Tetrahedron Letters, Vol. 33, No. 45, pp. 6807-6810, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

HIGHLY ENANTIOSELECTIVE CATALYTIC DIELS-ALDER ADDITION PROMOTED BY A CHIRAL BIS(OXAZOLINE)-MAGNESIUM COMPLEX

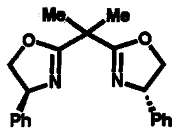
E. J. Corey and Kazuaki Ishihara

Department of Chemistry, Harvard University, Cambridge, Massachusetts, 02138

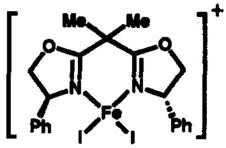
Summary: The new chiral bis(oxazoline) ligand 8 has been synthesized from (S)-phenylglycine and has been shown to form effective catalysts for enantioselective Diels-Alder addition in combination with ferric iodide, magnesium iodide or magnesium tetraphenylborate. Catalytic activation of the dienophile, 3-acryloyl-1,3-oxazolidine-2-one (4), in the magnesium system is proposed to involve tetrahedrally coordinated magnesium in a dipositive complex (10).

Recently the chiral bis(oxazoline) **1** has been synthesized and its unipositive complex with FeI_3 (**2**) has been shown to catalyze the formation of Diels-Alder adduct **3** from cyclopentadiene and 3-acryloyl-1,3-oxazolidine-2-one (**4**) with 91 : 9 enantioselectivity.[1,2] The formation of principal enantiomer **3** from **2** suggests that the major reaction path involves bidentate coordination of **4** with **2** at an axial and an equatorial site prior to reaction with cyclopentadiene,[1] since coordination at the two equatorial positions can be expected to lead mainly to the enantiomer of **3**.[1] In this paper we describe the synthesis of a new bis(oxazoline) (**8**), which is a more rigid version of **1** with respect to rotation of phenyl, and its use to effect Diels-Alder catalysis via tetrahedral coordination to a metal. The new catalytic system converts cyclopentadiene and **4** to the chiral adduct **3** with *ca.* 20 : 1 enantioselectivity, as expected on the basis of a unique tetrahedral coordination mode.

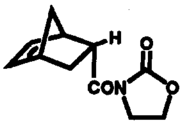
Ligand **8** (*S* form) was synthesized in the following manner. (*S*)-Phenylglycine methyl ester[3] and triethylamine (1.2 equiv) were treated with 1.2 equiv of trifluoroacetic anhydride (-78 °C, 1 h) to give the N-trifluoroacetyl derivative **5**, mp 71.4 °C, $[\alpha]_D^{27}$ + 191.3° (c=1, $CHCl_3$).[4] Reaction of **5** with 5 equiv of methyl magnesium iodide at 23 °C for 2.5 h afforded the corresponding tertiary alcohol (90%, mp 101.6°) which upon exposure to 2 equiv of KOH in methanol at 23 °C for 2 h provided the amino alcohol **6** (98% yield) as a colorless solid (mp 51° after recrystallization from ether–pentane). A solution of amino alcohol **6** and triethylamine (2 equiv) was treated dropwise with 0.5 molar equiv of dimethylmalonyl chloride in CH_2Cl_2



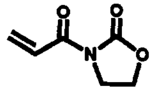
1



2



3

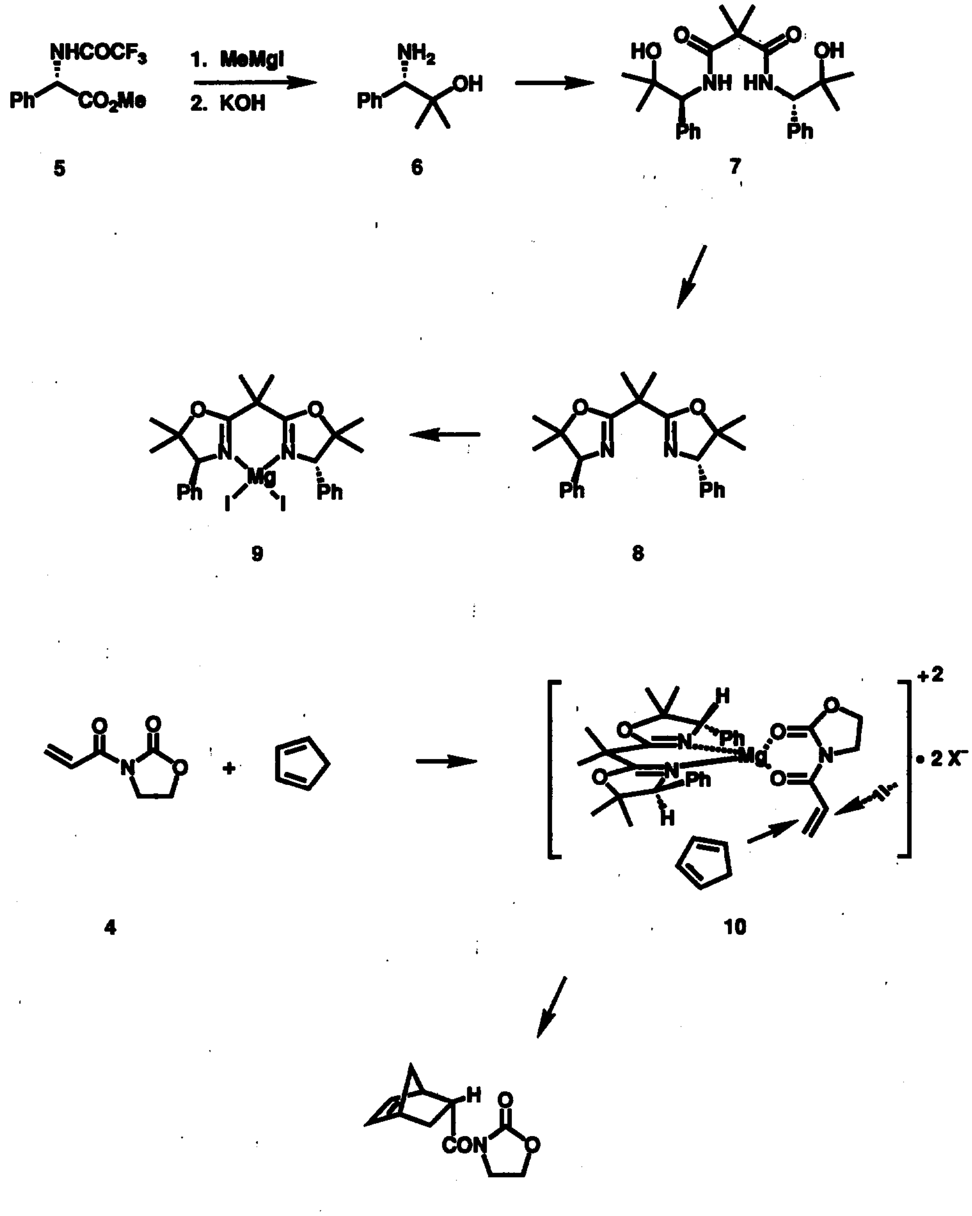


4

at -78 °C and then maintained at 0 °C for 1 h to yield, after extractive isolation and filtration through silica gel, the diamide **7** (98%), mp 190-190.5°. Cyclization to form the bis(oxazoline) system was effected by heating **7** at reflux in CH_2Cl_2 with 5 equiv of methanesulfonic acid for 5 h with continuous removal of water from the refluxing solvent with CaH_2. Extractive isolation and flash chromatography on silica gel provided the (*S*) ligand **8** (78%) as a colorless solid, mp 83-84°, $[\alpha]^{26}_{D}$ - 149.5° (c=1, $CHCl_3$), R_f 0.20 (tlc, silica gel, 5 : 2 hexane–EtOAc).[5]

An Fe(III)-containing catalyst was prepared by reaction of FeI_3 (made in situ from powdered iron and 1.5 mol equiv of I_2 in dry CH_3CN at 40 °C) and ligand **8** in dry CH_3CN at 23 °C, and evaporation of solvent to give a black solid which could be dissolved in dry CH_2Cl_2 or 1 : 1 CH_2Cl_2–$CH_3CH_2NO_2$. Reaction of 3-acryloyl-1,3-oxazolidine-2-one (1 equiv) and cyclopentadiene (4 equiv) in the presence of 0.1 equiv of **8**•FeI_3 and 1 equiv of I_2 (co-catalyst)[1] at -50 °C in CH_2Cl_2 for 19 h afforded 87% yield of the Diels-Alder adduct **3** with 92.5 : 7.5 enantioselectivity and 95 : 5 *endo* : *exo* selectivity. A similar result was obtained in 1 : 1 CH_2Cl_2–$CH_3CH_2NO_2$ as solvent. The enantioselectivities obtained for **8**•FeI_3/I_2 are slightly higher than observed in parallel experiments for the complex **1**•FeI_3/I_2 (*ca.* 91 : 9). The data for both **1** and **8** are consistent with the model[1] in which the catalyzed reaction proceeds by way of a pathway involving a unipositive complex of **1** or **8**, with FeI_2^+ and dienophile **4** in which **4** is coordinated to iron at an equatorial and an axial site (relative to the bis(oxazoline) plane).

Of greatest interest to us was the study of complexes of bis(oxazoline) **8** with metals capable of binding **8** and **4** in a tetrahedral manner. Very good results were obtained with **8** and magnesium iodide (made from Mg + I_2 in ether at ambient temperature followed by removal of solvent) or magnesium tetraphenylborate (prepared by reaction of anhydrous $MgCl_2$ with sodium tetraphenylborate in dry CH_3CN at 50 °C, removal of solvent *in vacuo*, addition of CH_2Cl_2 and filtration under dry N_2 to remove insoluble NaCl). (Removal of NaCl is unnecessary for the Diels-Alder reaction to form **3**.) Treatment of **8** in dry CH_2Cl_2 with 1 equiv each of MgI_2 and I_2 (co-catalyst for I^- removal) resulted in a dark red solution of the **8**•MgI_2 complex which was used as a catalyst (0.1 equiv) for the reaction of 3-acryloyloxazolidine-2-one (**4**) and cyclopentadiene (4 equiv) at -80 °C in CH_2Cl_2 for 24 h to give the Diels-Alder product **3** in 82% yield with 95.3 : 4.7 enantioselectivity and 97 : 3 *endo* : *exo* selectivity. Similarly, using 0.1 equiv of the catalyst **8**•MgI_2 and 0.2 equiv of $AgSbF_6$ co-catalyst with **4** and cyclopentadiene (4 equiv) in CH_2Cl_2 at -80 °C for 16 h adduct **3** was formed in 84% yield with 95.5 : 4.5 enantioselectivity and 98 : 2 *endo* : *exo* selectivity. The same reaction using **8**•MgI_2 as catalyst (0.1 equiv of **9** alone, no co-catalyst) afforded the Diels-Alder product **3** with somewhat lower enantioselectivity


NHCOCF₃
Ph
CO₂Me
1. MeMgI
2. KOH
NH₂
Ph
OH
HO
O
O
OH
NH
HN
Ph
Ph
5
6
7
O
N
Mg
I
I
Ph
Ph
9
8
N
+
+2
H
Ph
Mg
• 2 X⁻
H
4
10
CON
3

(90.6 : 9.4). The homogeneous Diels-Alder reaction of **4** and cyclopentadiene (4 equiv) with **8**•Mg(Ph_4B)$_2$ as catalyst in 2 : 1 CH_2Cl_2–*i*-$PrNO_2$ at -50 °C for 18 h produced adduct **3** with 95.4 : 4.6 enantioselectivity and 97 : 3 *endo* : *exo* selectivity.

There are a number of interesting implications of the catalytic effects of complexes of bis(oxazoline) **8** and Mg^{+2}. It is most likely that the reactive species in the Diels-Alder reaction is a 1 : 1 : 1 complex of **8**, Mg^{+2} and the dienophile **4** with a tetrahedral arrangement of donor groups about the metal and the *s-cis* arrangement of carbonyl and vinyl groups of the acryloyl subunit of **4**,[6] as shown in formula **10**. Apparently, the doubly positive magnesium complex **10** is readily formed under the reaction conditions because of the stabilization of Mg^{+2} by the four donor atoms coordinated to it. It is evident from our results the doubly positive **10**, in a non-coordinating medium such as CH_2Cl_2, can serve as a strong activator of oxazolidinone **4**. We believe that catalytic system disclosed herein should stimulate interest in traditionally weak Lewis acids such as MgX_2 for the design of catalysts. There is only one arrangement of the dienophilic ligand **4** which is possible from the tetrahedral magnesium complex **9**, making this a very simple system to interpret. Within this complex the rear face of the dienophilic double bond is blocked by phenyl with the result that diene approach from the front side of **10** is preferred. Thus, the combination of a C_2 symmetric chiral bidentate ligand **8**, a bidentate dienophile and tetrahedral magnesium leads to a single catalytically active species of well-defined geometry and a Diels-Alder product of predictable absolute configuration and excellent enantiomeric purity.[7,8]

References and Notes

1. Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728-729.
2. For other studies of chiral bis(oxazolines) for enantioselective catalysis see (a) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Letters* **1990**, *31*, 6005-6008; (b) Evans, D. A.; Woerpel, K. A.; Hinman, M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726-728; (c) Nishiyama, H.; Kondo, M.; Nakamura, T.; Itoh, K. *Organometallics* **1991**, *10*, 500-508; (d) Lowenthal, R. E.; Masamune, S. *Tetrahedron Letters* **1991**, *32*, 7373-7376.
3. Prepared in 91% yield by heating (*S*)-phenylglycine at reflux for 2.5 h with 5 equiv of trimethylchlorosilane and methanol to give the crystalline amino ester hydrochloride and subsequent extraction from sat. aq. NaCl containing $NaHCO_3$ with ethyl acetate.
4. Satisfactory infrared, ^1H and ^{13}C NMR and mass spectral data were obtained for new compounds using chromatographically homogeneous samples.
5. Found for **8**: IR (CCl_4) 2979, 2936, 1654 (C=N), 1124, 1102 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 0.84 (s, 6H, $2CH_3$), 1.54 (s, 6H, $2CH_3$), 1.66 (s, 6H, $2CH_3$), 4.83 (s, 2H, 2CH), 7.12 - 7.34 (m, 10H, $2C_6H_5$); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 23.72 (2C), 23.99 (2C), 29.08 (2C), 39.15, 77.72 (2C), 88.03 (2C), 127.38 (4C), 127.56 (2C), 128.21 (4C), 138.74 (2C), 169.62 (2C); MS m/z EI 390 (M^+).
6. Dienophile **4** is superior to 3-acryloyl-4,5-benzoxazolidine-2-one or 3-acryloyl-4,4-dimethyloxazolidine-2-one.
7. A brief investigation of complexes of **8** with lithium or zinc tetraphenylborate indicated that these systems were less effective than the magnesium case.
8. This work was assisted financially by the National Science Foundation, the National Institutes of Health and the Yamada Science Foundation.

(Received in USA 16 July 1992)