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# $C_2$-Symmetric Cu(II) Complexes as Chiral Lewis Acids. Catalytic, Enantioselective Cycloadditions of Silyl Ketenes

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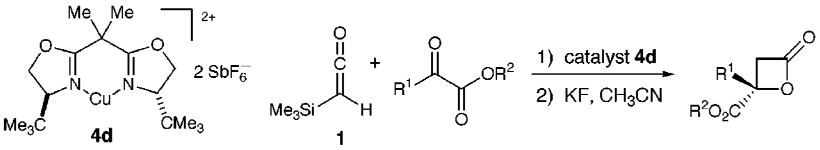
## ABSTRACT



**$C_2$-Symmetric bis(oxazoline)–Cu(II) complexes (4a–g) catalyze the enantioselective [2 + 2] cycloaddition between (silyl)ketenes and chelating carbonyl substrates. A range of substituted $\beta$-lactones can be produced in excellent yields and selectivities. It was also found that (trimethylsilyl)ketene (1) may also undergo a highly selective hetero Diels–Alder reaction with $\beta,\gamma$-unsaturated α-keto esters.**

The [2 + 2] cycloaddition between ketenes and carbonyl compounds serves as an expedient route to substituted $\beta$-lactones,[1] useful acetate enolate aldol equivalents.[2,3] Although there are numerous examples of Lewis acid catalyzed [2 + 2] reactions between ketenes and carbonyl substrates,[1,4] there are few general routes to enantiopure $\beta$-lactones.[5,6] We have recently demonstrated that $C_2$-symmetric Cu(II)−bis(oxazoline) complexes[7] serve as efficient catalysts[8] for enantioselective Diels−Alder,[9] hetero Diels−Alder,[10] Mu-

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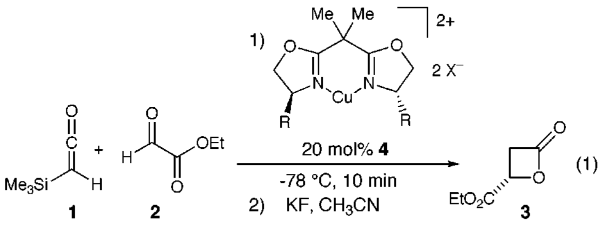
kaiyama aldol,[11] carbonyl ene reaction,[12] enol amination,[13] and Mukaiyama Michael addition reactions.[14] In each of these transformations, a chelating carbonyl substrate is required in order to impart a high level of structural organization in the transition state. We now present an extension of this strategy to the catalytic, enantioselective [2 + 2] cycloaddition reaction between nucleophilic silyl ketenes and chelating carbonyl substrates.

(Trimethylsilyl)ketene (**1**), a readily available,[15] stable ketene,[16] undergoes [2 + 2] cycloaddition with ethyl glyoxalate (**2**) in the presence of Cu(II)−bis(oxazoline) (box) complexes **4a**−**f** to afford $\beta$-lactone **3** (Table 1).[5b] Our preliminary catalyst screening revealed that [Cu{(*S*,*S*)-*t*-Bu-box}][$SbF_6$]$_2$ (20 mol % of **4d**, $CH_2Cl_2$, −78 °C) afforded cycloadduct **3** in 86% yield and 69% ee with 88:12 *cis*:*trans* diastereoselection (entry 4). Analogous reactions with hexafluoroantimonate catalysts **4a**−**d** all proceeded to completion in less than 10 min at −78 °C, and a subsequent in situ infrared spectroscopic experiment revealed that the **4d**-catalyzed cycloaddition is essentially instantaneous at this temperature. To attenuate catalyst reactivity, the reaction was conducted in the presence of catalyst **4e** containing the more coordinating trifluoromethanesulfonate (OTf) counterion.[9b] This catalyzed reaction (**4e**, −40 °C, $CH_2Cl_2$, 20 h) afforded the cycloadduct **3** in 93% yield and 77% ee (entry 5). In prior studies we have observed that solvent can have an influence on both the reactivity and selectivity of **4e** in the hetero Diels−Alder[10a,b] and Mukaiyama aldol additions to pyruvate esters,[11c] with donor solvents such as THF often affording superior results. When the [2 + 2] cycloaddition is performed with catalyst **4e** in THF (−78 °C, 20 h), the product **3** is obtained in >99% yield and 95% ee with >95:5 *cis*:*trans* diastereoselection (entry 6). As a consequence of this experiment, THF was selected as the optimal reaction solvent.

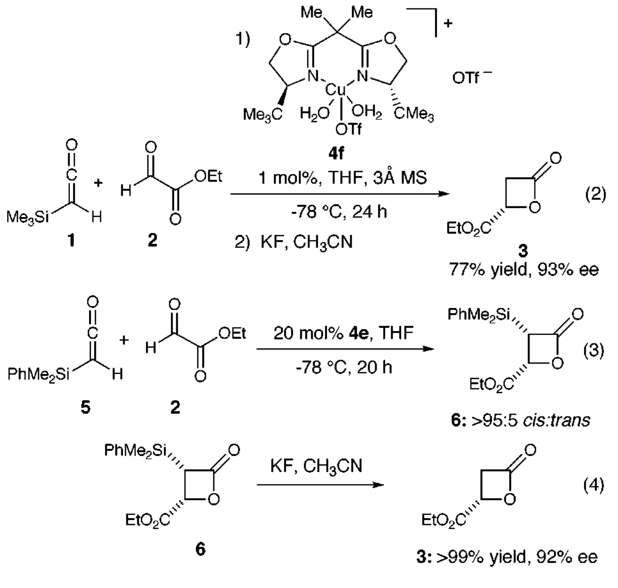
**Table 1.** Catalyst Screen for the Glyoxylate Cycloaddition (eq 1)



| entry | cat. **4** | R | X | solvent | *cis*:*trans*[a] | yield, % | ee, %[b,c] |
|---|---|---|---|---|---|---|---|
| 1 | **4a** | Ph | $SbF_6$ | $CH_2Cl_2$ | 88:12 | >99 | 17 (*R*) |
| 2 | **4b** | Bn | $SbF_6$ | $CH_2Cl_2$ | ND[d] | 92 | 0 |
| 3 | **4c** | $CHMe_2$ | $SbF_6$ | $CH_2Cl_2$ | 88:12 | 43 | 10 (*S*) |
| 4 | **4d** | $CMe_3$ | $SbF_6$ | $CH_2Cl_2$ | 91:9 | 86 | 69 (*S*) |
| 5[e] | **4e** | $CMe_3$ | OTf | $CH_2Cl_2$ | ND | 93 | 77 (*S*) |
| 6[f] | **4e** | $CMe_3$ | OTf | THF | >95:5 | >99 | 95 (*S*) |

[a] Diastereomeric ratio of silylated $\beta$-lactone determined by $^1$H NMR spectroscopy. [b] Enantiomeric excess determined by capillary GLC using a Cyclodex $\beta$ column. [c] Absolute configuration assigned by conversion to (*S*)-dimethyl malate (see Supporting Information). [d] ND = not determined. [e] Reaction conducted at −40 °C, 20 h. [f] Reaction conducted at −78 °C, 20 h.

We have recently reported the use of the hydrated [Cu{(*S*,*S*)-*t*-Bu-box}($H_2O$)$_2$(OTf)][OTf] catalyst **4f** for the hetero Diels−Alder reaction between $\beta$,$\gamma$-unsaturated α-keto esters and enol ethers.[10a,b] Catalyst **4f** is a bench-stable blue powder that may be activated in situ with powdered 3 Å molecular sieves. It was found that the [2 + 2] cycloaddition was effectively catalyzed by 1 mol % of hydrated catalyst **4f** (THF, −78 °C, 24 h) in the presence of 3 Å molecular sieves, affording the cycloadduct **3** in 77% yield and 93% ee (eq 2). The catalyzed [2 + 2] cycloaddition is tolerant of other silyl groups as well. The reaction of (dimethylphenylsilyl)ketene (**5**)[17] and ethyl glyoxylate (**2**), catalyzed by **4e**,



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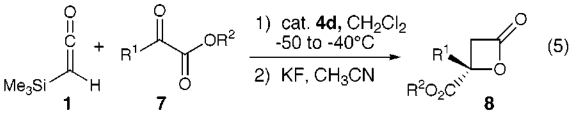
provided the silylated $\beta$-lactone **6** as a >95:5 ratio of diastereomers (eq 3). Attempts at oxidation of the silyl moiety under standard conditions[18] resulted in rapid protodesilylation. Desilylation of **6** using our usual procedure afforded **3** in >99% overall yield and 92% ee (eq 4).

**Reactions with α-Keto Esters.** [2 + 2] cycloaddition between (trimethylsilyl)ketene (**1**) and α-keto esters **7a**−**f** is also efficiently catalyzed by [Cu{(*S*,*S*)-*t*-Bu-box}][SbF$_6$]$_2$ **4d** (CH$_2$Cl$_2$ −50 °C, Table 2). For example, the reaction between **1** and methyl pyruvate (**7a**) in the presence of **4d** afforded cycloadduct **8a** in >99% yield and 95% ee[19] while the ethyl substituted α-keto ester **7b** gave cycloadduct **8b** in 92% yield and >99% ee. As the steric bulk of the acyl substituent is increased (R$^1$ = *i*Bu, *i*Pr, and Ph, **7c**−**e**), a slight decrease in enantioselection (79−87% ee) of the resulting $\beta$-lactones **8c**−**f** is observed. The reaction also accommodates the bromine-substituted pyruvate **7f**, affording **8f** in >99% yield and 91% ee. Cycloadducts **8a**−**f** provide convenient access to enantioenriched, hindered tertiary alcohols after ring opening.[2,3]

**Table 2.** Cycloadditions with α-Keto Esters (eq 5)

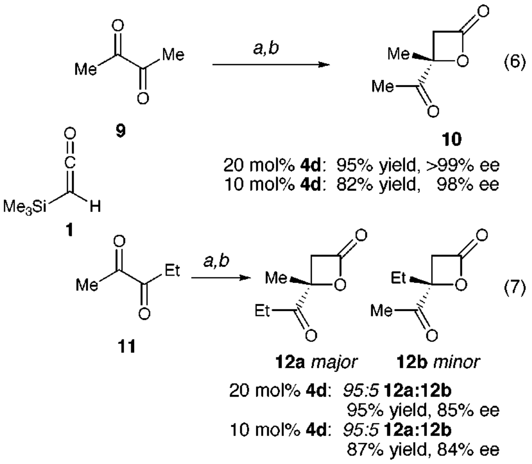


| α-keto ester | R$^1$ | R$^2$ | 20 mol % of **4d** % yield[a] (%ee[b,c]) | 10 mol % of **4d** % yield[d] (%ee[b,c]) |
|---|---|---|---|---|
| **a** | Me | Me | >99 (95) | 93[e] (95) |
| **b** | Et | Me | 92 (99) | 89 (93) |
| **c** | $^i$Bu | Me | 87 (83) | 89 (86) |
| **d** | $^i$Pr | Et | 86 (85) | 78 (88) |
| **e** | Ph | Me | 79[d] (87) | 76 (83) |
| **f** | BrCH$_2$ | Et | >99 (91) | 75 (91) |

[a] Reaction conducted over 24 h. [b] Enantiomeric excess determined by capillary GLC using a Cyclodex $\beta$ column or by HPLC using a Chiralcel OD-H column. [c] Absolute configurations assigned by analogy. [d] Reaction conducted over 48 h. [e] Reaction conducted over 24 h with 1 mol % of **4d**.

The effect of catalyst loading was also examined for these substrates. As shown, the reaction between **1** and methyl pyruvate (**7a**) proceeds at −40 °C over 24 h in the presence of 1 mol % of **4d**, affording cycloadduct **8a** with excellent yield and enantioselectivity. In contrast, a decrease in catalyst loading to 10 mol % of **4d** for the larger acyl substituents (**7b**−**f**) resulted in comparable enantioselection but longer reaction times (48 h) and lower yields in some instances.

The reaction scope has been extended to α-diketones. It was found that the cycloaddition between 2,3-butanedione (**9**) and **1** mediated by catalyst **4d** generated **10** in 95% yield with >99% ee (eq 6). In addition, the [Cu{(*S*,*S*)-*t*-Bu-box}][SbF$_6$]$_2$ complex **4d** is able to effectively discriminate between the ethyl and methyl substituents in 2,3-pentanedione (**11**) to the extent of 95% (eq 7). Notably, of the eight possible isomeric products that may be obtained in this cycloaddition, **12a** is formed with 95:5 regioselection, 95% yield, and with 85% ee. When catalyst loading was reduced to 10 mol %, a slight decrease in yield was noted; however, reaction stereoselectivity was maintained. In contrast, the analogous reaction catalyzed by BF$_3$·OEt$_2$ proceeds with 80:20 regioselection. The excellent level of selectivity observed is indicative of the high level of organizational control that may be obtained with Cu(II)−bis(oxazoline) complexes **4d** and dicarbonyl substrates.[11b,c]



20 mol% **4d**: 95% yield, >99% ee
10 mol% **4d**: 82% yield, 98% ee

20 mol% **4d**: *95:5* **12a**:**12b**
95% yield, 85% ee
10 mol% **4d**: *95:5* **12a**:**12b**
87% yield, 84% ee

We propose that high enantioselection for this [2 + 2] cycloaddition requires chelation of the carbonyl electrophile to the Lewis acid. The reaction of hydrocinnamaldehyde (**13**) with (trimethylsilyl)ketene (**1**) and catalyst **4d** affords cycloadduct **14** in poor yields (28%) and low selectivity (35% ee) (eq 8).[20] We have recently shown that [Cu{(*S*,*S*)-Ph-pybox}][SbF$_6$]$_2$ (**4g**)[21] catalyzes the Mukaiyama aldol addition of silyl ketene acetals to (benzyloxy)acetaldehyde with excellent levels of enantioselection and yield.[11d] Similarly, the reaction between **1** and (benzyloxy)acetaldehyde (**15**) is efficiently catalyzed by **4g**, affording cycloadduct **16** in 92% yield and 87% ee (eq 9).[22] This demonstrates that the electrophilic component requires a moiety capable of chelation in order to achieve an organized substrate−catalyst complex in the transition state.

**Hetero Diels−Alder Reaction.** Previous reports from us and others have documented the highly stereoselective hetero Diels−Alder reaction between $\beta$,$\gamma$-unsaturated α-keto esters and enol ethers.[10] In a similar manner, catalyst **4d** induces a highly diastereo- and enantioselective hetero Diels−Alder reaction between (trimethylsilyl)ketene (**1**) and keto ester **17**, providing $\delta$-lactone **18**[23] in 96% yield with >95:5 *endo*:*exo* diastereoselection and 97% ee (eq 10).

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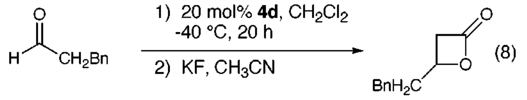
(19) Previous work with the Cu(II)−bis(oxazoline)-catalyzed Mukaiyama aldol reaction between silylketene acetals and pyruvate esters has shown that the ester substituent has little influence on the stereochemical course of the reaction, see ref 11c.

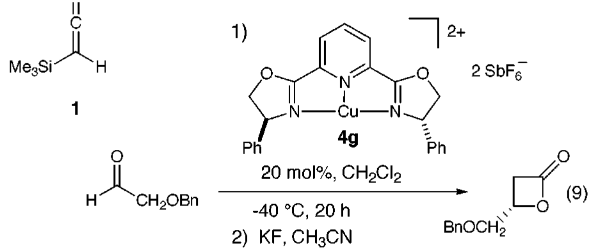
(20) The reaction of (trimethylsilyl)ketene (**1**) and hydrocinnamaldehyde (**13**) was not catalyzed by [Cu{(*S*,*S*)-Ph-pybox}][SbF$_6$]$_2$ (**4g**).

(21) For synthesis of the PyBox ligands, see: Nishiyama, H.; Kondo, M.; Nakamura, T.; Itoh, K. *Organometallics* **1991**, *10*, 500−508.

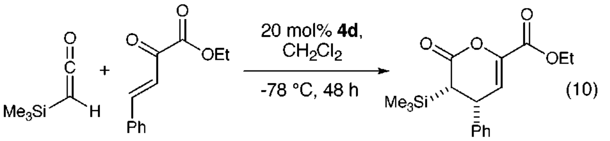
(22) The absolute configuration was determined by acyl ring opening of **16** with EtOH to yield the previously reported ethyl ester, see ref 11d and Supporting Information.



**13** **14:** 28% yield, 35% ee



**1** **15** **16:** 92% yield, 87% ee

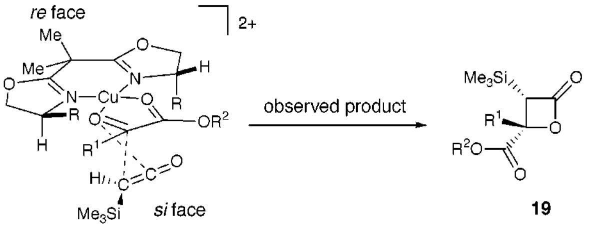


**1** **17** **18:** 96% yield, *endo:exo* >95:5
97% ee

The transition state for the Lewis acid catalyzed ketene–aldehyde [2 + 2] cycloaddition is believed to be a concerted, highly asynchronous $_{\pi}2_s + (_{\pi}2_s + _{\pi}2_s)$ interaction between the perpendicular HOMO and LUMO orbitals of the ketene and the LUMO of the activated carbonyl.[1b,24] The initial orbital interaction is between the HOMO of the ketene and the Lewis acid activated LUMO of the carbonyl substrate, followed by ring closure with the ambiphilic ketene.[24d,25] In this sense, (trimethylsilyl)ketene (**1**) can be regarded as a weak nucleophile.

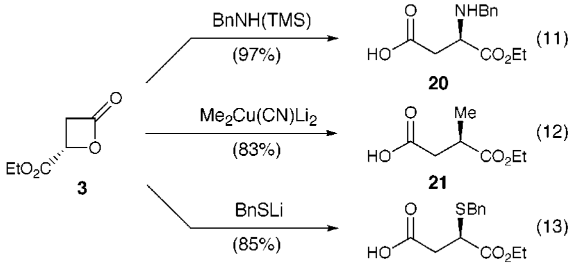
The geometric requirements of the ketene orbitals result in an orthogonal approach of the ketene onto the activated carbonyl. As shown in Scheme 1, approach of the ketene from the less hindered (bottom) *si* face of the catalyst complex would produce the observed stereochemistry. The observed *syn* diastereoselection of the silylated intermediate **19** can be explained by assuming placement of the TMS group away from the large catalyst–substrate complex. This model and the observed stereoselectivity are in accordance with other Cu(II)–bis(oxazoline) catalyzed nucleophilic additions and cycloadditions to chelating substrates.[8–14]

**Scheme 1**



**19**

***β*-Lactone Ring Opening.** *β*-Lactones may serve as a powerful synthon for a variety of substituted carboxylic acids via ring opening with the appropriate nucleophile. Opening may proceed through acyl–oxygen cleavage with "hard" nucleophiles, giving the free alcohol, or alkyl–oxygen cleavage with "soft" nucleophiles to give substituted carboxylic acids. When **3**, prepared from the above methodology or from lactonization of (*R*)-malic acid,[26] is treated with *N*-benzyl-*N*-(trimethylsilyl)amine, the protected aspartic acid **20** is generated in 97% yield (eq 11).[3a] In a similar manner, higher order cyanocuprates may also open the *β*-lactone.[3g] The reaction of **3** with $Me_2Cu(CN)Li_2$ provides the methyl-substituted carboxylic acid **21** in 83% yield (eq 12). Furthermore, lactone **3** may be treated with lithium benzylsulfide to give, in 85% yield, the benzylsulfide-substituted carboxylic acid **22** (eq 13).[3f]



In summary, we have found that Cu(II)–bis(oxazoline) complexes mediate a highly enantioselective [2 + 2] cycloaddition of (silyl)ketenes and chelating carbonyl substrates. It was also found that (trimethylsilyl)ketenes (**1**) may undergo a highly selective hetero Diels–Alder reaction to provide a substituted *δ*-lactone. (Silyl)ketenes act as component nucleophiles in Lewis acid catalyzed reactions, and it is the ambiphilic nature of the (silyl)ketene which provides the formal cycloaddition product. The cycloaddition tolerates a variety of substrates and yields lactones which may serve as an alternative entry into enantioenriched aldol addition products via ring opening.

**Acknowledgment.** Support has been provided by the National Science Foundation.

**Supporting Information Available:** Experimental procedures and characterization of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[23] The absolute and relative configuration of cycloadduct **18** was assigned by 2D $^1$H NMR and chemical correlation (see Supporting Information).

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