Organic LETTERS
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Origins of Diastereoselectivity in Lewis Acid Promoted Ketene–Alkene [2 + 2] Cycloadditions

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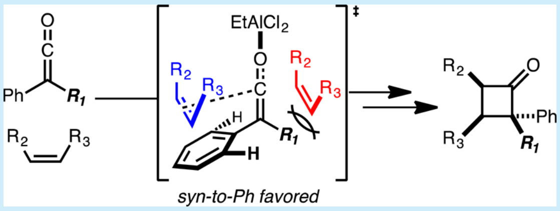
Supporting Information

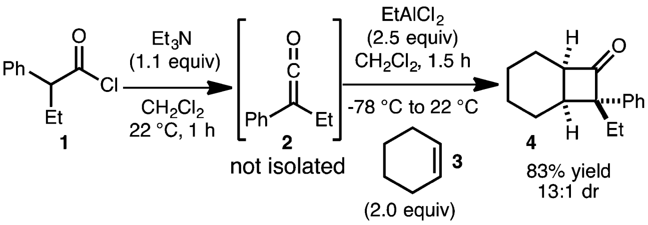
ABSTRACT: A detailed analysis of a Lewis acid promoted ketene–alkene [2 + 2] cycloaddition is reported. The studies have led to a rationalization for an observed inversion of diastereoselectivity between thermally induced and Lewis acid promoted ketene–alkene [2 + 2] cycloadditions. The model is supported with both experimental and computational results.



We recently reported a method for Lewis acid promoted ketene–alkene [2 + 2] cycloadditions.[1] This method offers a number of advantages relative to traditional thermally induced variants.[2] The advantages include increased reactivity, increased diastereoselectivity, increased regioselectivity, and, for certain cases, inverse diastereoselectivity.[1] The latter point raised interesting questions concerning issues of stereocontrol. Herein, we describe a mechanistic analysis of how the ketene substitution pattern affects the diastereoselectivity of cycloaddition. This analysis of experimental results is also supported with related computational data.

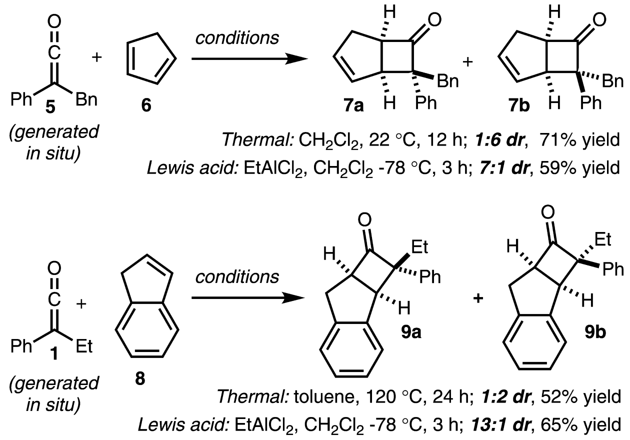
The standard conditions for cycloaddition are illustrated in Scheme 1.[1] Several points are important to note: (1) A stoichiometric Lewis acid is necessary due to severe product inhibition. (2) For reactions with disubstituted ketenes, Al(III) Lewis acids are uniquely effective. (3) The ketene can be either generated and used as a solution in dichloromethane without removal of the Et_3NHCl byproduct or isolated and purified with little change in yield or diastereoselectivity. In the former case ~2.5 equiv of $EtAlCl_2$ are necessary because 1 equiv of the Lewis acid reacts with Et_3NHCl. With the latter, if isolated and purified ketenes are used, 1.5 equiv of $EtAlCl_2$ is sufficient. (4) For many cases, the reactions proceed at −78 °C in <1 h.

Scheme 1. Lewis Acid Promoted Ketene–Alkene [2 + 2] Cycloadditions



During the course of our studies we made an interesting observation regarding the diastereoselectivity of the Lewis acid promoted [2 + 2] cycloaddition compared to traditional thermal cycloadditions (Scheme 2).[1] For reactions with activated alkenes and aryl/alkyl ketenes, different major diastereomers were observed depending on the reaction conditions. Under traditional thermal cycloaddition conditions the *endo*-Ph (**7b**, **9b**) adducts were obtained as the major products, while, under Lewis acid promoted conditions, the *exo*-Ph (**7a**, **9a**) product was preferentially generated. For example, the reaction of ketene **5** with cyclopentadiene at 22 °C for 12 h provides the *endo*-Ph product **7b** in 6:1 dr while conditions employing $EtAlCl_2$ lead to formation of the *exo*-Ph **7a** product in 7:1 dr. Similar observations were noted for cycloadditions with indene (Scheme 2, **1** + **8** → **9a**/**9b**). It

Scheme 2. Comparison of Lewis Acid Promoted and Thermally Induced [2 + 2] Cycloadditions

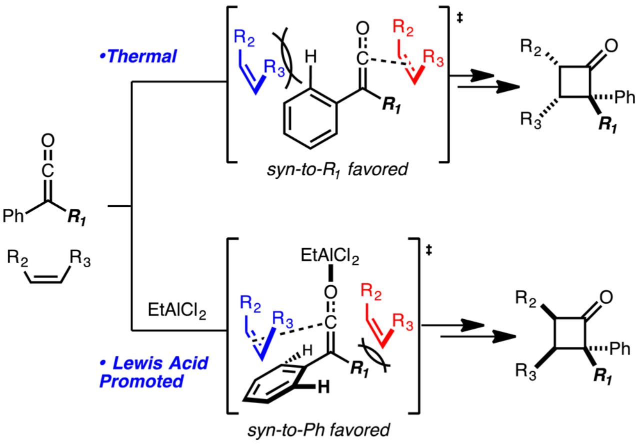


Received: August 26, 2014
Published: September 17, 2014

should be noted that control experiments confirm that the inversion in selectivity is not due to a solvent effect.[1]

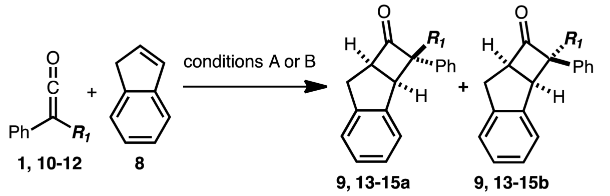
To rationalize the observed differences in diastereoselectivity, we proposed a mechanistic model (Scheme 3; R_1 = Et).[1] In accord with previous mechanistic data, under thermal conditions, the alkene likely approaches the ketene *syn* to the smaller Et-group (relative to the conjugated Ph-group). Under Lewis acid promoted conditions, the alkene must approach *syn*-to-Ph. A necessary component of this model is that the Ph-group must rotate out of plane to allow for the approach of the incoming alkene. Neither of these models assumes a concerted or stepwise cycloaddition. However, if the process is stepwise, the putative dipolar intermediate must be short-lived to limit bond rotations that may lead to changes in diastereoselectivity.

Scheme 3. Proposed Stereochemical Models[1]



To test the proposed models,[1] we carried out cycloadditions with modified ketenes. Since our original hypothesis for Lewis acid promoted reactions assumed that the alkene approaches *syn*-to-Ph, increasing the size of the alkyl group should lead to increased diastereoselectivities. Indeed, increasing the size of the alkyl group (R_1 in Table 1) from Me, Et, *i*-Bu, to *i*-Pr led to a significant increase in diastereoselectivity (compare entries 1–4, Table 1, conditions B). Thermal cycloaddition with Ph/Me or Ph/Et substituted ketenes predominantly generated the *endo*-Ph adducts (**9b**, **13b**) likely from the approach of the alkene *syn*-to-alkyl. However, when the steric bulk of the alkyl substituent was inceased to *i*-Pr, the *exo*-Ph isomer was generated in >20:1 dr. It seems that the steric bulk imposed by the *i*-Pr group is too significant to allow for the approach of the alkene.

Table 1. Effect of Substituent Size on Diastereoselectivity[a]

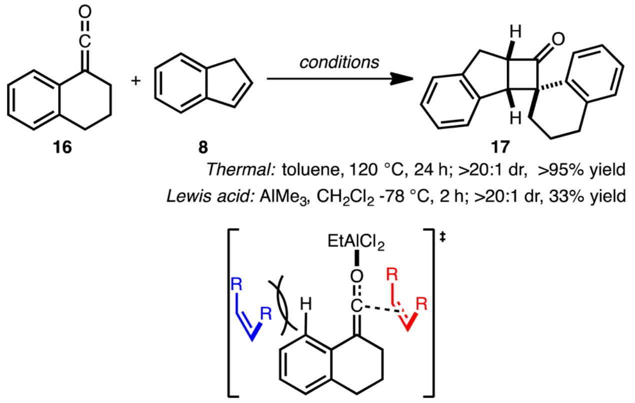


		conditions A toluene 120 °C, 24 h		conditions B EtAlCl$_2$, CH$_2$Cl$_2$, -78 °C, 2 h	
entry	ketene (R_1)	yield[b] (%)	dr[c]	yield[b] (%)	dr[c]
1[d]	Me (**10**)	82	1:7 (**13a**:**13b**)	23	3:1 (**13a**:**13b**)
2	Et (**1**)	>95	1:2 (**9a**:**9b**)	86	16:1 (**9a**:**9b**)
3	*i*-Bu (**11**)	>95	1:1 (**14a**:**14b**)	56	>20:1 (**14a**:**14b**)
4	*i*-Pr (**12**)	42	>20:1 (**15a**:**15b**)	80	>20:1 (**15a**:**15b**)

[a]See the Supporting Information (SI) for details. [b]Yields determined by ^{1}H NMR analysis with an with an internal standard. [c]Determined by ^{1}H NMR analysis of the unpurified reaction mixture. [d]Ketene was generated insitu. See the SI.

Reactions with ketene **16** were also investigated because it bears an aryl ring that is incapable of rotation out of plane. Thus, approach of the alkene can only occur from the less hindered face according to the model illustrated in Scheme 4.

Scheme 4. Controlling Facial Selectivity



Thermal: toluene, 120 °C, 24 h; >20:1 dr, >95% yield
Lewis acid: AlMe$_3$, CH$_2$Cl$_2$ -78 °C, 2 h; >20:1 dr, 33% yield

In accordance with this hypothesis, cycloadditions carried out under both thermal and Lewis acid promoted conditions provided the *endo*-Ar adduct **17** in excellent diastereoselectivity.

Based on the data described above it seems that the selectivity of the cycloaddition is dictated by the approach of the alkene to different faces of the ketene. A question that remained is why does the Lewis acid affect the approach of the alkene from difference faces of the ketene? To assist in our understanding, we turned toward computational evaluation[3] of the potential energy surfaces of both the thermal and Lewis acid promoted reactions.[4] A recent theoretical study by Wei, Tang and co-workers described many features of the potential energy surface for the reaction of phenylbenzylketene with cyclopentadiene (**5** + **6** in Scheme 2).[5] Herein, we describe results for **1** + **8**, comparing and contrasting our results with theirs and highlighting additional important features contributing to stereocontrol.

Initial computational investigations revealed that coordination of MeAlCl$_2$ to a ketene reduces the barrier to rotation of the aryl ring (Figure 1). This observation is consistent with the notion of aryl rotation for the Lewis acid promoted

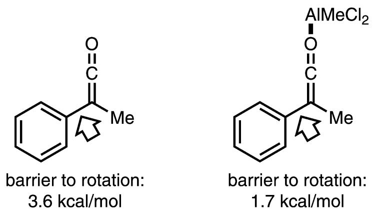
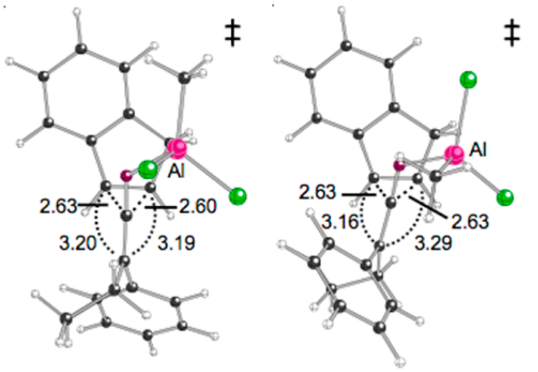


Figure 1. Barrier to rotation of Ph/Me ketene and Ph/Me ketene Lewis acid complex.

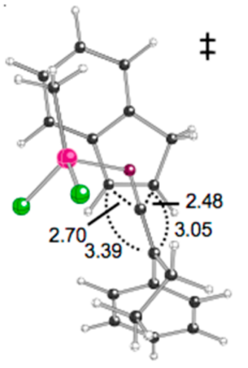
cycloadditions described above. Note that, in the Lewis acid complexed structure, the C═C bond of the ketene shortens slightly (from 1.33 to 1.31 Å) and the C−C$_{ipso}$ bond lengthens slightly (from 1.48 to 1.49 Å).

MeAlCl$_2$-promoted cycloaddition of **1** + **8** was found to involve reaction coordinates in the borderlands between stepwise and concerted asynchronous processes.[6] Pathways to the major and minor products were found, depending on the level of theory used, to involve either dipolar intermediates with very small barriers for cyclobutane ring closure (<2.5 kcal/mol) or no intermediates but very asynchronous formation of the two new C−C bonds (free energies, −78 °C, in CH$_2$Cl$_2$ or the gas phase). In either case, the lifetime of a dipolar species is expected to be very short and formation of the first new C−C bond occurs in the rate-determining transition state structures (Figure 2, top). Note that the central ketene carbons in these (very early) transition state structures sit over the center of the indene π-bond; only later along the reaction coordinates is this symmetrical bridging disrupted. In addition, the aryl groups in both transition state structures are indeed twisted out of conjugation: in the major transition state structure so as to avoid the indene (and possibly engage in favorable C−H···π interactions) and in the minor transition state structure so as to avoid the Lewis acid. The predicted free energy barriers (from MeAlCl$_2$ complexed **1** + free **8**) are 6.67 and 6.85 kcal/mol (M06-2X/6-31G(d)),[3] corresponding to a smaller product ratio than that observed experimentally (a 20:1 product ratio corresponds to a preference of 1.3 kcal/mol). A third transition state structure was located with a different orientation of the Lewis acid (Figure 2, bottom). This transition state structure is 2.00 kcal/mol lower in free energy than the lower energy transition state structure from the top of Figure 2. If this transition state structure leads to the major product, then a larger product ratio is expected. The pathway forward from this transition state structure leads to a flat portion of the energy surface, initially forming a dipolar intermediate with the appropriate C−C bond formed. However, an exit channel from this region of the energy surface leads to a regioisomer of **9a**.



*transition state structure for formation of **9a***

*transition state structure for formation of **9b***



transition state structure leading to flat portion of energy surface

Figure 2. Transition state structures for formation of diastereomers **9a**/**b** in the presence of MeAlCl$_2$. Selected distances shown in Å (M06-2X/6-31G(d)).[3]

The uncatalyzed thermal reaction was also predicted to be concerted with highly asynchronous bond forming events. Barriers for thermal cycloaddition were predicted to be much larger (37−38 kcal/mol), consistent with experiment. Transition state structures leading to **9a** and **9b** were predicted to be nearly equienergetic (low selectivity is observed experimentally, Scheme 2), although the transition state structure leading to **9a** was favored slightly (ΔΔG = 0.65 kcal/mol with M06-2X/6-31G(d)). In the transition state structure leading to **9a**, the phenyl ring twists out of conjugation, but in the transition state structure leading to **9b**, the phenyl ring does not twist out of conjugation (Figure 3), consistent with the twist in the transition state structure leading to Lewis acid complexed **9b** being dependent on the presence of the Lewis acid, likely the result of a steric effect.

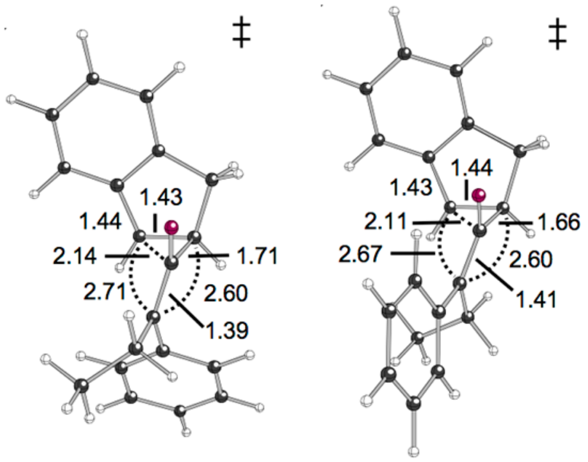


Figure 3. Transition state structures for formation of diastereomers **9a**/**b** in the absence of a Lewis acid. Selected distances shown in Å (M06-2X/6-31G(d)).[3]

Unusual energy surfaces have been described previously by Singleton and co-workers for other ketene−alkene and ketene−diene cycloadditions, and dynamics calculations have played an important role in understanding the origins of selectivity for these processes.[7] Dynamics calculations on the complex situation discussed above will be described in a future report, but our tentative diastereoselectivity model is summarized in Scheme 3. In short, selectivity for **9a** is increased in the Lewis acid promoted case due to steric clashes between the Lewis acid and phenyl groups that disfavor the **9b**-forming transition state structure.[8] These clashes induce a conformational change, which does not occur in the Lewis acid free system (Figure 3), that causes a reduction in conjugation between the phenyl ring and the C═C bond of the ketene.

In summary, we have provided both experimental and computational data that support the proposed pathway for diastereoselectivity. Subsequent studies will be directed toward utilizing this knowledge for future iterations of reaction development.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental data, computational data, and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge support from UC Davis and the National Science Foundation (CHE-030089 for computer time via the XSEDE program). Indiana University is also acknowledged for generous financial support.

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(8) Wei, Tang and co-workers also invoke steric effects in rationalizing the diastereoselectivity for the **5** + **6** reaction (see ref 5).