Enantioselective and Diastereoselective Mukaiyama−Michael Reactions Catalyzed by Bis(oxazoline) Copper(II) Complexes

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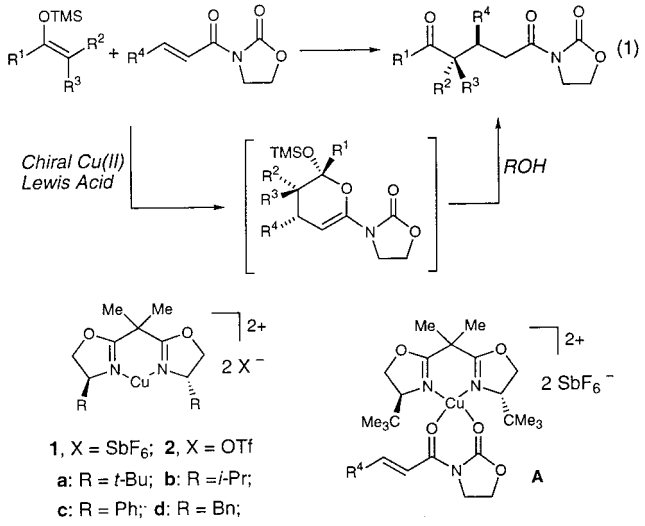
Abstract: The scope of highly enantioselective and diastereoselective Michael additions of enolsilanes to unsaturated imide derivatives has been developed with use of [Cu((*S*,*S*)-*t*-Bu-box)](SbF$_6$)$_2$ (**1a**) as a Lewis acid catalyst. The products of these additions are useful synthons that contain termini capable of differentiation under mild conditions. Michael acceptor π-facial selectivity is consistent with two-point binding of the imide substrate and can be viewed as an extension of substrate enantioselection in the corresponding Diels−Alder reactions. A model analogous to the one employed to describe the hetero Diels−Alder reaction is proposed to account for the observed relation between enolsilane geometry and product absolute diastereocontrol. Insights into modes of catalyst inactivation are given, including spectroscopic evidence for inhibition of the catalyst by a dihydropyran intermediate that evolves during the course of the reaction. A procedure is disclosed in which an alcohol additive is used to hydrolyze the inhibiting dihydropyran and afford the desilylated Michael adduct in significantly shortened reaction time.

Introduction

In 1974, Mukaiyama and co-workers reported the first examples of Lewis acid-catalyzed Michael reactions between enolsilanes and α,β-unsaturated carbonyl acceptors.[1] This reaction variant is an attractive alternative to the conventional metalloenolate process due to the mild reaction conditions and frequently superior regiocontrol (1,4- versus 1,2-addition).[2] While glutarate esters produced from this reaction have been heavily utilized in organic synthesis, few general methods of a catalytic asymmetric variant of this reaction have been reported.[3] This report describes the utilization of chiral copper Lewis acid **1a** to catalyze the addition of enolsilanes to substituted acryloyl oxazolidinones (eq 1) based on the proposed activated substrate−catalyst complex **A**. We have found that the reaction proceeds through a dihydropyran intermediate, which is subsequently hydrolyzed by an alcoholic additive.



Previous Contributions. Notable progress has been made toward the development of a general enantioselective catalytic Michael reaction. Mukaiyama recently documented the ability of [(*R*)-1,1′-bi-2-naphthalenediolato(2-)-*O*,*O*′]oxotitanium (**B**) to provide Michael adducts of thioester enolsilanes and enones in 36−90% ee (eq 2). Enantioselection was found to be highly sensitive to reactant structure, with modifications in either component resulting in a 20−40% drop in enantioselectivity.[4] Katsuki has employed a multitude of BINOL-lanthanide and bis(oxazoline) Cu(II) triflate catalysts to promote the addition of 3-methyl-1-trimethylsiloxy furan and 1-trimethylsiloxy furan to crotonyl oxazolidinone in which the maximum enantioselectivity of 95% was observed with modest diastereoselectivity (eq 3).[5] Barnes and co-workers have employed Mg(II) bis(oxazoline) catalyst **C** to promote the addition of β-keto esters to various nitroalkenes in high enantioselectivity (eq 4).[6] Most recently, Shibasaki has disclosed a "linked" lanthanum BINOL complex (**D**) that promotes the addition of malonate anions to various cyclic enones in greater than 98% ee (eq 5).[7] While the levels of diastereoselection and enantioselection for these

(1) Narasaki, K.; Soai, K.; Mukaiyama, T. *Chem. Lett.* **1974**, 1223−1224.

(2) (a) Oare, D. A.; Heathcock, C. A. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1991; Vol. 20, pp 124−170. (b) Oare, D. A.; Heathcock, C. A. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1989; Vo. 19, pp 227−407.

(3) For recent reviews, see: (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Chapter 31. (b) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171−196.

(4) Mukaiyama and co-workers have also developed a catalytic (10 mol %), asymmetric (40−70% ee) Michael addition reaction in which the active chiral species is believed to be a chiral diamine-tin(II) enolate: (a) Yura, T.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1988**, 1021−1024. (b) Yura, T.; Iwasawa, N.; Narasaka, K.; Mukaiyama, T. *Chem. Lett.* **1988**, 1025−1026.

(5) (a) Kitajima, H.; Katsuki, T. *Synlett* **1997**, 568−570. (b) Kitajima, H.; Ito, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 17015−17020.

(6) Ji, J.; Barnes, D. M.; Zhang, J.; King, S. A.; Wittenberger, S. J.; Morton, H. E. *J. Am. Chem. Soc.* **1999**, *121*, 10215−10216.

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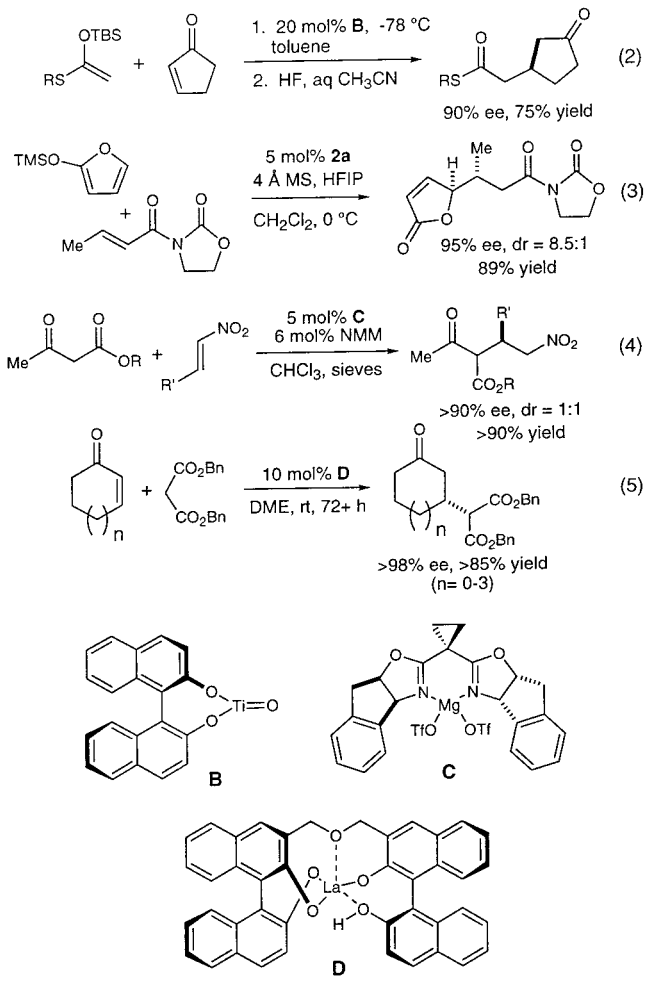
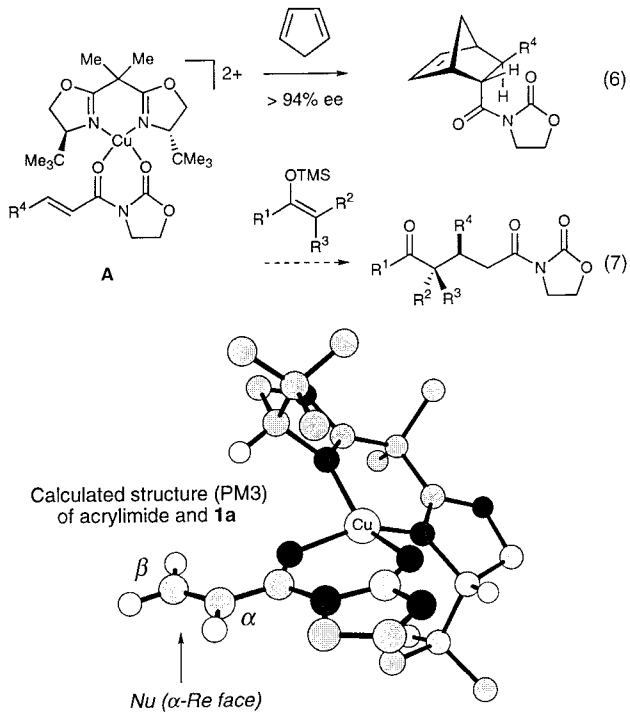
reactions are encouraging, more general catalysts are needed to provide a greater freedom in choice of nucleophile and electrophile.



Copper(II) Complexes. Bis(oxazoline) Cu(II) complexes[8,9] are practical[10] catalysts for a variety of carbon−carbon bond forming processes, such as Diels−Alder,[11] hetero Diels−Alder,[12] carbonyl-ene,[13] aldol,[14−16] enolsilane amination reactions,[17] and Michael reaction of alkylidene malonates.[18] Previous research from this laboratory has documented the elements of substrate architecture necessary for designing reactions that are both stereoselective and catalytic. Specifically, unsaturated acyl oxazolidinones are excellent substrates for Diels−Alder cycloadditions catalyzed by C_2-symmetric bis(oxazoline) Cu(II) Lewis acids (eq 6). Significant experimental data suggest that the imide substrate coordinates to **1a** in a distorted square-planar geometry placing the *s*-cis planar enamide proximate to the C_2-symmetric ligand substituent, thereby imparting α-*Re* π-facial selectivity in the Diels−Alder addition. We anticipated that the selectivity afforded by bis(oxazoline) Cu(II) complexes in the Diels−Alder reaction would be applicable to Michael reactions of enolsilanes and appropriately activated acyl oxazolidinones (eq 7). The details of this investigation, including scope, product elaboration, and mechanism, are reported herein.[19]



Results and Discussion

Reaction Development. Preliminary observations suggested that a reactive Michael acceptor as well as a strong Lewis acid catalyst were necessary to promote the addition process. Previous experiments from this laboratory indicated that fumaryl and acryloyl imides were the most reactive dieneophiles in the copper(II) catalyzed Diels−Alder reaction with cyclopentadiene and therefore initial efforts were focused on these two substrates. The Lewis acid selected was [Cu((*S*,*S*)-*t*Bu-box)]$(SbF_6)_2$ (**1a**) based on earlier catalytic asymmetric Diels−Alder investigations which demonstrated that this complex was exceptionally active (eq 6).[20] The additions of enolsilanes **4a**−**c** to fumarylimide **3** revealed that there was no correlation between enantioselection and reactivity of the nucleophile (Table 1). Silylketene acetals are the most reactive nucleophilic participants, but are generally nonselective in their additions (not shown). Conversely, thioester-derived ketene acetals and enolsilanes derived from both

(7) (a) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236−1256. (b) Kim, Y. S.; Matsunaga, S.; Das, J.; Sekine, A.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6505−6507.

(8) Evans, D. A.; Rovis, T.; Johnson, J. S. *Pure Appl. Chem.* **1999**, *71*, 1407−1415.

(9) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325−335.

(10) The copper chloride complex that serves as a bench-stable precursor to **1a** can be routinely prepared in batches of 30 g: Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541−4544.

(11) (a) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1993**, *115*, 6460−6461. (b) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559−7573. (c) Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582−7594.

(12) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635−1649 and references therein.

(13) Evans, D. A.; Tregay, S. W.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T. *J. Am. Chem. Soc.* **2000**, *122*, 7936−7943.

(14) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669−685.

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

(16) Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893−7894.

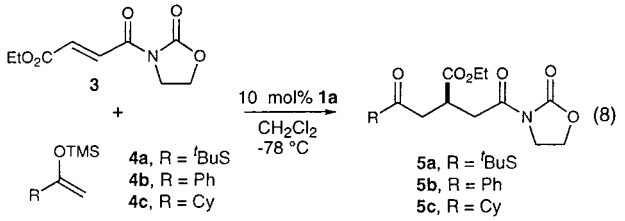
(17) Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, *1*, 595−598.

(18) Evans, D. A.; Rovis, T.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1999**, *121*, 1994−1995.

(19) A preliminary account of this work has been communicated: Evans, D. A.; Willis, M. C.; Johnston, J. N. *Org. Lett.* **1999**, *1*, 865−868.

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

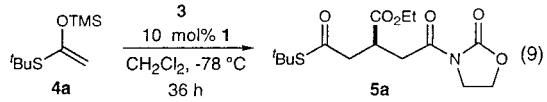
Table 1. Initial Michael Additions of Enolsilanes to Imide **3** Catalyzed by **1a** (Eq 8)[a]



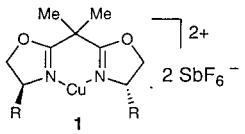
entry	Nu	yield (%)[b]	% conv[c]	ee (%)[d]	time
1	**4a**	86	100	89	36 h
2	**4b**	54	70	98	4 days
3	**4c**	31	52	99	4 days

[a] Reactions run at a concentration of 0.2 M. [b] Isolated yield. [c] Based on recovered **3**. [d] Enantiomeric excess determined by chiral HPLC.

Table 2. Effect of Catalyst Ligand Substituent on Michael Addition Enantioselectivity (Eq 9)[a]



cat. (**1**)	R	yield (%)[b]	% ee[c]
a	^{t}Bu	86	89
b	^{i}Pr	81	89
c	Ph	nd[d]	57
d	Bn	nd	78



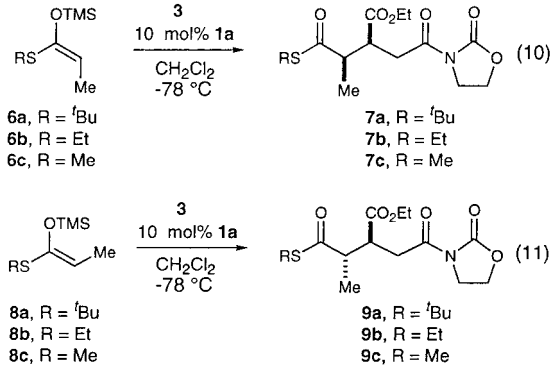
[a] Reactions run at a concentration of 0.2 M. [b] Isolated yield. [c] Enantiomeric excess determined by chiral HPLC. [d] Not determined.

aromatic and aliphatic ketones exhibit a high degree of selectivity, but initially lacked promising reaction profiles at −78 °C. Enolsilanes derived from linear ketones typically produce complex mixtures of products and were therefore not investigated.[21] Although yields for this reaction were initially modest, we were encouraged by the high levels of asymmetric induction exhibited by catalyst **1a** with fumaryl oxazolidinone as a substrate. Interestingly, silylated addition products are not detected in these reactions, thereby obviating a separate hydrolysis step.

Optimization of the reaction catalyst included a study of the effect of ligand substituent on enantioselectivity (Table 2). The addition of enolsilane **4a** to imide **3** is catalyzed by various bis(oxazoline) Cu(II) complexes to afford adduct **5a** (eq 9). Catalysts bearing sterically demanding aliphatic substituents (^{t}Bu, ^{i}Pr) exhibit higher enantioselectivity than their phenyl- and benzyl-substituted counterparts. Copper complexes with triflate counterions (**2**) are not efficient catalysts for this reaction, presumably due to reduced Lewis acidity.

The Michael additions of thioester-derived enolsilanes were further investigated for their favorable reactivity/selectivity profile (Table 3). The issue of reaction diastereoselection was next addressed. Selective generation of (*E*) and (*Z*) isomers of substituted thioester enolsilanes is possible by employing the Ireland (LDA, HMPA, then TMS-Cl)[22] or Collum (LiTMP, then TMS-Cl·Et_3N)[23] procedures, respectively. Particular care must be taken to distill the thioester immediately prior to generation

Table 3. Catalyzed Michael Additions of Isomeric Thioester Enolsilanes to Fumaryl Imide **3** (Eqs 10 and 11)[a]



entry	Nu	geometry	*syn:anti*[b]	ee (%)[b,c]	yield (%)[d]
1	**6a**	***Z***	**99:1**	**99**	**73**
2	**6b**	*Z*	75:25	92	91
3	**6c**	*Z*	66:34	90	90
4	**8a**	*E*	22:78	96	65
5	**8b**	*E*	14:86	91	77
6	**8c**	***E***	**5:95**	**90**	**90**

[a] Reactions run at a concentration of 0.2 M. [b] Determined by chiral HPLC. [c] Enantiomeric excess of the major diastereomer. [d] Isolated yield.

of the enolsilane to achieve high levels of stereoisomeric purity (>95:5).[24] The addition of isomeric enolsilanes derived from *tert*-butyl thiopropionate (**6a**, **8a**) proceeds efficiently to yield either anti or syn Michael adducts with good enantiomeric purity (>96% ee) after 4 days. Two trends are evident from the illustrated data. First, there is a general correlation between enolsilane geometry and reaction diastereoselection: (*Z*)-enolsilanes **6** exhibit syn diastereoselection (eq 10) while (*E*)-enolsilanes **8** are anti selective (eq 11). Second, reaction diastereoselection may be modulated by the size of the thioalkyl substituent: (*Z*)-*tert*-butylthio enolsilane **6a** is highly syn selective (>99:1) while the (*E*)-methylthio enolsilane **8b** is quite anti selective (95:5). Utilization of enolsilanes derived from ethyl thioesters provides levels of diastereoselectivity intermediate to methylthio and *tert*-butylthio enolsilanes.

Although synthetically useful levels of stereoselection are obtained by using the procedure described in Table 3, the reaction times are prohibitively long (*tert*-butylthio enolsilanes, 4 days; methylthio enolsilanes, 2 days).[25] A survey of additives guided by the known ability of alcohols to facilitate turnover in various catalytic reactions[26] yielded a modification of our initial experimental procedure that significantly reduced reaction times. A single equivalent of hexafluoro-2-propanol (HFIP) is

(21) Mayr's nucleophilicity scale is also consistent with our enolsilane reactivity profiles: Burfeindt, J.; Patz, M.; Müller, M.; Mayr, H. *J. Am. Chem. Soc.* **1998**, *120*, 3629−3634.

(22) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868−2877. (b) Ireland, R. E.; Wipf, P.; Armstrong, J. D., III *J. Org. Chem.* **1991**, *56*, 650−657.

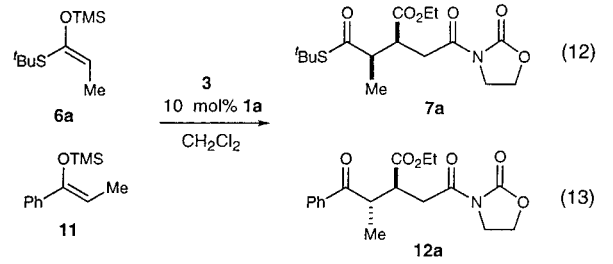
(23) Hall, P. L.; Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9571−9574.

(24) We have observed a dependence of selectivity on thioester age. In one case, the presence of the impurity (not detectable by ^{1}H NMR) was able to *reverse* the sense of selectivity by using the Ireland HMPA protocol. We thereby suggest strict adherence to the details outlined in the references and our experimental details.

(25) The (*Z*) phenyl thioester enolsilane derived from isovaleric acid gives the Michael adduct (dr = 85:15, both in >99% ee) in 72% yield (unoptimized) at a higher temperature of −50 °C.

(26) For representative examples of catalytic processes that utilize alcohols as additives see: (a) Kawara, A.; Taguchi, T. *Tetrahedron Lett.* **1994**, *35*, 8805−8808. (b) Kitajima, H.; Ito, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 17015−17028. (c) Yun, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 5640−5644. (d) Ishitani, H.; Yamashita, Y.; Shimizu, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 5403−5404. (e) Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1650−1652.

Table 4. Acceleration of Michael Reactions Using Hexafluoro-2-propanol (HFIP) (Eqs 12 and 13)



entry	Nu	T (°C)	additive	*syn:anti*[a]	ee (%)[a]	yield (%)[b]	time
1	**6a**	-78	none	99:1	97	73[c]	4 d
2	**6a**	-78	HFIP	99:1	99	94	36 h
3	**6a**	-20	HFIP	93:7	89	95	2 h
4	**11**	-40	none	1:99	96	95	4 d
5	**11**	-40	HFIP	1:99	96	94	3 h
6	**11**	-20	HFIP	3:97	95	95	1.5 h
7	**11**	-5	HFIP	3:97	94	94	1.2 h

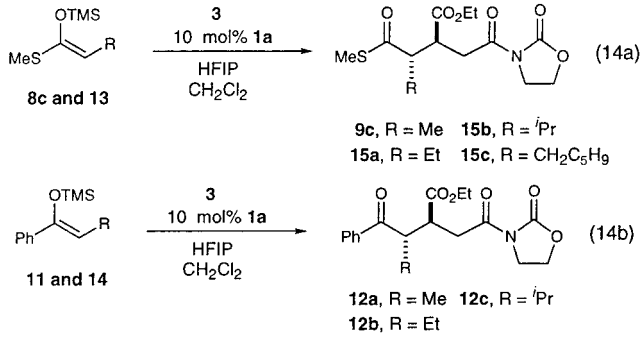
[a] Determined by chiral HPLC. [b] Isolated yield. [c] Incomplete conversion.

added to the catalyst−substrate solution prior to addition of the enolsilane. Hexafluoro-2-propanol has been successfully utilized as an additive in the enantioselective Cu(II)-catalyzed enol amination[17] and, subsequently, the enantioselective Cu(II)-catalyzed Michael reaction of alkylidene malonates.[18] Gratifyingly, the reaction times are reduced by an average of 70% without a detectable loss in stereoselectivity in most cases (Table 4).[27] The time required for complete conversion of the most unreactive enolsilane **6a** is reduced by 60% (4 d to 36 h) at −78 °C, concomitant with an increase in yield (73 to 94%, entries 1 and 2). A further increase in the reaction rate may be achieved by raising the temperature to −20 °C (entry 3) without drastically affecting stereoselectivity (99:1 ds, 99% ee at −78 °C vs 93:7 ds, 89% ee at −20 °C).[28] Michael additions of propiophenone enolsilane **11** to **3** (eq 13) are accelerated by the addition of HFIP, thereby decreasing the reaction time by 95% (entry 4 vs entry 5) and allowing for the use of ice bath reaction temperatures with only minor erosion in enantioselectivity and diastereoselectivity (entry 7).

The size of the pendant alkyl group on the enolsilane was varied to assess its impact on reaction stereoselection. Methyl thioester-derived enolsilanes (**8c** and **13**) and phenyl ketone enolsilanes (**11** and **14**) engage in highly stereoselective reactions with imide **3** (Table 5).[29] Stereoselection regularly increases with increasing substituent size. The attenuated reactivity of phenyl ketone enolsilanes requires higher temperatures, but these reactions are conveniently carried out at 0 °C with excellent diastereoselection (>95:5) and enantioselection (>92% ee).

In contrast to the (*E*)-substituted methyl thioester-derived enolsilanes, increasing the substituent size in the (*Z*)-*tert*-butyl thioester-derived enolsilanes (**6a**, **16**) results in a decrease in reaction diastereoselection (Table 6). The (*Z*)-*tert*-butyl thioester-derived enolsilanes are less nucleophilic than the methyl thioester-derived enolsilanes and occasionally require higher temperatures for efficient conversion.

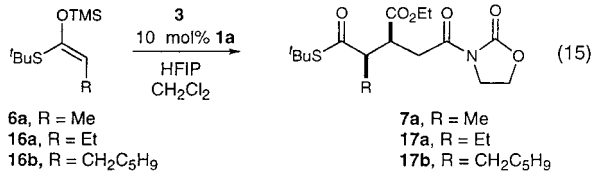
Table 5. Methylthioester and Phenyl ketone Enolsilane Additions to **3** (Eqs 14a and 14b)[a]



entry	Nu	R	*anti:syn*[b]	ee (%)[b]	yield (%)[c]	T (°C)	time
1	**8c**	Me	90:10	83	93	-78	2 h
2	**13a**	Et	95:5	90	89	-78	2 h
3	**13b**	^{i}Pr	99:1	98	93	-78	4.5 h
4	**13c**	$CH_2C_5H_9$[d]	96:4	97	84	-78	20 h
5	**11**	Me	95:1	92	99	0	10 min
6	**14a**	Et	99:1	94	99	0	20 min
7	**14b**	^{i}Pr	99:1	94	99	0	60 min

[a] Reactions run at a concentration of 0.2 M. [b] Measured using chiral HPLC. [c] Isolated yield. [d] C_5H_9 = cyclopentyl.

Table 6. Representative Michael Additions of *tert*-Butylthioester Enolsilanes Catalyzed by **1a** (Eq 15)



Nu	R	*syn:anti*[a]	ee (%)[a]	yield (%)[b]	T (°C)	time
6a	Me	99:1	91	94	-78	36 h
16a	Et	91:9	90	67	-78	4d
16b	$CH_2C_5H_9$	73:27[c]	99/88	92	-20	2 d

[a] Determined by chiral HPLC. [b] Isolated yield. [c] From a 88:12 *Z:E* mixture of enolsilanes. Recrystallization from hexanes gives the desired diastereomer (dr = 98:2, 99% ee) in 56% overall yield.

The need for more reactive enolsilanes became apparent during attempts to develop a more diverse set of Michael acceptors. For example, *tert*-butyl thioacetate enolsilane **4a** adds to crotonyl oxazolidinone **18a** catalyzed by **1a** in the presence of HFIP to afford only a 13% yield of **19** (44% ee) after 4 days at −20 °C (Table 7, eq 16). This observation led us to examine the use of pyrrole amide-derived enolsilanes as more nucleophilic reactants.[30] We initially observed the high reactivity of pyrrole amide enolsilanes when developing our Cu(II)-catalyzed enol amination.[17] Gratifyingly, the addition of acetyl pyrrole enolsilane **20** to **18a** afforded crystalline addition product **21a** in 91% ee and 90% yield after only 26 min at −20 °C (entry

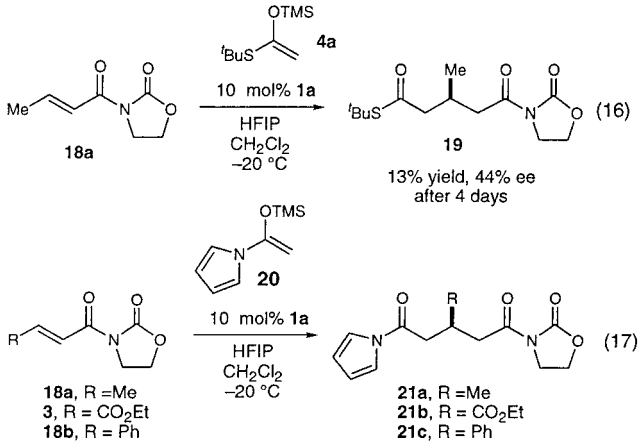
(27) Unless otherwise noted, the standard stoichiometry of the reported reactions is as follows: enolsilane (2 equiv), HFIP (1 equiv), imide acceptor (1 equiv), 10 mol % **1a**, and 0.2 M dichloromethane. See Supporting Information for more details.

(28) The integrity of stereoselection over a large temperature range is typical of this Cu(II) Lewis acid class: Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325−335.

(29) Michael addition of methylthiopropionate enolsilane was one of the few cases where a degradation of selectivity was observed when using HFIP (ds 90:10, 90% ee → ds 90:10, 83% ee).

(30) *N*-Acyl pyrroles have been used as acylating agents and can be regarded as activated carboxylic acid equivalents: (a) Brandange, S.; Rodrigues, B. *Acta Chem. Scand.* **1987**, *B41*, 710−744. (b) Brandange, S.; Holmgren, E.; Leijonmarck, H.; Rodriguez, B. *Acta Chem. Scand.* **1995**, *49*, 922−928. (c) Lee, S. D.; Brook, M. A.; Chan, T. H. *Tetrahedron Lett.* **1983**, *24*, 1569−1572. To our knowledge, only the silylketene aminal of acetyl pyrrole has been previously described: (d) Frick, U.; Simchen, G. *Leibigs Ann. Chem.* **1987**, 839−845.

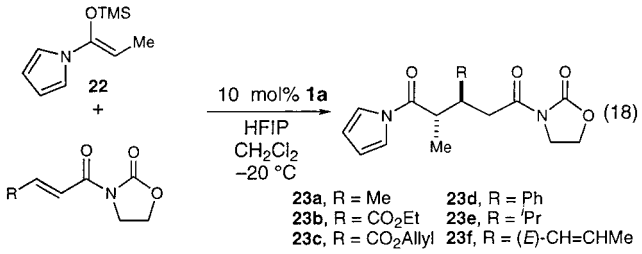
Table 7. Addition of Acetyl Pyrrole Enolsilane to Substituted Acrylimides (Eq 17)[a]



entry	Acceptor	R	ee (%)[b]	yield (%)[c]	time
1	**18a**	Me	91	90	26 min
2	**3**	CO_2Et	95	92	68 min
3	**18b**	Ph	90	94	2 h

[a] Reactions run at a concentration of 0.2 M. [b] Determined by chiral HPLC. [c] Isolated yield.

Table 8. Addition of *N*-Propionyl Pyrrole Enolsilane to Substituted Acrylimides (Eq 18)[a]



entry	R	*anti:syn*[b]	ee (%)[b]	yield (%)[c]	time
1	Me	99:1	98	88	5 min
2	CO_2Et	97:3	94	91	60 min
3	CO_2Allyl	98:2	97	80	60 min
4	Ph	99:1	94	97	16 h
5	^iPr	99:1	98	40	24 h[d]
6	(*E*)-CH=CHMe	99:1[e]	94	85	20 h[e]

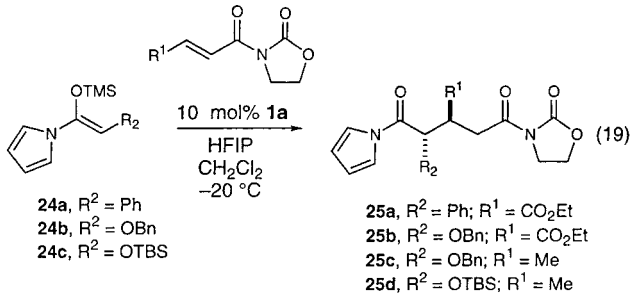
[a] Reactions run at a concentration of 0.2 M. [b] Determined by chiral HPLC. [c] Isolated yield. [d] Reaction did not go to completion. [e] Regiochemistry >95:5 as detected by ^1H NMR spectroscopy (500 MHz).

1). Also, the addition of **20** to fumaryl oxazolidinone **3** produces adduct **21b** (95% ee) after only 68 min (entry 2). The competence of this acetate enolate equivalent is exemplified by the addition of **20** to cinnamyl oxazolidinone **18b**, a very unreactive substrate, in excellent yield (94%) after 2 h (90% ee, entry 3).

α-Substitution of acylpyrrole-derived enolsilane **20** provides the opportunity to study diastereoselective reaction variants. The enolization of these substrates is highly (*Z*)-selective (>95:5) due to the inherent allylic (1,3) strain of α-substituted acylpyrroles.[31] Reactions of propionyl acylpyrrole enolsilane **22** exhibit exceedingly high levels of diastereoselection in concert with good enantioselection (Table 8). When the Michael acceptor is sterically hindered (R = isopropyl, entry 5), the reaction does not proceed to completion even with additional nucleophile (entry 5). The addition of **22** is also highly

(31) Evans, D. A.; Taber, T. R. *Tetrahedron Lett.* **1980**, *21*, 4675−4678.

Table 9. Addition of Substituted Pyrrole Enolsilanes to Fumaryl and Crotyloxazolidinones (Eq 19)



entry	Nuc	R_1	*anti:syn*[a]	ee (%)[a]	yield (%)[b]
1	**24a**	CO_2Et	75:25[c]	99	60
2	**24a**	Me	-	-	NR
3	**24b**	CO_2Et	92:8	99	93
4	**24b**	Me	98:2	99	86
5	**24c**	Me	98:2	95	75[d]

[a] Determined by chiral HPLC. [b] Isolated yield. [c] After one recrystallization, dr increased to 92:8 anti:syn. [d] 20 mol % catalyst used.

regioselective as seen in the addition to sorbyl imide (entry 6). We sought to extend the scope of these nucleophiles by utilizing α-phenyl and α-oxygenated acylpyrrole enolsilanes (Table 9). While phenyl-substituted enolsilane **24a** is only reactive enough to add to fumaryl oxazolidinone (75:25 dr, 99% ee, entry 1), both α-benzyloxy and α-(*tert*-butyldimethylsilyl)oxy acylpyrrole-derived enolsilanes (**24b** and **24c**, respectively) add to crotonyl oxazolidinone with high diastereo- and enantioselectivity (98:2 dr, >95% ee, entries 4 and 5). As a testament to the applicability of this reaction toward preparative scale synthesis, the addition of **22** to fumaryl oxazolidinone (**3**) can be performed on a 25-mmol scale with 5 mol % catalyst loading to provide **23b** in 97% yield (99:1 dr, 97% ee).[32]

In addition to substituted acryloyl oxazolidinone substrates, we sought to extend the developed methodology to parent acryloyl oxazolidinone **26**. In earlier experiments, this substrate tended to oligomerize. We hoped that alcoholic additives would attenuate the Lewis acidity of the catalyst complex and/or provide the same acceleration in reaction rate observed in the Michael additions to substituted acryloyl oxazolidinones. These affects might be pronounced enough to promote the desired reaction without the intervention of the alternate oligomerization pathway. Alcohol structure is pivotal to successful inhibition of the oligomerization pathway during the addition of triethylsilyl *tert*-butylthiopropionate enolsilane **27** to acryloyloxazolidinone **26** (Table 10). On the basis of these experiments, it is clear that (a) the alcohol inhibits polymerization (entries 6 and 7), (b) the pK_a of the alcohol is pivotal for efficacy (entries 2 and 4), and (c) silylating agents are generally unsuccessful in limiting the oligomerization manifold (entry 6).[33] Fortunately, the catalyst complex/HFIP mixture provided sufficient activity for these reactions which allowed for further optimization.[34]

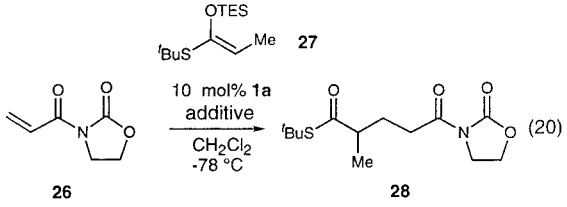
After identifying HFIP as the optimal additive, it was discovered that good yields of Michael adducts are obtained with a promising level of enantioselection (86% ee) and yield

(32) There was no exotherm observed for this reaction unlike the corresponding Cu(II) catalyzed aldol reactions (ref 14).

(33) TMS-OTf alone is also insufficient. This is in direct contrast to the beneficial affect that TMS-OTf exhibits in the Mukaiyama aldol reaction disclosed earlier: (ref 14).

(34) Interestingly, addition of HFIP (mp −4 °C) to a −78 °C reaction mixture of catalyst and substrate forms a precipitate that is consumed after several hours of reaction time. Identical yields and selectivities are observed.

Table 10. Additive Effect on Catalyzed Michael Additions to Acryloyl Oxazolidinone **26** (Eq 20)



entry	additive[a]	yield (%)[c]
1	none	20
2	**$(CF_3)_2CHOH$**	**80**[b]
3	CF_3CH_2OH	15
4	$(CH_3)_2CHOH$	37
5	$CH_3(CF_3)_2COH$	23
6	TMSOTf/HFIP	43
7	$TMSOCH_3$	12

[a] 2 equiv of additive was used. [b] The bis-Michael addition product was formed in 15% yield (dr = 3.2:1). [c] In most cases, the remainder consisted of a mixture of oligomers.

(80%) at *room temperature* when TIPS-enolsilane **29** is used as a representative nucleophile (eq 21). Confirmation that the alcohol was acting as a Brønsted acid and not as an agent of silyl transfer was obtained by using hexafluoro-2-propan(ol-*d*) (eq 22). The high degree of deuterium incorporation eliminates the possibility that hydrolysis occurs during the workup procedure.

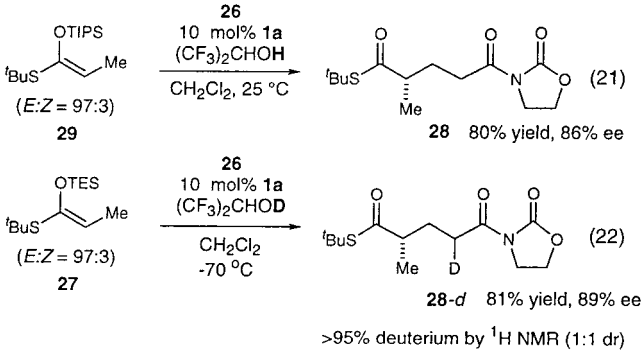
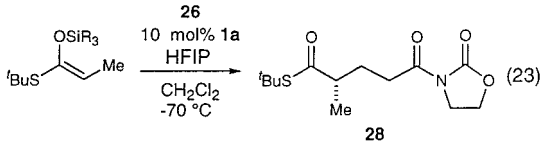


Table 11. Impact of Enolsilane Silicon Substituent Size on the Michael Addition to Acryloyl Oxazolidinone **26** (Eq 23)

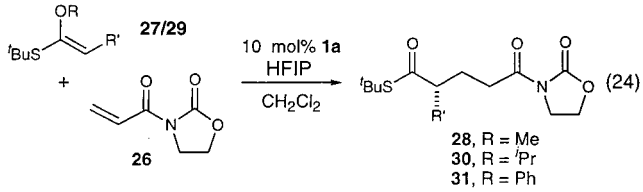


entry	R	ee (%)[a]	yield (%)[b]
1	Me	69	80
2	Et	89	80
3	^{i}Pr	88	61[c]

[a] Determined using chiral HPLC. [b] Isolated yield. [c] Reaction not complete after 4 days.

Among the variations studied within the enolsilane subunit, the silicon substituent size emerged as an important stereocontrol element (Table 11). Both triethyl- and triisopropylsilyl enolsilane nucleophiles provide encouraging levels of enantioselection (>88%) in these Michael additions (entries 2 and 3). Again, omission of the alcohol additive from the reaction allows the oligomerization pathway to dominate, and the desired Michael adducts are isolated in <20% yield. It was also discovered that

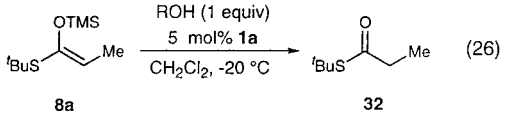
Table 12. Catalyzed Michael Additions to Acryloyl Oxazolidinone (Eq 24)



entry	R	R'	*E:Z* of **27/29**[a]	T (°C)	ee (%)[b]	yield (%)[c]
1	TES	Me	98:2	-78	89	80
2	TIPS	Me	95:5	-20	86	80
3	TES	^{i}Pr	90:10	-78	94	76
4	TIPS	^{i}Pr	95:5	-20	92	84
5	TES	Ph	97:3	-78	83	83
6	TIPS	Ph	92:8	-20	40	93

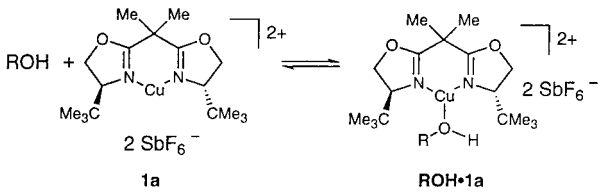
[a] Thioketene acetal isomeric ratio determined by ^{1}H NMR (500 MHz). [b] Determined by chiral HPLC. [c] Isolated yields.

Table 13. Catalytic Hydrolysis of Enolsilanes (Eq 26)



ROH	$t_{1/2}$[a]
2-propanol	30 min
hexafluoro-2-propanol (HFIP)	6 h

[a] Measured by *in situ* IR.



a large sulfur substituent (*tert*-butyl) and (*E*)-enolsilane geometry are necessary for high yield and good enantioselection.

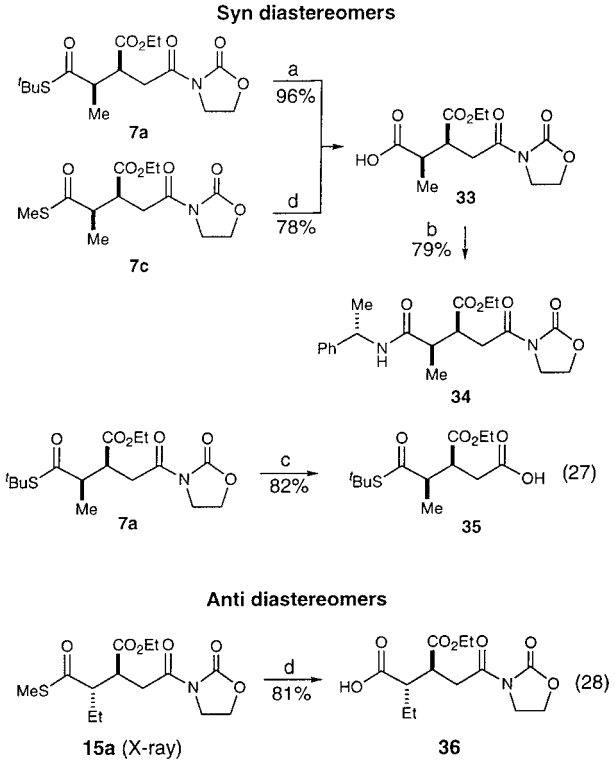
Whereas reactions employing TES-enolsilanes proceed to completion in 1−3 days at −78 °C, TIPS-enolsilanes require a reaction temperature of −20 °C for similar reaction times. Accordingly, enolsilanes containing both trialkylsilyl substituents were more thoroughly examined (Table 12). No general trends regarding the optimal silicon substituent/enolsilane α-substituent are apparent from these data. Nevertheless, good levels of enantioselection and yield can be realized.

A potential problem in using alcohol additives in Lewis acid-catalyzed reactions involving enolsilanes is the destructive enolsilane hydrolysis pathway. Surprisingly, in the presence of **1a**, *alcohols of greater Brønsted acidity result in slower enolsilane hydrolysis* (Table 13). This observation is in direct contrast to conventional wisdom. We suggest that the rate of enolsilane hydrolysis correlates to the Lewis basicity of the unbound carbinol oxygen and not to the Brønsted acidity of the alcohol additive. When combined with complex **1a**, the observed pK_a of 2-propanol is lower than HFIP due to the higher equilibrium constant between bound alcohol and free alcohol (the pK_a value in Me_2SO for 2-propanol is 30.3[35] while the pK_a value of hexafluoro-2-propanol in Me_2SO is 17.9).[36]

(35) Olmstead, W. N.; Margolin, Z.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3295−3299.

(36) http://www.msn.fullfeed.com/~plt/pkatable.

Scheme 1. Determination of Relative and Absolute Stereochemistry of Michael Adduct from Thioester Enolsilanes[a]



[a] Reaction conditions: (a) NBS, 5:1 THF−H_2O, 25 °C; (b) isobutylchloroformate, (*S*)-α-methylbenzylamine, NMM, EtOAc, 0 °C; (c) LiOH, THF−H_2O, 0 °C; (d) Br_2, THF−H_2O.

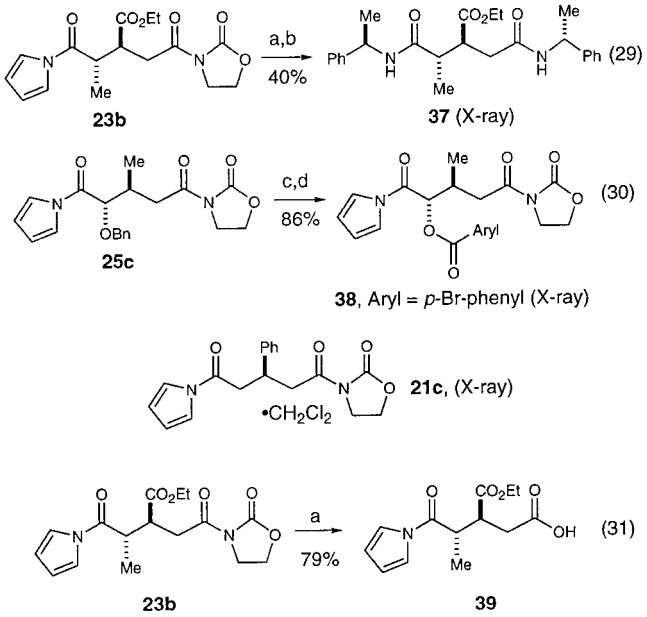
Determination of Absolute Stereochemistry. Reports of the synthesis and use of thioesters are increasingly widespread and are testament to the increasing value of these subunits in organic synthesis. The thioester termini of **7a** and **7c** were selectively hydrolyzed to the corresponding acid **33** by using either aqueous NBS in THF or aqueous Br_2 in THF (Scheme 1).[37] Conversion of this acid to (*S*)-(α)-methyl benzylamide **34** provided a crystalline derivative suitable for X-ray analysis, which established both the absolute and relative configuration at the two centers generated during the Michael addition. Likewise, a combination of X-ray crystallography and chemical correlation was then utilized for determination of representative anti adduct **15a**. Alternatively, basic hydrogen peroxide, or occasionally lithium hydroxide, may also be used to selectively saponify the imide terminus without detectable levels of epimerization at either of the two newly generated stereocenters (eq 27).

The relative and absolute stereochemistry of the Michael adducts from the addition of acylpyrrole enolsilanes was determined in a manner analogous to the thioester enolsilane additions. Michael adduct **23b** was treated with excess LiOOH to afford the diacid, which was then directly coupled with (*R*)-(α)-methylbenzylamine to yield the crystalline diamide in 40% yield (eq 29). Alternatively, the benzyl ether of **25b** was removed with boron trichloride and immediately acylated with *p*-bromobenzoyl chloride to yield a crystalline solid in 86% yield (eq 30). Remarkably, the intermediate hydroxy imide generated from the benzyl group cleavage can be manipulated without spontaneous closure to the five-membered lactone. This process has been used to replace the benzyl ether with alternative protecting groups not compatible with this catalytic process for synthetic endeavors. The absolute stereochemistry of the parent acetylpyrrole adducts was confirmed by X-ray analysis of the cinnamyl adduct **21c** with an occluded molecule of dichloromethane in the unit cell. In most cases, the imide could be hydrolyzed with basic hydrogen peroxide to provide the acylpyrrole carboxylic acid (eq 31). Acrylate products **28** and **31** were converted to the diacids in a two-step procedure employing the established NBS-mediated hydrolysis followed by treatment with lithium hydroperoxide to afford (*S*)-(+)-methylglutaric acid **40** and (*R*)-(−)-phenylglutaric acid **41**, respectively, in good overall yields (Table 14). The optical rotations of **40** and **41** correlate with reported values.[38]

Mechanistic Details. The preference for nucleophilic attack on the α-*Re* face of acyl oxazolidinones has been documented for the Diels−Alder reaction with bis(oxazoline) Cu(II) catalysts. Arguably similar substrates, such as α-keto phosphonates and α-keto esters,[12] exhibit the same π-facial selectivity in [4+2]

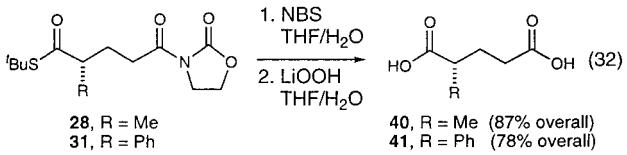
(37) (a) Minato, H.; Kodama, H.; Miura, T.; Kobayashi, M. *Chem. Lett.* **1977**, 413−418. (b) Minato, H.; Takeda, K.; Miura, T.; Kobayashi, M. *Chem. Lett.* **1977**, 1095−1099.

Scheme 2. Determination of Relative and Absolute Stereochemistry of Michael Adduct from Acylpyrrole Enolsilanes[a]



[a] Reaction conditions: (a) LiOH·H_2O, H_2O_2, THF/H_2O, 0 °C; (b) (*R*)-α-methylbenzylamine, EDCI, *i*-Pr_2NEt_2, DMF; (c) BCl_3, CH_2Cl_2, −40 °C; (d) *p*-bromobenzoyl chloride, DMAP, pyridine, CH_2Cl_2.

Table 14. Determination of Acrylate Michael Adduct Absolute Stereochemistry by Chemical Correlation (Eq 32)



R	$[\alpha]_D$ (config.)	lit.[a] $[\alpha]_D$ (config.)	solvent
Me (**40**)	+18.1° (*S*)	+24.2° (*S*)	$CHCl_3$
Ph (**41**)	−50.4° (*R*)	+86.9° (*S*)	$CHCl_3$

[a] See ref 38.

(38) (a) For the optical rotation of (*S*)-(+)-methylglutaric acid see: Eisenbraun, E. J.; McElvain, S. M. *J. Am. Chem. Soc.* **1955**, *77*, 3383−3385. (b) For the optical rotation of (*S*)-(−)-phenylglutaric acid see: Kawazu, K.; Fujita, T.; Mitsui, T. *J. Am. Chem. Soc.* **1959**, *81*, 932−935. Westman, L. *Arkiv. Kemi* **1957**, *11*, 431−440.

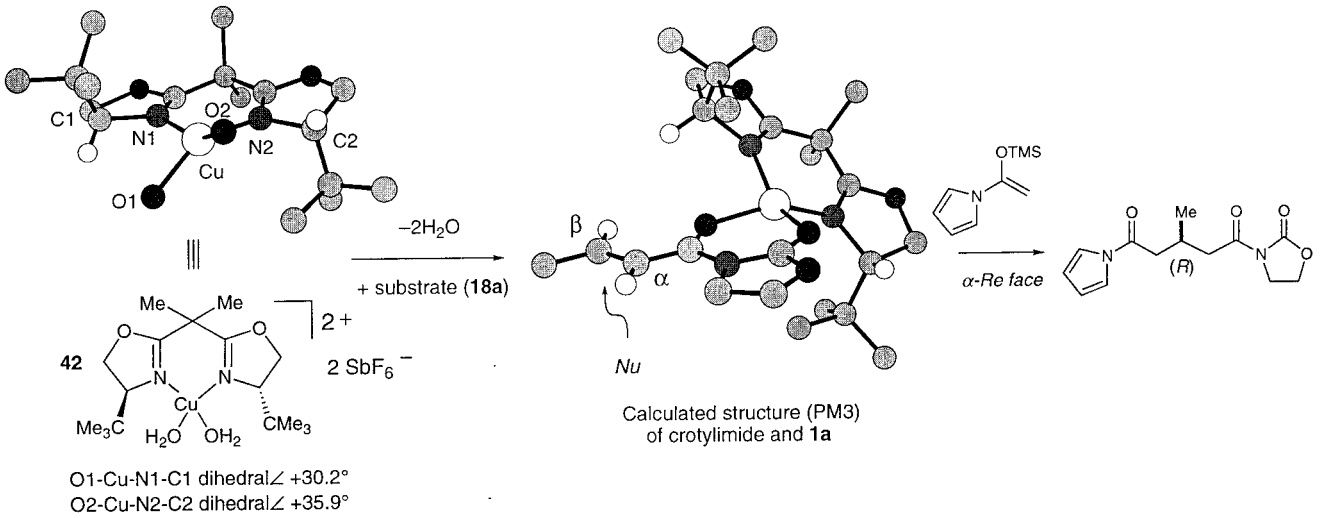


Figure 1. Origin of enantioselectivity inferred from the X-ray crystal structure of [Cu(*t*-Bu-box)(H_2O)$_2$](SbF_6)$_2$ (**42**) (ref 12) by replacement of H_2O ligands with substrate **18a** (counterions for **42** omitted for clarity).

cycloadditions with vinyl ethers.[39] The stereoregular behavior exhibited by these substrates implies similar substrate−catalyst complexes, and several solid-state structures of bis(oxazoline) Cu(II) complexes have now been disclosed that implicate a square-planar or distorted square-planar coordination geometry at the metal center. As in the stereochemical models for enantioselection in the Diels−Alder reaction, we have inferred from the crystalline hydrated complex [Cu((*S*,*S*)-*t*-Bu-box)]-(SbF_6)$_2$·2H_2O (**42**) that these Cu(II) Lewis acids will accept complementary carbonyl oxygen atoms in the substrate through dative bonds to the metal center (Figure 1). The six-membered chelate thus formed is activated toward nucleophilic donors and positioned in a manner that promotes a subsequent face-selective process.[8,9]

Analysis of this reaction was initially hampered by the inability to grow single crystals of the imide−Lewis acid complex. As an alternative to analyzing crystalline complexes incorporating imide substrates, in situ infrared spectroscopy was utilized to observe the proposed complex **A** (Figure 2).[40] Accordingly, Lewis acid **1a** (1 equiv) was added to a solution of the imide substrate (1 equiv) in 5 equal aliquots between sampling intervals (2 min) (Lewis acid:imide substrate = 1:1).[41] This experiment reveals that as Lewis acid is added, the absorptions at 1783 (urethane C=O stretch) and 1687 cm^{-1} (amide C=O stretch) decrease in intensity while two absorptions, 1738 and 1644 cm^{-1}, simultaneously increase in intensity. This behavior is consistent with our hypothesis that the Lewis acidic Cu(II) coordinates with these two carbonyls to form a six-membered chelate as in complex **A**. The ester carbonyl stretching frequency (1725 cm^{-1}) does not change during the experiment, suggesting that no significant interaction exists between the metal and this functional group. Hence, the Lewis acid binds imide substrates preferentially in a chelate fashion despite the presence of additional Lewis basic functionality.

In a separate experiment, a catalytic amount of Lewis acid **1a** was then used to promote the Michael addition reaction while being monitored by in situ IR spectroscopy to probe the identity and amount of carbonyl present throughout the reaction. In a representative experiment,[42] the reaction of propiophenone enolsilane **11** to fumarylimide **3** was monitored as a function of time (Figure 3). Immediately following addition of enolsilane to a solution of the imide substrate (1 equiv) and Lewis acid **1a** (0.1 equiv), a time-dependent decrease in the absorption diagnostic for the urethane (1783 cm^{-1}) was observed. The

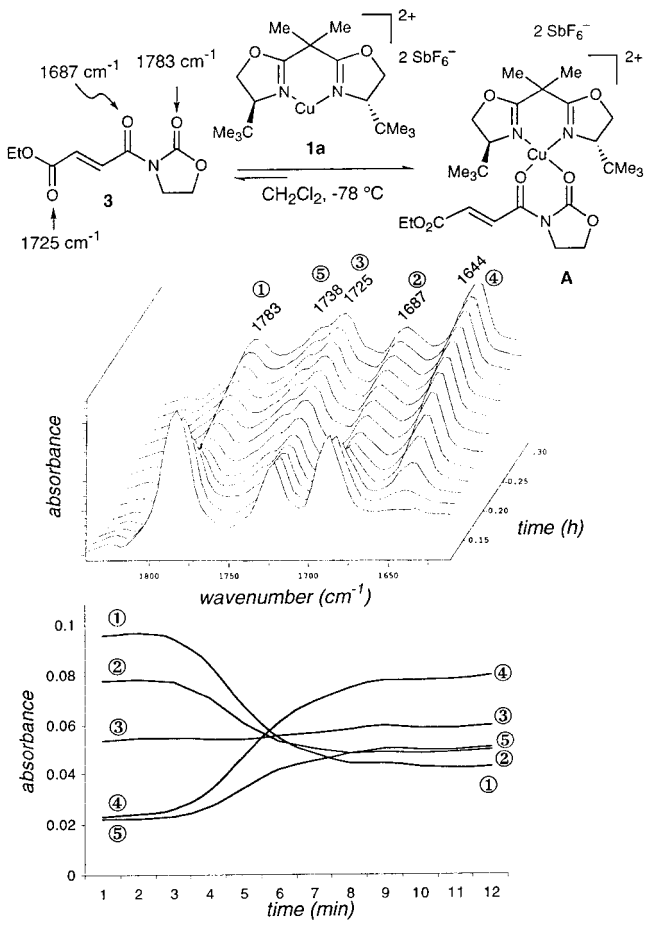


Figure 2. Imide complexation by copper(II) bis(oxazoline) monitored by in situ IR spectroscopy.

(39) Note that a turnover in π-facial selectivity is observed in hetero Diels−Alder reactions, but not in the Michael additions or Diels−Alder reactions. For a discussion of this phenomenon, see: Evans, D. A.; Johnson, J. S.; Burgey, C. S.; Campos, K. R. *Tetrahedron Lett.* **1999**, *40*, 2879−2882.

(40) In situ IR spectra were recorded on a ReactIR 1000 instrument from ASI Applied Systems. See Supporting Information for more details.

(41) In the graph and reaction plot for all figures with IR data, data points (=IR spectrum) represent actual samplings.

(42) Identical spectroscopic behavior is documented for thioester enolsilane Michael additions.

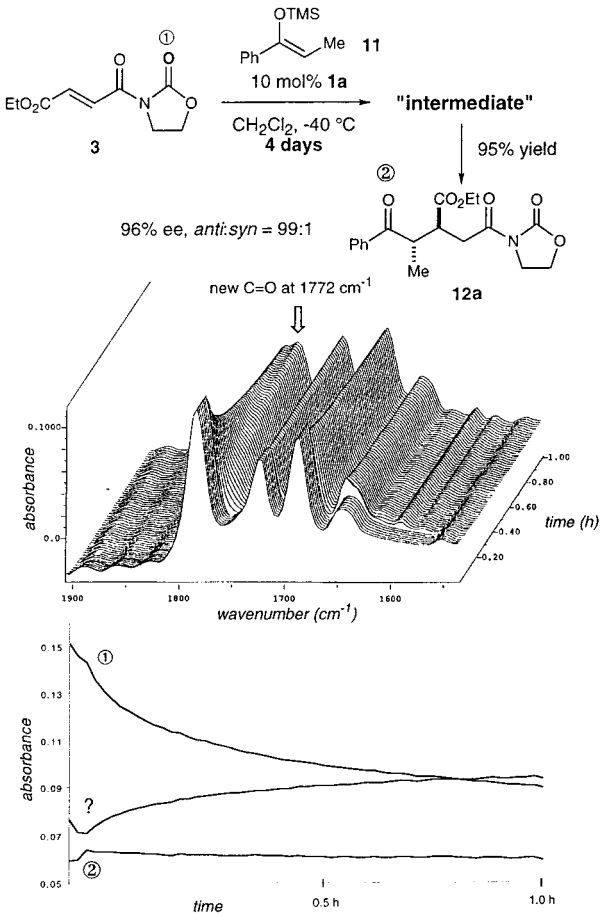


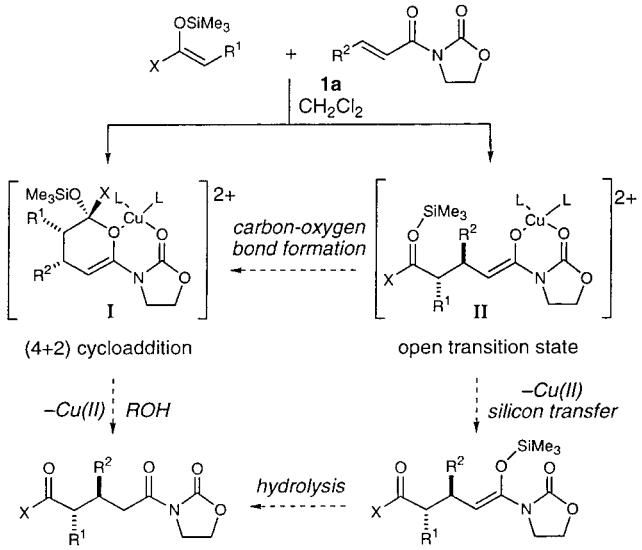
Figure 3. Monitoring the reaction by IR spectroscopy reveals the formation of an intermediate and stalling of the reaction.

generation and subsequent increase of a new absorption at 1772 cm^{-1} that appeared as a shoulder was also observed. The imide was consumed at a reasonable pace for the first hour, but the reaction then slowed dramatically. When the reaction was quenched after 2 h, a mixture containing **3** and product **12** in ca. a 70:30 ratio was detected. Clearly the catalyst had completed three cycles, but became inhibited as the reaction proceeded. In this particular case, a reaction time of 4 days was necessary to achieve complete substrate conversion (or 10 catalyst turnovers). *Interestingly, a plot of the nascent phenyl ketone carbonyl suggested it was not formed during the course of the reaction.*

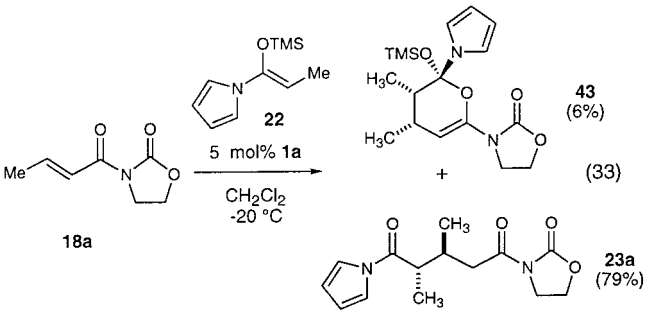
There are two plausible mechanistic pathways for this reaction (Scheme 3). The first is the "classical" Mukaiyama−Michael mechanism, in which the approach of the nucleophile occurs via an "open" transition state, either in a synclinal or antiperiplanar fashion.[43] Subsequent silicon transfer from the transient oxocarbenium ion in intermediate **II** to the copper enolate followed by hydrolysis would provide the product. However, the absence of product phenyl ketone in Figure 3 suggests that either (a) intermediate **II** collapses to dihydropyran **I** at a rate unobservable due to the spectral sampling rate or (b) the reaction proceeds directly to dihydropyran **I** by a hetero Diels−Alder [4+2] cycloaddition, followed by breakdown to product. Indeed, this cycloaddition manifold has precedent in our previous reports of the hetero Diels−Alder reaction between vinyl ethers and α-keto phosphonates or esters mediated by bis(oxazoline) Cu(II) catalysis.[44] Consistent with the [4+2] mechanism is the fact that in no instance do we observe the Michael

(43) For discussions of this possibility, see ref 2 and references therein.

Scheme 3. Possible Mechanistic Pathways of the Michael Addition of Enolsilanes to Unsaturated Acyloxazolinones



Scheme 4. Isolation of Dihydropyran **43** from Michael Reaction (Eq 33)



adduct enolsilane in unpurified reaction mixtures. An important feature of this work is that no evidence has been observed for the transmetalation pathway to form the Cu(II) enolate as the reactive species. Unpurified reaction mixtures were analyzed by ^{1}H NMR spectroscopy and in all cases, including reactions taken to only partial conversion, any excess enolsilane could be analyzed and shown to possess an *E/Z* ratio identical with that of the starting enolsilane.

While we have been unable to identify the intermediate dihydropyran **I** in the fumaryl imide series (outside of IR spectroscopy), it is possible to isolate and fully characterize the dihydropyran intermediate in Michael additions to crotonyl oxazolidinone (eq 33) when no additive is present. The relative stereochemistry of **43** was determined by using ^{1}H NMR spectroscopy (GOESY pulse program).[45] An important aspect of the reaction mechanism is the ability of the dihydropyran intermediate to inhibit the catalyst (Figure 4). The Lewis basicity of the resulting urethane carbonyl is increased in **III** relative to either starting material or product, but the superior chelating ability of the starting material might be expected to offset this basicity when considering their relative binding affinities. However, one might also consider that the fifth coordination

(44) Our findings most closely parallel those of Evans, but it is possible that numerous such observations have been made: (a) Toon, L. A.; Poon, C.-D.; Evans, S. A., Jr. *J. Org. Chem.* **1996**, *61*, 7455−7462. (b) Birkinshaw, T. N.; Tabor, A. B.; Holmes, A. B.; Kaye, P.; Mayne, P. M.; Raithby, P. R. *J. Chem. Soc., Chem. Commun.* **1988**, 1599−1601.

(45) (a) Stott, K.; Stonehouse, J.; Keeler, J.; Hwang, T.-L.; Shaka, A. J. *J. Am. Chem. Soc.* **1995**, *117*, 4199−4200. (b) Stonehouse, J.; Adell, P.; Keeler, J.; Shaka, A. J. *J. Am. Chem. Soc.* **1994**, *116*, 6037−6038.

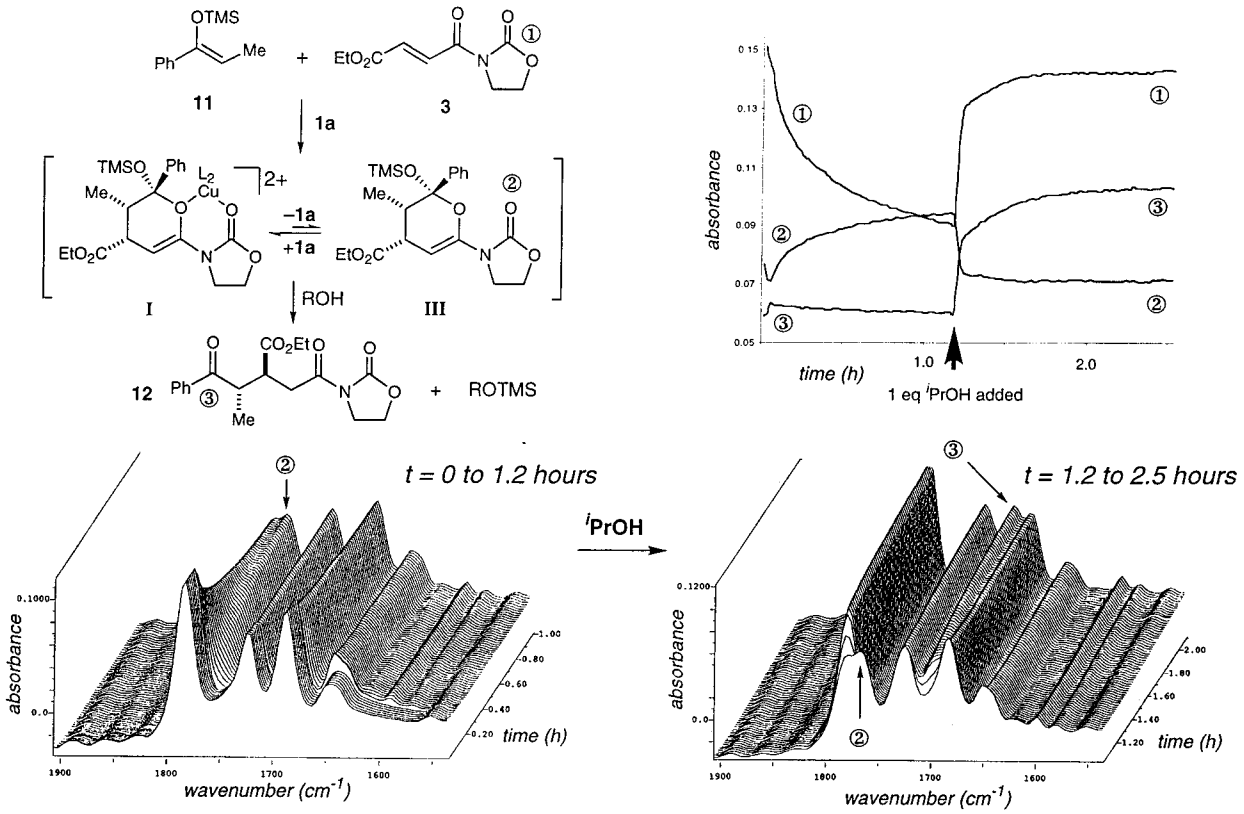
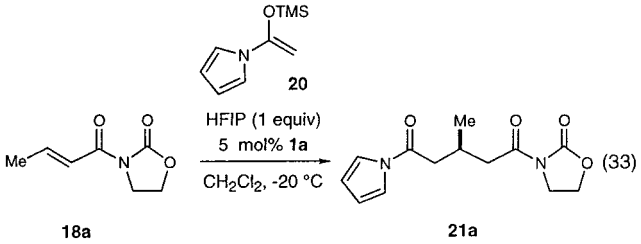


Figure 4. Monitoring the catalyzed Michael addition by in situ IR spectroscopy: characterization of an inhibiting intermediate.

site on square-pyramidal bis(oxazoline) Cu(II) is capable of accepting a monodentate Lewis base. The resulting interaction would substantially attenuate the Lewis acidity of the metal center, and result in an overall slowing of the reaction. The rate enhancement observed upon addition of HFIP to reactions catalyzed by **1a** can then be rationalized by the rapid hydrolysis of the inhibiting dihydropyran.[46] This observation is documented in Figure 4 by showing immediate formation of the product phenyl ketone carbonyl upon addition of an alcohol to a stalled reaction. The peaks corresponding to dihydropyran disappear, the product appears, and the catalyst turns over until the reaction is complete (ca. 2 h). The observation that the alcohol is the ultimate silicon acceptor in the acid hydrolysis of dihydropyran **III** could be monitored by IR spectroscopy. The latter behavior was also documented by IR spectroscopy in experiments with 2-propanol. The distinction between carbinol modes of action (Brønsted acid vs silicon shuttle) is important since most of our efforts were originally directed toward discovering effective silicon shuttles. In retrospect, discovery of an efficient silicon shuttle[47] would be of little practical value since it would produce a product that would similarly inhibit the catalyst.

In an experiment designed to test the ability of intermediate **III** to inhibit the catalyst, *N*-methyl oxazolidinone was added to the catalyzed Michael addition of enolsilane **20** to crotonyl imide (**18a**) (Table 15). The standard procedure normally affords the Michael adduct in 26 min with good enantioselection. However, catalyst activity is severely diminished in the presence of the urethane additive such that only 15% conversion is achieved after 3 h. Although *N*-methyl oxazolidinone is not electronically identical to **III**, it is clear that minor electronic perturbation of the urethane carbonyl unit of **III** can strongly inhibit this reaction. It is surprising that dihydropyran **III** is such a potent inhibitor when similar products from our Cu(II)-catalyzed hetero Diels−Alder reactions bearing phosphonate and ester groups do not seem to pose the same problem.

Table 15. Rate Comparison between Selected Catalyzed Michael Addition Reactions (Eq 33)



entry	R	additive	% conv	yield (%)[a]	time	ee (%)[b]
1	Me	−	100	90	26 min	89
2	Me	*N*-methyl oxazolidinone	15	11	3 h	95

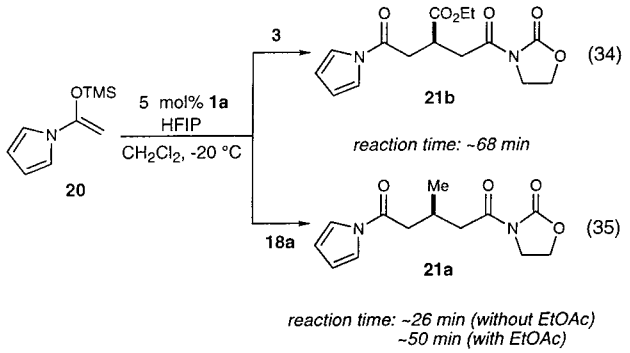
[a] Isolated yield. [b] Determined by chiral HPLC.

Overall rate differences between substrates of largely different electrophilicity have also been observed. For example, in the addition of *N*-acetylpyrrole enolsilane to oxazolidinones **3** and **18a** catalyzed by **1a** with an alcohol additive, the overall reaction times were found to be 68 and 26 min, respectively (Scheme 5). On the basis of the electronically activating effect (toward nucleophiles) the ethoxycarbonyl subunit of **3** imparts to the β carbon, the opposite relative reaction times are expected. Investigation of this phenomenon by charting reaction progress by IR spectroscopy led to the suggestion that it is the ester carbonyl that might competitively inhibit the Lewis acid catalyst.

(46) This conclusion is contrary to that reached by Katsuki (ref 5b), who postulates that the alcohol is quenching the nascent enolate.

(47) (a) Parmee, E. R.; Tempkin, O.; Masamune, S.; Abiko, A. *J. Am. Chem. Soc.* **1991**, *113*, 9365. (b) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837. (c) Hollis, T. K.; Bosnich, B. *J. Am. Chem. Soc.* **1995**, *117*, 4570−4581.

Scheme 5. Approximate Reaction Progress for Catalyzed Michael Additions (Eqs 34 and 35)



To test this hypothesis, a single equivalent of ethyl acetate was added to the oxazolidinone-catalyst solution prior to addition of enolsilane **20**. Reaction progress was again monitored by IR, revealing an overall reaction time for the crotonyl substrate that now approximates that for the fumaryl substrate. While it is not surprising that a polar functional group will interact with the Lewis acidic Cu(II) metal center, it is interesting that this *deactivating* interaction is observable and perhaps capable of overcoming the *activating* inductive effect from a functional group within the substrate. Fortunately, these effects are aptly balanced in substrate **3** for Michael additions with **1a** so that a synthetically useful reaction has been developed.

Reaction Diastereoselectivity. The implication of a hetero Diels−Alder reaction pathway provides an opportunity to explain the correlation between diastereoselection and enolsilane geometry. Generally, enolsilanes derived from the trans enolate[48] provide the syn diastereomeric products (eq 36) while enolsilanes from cis enolates afford the anti diastereomers (eq 37) with high levels of diastereoselectivity (Figure 5). This correlation of enolate geometry and product stereochemistry suggests that frontier orbital control and/or electrostatic effects could be playing an organizational role in this reaction (Figure 6). The observed endo preference is most likely the result of stabilization due to a secondary orbital overlap between the C-2 of the oxadiene (LUMO) and the trimethylsiloxy subunit (HOMO) of the enolsilane. The relative stereochemistry of intermediate **III** (Figure 4) is consistent with a strong endo bias for the trimethylsiloxy subunit. Importantly, this relation holds only for enolsilanes in which the trimethylsiloxy moiety is a more effective stereoelectronic control element than the geminal substituent (Ph, RS, or C_4H_4N) in stabilizing the endo stereoisomeric transition state structure. When ester enolsilanes are employed, low levels of enantioselectivity and diastereoselectivity are observed, most likely due to the comparable electronic properties of the trimethylsiloxy and alkoxy substituents.

REDOX Side Reactions. In no instance did we observe redox chemistry of the Cu(II) complex. Reaction temperatures as high as 0 °C were routinely implemented without complication. When the catalyzed Michael addition of enolsilanes to imide acceptors is performed in the absence of alcohol, the reaction mixture often undergoes a series of color changes that conclude with a predominantly brown endpoint. This color change appears to be correlated to the formation of Lewis acid−dihydropyran complex **I** and is not indicative of a reduced form of copper. The addition of alcohol hydrolyzes the dihydropyran and releases the catalyst back into the reaction, concomitant with a color change from brown to green or blue. Reactions utilizing an alcohol additive typically remain either blue or green in color throughout the reaction course.

(48) The trans and cis enolate nomenclature refers to the relationship between the *O*-metal bond of the enolate and the α-substituents and therefore remains consistent between thioesters, pyrrole amides and ketones, see: Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley and Sons: New York, 1994; Chapter 12.

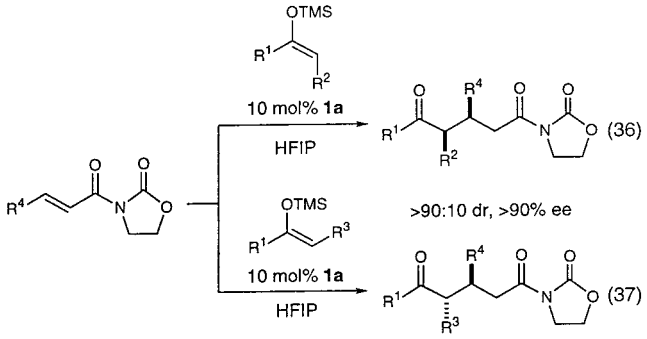


Figure 5. Stereochemical course of Mukaiyama−Michael additions catalylzed by **1a** (eqs 36 and 37).

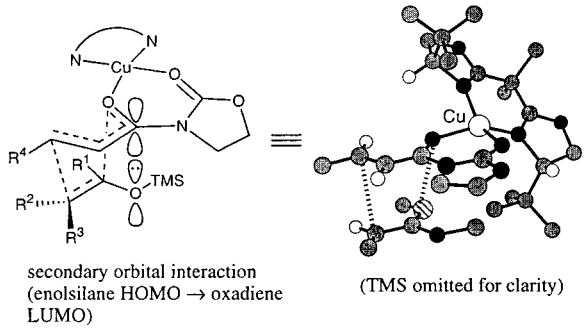


Figure 6. Qualitative model of the Mukaiyama−Michael transition state.

Conclusions

A highly enantioselective and diastereoselective Mukaiyama−Michael reaction of enolsilanes and substituted acryloyl oxazolidinones is catalyzed by C_2-symmetric bis(oxazoline) Cu(II) complexes. The enolsilane component of the reaction includes derivatives of phenyl ketones, thioesters, and acylpyrroles with or without substitution at the α-position. The Michael acceptor structure is confined to an unsaturated acylimide to promote chelation to the copper Lewis acid, but substitution at the β carbon includes fumarate esters, alkyl and aryl substituents, as well as the parent acrylate. The reactions described herein have been executed with low catalyst loadings (≤10 mol %) of an easily prepared Cu(II) complex at convenient temperatures (−20 °C). These attributes are particularly attractive when considering preparative scale use.

The high enantioselectivity of this reaction can be explained by the participation of a distorted square-planar substrate−catalyst complex which effectively shields one face of the activated Michael acceptor. The absolute and relative configurations of the Michael adducts were determined by X-ray crystallography and chemical correlation and are consistent with a hetero Diels−Alder reaction in which the incoming enolsilane exhibits a strong endo preference with respect to the silyloxy substituent. This preference explains the correlation of enolsilane geometry and diastereoselectivity. The methodology described herein is an efficient and highly selective entry into substituted glutaric acid derivatives and should find wide application in organic synthesis.

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

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