Enantioselective Lewis Acid Catalyzed Michael Reactions of Alkylidene Malonates. Catalysis by C_2-Symmetric Bis(oxazoline) Copper(II) Complexes in the Synthesis of Chiral, Differentiated Glutarate Esters

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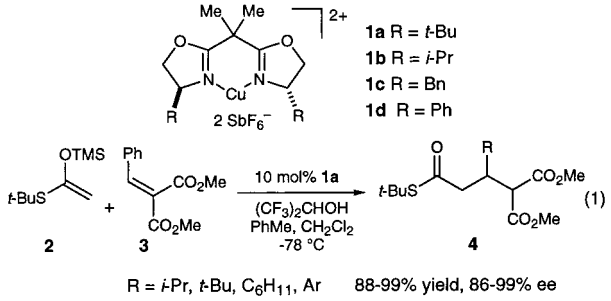
Abstract: C_2-symmetric bis(oxazoline)−Cu(II) complexes **1** catalyze the Mukaiyama Michael reaction of alkylidene malonates and enolsilanes. The use of hexafluoro-2-propanol is essential to induce catalyst turnover. High enantioselectivities are exhibited by bulky alkylidene malonate β-substituents using catalyst **1a**. The glutarate ester products are readily decarboxylated to provide chiral 1,5-dicarbonyl synthons. Crystallographic characterization of substrate−catalyst complexes provides insight into the binding event with these catalysts and affords a rationale for the observed facial selectivities.

Introduction

The increasing demand for efficient methods to control stereochemical relationships has mandated the development of catalytic asymmetric bond-forming reactions. Lewis acids have been documented to accelerate numerous bond-forming events, and hence efforts have been directed at developing chiral versions to control the overall process in an absolute sense. Recent reports from this laboratory and others have focused on the development of cationic bis(oxazoline)−Cu(II) complexes as chiral Lewis acids[1] in a variety of organic transformations including Diels−Alder,[2] hetero-Diels−Alder,[3] aldol,[4] Michael,[5] ene,[6] and enol amination[7] reactions. The Mukaiyama Michael reaction,[8] the addition of an enolsilane to an α,β-unsaturated carbonyl induced by a Lewis acid, is a particularly attractive target for development. Despite its importance, few methods have been reported for controlling this process in an absolute sense.[9] This report provides a full account of the development of the addition reactions of enolsilanes to alkylidene malonates catalyzed by the chiral copper complex **1a** (eq 1).



At the outset of this work, we speculated that the preorganization afforded by bis(oxazoline)−Cu(II) complexes **1** in

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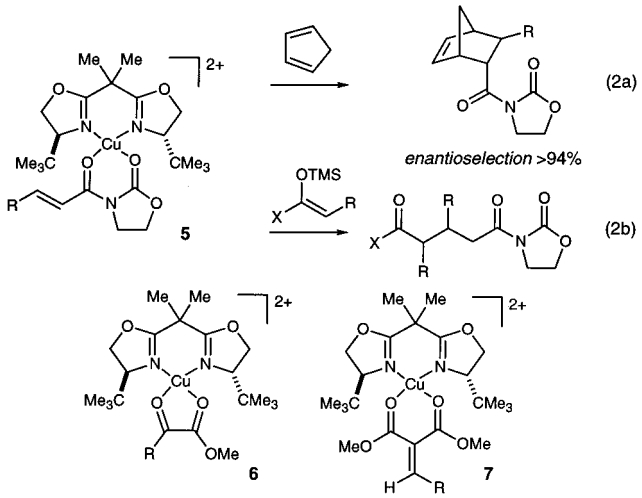
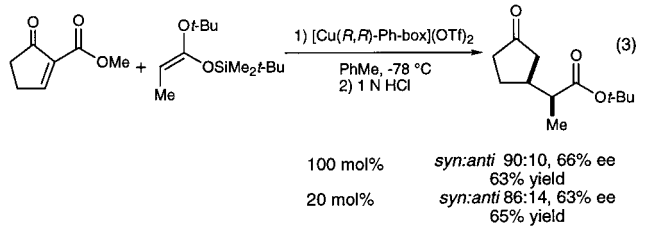


Figure 1. Binding motifs of 1,2 and 1,3 dicarbonyl substrates with bis(oxazoline)−Cu(II) complexes.

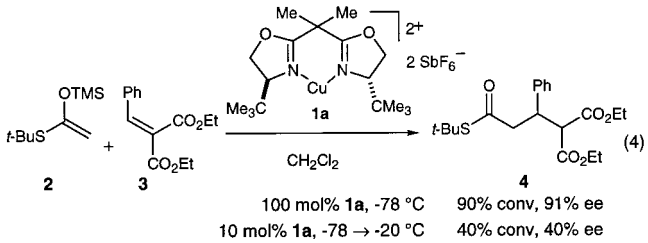
controlling π-facial discrimination in the Diels−Alder process (eq 2a) via substrate−catalyst complex **5** should be transferable to Michael reactions of enolsilanes (eq 2b). While this analogy has stimulated the development of these valuable addition processes,[5a] we have also explored the even more reactive alkylidene malonate Michael acceptors using this family of catalyst complexes.

It was felt that the enhanced reactivity of substituted alkylidene malonates might accommodate the inclusion of a wider range of β-substituents into the Michael acceptor. However, the analogies for asymmetric induction in this process are not well developed. While the unsaturated imide and α-keto ester−Cu(II) complexes **5** and **6** place the ligand chirality close to the prochiral centers in the bound reactants, the putative catalyst−substrate complex **7** positions the ligand some distance from the resident prochiral center in the Michael acceptor. However, conformational effects within the complex were not discounted as a potential element in the transmission of ligand chirality to the reaction.[10]

Concurrent with this investigation, Bernardi and Scolastico had shown that α-alkylidene keto esters undergo Michael addition with enolsilanes mediated by bis(oxazoline)−Cu(II) complexes.[11] This reaction is stoichiometric in Cu(II) complex, with one exception (eq 3). In another relevant investigation, Tietze has demonstrated that Lewis acid-mediated intramolecular allylsilane additions to alkylidene malonates are effectively controlled by an oxazolidinone auxiliary.[12]



Reaction Development. Initial addition reactions with the phenyl-substituted alkylidene malonates and enolsilane **2** in the presence of [Cu(*S*,*S*)-*t*-Bu-box](SbF$_6$)$_2$ revealed that the stoichiometric process provides the Michael adduct in 91% ee (90% conversion) (eq 4); however, under catalytic conditions, no turnover is observed. Upon warming the reaction mixture to −20 °C, the adduct is formed (40% conversion) with a significant decrease in selectivity (40% ee). A number of literature reports have appeared documenting the dramatic impact of alcoholic additives on catalyst turnover[13] and work within our group had shown that these Cu(II) catalysts retain their activity in the presence of such addends.[14] Accordingly, we evaluated a number of alcohols in an attempt to promote reaction turnover (Table 1). As the data indicate, enantioselectivities increase significantly in the presence of alcoholic additives, suggesting that turnover in their absence was due to the intervention of a second, less selective pathway.



Hexafluoro-2-propanol (HFIP) proved to be the most efficient alcohol in promoting turnover in this reaction. However, considerable starting alkylidene malonate still remained. We speculated that the enolsilane was being competitively hydrolyzed during the course of the reaction. To test this hypothesis, the reaction of enolsilane **2** and HFIP in CH_2Cl_2 (−78 °C) was monitored by in situ IR spectroscopy (eq 6a). No change was observed over the course of 1 h. Upon addition of complex **1a** to this solution, the immediate appearance of the carbonyl stretch of *tert*-butylthioacetate (1675 cm^{-1}) was noted and complete hydrolysis of the enolsilane was observed within 40 min at −78 °C. This suggests that coordination of HFIP to the Lewis acid is required to produce a species acidic enough to decompose the enolsilane.[15] This hypothesis was validated by the observation that 2-propanol leads to *faster* hydrolysis (and lower conversion to product) than the more acidic HFIP, despite the significant difference in the pK_a's of these two alcohols (30.3 vs 17.9 in DMSO,[16] respectively). We suggest that, in the presence of complex **1a**, the pK_a of 2-propanol is effectively lower because of the higher equilibrium constant between bound alcohol (**1a·ROH**) and free alcohol (eq 6b).

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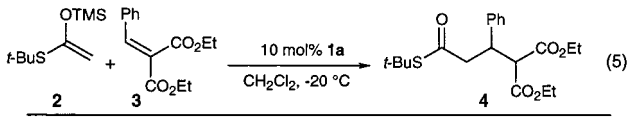
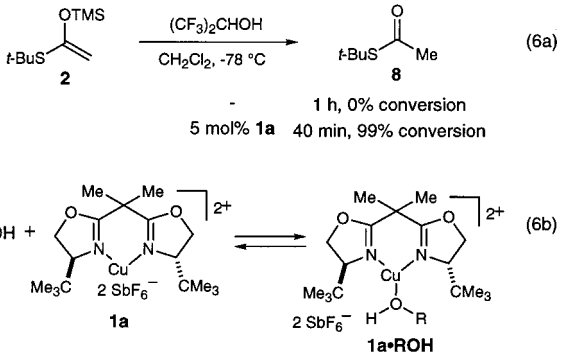
Table 1. Effect of Additives on the Michael Reaction of **2** and Benzylidene Malonate **3**[a]



entry	additive	conversion(%)[b]	% ee[c]
1	none	40	40
2	*i*-PrOH	15	90
3	$(CF_3)_2CHOH$	70	84
4	$(CF_3)_2CCH_3OH$	40	82
5	phenol	60	85

[a] Enolsilane (2 equiv) added to a solution of substrate, catalyst and additive (1.5 equiv). [b] Determined by ^1H NMR. [c] Enantiomeric excess determined by HPLC on Chiralcel AD column. (**1a**): [Cu(*S,S*)-*t*-Bu-box]$(SbF_6)_2$.



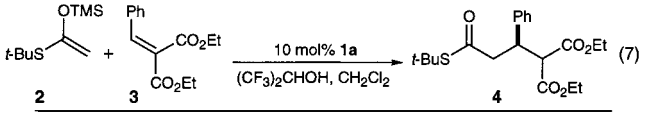
In an attempt to minimize enolsilane decomposition, we investigated the use of a slow addition procedure. Syringe pump addition of the enolsilane to a catalyst−malonate mixture over the course of 10 h at −20 °C resulted in complete conversion to product (entry 2 in Table 2) affording the Michael adduct in 89% ee. This reaction was also conducted at a lower temperature with the aim of improving selectivities. Unfortunately, this strategy proved untenable as slow addition over 18 h was insufficient to achieve complete conversion.[17]

Ester Gearing. At the outset of this study, it was not evident how the bis(oxazoline)−Cu(II) complex **7** might impart π-facial selectivity to the alkylidene malonate acceptors. Examination of models (PM3) of alkylidene malonate−copper complexes provided little insight into the potential origins of π-facial selectivity (Figure 1). In one possible option, it was speculated that the ligand substituents might influence the conformation of the ester substituents thereby relaying the influence of the chiral ligand closer to the reaction center, Figure 2. As such, an increase in the size of this substituent might lead to an increase in reaction enantioselectivity. Correspondingly, a smaller ester should lead to lower selectivity if this "gearing premise" is valid.

To test this gearing hypothesis, a number of benzylidene malonates with varying ester substituents were synthesized. When these substrates were subjected to the catalyzed reaction at ambient temperature, the Michael adduct was formed in good yield (Table 3). Enantioselectivity increases as a function of increasing ester size. Isopropyl esters reverse this trend while the bulky *tert*-butyl esters proved to be unreactive under these conditions. Upon cooling this reaction to −20 °C, however, we

(17) Addition times varied between 8 and 16 h. Changing the substrate required reoptimization of addition times. Alkylidene malonate **10i** proved resilient to this protocol, affording only 55% conversion under the optimized addition time of 16 h. We suggest that the bulk of this substrate is responsible. From this and other data, we concluded that slow addition would prove insufficient as a general solution.

Table 2. Slow Addition of Nucleophile Increases Turnover[a]



entry	addn time (h)[b]	temp (°C)	conv (%)[c]	% ee[d]
1	0	-20	70	84
2	10	-20	>98	89
3	10	-40	30	92
4	18	-40	90	93

[a] Enolsilane added to a solution of substrate, catalyst, and additive. [b] Addition time for delivery of enolsilane **2** to reaction flask via syringe pump. [c] Conversion determined by ^1H NMR. [d] Enantiomeric excess determined by HPLC using a Chiralcel AD column. (**1a**): [Cu(*S,S*)-*t*-Bu-box]$(SbF_6)_2$.

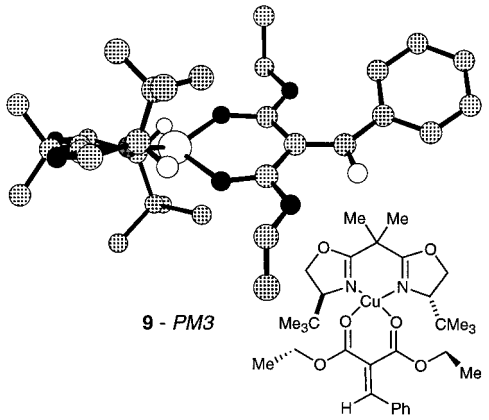
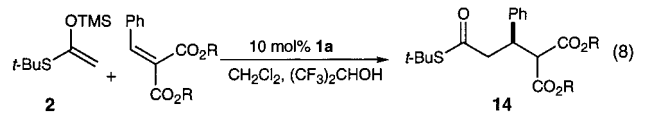


Figure 2. PM3 model of [Cu(*S,S*)-*t*-Bu-box]·**3** $(X)_2$ illustrating a predicted gearing of the ester group by the ligand substituent.

Table 3. Effect of Ester Substituent on the Michael Reaction of **2** and Benzylidene Malonates

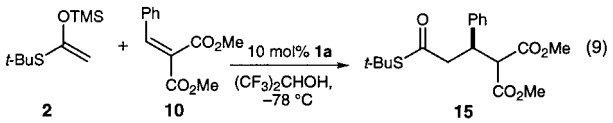


		% ee (% conversion)[a]		
entry	R	25 °C[b]	-20 °C[c]	-78°C[d]
1	Me (**10**)	60 (>98)	78 (>98)	91 (>98)
2	Et (**3**)	70 (>98)	88 (>98)	93 (30)
3	*i*-Bu (**11**)	79 (70)	88 (50)	94 (24)
4	*i*-Pr (**12**)	58 (80)	-	-
5	*t*-Bu (**13**)	NR	-	-

[a] Enantiomeric excesses were determined by chiral HPLC using a Chiralcel AD column. [b] Enolsilane added to substrate, catalyst, and alcohol over the course of 1−15 s. [c] Enolsilane added to substrate, catalyst, and alcohol over the course of 10 h. [d] Enolsilane added to substrate, catalyst, and alcohol over 16 h. (**1a**): [Cu(*S,S*)-*t*-Bu-box]$(SbF_6)_2$.

noted that the ethyl and isobutyl esters provide the Michael adduct in identical enantioselectivity, despite the significant difference observed between these two substrates at ambient temperature. Furthermore, the bulkier isobutyl ester provides the Michael adduct in lower conversion even with slow addition of enolsilane. Accordingly, it was concluded that enantioselectivities in these reactions were governed by factors other than ester size and that the gearing hypothesis could not account for the observed selectivities at lower temperatures. As such, we wondered whether the methyl ester could provide the conjugate adduct in equivalent selectivities as the larger esters at a lower temperature. This was particularly attractive because conversion using the smaller ester was invariably higher under identical conditions. Indeed, at −78 °C, the methyl ester affords the

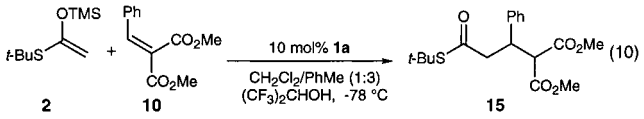
Table 4. Effect of Solvent and Concentration on the Michael Reaction of **2** and Benzylidene Malonates[a]



entry	solvent	concentration[b]	conv (%)[c]	% ee[d]
1	CH_2Cl_2	0.2 M	40	90
2	CH_2Cl_2	0.5 M	87	91
3	CH_2Cl_2/PhMe (1:1)	0.2 M	99	93
4	CH_2Cl_2/PhMe (1:3)	0.2 M	99	93
5	PhMe	0.2 M	99	92

[a] Enolsilane added to a solution of substrate, catalyst, and additive. [b] In substrate. [c] Determined by ^{1}H NMR. [d] Enantiomeric excess determined by HPLC. (**1a**): [Cu(*S*,*S*)-*t*-Bu-box]$(SbF_6)_2$.

Table 5. Catalyst Survey[a]



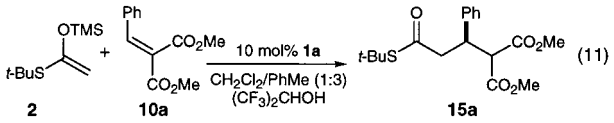
entry	R	% conversion[c]	% ee(config)[d]
1	CMe_3	99	93 (*R*)
2	$CHMe_2$	34	41 (*R*)
3	Bn	55	60 (*R*)
4	Ph	99	52 (*S*)

[a] Enolsilane added to a solution of substrate, catalyst, and additive. [b] In substrate. [c] Determined by ^{1}H NMR. [d] Enantiomeric excess determined by HPLC. Absolute configuration determined by X-ray crystallography. (**1a**): [Cu(*S*,*S*)-*t*-Bu-box]$(SbF_6)_2$.

Michael adduct in 91% ee and quantitative conversion. Under identical conditions, the ethyl and isobutyl esters exhibited little reaction.

Solvent Polarity. During the course of these investigations, it was noted that hexafluoro-2-propanol is sparingly soluble in CH_2Cl_2 at low temperatures. Since the success of the slow addition procedure was presumably due to a reduction in the rate of the destructive enolsilane hydrolysis by maintaining a low local concentration of one of the reactants, we wondered whether we could take advantage of the solubility properties of HFIP to lower its concentration in solution relative to the other reagents, thus favoring the productive Michael pathway (Table 4). A decrease in the amount of solvent used and, hence, an increase in the concentrations of electrophile, nucleophile, and catalyst resulted in a significant increase in conversion to 87% (0.5 M vs 0.2 M in substrate). The use of a less polar reaction medium (CH_2Cl_2/PhMe mixtures, entries 3 and 4 in Table 4) resulted in complete conversion to product at 0.2 M concentration. Reactions in toluene afford no discernible benefits. Therefore, given that the active catalyst must be made in CH_2Cl_2, the mixed solvent system was chosen for further development. With the optimized reaction conditions in hand, the effect of ligand architecture on the reaction of enolsilane **2** and benzylidene malonate **10** (Table 5) was investigated. *tert*-Butyl bis(oxazoline) proved to be the optimal ligand for copper(II) in this reaction. It is interesting that the copper complex derived from phenyl bis(oxazoline) provides the Michael adduct of opposite configuration. This effect had previously been observed in several other reactions.[3a−c,h,6a] Although various rationales have been advanced to account for this reversal (vide infra), it remains an unresolved issue in the field. As will be discussed below, some insight into this effect has been gained from crystallographic studies of catalyst−substrate complexes.

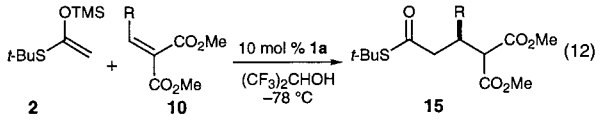
Table 6. Temperature Profile[a]



entry	temperature (°C)	% conversion[b]	% ee[c]
1	-78	99	93
2	-60	99	88
3	-30	99	84
4	0	67	79
5	25	46	68

[a] Enolsilane added to a solution of substrate, catalyst, and additive. [b] Determined by ^{1}H NMR. [c] Enantiomeric excess determined by HPLC. (**1a**): [Cu(*S*,*S*)-*t*-Bu-box]$(SbF_6)_2$.

Table 7. Scope of the Catalyzed Michael Reaction between **2** and **10**: Aryl Substituents (Eq 12)[a]



entry	R	time (h)	yield (%)[b]	ee (%)[c]
1	Phenyl (**a**)	3	91	93
2	2-Furyl (**b**)	5	88	94
3	1-Naphthyl (**c**)	16	82	0
4	2-Naphthyl (**d**)	10	90	93
5	3-Ts-Indolyl (**e**)	48	99[d]	86
6	2-MeOPh (**f**)	12	92	99

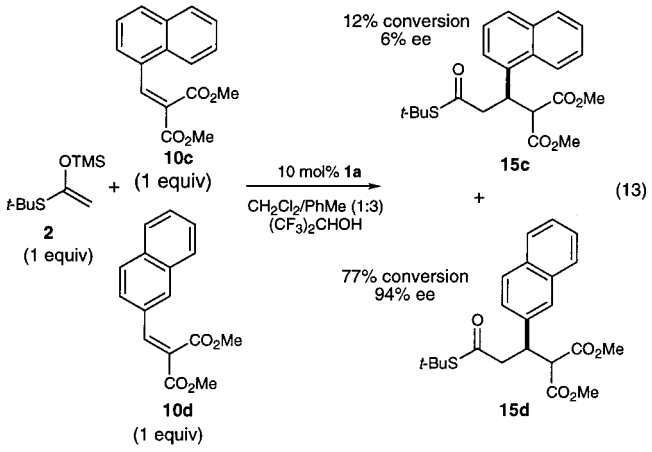
[a] Reaction conducted with 2.2 equiv of **2** and 2 equiv of hexafluoro-2-propanol (HFIP) relative to **10** in PhMe/CH_2Cl_2 (3:1). [b] Isolated yield. [c] Determined by chiral HPLC (see Supporting Information). Absolute configuration as indicated. [d] 20 mol % catalyst used and 2.5 equiv of **2** added. (**1a**): [Cu(*S*,*S*)-*t*-Bu-box]$(SbF_6)_2$.

The temperature profile of this reaction reveals descending selectivity with ascending temperature. However, conversion does not respond linearly to temperature (Table 6). At temperatures above −30 °C, the reaction does not proceed to completion. We believe this supports our assertion of the importance of alcohol solubility to the success of this process.

Electrophile Scope. A variety of alkylidene malonates were evaluated as substrates. The reaction affords high enantioselectivities for aryl (phenyl = 93% ee, 2-methoxyphenyl = 99% ee, 2-naphthyl = 93% ee) and heteroaryl (2-furyl = 94% ee, 3-indolyl = 86% ee) alkylidene malonates, Table 7. 1-Naphthyl alkylidene malonate proved to be nonselective (0−5% ee) under these conditions for reasons that remain unclear (entry 3). To evaluate relative reactivity of this substrate with the related 2-naphthyl alkylidene malonate, 1 equiv of enolsilane and a 1:1 mixture of these two alkylidene malonates (**10c** and **10d**) were subjected to 10 mol % catalyst under the standard reaction conditions in a competition experiment (eq 13). 2-Naphthyl alkylidene malonate provides the Michael adduct in 77% conversion with 94% ee, while 1-naphthyl alkylidene malonate affords only 12% conversion and 6% ee product.

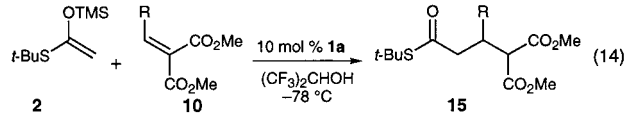
Branched alkyl substrates also give Michael adducts in high enantioselectivity (cyclohexyl = 95% ee, isopropyl = 93% ee, *tert*-butyl = 90% ee, Table 8). This reaction proceeds with equal facility at lower catalyst loading (5 mol %, entry 2) and on a 1-g scale (entry 3), affording adducts in 95% ee and quantitative yield. Unbranched alkyl substrates are far less effective as substrates in this reaction. Ethylidene malonate gives the Michael adduct in only 43% ee. In an attempt to delineate the limits of acceptable substitution patterns, alkyl substituents

intermediate in size between methyl and isopropyl were screened. Each substrate examined afforded lower enantioselectivities than methyl itself (ethyl = 22% ee, *n*-propyl = 27%



ee, isobutyl = 33% ee). We speculated that the absolute stereochemistry of the Michael adduct derived from benzylidene

Table 8. Scope of the Catalyzed Michael Reaction between **2** and **10**: Alkyl Substituents (Eq 14)

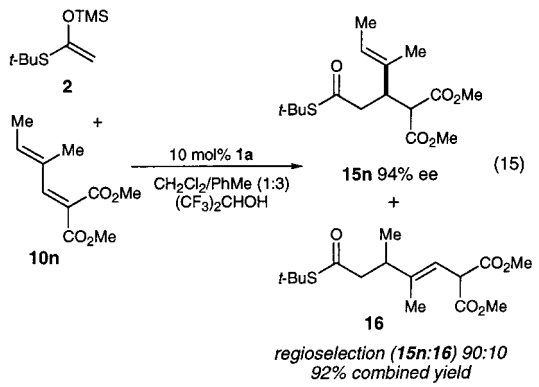


entry	R	time (h)	yield (%)[b]	ee (%)[c]
1	cyclohexyl (**g**)	5	95	95(*S*)
2	cyclohexyl (**g**)	12	96[d]	93(*S*)
3	cyclohexyl (**g**)	20	99[e]	95(*S*)
4	isopropyl (**h**)	6	93	93(*S*)
5	*t*-butyl (**i**)	8	89	90(*R*)
6	methyl (**j**)	5	91	43(*S*)
7	ethyl (**k**)	5	82	22
8	*n*-propyl (**l**)	5	87	27
9	isobutyl (**m**)	8	99[f]	33

[a] Reaction conducted with 2.2 equiv of **2** and 2 equiv of hexafluoro-2-propanol (HFIP) relative to **10** in PhMe/CH_2Cl_2 (3:1). [b] Isolated yield. [c] Determined by chiral HPLC (see Supporting Information). Configuration provided in parantheses, where assigned. [d] 5 mol % catalyst used. [e] 5 mol % catalyst used on a 5-mmol scale. [f] Conversion (as determined by ^{1}H NMR). (**1a**): [Cu(*S*,*S*)-*t*-Bu-box](SbF_6)$_2$.

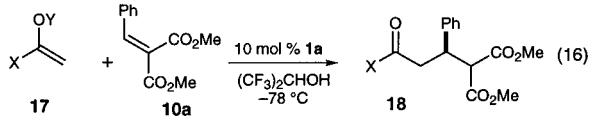
and ethylidene malonate corresponded to opposite facial attack by the nucleophile. As such, substituents larger than methyl would, in principle, provide selectivities intermediate between phenyl (+93) and methyl (−43). Indeed, this proved to be the case (vide infra).

One dienic ester was also evaluated (eq 15). With such



substrates, the reaction is potentially complicated by competing

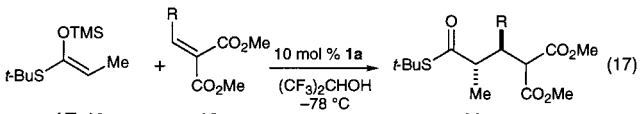
Table 9. Variation of the Nucleophile in the Catalyzed Michael Reaction between **17** and **10** (Eq 16)[a]



entry	substrate	X	Y	conv (%)[b]	ee (%)[c]
1	**17a**	*t*-Bu	TMS	15	58
2	**17b**	Ph	TMS	50	34
3	**17c**	S-Ph	TMS	60	73
4	**17d**	S-*t*-Bu	TES	10	92

[a] Reaction conducted with 2.2 equiv of **17** and 2 equiv of hexafluoro-2-propanol (HFIP) relative to **10a** in CH_2Cl_2. [b] Determined by ^{1}H NMR of the unpurified reaction mixture. [c] Determined by chiral HPLC on a Chiralcel AD column. Configuration assigned by analogy. [d] Reaction conducted at −50 °C with slow addition of nucleophile (16 h). (**1a**): [Cu(*S*,*S*)-*t*-Bu-box](SbF_6)$_2$.

Table 10. Diastereoselectivity in the Michael Reaction of Propionate Enolsilane and Alkylidene Malonates (Eq 17)[a]



entry	substrate	*E*:*Z*[b]	R	*anti*:*syn*[c]	ee (%)[d]
1	**10a**	97:3	Ph	55:45	<5/<5
2	**10a**	5:95	Ph	92:8	80/70
3	**10j**	97:3	Me	95:5	68/30
4	**10j**	5:95	Me	29:71	10/62

[a] Reaction conducted with 2.2 equiv of **19** and 2 equiv of hexafluoro-2-propanol (HFIP) relative to **10** in CH_2Cl_2. [b] Ratio of enolsilane geometry. [c] Determined by ^{1}H NMR of the unpurified reaction mixture. [d] Determined by chiral HPLC on Chiralcel OJ and AD columns. Absolute configuration not assigned. (**1a**): [Cu(*S*,*S*)-*t*-Bu-box](SbF_6)$_2$.

1,4- and 1,6-addition pathways. The tiglic aldehyde-derived alkylidene malonate **10n** affords high yields of the Michael adduct. The regioselectivity of the addition was found to be 90:10 in favor of the 1,4 product which was formed in 94% ee and good yield (eq 15).

Nucleophile Scope. In an effort to expand the scope of acceptable nucleophiles, we examined the reaction of a number of unsubstituted ketone-derived enolsilanes. Within this series, pinacolone- and acetophenone-derived enolsilanes were less reactive[18] and considerably less selective. *S*-Phenyl thioester derived enolsilane was also less selective than the *S*-*tert*-butyl thioacetate analogue illustrating the importance of steric hindrance at that position. We briefly examined the effect of the silyl moiety (entry 4) and found that TES enolsilane derived from *S*-*tert*-butyl thioacetate, while very selective at a slightly higher temperature,was not amenable to catalyst turnover. Diastereoselective Michael reactions were examined using propionate-derived enolsilanes. Selectivities were found to depend significantly on enolsilane geometry. Benzylidene malonate **10a** afforded anti-Michael adduct with either the (*E*) or (*Z*) enolsilane, but only the latter was selective (92:8 vs 55:45). Enantioselectivity in this reaction is moderate, providing the anti diastereomer in 80% ee. The results with ethylidene malonate were complementary: (*E*) enolsilane affords a highly anti-selective Michael adduct (95:5) while the (*Z*) enolsilane leads to poor syn selectivity (71:29).

Stereochemical Models. The departure from previously exploited binding motifs (**5** and **6** in Figure 1) necessitated the

(18) Mayr, H.; Patz, M. *Angew. Chem., Int. Ed.* **1994**, *33*, 938.

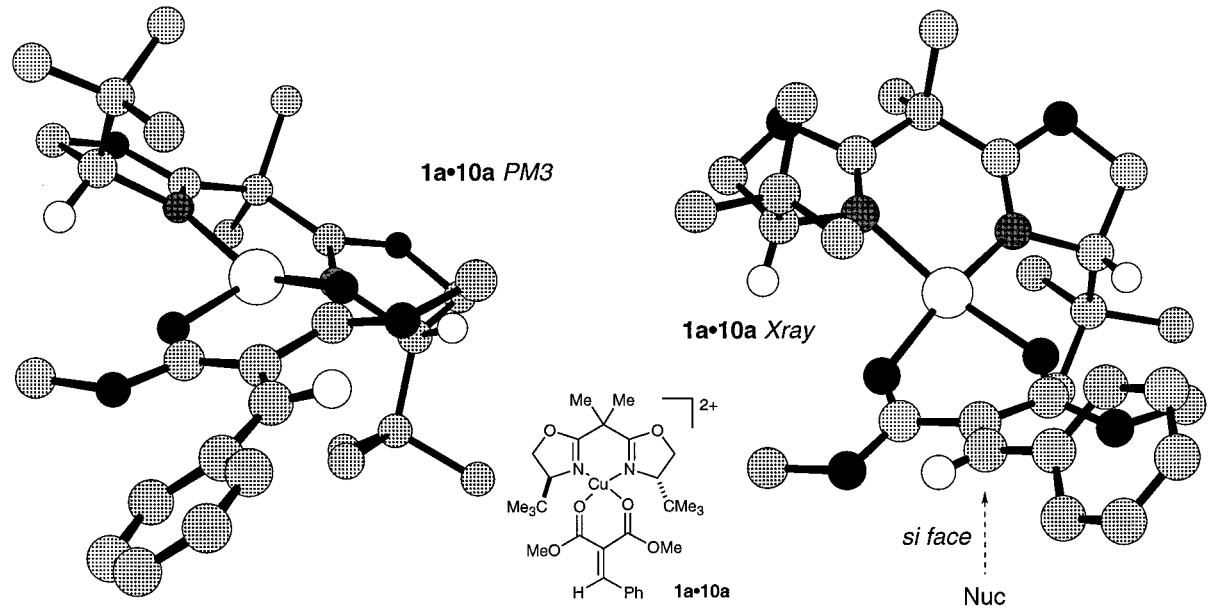
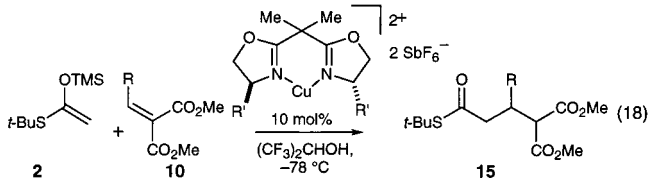


Figure 3. PM3 model and X-ray structure of [Cu(*S*,*S*)-*t*-Bu-box](SbF$_6$)$_2$ complex **1a** with alkylidene malonate **10a** (counterions omitted for clarity).

development of a new model to explain the observed product stereochemistry. PM3-level calculations predicted a complex devoid of obvious steric impediment to incoming nucleophiles from either face of the coordinated alkylidene malonate complex (Figure 3).[19] Fortuitously, attempts to induce the formation of X-ray-quality crystals of substrate−catalyst complexes were successful. The crystal structure provided considerable impetus for the development of a stereochemical model.

The crystal structure of {Cu[(*S*,*S*)-*t*-Bu-box](**10a**)}(SbF$_6$)$_2$ (**1a·10a**) depicted in Figure 3 is the first crystallographically characterized bis(oxazoline)−Cu(II) complex containing a bound substrate. It provides evidence in support of our hypothesis[1] that substrates bind to this complex in a distorted square-planar geometry analogous to the coordination geometry observed in the aquo complex {Cu[(*S*,*S*)-*t*-Bu-box](OH$_2$)$_2$}(SbF$_6$)$_2$.[20] The magnitudes of the O−Cu−N−C dihedral angle distortions are different for the alkylidene malonate complex than that observed in the dihydrate crystal structure (13.6 and 17.4° vs 29.3 and 30.4°, respectively). In contrast to the PM3 model, the crystal structure depicts the alkylidene malonate as being significantly distorted from planarity in the metal−substrate complex. The six-membered ring formed by the dicarbonyl, alkene carbon, and copper atom is in a boat conformation with the alkene carbon and metal at the apexes.[21] The ligand sits preferentially on one face of the olefin, positioning the β-phenyl substituent in the substrate away from the proximal *tert*-butyl substituent on the ligand. A small pyramidalization of the α-carbon of the olefin (3°) is noted in this structure. A similar pyramidalization has been used to rationalize facial selectivity in an auxiliary-controlled alkylidene malonate Diels−Alder reaction.[22] Pyramidalization has also been invoked to explain diastereoselectivity in chiral dioxolenone functionalization.[23] While it is hazardous to extrapolate from solid state to solution structures, it should be noted that the sterically more accessible face of the prochiral carbon in **1a·10a** (Figure 3) correlates with the stereochemical outcome of the Michael adducts themselves. In an attempt to optimize Michael additions to *n*-alkyl-substituted alkylidene malonates, we examined their reactions with enolsilane **2** in the presence of varying bis(oxazoline) copper(II) catalysts. A comparison of benzylidene malonate and several alkylidene malonates (Me, *n*-Pr, *i*-Bu) in the presence of *t*-Bu, Ph, *i*-Pr, and Bn bis(oxazoline)−Cu(II) catalysts is illustrated in Table 11. The results varied as illustrated above: *t*-Bu-box was optimal for benzylidene malonate (93% ee), *i*-Pr-box for ethylidene malonate (50% ee), and Ph-box was best for malonates **10l** and **10m** (43% and 72% ee), respectively. It is significant that facial selectivities exhibited by *i*-Pr- and Bn-box are always identical, similar to *t*-Bu-box with **10a** and **10l** and with Ph-box for **10j** and **10m**. Ph-box and *t*-Bu-box *always* display opposite facial selectivity.

Table 11. Correlation of Ligand Substituents with Selectivity (Eq 18)[a]



			% ee for R'[b]			
entry	substrate	R	CMe_3	Ph	$CHMe_2$	Bn
1	**10a**	Ph	93	-52	41	60
2	**10j**	Me	44	-40	-50	-40
3	**10l**	*n*-Pr	27	-43	21	14
4	**10m**	*i*-Bu	33	-72	-36	-24

[a] Reaction conducted with 2.2 equiv of **2** and 2 equiv of hexafluoro-2-propanol (HFIP) relative to **10** in PhMe/CH_2Cl_2 (3:1). [b] Enantioselectivity afforded by ligand−Cu complex. Determined by chiral HPLC (see Supporting Information).

(19) Geometry optimizations were performed at the PM3(tm) level using the Spartan Semiempirical Program 5.0 (Wavefunction Inc., Irvine, CA 92612) on a Silicon Graphics Impact 10000 (195 MHz, 128 M RAM) running IRIX 6.2. Calculations were performed without counterions or solvent using the following parameters: optcycle = 5000, maxcycle = 10000, charge = 2, multiplicity = 2. Calculations converged (energy difference between cycles <0.0005 kcal/mol) in ≤4 h CPU time.

(20) Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541.

(21) This is not suprising considering that this ring needs to accommodate five 120° angles (C−C−O, C−C−C, and C−O−Cu), one 90° angle (square planar Cu), and two long bonds (2.0 Å, Cu−O). Indeed, a molecular mechanics geometry optimization of this ring alone predicts an identical conformation despite the failure of PM3 to do likewise.

(22) Katagiri, N.; Watanabe, N.; Sakaki, J.-i.; Kawai, T.; Kaneko, C. *Tetrahedron Lett.* **1990**, *31*, 4633.

(23) Seebach, D.; Zimmermann, J.; Gysel, U.; Ziegler, R.; Ha, T.-K. *J. Am. Chem. Soc.* **1988**, *110*, 4763.

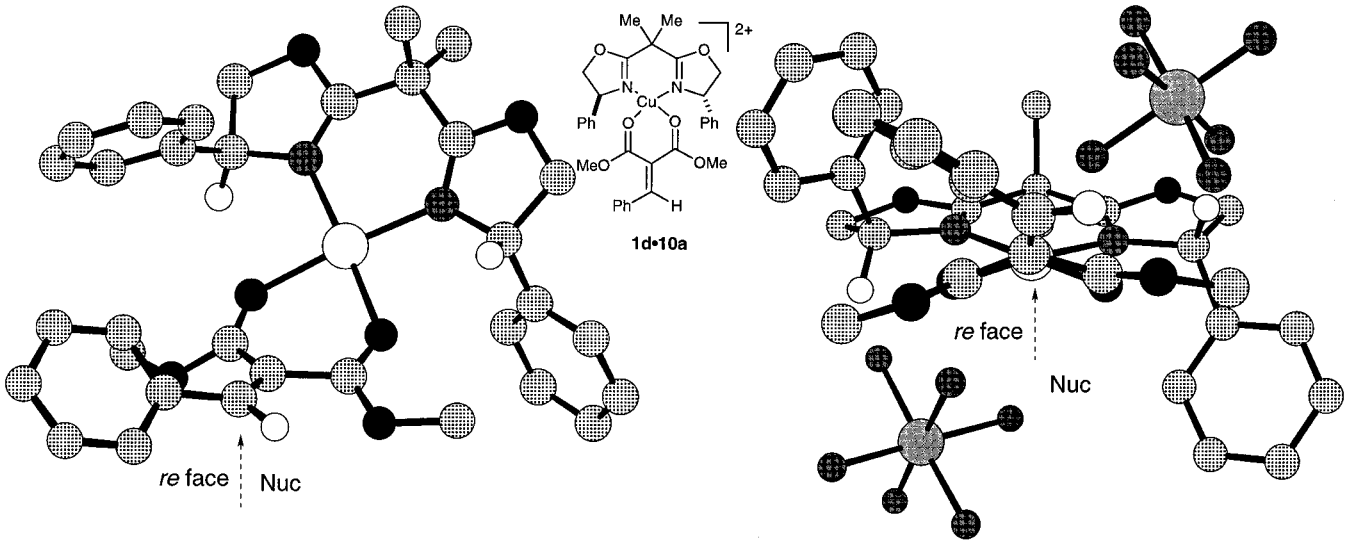


Figure 4. Two views of the X-ray crystal structure of the [Cu(*S,S*)-Ph-box]$(SbF_6)_2$ complex of malonate **10a** (counterions omitted in the left view for clarity).

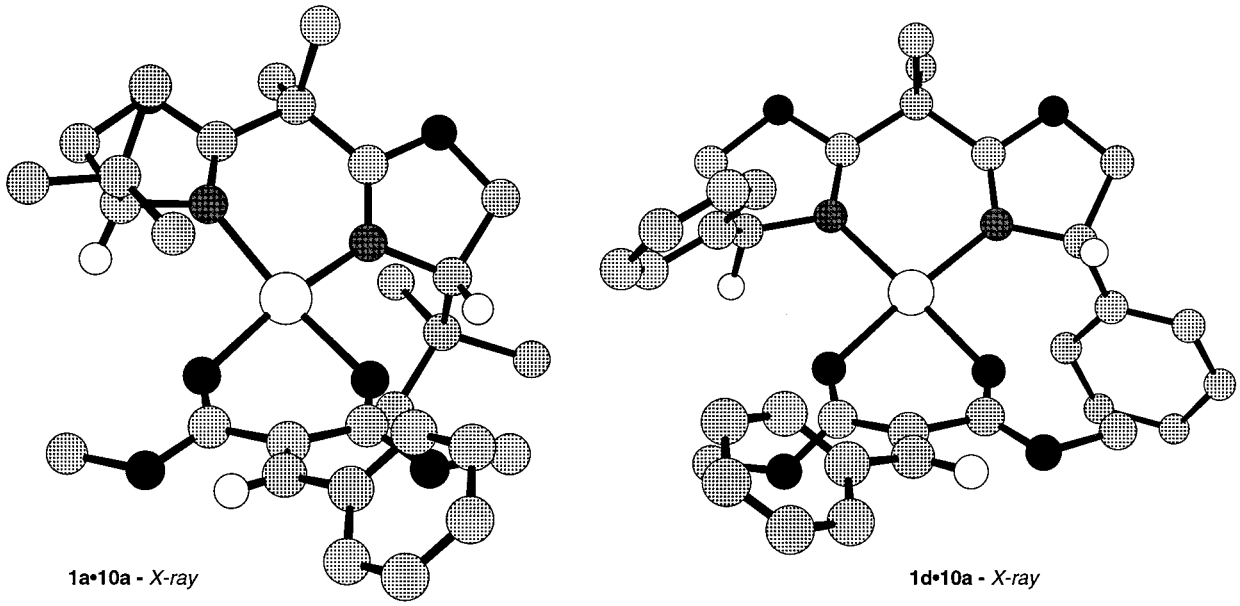


Figure 5. Comparison of the X-ray crystal structures of [Cu(*S,S*)-*t*-Bu-box]$(SbF_6)_2$ and [Cu(*S,S*)-Ph-box]$(SbF_6)_2$ complexes of malonate **10a**.

As mentioned previously, the reversal of facial selectivity exhibited by *t*-Bu-box and Ph-box Cu(II) complexes is an unsolved problem in this field and has been observed in the ene[3h,6c] and hetero-Diels−Alder[3c] reactions. The primary rationale that has been posited to account for this observation involves a change in geometry of the catalyst−substrate complex from distorted square planar to tetrahedral.[24] This proposal is unsatisfying in the face of structural and circumstantial evidence against this metal geometry.[25] We speculated that there could be a structural difference in the solid-state geometries of catalyst−substrate complexes of *t*-Bu-box and Ph-box, which may provide some insight into π-facial discrimination in these reactions. Suitable X-ray-quality crystals of malonate bound to [Cu(*S,S*)-Ph-box]$(SbF_6)_2$ complex were obtained from pentane/dichloromethane solution; the structure is illustrated in Figure 4.

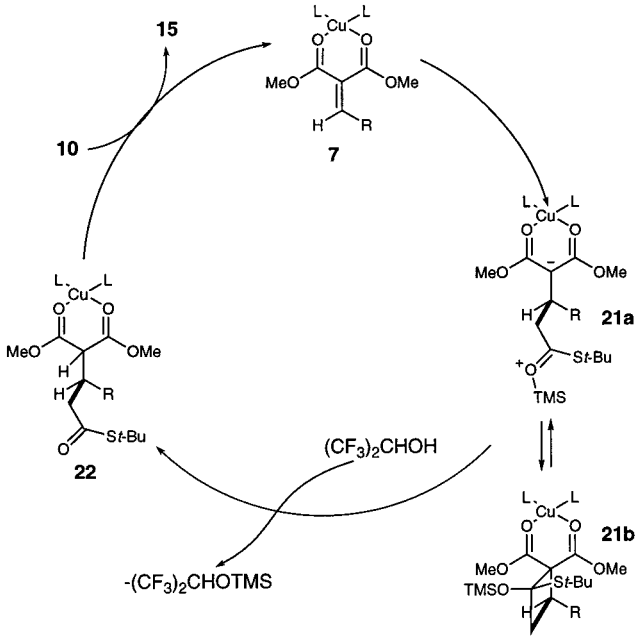
The crystal structure of [Cu(*S,S*)-Ph-box(**10a**)]$(SbF_6)_2$ (**1d·10a**) reveals a distorted octahedral geometry at the copper center with each SbF_6 counterion in a weak bonding interaction (2.35 and 2.65 Å). The metal geometry and counterion contact distances correlate well with the crystal structure of the corresponding dihydrate, suggesting that this may be a general phenomenon for these complexes.[14a] The dicarbonyl is bound in the equatorial plane with a small distortion (1.4 and 2.3°) from the N−Cu−N plane. The β-phenyl substituent is bent toward the phenyl group on the ligand backbone, thereby exposing the convex *re* face toward nucleophilic attack. This corresponds to facial selectivity complementary to that exhibited by the crystal structure of {Cu[(*S,S*)-*t*-Bu-box](**10a**)}$(SbF_6)_2$ complex (vide supra). The source of this turnover is unclear. It is tempting to invoke an edge−face interaction between the alkylidene malonate phenyl group and the ligand substituent, validated by a reasonable ortho hydrogen−arene centroid distance of ~3.1 Å and a centroid−centroid distance of 5.4 Å.[26] However, turnover between the Ph-box and *t*-Bu-box catalysts is observed with both aryl and alkyl alkylidene malonates

(24) (a) Johannsen, M.; Yao, S.; Graven, A.; Jørgensen, K. A. *Pure Appl. Chem.* **1998**, *70*, 1117. (b) References 3f and 3h.

(25) (a) Evans, D. A.; Johnson, J. S.; Burgey, C. S.; Campos, K. R. *Tetrahedron Lett.* **1999**, *40*, 2879. (b) See also refs 3c and 2l.

(26) Centroid distances in documented edge-face complexes span a range from 4.5 to 7 Å; see: Quan, R. W.; Li, Z.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 8156 and references therein.

Scheme 1



suggesting edge−face interaction may not be the exclusive factor influencing π-facial selectivity.

The turnover in facial selectivity exhibited by the catalyst [Cu(*S*,*S*)-*t*-Bu-box](SbF$_6$)$_2$ (**1a**) in the Mukaiyama Michael reaction of ethylidene malonate **10j** as compared to bulky alkylidene malonates was also an aspect of this reaction that required further analysis. We hoped that the elucidation of the solid state structure of its complex with the catalyst would provide some insight into the significantly lower selectivities exhibited by unbranched alkyl substituents. X-ray-quality crystals of {Cu[(*S*,*S*)-*t*-Bu-box](**10j**)}(SbF$_6$)$_2$ were obtained from pentane/dichloromethane and the solved structure is shown in Figure 6. This structure has the closest SbF$_6$−Cu contact distance observed to date in the *t*-Bu-box series (2.73 Å vs 3.30 Å for {Cu[(*S*,*S*)-*t*-Bu-box](OH$_2$)$_2$}(SbF$_6$)$_2$ and 4.60 Å for {Cu-[(*S*,*S*)-*t*-Bu-box](**10a**)}(SbF$_6$)$_2$). The dicarbonyl binds to the metal in a distorted square-planar geometry similar to the benzylidene malonate Cu(II) complex (15.1 and 16.5°). The

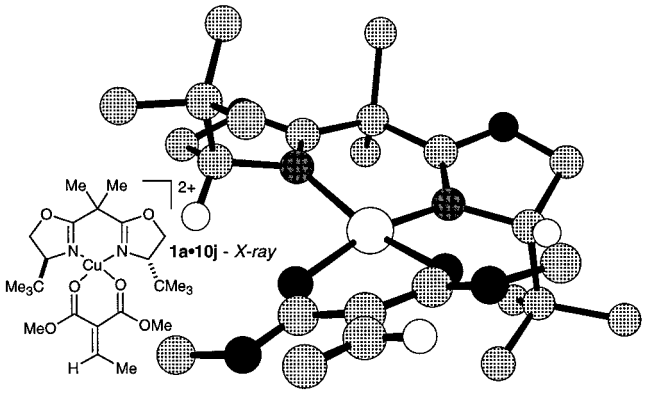


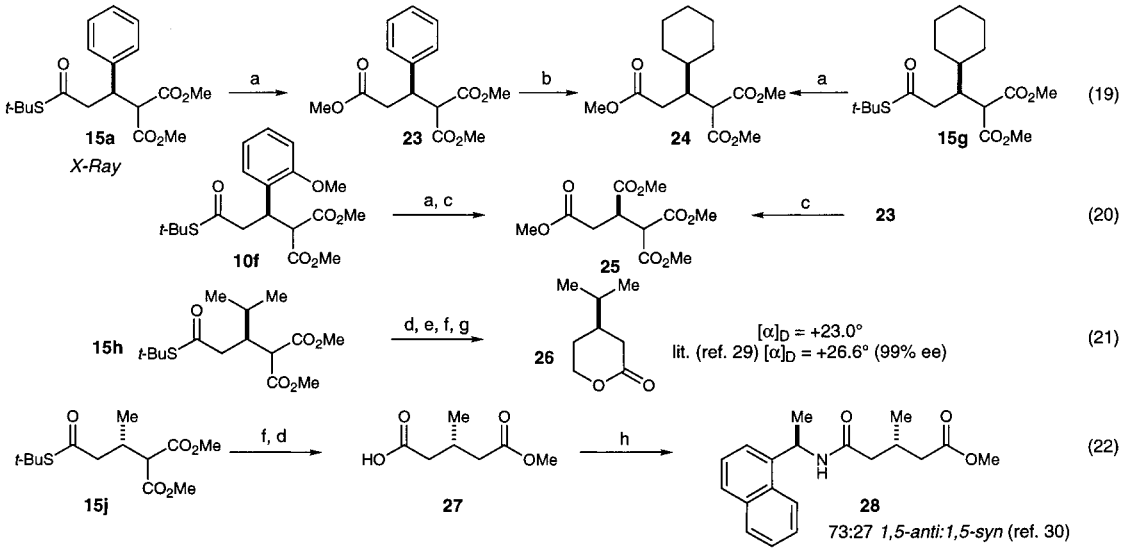
Figure 6. X-ray crystal structure of [Cu(*S*,*S*)-*t*-Bu-box](SbF$_6$)$_2$ complex **1a** with alkylidene malonate **10j**.

curvature in the six-membered ring formed by the dicarbonyl and copper atom is not as pronounced in this structure as in the benzylidene malonate−Cu(II) complex and presents the opposite face toward nucleophilic attack, corresponding to the observed absolute stereochemistry of the major enantiomer.

Mechanistic Considerations. A coherent mechanistic explanation of this reaction begins to emerge from consideration of the results described above. Two-point binding of the alkylidene malonate to the bis(oxazoline)−copper complex is presumed since this affords the most reactive of the possible catalyst−substrate complexes. This assumption is reinforced by crystallographic characterization of these substrate−catalyst complexes. A possible rationale for the poor results afforded by the extremely bulky 1-naphthyl alkylidene malonate is that it does not react by the two-point binding motif but rather by single-point coordination, accounting for its lower reactivity and complete lack of selectivity.

The broad outline of a catalytic cycle is provided in Scheme 1. Addition of the enolsilane to the alkylidene malonate may proceed by an open transition state. The intermediate silyloxy−carbenium/malonyl enolate zwitterion may either exist as ion pair **21a** or close reversibly to form the cyclobutane **21b**.[27] Hexafluoro-2-propanol serves as the proton source and ultimate silicon acceptor. The order of these two events remains undetermined. Dissociation of the neutral product from the

Scheme 2

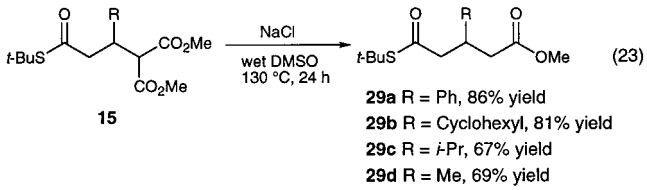


[a] Br$_2$, MeOH, CH$_2$Cl$_2$. [b] Rh/Al$_2$O$_3$, H$_2$, MeOH. [c] RuCl$_3$·H$_2$O, NaIO$_4$, MeCN/CCl$_4$/H$_2$O; then CH$_2$N$_2$. [d] Br$_2$, THF/H$_2$O. [e] BH$_3$·DMS, THF. [f] NaCl, wet DMSO, 130 °C. [g] TFA, CH$_2$Cl$_2$. [h] (*R*)-*a*-Naphthylmethylbenzylamine, EDCI, DMAP, CH$_2$Cl$_2$.

copper complex allows for catalyst turnover. The competing hydrolysis must proceed by alcohol coordination to copper. The strong Lewis acid activation of HFIP by Cu(II) significantly changes the acidity of this proton.[28]

Stereochemical Proof. Absolute stereochemistry was unambiguously assigned for compounds **15a**, **15f**, **15g**, **15h**, and **15j** by the procedures illustrated in Scheme 2. An X-ray crystal structure of **15a** allowed the assignment of the stereochemistry of this adduct as depicted. Chemical correlation of adducts **15f** and **15g** to this structure was accomplished. Correlation of **15h** to the known lactone **26**[29] confirmed that the absolute stereochemistry of this adduct was as assigned. The absolute stereochemistry of the methyl substrate **15j** was assigned by chemical correlation with glutarate amide **28**,[30] formed from the Michael adduct (44% ee) as a 73:27 ratio of 1,5-*anti* to 1,5-*syn* diastereomers (46% de). The stereochemical assignment for the aryl and branched alkyl Michael adducts conforms to a conserved π-facial selectivity for the corresponding alkylidene malonate substrates. As expected, absolute stereochemistry of the methyl-substituted Michael adduct corresponds to a reversal in π-facial selectivity.

Product Elaboration. The Michael adducts undergo facile monodecarbomethoxylation under Krapcho conditions[31] to afford chiral differentiated glutarate esters. Optimal decarboxylation conditions involved heating the malonate ester in wet DMSO at 130 °C in the presence of NaCl. Higher temperatures consistently led to lower yields, presumably due to competing thioester hydrolysis. Selective hydrolyis or alcoholysis of the thioester is possible using documented procedures.[32]



(23)

Conclusion. The Mukaiyama Michael reaction of alkylidene malonates and enolsilanes is efficiently catalyzed by bis(oxazoline)−Cu(II) complexes. Catalyst turnover in this reaction is not observed in the absence of protic additives and high conversion is achieved in the presence of hexafluoro-2-propanol. A competing enolsilane decomposition pathway is effectively minimized in low-polarity solvents relying on the poor solubility of the fluorinated alcohol at low temperature. Large β-substituents afforded highest enantioselectivities in this reaction, typically >90% ee. Crystallographic characterization of substrate−catalyst complexes has provided considerable insight into how these complexes may behave in solution and into the source of enantioselectivity. The Michael adducts are formed in high yields and may be readily decarboxylated to afford chiral, differentiated glutarate esters.

Acknowledgment. Support for this research was provided by the NSF and the NIH (GM-33328). Postdoctoral fellowships from NSERC (T.R.) and NSF (M.C.K) are gratefully acknowledged. The amino alcohols and acids utilized in the preparation of the box ligands were generously provided by NSC Technologies.

Supporting Information Available: Complete experimental procedures, crystallographic data, and characterization of new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) Electron-deficient alkylidene malonates form cyclobutanes upon reaction with electron-rich olefins, see: Evans, S. B.; Abdelkader, M.; Padias, A. B.; Hall, H. K., Jr. *J. Org. Chem.* **1989**, *54*, 2848.

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