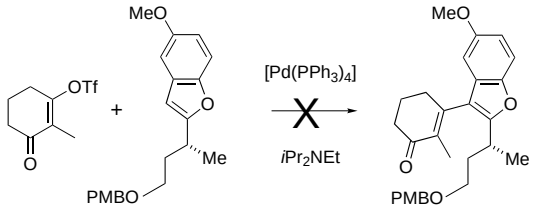
[9] All attempts to effect a Friedel–Crafts type cyclization of the sensitive diketone **14** with polyphosphoric acid were unsuccessful.
[10] Interestingly, no product was observed for intermolecular versions of this reaction, see for example Equation (1).



(1)

[11] At elevated temperature (110 °C) partial racemization was observed to afford the cyclized product (−)-**6** in 86% *ee*.
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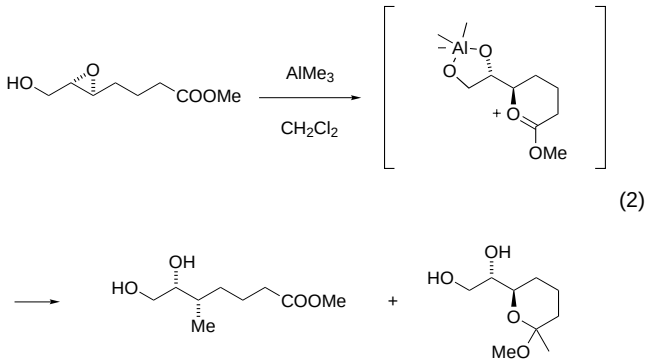
[16] Complete inversion would imply a highly stereoselective protonation of enol ether **16** since a suprafacial [1,3]-hydrogen shift is thermally not allowed.
[17] The most likely candidate for such a switch is the nucleophilic opening of an epoxy alcohol with trimethylaluminum, which probably proceeded with unwanted retention of configuration through participation of the ester carbonyl group [Eq. (2)]. See also footnote 42 in reference [2b]. In fact, a case of retention of configuration is already documented in the original publication on the ring opening of epoxy alcohols with organoaluminum compounds: T. Suzuki, H. Saimoto, H. Tomioka, K. Oshima, H. Nozaki, *Tetrahedron Lett.* **1982**, *23*, 3597–3600.



(2)

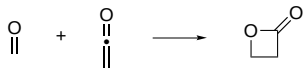
[18] Attempts to assign the absolute configuration of frondosin B independently by X-ray crystallographic analysis of its bromobenzoate and camphanoyl ester have thus far been unsuccessful.

Mechanism and Origin of Stereoselectivity in Lewis Acid Catalyzed [2 + 2] Cycloadditions of Ketenes with Aldehydes**

Daniel A. Singleton,* Yingcai Wang, Hong Woon Yang, and Daniel Romo*

Stereoselectivity as a general phenomenon arises from differences in free energy associated with diastereomeric transition states or diastereomeric products. Free-energy differences between diastereomeric pathways are a requirement for stereoselectivity, but they are not sufficient in themselves. For example, high kinetic enantioselectivity may be compromised by product racemization. Another common situation is when stereoisomeric products are formed by differing mechanisms, so the inhibition of alternative mechanisms is often pivotal in the development of stereoselective methodology. A more complex possibility is that stereoisomeric pathways may have different rate-limiting steps.[1] We describe here evidence for such an event in a cycloaddition in which diastereomeric products are formed, and we discuss the impact of divergent rate-limiting steps on selectivity.

β-Lactones are exceptionally versatile intermediates in organic synthesis,[2] and there has been considerable interest in their direct synthesis from the [2 + 2] cycloaddition of ketenes with carbonyl compounds [Eq. (1)] .[3] A growing number of variants employ achiral[4] or chiral[5] Lewis acids catalysts to afford optically enriched β-lactones by substrate or reagent control, respectively.



(1)

The synthetic utility and fundamental allure of these formally forbidden cycloadditions make their mechanism of considerable interest. Experimental studies have been limited to substituent, solvent, and stereochemical effects in the uncatalyzed reaction,[6] but several theoretical studies have

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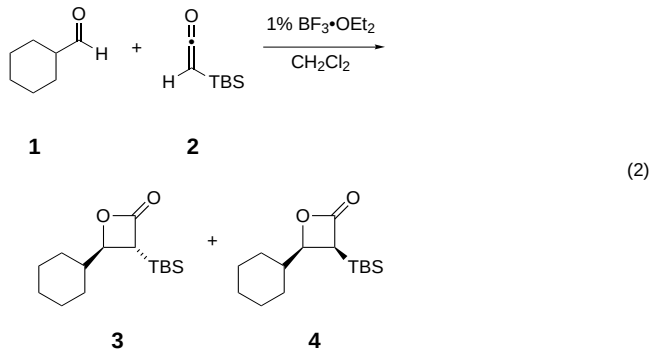
looked at both the uncatalyzed and Lewis acid catalyzed cycloadditions. For the uncatalyzed process, AM1 calculations predict a stepwise process but Hartree-Fock (HF), CASSCF, and denisty functional theory (DFT) calculations all favor a concerted mechanism involving a $[\pi 2_s + (\pi 2_s + \pi 2_s)]$ transition state.[7] Similarly for Lewis acid catalyzed reactions, AM1 calculations on the reaction of formaldehyde · BF_3 with ketene predict a stepwise process involving a zwitterionic intermediate,[8] while HF calculations employing an Onsager-type solvent model for the cycloaddition of acetaldehyde · BH_3 with chloroketene favor a concerted asynchronous mechanism.[7c] The conflicting predictions, the use of simplified model systems, and intrinsic limitations of the calculational methods employed combine to impede a secure understanding of mechanism and selectivity in the Lewis acid catalyzed reaction.

Our goal was to define the stepwise versus concerted nature of the cycloaddition in a synthetically relevant example and to gain insight into its stereoselectivity. Toward that end, the clean, high-yielding BF_3-catalyzed cycloaddition of cyclohexanecarboxaldehyde (**1**) with *tert*-butyldimethylsilylketene (**2**) was chosen for study [Eq. (2); TBS = *tert*-butyldimethylsilyl]. This reaction had previously been reported to afford a 62% yield of a 96:4 ratio of the *trans* and *cis* diastereomeric



(2)

products **3** and **4** (−20 °C, "catalytic" $BF_3 \cdot OEt_2$, 1M HCl workup).[3c] Under our conditions (0 °C, 1 mol% $BF_3 \cdot OEt_2$, buffered workup) the yield of isolated product was as high as 98% and typically >90%. An intriguing observation in this reaction is that the ratio of **3**:**4** varies substantially with temperature, and the selectivity *decreased* with decreasing temperature (Table 1). No isomerization was observed under the reaction conditions, and all of the reactions appeared devoid of side products by NMR analyses.

The ^{13}C kinetic isotope effects (KIEs) for this reaction were determined at natural abundance by NMR spectroscopy.[9] To determine the ^{13}C KIE for the carbonyl carbon atom of **1**, reactions using a limiting amount of **2** and 1% (versus **1**) $BF_3 \cdot OEt_2$ at 0 °C were taken to 10–20% aldehyde conversion. Similarly, the ^{13}C KIEs for **2** were determined from reactions using excess **2** and a limiting amount of **1** taken to approximately 10–20% conversion of **2**. Isotope effects were then calculated from the difference in ^{13}C isotopic composition of the products **3** and **4**, compared to standard samples of products from reactions taken to completion. In the ^{13}C NMR analysis of these samples, the tertiary cyclohexyl ring carbon and the dimethylsilyl carbon signals were used as "internal standards" with the assumption of a negligible isotope effect in these positions. The results from three independent reactions are summarized in Figure 1. The KIEs obtained are directly limited in precision by the precision of the NMR integrations, and these are the most complex molecules analyzed in this manner so far. Given this, the reproducibility of the experimental KIEs from independent measurements is very reasonable.

Table 1. Effect of temperature on *cis*/*trans* diastereoselectivity of the Lewis acid catalyzed [2+2] cycloaddition of **1** with **2** [Eq. (2)].

Entry	Reaction temperature [°C]	**3**:**4**
1	+23	2.7–3.1:1
2	0	1.4–1.7:1
3	−21	1.3:1
4	−42 → +23	1.1:1

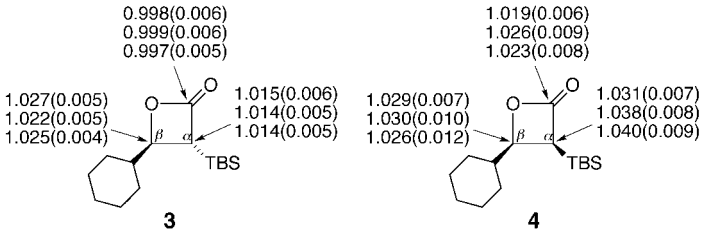
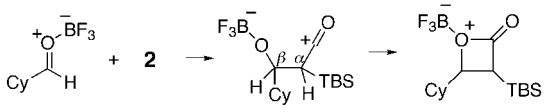


Figure 1. ^{13}C KIEs (k_{12C}/k_{13C}, 0 °C) for the $BF_3 \cdot OEt_2$-catalyzed [2+2] cycloaddition of **1** with **2**, measured in three independent reactions. Standard deviations from six measurements on each sample are shown in parentheses.

The most striking observation is that the KIEs for the formation of diastereomers **3** versus **4** differ substantially. This is indicative of significantly differing mechanisms or rate-limiting steps in the formation of these products. This is unusual—the Ockham's-razor assumption is that diastereomeric products are formed by stereoisomeric but otherwise identical pathways. Clearly something more intricate is occurring here.

Qualitatively, the observation of significant ^{13}C KIEs at the α-and β-carbon atoms of **3**, but no KIE at the carbonyl carbon atom, is suggestive of rate-limiting formation of the C_α–C_β bond of the impending *trans*-β-lactone. This does not preclude a highly asynchronous concerted [2+2] cycloaddition, but the most economical hypothesis would be rate-limiting (irreversible) C_α–C_β bond formation [Eq (3); Cy = cyclohexyl]. In the

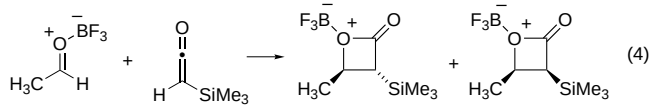


(3)

formation of the *cis* product **4**, the substantial ^{13}C KIEs at all ring carbon atoms would customarily be associated with a concerted cycloaddition. However, it has been recently observed that large secondary ^{13}C isotope effects, mimicking primary ^{13}C KIEs, can result from the weakened bonds $\alpha-\beta$

to charged atoms in reactive intermediates.[10] Thus a stepwise mechanism can account for significant C_α and C_β KIEs. The KIE of the carbonyl carbon atom in **4** would then be consistent with a rate-limiting second step for a stepwise mechanism.

Theoretical studies buttress these ideas. The model cycloaddition of *anti*-acetaldehyde · BF_3 (**5**) with trimethylsilylketene (**6**) [Eq. (4)] was studied in B3LYP/6-31 + G* calculations, employing an Onsager-type continuum solvent model[11] for geometry optimizations and a polarizable continuum model (PCM) solvent model for single-point energy calculations.[12] Both the solvent model and diffuse functions were



5 **6** **7** **8**

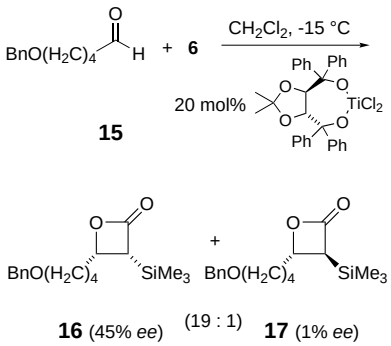
required for chemically reasonable results. In the absence of the solvent model, stationary points on the *cis* pathway could not be located, while without diffuse functions the apparent *trans* pathway gave rise to an open-chain acyl fluoride product. A pathway involving *syn*-acetaldehyde · BF_3 had a 5.3 kcal mol^{-1} higher barrier than those with **5** (see Supporting Information). Efforts to locate transition structures for concerted cycloadditions or for reaction of acetaldehyde with **6** · BF_3 were unsuccessful.

In contrast to previous theoretical studies, the calculations here predict a stepwise cycloaddition mechanism (Figure 2). In this mechanism, initial C–C bond formation via transition structures **9** and **12** leads to zwitterionic intermediates **10** and **13**. Subsequent ring closure forms the *trans*- and *cis*-β-lactone products via the C–O bond-forming transition structures **11** and **14**, respectively.

Most notably, the calculations predict that the first step will be rate limiting for formation of the *trans* product and the second step will be rate limiting for formation of the *cis* product.[13] The predicted activation barriers of 9.3 and 10 kcal mol^{-1} are consistent with a reaction that proceeds to completion in a few minutes at 0 °C using 1 mol % catalyst. In accord with the experiment, the activation barriers are predicted to be similar.[14] It should be noted that the predicted selectivity is very different than if either the first step or the second step were considered by themselves.

The aforementioned decrease in selectivity with decreasing temperature also supports the idea of differing mechanisms or rate-limiting steps in the formation of **3** versus **4**. If **3** and **4** were formed by similar rate-limiting transition states with comparable activation entropies, the selectivity would exhibit the normal tendency to increase with decreasing temperature. The increased preference for **3** at higher temperatures indicates that it is "entropically favored." This fits with a rate-limiting first step. The confounding effect of solvent entropy imperils predictions of activation entropies for charged reactions, but one might normally expect that the looser first transition state in a stepwise cycloaddition would have greater entropy than the second.

An observation from the closely related TADDOL-$TiCl_2$ catalyzed cycloadditions of **6** with aldehydes appears relevant. These reactions afford predominantly *cis* α-silylated β-lactones, with moderate enantiomeric excesses determined after separation and desilylation.[15] The *trans*-β-lactone is formed with much lower enantioselectivity [Eq. (5)]. This is again



consistent with very dissimilar selectivity-determining steps in the formation of the *cis* versus *trans* products.

The results described here suggest a very different rationale for the stereoselectivity of this class of cycloadditions from that proposed by Cossio and co-workers for the reaction of chloroketene with acetaldehyde · BH_3.[7c] In that work, a preference for the *cis* product with bulky catalysts was attributed to a steric interaction of the catalyst with H versus R^1 in the concerted transition state model **18** (Figure 3a). The present study suggests that formation of *trans* β-lactones proceeds via rate-limiting transition state **9** (Figure 2, cf. **19**, Figure 3b) in which the aldehydic

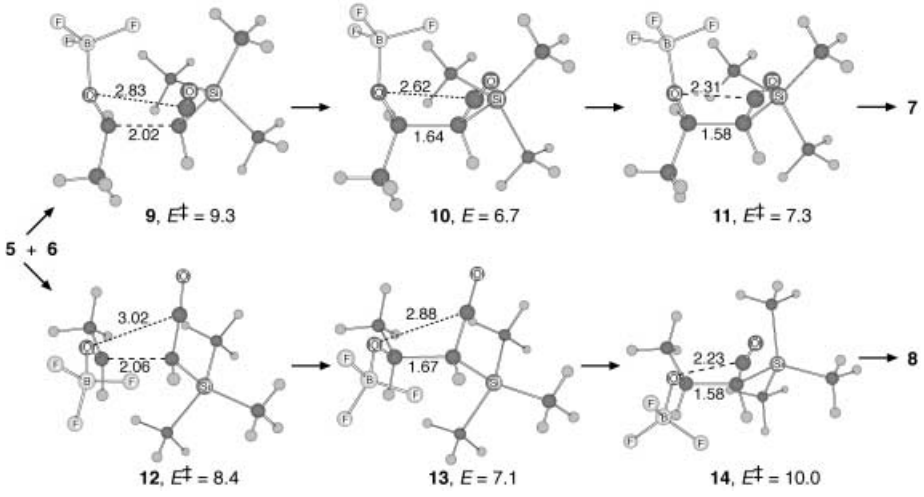


Figure 2. Calculated structures and energies for the cycloaddition of **5** with **6**. Selected distances are given in Å—for complete structures see Supporting Information. Energies are kcal mol^{-1}, relative to **5** + **6**.

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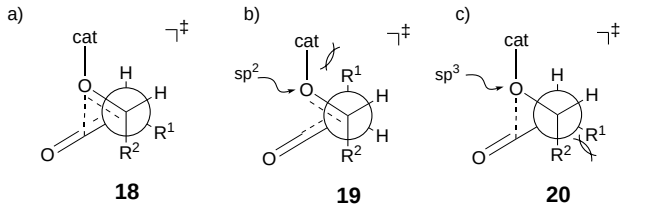

Figure 3. Transition state models for rationalizing stereoselectivity in the [2 + 2] cycloaddition: a) Cossio's model[7c]], b) revised model leading to *trans* diastereomer with C–C bond formation as rate-limiting and selectivity-determining step, c) revised model leading to *cis* diastereomer with C–O bond formation as rate-limiting and selectivity-determining step.

oxygen atom is sp^2 hybridized and the Lewis acid is not free to rotate away from steric interactions with the silyl group. Alternatively, transition state structure **14** (Figure 2, cf. **20**, Figure 3c) is rate limiting for the formation of the *cis* product and in this case, the aldehydic oxygen atom is sp^3 hybridized and the Lewis acid can rotate away from steric interactions. Thus, catalyst bulk would have a greater inhibiting effect on formation of the *trans* product (i.e. greater cat./R^1 interaction) and lead to higher *cis* selectivity as observed. The observation by Yamamoto[3c] that bulky groups (R^1) on the ketene favor the *trans* product would be explained by an unfavorable steric interaction with the aldehydic substituent R^2 in **14** (Figure 2, cf. **20**, Figure 3c) which takes on added importance when one considers that C–C bond formation is rate limiting. This observation is not so readily understood from Cossio's model **20** (Figure 3a). Overall, one can conclude that R^1/R^2 interactions are most important during the formation of *cis*-β-lactone diastereomers since these impending eclipsed interactions have the greatest impact on the rate-limiting ring closure (C–O bond formation) following C–C bond rotation. On the other hand, catalyst/R^1 interactions predominate for the reaction pathway leading to the *trans* diastereomer.

More generally, the observations made in this study highlight that a broad range of factors must be pondered in order to understand and control stereoselectivity in a multistep reaction. Selectivity among competitive pathways may be determined by dissimilar transition states or divergent rate-limiting steps, and a strong energetic preference for one transition state over a stereoisomeric partner is not sufficient to guarantee high stereoselectivity. Rather, stereoselectivity must be controlled throughout a mechanism.

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[13] A comparison of the experimental and predicted KIEs provides ambiguous support for the calculated structures. The predicted ^{13}C KIEs for **9** are 1.034, 1.028, and 1.000 for C_β, C_α, and $C_{C=O}$, respectively, in qualitative agreement with the experimental values. The predicted ^{13}C KIEs for **14** are 1.017, 1.000, and 1.028 for C_β, C_α, and $C_{C=O}$, respectively. The qualitative discrepancy at C_α may mean that the KIEs for **4** are best interpreted as a concerted mechanism, or it may just reflect the difficulties of calculations on charged intermediates.
[14] Owing to a referee's concern over using an unbranched aldehyde as a theoretical model, we have repeated our calculations with isobutyraldehyde instead of acetaldehyde and the results are qualitatively identical (see Supporting Information). The energies for the isobutyl analogues of **9**–**14** (B3LYP/6-31G*/PCM//B3LYP/6-31G*/Onsager + zpe, versus starting materials) are 13.1, 11.0, 11.3, 12.5, 11.6, and 14.6 kcal mol^{-1}, respectively.
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Cyclotetrasilenide Ion: A Reversible Redox System of Cyclotetrasilenyl Cation, Radical, and Anion**

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Alkali metal derivatives of organosilicon compounds are useful not only in organosilicon chemistry, but also in organic synthesis. The synthesis, reactivity, and structural aspects of silyllithium compounds are the most studied of alkali metal derivatives.[1] Numerous anionic organosilicon compounds are

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