Catalytic Enantioselective Hetero Diels−Alder Reactions of α,β-Unsaturated Acyl Phosphonates with Enol Ethers

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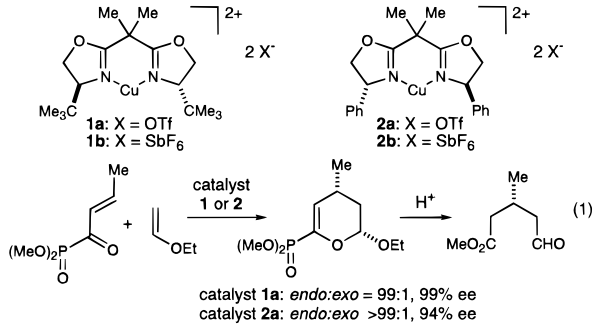
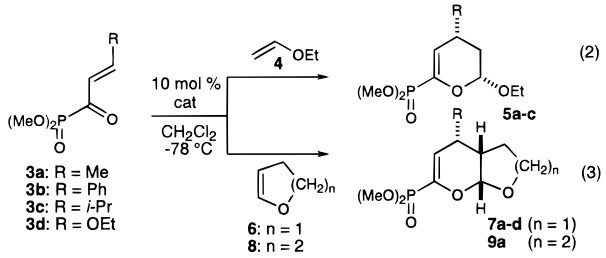
Previous reports from this laboratory have documented the utility of cationic C_2-symmetric Cu(II)bis(oxazoline)[1] complexes **1** and **2** as chiral Lewis acids capable of catalyzing a number of Diels−Alder[2] and aldol[3] reactions with high enantioselectivities. In these processes, the unifying organizational motif is that the substrate undergoing activation is capable of chelating to the chiral cationic Cu(II) catalyst, a condition that frequently affords high enantioselection.[4] The purpose of this paper is to present our findings that α,β-unsaturated acyl phosphonates undergo enantioselective hetero Diels−Alder reactions[5] with enol ethers catalyzed by chiral Cu(II) complexes **1** and **2** to afford cyclic enol phosphonates (eq 1), chemical entities that are shown to be useful building blocks for asymmetric synthesis.



The selection of acyl phosphonates for this study was made on the premise that favorable acyl phosphonate−catalyst association might be achieved via complexation between the vicinal C═O and P═O functional groups. Indeed, it was found that complexes **1** and **2** activate acyl phosphonates **3a**−**d** to the extent that they undergo facile cycloaddition reactions with electron-rich alkenes (Table 1).[6−8] The reaction of ethyl vinyl ether (**4**) with crotonyl phosphonate **3a** in the presence of [Cu((*S*,*S*)-*tert*-Bu-box)](OTf)$_2$ complex (**1a**) (10 mol % catalyst, CH_2Cl_2, 48 h, −78 °C) afforded cycloadduct **5a** in 89% yield with exceptional stereoselectivity (entry 1; *endo*/*exo* = 99:1, 99% ee). In contrast to previous studies,[2b] reaction with [Cu((*S*,*S*)-*tert*-Bu-box)](SbF$_6$)$_2$ complex (**1b**) afforded cycloadduct **5a** (84%) in moderately lower diastereo- and enantioselectivities (entry 2), although the expected rate acceleration was observed (48 h for **1a** vs 22 h for **1b**).[9] Interestingly, [Cu((*R*,*R*)-Ph-box)](X)$_2$ complexes **2**, possessing the opposite stereochemistry of **1**, afforded the *same antipode of* ***5a***, again in high stereoselectivity and yield (entries 3 and 4).[10,11] It is of some practical import that the cycloaddition between **3a**

Table 1. Cycloaddition of Acyl Phosphonates **3a-d** and Enol Ethers Catalyzed by **1** and **2** (eqs 2 and 3)



entry	R	enol ether[a]	catalyst	product (*endo*/*exo*)[b]	yield (%)[c]	ee (%)[b]
1	Me	**4**	**1a**	**5a** (99:1)	89	99
2	Me	**4**	**1b**	**5a** (69:1)	84	93
3	Me	**4**	**2a**	**5a** (>99:1)	85	94
4	Me	**4**	**2b**	**5a** (>99:1)	100	93
5	Me	**6**	**1a**	**7a** (>99:1)	91	95
6	Me	**8**	**1b**	**9a** (98:2)	55	92
7	Me	**8**	**1b**	**9a** (93:7)[d]	100	89
8	Ph	**4**	**2b**	**5b** (167:1)	98	98
9	Ph	**6**	**2a**	**7b** (171:1)	100	93
10	*i*-Pr	**4**	**2b**	**5c** (146:1)	99	96
11	*i*-Pr	**6**	**1b**	**7c** (98:2)	79	90
12	OEt	**6**	**1b**	**7d** (>99:1)	98	97

[a] Reaction conducted with 3 equiv of enol ether relative to **3**. [b] Determined by capillary GLC or chiral HPLC (see the Supporting Information). [c] Isolated yield. [d] Reaction run at −40 °C.

(1) The bis(oxazoline) ligands will be abbreviated as box in the following discussion. Syntheses of the (*S*,*S*)-*tert*-butyl-box and (*S*,*S*)-phenyl-box ligands are included in the Supporting Information. For catalyst preparation, see ref 2d, footnote 6, or the Supporting Information.

(2) (a) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460−6461. (b) Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798−800. (c) Evans, D. A.; Kozlowski, M. C.; Tedrow, J. S. *Tetrahedron Lett.* **1996**, *37*, 7481−7484. (d) Evans, D. A.; Barnes, D. M. *Tetrahedron Lett.* **1997**, *38*, 57−58. (e) Evans, D. A.; Johnson, J. S. *J. Org. Chem.* **1997**, *62*, 786−787. (f) Evans, D. A.; Shaughnessy, E. A.; Barnes, D. M. *Tetrahedron Lett.* **1997**, *38*, 3193−3194.

(3) (a) Evans, D. A.; Murry, J. A. *J. Am. Chem. Soc.* **1996**, *118*, 5814−5815. (b) Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893−7894.

(4) Those substrates that appear to effectively chelate with these Lewis acids are α,β-unsaturated imide dienophiles in Diels−Alder reactions (ref 2) and α-alkoxy aldehydes, α-diketones, and glyoxylate and pyruvate esters in aldol reactions (ref 3).

(5) Formal hetero Diels−Alder reactions between electron-rich dienes and pyruvate have recently been reported with these complexes: Johannsen, M.; Jørgensen, K. A. *J. Chem. Soc., Chem. Commun.* **1997**, 2169−2170.

(6) Cycloadditions of an α,β-unsaturated acyl phosphonate with alkylidene dithianes have been reported: Schuster, T.; Evans, S. A., Jr. *Phosphorous, Sulfur, Silicon* **1995**, *103*, 259−271.

(7) Hetero Diels−Alder reactions of α,β-unsaturated carbonyls with enol ethers: (a) McRae, K. J.; Rizzacasa, M. A. *J. Org. Chem.* **1997**, *62*, 1196−1197. (b) Dondoni, A.; Kniezo, L.; Martinkova, M.; Imrich, J. *Chem. Eur. J.* **1997**, *3*, 424−430. (c) Wada, E.; Pei, W.; Yasuoka, H.; Chin, U.; Kanemasa, S. *Tetrahedron* **1996**, *52*, 1205−1220 and references therein. (d) Tietze, L. F.; Schneider, C.; Grote, A. *Chem. Eur. J.* **1996**, *2*, 139−148 and references therein. (e) Gaudenzi, L. D.; Apparao, S.; Schmidt, R. R. *Tetrahedron* **1990**, *46*, 277−290 and references therein. (f) Boger, D. L.; Robarge, K. D. *J. Org. Chem.* **1988**, *53*, 5796−5798. (g) Boger, D. L.; Robarge, K. D. *J. Org. Chem.* **1988**, *53*, 3373−3377.

(8) For general references on the hetero Diels−Alder reaction, see: (a) Boger, D. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 451−512. (b) Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: San Diego, CA, 1987.

(9) Representative procedure for catalyzed cycloadditions: To a 0.02 M solution of 0.1 equiv of [Cu((*S*,*S*)-*tert*-Bu-box)](SbF$_6$)$_2$ in CH_2Cl_2 at −78 °C was added sequentially acyl phosphonate **2** (1.0 equiv) and enol ether (3.0 equiv). After the reaction was complete, the reaction mixture was partitioned between 20 mL of EtOAc and 10 mL of 2:1 (v/v) 3 M NH_4OH/saturated aqueous NaCl. After extraction, the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. A small aliquot was analyzed by capillary GC and chiral HPLC to determine the de and ee, respectively, of the cycloaddition. Flash chromatography on silica gel afforded the pure cycloadducts.

(10) In practice, [Cu((*S*,*S*)-Ph-box)](X)$_2$ (*ent*-**2a**, X = OTf; *ent*-**2b**, X = SbF$_6$) were used to afford cycloadducts *ent*-**5**, *ent*-**7**, and *ent*-**9**. For the sake of clarity, we have chosen to show the (*S*,*S*)-*tert*-Bu ligand and the (*R*,*R*)-Ph ligand affording the *same* products. The source of this divergent stereochemical outcome is not apparent at this time and is the subject of continuing investigation.

(11) Cu[(*S*,*S*)-Bn-box)](SbF$_6$)$_2$ afforded *ent*-**5a** in 58% ee (98:2 *endo*/*exo*); Cu[(*S*,*S*)-*i*-Pr-box)](SbF$_6$)$_2$ afforded *ent*-**5a** in 39% ee (97:3 *endo*/*exo*).

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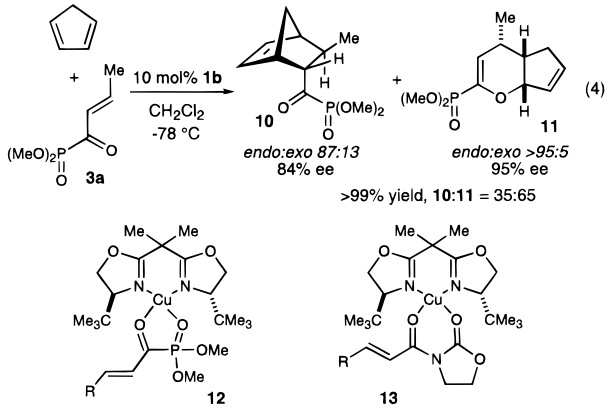
and ethyl vinyl ether could be conducted with as little as 0.2 mol % of catalyst **2b** with minimal drop in yield and no loss of stereoselectivity (93% yield, *endo/exo* > 99:1, 93% ee). Consistent with previous observations,[2c,3b] complexes **1** and **2** may be employed as effective catalysts over a broad range of temperatures as evidenced by an enantioselectivity/temperature profile (eq 1, **1a**, −78 °C, *endo/exo* = 99:1, 99% ee; −20 °C, *endo/exo* = 97:3, 94% ee; 25 °C, *endo/exo* = 95:5, 89% ee).[12]

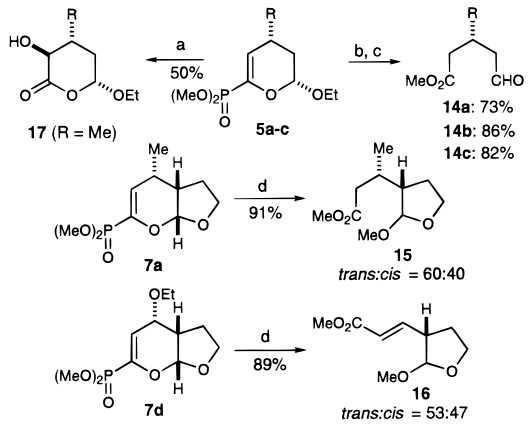
Cyclic enol ethers also undergo stereoselective reactions with acyl phosphonate **3a**.[13] Specifically, 2,3-dihydrofuran (**6**) reacted with **3a** in the presence of [Cu((*S*,*S*)-*tert*-Bu-box)](OTf)$_2$ complex (**1a**) to deliver bicyclic enol phosphonate **7a** (entry 5), while the reaction of 2,3-dihydropyran (**8**) and **3a** afforded adduct **9a** (entry 6), both in good diastereo- and enantioselectivities. The hetero Diels−Alder reaction was general with respect to the β-substituent on the unsaturated acyl phosphonate (entries 8−12). Of particular merit is the fact that phenyl (entries 8 and 9), isopropyl (entries 10 and 11), and alkoxy (entry 12) substituents may all be tolerated with no loss in selectivity for the derived cycloadducts.[14] Cycloadduct **5b** has been produced on multigram scale using 2.5 mol % of catalyst **2b**, indicating the preparative utility of the reaction.

The electron-withdrawing capability of the phosphonate group manifests itself when acyl phosphonates **3** undergo reaction with dienes. Specifically, when acyl phosphonate **3a** was treated with cyclopentadiene in the presence of complex **1b**, two products were obtained in quantitative yield (**10**/**11** = 35:65, eq 4). The expected



Diels−Alder adduct **10** was obtained as the minor product (*endo/exo* = 87:13, *endo* ee = 84%). Surprisingly, the major reaction product **11** was the result of an inverse electron demand hetero Diels−Alder reaction in which *cyclopentadiene acted as the dienophile in the cycloaddition process.* To our knowledge, this is the first example of cyclopentadiene behaving as the 2π component in a hetero [4π + 2π] reaction with an unsaturated carbonyl compound.[15] Enol phosphonate **11** was isolated as a single diastereomer in 95% ee, indicating that both cycloaddition processes are highly stereoselective.

Scheme 1[a]



[a] Key: (a) 10 mol % OsO_4, *N*-methylmorpholine *N*-oxide, *t*-BuOH/H_2O (10:1); (b) HCl(g)/MeOH, reflux; (c) pyridinium *p*-toluenesulfonate (cat.), 4:1 acetone/H_2O, reflux; (d) 5 mol % Sm(OTf)$_3$, MeOH, reflux.

The sense of asymmetric induction observed for all reported reactions catalyzed by the [Cu((*S*,*S*)-*tert*-Bu-box)](X)$_2$ complexes (**1**) is consistent with the intervention of catalyst−acyl phosphonate complex **12** in direct analogy to the related Diels−Alder imide-derived catalyst−dienophile complex **13**.[2] In contrast, we have no adequate model that rationalizes the sense of asymmetric induction for the analogous [Cu((*S*,*S*)-Ph-box)](X)$_2$ complexes (**2**).

The cycloadducts described in this study afford useful chiral synthons (Scheme 1). Upon treatment of **5** with protic (anhydrous HCl) or Lewis (Sm(OTf)$_3$) acid in MeOH, solvolysis of the lactol ethyl ether and decomposition of the intermediate enol phosphonate occurred to deliver acetal esters which, after brief treatment with aqueous acid (PPTS, acetone/H_2O), afforded aldehydic esters in good overall yield. Oxo esters **14a**−**c** are formally conjugate adducts of aldehyde enolates with β-substituted acrylates, a process for which no catalytic asymmetric variant exists. Bicyclic enol phosphonates were also transformed into useful compounds. Under the influence of catalytic quantities of Sm(OTf)$_3$ in MeOH, adduct **7a** was transformed to lactol methyl ether **15** in 91% yield. Alkoxy-substituted adduct **7d** undergoes a similar Lewis acid catalyzed solvolysis reaction, but undergoes elimination of EtOH to afford α,β-unsaturated ester **16**, formed exclusively as the *E* isomer, in 89% yield. The double bond in the cyclic enol phosphonate may also be manipulated. Reaction of cycloadduct **5a** under standard dihydroxylation conditions (cat. OsO_4, NMO, *tert*-BuOH/H_2O) afforded lactone **17** as a single diastereomer.

In summary, the stereoselective hetero Diels−Alder reaction between α,β-unsaturated acyl phosphonates and enol ethers catalyzed by C_2-symmetric Cu(II)bis(oxazoline) complexes reported in this study provides access to a range of useful bifunctional chiral synthons not readily accessible by other current reaction methodology.

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Supporting Information Available: Ligand syntheses, experimental procedures, spectral data for all compounds, and stereochemical proofs (16 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(12) Complex **2a** catalyzed the same reaction and gave the following ee−temperature profile: −78 °C, > 99:1 *endo/exo*, 94% ee; −20 °C, >99:1 *endo/exo*, 86% ee. At 25 °C, catalyst decomposition and low conversion (<40%) was observed.

(13) The optimal catalyst is reported for each particular reaction; however, we have observed that any of the four catalysts (**1** or **2**) will consistently catalyze the indicated cycloadditions in >80% ee. See the Supporting Information.

(14) The absolute configurations of **5a**−**c**, **7a**, and **10** were unambiguously determined either by X-ray crystallography or by correlation with structures of known configuration as described in the Supporting Information.

(15) For a hetero Diels−Alder reaction between an aryl imine and cyclopentadiene, see: Ishitani, H.; Kobayashi, S. *Tetrahedron Lett.* **1996**, *37*, 7357−7360.