C_2-Symmetric Cu(II) Complexes as Chiral Lewis Acids. Catalytic Enantioselective Michael Addition of Silylketene Acetals to Alkylidene Malonates

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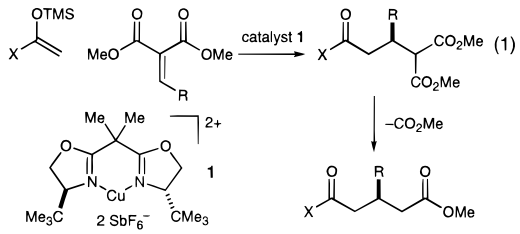
The conjugate addition of silylketene acetals and enolsilanes to α,β-unsaturated carbonyl derivatives, the Mukaiyama−Michael reaction, has been shown to be a mild, versatile method for carbon−carbon bond formation.[1] While the development of catalytic asymmetric variants of this process would provide access to chiral enantioenriched 1,5-dicarbonyl synthons, success in such endeavors has proven elusive.[2] C_2-symmetric bisoxazoline copper(II) complexes have been shown to be highly effective as chiral Lewis acids in such transformations as the Diels−Alder,[3] hetero Diels−Alder,[4] the Mukaiyama aldol,[5] and carbonyl ene reactions.[6] The unifying structural motif in these studies has been the presence of functional groups in the substrate capable of bidentate chelation to the metal center. We had two goals in initiating this study: to extend the range of substrates meeting this criterion and to develop a catalytic asymmetric Mukaiyama−Michael reaction of silylketene acetals to alkylidene malonates (Scheme 1, eq 1).[7] The alkylmalonate products of these reactions may be induced to undergo decarboxylation to afford differentiated chiral glutarate esters, a valuable set of chiral synthons.[8]

Initial experiments revealed that the [Cu((*S*,*S*)-*t*-Bu-box)]-$(SbF_6)_2$ complex **1**[9] (100 mol %) efficiently mediates the enantioselective addition of silylketene acetal **3**[10] to the phenyl-substituted alkylidene malonate **2a** (CH_2Cl_2, −78 °C) to give the expected adduct **4a** in 86% ee. However, attempts to render the process catalytic were unsuccessful, presumably as a consequence of the stability of the product Cu(II)−malonyl enolate complex.[11] After a number of strategies for promoting catalyst turnover were investigated, it was discovered that addition of 2 equiv of hexafluoro-2-propanol (HFIP) to the reaction mixture increased conversion from 10 to 40% (Table 1, entry 1).[12] Although catalyst turnover was achieved, conversion suffered due to competitive HFIP-induced hydrolysis of the silylketene acetal mediated by the copper catalyst. This side reaction could be minimized by the slow addition of the nucleophile (entry 2); however, this failed to provide a general solution.[13] Taking advantage of the limited solubility of HFIP at low temperatures, we found that an increase in the concentration of alkylidene malonate from 0.2 to 0.5 M resulted in an increase in conversion from 40 to 87% without recourse to a slow addition procedure (Table 1, entry 3). When the dielectric constant of the medium was lowered using a dichloromethane/toluene mixture complete conversion at 0.2 M concentration (entries 4 and 5) was observed. The use of toluene without a cosolvent led to slightly longer reaction times with no discernible benefits (entry 6).[14]

Scheme 1



A variety of β-substituted alkylidene malonates were examined in this reaction using the optimized conditions (Table 2). Aromatic substituents such as phenyl, 2-furyl, β-naphthyl and 3-indolyl provide high selectivities in the reaction, (entries 1−4). Ortho substitution on the aromatic ring is well-tolerated, with the *ortho*-anisyl substituent affording the addition product **4e** in 99% ee, (entry 5). Sterically demanding alkyl substituents are also well-tolerated. Cyclohexyl, isopropyl, and even *tert*-butyl alkylidene malonates all provide the addition products in enantioselectivities of 95, 93, and 90% respectively, (entries 6, 9, 10). Interestingly, the methyl-substituted derivative **2i** provides the addition adduct **4i** in only 43% ee with opposite facial selectivity, (entry 11). The reasons for this turnover in selectivity are not clear at this time. From a practical standpoint, it is important to note that the reaction can be conducted using lower catalyst loadings (5 mol %), (Table 2, entry 7). Under these conditions, the cyclohexyl alkylidene malonate **2f** provides a 99% yield of the addition product **4f** in 95% ee on a gram scale (Table 2, entry 8).[15] The absolute stereochemistry of the adducts was established by X-ray crystallography for **4a**, and by chemical correlation for **4e**, **4f**, **4g**, and **4i**. The other products were assigned by analogy.

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(10) For an analogy to the preparation of **3** see: Kuwajima, I.; Kato, M.; Sato, T. *J. Chem. Soc., Chem. Commun.* **1978**, 478−479.

(11) Trimethylsilyl trifluoromethanesulfonate (TMSOTf) was ineffective as an additive. For its effectiveness in promoting turnover in the Mukaiyama aldol reaction, see ref 5b.

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(13) Variation of the β-substituent on the alkylidene malonate necessitated reoptimization of addition times.

(14) The use of the cosolvent is preferred for reasons of operational simplicity. The catalyst cannot be formed in toluene, and although the dichloromethane can be removed once the catalyst is formed, we have found the mixed solvent system to be superior in certain cases likely owing to solubility issues. Full details of this work will be published in due course.

(15) Ligand recovery was 63%: see Supporting Information for details.

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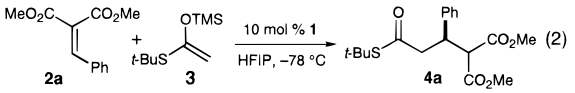
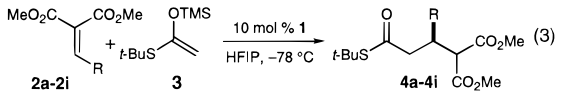
Table 1. Effect of Concentration and Solvent on Conversion in the Michael Reaction between **2** and **3** (eq 2)[a]



entry	concn (M)	solvent	conversion (%)[b]	ee (%)[c]
1	0.2	CH_2Cl_2	40	90
2	0.2	CH_2Cl_2	>98[d]	91
3	0.5	CH_2Cl_2	87	91
4	0.2	CH_2Cl_2/PhMe(1:1)	>98[e]	93
5	0.2	CH_2Cl_2/PhMe(1:3)	>98	93
6	0.2	PhMe	>98	92

[a] Reaction conducted with 2.2 equiv of **3** and 2 equiv of hexafluoro-2-propanol (HFIP) relative to **2**. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral HPLC (see Supporting Information). [d] Slow addition of **3** to the reaction over a period of 8 h. [e] Isolated yield is 88%.

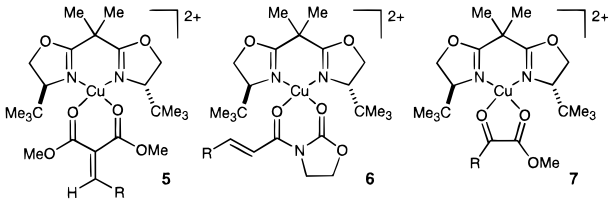
Table 2. Scope of the Catalyzed Michael Reaction between **2** and **3** (eq 3)[a]



entry	substrate	R	time (h)	yield (%)[b]	ee (%)[c]
1	**2a**	Phenyl	3	91	93
2	**2b**	2-Furyl	5	88	94
3	**2c**	2-Naphthyl	10	90	93
4	**2d**	3-Ts-Indolyl	48	99[d]	86
5	**2e**	2-MeOPh	12	92	99
6	**2f**	Cyclohexyl	5	95	95
7	**2f**	Cyclohexyl	12	96[e]	93
8	**2f**	Cyclohexyl	20	99[f]	95
9	**2g**	*i*-Pr	6	93	93
10	**2h**	*t*-Bu	8	89	90
11	**2i**	Methyl	5	91	−43

[a] Reaction conducted with 2.2 equiv of **3** and 2 equiv of hexafluoro-2-propanol (HFIP) relative to **2** in PhMe/CH_2Cl_2 (3:1). [b] Isolated yield. [c] Determined by chiral HPLC (see Supporting Information). [d] 20 mol % catalyst used and 2.5 equiv of **3** added. [e] Five mol % catalyst used. [f] Five mol % catalyst used on a 5-mmol scale.

At the outset of this investigation, it was not clear that the [Cu((*S*,*S*)-*t*-Bu-box)](2+) complex **1** would provide an effective facial bias upon binding the alkylidene malonate substrate since the prochiral carbon in the undergoing reaction lies along the C_2 axis of the chiral ligand. This is to be contrasted with the analogous complexes of unsaturated imides **6**, pyruvates, **7** (R = Me),



and glyoxylate esters **7** (R = H), that exhibit high levels of asymmetric induction in the Diels−Alder,[3a,3b] aldol,[5] and ene[5] reactions.

Direct evidence for the structure of the catalyst−alkylidene malonate complex **5** was obtained by single-crystal X-ray diffraction (Figure 1).[16] Interestingly, there is significant distortion in the alkylidene malonate−catalyst complex **5**. The chelated substrate forms a boat conformation with the copper atom at the apex.[17] This distortion of the bis(oxazoline) ligand out of the plane approximately defined by the coordinated ester carbonyls is probably essential for good levels of asymmetric induction. This represents the first crystallographic characterization of a substrate−bisoxazoline copper(II) complex and confirms our hypothesis[3−6] that the substrate binds to copper in a distorted square planar geometry in analogy to that observed in the X-ray structure of the analogous dihydrate complex [Cu((*S*,*S*)-*t*-Bu-box)$(H_2O)_2$]-

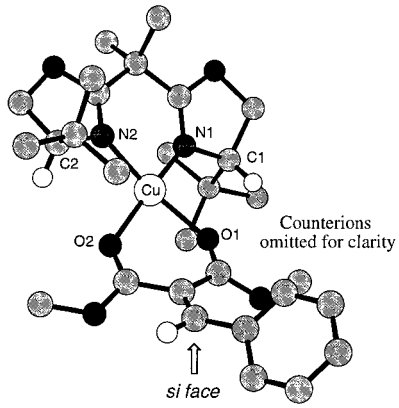
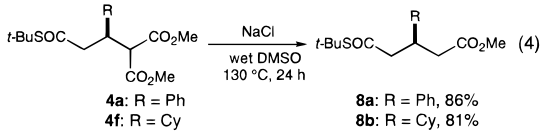


Figure 1. X-ray structure of [Cu(*t*-Bubox)·**2a**]$(SbF_6)_2$ (**5**). Selected bond lengths and angles: Cu−N1, 1.926 Å; Cu−N2, 1.955 Å; Cu−O1, 1.964 Å; Cu−O2, 1.950 Å; C1−N1−Cu−O1, 16.6°; C2−N2−Cu−O2, 7.0°.

$(SbF_6)_2$.[10] The sense of asymmetric induction is consistent with attack of the silylketene acetal nucleophile from the less hindered *si*-face of the complexed alkylidene malonate, the stereochemical outcome predicted from the crystal structure (Figure 1). In cases where the β-substituent (R) on the Michael acceptor is sterically demanding, we speculate that the trajectory of the nucleophilic addition could also be important in achieving asymmetric induction. As the nucleophile is forced to approach the Michael acceptor on a nonvertical trajectory to avoid nonbonding interactions with substituent (R), the ligand is able to provide π-facial discrimination since the nucleophile is now forced to interact with the two ligand substituents unequally.[18]

The malonate adducts readily undergo Krapcho decarboxylation[19] (NaCl, wet DMSO, 130 °C, 24 h) to afford the differentiated glutarate esters **8** in high yield, formally the conjugate adducts



of ester enolates and substituted acrylate esters (eq 4). As a demonstration of the orthogonality of the ester groups, oxidative hydrolysis (Br_2 or NBS in THF/H_2O)[20] of the thioester yields the corresponding free acid without interference from the methyl ester.

While space constraints do not permit a more detailed discussion of the role of alcohol addends in rendering the preceding process catalytic, it is noteworthy that this variant of the Mukaiyama−Michael reaction has now been generalized to two other processes that will be reported in due course.

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Supporting Information Available: Experimental procedures, spectral data for all compounds, crystallographic data, and stereochemical proofs (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) X-ray data for Cu(*t*-Bubox)·**2a**$(SbF_6)_2$: blue-green crystal, fw 1049.69, crystal system trigonal, space group $P3_2$, a = 12.9635(4) Å, b = 12.9635(4) Å, c = 20.4970(8) Å, α = 90°, β = 90°, γ = 120°, V = 2983.1(2) Å^3, Z = 3, R1 = 0.0397, wR2 = 0.0980, data/parameters = 7940/469, GOF = 1.019.

(17) For an X-ray structure of an alkylidene malonate bound to $TiCl_4$, see: Kakkonen, H. J.; Pursuiainen, J.; Pakkanen, T. A.; Ahlgrén, M.; Iiskola, E. *J. Organomet. Chem.* **1993**, *453*, 175−184.

(18) In a related case the impact of nonbonding interactions imposed by carbonyl substituents in diastereoselective carbonyl addition has previously been noted: (a) Heathcock, C. H.; Flippin, L. A. *J. Am. Chem. Soc.* **1983**, *105*, 1667−1668. (b) Heathcock, C. H. *Aldrichimica Acta* **1990**, *23*, 99−111.

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