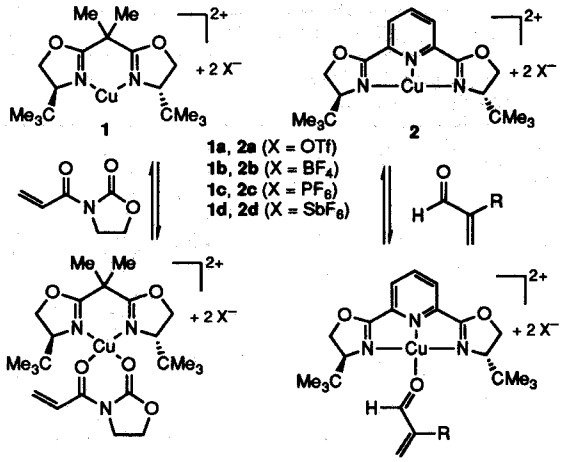

Scheme 1. Chiral Lewis acids derived from square-planar Cu^{II} complexes and their associated coordination complexes with complementary one- and two-point binding dienophiles.

C_2-Symmetric Cationic Copper(II) Complexes as Chiral Lewis Acids: Counterion Effects in the Enantioselective Diels–Alder Reaction**

David A. Evans,* Jerry A. Murry, Peter von Matt, Roger D. Norcross, and Scott J. Miller

We have recently documented the utility of chiral bis(oxazoline)copper(II) complexes **1** (oxazoline = dihydrooxazole) in the catalysis of asymmetric group transfer reactions such as cyclopropanation[1, 2] and aziridination.[3, 4] In addition, we have demonstrated that the C_2-symmetric bis(oxazoline)copper(II) triflate complex **1a** (triflate = trifluoromethanesulfonate = OTf) is also capable of functioning as an effective chiral Lewis acid in the Diels–Alder reaction with two-point binding *N*-acylimide dienophiles.[5] In an effort to broaden the utility of Lewis acidic chiral Cu^{II} complexes, we have prepared Cu^{II} complexes with tridentate bis(oxazolinyl)pyridine[6] (pybox) ligands, [Cu^{II}(pybox)X_2] (**2**) and probed their reactivity as chiral Lewis acids (Scheme 1). In conjunction with this investigation, we have uncovered dramatic counterion effects that strongly influence the reactivity of these Lewis acids. In this communication, we document the scope of these catalysts in enantioselective Diels–Alder reactions with unsaturated aldehyde and imide-derived dienophiles.

We began with an investigation of [Cu^{II}(pybox)] complexes which we anticipated would possess a preferred square-planar coordination geometry with a single accessible coordination site for carbonyl-derived dienophiles such as α,β-unsaturated aldehydes. Indeed, we have found that [Cu^{II}(pybox)] complexes **2** serve as effective chiral Lewis acids with aldehyde-derived dienophiles. For example, the cycloaddition of methacrolein with cyclopentadiene catalyzed by (pybox)Cu(OTf)$_2$ (**2a**) (5 mol%, CH_2Cl_2, −20 °C) afforded the desired cycloadducts with good *exo*:*endo* selectivity (96:4) and enantioselectivity (*exo* adduct: 85% ee).[7] However, extended reaction times (120 h) were required for complete conversion.

In an effort to increase catalyst reactivity, the cationic complexes **2b**–**2d** were prepared[6] and evaluated. As illustrated in Figure 1, a large counterion effect was observed in these reactions. For example, the cycloaddition of methacrolein with cyclopentadiene that required 120 hours for complete conversion with catalyst **2a** (X = OTf) was complete in 8 hours with catalyst **2d** (X = SbF_6). This comparison reveals that the counterion structure dramatically affects catalyst efficiency and that the "noncoordinating" counterions SbF_6^-, PF_6^-, and BF_4^-, strongly differ in degree of interaction with the Lewis acidic Cu^{II} center.[8]

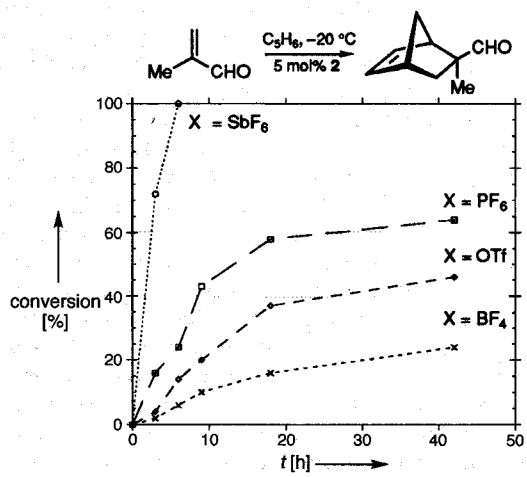

Fig. 1. Plot of the conversion [%] as a function of the reaction time [h] for the Diels–Alder reaction of methacrolein with cyclopentadiene catalyzed by **2** at −20 °C.

From the results of the preceding study, the cationic (pybox)Cu(SbF_6)$_2$ complex (**2d**) was determined to be the catalyst of choice, and its optimized performance in the Diels–Alder reactions of cyclopentadiene with representative aldehyde dienophiles is given in Table 1. The *tert*-butyl ligand **2** was originally chosen in analogy with the acrylimide results and provides enantioselectivities comparable to those reported in the literature.[9] Importantly, we have also found that the (*S*)-benzyl-pybox ligand, derived from L-phenylalanine, provides comparable

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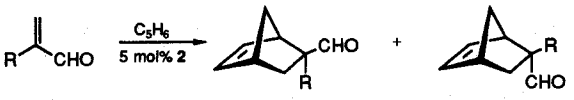
Table 1. Enantioselective Diels–Alder reactions of α-substituted acroleins with cyclopentadiene catalyzed by Cu^{II} complexes **2a** and **2d** [a].

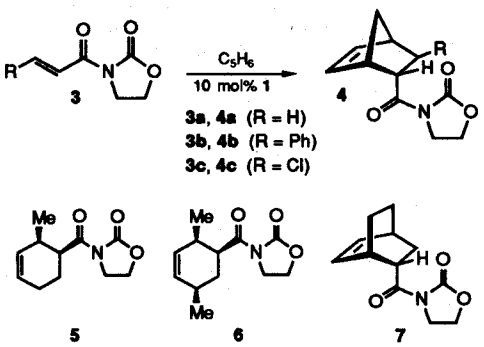


R	Catalyst	T[°C]	t[h]	*exo*:*endo*	*ee*[%]
H	**2d**	−20	18	6:94	85
Br	**2a**	−40	60	97:3	87
Br	**2d**	−78	12	98:2	96
Me	**2a**	−20	120	96:4	85
Me	**2d**	−40	8	97:3	92

[a] Reactions were performed in 4 mL CH_2Cl_2 with 2.0 mmol dienophile, 2.4 mmol cyclopentadiene, and 5 mol% catalyst. The *exo*:*endo* ratios determined by GLC. The enantiomeric excesses were determined by GLC after conversion of products to the (*R*,*R*)-pentanediol acetals (see ref. [10]).

enantioselectivities. For example, the Diels–Alder reaction of α-bromoacrolein with cyclopentadiene in the presence of the benzyl-pybox ligand provides the adduct in 95% enantiomeric excess. This readily available ligand is an attractive alternative to the more expensive *tert*-butylglycine derived variant.

The correlation of catalyst reactivity with the coordinating ability of the counterion for the [(pybox)$Cu(X)_2$] catalysts **2** led us to reinvestigate the bis(oxazoline)copper(II) catalyzed Diels–Alder reactions of acrylimides **3**. The bis(oxazoline)copper triflate complex **1a** was originally chosen with the expectation that the imide dienophile would successively displace both of the electronegative triflate ligands from the metal center in conjunction with the bidentate ligation of dienophile and Lewis acid.[5]



To the extent that the triflate counterion impairs the two-point dienophile binding motif, other coordination geometries could lead to diminished enantioselection. Accordingly, complexes **1b**–**d** were prepared and evaluated as catalysts in the Diels–Alder reaction of acrylimide **3a** (R = H) with cyclopentadiene (Table 2). As in the preceding study, catalysts **1a**–**1d** exhibited significantly different levels of activity in the Diels–Alder reaction. Again, the SbF_6-derived complex **1d** was found to be the catalyst of choice. For example, the rate of the Diels–Alder reaction of **3a** with cyclopentadiene catalyzed by **1d** (X = SbF_6) was approximately 20 times faster (−78 °C, 99% *ee*) than the rate of the analogous reaction promoted by the less efficient triflate complex **1a**. The cationic bis(oxazoline) complex **1d** was then probed for generality with a selection of cyclic and acyclic dienes.

Inspection of Table 2 reveals that the Diels–Alder reactions of these substrates are significantly improved with the more reactive cationic catalyst. The cycloadditions of the less reactive

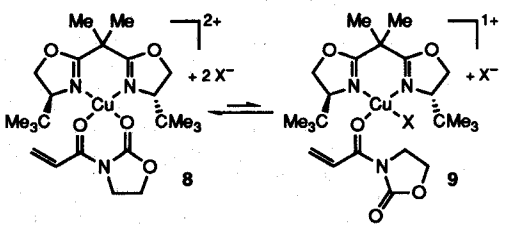
Table 2. Enantioselective Diels–Alder reactions of imide-derived dienophiles **3a**–**c** with dienes catalyzed by **1a** (X = OTf) and **1d** (X = SbF_6) at 25 °C [a].

Dienophile	R	Diene	Catalyst	t[h]	Yield [%] [b]	*endo*:*exo* [c]	*endo ee* [%] [d	Product
3b	Ph		**1a**	24	85	90:10	99	**4b**
			1d	24	96	91:19	96	**4b**
3c	Cl		**1a**	24	<10	93:7	53	**4c**
			1d [e]	24	96	86:14	95	**4c**
3a	H		**1a**	12	72	75:25 [f]	86	**5**
			1d	12	70	91:9 [f]	94	**5**
3a	H		**1a**	36	66	78:22	84	**6**
			1d	12	59	77:23	93	**6**
3a	H		**1a**	48	90	98:2	82	**7**
			1d	5	90	95:5	93	**7**

[a] All reactions were carried out in CH_2Cl_2 (0.3 M in substrate) at 25 °C with 10 mol% catalyst. [b] Values refer to isolated yields. [c] Determined by ^1H NMR spectroscopy and/or GLC or HPLC. [d] Determined by chiral HPLC or GLC. [e] This reaction was performed on 11.0 g (62.4 mmol) of **3c** to give 14.5 g of **4c** (96% yield, 95% ee). [f] Ratio of **5** to all other isomers.

β-substituted dienophiles **3b** (R = Ph) and **3c** (R = Cl) with cyclopentadiene proceed with excellent selectivities (95–96% *ee*) at room temperature. In particular, the performance of the latter dienophile, a potentially useful acetylene surrogate, was significantly enhanced with the cationic catalyst. Complex **1d** (X = SbF_6) is also an excellent catalyst for less reactive dienes. For example, the two acyclic dienes and cyclohexadiene underwent catalyzed cycloadditions with the imide **3a** to afford the derived cycloadducts in good yields and enantioselectivities in the 93–94% range at room temperature.

In all instances, the cationic Cu^{II} complex **1d** (X = SbF_6) affords higher levels of asymmetric induction than the analogous triflate complex **1a**. The sense of asymmetric induction is fully consistent with the intervention of a square-planar catalyst-substrate complex **8**,[5] featuring the chelated dienophile in the s-*cis* conformation. We speculate that the moderately lower enantioselection exhibited by the triflate-based catalyst might be due to the intervention of a competing cycloaddition from a less highly organized one-point catalyst–dienophile complex such as **9**.



In summary, this study provides a rational basis for the design of Lewis acids based on the coordinating capacity of cationic Cu^{II} complexes which possess sufficient Lewis acidity to catalyze a range of synthetically useful Diels–Alder reactions. In particular, documentation of the importance of counterion structure in the use of cationic metal centers as Lewis acids has been made for the first time. Investigations on the scope of these complexes as chiral Lewis acids are ongoing.

Experimental Procedure

Diels–Alder reaction of methacrolein with cyclopentadiene catalyzed by **2d**: To a dry flask in an inert atmosphere dry box was added $CuBr_2$ (22 mg, 0.10 mmol), $AgSbF_6$ (69 mg, 0.20 mmol) and *tert*-butyl[pyridine-bis(oxazoline)] **2** (33 mg, 0.10 mmol). The flask was fitted with a serum cap, removed from the dry box and charged with 4 mL CH_2Cl_2. The resulting heterogenous mixture was allowed to stir for 6 h and then filtered through a plug of cotton to give a clear blue-green solution. This solution was then cooled to −40 °C and cyclopentadiene (2.4 mmol, 158 mg, 164 mL) was added followed by methacrolein (140 mg, 166 mL, 2.0 mmol). The reaction was monitored by taking a 100 μL aliquot and filtering through a small plug of silica gel eluting with 2 mL of diethyl ether. The solvent was removed in vacuo and the resulting oil dissolved in $CDCl_3$ and analyzed by ^1H NMR spectroscopy. The reaction mixture was monitored until the conversion was ≥95%. The crude reaction mixture was filtered through a plug of silica gel eluting with diethyl ether. The resulting solution was concentrated to give (1*R*,2*S*, 4*R*)-2-methylbicyclo-[2.2.1]hept-5-ene-2-carboxaldehyde as a clear colorless oil. $[\alpha]_D = +21.4$ ($c = 2.3$, EtOH); $R_f = 0.5$ (40% hexane/CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.69$ (s, 1H, CHO), 6.29 (dd, $J = 5.6$, 3.0 Hz, 1H, C(6)-H), 6.11 (dd, $J = 5.6$, 3.0 Hz, 1H C(5)-H), 2.89 (br s, 1H, C(1)-H), 2.82 (br s, 1H, C(4)-H), 2.25 (dd, $J = 11.9$, 3.8 Hz, 1H, C(3)HXH_Y), 1.39 (m, 2H, C(7)H_2), 1.01 (s, 3H, Me), 0.76 (d, $J = 11.9$ Hz, 1H, C(3)H_XH**Y**); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 205.8$, 139.5, 133.1, 53.9, 48.5, 47.6, 43.2, 34.6, 20.0; IR (neat): $\tilde{\nu} = 2973$, 2870, 2705, 1720, 1448, 1333, 1119 cm^{-1}; Exact mass calcd for $C_9H_{12}O$ 136.0893; found 136.0888 (EI). At this point the *exo*:*endo* product ratio was ascertained by GLC: DB-1701, 110 °C, 5 psi, t_r(*exo*) = 5.40, t_r(*endo*) = 6.01. This aliquot was then derivatized and used for determination of the enantioselectivity of the reaction. The cycloaddition product (14 mg, 0.10 mmol) was diluted with CH_2Cl_2 (0.5 mL) and (−)-(2*R*,4*R*)-pentanediol (20 mg, 0.20 mmol) and a few crystals of *p*-TsOH were added. After stirring for 6 h at room temperature, tlc analysis indicated that acetalization was complete. The reaction mixture was eluted through a short plug of silica with ether and analysed by capillary GLC. In this way the enantiomeric excess of the *exo* cycloaddition product was determined. Using the enantiomer of the diol, (+)-(2*S*,4*S*)-pentanediol, gave the same numeric value for the *exo* enantiomeric excess (within ±2% ee) indicating that there was negligible kinetic resolution during the acetalization reaction. Purification by flash chromatography gave the pure (2(1*R*,2*S*, 4*R*),9*R*,11*R*)-4,6-dimethyl-2-(2-methylbicyclo[2.2.1]hept-5-ene-2-yl)-1,3-dioxane. R_f 0.42 (20% EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.13$–6.07 (m, 2H, C(5)-H, C(6)-H), 4.69 (s, 1H, C(8)-H), 4.32–4.28 (m, 1H, C(9)-H) 3.91–3.84 (m, 1H, C(11)-H) 2.73 (br s, 1H, C(1)-H), 2.65 (br s, 1H, C(4)-H), 1.76–1.55 (m, 3H, C(7)-CH_2, C(3)-HxH_y), 1.36 (d, $J = 7.0$ Hz, 3H, C(9)-CH_3), 1.28-1.33 (m, 2H, C(10)-CH_2), 1.20 (d, $J = 6.2$ Hz, 3H, C(11)-CH_3), 0.86 (s, 3H, C(2)-CH_3), 0.74 (dd, $J = 2.7$, 12.0 Hz, 1H, C(3)-H$_x$Hy); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 137.2$, 135.7, 99.5, 67.9, 67.7, 47.9, 47.4, 45.5, 37.2, 36.9, 21.9, 18.8, 17.3; IR (neat): $\tilde{\nu} = 3058$, 2969, 1449, 1375, 1334, 1240, 1136, 1058, 1004 cm^{-1}; Exact mass calcd for $C_{14}H_{22}O_2$ 222.1625; found 222.1620 (EI); GLC, DB-1701, 110°C, 5 psi, t_r(minor product) = 29.89, t_r (major product) = 30.63 min.

Diels–Alder reaction of β-chloroimide **3c** with cyclopentadiene. A solution of catalyst **1d** (X = SbF_6) was prepared by mixing $CuCl_2$ (766 mg, 5.7 mmol), *tert*-butylbis(oxazoline) **1** (1.89 g, 6.3 mmol), and $AgSbF_6$ (3.92 g, 11.4 mmol) in CH_2Cl_2 (57 mL), stirring for 8 h at ambient temperature and filtering through celite. Imide **3c** (10.96 g, 62.4 mmol) was then added as a solution in CH_2Cl_2 (60 mL) by cannula (5 mL rinse of CH_2Cl_2). Immediately thereafter, cyclopentadiene (62 mL, 744 mmol) was added by syringe. The resulting solution was stirred at room temperature for 24 h. The reaction mixture was directly applied to a short column of silica gel (6 × 6 cm) and eluted with approximately 1 L of 1:1 ethyl acetate/hexane. Concentration afforded the unpurified product **4c** which was analyzed. ^1H NMR analysis indicated that the reaction had proceeded to >98% conversion. The unpurified reaction mixture was analyzed directly by chiral GLC, which showed the *endo*/*exo* ratio to be 87:13 (*endo* isomer 96% ee, chiraldex G-TA column; oven temperature = 150 °C, flow rate = 20 psi; t_r(*endo* major enantiomer) = 47.40, t_r (*endo* minor enantiomer) = 57.62, t_r(*exo* enantiomer 1) = 50.27, t_r(*exo* enantiomer 2) = 51.85). The product mixture was then purified by chromatography (8 × 32 cm silica gel, 30% ethyl acetate/hexane) to afford 14.45 g (59.8 mmol, 96%) of **4c** as a white solid. Recrystallization from ethyl acetate/hexane yielded enantiomerically pure **4c**: $[\alpha]_D = -113$ ($c = 1.10$, CH_2Cl_2); IR (CH_2Cl_2): $\tilde{\nu}$ 3000, 1781, 1699, 1480, 1387 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.23$ (dd, 1H, $J = 5.6$, 3.3 Hz, C*H*=CH), 5.90 (dd, 1H, $J = 5.6$, 2.7 Hz, CH=C*H*), 4.41 (t, 2H, $J = 7.8$ Hz, OCH_2), 4.24 (m, 1H, -CH-), 4.13 (m, 1H, -CH-), 4.05–3.87 (m, 2H, -NCH_2), 3.39 (br d, 1H, $J = 1.4$ Hz, bridgehead H), 3.06 (br s, 1H, bridgehead H), 2.10 (br d, 1H, $J = 9.1$ Hz, one of -CH_2-), 1.72 (dd, 1H, $J = 9.0$, 1.7 Hz, one of -CH_2-); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 172.0$, 153.2, 136.2, 134.4, 62.1, 58.8, 54.8, 52.4, 48.1, 46.9, 42.8; exact mass calcd for $C_{11}H_{12}N_1O_3Cl_1$ requires *m/z* 241.0506; found *m/z* 241.0494 (EI).

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[10] *exo*:*endo* Ratios determined by GLC analysis. (DB-1701, 110 °C, 5 psi) For acrolein: t_r(major product) = 5.32, t_r(minor product) = 5.92 min. For methacrolein: t_r(major product) = 5.40, t_r(minor product) = 6.01 min.; for bromoacrolein: t_r(starting aldehyde) = 2.33, t_r(major product) = 9.59, t_r(minor product) = 10.76 min. Enantiomeric excesses for acrolein and methacrolein adduct were determined by GLC analysis after conversion to the acetal of (*R*,*R*)-pentanediol (DB-1701, 110 °C, 5 psi) For the acrolein adduct-derived acetal: t_r(major product) = 28.15, t_r(minor product) = 28.91. For the methacrolein adduct-derived acetal: t_r(major product) = 29.89, t_r(minor product) = 30.55. For the bromoacrolein adduct, the enantiomeric excess was determined by GLC of the dimethyl acetal (GTA, 110 °C, 5 psi, t_r(minor product) = 62.95, t_r(major product) = 64.43 min and by ^{19}F NMR of the corresponding Mosher ester.

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