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Cationic Bis(oxazoline)Cu(II) Lewis Acid Catalysts. Enantioselective Furan Diels-Alder Reaction in the Synthesis of *ent*-Shikimic Acid

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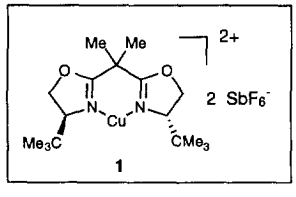
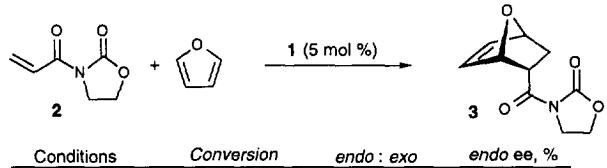
Abstract: The highly enantioselective Diels-Alder reaction between acryloyl oxazolidinone and furan, catalyzed by cationic bis(4-*tert*-butyloxazoline)Cu(II) complex **1**, is presented. Though the reaction equilibrates rapidly at -20 °C, reaction at -78 °C permits isolation of the kinetic product mixture. The synthetic utility of the reaction is demonstrated by the conversion of the cycloadduct to *ent*-shikimic acid.

Recent publications from this laboratory have documented the development of cationic copper(II) complexes as chiral Lewis acids in the Diels-Alder[1] and Mukaiyama aldol[2] reactions. In particular, complex **1** has been found to be the optimal catalyst for a number of Diels-Alder reactions. In this Letter, we demonstrate the utility of this catalyst system in the reaction of acrylimide **2** with furan to yield cycloadduct **3**, as well as the conversion of the latter to shikimic acid.

Scheme I



1



2 **3**

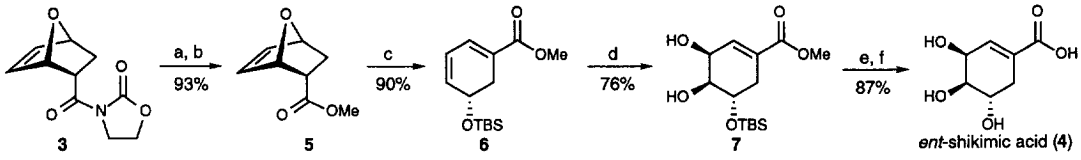
Conditions	*Conversion*	*endo* : *exo*	*endo* ee, %
-20 °C, 24 h	98%	10:90	0
-20 °C, 2.5 h	88%	66:34	59
-78 °C, 42 h	97%	80:20	97

Although 7-oxabicyclo[2.2.1]hept-2-enes are useful synthetic intermediates,[3] only two examples of catalytic asymmetric Diels-Alder reactions with furan or substituted furans have been reported, one employing α-haloacroleins as the dienophiles,[4] and the other requiring the more reactive 3-(methylthio)furan as the diene component.[5] Our investigation of this system began with the investigation of acrylimide **2** with furan in the presence of 5 mol% of complex **1** at -20 °C for 24 h. Cycloadduct **3** was isolated as a 9:1 mixture of *exo* to *endo* diastereomers. Surprisingly, both cycloadducts were found to be racemic. However, when the reaction was terminated after 2.5 h (88% conversion), the *endo*:*exo* ratio had reversed to 66:34, with the major *endo* adduct obtained in 59% ee. These results suggested that at -20 °C, the reaction was equilibrating rapidly to generate a thermodynamic mixture of products. Accordingly, when the reaction was performed at -78 °C, the *endo*:*exo* diastereomer ratio climbed to 80:20, and the *endo* isomer was obtained in 97% ee. Recrystallization of a 20 mmol scale reaction delivered enantiomerically pure **3** , mp 89 °C, $[\alpha]_D^{25}$ +99.1° (c = 1.0, $CDCl_3$)], in 67% yield.[6]

In order to demonstrate the synthetic utility of this transformation, the elaboration of cycloadduct **3** to shikimic acid (**4**) was undertaken (Scheme II).[7] Previous syntheses of racemic shikimic acid and related derivatives have originated from Diels-Alder adducts of furan with acrylonitrile[8] or methyl acrylate.[9] Attempted ring opening of imide **3** with LiHMDS proved unsuccessful under a variety of conditions; therefore, the imide was converted to methyl ester **5** *via* the derived intermediate ethylthio ester [a) LiSEt;[10] b) Cs_2CO_3, MeOH] in 93% overall yield. In a modification of the procedure of Campbell,[9c] the product of the LiHMDS

induced ring opening of **5** was trapped *in situ* with TBSOTf to give **6** in 90% yield. Dihydroxylation (OsO_4, NMO, THF, H_2O) of diene **6** proceeded with good diastereoselectivity (10:1) to deliver diol **7** in 76% isolated yield. Desilylation proceeded in 97% yield to provide *ent*-methyl shikimate. Although the saponification of methyl shikimate is reported to be capricious due to varying levels of aromatized products,[7] it was found that potassium trimethylsilanolate cleanly afforded *ent*-shikimic acid (**4**),[11] which was purified by ion-exchange chromatography (IR-120, H_2O)[12] in 90% yield. This material exhibited spectroscopic data comparable to that of a natural sample, with the exception of the rotation, which was opposite in sign $[\alpha]_D^{25}$ (Aldrich) -150° (c = 0.80, MeOH); $[\alpha]_D^{25}$ (synthetic) +142° (c = 0.80, MeOH)].

Scheme II[a]



[a](a) LiSEt, THF, -20 °C; (b) Cs_2CO_3, MeOH, 0 °C; (c) LiHMDS, THF, -78 to 0 °C, then TBSOTf, 2,6-lutidine, -78 °C; (d) OsO_4, NMO, THF, H_2O, 0 °C; (e) TBAF, THF; (f) TMSOK, THF, then IR-120, H_2O.

In summary, the unnatural enantiomer of shikimic acid has been synthesized in 7 steps and 37% overall yield from imide **2**. The key transformation was the bis(oxazoline)Cu(II)-catalyzed Diels-Alder reaction of acrylimide **2** with furan, which proceeded with excellent enantioselectivity. This route provides a rapid entry into the asymmetric synthesis of this class of compounds.

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6) Experimental details are as follows: To a mixture of bis(oxazoline)$CuCl_2$•CH_2Cl_2 (511 mg, 1 mmol) and $AgSbF_6$ (687 mg, 2 mmol) was added CH_2Cl_2 (15 mL); the mixture was stirred for 3.5 h in the dark. A solution of imide **3** (2.82 g, 20 mmol) in CH_2Cl_2 (25 mL) was cooled to -78 °C, and furan (14.5 ml, 200 mmol) was added. The deep-green catalyst solution was filtered through celite into the reaction over 5 min; an additional 5 ml of CH_2Cl_2 was used to wash the celite. After 42 h, the reaction was quenched by the addition of 5 mL conc. NH_4OH solution. On warming, the mixture was diluted with H_2O and extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting crystalline solid was dissolved at room temperature in EtOAc, and hexanes were slowly added. After standing overnight at -20 °C, the crystals were collected. Yield = 2.76 g (67%). Diastereomer and enantiomer ratios were determined by NMR and chiral HPLC (Chiracel OD-H, 70:30 hexanes:EtOAc, 0.65 mL/min; t^R (major) = 24.8 min, t^R (minor) = 30.5 min).

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