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

Arun K. Ghosh, Packiarajan Mathivanan, and John Cappiello

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607.

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, C₂-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 group⁷ on the synthesis and application of (1*S*, 2*R*)-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-indanols⁸ 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 available⁹ 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 (1*R*, 2*S*)-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, CHCl₃) after

recrystallization from a mixture (1:1) of chloroform and methanol (60 % yield). Similarly, (1*S*, 2*R*)-1-amino-2-indanol **3** was converted to constrained bis(oxazoline) **5** (m.p. 207–209°C; $\alpha_D^{23^\circ} - 352.7$, c, 3.0, CHCl₃). 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 CH₂Cl₂ 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 NH₄Cl solution and chromatography over silica gel, the resulting Diels-Alder cycloadducts were analyzed by ¹H-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 1. 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 $\alpha_D^{23^\circ} +172$, c 6.1, CHCl₃; lit.¹²; $\alpha_D^{23^\circ} +171.05^\circ$, c, 1.04, CHCl₃) 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** (2*R*-configuration) and **8a** (2*S*-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** ($\alpha_D^{23^\circ} -39.2$, c 4.65, CHCl₃; lit.^{5c}; $\alpha_D^{23^\circ} +40^\circ$, ee, c, 1.78, CHCl₃).^{14, 15}

The high degree of enantioface selection in the current Cu(II)-bis(oxazoline) catalyzed DielsAlder 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 2*R*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 (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 2*S*-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-

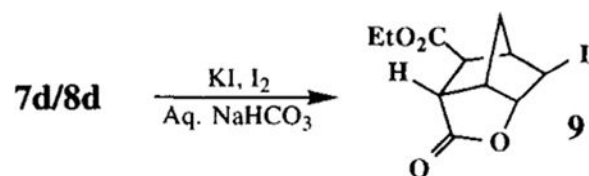
indanol, the current catalytic Diels-Alder technology provides a convenient access to either enantiomer of the cycloadducts in a stereopredictable fashion with high optical purity and isolated yields. Application of these chiral catalysts in synthesis is currently on going in our laboratory,

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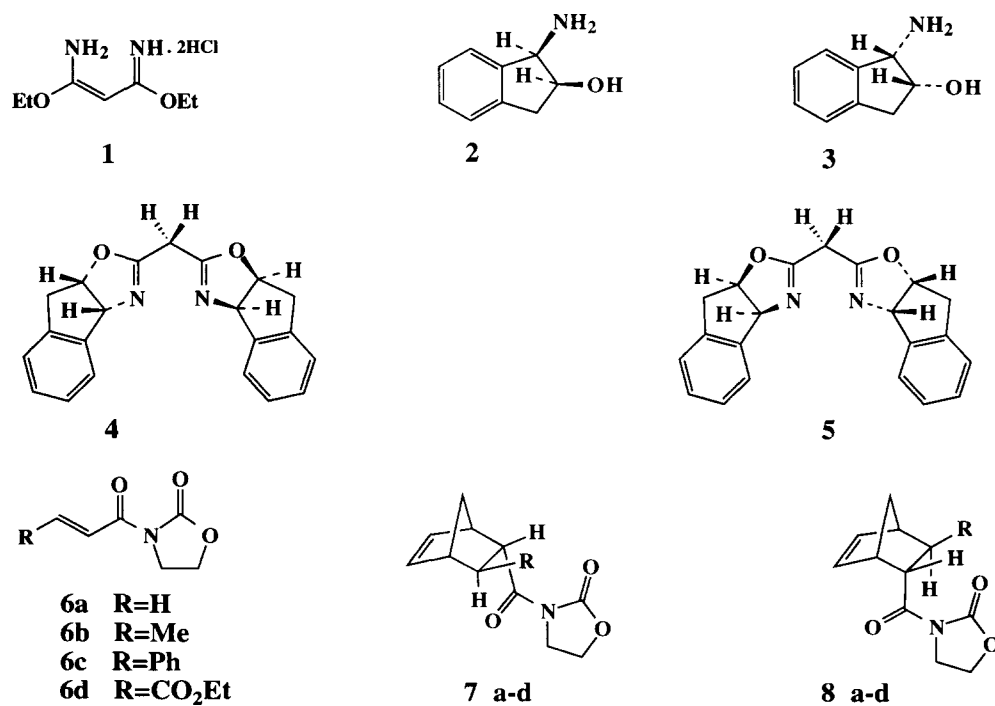
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- The iodolactone **9** was conveniently prepared by exposure of the adducts to iodine, KI and NaHCO₃ in aqueous CH₂Cl₂ at 23°C for 16 h (72% yield).



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.



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=C ₀ Et)	Cu (10)	-45°C (8)	75	93 : 7	94 (2S)

^aIsolated yield after silica gel chromatography.^bWith IS, 2R-bisoxazoline ligand.^cBased on recovered starting material.^dEndo/exo ratios were determined by ¹H-NMR and HPLC.^eEnantiomeric excess was determined by HPLC and comparison of known optical rotation.^fAt -78°C, no reaction or very little conversion was obtained.