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Lewis Acid-Promoted Ketene–Alkene [2 + 2] Cycloadditions

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Ⓢ *Supporting Information*

ABSTRACT: Described are the first examples of ketene–alkene [2 + 2] cycloadditions promoted by Lewis acids. Notable features of this method include (1) substantial rate acceleration relative to traditional thermal reactions, (2) good diastereoselectivities and yields for the formation of the cyclobutanone products, and (3) inverse diastereoselectivity compared with related thermal cycloadditions for many examples. These studies not only provide access to synthetically versatile cyclobutanones that cannot be prepared by traditional thermal cycloadditions but also address important mechanistic questions regarding ketene–alkene [2 + 2] cycloaddition reactions.

Ketene–alkene [2 + 2] cycloadditions are an important class of transformations for chemical synthesis.[1,2] This is largely due to the synthetic utility of the resultant cyclobutanone products and is evidenced by the numerous reports regarding their use in total synthesis.[3,4] Many modifications and improvements introduced over the last several decades have extended the versatility of these cycloadditions.[1] Despite such advances, significant limitations still remain in regard to the range of ketenes and alkenes capable of undergoing [2 + 2] cycloadditions. For example, current methods for thermal ketene–alkene [2 + 2] cycloadditions between relatively unreactive reaction partners typically require forcing conditions (>120 °C, >24 h, large excess of alkene or ketene) that at best result in low isolated yields of the desired products (eq 1 and Table 1, entries 1 and 2).[5] Such reaction conditions are likely detrimental in cases where diastereomers are produced, ultimately leading to poor control of the selectivity.[5b] As part of a program aimed at developing diastereo- and enantioselective reactions involving allenes and heteroallenes,[6] we became interested in extending the utility of ketene–alkene [2 + 2] cycloadditions by specifically addressing some of the deficiencies outlined above.

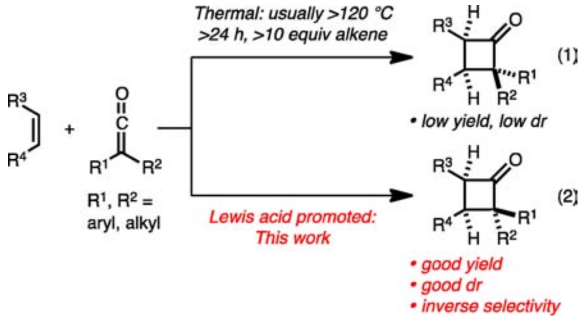
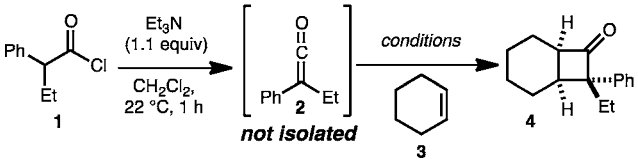


Table 1. Initial Evaluation of Reaction Conditions[a]



entry	temp (°C)	time (h)	equiv of 3	Lewis acid	yield (%)[b]	dr[c]
1	120	48	10	–	<2	–
2	180	48	10	–	∼10[d]	∼1:1
3	**−78**	**1**	**2**	**$EtAlCl_2$ (2.5 equiv)**	**70**	**13:1**

[a] See the Supporting Information (SI) for experimental details. [b] Determined by ^1H NMR analysis with an internal standard. [c] Determined by ^1H NMR analysis. [d] ^1H NMR analysis of the unpurified reaction mixture showed a complex mixture of products.

Nearly all ketene–alkene [2 + 2] cycloadditions rely solely on the inherent reactivity of the reacting partners. Modulation of this reactivity can be achieved by variation of the reaction solvent[7] and/or temperature[8] with moderate degrees of success. In contrast, reagent- or catalyst-controlled variants of these reactions have largely been neglected in the chemical literature. The introduction of such an advance holds the potential to transform the way ketene–alkene [2 + 2] cycloadditions are carried out and could significantly expand the scope of the reaction. To the best of our knowledge, only one example regarding the use of reagent or catalyst control in a ketene–alkene [2 + 2] cycloaddition has been reported. Dickinson and co-workers demonstrated that Pd(II) salts [although Pd(0) was implicated as the active catalyst] can slightly influence the diastereoselectivity and improve the yield of ketene–alkene [2 + 2] cycloadditions relative to thermal reactions.[9] However, the method appears to be limited to reactions between very specific *n*-alkyl/bromo-substituted ketenes and cyclopentadiene and provides access to cyclobutanones that can be prepared readily under traditional thermal conditions.

Herein we introduce a new paradigm in ketene–alkene [2 + 2] cycloadditions that relies on the use of Lewis acid-based reagent control (eq 2). This method is notable for not only the high yields and diastereoselectivities obtained for the cyclobutanone product but also the inverse selectivity relative to traditional thermal cycloadditions observed for many ketene–alkene cycloadditions. Furthermore, this method provides access to synthetically versatile, highly substituted cyclobutanones that are difficult to access through current methods.[4]

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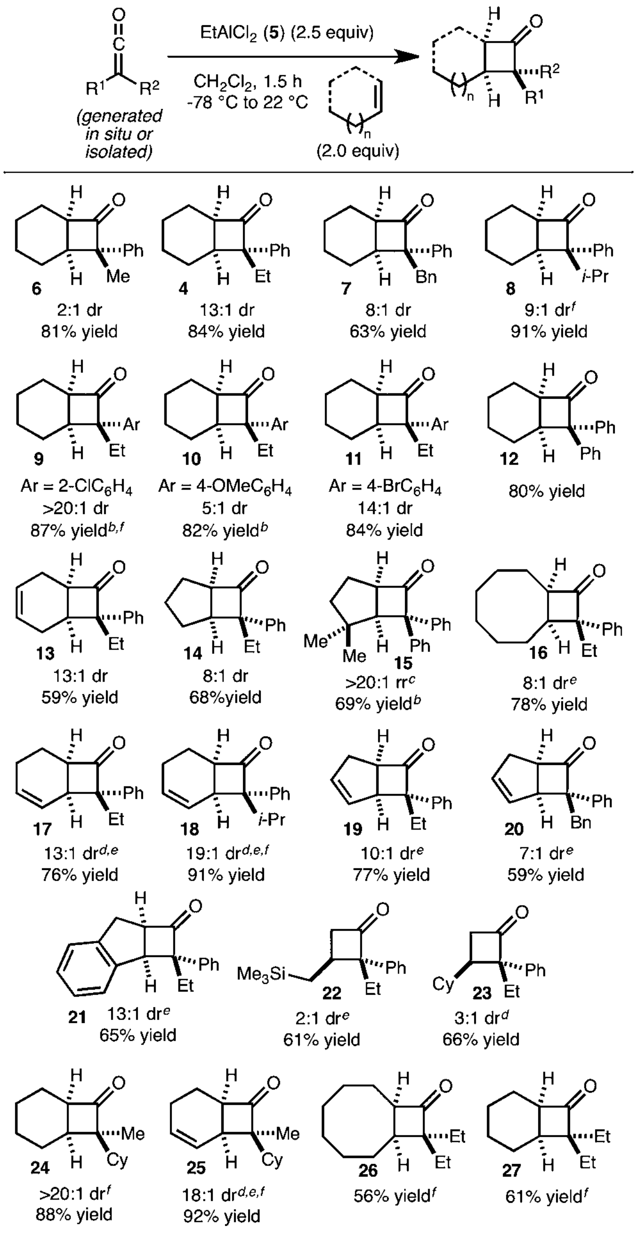
Chart 1. Substrate Scope[a]



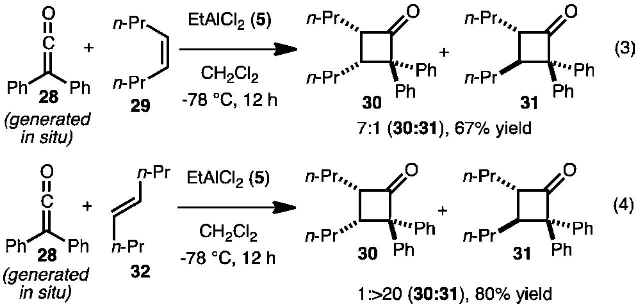
[a] See the SI for experimental details. Isolated yields are shown, unless otherwise indicated. Diastereomeric ratios (dr) were determined by ^1H NMR analysis of the unpurified reaction mixtures. [b] Determined by ^1H NMR analysis of the unpurified reaction mixture with an internal standard. [c] Regioisomeric ratio (rr) determined by ^1H NMR analysis of the unpurified reaction mixtures. [d] Formation of ~15% of the regioisomeric product was observed (see the SI for details). [e] Reaction was kept at −78 °C for 3 h. [f] The corresponding ketene was isolated and purified prior to use.

Contemporary mechanistic data regarding thermal ketene−alkene [2 + 2] cycloadditions point toward a reaction that is likely either stepwise, with involvement of a dipolar intermediate, or concerted yet highly asynchronous.[1,2,10,11] On the basis of these potential reaction pathways, it seemed plausible that Lewis acids could accelerate the cycloaddition.[12−14] We envisioned that interaction of a Lewis acid with the electrophilic ketene would effectively lower the energy of the lowest unoccupied molecular orbital and render these adducts more reactive.[15,16] To the best of our knowledge, definitive Lewis acid acceleration of ketene−alkene [2 + 2] cycloadditions has not previously been established.[17]

To initiate our studies, the cycloaddition of ketene **2** (generated in situ by treatment of acid chloride **1** with Et_3N) and cyclohexene (**3**) was examined. In the traditional thermal approach, forcing conditions (180 °C, 48 h, 10 equiv of alkene) were needed to generate cyclobutanone **4**, albeit in low yield (~10%) and with poor diastereoselectivity (~1:1) (Table 1, entry 2). The reaction in the presence of the Lewis acid ethylaluminum dichloride ($EtAlCl_2$, **5**) gave rise to a substantial rate enhancement, resulting in the formation of **4** in <1 h at −78 °C in 70% yield with 13:1 dr using only 2.0 equiv of alkene (Table 1, entry 3). Several points regarding this result warrant further mention: (1) Al-based Lewis acids are uniquely effective at promoting this reaction.[18] (2) At present, excess Lewis acid (2.5 equiv) is required because of product inhibition[18] and unavoidable reaction with $Et_3N{\cdot}HCl$ (a byproduct of ketene generation). Fortunately, **5** is inexpensive, readily available, and easy to use. (3) Ketene **2** can be prepared and used in situ (without removal of $Et_3N{\cdot}HCl$). This procedure avoids the cumbersome isolation of the ketene.[19]

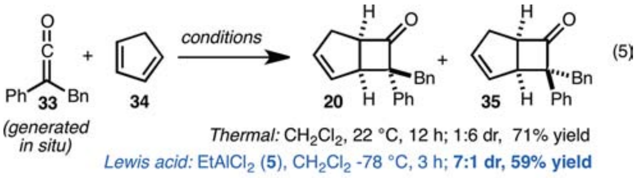
The scope of this process with respect to both the ketene and the alkene was examined (Chart 1). Several points regarding the ketene substrate scope are noteworthy: (1) Diaryl, dialkyl, and alkyl/aryl ketenes undergo the reaction to provide the desired products in good to moderate yields and diastereoselectivities. (2) Reactions with monosubstituted ketenes do not provide any desired product, likely because of the instability associated with these highly reactive ketenes. (3) The reaction of **3** with Me/Ph ketene is less selective (2:1 dr, **6**) than the reactions with Et/Ph (13:1 dr, **4**), Bn/Ph (8:1 dr, **7**), and *i*-Pr/Ph (9:1 dr, **8**) ketenes. (4) Electron-rich (e.g., **10**), electron-deficient (e.g., **11**), and sterically hindered aryl ketenes (e.g., **9**) undergo the reaction in good yield and selectivity. (5) Because of difficulties associated with the in situ preparation of *i*-Pr/Ph ketene, 2-ClC_6H_4/Et ketene, and all of the dialkyl ketenes, these were isolated and purified prior to use.[18] (6) The synthesis of **4** can be carried out on a gram scale with only 1.1 equiv of nondistilled **3** in 85% yield with 13:1 dr.

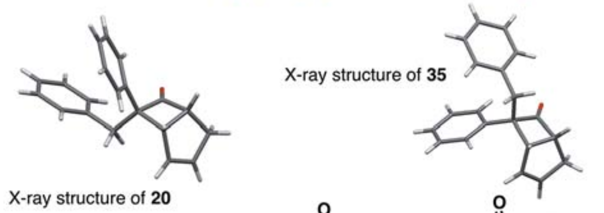
A wide range of cyclic disubstituted alkenes and dienes underwent the reaction to provide the cyclobutanone products (**13**−**21** and **24**−**27**) with uniformly good diastereoselectivities (>7:1) and yields (>60%) (Chart 1). A limitation of this method is that reactions with trisubstituted alkenes gave product yields of <5% under a variety of conditions. This is likely due to the severe steric interaction that results when vicinal quaternary carbons are generated. Reactions with terminal alkenes led to the formation of **22** and **23** in good to moderate yields, but the diastereoselectivities of the reactions suffered (2:1−3:1). Acyclic disubstituted alkenes are also suitable substrates for this process (eqs 3 and 4). For example, the reaction of diphenyl ketene (**28**) with *cis*-4-octene (**29**) led to the formation of both **30** and **31** (7:1) (eq 3), while the reaction with *trans*-4-octene (**32**) generated **31** exclusively (>20:1) (eq 4). The formation of *trans*-cyclobutanone **31** by the reaction with *cis*-alkene **29** (eq 3) may be the result of a Lewis acid-promoted *E*/*Z* alkene isomerization or product equilibration rather than a stepwise cycloaddition reaction.[18] Finally, the regioselectivity of cycloadditions with unsymmetrical alkenes can be controlled not only through electronic activation (e.g., cyclopentadiene) but also with sterics. For example, the synthesis of **15** under Lewis acid-promoted conditions resulted in the formation of a single regioisomer

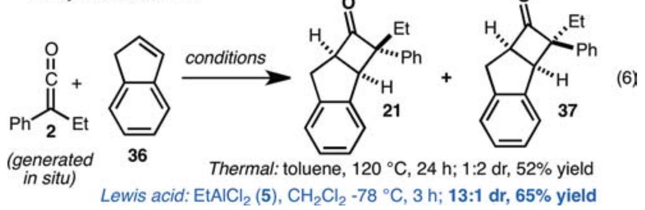


(>20:1). Thermal cycloaddition to access **15** requires heating of the corresponding alkene and **28** for 10 days at 100 °C and delivers the product in 90% yield as a 6:1 mixture of regioisomers.[20]

A notable aspect of this study is the inversion of diastereoselectivity for the Lewis acid-promoted reactions of *alkyl/aryl ketenes* in comparison with the thermal reactions (eqs 5 and 6).[21] When cyclopentadiene (**34**) was allowed to react with ketene **33** at 22 °C, a 1:6 mixture of diastereomers **20** and **35** was generated (eq 5). With most ketene−alkene [2 + 2] cycloaddition reactions, the diastereomer in which the larger group is in the endo position is preferentially generated.[1] *Remarkably, under Lewis acid-promoted conditions, the opposite diastereomer* ***20*** *was generated with good selectivity (7:1 dr)* (eq 5).[22] This behavior was not limited to reactions of dienes but was observed for all of the “activated” alkenes[23] investigated.[18] For example, the Lewis acid-promoted cycloaddition of ketene **2** and indene (**36**) resulted in the formation of **21** in reasonable yield (65%) with excellent diastereoselectivity (13:1 dr) (eq 6). The corresponding thermal reaction provides the opposite diastereomer **37** as the major product, albeit with low diastereoselectivity (1:2 dr) (eq 6).[7]

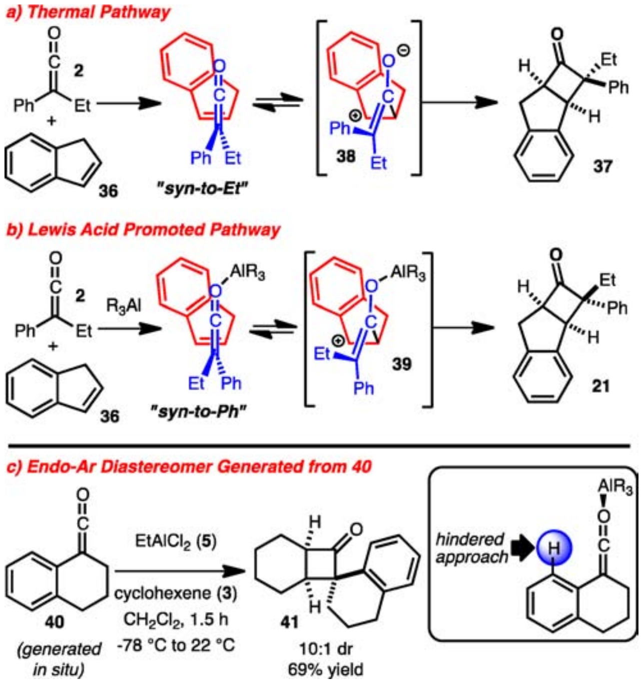






A rationale that accounts for the reversal of diastereoselectivity is presented in Scheme 1. Thermal ketene−alkene [2 + 2] cycloadditions with “activated” alkenes[23] likely proceed by a stepwise mechanism, and the diastereoselectivity of such processes has been explained according to the model illustrated in Scheme 1a.[1c,d,f] Addition of the alkene orthogonal to the C1−C2 π system of ketene **2** and syn to the sterically smaller ethyl substituent (relative to phenyl) generates dipolar intermediate **38**. Direct ring closure of this intermediate gives rise to the observed *endo*-Ph diastereomer **37**.[1c,d,f]

Scheme 1. Model for Reversal of Diastereoselectivity in the Lewis Acid-Promoted Reaction



The Lewis acid-mediated ketene−alkene [2 + 2] cycloaddition likely is mechanistically similar to the thermal process, with the primary difference being that the alkene now adds to a Lewis acid-activated ketene (Scheme 1b). The observed inversion in diastereoselectivity relative to the thermal reaction may be the result of a “syn-to-Ph” approach of the alkene (Scheme 1b). A necessary requirement of this model is that the Ph group must rotate out of conjugation to allow for approach of the alkene. To test this hypothesis, we carried out the Lewis acid-promoted reaction with an aryl ketene incapable of out-of-plane rotation (i.e., **40**), which would block the approach of the alkene syn to the aryl group and favor the formation of the *endo*-aryl diastereomer (Scheme 1c). Indeed, the Lewis acid-promoted [2 + 2] cycloaddition of **40** and **3** generated *endo*-aryl isomer **41** with good diastereoselectivity (10:1), thus supporting the model proposed in Scheme 1b. While this model is certainly consistent with the data, the mechanistic subtleties of this process are likely complex because of the possibility of bifurcated transition states[11e,f] and C2-bound Lewis acid−ketene complexes.[16] Further studies will be necessary to delineate fully these interesting possibilities.

In summary, the first definitive examples of a Lewis acid-promoted ketene−alkene [2 + 2] cycloaddition reaction have been demonstrated. We have discovered that this reaction not only results in improved yields and diastereoselectivities but also furnishes inverse selectivity relative to thermal reactions for many of the substrates investigated. Furthermore, these studies have established that rate acceleration of a ketene−alkene [2 + 2] cycloaddition is possible and sets the stage for the development of related catalytic as well as catalytic enantioselective variants. Studies along these lines are currently in progress.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, analytical data for all compounds, and crystallographic data (CIF). 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.

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(21) Lewis acid-promoted reactions with dialkyl ketenes provided the same major diastereomers as the analogous thermal processes. The diastereoselectivities and yields, however, were significantly higher under the Lewis acid-promoted conditions. For example, the synthesis of **25** under thermal conditions required heating for 48 h at 60 °C to give a yield of 42% with 2:1 dr. See the SI for details.

(22) Control experiments confirmed the observed selectivity to be the result of a Lewis acid-promoted cycloaddition reaction rather than a Lewis acid-promoted isomerization between diastereomers. See the SI for details.

(23) Here "activated" alkenes are dienes, styrenes, and allylsilanes.