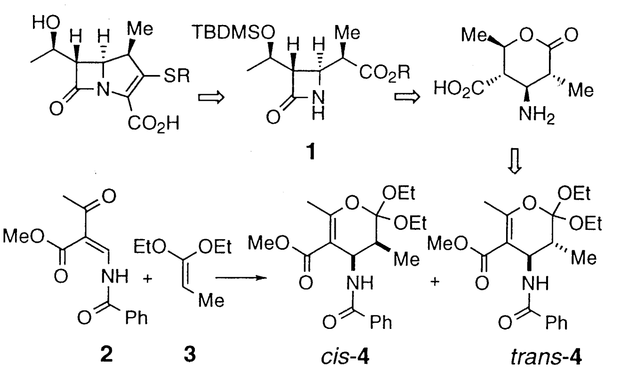
Stereocontrol by Lewis Acids in the Hetero-Diels-Alder Reaction Leading to a Key 1*β*-Methylcarbapenem Intermediate

Masaki Nishiuchi,[#] Keisuke Honda, and Takeshi Nakai*
Department of Chemical Technology, Tokyo Institute of Technology, Meguro-ku, Tokyo 152

(Received January 22, 1996)

The Lewis acid-promoted versions of the cycloaddition reaction between methyl 2-(benzoylamino)methylene-3-oxobutanoate and methylketene diethyl acetal are shown to provide a 1*β*-methylcarbapenem intermediate with high diastereoselectivity and moderate enantioselectivity.

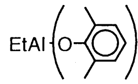
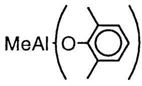
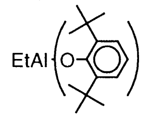
Since the Merck group discovered that the introduction of 1*β*-methyl group onto the carbapenem skeleton remarkably enhanced the chemical and metabolic stability,[1] a number of synthetic methods for the key 1*β*-methylcarbapenem intermediate **1** have been reported.[2] While most of the reported methods employ the optically active 4-acetoxy-2-azetidinone as the precursor, the ICI group has reported an interesting alternative route to **1** which involves as the key step the *thermal* hetero-Diels-Alder reaction between 2-(acylamino)methylene-3-oxobutanoates (e.g, **2**) and ketene acetal **3** (Scheme 1).[3] However, the thermal cycloaddition of **2** and **3** is non-diastereoselective to give a nearly 1:1 mixture of the *cis*- and *trans*-cycloadducts **4**, of course, in racemic forms.[3,4] Thus, we became interested in stereocontrol of the important cycloaddition process by using appropriate Lewis acids to obtain the desired cycloadduct *trans*-**4** in a highly diastereo- and enanioselective fashion. Reported herein are the Lewis acid-promoted versions of the hetero-Diels-Alder reaction which afford *trans*-**4** in high diastereoselectivity and moderate enantioselectivity.



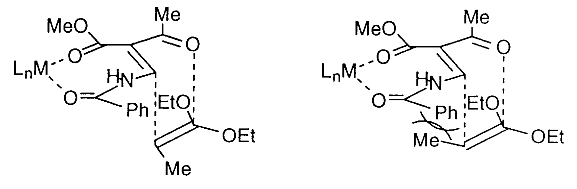
Scheme 1.

First, we examined the diastereoselectivity in the cycloaddition between **2** and **3** promoted by a variety of *achiral* Lewis acids. Since the cycloaddition was found to proceed thermally even at -30 °C,[4] the Lewis acid-promoted reactions were carried out in dichloromethane at -78 °C where no reaction occurred in the *absence* of Lewis acids. Table 1 summarizes the results thus obtained. The *cis*/*trans* ratios were determined by ^{1}H NMR analysis, and the relative stereochemistry of *cis*- and *trans*-**4**, separated by column chromatography (silica gel, hexane/ether = 1:1), was confirmed by comparisons of the NMR data with the reported ones.[3c,5] Among the Lewis acids examined, the use of methylaluminum bis(2,6-dimethylphenoxide)[6] provided the highest diastereoselectivity (89%) to afford *trans*-**4** in 76% yield (entry 6). The high *trans* selectivity is explicable as a result that the coordination of **2** to the Lewis acid would reduce the geometrical flexibility of **2**, thus making the transition state **A** thermodynamically more favorable than **B**.

Table 1. The Lewis acid-promoted reactions of **2** and **3**[a]

Entry	Lewis Acid	Time / h	Yield / %	*cis*-**4**:*trans*-**4**[b]
1	Et$_2$Zn	44	80	24 : 76
2	ZnBr$_2$	10	100	25 : 75
3	Ti(O^{i}Pr)$_2$Cl$_2$	45	43	15 : 85
4	Et$_3$Al	2	100	27 : 73
5		28	73	11 : 89
6		2	76	11 : 89
7		16	77	15 : 85

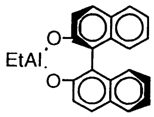
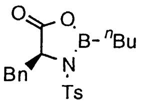
[a]All reactions were run in CH$_2$Cl$_2$ at -78 °C using 10 equiv. of **3** and 1.0 equiv. of the Lewis acid. [b]Determined by ^{1}H NMR assay (see the text).



A → *trans*-**4** **B** → *cis*-**4**

Encouraged by these observations, we next attempted enantiocontrol by using *chiral* Lewis acids, including (*S*)-BINOL-derived aluminum[6] and titanium complexes[7] (Table 2). Among the chiral Lewis acids examined, the use of the (*S*)-BINOL-aluminum complex gave the best result, although the %ee was still unsatisfactory. Quite fortunately, however, crystallization of *trans*-**4** from the product mixture (entry 1) by adding a mixture of hexane and 2-propanol (v/v = 50:1) was found to afford *ca.* 20% yield of *trans*-**4** of a remarkably enhanced optical purity up to 74%ee, suggesting that a sort of optical resolution takes place during the crystallization.

Table 2. The chiral Lewis acid-promoted reactions of **2** and **3**[a]

Entry	Lewis Acid	Time / h	Yield / %	*cis*-**4**:*trans*-**4** (%ee)[b]
1		43	76	11 : 89 (16) : (26) [74][c]
2	"(S)-BINOL-Ti-Oxo"	[d]	100	24 : 76 (17) : (9)
3	(S)-BINOL-Ti$(O^{i}Pr)_2$	52	51	18 : 82 (3) : (1)
4		28	49	20 : 80 (0) : (1)

[a] All reactions were run under the same conditions as described in Table 1. [b] Determined by HPLC analysis using a Daicel chiralcel OD column [4.6 mm x 25 cm, eluent: 2% 2-propanol in hexane, flow rate: 0.5 ml min^{-1}]. [c] See the text. [d] The reaction was run at -78 °C for 23 h and then at -30 °C for 7 h.

Finally, it should be noted that any attempts to make this reaction catalytic by using the chiral Lewis acids shown in Table 2 were unsuccessful. For instance, the reaction at -78 °C in the presence of 10 mol% of the (*S*)-BINOL-derived ethylaluminum complex gave the cycloadducts in less than 10% yield. When the catalytic reaction was carried out at -30 °C, the cycloadducts were obtained quantitatively, but in essentially racemic forms.[8]

In summary, we have developed the Lewis acid-promoted hetero-Diels-Alder reactions which provide a 1β-methylcarbapenem intermediate in high diastereoselectivity and moderate enantioselectivity. We continue to search for an efficient asymmetric catalyst for the hetero-Diels-Alder reaction.

The authors thank Takasago International Corp. for providing reactant 2 and Dr. Noboru Sayo of the company for his helpful discussions. This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Science and Culture, Japan.

References and Notes

[#] JSPS Postdoctral Fellow, 1994-1996.

1 D. H. Shih, F. Backer, L. Cama, and B. G. Christensen, *Heterocycles*, **21**, 29 (1984).

2 For a pertinent list of references, see: N. Tsukada, T. Shimada, Y. S. Gyoung, N. Asao, and Y. Yamamoto, *J. Org. Chem.*, **60**, 143 (1995); H. Itani and S. Uyeo, *Synlett*, **1995**, 213; H. Ishibashi, K. Kodama, C. Kameoka, H. Kawanami, and M. Ikeda, *Synlett*, **1995**, 912; H. Ishibashi, C. Kameoka, K. Kodama, and M. Ikeda, *Synlett*, **1995**, 915; T. Fujisawa, R. Hayakawa, and M. Shimizu, *Chem. Lett.*, **1995**, 1013; and references cited therein.

3 a) R. Bayles, A. P. Flynm, R. H. B. Galt, S. Kirby, and R. W. Turner, *Tetrahedron Lett.*, **29**, 6341 (1988); b) R. Bayles, A. P. Flynm, R. H. B. Galt, S. Kirby, and R. W. Turner, *Tetrahedron Lett.*, **29**, 6345 (1988); c) R. Bayles, A. P. Flynm, and R. W. Turner, *European Patent EP*, **230**, 771 (1991).

4 In our hands, the thermal reaction in toluene at -30 °C gave a 46:54 mixture of *cis*- and *trans*-**4**.

5 The NMR data for the diastereomeric pair of **4** are as follows. *Trans*-**4**: ^{1}H NMR ($CDCl_3$, 300 MHz), δ 1.01 (d, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.0 Hz, 3H), 1.28 (t, *J* = 7.0 Hz, 3H), 2.33 (s, 3H), 2.41 (dq, *J* = 1.1, 6.8 Hz, 1H), 3.54 (q, *J* = 7.0 Hz, 2H), 3.65 (s, 3H), 3.66 (q, *J* = 7.0 Hz, 2H), 5.07 (dd, *J* = 1.1, 9.8 Hz, 1H), 6.90 (d, *J* = 9.8 Hz, 1H), 7.35 - 7.51 (m, 3H), 7.72 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 13.2, 14.9, 15.3, 19.4, 36.8, 47.5, 51.4, 56.8, 58.1, 103.0, 114.2, 126.6, 128.4, 131.0, 134.7, 162.1, 165.2, 167.7. *Cis*-**4**: ^{1}H NMR ($CDCl_3$, 300 MHz), δ 1.09 (d, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.0 Hz, 3H), 1.28 (t, *J* = 7.0 Hz, 3H), 2.29 (s, 3H), 2.41 (dq, *J* = 1.1, 6.8 Hz, 1H), 3.54 (q, *J* = 7.0 Hz, 2H), 3.65 (s, 3H), 3.66 (q, *J* = 7.0 Hz, 2H), 5.32 (dd, *J* = 5.5, 10.2 Hz, 1H), 6.80 (d, *J* = 10.2 H, 1H), 7.35 - 7.51 (m, 3H), 7.72 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz), δ 9.7, 15.1, 15.5, 19.5, 35.2, 45.6, 51.3, 57.0, 59.7, 104.8, 114.4, 126.6, 131.1, 131.2, 135.0, 163.4, 166.1, 167.6.

6 The bis(phenoxy)aluminum complexes were prepared according to the literature procedure: K. Maruoka, T. Itoh, M. Sakurai, K. Nonoshita, and H. Yamamoto, *J. Am. Chem. Soc.*, **110**, 3588 (1988).

7 The BINOL-derived titanium complexes were prepared according to our reported procedures: D. Kitamoto, H. Imma, and T. Nakai, *Tetrahedron Lett.*, **36**, 1861 (1995). The chiral boron complex has been reported to serve as an efficient asymmetric catalyst for some Diels-Alder reactions: J.-P. G. Seerden, J. W. Scheeren, *Tetrahedron Lett.*, **34**, 2669 (1993).

8 For instance, *trans*-**4** obtained from the reaction catalyzed by "(S)-BINOL-Ti-Oxo" (10 mol%) was of only 4%ee.