Chiral C_2-Symmetric Cu(II) Complexes as Catalysts for Enantioselective Intramolecular Diels−Alder Reactions. Asymmetric Synthesis of (−)-Isopulo'upone

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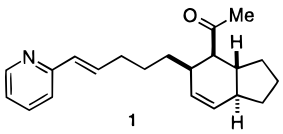
Important advances are being made in the development of catalytic, asymmetric variants of the Diels−Alder reaction.[1] A number of systems have been reported that effect this powerful transformation, with variable tolerance for changes in diene and dienophile structure; however, the intermolecular version 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,[2] but only a handful of *enantioselective* variants have been systematically investigated.[3] In this paper, we report that cationic Cu(II) bis(oxazoline) complexes effectively catalyze the IMDA reactions of a variety of substrates, affording bicyclic products with as many as four contiguous stereogenic centers in high enantioselectivity. The synthetic utility of this system is demonstrated by the synthesis of the marine toxin (-)-isopulo'upone (**1**).



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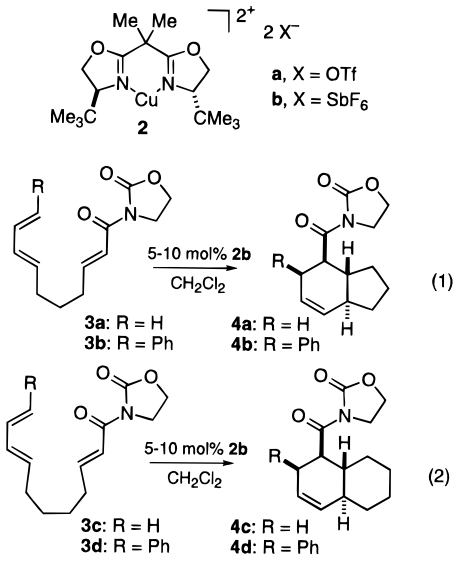
(-)-Isopulo'upone

Previous reports from this laboratory have documented the use of C_2-symmetric Cu(II) complexes as catalysts for enantioselective Diels−Alder[4] and Mukaiyama aldol reactions.[5] With regard to the Diels−Alder catalysts, the nature of counterion structure in complex **2**, constructed from the (*S*,*S*)-*tert*-butylbis(oxazoline) ligand,[6] has been shown to be critical, with the hexafluoroantimonate (SbF_6^-) counterion consistently displaying higher reactivity and enantioselectivity than the analogous triflate ($^-$OTf)-derived catalyst.[7] In initial experiments, it was observed that, in the presence of 10 mol % of the triflate complex **2a**, trienimide **3a**[8] afforded less than 20% of the expected cycloadduct **4a** after 5 days at room temperature; however, when trienimide **3a** was treated with the SbF_6^--derived complex **2b** (10 mol %, CH_2Cl_2), 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, $[\alpha]^{25}_D$ −23.8° (c = 0.90, $CHCl_3$),[9] and is in agreement with our previously proposed model for asymmetric induction involving a four-coordinate square planar Cu(II)−ligand−substrate complex.[4]

Scheme 1



A representative set of trienimides was synthesized, and their catalyzed cycloadditions with 5−10 mol % complex **2b** were evaluated.[10] 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.[11] Curiously, the unsubstituted imide **3c** failed to cyclize to a significant degree over extended periods of time. The source of this

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(3) (a) Iwasawa, N.; Sugimori, J.; Kawase, Y; Narasaka, K. *Chem. Lett.* **1989**, 1947−1950. (b) Furuta, K.; Kanematsu, A.; Yamamoto, H. *Tetrahedron Lett.* **1989**, *30*, 7231−7232. (c) Narasaka, K.; Saitou, M.; Iwasawa, N. *Tetrahedron Asymm.* **1991**, *2*, 1305−1318. (d) Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 3049−3050.

(4) (a) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460−6461. (b) Evans, D. A.; Lectka, T.; Miller, S. J. *Tetrahedron Lett.* **1993**, *34*, 7027−7030.

(5) Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814−5815.

(6) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726−728. The synthesis of the (*S*,*S*)-bis(oxazoline) ligand, as well as its enantiomer, is provided in the Supporting Information.

(7) Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798−800.

(8) Prepared from Octa-5(*E*),7-dienenitrile: Roush, W. R.; Gillis, H. R.; Ko, A. I. *J. Am. Chem. Soc.* **1982**, *104*, 2269−2283. Details of the synthesis and characterization of all compounds can be found in the Supporting Information.

(9) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238−1256.

(10) **Representative Procedure. Catalyst Preparation.** To a dry flask in an inert atmosphere drybox was added 5.0 mg (0.037 mmol) of $CuCl_2$, 25.5 mg (0.074 mmol) of $AgSbF_6$, and 12.1 mg (0.041 mmol) of (*S*)-*tert*-butylbis(oxazoline) (ref 6). The flask was fitted with a serum cap, removed from the drybox, and charged with 2 mL of CH_2Cl_2. 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; the resulting blue solution was used as a 0.019 M catalyst solution. **Cycloaddition.** To 309 mg (0.734 mmol, 1.0 equiv) of trienimide **10** was added via syringe 2 mL (0.037 mmol, 0.05 equiv) of the catalyst solution. After 24 h at room temperature, the reaction solution was 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**.

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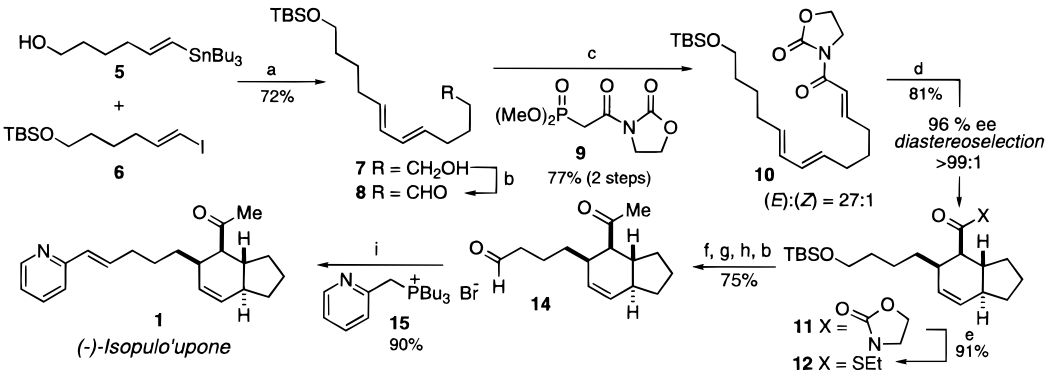
Scheme 2[a]



[a] Key: (a) 4 mol % $Pd_2(dba)_3 \cdot CHCl_3$, DMF, rt, 16 h; (b) $(COCl)_2$, DMSO, Et_3N, $-78 \rightarrow -40$ °C; (c) NaHMDS, THF, rt, 26 h; (d) 5 mol % **2b**, CH_2Cl_2, rt, 24 h; (e) LiSEt, THF, 0 °C, 15 min; (f) Et_3SiH, 5% Pd/$CaCO_3$/PbO/quinoline, 1-decene, acetone, rt, 2 h; (g) MeMgCl, THF, −78 °C; (h) 1% HCl/EtOH, rt, 10 min; (i) **15**, *n*-BuLi, THF, −20 °C, then **14**, rt, 45 min.

Table 1. Enantioselective Intramolecular Diels−Alder Reactions Catalyzed by 2 at 25 °C in CH_2Cl_2 (Eqs 1 and 2)

trienimide	catalyst (mol %)	% yield (time, h)	ratio *endo*:*exo*[a]	product % ee[b]
3a	**2a** (10)	<20 (120)		
3a	**2b** (10)	89 (24)	>99:1	**4a**, 86
3b	**2b** (5)	86 (5)	>95:5	**4b**, 92
3c	**2b** (10)	<20 (24)		
3d	**2b** (10)	97 (14)	84:16	**4d**, 97
10	**2b** (5)	81 (24)	>99:1	**11**, 96

[a] *Endo*/*exo* ratios determined by GLC, HPLC or NMR spectroscopy. [b] Enantiomeric excess determined by GLC or HPLC. See the Supporting Information for details.

lack of reactivity is not apparent at this time; indeed, this is the only trienimide we have found to be unreactive toward catalyst **2b**.

The tolerance of catalyst **2b** to increased substrate complexity was tested in the context of a projected asymmetric synthesis of (−)-isopulo'upone (**1**), a marine natural product isolated in 1993 from mollusks *Navanax inermis* and *Bulla Gouldiana* (Scheme 2).[12] The synthesis of the cyclization precursor **10** was initiated by the Pd(0)-catalyzed coupling of vinylstannane **5** and vinyl iodide **6**, both available from 5-hexyn-1-ol,[13] to afford a 72% yield of the pseudosymmetrical diene **7**. Alcohol **7** was subjected to Swern oxidation,[14] and the derived aldehyde **8** was immediately treated with phosphonate reagent **9** (NaHMDS, THF) to afford trienimide **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 **10** was found to undergo cycloaddition with as little as 5 mol % of catalyst **2b** (24 h, 25 °C) to provide cycloadduct **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 **11**.[15] Thioesterification of **11** (LiSEt, THF, 15 min, 0 °C)[16] provided **12** in 90% yield. While initial attempts to reduce the thioester under standard Pd(0)/triethylsilane conditions[17] afforded variable amounts of concomitant endocyclic olefin reduction, modified conditions using Lindlar's catalyst with triethylsilane[15] 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 8:1 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 diol **13** (not shown) in 90% yield (three steps) from thioester **12**. An X-ray structure of the major isomer confirmed the relative stereochemical assignments made previously.[18] Diol **13** (as a mixture of diastereomers) was oxidized under Swern conditions to provide keto aldehyde **14** in 83% yield. After considerable experimentation with olefination methods, it was found that treatment of **14** with the ylide derived from tributylphosphonium salt **15** afforded a 90% yield of (−)-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 **5** and 14 steps and 14% overall yield from 5-hexyn-1-ol.

In summary, cationic Cu(II)bis(oxazoline) complex **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 **4b** and **13** (11 pages).

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(11) See the Supporting Information for details on stereochemical proofs.

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(17) Fukuyama, T.; Lin, S.-C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050−7051.

(18) The author has deposited atomic coordinates for **4b** and **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, CH2 1EZ, UK.