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Lewis Acid-Promoted [2+2] Cycloadditions of Alkenes with Arylketenes

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Abstract

A method for the [2+2] cycloaddition of arylketenes and alkenes is presented. The process involves the in situ generation of a ketene in the presence of a Lewis acid. The utility of products is demonstrated towards the synthesis of a common scaffold found in several natural product families.

Ketene-alkene [2+2] cycloadditions have been established to be important reactions for chemical synthesis.¹ These reactions, however, do not function well with poorly reactive and unstable monosubstituted aryl ketenes.^{2,3} For example, cycloaddition of phenylketene with cyclopentadiene only provides the cycloadduct in 26% yield (Scheme 1).² Cycloaddition of this type are significant, as the cyclobutanone products generated would represent an important scaffold for chemical synthesis.⁴ Herein, we provide a solution to this problem through the development of a Lewis acid-promoted [2+2] cycloaddition with *monosubstituted aryl ketenes* (Scheme 2b). The utility of this method is also demonstrated by the synthesis of a scaffold that is common to several natural product families.

As part of a program toward developing new methods for the synthesis of cyclobutanes, we have introduced Lewis acid- promoted ketene-alkene [2+2] cycloadditions.⁵ In our initial installment, we developed a method for cycloaddition of “stable” disubstituted ketenes (Scheme 2a).^{5a} In these reactions the ketene is fully generated prior to addition of alkene and Lewis acid. To extend the utility of this method towards use of unstable ketenes, like monosubstituted aryl ketenes, a new protocol was developed as pregeneration of the ketene was not possible. This initiative led to the identification of conditions that allow for the in situ generation of a monosubstituted aryl ketene in the presence of a Lewis acid (Scheme 2b).⁶

[§]These authors contributed equally to the completion of this work

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Due to efforts towards the total synthesis of gracilioether F (**5**), a method for cycloaddition with an “unstable” vinyl-ketene (Scheme 3) was developed.^{5c} In this reaction, because mono-substituted ketenes undergo dimerization, the ketene needed to be generated in situ at low concentrations. This was achieved by slow addition of acid chloride **1** to a solution of Lewis acid, *i*-Pr NEt, and alkene **2**.^{5b}

Due to the known instability of monosubstituted aryl ketenes, the method illustrated in Scheme 3 seemed appropriate for initial reaction development.^{5c} The optimization of the test reaction is outlined in Table 1. We found that the dropwise addition of a solution of acid chloride **6** to a mixture of alkene, base, and Lewis acid at $-78\text{ }^{\circ}\text{C}$ then warming to $-45\text{ }^{\circ}\text{C}$ was critical to success for formation of cyclobutanone **8**. Entries 1-3 show that weaker aluminum Lewis acids provided the highest yield of the cycloadduct **8**, which led to our use of Me_3Al . Higher equivalents of alkene afforded the cyclobutanone product **8** in excellent yields; however, as low as two equivalents of alkene still provided good yields of the desired product (Table 1, entries 3-4). We propose the success of this method is due to the ephemeral formation of a highly reactive monosubstituted ketene-Lewis acid adduct (*e.g.*, intermediate analogous to **3**, Scheme 2b). By maintaining a low concentration of the reactive intermediate and relatively high concentration of the alkene, [2+2] cycloadditions can occur with low rates of ketene dimerization and decomposition. Alternatively, the acid chloride can be used in excess if desired (Table 1, entry 5), albeit with lower yields.

Chart 1 displays the substrate scope of the optimized reaction. All reactions, except where noted, were performed with 20 equivalents of alkene. However, as noted in Table 1, entry 4, fewer equivalents of alkene provided the product in reduced but useful yield. This method has proven successful with both cyclic and acyclic alkenes. The scope of this reaction includes both activated (*e.g.*, diene, allyl silane) and unactivated alkenes (*e.g.*, 1-hexene, cyclopentene). Trisubstituted olefins are also suitable substrates for this reaction (product **13**). Aryl acid chlorides of varying steric (*vide infra*, product **20**) and electronic properties (products **15-16**) were also found to be viable substrates. Attempted cycloaddition with either acylchloride or butanoyl chloride resulted in low yields of the cycloaddition. This can be attributed to the slower rate of ketene formation with the less acidic acid chloride. Finally, the observed diastereomeric ratios are likely, in part, due to equilibration under the reaction or workup conditions. This is due to the known configurationally instability of the aryl substituted stereocenter.^{7,8} Furthermore, equilibrium diastereomeric ratios for bicyclic systems such as **8** are known to be near 1:1 dr.⁷

Reaction with chiral allylsilane **17** led to formation of cyclobutanone **18** with excellent levels of diastereoselectivity (Scheme 4).⁹ In this example, the precious alkene component was used as the limiting reagent.

To demonstrate the utility of the method, a scaffold that is prevalent in several natural product families was prepared. The synthesis commences with [2+2] cycloaddition of *o*-bromoaryl substituted ketene derived from acid chloride **19**. Cyclobutanone **20** was accessed in 80% yield on gram scale. Subsequent deprotonation with KHMDS and alkylation with methyl iodide afforded a single diastereomer of product. Baeyer-Villiger oxidation provided lactone **21** in good yield over two steps.^{5c} Upon addition of *t*-butyllithium, lithium-halogen

exchange occurred followed by an intramolecular acyl substitution to generate **22**. Structures related to **22** are common to several natural products such as **25**,¹⁰ **24**,¹¹ and **23**.¹²

Conclusions

In summary, we have developed a method for the cycloaddition of arylketenes and alkenes. This process shows broad scope, includes highly diastereoselective variants, and has enabled the synthesis of a scaffold that is common to several natural product families.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.
[2+2] Cycloadditions with Arylketenes

a) Previous Work: Pregenerated "Stable" Ketenes **b) This Work: In situ Generated "Unstable" Ketenes** **Scheme 2.**

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

Scheme 3.
Summary of Related Work

Chart 1.
Substrate Scope^a

^a See the Supporting Information for experimental details, yield refers to yield of isolated product. dr = diastereomeric ratio - determined by ^1H NMR analysis of the un purified reaction mixtures. In all cases, expect where noted, the dr of the unpurified reaction mixtures and purified samples are the same. ^b Reactions with two equiv alkene. ^c dr of the purified mixture, dr of the unpurified mixture is 14:1. ^d Reaction run for 3 hr. ~10% of a regioisomeric product was formed.

Figure 0005

Figure 0006

Scheme 4.
Reaction with Chiral Alkene

Table 1Optimization of Reactions Conditions^a

entry	Lewis Acid	acid chloride equiv	alkene equiv	yield (%) ^b
1	EtAlCl ₂	1	20	22
2	Me ₂ AlCl	1	20	20
3	Me ₃ Al	1	20	91
4	Me ₃ Al	1	2	74
5	Me ₃ Al	3	1	40

^aSee the Supporting Information for experimental details^bYield determined by ¹H NMR analysis of the unpurified reaction mixture with an internal standard.