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

David A. Evans* and David M. Barnes

Department of Chemistry & Chemical Biology, Harvard University, Cambridge, MA 02138, USA

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. Copyright © 1996 Published by Elsevier Science Ltd

Recent publications from this laboratory have documented the development of cationic copper(II) complexes as chiral Lewis acids in the Diels-Alder¹ and Mukaiyama aldol² 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.





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 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, CDCl₃)], 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 acrylonitrile⁸ 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) Cs₂CO₃, 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 (OsO₄, NMO, THF, H₂O) 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, H₂O)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



⁵(a) LISE1, THF, -20 °C; (b) Cs₂CO₃, MeOH, 0 °C; (c) LIHMDS, THF, -78 to 0 °C, then TBSOT1, 2,6-lutidine, -78 °C; (d) OsO4, NMO, THF, H₂O, 0 °C; (e) TBAF, THF; (f) TMSOK, THF, then IR-120, H₂O.

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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