Chiral C₂-Symmetric Cu(II) Complexes as Catalysts for Enantioselective Intramolecular Diels–Alder Reactions. Asymmetric Synthesis of (−)-Isopulopone

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Important advances are being made in the development of catalytic, asymmetric variants of the Diels–Alder reaction. A number of systems have been reported that effect this powerful transformation, with variable tolerance for changes in diene and dienophile structure; however, the intermolecular version of the Diels–Alder reaction has been developed in almost exclusive preference to its intramolecular counterpart. Examples of diastereoselective intramolecular Diels–Alder (IMDA) reactions are abundant, but only a handful of enantioselective variants have been systematically investigated. In this paper, we report that cationic Cu(II) complex (SbF₆⁻) shown to be critical, with the hexafluoroantimonate counterion consistently displaying higher reactivity and enantioselectivity than the analogous triflate counterion structure in complex (SbF₆⁻)-derived catalyst. In initial experiments, it was observed that, in the presence of 10 mol % of the triflate complex 2a, trienimide 3a afforded less than 20% of the expected cycloadduct 4a after 5 days at room temperature; however, when trienimide 3a was treated with the SbF₆⁻-derived complex 2b (10 mol % CH₃Cl), the desired cycloadduct 4a was isolated as a single diastereomer in 89% yield and 86% ee after 24 h at ambient temperature (Scheme 1). The absolute configuration of this adduct was established by transformation to the known benzyl ester, [α]D₂₀ = −23.8° (c = 0.90, CHCl₃), and in agreement with our previously proposed model for asymmetric induction involving a four-coordinate square planar Cu(II)-ligand-substrate complex.

A representative set of trienimides was synthesized, and their catalyzed cycloadditions with 5–10 mol % complex 2b were evaluated. The results summarized in Table 1 indicate that both 4.3.0- and 4.4.0-bicyclic ring systems may be constructed with good levels of asymmetric induction and that terminally substituted dienes reacted with equal or greater facility than their unsubstituted counterparts. Specifically, phenyl-substituted trienimide 3b reacted in the presence of 5 mol % 2b with complete diastereoselectivity in 86% yield after only 5 h, affording cycloadduct 4b in 92% ee. The higher homologue 3d was transformed in 97% yield to the corresponding cycloadduct 4d with somewhat disappointing diastereoselectivity (endo:exo = 84:16); however, the endo isomer was delivered in 97% ee. Curiously, the unsubstituted imide 3c failed to cyclize to a significant degree over extended periods of time. The source of this


(10) Representative Procedure, Catalyst Preparation. To a dry flask in an inert atmosphere drybox was added 5.0 mg (0.037 mmol) of CuCl₂, 25.5 mg (0.074 mmol) of AgSbF₆, and 12.1 mg (0.041 mmol) of (S,S)-tert-butylbis(oxazoline) (ref 6). The flask was fitted with a serum cap, removed from the drybox, and charged with 2 mL of CH₂Cl₂. The resulting heterogeneous mixture was stirred for 12 h in the absence of light and then filtered through Celite and cotton into a dry flask; this was washed with an additional 2 mL of CH₂Cl₂. The resulting homogeneous mixture was stirred for 24 h at room temperature, the reaction solution filtered through a plug of silica gel, eluting with diethyl ether. The product and starting material were separated by flash chromatography (15% EtOAc/hexanes) to afford 251 mg (81%) of 11 as a clear oil, followed by 25.5 mg (8%) of 10.
a Key: (a) 4 mol % Pd(0)-catalyzed coupling of vinylstannane \[ \text{1}\] and vinyl iodide \[ \text{6}\], both available from 5-hexyn-1-ol, \[ \text{13}\] to afford a 90% yield of (1)-isopulo'upone \[ \text{1}\]. Alcohol \[ \text{8}\] was subjected to Swern oxidation, \[ \text{14}\] and the derived \[ \text{7}\] afforded a 72% yield of the pseudosymmetrical diene \[ \text{7}\]. Alcohol \[ \text{7}\], both available from 5-hexyn-1-ol, \[ \text{13}\] to afford a 72% yield of the pseudosymmetrical diene \[ \text{7}\]. Alcohol \[ \text{7}\] was subjected to Swern oxidation, \[ \text{14}\] and the derived aldehyde \[ \text{8}\] was immediately treated with phosphonate reagent \[ \text{9}\] (NaHMD, THF) to afford trienimide \[ \text{10}\] in 77% yield as a separable 27:1 mixture of E- and Z-isomers.

With the requisite trienic substrate in hand, the key catalytic IMDA reaction was attempted. Trienimide \[ \text{10}\] was found to undergo cycloaddition with as little as 5 mol % of catalyst \[ \text{2b}\] (24 h, 25 °C) to provide cycloadduct \[ \text{11}\] in 81% yield. The cycloaddition proceeded with high diastereo- and enantioselectivity (99:1 endo:exo; 96% ee) to provide the bicyclic isopulo'upone precursor in the required relative and absolute configuration. It is noteworthy that these intramolecular cycloadditions can be performed at high concentration (1 M in substrate) without interference from competing intermolecular processes.

Previous work from this laboratory has established a protocol for the manipulation of hindered imides such as \[ \text{11}\]. \[ \text{15}\] Thioesterification of \[ \text{11}\] (LiSEt, THF, 15 min, 0 °C) \[ \text{16}\] provided \[ \text{12}\] in 90% yield. While initial attempts to reduce the thioester under standard Pd(0)/triethylsilane conditions \[ \text{17}\] afforded variable amounts of concomitant endocyclic olefin reduction, modified conditions using Lindlar’s catalyst with triethylsilane \[ \text{18}\] in the presence of 1-decene completely suppressed olefin reduction and cleanly provided the desired aldehyde. The aldehyde, carried forward without purification, was treated with excess methylmagnesium chloride (THF, -78 °C), yielding an 81% mixture of diastereomers at the newly-formed hydroxyl stereocenter. The unpurified alcohol was treated with acid (1% HCl/EtOH, 10 min, 25 °C) to effect silyl ether deprotection and provide \[ \text{13}\] (not shown) in 90% yield (three steps) from thioester \[ \text{12}\]. An X-ray structure of the major isomer confirmed the relative stereochemical assignments made previously. \[ \text{18}\] Diol \[ \text{13}\] (as a mixture of diastereomers) was oxidized under Swern conditions to provide keto aldehyde \[ \text{14}\] in 83% yield. After considerable experimentation with definition methods, it was found that treatment of \[ \text{14}\] with the ylide derived from tributylphosphonium salt \[ \text{15}\] afforded a 90% yield of (1)-isopulo'upone with excellent olefin selectivity (E/Z = 12: 1). The synthesis was thus achieved in 10 steps and 28% overall yield from known stannane \[ \text{5}\] and 14 steps and 14% overall yield from 5-hexyn-1-ol.

In summary, cationic Cu(I) bis(oxazoline) complex \[ \text{2b}\] is an effective catalyst that exhibits excellent enantioselectivity for intramolecular Diels–Alder reactions carried out at ambient temperatures.

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**Supporting Information Available:** Experimental procedures and spectral data for all compounds and X-ray crystal structures of \[ \text{4b}\] and \[ \text{13}\] (11 pages).

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(14) The author has deposited atomic coordinates for \[ \text{4b}\] and \[ \text{13}\] with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.