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ASYMMETRIC HETERO DIELS-ALDER REACTIONS OF DANISHEFSKY'S DIENE AND GLYOXYLATE ESTERS CATALYZED BY CHIRAL BISOXAZOLINE DERIVED CATALYSTS

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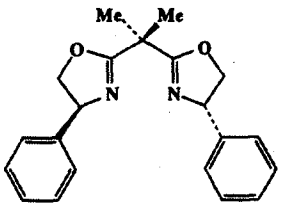
Summary. Asymmetric hetero Diels-Alder reactions of Danishefsky's diene and glyoxylate esters catalyzed by bis(oxazoline)-metal complex afforded the corresponding aldol adduct which upon treatment with trifluoroacetic acid furnished the hetero Diels-Alder product in 72% enantiomeric excess and 70% isolated yield. Copyright © 1996 Elsevier Science Ltd

The development of chiral catalysts for asymmetric syntheses is of tremendous synthetic importance.[1] In this context, catalytic enantioselective carbon-carbon bond forming reactions have received special attention. Particularly notable is the recent development of a number of remarkably effective catalytic processes for the enantioselective Diels-Alder reactions.[2] The Diels-Alder reaction is one of the most powerful and versatile methods in organic synthesis and there have been numerous applications of this reaction in the construction of complex organic molecules.[3] Chiral Lewis acid catalyzed hetero Diels-Alder reaction of aldehyde with diene is also of particular interest since the cycloadducts are potential intermediates of a variety of natural products.[4] Previous rigorous investigations by Danishefsky and coworkers have established various mechanistic aspects as well as immense synthetic utility of this reaction.[5] As part of our studies aimed at the design and synthesis of various nonpeptidal ligands for the HIV protease substrate binding site, we required a range of functionalized tetrahydropyran derivatives in optically active form. In light of recent reports[6] on asymmetric hetero Diels-Alder reactions with 1-methoxy butadiene or Danishefsky's diene with various chiral ligand-metal complexes, we have investigated the degree of enantioselection associated with various chiral bis(oxazoline) derived chiral Lewis acids as the catalysts. Herein we report that the reactions of Danishefsky's diene and the glyoxylate esters catalyzed by (1R, 2S)-bis(oxazoline)-metal complex afforded the corresponding aldol adduct which upon treatment with trifluoroacetic acid furnished the enantiomerically enriched hetero Diels-Alder product in good yields. Among various ligand-metal complexes examined, recently described[7] conformationally constrained bis(oxazoline)-Cu(II)-triflate afforded 72% enantiomeric excess and 70% isolated yield. Such constrained ligands are particularly attractive because of their ready availability in both enantiomeric forms from the corresponding commercially available optically active cis-1-amino-2-indanols.[8]

Chiral bis(oxazoline) ligands **1** and **2** were obtained commercially.[8] Preparation of constrained bis(oxazoline) **3** has been reported[7] recently in connection with our investigations into chiral Lewis acid catalyzed Diels-Alder reactions of cyclopentadiene and various bidentate dienophiles affording



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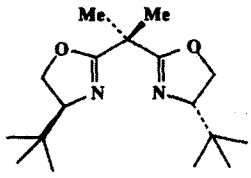

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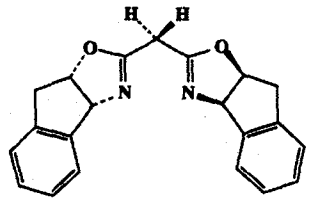

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excellent endo/exo selectivity as well as endo enantioselectivity. Methyl and ethyl glyoxylate esters **5** and **6** were prepared by ozonolysis of the corresponding maleate esters according to the procedure of Jung and coworkers.[9] The chiral catalysts were prepared by reaction of an equimolar mixture of metal triflate and bis(oxazoline) ligands in dry CH_2Cl_2 at 23°C under nitrogen atmosphere. Typically, cyclocondensation was effected by addition of 1 equiv. of glyoxalate ester to the chiral catalyst at the specified temperature followed by addition of 2 equiv. of Danishefsky's diene **4**.[10] The resulting mixture was stirred at the specified temperature and the progress of the reaction was monitored by TLC (5-9 h). The reaction was quenched with aqueous saturated $NaHCO_3$ solution to provide the mixture of corresponding Mukaiyama aldol product **7** as well as the pyranone derivative **8** (Scheme 1) after standard workup. The crude mixture upon treatment with excess of trifluoroacetic acid in CH_2Cl_2 at 23°C for 1 h furnished the cyclocondensation product **8**. The level of enantioselection associated with various hetero Diels-Alder cycloadducts was analyzed by chiral HPLC analysis (Daicel OD column,[11] 10% isopropanol/hexane as the eluent) as well as by comparison of optical rotation with the authentic material. The results of various metal-ligand catalyzed hetero Diels-Alder reactions with glyoxalate esters and Danishefsky's diene **4** are summarized in Table 1. As shown, the reaction of methyl glyoxylate **5** and Danishefsky's diene in the presence of 10 mol% chiral catalyst derived from bis(oxazoline) **1** and

Scheme 1

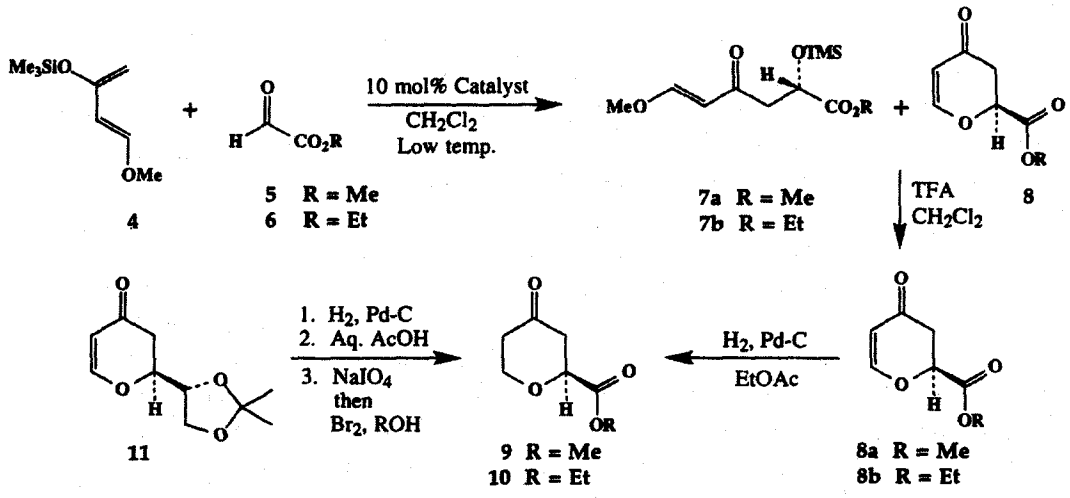

Table 1. Enantioselective Hetero Diels-Alder Reaction of glyoxalate esters and diene **4**

Entry	R	Metal	Ligand	temp (time, h)	% Yield[a]	% ee[b]	Abs. config.[c]
1.	Et	Cu	1	-78°C (9)	27	44	2S
2.	Me	Cu	1	-78°C (9)	40	47	2S
3.	Et	Cu	2	-78°C (8)	42	17	2R
4.	Me	Cu	2	-78°C (9)	37	2	2R
5.	Et	Cu	3	-78°C (9)	70	72	2S
6.	Me	Cu	3	-78°C (9)	67	70	2S
7.	Et	Cu	3	23°C (9)	76	50	2S
8.	Et	Mg	3	0°C (5)	70	12	2R
9.	Et	Sn	3	0°C (5)	40	2	2R

[a] Isolated yield after silica gel chromatography. [b] Enantiomeric excess was determined by chiral HPLC and comparison of optical rotation. [c] By comparison of optical rotation.

$Cu(OTf)_2$ at -78°C in CH_2Cl_2 for 9 h, followed by trifluoroacetic acid afforded cycloadduct **8** in 47% enantiomeric excess and 40% isolated yield (entry 2). Chiral catalyst derived from bis(oxazoline) **2** is very ineffective (entry 3 and 4) in this study. Consistent with our previous observation, conformationally constrained bis(oxazoline) ligand **3** in which the rotational freedom of the phenyl ring in bis(oxazoline) **1** is constrained, has shown improved enantioselectivity. Reaction of ethyl glyoxalate **6** with 10 mol% Cu(II)-bis(oxazoline) **3** complex resulted in **8b** (entry 5) in 72% ee and 70% yield after silica gel chromatography. Methyl glyoxalate **5** has also shown similar results (entry 6). The ligand-metal complexes derived from $Sn(OTf)_2$ or $Mg(OTf)_2$ were found to be ineffective.

As evidenced in Scheme 1, the present chiral bis(oxazoline)-metal complex catalyzed cyclocondensation reaction proceeds via Mukaiyama's aldol reaction. The aldol product **8** has been isolated and fully characterized.[12] The observed enantioselectivies can be rationalized as proposed by Johannsen and Jorgensen.[6g] The glyoxalate ester presumably forms a square planar complex with Cu(II)-bis(oxazoline) complex and the addition of activated diene occurs from the less hindered site of the carbonyl group leading to initial formation of the Mukaiyama aldol product which is further cyclized to cycloadduct **8** with trifluoroacetic acid. The absolute configuration of the cycloadducts were established by comparison of the optical rotation of the the corresponding hydrogenated cycloadducts **9** and **10** with those of the authentic samples prepared from the known optically pure dihydropyranone derivative **11**.[13] Hydrogenation of the cycloadduct **11** with 10% Pd-C in EtOAc followed by removal of the isopropylidene group by treatment with 40% aqueous acetic acid at 90°C provided the corresponding diol in 66% yield. Diol cleavage with sodium periodate in methanol in the presence of aqueous $NaHCO_3$ afforded the corresponding aldehyde which was further oxidized[14] with bromine in methanol or ethanol to furnish the reference methyl ester **9** ($\alpha_D^{23°}$ -26.4; c, 1.7, $CHCl_3$) and ethyl ester **10** ($\alpha_D^{23°}$ -24; c, 1.25, $CHCl_3$) respectively (65-68% yield).[15]

In conclusion, the present study has further demonstrated the utility of bis(oxazoline) derived chiral catalysts in hetero Diels-Alder reactions with glyoxalate esters. Of three different bis(oxazoline) ligands examined, conformationally constrained bis(oxazoline) **3** has been most effective providing maximum of 72% enantiomeric excess. The scope and utility of this asymmetric process is the subject of ongoing research in our laboratory.

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References:

1. Ojima, I. *Catalytic Asymmetric synthesis*, **1993,** VCH Publications, New York.
2. (a) Corey, E. J.; Imwinkelreid, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493; (b) Corey, E. J. ; Imai, N.; Zhang, H-Y. *ibid.* **1991**, *113*, 728; (c) Corey, E. J.; Isihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807; (d) Narasaka, K. *Synthesis* **1991**, 1; (e) Corey, E. J.; Sarshar, S.; Bordner, J. *J. Am. Chem. Soc.* **1992**, *114*, 7938; (f) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007; (g) Corey, E. J.; Sarshar, S.; Lee, D.-H. *J. Am. Chem. Soc.* **1994**, *116*, 12089; (h) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741; (i) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763; (j) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460; (k) Evans, D. A.; Murry, J. A.; Mat, P. V.; Norcross, R. D.; Miller, S. J. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 798; (l) Togni, A.; Venanzi, L. M. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 497; (m) Oh, T.; Reilly, M. *Org. Prep. Proceed. Int.* **1994**, *26*, 129 and references cited therein.
3. (a) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*, **1990,** Pergamon press; (b) Giuliano, R. M. *Cycloaddition Reactions in Carbohydrate Chemistry*, **1992**, American Chemical Society, washington, DC and references cited therein.
4. (a) Bednarski, M. D.; Lyssikatos, J. P. *Comprehensive Organic Synthesis*: *Selectivity, Strategy and Efficiency in Modern Organic Chemistry*, Trost, B. M. Ed., **1991**, *2*, 661; (b) Bednarski, M. D.; Danishefsky, S. J. *Tetrahedron Lett.*, **1983**, *24*, 3451; (c) Bednarski, M. D.; Maring, C.; Danishefsky, S. J. *J. Am. Chem. Soc.*, **1983**, *105*, 6968; (d) Waldmann, H. *Synthesis* **1994**, 535.
5. (a) Danishefsky, S. J.; Larson, E. R.; Askin, D. *J. Am. Chem. Soc.*, **1982**, *104*, 6437; (b) Larson, E. R.; Danishefsky, S. J. *ibid*, **1982**, *104*, 6458; (c) Danishefsky, S. J.; Kato, N.; Askin, D.; Kerwin, Jr., J. F. *ibid*, **1982**, *104*, 360; (d) Danishefsky, S. J.; Larson, E. R.; Askin, D.; Kato, N. *ibid*, **1985**, *107*, 1246. Also see reference 3a.
6. (a) Terada, M.; Mikami, K.; Nakai, T. *Tetrahedron Lett.* **1991**, *32*, 935; (b) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907; (c) Gao, Q.; Maruyama, T.; Mouri, M.; Yamamoto, H. *J. Org. Chem.* **1992**, *57*, 1957; (d) Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem. Soc.*, **1994**, *116*, 2811; (e) Motoyama, Y. Mikami, K. *J. Chem. Soc. Chem. Commun.*, **1994**, 1563; (f) Keck, G. E.; Li , X-Y.; Krishnamurthy, D. *J. Org. Chem.* **1995**, *60*, 5998; (g) Johannsen, M.; Jorgensen, K. A. *J. Org. Chem.* **1995**, *60*, 5757.
7. Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* In Press.
8. Available from Aldrich Chemical Co., Milwaukee, WI 53201.
9. Jung, M. E.; Shishido, K.; Davis, L. H. *J. Org. Chem.* **1982**, *47*, 891.
10. Danishefsky, S. J.; Kitahara, T. *J. Am. Chem. Soc.*, **1974**, *96*, 7807.
11. Daicel OD column was purchased from Chiral Technologies, 730 Springdale Dr, Exton, PA.
12. **7b:** $[\alpha]_D^{23}$ -27.1 (c, 2.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ ; 7.58(d, 1H, J=12.8 Hz), 5.58 (d, 1H, J=12.8 Hz), 4.68 (t, 1H, J=5.4 Hz), 4.16 (q, 2H, J=7.2 Hz), 3.7 (s, 3H), 2.85 (d, 2H, J=3 Hz), 1.25 (t, 3H, J=7.2 Hz), 0.1 (s, 9H); **8b** (entry 5): $[\alpha]_D^{23}$ +107.8 (c, 1.8, $CHCl_3$); ^1H NMR(400 MHz, $CDCl_3$) δ ; 7.4 (d, 1H, J=6 Hz), 5.48 (d, 1H, J=6 Hz), 5.0 (t, 1H, J=7.8 Hz), 4.3 (q, 2H, J=7.2 Hz), 2.85 (d, 2H, J=4.3 Hz), 1.32 (t, 3H, J=7.2 Hz).
13. Danishefsky, S. J.; Kobayashi, S.; Kerwin, Jr., J. F. *J. Org. Chem.* **1982**, *47*, 1981.
14. Lichtenthaler, F. W.; Jarglis, P.; Lorenz K. *Synthesis* **1988**, 790.
15. All new compounds gave satisfactory spectroscopic and analytical results.

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