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Bis(oxazoline)copper(II) Complexes as Chiral Catalysts for the Enantioselective Diels–Alder Reaction

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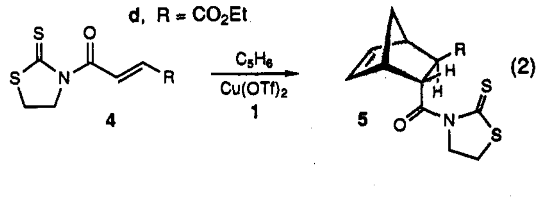
C_2-symmetric bis(oxazoline)copper complexes have proven to be excellent catalysts for enantioselective olefin cyclopropanation[2] and aziridination.[3] In addition, Corey has demonstrated that the Mg(II) and Fe(III) complexes[4] of these same ligands show promise as chiral Lewis acid catalysts for the Diels–Alder reaction[5] of unsubstituted acrylimides. The purpose of this communication is to report our observations on the utility of chiral Cu(II) bis(oxazoline) complexes as Lewis acids in the catalysis of these reactions. Attractive attributes of this catalyst system include an expanded scope of utilizable dienophiles and a clearly interpretable geometry for the catalyst–dienophile complex which rationalizes the sense of asymmetric induction for the cycloaddition process.

The range of dienophiles covered in this study include imides **2a–d** and the thiazolidine-2-thione analogs **4a–d** which exhibit enhanced dienophilic reactivity.[6] Catalyst–dienophile topography was probed in the context of the illustrated reactions with cyclopentadiene (eqs 1, 2).



One-to-one complexes of the ligands **1a–c** and $Cu(OTf)_2$[7] were prepared at ambient temperature in CH_2Cl_2 (0.03 M). The resulting green solution of catalyst (5–10 mol %) was then combined with 1.0 equiv of dienophile and 5–10 equiv of cyclopentadiene at the specified temperature (Table I).[8] After the indicated reaction time, the products were isolated by filtration through silica. *Endo–exo* ratios were determined by ^{1}H NMR spectroscopy and confirmed by either GLC or HPLC. Enantiomer compositions were determined either by HPLC (Daicel Chiralcel OD column) or GLC (Astec chiraldex G-TA, γ-cyclodextrin column). Absolute stereochemical assignments of the cycloaddition products **3a–d** and **5a–d** were made by correlation of these adducts with the products of the related Diels–Alder reactions of the chiral *N*-acyloxazolidones.[9]

From the data in Table I, it is evident that reaction enantioselectivity is strongly dependent upon the nature of the bis(oxazoline) ligand substituent R (entries A–C). Whereas the phenyl-substituted ligand **1a** performs well in the analogous Fe(III)-catalyzed reaction,[4a] the analogous catalyst prepared from **1a** and $Cu(OTf)_2$ exhibited low enantioselectivity (30% ee, entry A). On the other hand, dramatic enhancement in *endo* enantioselection was noted when the *tert*-butyl-derived bis(oxazoline) **1c** was employed,[10] and at −78 °C the minor *endo* enantiomer could not be detected (entry C). The fidelity of ligand **1c** holds throughout the survey of the other dienophiles. The crotonate derivative **2b** undergoes a highly enantioselective reaction (97% ee) at somewhat higher temperatures (−15 °C), while the thiazolidine-2-thione analog **4b** undergoes reaction at a somewhat lower temperature (−45 °C) but with modestly diminished enantioselection (94% ee). However, this trend is reversed with the cinnamate dienophiles, where the sulfur analog **4c** exhibits the higher *endo* enantioselection (97% ee, −35 °C). Finally, the Cu(II)-catalyzed reaction of the mixed fumarate dienophile **2d** (entry I) performs as well (5 mol % catalyst, 95% ee) as that reported for the recently modified Narasaka $(RO)_2TiCl_2$ catalyst (20 mol % catalyst, 91% ee).[11] In summary, this catalyst system exhibits selectivities competitive with the best values reported for catalyzed Diels–Alder reactions between cyclopentadiene and both unsubstituted and β-substituted acrylimides.[12]

The sense of asymmetric induction in the preceding reactions can be rationalized by assuming that the reaction proceeds via the intermediacy of a square-planar (eq 3) rather than tetrahedral Cu(II)–dienophile complex (eq 4).[13,14] In each of these complexes, the sterically accessible dienophile diastereoface is readily deduced. Double stereodifferentiating experiments using the enantiomeric chiral imides (*R*)- and (*S*)-**8** were carried out to probe the nature of the proposed catalyst–substrate complex.

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[1] (a) National Science Foundation Predoctoral Fellow. (b) National Institutes of Health Postdoctoral Fellow.

[2] (a) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991,** *113,* 726–728. (b) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990,** *31,* 6005–6008. (c) Müller, D.; Umbricht, B. W.; Pfaltz, A. *Helv. Chim. Acta* **1991,** *74,* 232–240.

[3] Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993,** *115,* 5328–5329.

[4] (a) Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991,** *113,* 728–729. Conversely, we have found that the *tert*-butyl ligand **1c** is not effective in either the Fe(III) or Mg(II) catalyst systems. (b) Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992,** *33,* 6807–6810.

[5] For an excellent chiral titanium catalyst for this reaction, see: Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989,** *111,* 5340–5345, and references cited therein.

[6] Competition studies with cyclopentadiene indicate that **4b** is 20 times more reactive than **2b**, while **4c** is 30 times that of **2c** in these catalyzed cycloaddition reactions, *vide infra.* We anticipated the enhanced dienophilic reactivity of **4** from its known elevated carbonyl reactivity in acyl-transfer reactions.

[7] $Cu(OTf)_2$ was obtained from the Aldrich Chemical Company. The minimum time allotted for metal–ligand complexation was found to be critical for catalyst formation. Typically the ligand and $Cu(OTf)_2$ were stirred until the dissolution of the solid metal triflate (1–3 h). The efficacy of the resulting catalyst was neither eroded nor enhanced with longer complexation times. In speculating on the nature of the catalyst, we have observed that neither the two-to-one complex $(\mathbf{1c})_2$–$Cu(OTf)_2$ nor $Cu(OTf)_2$ alone is a catalyst for the reaction.

[8] For the substituted dienophiles **2**/**4b–d** an increase in catalyst from 5 to 10 mol % and an increase in diene equivalents from 5 to 10 was done to decrease reaction times.

[9] Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988,** *110,* 1238–1256. Product correlations were made through the derived benzyl esters.

[10] See the supplementary material associated with ref 2a for the experimental procedures for the preparation of **1c** and its enantiomer.

[11] For example, see the recent study on improved versions of the Narasaka titanium catalyst system: Corey, E. J.; Matsumura, Y. *Tetrahedron Lett.* **1991,** *32,* 6289–6292.

[12] A number of other metal triflates were screened in the reaction and were found to be inferior to the **1c**–$Cu(OTf)_2$ system reported herein. Full experimental details will be reported shortly.

[13] For the sake of the ensuing analysis, it is assumed without corroborating evidence that both triflate ligands are dissociated from the metal center. For an X-ray structure of the related **1c**–Cu(I)OTf complex see: Evans, D. A.; Woerpel, K. A.; Scott, M. S. *Angew. Chem., Int. Ed. Engl.* **1992,** *31,* 430–432.

[14] Structures **6** and **7** are Chem 3D representations.

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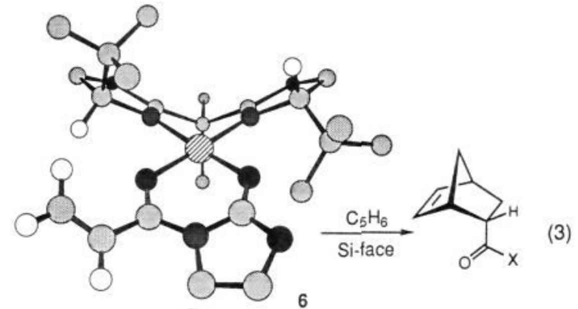
Table I. Enantioselective Diels–Alder Reactions of Imides **1** and **2** with Cyclopentadiene (eqs 1, 2)

entry	dienophile	ligand	time, h (temp, °C)	yield, %[a]	endo:exo ds	endo[b] ee	product
A[c]	**2a** (R = H)	**1a** (R = Ph)	1 (−78), 3 (−50)	92	95:5	30	**3a** (R = H)
B[c]		**1b** (R = $CHMe_2$)	1 (−78), 3 (−50)	93	96:4	58	
C[c]		**1c** (R = CMe_3)	18 (−78)	86	98:2	>98	
D[d]		**1c** (R = CMe_3)	18 (−50)	87	97:3	96	
E[e]	**2b** (R = Me)	**1c** (R = CMe_3)	30 (−15)[f]	85	96:4	97	**3b** (R = Me)
F[e]	**4b** (R = Me)	**1c** (R = CMe_3)	36 (−45)[f]	82	96:4	94	**5b** (R = Me)
G[e]	**2c** (R = Ph)	**1c** (R = CMe_3)	24 (25)[f]	85	90:10	90	**3c** (R = Ph)
H[e]	**4c** (R = Ph)	**1c** (R = CMe_3)	72 (−35)[f]	86	92:8	97	**5c** (R = Ph)
I[d]	**2d** (R = CO_2Et)	**1c** (R = CMe_3)	20 (−55)	92	94:6	95[g]	**3d** (R = CO_2Et)
J[d]	**4d** (R = CO_2Et)	**1c** (R = CMe_3)	20 (−55)	88	84:16	96[g]	**5d** (R = CO_2Et)

[a] Values refer to isolated yields of cycloadducts. [b] Enantiomer ratios determined either by chiral GLC or chiral HPLC. [c] Reactions performed in CH_2Cl_2 in the presence of 11 mol % ligand and 10 mol % $Cu(OTf)_2$. [d] Reactions performed in CH_2Cl_2 in the presence of 5.5 mol % ligand and 5 mol % $Cu(OTf)_2$. [e] Reaction run in the presence of 10 mol % ligand and 8 mol % $Cu(OTf)_2$. [f] The optimal temperatures for the indicated reactions. [g] The ee's of this cycloadduct determined on the derived iodolactone by chiral GLC.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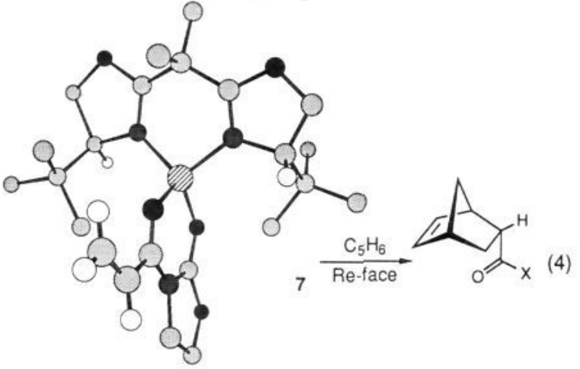
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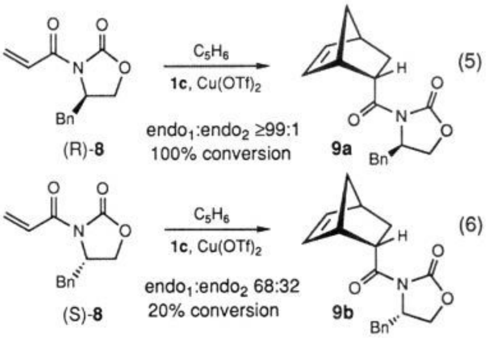

Diels–Alder reactions between (*R*)- and (*S*)-**8** and cyclopentadiene, catalyzed by 10 mol % of ligand **1c**–$Cu(OTf)_2$ complex, were performed under identical conditions (CH_2Cl_2, −78 °C, 11 h). In the stereochemically matched case (eq 5), the reaction proceeded to completion with undiminished stereoselectivity to afford adduct **9a** in an 87% isolated yield. In contrast, the catalyzed reaction with dienophile (*S*)-**8** only proceeded to 20% conversion (~10% isolated yield of **9b**) with very low diastereoselectivity (eq 6). *It is noteworthy that the principal adduct* ***9b*** *in this mismatched case is that cycloadduct derived from the catalyst-dominated rather than the substrate-controlled process.* These results are compatible with the intermediacy of either a square-planar or a square-pyramidal catalyst–substrate complex with two-point binding of dienophile to the metal center.[15]

Chiral Cu(II)–neutral ligand complexes have not previously been evaluated for their use as chiral Lewis acids. The present study provides the first evidence that such complexes might possess general utility for the enantioselective catalysis of a variety of useful processes. Further studies in this area will be forthcoming.

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Supplementary Material Available: Experimental procedures and spectral data for all compounds (8 pages). Ordering information is given on any current masthead page.

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[15] Two-point binding of Lewis acids to this family of dienophiles was first postulated in earlier studies, ref 8 and references cited therein. This point has recently been confirmed experimentally: Castelleno, S.; Dwight, W. J. *J. Am. Chem. Soc.* **1993**, *115*, 2986–2987.