Pergamon

Tetrahedron Letters, Vol. 37, No. 22, pp. 3815-3818, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00721-6

Conformationally Constrained Bis(oxazoline) Derived Chiral Catalyst: A Highly Effective Enantioselective Diels-Alder Reaction

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Abstract: The reaction of cyclopentadiene with various bidentate dienophiles in the presence of 4-10 mol% of copper(II)-bis(oxazoline) complexes afforded excellent endo/exo selectivity as well as endo enantioselectivity (95-99% ee) and isolated yields. On the other hand, Diels-Alder reaction with Mg(II)-complexes afforded a modest (61% ee) reversal in enantioselectivity.

The enantioselective Diels-Alder reaction is of paramount interest in organic synthesis.[1] As a consequence, a number of effective enantioselective processes have been developed over the years.[2] Recent discoveries of various catalytic processes have added a new dimension to the enantioselective Diels-Alder reaction.[3,4] Of particular interest, C_2-symmetric chiral bis(oxazoline)-metal complexes have shown exceptional promise as chiral catalysts for enantioselective Diels-Alder reactions.[5] As part of our interests in various ligand assisted asymmetric syntheses,[6] we have synthesized conformationally constrained chiral bis(oxazoline) ligands and investigated their effectiveness as chiral catalysts in asymmetric Diels-Alder reactions. Recent reports by Merck group[7] on the synthesis and application of (1S, 2R)-1-amino-2-indanol derived other bis(oxazoline) ligands in catalytic Diels-Alder reaction, prompted us to disclose our results in this area. Herein, we report that various metal-ligand complexes of conformationally constrained bis(oxazoline) ligands derived from phenylglycinol surrogates, *cis*-1-amino-2-indanols[8] are indeed highly effective catalysts for the enantioselective Diels-Alder reaction. Among various metal complexes examined, bis(oxazoline)-copper(II) complex is particularly effective. Reaction of cyclopentadiene with various bidentate dienophiles **6** in the presence of 4-10 mol% of bis(oxazoline)-copper(II) complexes afforded excellent endo/exo selectivity as well as endo enantioselectivity and excellent isolated yields. Since either enantiomer of constrained bis(oxazoline) is readily prepared from commercially available[9] optically active cis-1-amino-2-indanols, the current methodology provides a convenient access to either enantiomer of various cyclopentadiene based Diels-Alder adducts in a stereopredictable fashion.

Conformationally constrained ligand **4** was readily prepared on a multi gram scale according to the procedure of Lehn.[10] Treatment of malononitrile and ethanol in dioxane in the presence of anhydrous HCl afforded the amide enol ether hydrochloride salt **1** (Scheme I). Reaction of **1** with (1R, 2S)-1-amino-2-indanol **2** in DMF at 23°C provided the bis(oxazoline) **4** as a white solid (m.p.206-208°C; $\alpha_D^{23°}$ + 352, c, 3.7, $CHCl_3$) after recrystallization from a mixture (1:1) of chloroform and methanol (60 % yield). Similarly, (1S, 2R)-1-amino-2-indanol **3** was converted to constrained bis(oxazoline) **5** (m.p. 207-209°C; $\alpha_D^{23°}$ - 352.7, c, 3.0, $CHCl_3$). The Diels-Alder reactions of bidentate dienophiles **6a-d** and cyclopentadiene in the presence of various chiral catalysts derived from the above ligands and metal triflates or halides, were investigated. For the Cu(II)-catalyzed reaction, the metal-ligand complex was prepared[5c] by reaction of an equimolar mixture of Cu(II) triflate and bis(oxazoline) **4** in dry CH_2Cl_2 at 23°C under nitrogen atmosphere.

The resulting dark blue solution of the catalyst (4-50 mol%) was stirred for 1 h at 23°C and then cooled to the specified temperature and 1 equiv of dienophile (**6 a-d**) followed by 4-6 equiv of freshly cracked cyclopentadiene were added. After workup with saturated aqueous NH_4Cl solution and chromatography over silica gel, the resulting Diels-Alder cycloadducts were analyzed by ^{1}H-NMR (400MHz) and chiral HPLC analysis (Daicel Chiracel OD column,[11] 10% isopropanol/hexane as the eluent). The results of various metal catalyzed Diels-Alder reaction with a range of bidentate dienophiles are summarized in Table I. As shown, Cu(II)-catalyzed reaction with acryloyl-N-oxazolidinone **6a** proceeded with virtually complete endo selectivity (endo/exo ratio >99 :1) as well as excellent endo enantioselectivity (97-99% ee) and isolated yields. Such selectivity can even be observed with 4 mol% catalyst (entry 4). The endo adduct **7a** was formed exclusively with 99% enantiomeric excess ($\alpha_D^{23°}$ +172, c 6.1, $CHCl_3$; lit.[12]; $\alpha_D^{23°}$ +171.05°, c, 1.04, $CHCl_3$) and 90% yield after silica gel chromatography. The identities of endo and exo isomers as well as endo enantioselectivities of the cycloadducts **7a** and **8a** were determined by chiral HPLC analysis. The absolute configuration of the cycloadducts **7a** (2R-configuration) and **8a** (2S-configuration) was assigned based upon the comparison of optical rotations with the literature values.[12] The Diels-Alder reaction of fumaroyl-N-oxazolidinone **6d**[13] with 10 mol% Cu(II)-catalyst (entry 12) proceeded well at -45°C for 8 h providing a 93:7 endo/exo mixture ratio and 94% endo enantiomeric excess. The enantiomeric excess of endo adduct was determined after conversion of the cycloadducts to the corresponding iodolactone **9** ($\alpha_D^{23°}$ -39.2, c 4.65, $CHCl_3$; lit.[5c]; $\alpha_D^{23°}$ +40°, 96% ee, c, 1.78, $CHCl_3$).[14, 15]

Scheme I

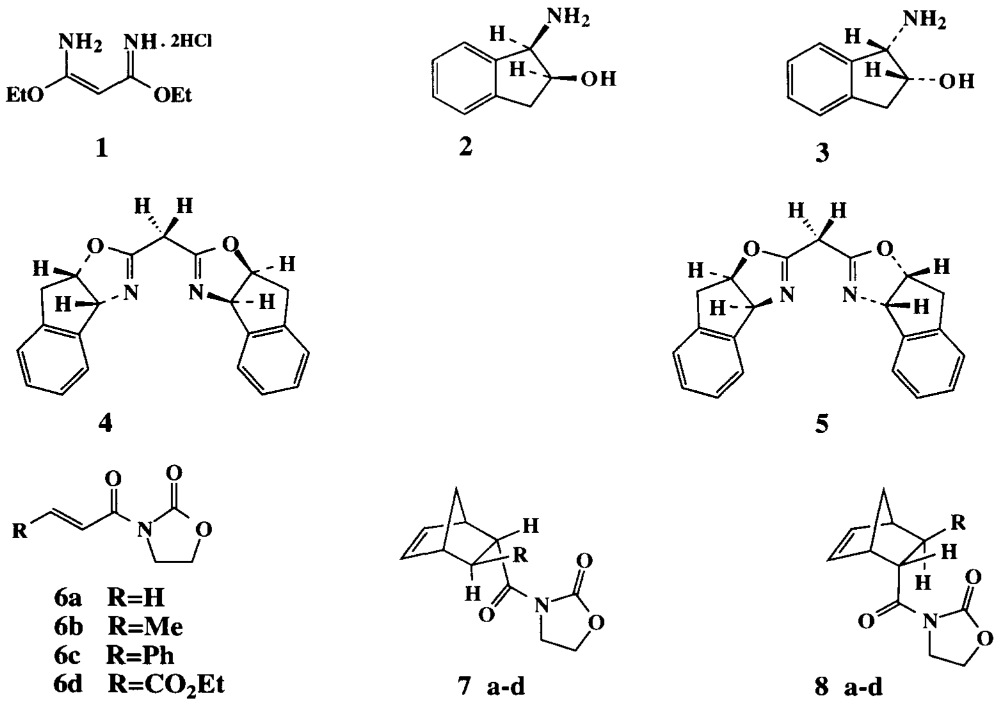

Table 1. Enantioselective Diels-Alder Reaction of Imides **6** with cyclopentadiene

Entry	Dienophile	Metal (mol %)	temp (time,h)	% Yield[a]	endo/exo[d]	endo ee (config.)[e]
1.	6a (R=H)	Cu (50)	-78°C (6)	78	>99 : 1	97 (2R)
2.	6a (R=H)	Cu (8)	-78°C (8)	94	>99 : 1	98 (2R)
3.	6a (R=H)	Cu (8)[b]	-78°C (8)	98	>99 : 1	94 (2S)[b]
4.	6a (R=H)	Cu (4)	-78°C (8)	90	>99 : 1	99 (2R)
5.	6a (R=H)	Mg (100)	-78°C (7)	81	98 : 2	61 (2S)
6.	6a (R=H)	Mg (10)	-78°C (7)	76	95 : 5	34 (2S)
7.	6a (R=H)	Fe (100)	-78°C (7)	79	94 : 6	65 (2R)
8.	6b (R=Me)	Cu (40)	0°C (26)[f]	84	92 : 8	94 (2R)
9.	6b (R=Me)	Cu (10)	0°C (48)[f]	77	90 : 10	84 (2R)
10.	6b (R=Me)	Mg (10)	0°C (48)[f]	76[c]	92 : 8	55 (2S)
11.	6c (R=Ph)	Cu (10)	23°C (72)[f]	78	80 : 20	35 (2S)
12.	6d (R=CO_2Et)	Cu (10)	-45°C (8)	75	93 : 7	94 (2S)

[a] Isolated yield after silica gel chromatography. [b] With 1S, 2R-bisoxazoline ligand. [c] Based on recovered starting material. [d] Endo/exo ratios were determined by ^{1}H-NMR and HPLC. [e] Enantiomeric excess was determined by HPLC and comparison of known optical rotation. [f] At -78°C, no reaction or very little conversion was obtained.

The high degree of enantioface selection in the current Cu(II)-bis(oxazoline) catalyzed Diels-Alder reaction can be rationalized based on transition state models proposed by Corey and Evans in which Cu(II) assumes a square planar complex with the bis(oxazoline) ligand **4** and bidentate dienophile while the dienophile assumes a s-cis conformation.[5] Based on such a model, the endo-*Si*-face attack of cyclopentadiene is favored and this leads to the observed 2R-enantioselectivity (for **6a-b**) with ligand **4**. The reversal of enantioselectivity with the Mg(II)-bis(oxazoline) catalyzed reaction (for **6a-b**) could be explained by a Corey-Isihara type transition state[5b] model in which the Mg(II)-complex (with **4**) assumes a tetrahedral geometry rather than a square planar geometry most probable for Cu(II). Now, based on such molecular arrangements, it appears that the endo-*Re*-face attack of the diene is favored providing 2S-enantioselectivity.[16]

In summary, the present conformationally constrained bis(oxazoline) based metal-ligand complexes particularly Cu(II)-complexes represent a highly effective catalytic system for enantioselective Diels-Alder reactions. Since both enantiomers of the bis(oxazoline) ligand are readily prepared from the commercially available optically active cis-1-amino-2-indanols, the current catalytic Diels-Alder technology provides a convenient access to either enantiomer of the cycloadducts in a stereopredictable fashion with high optical purity and isolated yields. Application of these chiral catalysts in synthesis is currently on going in our laboratory.

Acknowledgment: Financial support for this work was provided by the University of Illinois at Chicago. The authors thank Dr. Kurt Ritter of BASF, Germany for a gift of optically active cis-1-amino-2-indanol and Professor Robert Moriarty for helpful discussions.

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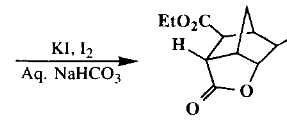
14. The iodolactone **9** was conveniently prepared by exposure of the adducts to iodine, KI and $NaHCO_3$ in aqueous CH_2Cl_2 at 23°C for 16 h (72% yield).

7d/8d



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15. All new compounds gave satisfactory spectroscopic and analytical results.

16. The scope of the current constrained ligand in the Diels-Alder reactions with other dienes and counter ions has not been investigated.

(*Received in USA* 29 *March* 1996; *revised* 15 *April* 1996; *accepted* 16 *April* 1996)