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ARTICLE

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A Practical Synthesis of 3-Acyl Cyclobutanones by [2 + 2] Annulation. Mechanism and Utility of the Zn(II)-Catalyzed Condensation of α-Chloroenamines with Electron-Deficient Alkenes

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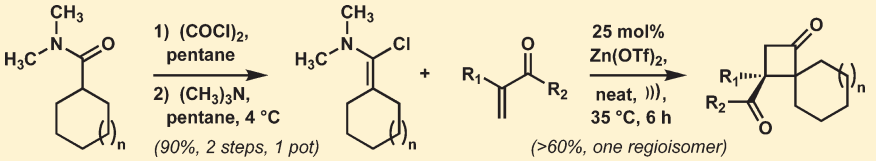
Supporting Information

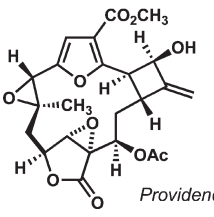
ABSTRACT:

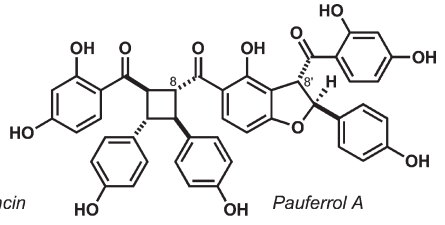


New conditions for the conversion of simple tertiary amides to α-chloroenamines and their use in Zn(II)-catalyzed cycloaddition reactions with commercial α,β-unsaturated carbonyl compounds allows rapid, regiocontrolled access to 3-acyl cyclobutanones. Reactions take place at ambient temperature without solvent, giving strained [2 + 2] adducts with all-carbon-substituted quaternary carbon atoms. Ab initio calculations of the putative keteniminium intermediate and studies with styrenyl olefins suggest a dual role for $Zn(OTf)_2$ during catalysis.

INTRODUCTION

Complexity and diversity among bioactive natural products with a four-carbon ring continue to stimulate the development of improved methods[1] for [2 + 2] annulation.[2] Providencin[3] and pauferrol A,[4] for instance, are both unmet synthetic challenges[5] and important lead structures for the treatment of human cancers. In this article, we describe a catalytic, solvent-free synthesis of 3-acyl cyclobutanones[6] (**A**) from simple α,β-unsaturated ketones, carboxylic esters, and amides (**B**, Scheme 1) as substrates. Our approach is based on an underutilized variant of the keteniminium−olefin cycloaddition developed by Ghosez and co-workers.[7] Not only do the products **A** represent versatile intermediates for chemical synthesis, but the presence of a 1,4-dicarbonyl points to an unusual pattern of reactivity. As opening examples of catalysis for this transformation, it is hoped that this work can inspire modern enantioselective entries to substituted cyclobutanones since prior strategies have relied exclusively on pyrrolidine-based chiral auxiliaries.[7d,e,g]


Providencin


Pauferrol A

The synthesis of cyclobutanones from aldo- and keto-keteniminium salts is a valuable complement to the ketene−olefin [2 + 2] cycloaddition reaction.[8] Each process generates four-carbon ring strain and formally accomplishes the *vicinal carbofunctionalization* of an alkene. Although assertions have been made in support of concerted $[\pi 2_s + \pi 2_a]$ pericyclic mechanisms[7a,9] involving the C=C double bond and low-lying unoccupied $\pi^*_{C=N}$ (or $\pi^*_{C=O}$) orbitals, the literature records ample evidence in favor of asynchronous[10] or even stepwise bond-forming events.[7a,f] For instance, keteniminium ions show marked nonstereospecificity in intermolecular cycloaddition with acyclic *cis*-substituted olefins.[7e] As shown in Scheme 2, a stepwise mechanistic model also adequately explains the high levels of asymmetric induction attainable in reaction of small cycloalkenes (cyclopentene) or acyclic *trans*-alkenes with the chiral, proline-derived keteniminium **3**, namely: (1) least-hindered approach of the reactants to facilitate initial bonding at C1; (2) sterically preferred bond rotations (as indicated) in carbonium ion **4** to establish the nucleophilic enamine system prior to formation of the second C−C bond (→**5**); and finally (3) hydrolytic removal of the pyrrolidine auxiliary to reveal enantiomerically pure bicycloheptanone **6**, whose absolute configuration at the ring juncture was shown to be (1*R*,5*S*).[7d] The electrophiles have been accessed by stoichiometric Zn-promoted dechlorination of α-chloroenamines (see **2**, prepared by chlorination−deprotonation of **1**)[7b,e] or by direct dehydration of the tertiary amides **1** with Tf_2O and 2,4,6-collidine.[7c,f]

In 1981, it was reported that keteniminium cations cycloadd to *electron-poor* double bonds, as well.[11] As an example, α-chloroenamine **7** reacts with isopropenyl methyl ketone upon treatment with 1.2 equiv of $ZnCl_2$, presumably through the intermediacy of keteniminium salt **8** (Scheme 3).[11] Product is isolated

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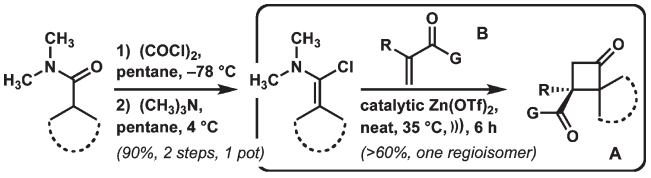
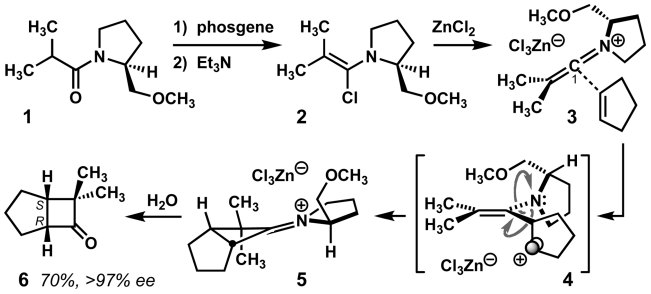
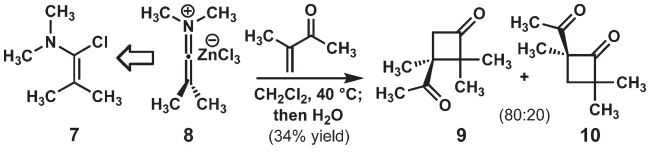
Scheme 1



Scheme 2. Ghosez's Enantioselective Intermolecular 4-C Annulation through Cation−π Reaction in the Intermediate Chiral Keteniminium 3



Scheme 3. Stoichiometric [2 + 2] Annulation with an α,β-Enone



in 34% yield as an 80:20 mixture of regioisomers **9** and **10**. To the best of our knowledge, no other reports in this area have followed in support of an alternative reaction pathway. We found the issue of mechanism to be quite intriguing since an analogous stepwise explanation invokes a carbocation that is either primary (for minor regioisomer **10**) or α to a carbonyl group (for **9**). Because of the simplicity of this approach to cyclobutane rings with a versatile 1,4-dicarbonyl function and the chance that it might be of value in the stereocontrolled synthesis of more complex derivatives, the following studies were undertaken. Our results show that the reaction can be catalytic in zinc(II) triflate and that its strained cycloadducts participate in a variety of enabling synthetic transformations.

RESULTS AND DISCUSSION

Catalysis of the Reaction with Electron-Poor Olefins. We began our investigation by optimizing reaction conditions for the preparation of 3-acetyl-2,2-dimethylcyclobutanone (see **11**, Table 2) from α-chloroenamine **7** and methyl vinyl ketone (MVK). These experiments were facilitated by the commercial availability of **7**, a reagent useful in other contexts, including acid chloride generation under neutral conditions[12] and the halogenation of delicate medium ring ethers and lactones.[13] As shown in entry 1 of Table 1, prolonged stirring of a sealed CH_2Cl_2 solution

Table 1. Optimization of the Synthesis of 3-Acetyl-2,2-dimethylcyclobutanone from MVK and 1-Chloro-1-*N*,*N*,2-trimethylpropenylamine

entry	catalyst	loading	solvent	temp (°C)	time	conv (%)[a]	yield (%)[b]
1	$ZnCl_2$	1 equiv	CH_2Cl_2	50	24 h	97	81
2	AgOTf	1 equiv	CH_2Cl_2	50	24 h	53	nd
3	$ZnCl_2$	1 equiv	neat	50	24 h	95	80
4	$Zn(OTf)_2$	20 mol %	neat	50	24 h	89	nd
5	$Zn(OTf)_2$	10 mol %	neat	50	24 h	51	nd
6	$Zn(OTf)_2$	20 mol %	neat	23	6 days	85	nd
7	$Zn(OTf)_2$	20 mol %	neat	35	6 h	80	72
8	$Zn(OTf)_2$	25 mol %	neat	35	6 h	89	86

[a] Determined by ^{1}H NMR analysis. [b] After chromatography on silica gel.

of MVK, **7**, and $ZnCl_2$ (ratio 1.2:1:1) at 50 °C under nitrogen gives ketone **11** as a single regioisomer after a brief hydrolytic workup with H_2O.[11] Several Ag(I) salts,[7a,14] including AgOTf, are effective promoters too, but conversion is lower under identical conditions (entry 2). After seeing the benefit of higher concentrations, a run was performed without solvent. As shown in entry 3, high efficiency is maintained. We then surveyed a number[15] of other Lewis acids aiming to improve solubility (over $ZnCl_2$) in the oily reactant mixture. $Zn(OTf)_2$ proved superior, and an early attempt at catalysis was favorable; smooth conversion to **11** is observed as shown in entry 4. Attempts to lower either the catalyst loading or temperature led, respectively, to lower conversion (51%, entry 5) or an exceedingly long reaction (6 days, entry 6). However, we were able to shorten reaction time and enhance efficiency by sonicating[16] the neat mixture at 35 °C (entry 7). As a final refinement, a slight increase in the catalyst loading (25 mol %, entry 8) provides **11** in 86% yield at 89% conversion. On both milligram and gram scale, reaction is clean and regioselective. The only detectable impurity under the conditions of entry 8 is 8−10% (isolated yield) of *N*,*N*-dimethylisobutyramide derived from the hydrolysis of unreacted **7** during aqueous workup.

Having arrived at practical conditions for efficient [2 + 2] cycloaddition, the scope with regard to the alkene reaction component was evaluated, with results summarized in Table 2. Thermal bicyclization is reported[11] to give a 4:1 ratio of **9** and its regioisomer **10** in low yield, yet Zn-catalyzed reaction of **7** and 2-propenyl methyl ketone provides only **9** (73% distilled yield at 87% conv) with sonication in the absence of solvent (entry 2). Both methyl acrylate and methyl methacrylate are acceptable[17] donor alkenes, affording cyclobutanones **12** and **13** in >60% isolated yields (entries 3 and 4). A minor 2-acyl isomer was finally observed for *N*,*N*-dimethylmethacrylamide as substrate (80% yield, 3:1 ratio favoring **15**, entry 6) in an event that was of comparable efficiency to that involving the unsubstituted acrylic amide (83% of **14**, entry 5). The Weinreb amides of acrylic and methacrylic acid are also suitable. Cyclobutanone **16** was isolated in 64% distilled yield at 85% conversion as one regioisomer (entry 7), and its quaternary variant **17** was recovered in 57% yield (87% conv), again with perfect regiocontrol (entry 8). At this time, the method is limited to reactants lacking substitution at the β position; *trans*-methyl crotonate and cyclohexenone fail to react. α,β-Unsaturated nitriles were also tested but did not result in a productive transformation. It deserves note that in the one case in which a minor product is observed (entry 6), the regioisomers are separable by silica gel chromatography, yet distillation remains an attractive purification method.

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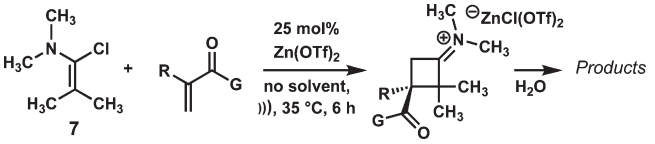
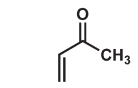
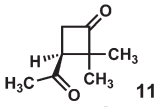
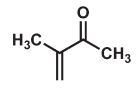
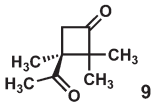
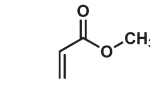
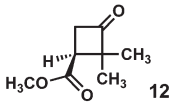
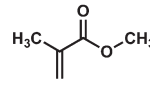
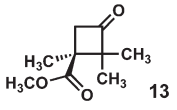
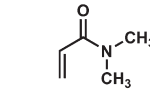
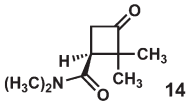
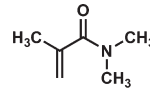
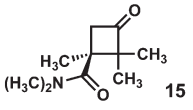
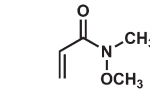
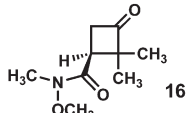
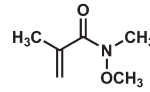
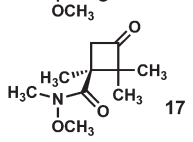
Table 2. Zn-Catalyzed, Solvent-Free Access to 3-Acyl Cyclobutanones



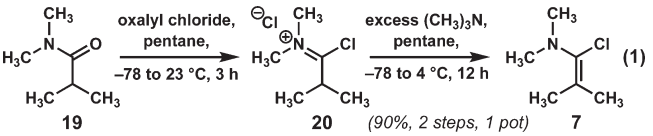
entry	reaction partner	cycloadduct	conv (%) [a]	yield (%)
1		 11	89	86 [b]
2		 9	87	73 [c]
3		 12	99	66 [b]
4		 13	91	63 [b]
5		 14	96	83 [c]
6		 15	90	80 [c,d]
7		 16	85	64 [c]
8		 17	87	57 [c]

[a] Determined by ^{1}H NMR analysis. [b] After chromatography on silica gel. [c] After vacuum distillation. [d] With a 3:1 regioisomeric ratio favoring that shown.

Several ketones in Table 2 are waxy solids below 23 °C, but attempts to obtain single crystals suitable for diffraction met with difficulty. An X-ray structure was eventually obtained for carboxylic acid **18**, confirming regiochemical assignments across the series (Scheme 4). Since **18** is soluble in water, conditions for ester hydrolysis in **12** were needed that avoided an aqueous workup altogether. A simple solution emerged involving: (1) treatment with LiOH in wet THF (23 °C, 18 h); (2) removal of solvent to provide lithium 2,2-dimethyl-3-oxocyclobutanecarboxylate as an off-white solid; and (3) dissolution in cold THF, protonation by brief treatment with anhydrous HCl, filtration of insoluble LiCl, and concentration to a white solid (91% yield). As shown, **18** packs as a dimer in the solid state with intermolecular CO_2H hydrogen bonding. Noteworthy is the considerable bond length distortion evident in the four-membered ring. At 1.583 Å, the bond between C3 and C4 is significantly longer than the remaining three: C1−C2 1.513 Å, C1−C4 1.526 Å, and C2−C3 1.537 Å. Although steric congestion imparted by the *gem*-dimethyl unit could partly account for this, a stabilizing FMO interaction involving the C3−C4 linkage and the carboxylic $\pi^*_{C=O}$ orbital is likely to be present given its favorable alignment and the shortened distance between C3 and C5 (1.494 Å). Whether this constitutes an incipient potential for substitution events at the quaternary carbon is an interesting prospect for future study.

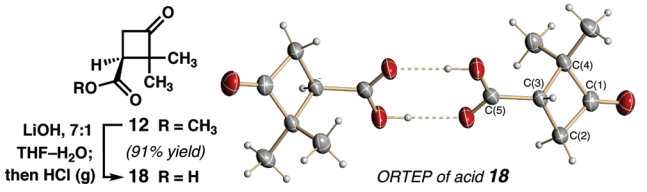
Synthesis and Participation of Other α-Chloroenamines. Further exploration on the scope of this transformation, especially with respect to the α-chloroenamine component, has been challenging for several reasons: (1) **7** is the only commercial available derivative bearing the reactive function; (2) existing protocols[18] for α-chloroenamine synthesis are complicated by moisture sensitivity and tedious purifications (see below); and finally, (3) β-monosubstituted chloroenamines—precursors for putative access to aldo-keteniminium cations—are reportedly[18b] unstable; they undergo self-condensation upon concentration and are best prepared and used in solution at low temperature.[19] Still, we wish to relay some progress on this challenging front, beginning with useful changes to the reported synthesis of **7** that translate well to the preparation of other β-disubstituted α-chloroenamines.

As shown below in eq 1, the required events are amide chlorination and proton loss from the resulting chloroimidate. Because of the hazards associated with phosgene (see Scheme 2), $POCl_3$ has been recommended as an alternative reagent for chlorination. However, in certain cases,[18b] it is necessary to remove unreacted $POCl_3$ before addition of the base (typically Et_3N), and several standard chlorinating agents are known to react with tertiary amides. We decided upon oxalyl chloride since the byproducts of chlorination are gaseous and preliminary experiments with **19** gave high efficiency even in the absence of DMF as a catalyst. A hydrocarbon solvent was chosen to promote precipitation of the crystalline iminium salt **20** as it forms, allowing for quantitative recovery by cannula filtration. In the same flask, **20** is suspended in pentane at −78 °C and treated with a solution of anhydrous trimethylamine. Upon warming, the insoluble chloroimidate gradually reacts to form **7** with simultaneous precipitation of trimethylammonium chloride. Filtration and concentration under inert conditions gives pure, colorless product with no contamination from the base or its hydrochloride. This alternative is an improvement over the original use of Et_3N, which in our hands afforded discolored samples of **7** and proved difficult to cleanly separate from the product by distillation (bp 129−130 °C).[20]

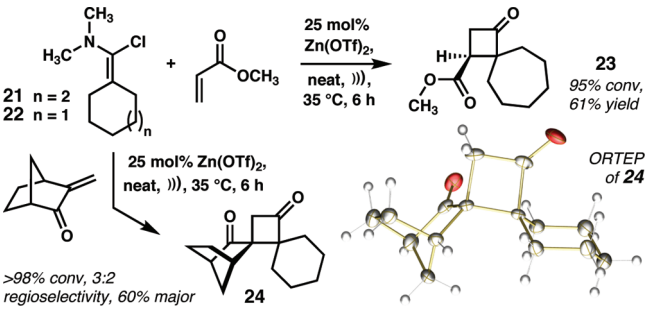


Evidence for the utility of the new haloenamine synthesis is provided in Scheme 5. Cyclic derivatives **21** and **22**, prepared in high yield by the operations just detailed, were without purification subjected to the optimized conditions for Zn-catalyzed [2 + 2] annulation. In the presence of methyl acrylate, **21** provides spirocycle **23** in 61% isolated yield. Exposure of **22** to 3-methylene-2-norbornanone gives tetracyclic diketone **24** (60%, 3:2 rr, 40% minor), whose structure was secured by

Scheme 4



Scheme 5. Zn-Catalyzed Synthesis of Spirocyclic Cyclobutanones

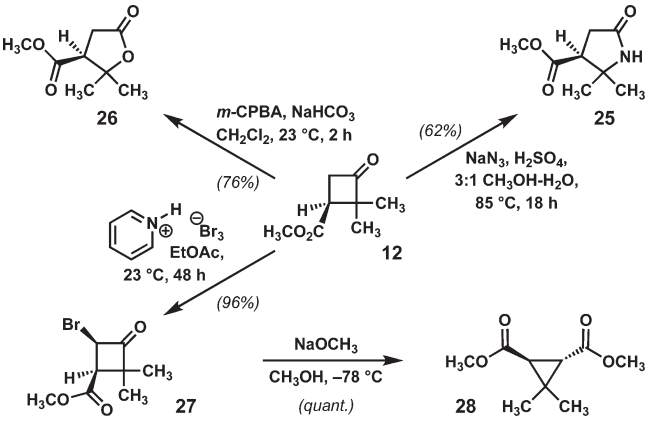


X-ray crystallography following crystallization from heptane. The ready availability of the starting materials and mild conditions associated with this reaction are advantageous. Another salient feature pertains to rapid buildup of sterically crowded all-carbon-substituted quaternary carbon atoms, some contiguous. Both carbonyl groups in any of the products seem poised for additional stereoselective bond-forming events, and ring strain can also be quite serviceable for further elaboration.

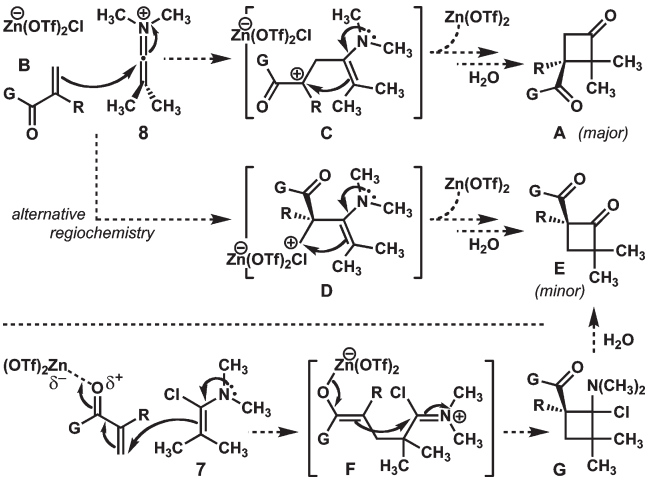
Synthetic Utility of 3-Acyl Cyclobutanones. In support of these assertions, we investigated the reactions shown in Scheme 6 starting with ketoester **12** as a representative synthon. After some experimentation, Schmidt nitrogen insertion was achieved in wet methanol with sulfuric acid as a promoter, giving **25** as a single regioisomer. Baeyer–Villiger oxidation under standard conditions provides **26** in 76% yield. Room temperature α-bromination with pyridinium perbromide proceeds quantitatively to give **27**, a structure assigned as the unexpected *cis*-diastereomer on the basis of NOE experiments. Subsequent ring contraction[21] with sodium methoxide affords dimethylcyclopropane dimethyl ester **28**, a C_2-symmetric structure possibly useful for making rigidified diol ligands with altered bite angles. Although the basis for diastereocontrol in the bromination event is not clear, we note that a similar contrasteric outcome in α-hydroxylation would be of relevance to the complex enecyclobutane core of providencin.[3]

Mechanistic Considerations for Cyclobutannulation. The exclusive or predominant products of the Zn-catalyzed process contain a 1,4-dicarbonyl and seem to derive from a polarity inversion. As mentioned previously and depicted in Scheme 7, a conventional ionic mechanism that invokes keteniminium **8** as a potent electrophile appears unlikely; participation of the electron-poor olefin **B** as a nucleophile results in a buildup of positive charge α to the carbonyl group (**C**), or in the case of minor regioisomer **E**, at the β position which is necessarily a primary carbon for substrates currently within the scope of this transformation (see **D**). It is also worth noting that were the Zn catalyst

Scheme 6. Initial Studies on the Versatility of 3-Acyl Cyclobutanones



Scheme 7. Seemingly Unlikely Paths for Regioselective [2 + 2] Annulation



to act as a Lewis acid for the carbonyl group, rather than removing chloride from the starting α-chloroenamine **7**, a straightforward path to a cyclobutanone can be drawn with the enamine unit in **7** through intermediates **F** and **G** (bottom of Scheme 7). However, the 2-acyl isomer (**E**) would form if this mechanism were operative, and the co-product is only observed in two seemingly unrelated cases of cyclocondensation.

We therefore began to consider alternative mechanisms for product formation that start with Zn-catalyzed dehalogenation to give the putative keteniminium cation **8**. Since the method is general for mono- and disubstituted α-olefins with a ketone, ester, or amide substituent (**B**, G = CH_3, OCH_3, or $N(CH_3)_2$), we judged that initial association of a Lewis basic oxygen lone pair at C1 of **8** would be facile (→**H**, Scheme 8). Further processing of ion pair **H** is then possible in either of two ways. The 5-*exo*-trig cyclization gives a tertiary cation (**I**) that could be quickly trapped internally to give [2.1.1]bicyclic oxonium ion **J**, a species that derives additional resonance stabilization if substituent G is electron-donating. Subsequent iminium ion formation and hydrolysis deliver the observed regioisomer **A**. Alternatively, 6-*endo*-trig cyclization gives α-alkoxy iminium ion **K** in a step

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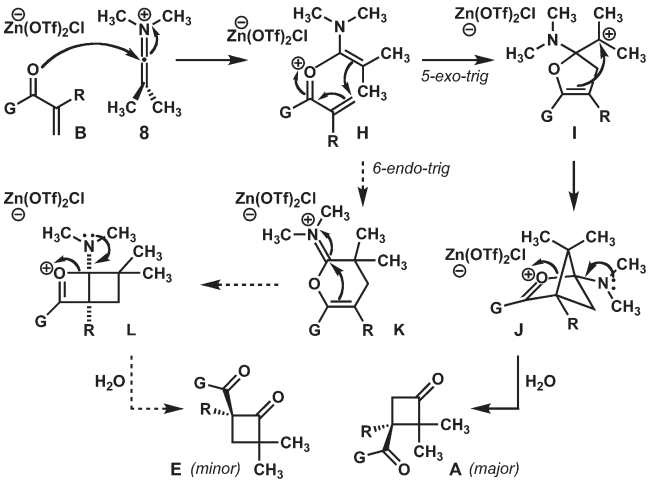
Scheme 8. Plausible Mechanism Based on Initial Cl^- Abstraction by Zn(II)



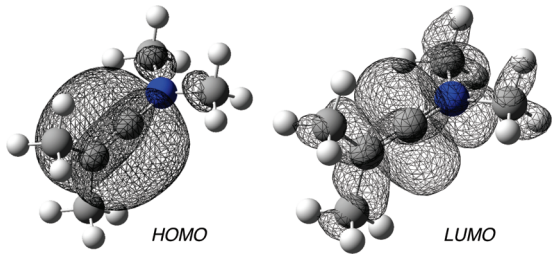
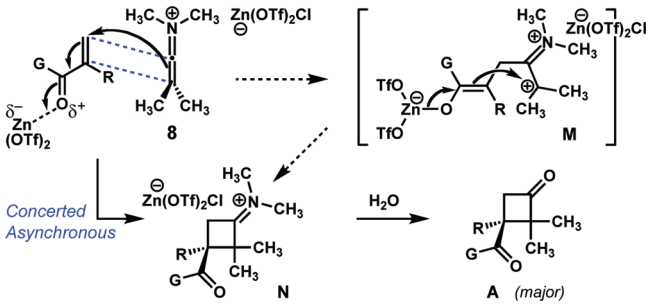


Figure 1. DFT calculations for keteniminium HOMO and LUMO.

Scheme 9. Viable Mechanism Based on Lewis Acid−Carbonyl Activation



that could also be viewed as a 6-π electrocyclic ring closure. A stereoelectronically disfavored 4-*endo*-trig bicyclization would then be needed to reach intermediate **L**, a potential precursor to the unusual 2-acyl regioisomer **E**. This, together with the forbidden nature of the ring closure when viewed as a disrotatory 4-π electrocyclization, can adequately explain the exclusive formation of 3-acyl cyclobutanone **A**.

At this point, a cationic path through **H**, **I**, and **J** was viewed as a possible scenario for Zn-catalyzed merger of the reactants, and we could account for the production of small amounts of regioisomer **E** in the cases of entry 6 (Table 2) and **22**→**24** (Scheme 5) by invoking the Michael addition/Mannich closure pathway described above (bottom of Scheme 7). The fact that cations **H**−**J** are either tertiary or resonance-stabilized, and thus more stable than those in **C** or **D** (Scheme 7), lends additional support to the mechanism in Scheme 8. However, it involves a reactivity inversion for the enamine function, and it is not clear why such a reversal would occur. The strained and congested nature of bridged bicyclic intermediate **J** was also a concern. A computational approach toward probing the electronic structure in the keteniminium species **8** thus seemed appropriate for gaining more insight on its role in this process.

DFT Calculations and Their Mechanistic Implications. DFT calculations at the B3LYP/6-31G* level show that the HOMO−LUMO gap in tetramethylketeniminium cation is 7.17 kcal/mol (Figure 1). This compares favorably to the result for ketene itself of 7.26 kcal/mol. More noticeable differences can be found upon comparison of the Mulliken populations in each electrophile. Our calculations show that, for ketene, Mulliken charges on the α and β carbon atoms are, respectively, 0.153 and 0.021, and the charge on the carbonyl oxygen is −0.241. In contrast, the keteniminium bears charges of 0.074 and −0.092 at the α and β positions and 0.166 for the nitrogen atom. The localization of partial anionic charge at the β carbon is unusual considering that the nitrogen lone pair is disposed completely orthogonal to the C−C π bond, but we were more intrigued by the apparent attenuation of electrophilicity at the α carbon of keteniminium (relative to ketene). Each of the mechanisms considered thus far begins by interaction of the α,β-unsaturated carbonyl with the keteniminium LUMO. However, there is no reason to suspect that the reaction could not involve the keteniminium HOMO and the vacant π^* orbital on the electron-deficient alkene.

Another mechanistic scenario therefore emerges based on the alternative role for keteniminium as a nucleophile (Scheme 9). The π component in **8** may engage the electrophilic β carbon of substrate in an addition subject to LUMO lowering by the Lewis acid. Subsequent internal trapping of the tertiary cation by the Zn enolate (in **M**) would generate dimethyliminium **N**, the direct product prior to the addition of water upon workup. Scrutiny reveals vicinal dication character in intermediate **M**, so it is probably best to view this as a concerted asynchronous process. Importantly, the *regiochemistry* and *timing* of C−C bond formation with respect to keteniminium ion **8** is the same here as that given in Scheme 8. However, the two mechanisms differ greatly in their underlying basis for zinc(II) catalysis; the latter clearly implies a dual role for $Zn(OTf)_2$ in assisting both generation of the keteniminium cation (**8**) and acceleration of its addition to the various electrophilic Michael acceptors.

Evidence To Support a Dual Role for the Zinc(II) Catalyst. In an effort to validate one of the two mechanistic pathways, we searched for a means to separately evaluate the catalyst's role in both chloride abstraction from α-chloroenamine **7** and carbonyl activation. It was known from work by Ghosez[7a] and Weingarten[14] that keteniminium salts form quantitatively (and can indeed be observed and characterized spectroscopically) upon exposure of **7** to an appropriate silver(I) salt in CH_2Cl_2 or acetonitrile ($AgBF_4$ and $AgPF_6$). We chose to experiment with AgOTf since triflate may best approximate the true counterion under our reaction conditions. As indicated below, treatment of **7** with an equimolar amount of AgOTf in CH_2Cl_2 at 0 °C immediately gives a voluminous AgCl precipitate that can be filtered off under inert conditions; variable processing of the supernatant **8** then gave the results entered in Table 3. In the absence of $Zn(OTf)_2$, a mixture of tetramethylketeniminium **8**

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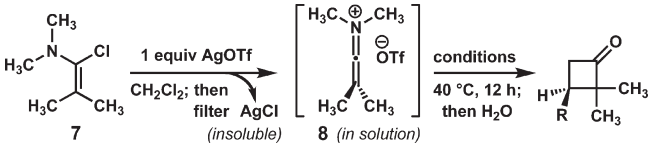
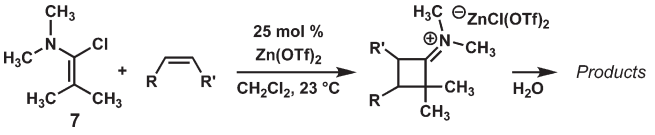
Table 3. Transformations of Keteniminium Formed by a Ag(I) Promoter

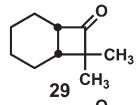
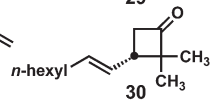
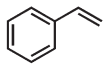
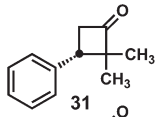
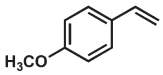
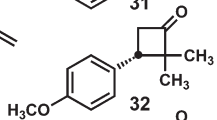
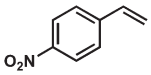
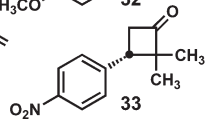


entry	conditions	"R" in product	conv to product (%)[a]
1	1 equiv of MVK, no catalyst	Ac	<5
2	1 equiv of MVK, 25 mol % of $Zn(OTf)_2$	Ac	80
3	1 equiv of MVK, 1.25 equiv of AgOTf (@ start)	Ac	75
4	1 equiv of styrene, no catalytst	Ph	83

[a] Determined by ^{1}H NMR analysis of the unpurified reaction mixture.

Table 4. Extending the Catalytic [2 + 2] Annulation to Nucleophilic Olefins



entry	reaction partner	cycloadduct	time	conv (%)[a]	yield (%)[b]
1		 29	36 h	98	88
2	*n*-hexyl 	 30	18 h	>98	85
3		 31	12 h	>98	94
4	H_3CO 	 32	12 h	>98	86
5[c]	O_2N 	 33	24 h	>98	90

[a] By ^{1}H NMR analysis. [b] After silica gel chromatography. [c] Run at 40 °C.

and MVK gives <5% of 3-acetyl-2,2-dimethylcyclobutanone (entry 1). In stark contrast, addition of substrate and 25 mol % of catalyst to the solution of **8** allows for smooth conversion to product, measured at 80% after 12 h at 40 °C (entry 2). These two outcomes clearly implicate a Lewis acid−base association between substrate and Zn(II) as a requirement for annulation, and the closing entries of Table 3 further corroborate this idea. If the experiment is initiated by a 25 mol % excess of AgOTf, a comparable 75% conversion to product is observed (entry 3). This suggests that $Zn(OTf)_2$ is not alone in its ability to activate the α,β-unsaturated carbonyl substrate as a Lewis acid. Finally, if a less electron-poor olefin such as styrene is added to **8** instead of MVK, 83% conversion to 3-phenyl-2,2-dimethylcyclobutanone is observed in the absence of $Zn(OTf)_2$ (entry 4). This last result implies that more electron-rich donor alkenes freely engage the keteniminium through the typical electrophilic mechanism (see Scheme 7); in the case of styrene, the penultimate cationic intermediate is a stable benzylic cation. This finding also points to a way to probe $Zn(OTf)_2$'s role in keteniminium ion formation, namely, success in catalyzing the synthesis of cyclobutanones starting from non-carbonyl-substituted olefins.

Data compiled in Table 4 indeed confirm that the Ghosez cyclobutanone annulation with simple mono- and disubstituted olefins is subject to catalysis by $Zn(OTf)_2$. As entry 1 shows, a stirred solution of cyclohexene, **7**, and 25 mol % catalyst gives 88% of bicyclooctanone **29** after 36 h at ambient temperature. Cycloaddition of *trans*-1,3-decadiene proceeds to >98% conversion in 18 h at 23 °C, affording the 1-octenyl-substituted ketone **30** in 85% yield as a single regioisomer (entry 2). Additionally, styrene, *p*-methoxystyrene, and *p*-nitrostyrene condense smoothly with chloroenamine **7** to give the respective [2 + 2] adducts in good yield. All three of the latter reactions give quantitative conversion under the indicated conditions (entries 3−5), but monitoring each prior to completion allows for manifestation of the expected rate differences. For instance, at a concentration of 0.25 M in $CDCl_3$, *p*-nitrostyrene gives 14% conversion to **33** in the same time (2 h) that *p*-methoxystyrene gives 75% conversion to **32**. Again, these data seem to be consistent with the hypothesis that non-carbonyl-substituted alkene substrates react with the keteniminium ion through a conventional ionic pathway in which charge buildup at the benzylic position of the nucleophile is influenced by the electron-releasing or electron-withdrawing effects of the *para*-substituent.

CONCLUSIONS

We demonstrate zinc(II) catalysis in an unusual merger of keteniminium ions[22] and electron-poor alkenes. The former are accessed by catalytic halogen abstraction from α-chloroenamines, themselves prepared by an improved one-pot protocol from the corresponding tertiary amide. In all but two cases studied to date, a 3-acyl cyclobutanone is the exclusive regioisomer formed, and we have shown such adducts to be useful in the context of strain release. More importantly, a 1,4-dicarbonyl inherent to the product structure points to an umpolung in reactivity.[23] On the basis of DFT calculations and empirical studies, a mechanism in which $Zn(OTf)_2$ serves two functions is

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currently favored. The first involves abstraction of chloride anion from the enamine starting material, giving tetrasubstituted keteniminium ions as reactive intermediates. The second role for the Lewis acid is to activate the α,β-unsaturated carbonyl toward Michael addition by the modestly nucleophilic α carbon of the keteniminium. This mechanistic proposal is supported by the following facts: (1) β-substituted enones, acrylic esters, and amides fail to react under the standard reaction conditions; (2) the optimal catalyst loading (25 mol %) is relatively high, reflecting its need to accomplish separate tasks during formal [2 + 2] cycloaddition; and (3) donor olefins that are poised to react in accordance with an established[7] stepwise pathway in which keteniminium is the electrophile also react efficiently under mild conditions with substoichiometric amounts of Zn(OTf)$_2$. Some questions on scope and generality of the Zn-catalyzed [2 + 2] cycloaddition remain unanswered at this time, including the performance of β-monosubstituted chloroenamines in the transformation and its preferred means of enantiocontrol.

EXPERIMENTAL SECTION

Materials and Methods. Unless stated otherwise, reactions were carried out in flame-dried glassware under an atmosphere of nitrogen with standard Schlenk or vacuum line techniques. A preferred experimental setup for sonication consists of a variable output Misonix 3000 sonicator equipped with an external water circulator to control the temperature of the bath in which the cup horn (sonar probe) is immersed. Dry and degassed solvents (CH_2Cl_2, pentane, and THF) were dispensed from a solvent purification system based on activated alumina columns.[24] Materials obtained from commercial sources were usually purified before use. 1-Chloro-1-*N*,*N*,2-trimethylpropenylamine was carefully degassed under vacuum at −78 °C and then distilled with warming to 23 °C through a short path with the receiving flask cooled to −78 °C. A dry trimethylamine solution (2.0 M in pentane) was prepared as follows: (1) commercial gas was condensed onto potassium hydroxide pellets at −78 °C; (2) the resulting colorless mixture was stirred cold for 10 min and then distilled through a short path with warming into a preweighed flask kept at −78 °C; and (3) the resulting colorless liquid (8.87 g, 150 mmol) was dissolved in 75.0 mL of pentane and transferred by cannula to a dry Shlenk flask that could be stored at −20 °C for repeated use. *N*,*N*-Dimethylisobutyramide was distilled under vacuum over calcium hydride. Zinc(II) triflate was rigorously dried under vacuum in an Abderhalden pistol containing P_2O_5 at 80 °C. *N*,*N*-Dimethylcyclohexanecarboxamide was prepared by catalytic hydrogenation of benzoic acid[25] and subsequent chlorination/amidation according to a procedure given below for *N*,*N*-dimethylcycloheptanecarboxamide. Methyl vinyl ketone, 3-methyl-3-buten-2-one, methyl methacrylate, methyl acrylate, *N*,*N*-dimethylmethacrylamide, and *N*,*N*-dimethylacrylamide were freed of stabilizers by vacuum distillation at 23 °C over calcium sulfate through a short path with the receiving flask kept at −78 °C. Oxalyl chloride was distilled under nitrogen. Anhydrous ethyl acetate (for the bromination of **12**) was distilled under nitrogen from CaH_2. Pyridinium perbromide recrystallized as bright orange needles from cyclohexane. Cyclohexene was distilled under nitrogen. *trans*-1,3-Decadiene, styrene, *p*-methoxystyrene, and *p*-nitrostyrene were vacuum distilled.

Column chromatography was performed with normal phase silica gel 60 (230−400 mesh ASTM) and driven with compressed air. Analytical thin-layer chromatography was carried out with silica gel 60 F_{254} precoated plates (250 μm thickness) and potassium permanganate or ceric ammonium molybdate (CAM) stains for spot visualization.

Infrared spectra were recorded on a FT-IR spectrophotometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^1H NMR spectra were recorded on 400 or 500 MHz spectrometers and are reported relative to deuterated solvent signals ($CDCl_3$: δ 7.26 ppm; C_6D_6: δ 7.16 ppm). Data are reported as follows: chemical shift, multiplicity, coupling constant (hertz), and integration. ^{13}C NMR spectra were recorded on 100 or 125 MHz spectrometers with complete proton decoupling. Chemical shifts are reported in parts per million from tetramethylsilane with solvent as the internal reference ($CDCl_3$: δ 77.16 ppm; C_6D_6: δ 128.39 ppm). High-resolution mass spectra were obtained using the electrospray ionization method in positive ion mode.

Experimental Procedures. *1-Chloro-N,N,2-trimethyl-1-propenylamine (**7**).* To a solution of *N*,*N*-dimethylisobutyramide (**19**, 0.500 mL, 3.87 mmol) in 3.87 mL of pentane under nitrogen at −78 °C was added dropwise from a syringe neat oxalyl chloride (0.327 mL, 3.87 mmol, 1.0 equiv). Upon slow (2 h) warming to 23 °C, a heterogeneous mixture was obtained that showed no starting material remaining according to TLC analysis. The supernatant was removed by cannula filtration under postitive nitrogen pressure, and the solid was washed with three 5 mL volumes of pentane. After removing the last pentane wash, the white solid was suspended in 3.87 mL of pentane and cooled to −78 °C. With vigorous stirring, cold trimethylamine (1.94 mL of 2.0 M solution, 3.87 mmol, 1.0 equiv) was then added dropwise and the heterogeneous mixture was transferred to a cold room (4 °C) for 12 h. The reaction never achieves homogeneity since trimethylamine hydrochloride precipitates as the intermediate chloroimidate (**20**) enters solution by deprotonation. Upon taking the sample into a glovebox, additional pentane was used to filter the mixture through a fine frit, affording a colorless filtrate that was concentrated in vacuo at −78 °C (to discourage violent bumping). This operation provided 0.465 g of a colorless, ready-to-use sample of α-chloroeneamine **7** (90% yield), which can be stored for iterative use at −30 °C in a glovebox freezer. ^1H and ^{13}C NMR data for this compound are identical to that of vacuum-distilled commercial samples.

*3-Acetyl-2,2-dimethylcyclobutanone (**11**)*

Representative Thermal Procedure for Formal [2 + 2] Cycloaddition. In a glovebox, a flame-dried 2 dram (7.4 mL) vial equipped with a stir bar was charged successively with methyl vinyl ketone (0.254 mL, 3.13 mmol, 1.25 equiv), 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine (**7**, 0.331 mL, 2.50 mmol), and zinc(II) chloride (0.341 g, 2.50 mmol, 1.0 equiv). After sealing the vial with a rubber septum and removing it from the glovebox, 2.5 mL of CH_2Cl_2 was added under positive nitrogen pressure in a fume hood. The resulting heterogeneous mixture was tightly capped and stirred at 50 °C for 24 h, a point at which the solids had dissolved to form a yellow solution; 1.1 mL of 10:1 THF−H_2O was then added to the solution to hydrolyze the iminium salt of the product. After 1 h of stirring, the mixture was diluted with 20 mL of CH_2Cl_2 and dried over magnesium sulfate. Vacuum filtration and concentration afforded a yellow oil which showed 97% conversion to product ketone (based on relative integration of ^1H NMR signals corresponding to *N*,*N*-dimethylisobutyramide (**19**), the product of α-chloroenamine hydrolysis). Purification was achieved by passage through a short plug (2.5 cm height, 7.5 cm diameter) of silica gel in 3:1 hexanes/ethyl acetate (TLC R_f = 0.34 for ketone, 0.08 for amide). Concentration of the chromatography fractions yielded 0.283 g of product (81% yield) as a colorless oil: IR (thin film) 2966 (s), 2924 (m), 2869 (w), 1782 (s), 1708 (s), 1641 (w), 1464 (m), 1442 (w), 1383 (m), 1364 (s), 1176 (s), 1160 (m), 1126 (m), 1066 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 3.56 (dd, *J* = 17.9, 7.9 Hz, 1H), 3.09 (dd, *J* = 8.4, 7.9 Hz, 1H), 2.78 (dd, *J* = 17.9, 8.4 Hz, 1H), 2.16 (s, 3H), 1.32 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.3, 205.4, 64.1, 47.7, 43.1, 31.2, 23.2, 18.2; HRMS (ESI+) calcd for $C_8H_{13}O_2^+$ $[M + H]^+$ 141.0916, found 141.0915.

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*Methyl 2,2-dimethyl-3-oxocyclobutanecarboxylate (**12**)*

Representative Sonication Procedure for Formal [2 + 2] Cycloaddition. In a glovebox, a flame-dried 2 dram (7.4 mL) vial equipped with a stir bar was charged successively with methyl acrylate (0.281 mL, 3.12 mmol, 1.25 equiv), 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine (**7**, 0.331 mL, 2.50 mmol), and zinc(II) triflate (0.227 g, 0.625 mmol, 0.25 equiv). The mixture was briefly stirred to blend its contents, and the vial was sealed tightly with a Teflon-lined screw cap. After removing the sample from the glovebox, the reaction was sonicated at 35 °C for 6 h (180 W, Misonix Sonicator 3000), during which time the solution turned yellow and, after 2 h, solidified; 1.1 mL of 10:1 THF−H_2O was then added to the mixture to hydrolyze the iminium salt of the product. After 1 h of stirring, the mixture was diluted with 20 mL of CH_2Cl_2 and dried over magnesium sulfate. Vacuum filtration and solvent removal on a rotary evaporator afforded a yellow oil showing >98% conversion to product ketone based on the lack of detectable signals corresponding to *N*,*N*-dimethylisobutyramide (**19**), the product of α-chloroenamine hydrolysis. Purification was achieved by filtration through a short plug (2.5 cm height, 7.5 cm diameter) of silica gel in 9:1 hexanes/ethyl acetate (TLC R_f = 0.31 for ketone, 0.0 for amide). Concentration of fractions gave 0.257 g of a colorless oil (66% yield): IR (thin film) 2965 (s), 2930 (m), 2870 (w), 1788 (s), 1735 (s), 1463 (m), 1438 (s), 1383 (m), 1353 (m), 1273 (w), 1208 (s), 1180 (s), 1163 (m), 1131 (w), 1110 (w), 1065 (m), 1040 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.52 (dd, J = 17.9, 7.3 Hz, 1H), 3.08 (dd, J = 17.9, 9.0 Hz, 1H), 2.94 (dd, J = 9.0, 7.3 Hz, 1H), 1.29 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.0, 172.5, 64.3, 51.9, 44.7, 40.6, 23.0, 18.4; HRMS (ESI+) calcd for $C_8H_{13}O_3^+$ $[M + H]^+$ 157.0865, found 157.0858.

*3-Acetyl-2,2,3-trimethylcyclobutanone (**9**).* The sonication procedure described above was applied with 0.252 g of 3-methyl-3-buten-2-one (3.00 mmol, 1.2 equiv), 0.331 mL of 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine (**7**, 2.50 mmol), and 0.227 g of zinc(II) triflate (0.625 mmol, 0.25 equiv). Upon obtaining a yellow oil after the hydrolytic workup (87% conversion by ^{1}H NMR analysis), a Kugelrohr distillation apparatus was used for purification. First, *N*,*N*-dimethylisobutyramide (**19**) and the unreacted 3-methyl-3-buten-2-one was removed at 1.8 Torr and 50 °C without isolation. Upon raising the temperature to 75 °C, the product distilled at 1.8 Torr over 6 h. Careful transfer and weighing of this distilled fraction delivered 0.283 g of a colorless oil (73% yield): IR (thin film) 2968 (m), 2929 (m), 2874 (w), 1779 (s), 1702 (s), 1460 (m), 1424 (w), 1404 (w), 1386 (m), 1381 (m), 1357 (m), 1279 (w), 1184 (w), 1154 (m), 1122 (w), 1099 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (d, J = 17.4 Hz, 1H), 2.38 (d, J = 17.4 Hz, 1H), 2.17 (s, 3H), 1.40 (s, 3H), 1.18 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.7, 208.3, 64.0, 50.8, 48.1, 27.9, 20.9, 19.9, 17.3; HRMS (ESI+) calcd for $C_9H_{15}O_2^+$ $[M + H]^+$ 155.1072, found 155.1077.

*Methyl 1,2,2-trimethyl-3-oxocyclobutanecarboxylate (**13**).* The sonication procedure described above was applied with 0.321 mL of methyl methacrylate (3.00 mmol, 1.2 equiv), 0.331 mL of 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine (**7**, 2.50 mmol), and 0.227 g of zinc(II) triflate (0.625 mmol, 0.25 equiv). Upon obtaining an orange oil (91% conversion by ^{1}H NMR analysis) after the hydrolytic workup, purification was achieved by filtration through a short plug (2.5 cm height, 7.5 cm diameter) of silica gel in 10:1 hexanes/ethyl acetate (TLC R_f = 0.32 for ketone, 0.0 for amide). Concentration of fractions yielded 0.269 g of a light yellow oil (63% yield): IR (thin film) 2970 (m), 2938 (m), 2874 (w), 1785 (s), 1732 (s), 1460 (m), 1436 (m), 1403 (w), 1384 (m), 1365 (w), 1296 (s), 1200 (s), 1157 (m), 1134 (s), 1104 (m), 1062 (m), 993 (w); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.78 (d, J = 17.4 Hz, 1H), 3.72 (br s, 3H), 2.62 (dd, J = 17.6, 11.5 Hz, 1H), 1.38 (s, 3H), 1.11 (d, J = 1.5 Hz, 3H), 1.10 (d, J = 1.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.5, 174.9, 64.7, 52.6, 52.1, 42.5, 20.9, 20.0, 17.5; HRMS (ESI+) calcd for $C_9H_{15}O_3^+$ $[M + H]^+$ 171.1021, found 171.1022.

*N,N,2,2-Tetramethyl-3-oxocyclobutanecarboxamide (**14**).* The sonication procedure described above was applied with 0.310 g of *N*,*N*-dimethylacrylamide (3.13 mmol, 1.25 equiv), 0.331 mL of 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine (**7**, 2.50 mmol), and 0.227 g of zinc(II) triflate (0.625 mmol, 0.25 equiv). Upon obtaining an orange oil after the hydrolytic workup (96% conversion by ^{1}H NMR analysis), a Kugelrohr distillation apparatus was used for purification. First, *N*,*N*-dimethylisobutyramide (**19**) and the unreacted *N*,*N*-dimethylacrylamide were removed at 1.8 Torr and 50 °C without isolation. Upon raising the temperature to 125 °C, the product distilled at 1.8 Torr over 6 h. Careful transfer and weighing of this distilled fraction delivered 0.353 g of a colorless oil (83% yield): IR (thin film) 2964 (w), 2929 (w), 2868 (w), 1779 (s), 1636 (s), 1499 (w), 1463 (w), 1401 (w), 1263 (w), 1153 (m), 1072 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (dd, J = 18.1, 7.1 Hz, 1H), 3.18 (dd, J = 8.8, 7.1 Hz, 1H), 3.06 (s, 3H), 3.02 (s, 3H), 3.01 (dd, J = 18.1, 8.8 Hz, 1H), 1.37 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.2, 170.7, 63.5, 45.7, 39.2, 37.4, 35.9, 23.3, 18.4; HRMS (ESI+) calcd for $C_9H_{16}NO_2^+$ $[M + H]^+$ 170.1181, found 170.1173.

*N,N,1,2,2-Pentamethyl-3-oxocyclobutanecarboxamide (**15**).* The sonication procedure described above was applied with 0.376 mL of *N*,*N*-dimethylmethacrylamide (3.00 mmol, 1.2 equiv), 0.331 mL of 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine (**7**, 2.50 mmol), and 0.227 g of zinc(II) triflate (0.625 mmol, 0.25 equiv). Upon obtaining an orange oil after the hydrolytic workup (90% conversion by ^{1}H NMR analysis), a Kugelrohr distillation apparatus was used for purification. First, *N*,*N*-dimethylisobutyramide (**19**) and the unreacted *N*,*N*-dimethylmethacrylamide were removed at 1.8 Torr and 50 °C without isolation. Upon raising the temperature to 150 °C, the product distilled at 1.8 Torr over 6 h. Careful transfer and weighing of this distilled fraction delivered 0.330 g (80% yield) of a colorless oil that consisted of a pure 3:1 mixture of regioisomeric cyclobutanones. Characterization follows for the major isomer, separable with 2:2:3:1 CH_2Cl_2/Et_2O/hexanes/NH_4OH as chromatographic eluant (TLC R_f = 0.33): IR (thin film) 2962 (w), 2928 (w), 2971 (w), 1779 (s), 1628 (s), 1496 (w), 1462 (w), 1396 (m), 1382 (m), 1270 (w), 1158 (w), 1144 (w), 1114 (w), 1093 (m), 1065 (w), 938 (w), 671 (w); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.17 (d, J = 17.6 Hz, 1H), 2.99 (s, 3H), 2.99 (s, 3H), 2.62 (d, J = 17.6 Hz, 1H), 1.41 (s, 3H), 1.22 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.6, 173.8, 63.0, 55.9, 43.7, 37.7, 36.6, 21.7, 21.2, 17.1; HRMS (ESI+) calcd for $C_{10}H_{18}NO_2^+$ $[M + H]^+$ 184.1338, found 184.1341.

*N-Methoxy-N,2,2-trimethyl-3-oxocyclobutanecarboxamide (**16**).* The sonication procedure described above was applied with 0.345 g of *N*-methoxy-*N*-methylacrylamide (3.00 mmol, 1.2 equiv), 0.331 mL of 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine (**7**, 2.50 mmol), and 0.227 g of zinc(II) triflate (0.625 mmol, 0.25 equiv). Upon obtaining an oil after the hydrolytic workup (85% conversion by ^{1}H NMR analysis), a Kugelrohr distillation apparatus was used for purification. First, *N*,*N*-dimethylisobutyramide (**19**) and the unreacted *N*-methoxy-*N*-methylacrylamide were removed at 1.8 Torr and 50 °C without isolation. Upon raising the temperature to 125 °C, the product distilled at 1.8 Torr over 6 h. Careful transfer and weighing of this distilled fraction delivered 0.294 g of a colorless oil (64% yield): IR (thin film) 2967 (w), 2931 (w), 2870 (w), 1779 (s), 1655 (s), 1462 (m), 1444 (m), 1420 (m), 1383 (m), 1298 (w), 1258 (w), 1178 (w), 1163 (w), 1119 (w), 1067 (m), 1023 (w), 977 (w), 955 (w); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (dd, J = 17.9, 7.6 Hz, 1H), 3.71 (s, 3H), 3.23−3.18 (m, 4H), 2.97 (dd, J = 18.1, 8.8 Hz, 1H), 1.31 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.8, 172.8, 64.5, 61.1, 44.0, 39.0, 39.1, 32.5, 23.0, 18.3; HRMS (ESI+) calcd for $C_9H_{16}NO_3^+$ $[M + H]^+$ 186.1130, found 186.1127.

N-Methoxy-N-methylmethacrylamide. A synthesis was adapted from that reported for *N*-methoxy-*N*-methylacrylamide.[26] The following modifications were made: (1) the reaction was carried out on 12.3 mmol scale with respect to the acid chloride; (2) 2.0 equiv of *N*,*O*-dimethylhydroxylamine hydrochloride was used; (3) 4.0 equiv of triethylamine was substituted for pyridine; and (4) THF was the solvent (0.5 M): IR (thin

film) 2973 (w), 2937 (w), 1655 (s), 1629 (m), 1458 (m), 1421 (w), 1377 (m), 1262 (w), 1177 (w), 1149 (w), 1118 (w), 1092 (w), 998 (w), 945 (w), 917 (w), 888 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29 (quartet, J = 1.1 Hz, 1H), 5.22 (quintet, J = 1.7 Hz, 1H), 3.64 (s, 3H), 3.23 (s, 3H), 1.97 (dd, J = 1.7, 1.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 140.3, 117.5, 61.4, 33.5, 20.1; HRMS (ESI+) calcd for $C_6H_{12}NO_2^+$ $[M + H]^+$ 130.0868, found 130.0861.

N-Methoxy-N,1,2,2-tetramethyl-3-oxocyclobutanecarboxamide (***17***). The sonication procedure described above was applied with 0.387 g of *N*-methoxy-*N*-methylmethacrylamide (3.00 mmol, 1.2 equiv), 0.331 mL of 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine (**7**, 2.50 mmol), and 0.227 g of zinc(II) triflate (0.625 mmol, 0.25 equiv). Upon obtaining a yellow oil after the hydrolytic workup (87% conversion by ^{1}H NMR analysis), a Kugelrohr distillation apparatus was used for purification. First, *N*,*N*-dimethylisobutyramide (**19**) and the unreacted *N*-methoxy-*N*-methylmethacrylamide were removed at 1.8 Torr and 50 °C without isolation. Upon raising the temperature to 150 °C, the product distilled at 1.8 Torr over 6 h. Careful transfer and weighing of this distilled fraction delivered 0.283 g of a colorless oil (57% yield): IR (thin film) 2968 (w), 2935 (w), 2873 (w), 1777 (s), 1716 (w), 1648 (s), 1459 (m), 1406 (w), 1375 (m), 1362 (m), 1261 (w), 1154 (m), 1110 (w), 1063 (w), 1002 (m), 751 (w), 730 (w), 657 (w), 426 (w); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.00 (d, J = 17.6 Hz, 1H), 3.72 (s, 3H), 3.21 (s, 3H), 2.51 (d, J = 17.6 Hz, 1H), 1.40 (s, 3H), 1.13 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.4, 176.6, 64.3, 60.7, 54.1, 43.6, 33.1, 21.1, 20.4, 16.8; HRMS (ESI+) calcd for $C_{10}H_{18}NO_3^+$ $[M + H]^+$ 200.1287, found 200.1285.

2,2-Dimethyl-3-oxocyclobutanecarboxylic acid (***18***). To a solution of 0.570 g (3.65 mmol) of **12** in 5.1 mL of 7:1 THF−H_2O was added lithium hydroxide (0.087 g, 3.65 mmol, 1.0 equiv). The solution was stirred for 18 h sealed under nitrogen at 23 °C, and the solvent was removed in vacuo. The off-white solid residue that remained (lithium 2,2-dimethyl-3-oxocyclobutanecarboxylate) was then dissolved in 7.3 mL of THF at 0 °C and protonated by brief treatment (5 min) with anhydrous HCl (generated from NaCl and H_2SO_4 and gently bubbled through the solution). Passage through a cotton plug (to remove insoluble lithium chloride) and concentration afforded 0.470 g (91% yield) of the acid as a white solid (mp = 66−69 °C): IR (thin film) 3176 (br), 2967 (w), 2928 (w), 2871 (w), 1786 (s), 1706 (s), 1494 (w), 1464 (w), 1444 (w), 1383 (w), 1327 (w), 1280 (w), 1188 (w), 1130 (w), 1065 (w), 796 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.00 (br, 1H), 3.51 (dd, J = 18.0, 7.2 Hz, 1H), 3.12 (dd, J = 18.0, 8.8 Hz, 1H), 3.01 (dd, J = 8.8, 7.2 Hz, 1H), 1.34 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.6, 178.0, 64.9, 44.7, 40.8, 23.3, 18.5; HRMS (ESI+) calcd for $C_7H_{11}O_3^+$ $[M + H]^+$ 143.0708, found 143.0705.

N,N-Dimethylcycloheptanecarboxamide. To a stirring solution of oxalyl chloride (3.33 mL, 39.3 mmol, 1.0 equiv) in pentane (78.6 mL, 0.5 M) at −78 °C was added dropwise 5.40 mL of cycloheptanecarboxylic acid (Aldrich, 39.3 mmol, 1.0 equiv). After stirring for 2 h with slow warming of the reaction to 23 °C, all starting material was judged to be consumed by TLC analysis. At this point, the solution was recooled to −78 °C and treated with 49.1 mL (98.3 mmol, 2.5 equiv) of a 2.0 M solution of dimethylamine in pentane. A white precipitate formed immediately, and the solution was stirred at −78 °C for an additional 6 h before cannula filtration and concentration of the filtrate on a rotovap. Column chromatography in 1:1 hexanes/ethyl acetate (TLC R_f = 0.33) furnished a light yellow oil that was further purified by short path vacuum distillation to give 5.55 g of a colorless oil (84% yield): IR (thin film) 2921 (m), 2856 (m), 1640 (s), 1495 (w), 1461 (w), 1411 (w), 1397 (w), 1362 (w), 1255 (w), 1178 (w), 1135 (w), 1107 (w), 1056 (w), 1024 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.03 (s, 3H), 2.92 (s, 3H), 2.68−2.62 (m, 1H), 1.82−1.40 (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.6, 42.0, 37.4, 35.7, 31.4, 28.4, 27.0; HRMS (ESI+) calcd for $C_{10}H_{20}NO^+$ $[M + H]^+$ 170.1545, found 170.1550.

1-Chloro-1-cycloheptylidene-N,N-dimethylmethanamine (***21***). This α-chloroenamine is prepared from 0.846 g (5.0 mmol) of *N*,*N*-dimethylcycloheptanecarboxamide by direct analogy to the synthesis of **7**, yielding 0.798 g (85% yield) of **21** as a colorless oil: ^{1}H NMR (400 MHz, C_6D_6) δ 2.42 (dt, J = 17.6, 6.2 Hz, 2H), 2.28 (s, 6H), 1.57−1.15 (m, 8H), 0.87 (dd, J = 7.1, 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.6, 43.3, 33.0, 32.1, 30.2, 29.7, 28.9, 27.2. IR and mass spectral data are not recorded; the compound undergoes rapid and quantitative hydrolysis upon exposure to air and moisture.

Methyl 3-Oxospiro[3.6]decane-1-carboxylate (***23***). The sonication procedure described above was applied with 0.281 mL of methyl acrylate (3.00 mmol, 1.2 equiv), 0.469 g of **21** (2.50 mmol), and 0.227 g of zinc(II) triflate (0.625 mmol, 0.25 equiv). Upon obtaining a light orange oil after the hydrolytic workup (95% conversion by ^{1}H NMR analysis), **21** and the unreacted methyl acrylate were removed at 1.8 Torr and 80 °C without isolation. Passage of the remaining undistilled fraction through a plug of silica gel in 10:1 hexanes/ethyl acetate (TLC R_f = 0.30) provided 0.320 g of a colorless oil (61% yield): IR (thin film) 2926 (m), 2857 (w), 1781 (s), 1732 (s), 1645 (w), 1461 (w), 1438 (w), 1353 (w), 1267 (w), 1200 (m), 1174 (m), 1089 (w), 1029 (w); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (s, 3H), 3.42 (dd, J = 17.7, 7.2 Hz, 1H), 3.02 (dd, J = 17.7, 8.9 Hz, 1H), 2.91 (dd, J = 8.9, 7.2 Hz, 1H), 1.95 (ddd, J = 11.5, 9.5, 2.2 Hz, 1H), 1.81−1.46 (m, 10H), 1.40 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.6, 172.9, 72.5, 52.0, 44.4, 41.5, 35.9, 30.8, 29.3, 29.1, 23.4, 23.2; HRMS (ESI+) calcd for $C_{12}H_{19}O_3^+$ $[M + H]^+$ 211.1334, found 211.1341.

1-Chloro-1-cyclohexylidene-N,N-dimethylmethanamine (***22***). This α-chloroeneamine is prepared from 0.776 g (5.0 mmol) of *N*,*N*-dimethylcyclohexanecarboxamide by direct analogy to the synthesis of **7**, yielding 0.485 g (56% yield) of **22** as a colorless oil: ^{1}H NMR (400 MHz, C_6D_6) δ 2.33 (dd, J = 38.8, 1.2 Hz, 1H), 2.24−2.19 (m, 2H), 1.63 (s, 6H), 1.33−1.04 (m, 6H), 0.73 (dd, J = 7.2, 6.8 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 138.9, 131.7, 43.4, 31. 5, 31.2, 28.5, 27.7, 27.3. IR and mass spectral data are not recorded; the compound undergoes rapid and quantitative hydrolysis upon exposure to air and moisture.

Pentacyclic Diketone ***24***. The sonication procedure described above was applied with 0.0350 mL of 3-methylene-2-norbornanone (0.286 mmol, 1.0 equiv), 0.0500 g of 1-chloro-1-cyclohexylidene-*N*,*N*-dimethylmethanamine (**22**, 0.286 mmol, 1.0 equiv), and 0.026 g of zinc(II) triflate (0.072 mmol, 0.25 equiv). Upon obtaining a yellow oil after the hydrolytic workup (>98% conversion by ^{1}H NMR analysis), column chromatography in 10:1 hexanes/ethyl acetate (TLC R_f = 0.20 for minor regioisomer, 0.27 for major regioisomer) furnished 0.041 g of major product (60% yield) and 0.027 g of minor product (40% yield), both as colorless crystalline solids. Major regioisomer (mp = 74−75 °C): IR (thin film) 2932 (m), 2877 (w), 2856 (w), 1773 (s), 1735 (s), 1451 (w), 1382 (w), 1304 (w), 1291 (w), 1276 (w), 1108 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.93 (d, J = 17.4 Hz, 1H), 2.87 (d, J = 17.4 Hz, 1H), 2.77 (br m, 1H), 2.63 (br m, 1H), 2.21 (br d, J = 16.4 Hz, 1H), 1.96 (br d, J = 12.0 Hz, 1H), 1.90−0.82 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.1, 210.3, 68.1, 53.9, 49.7, 47.3, 40.9, 36.2, 31.0, 30.3, 26.8, 25.8, 23.8, 23.7, 23.5; HRMS (ESI+) calcd for $C_{15}H_{21}O_2^+$ $[M + H]^+$ 233.1542, found 233.1543. Minor regioisomer (mp = 72−74 °C): IR (thin film) 2930 (m), 2877 (w), 2856 (w), 1769 (s), 1732 (s), 1447 (m), 1392 (w), 1274 (w), 1204 (w), 1167 (w), 1151 (w), 1097 (m), 1041 (m), 1021 (m), 948 (w), 910 (w); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.02 (d, J = 16.6 Hz, 1H), 2.71 (d, J = 16.4 Hz, 1H), 2.68 (ddd, J = 19.8, 4.6, 1.2 Hz 1H), 2.45 (br d, J = 13.2 Hz, 1H), 1.96 (br d, J = 13.0 Hz, 1H), 1.92−1.42 (m, 13H), 1.11 (qt, J = 13.5, 4.2 Hz, 1H), 0.85 (ddd, J = 13.0, 8.8, 4.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 218.8, 208.6, 66.8, 52.3, 50.9, 50.8, 42.7, 35.8, 30.9, 29.3, 26.0, 24.4, 23.9, 23.6, 23.5; HRMS (ESI+) calcd for $C_{15}H_{21}O_2^+$ $[M + H]^+$ 233.1542, found 233.1548.

Methyl 2,2-Dimethyl-5-oxopyrrolidine-3-carboxylate (***25***). To a stirring solution of **12** (17.0 mg, 0.106 mmol) in 0.42 mL of 3:1

MeOH−H_2O, was added 60.0 μL of sulfuric acid (0.211 mmol, 2.0 equiv) at 23 °C. Commercial sodium azide was then added directly to the reaction mixture as a solid in one portion (8.0 mg, 0.13 mmol, 1.2 equiv), and the mixture was heated to 85 °C. After 3 h of stirring, an additional 1.2 equiv of sodium azide was added, and the reaction was stirred for 15 h. The sulfuric acid was then quenched by the dropwise addition of 1 mL of saturated sodium bicarbonate at 0 °C, and the mixture was transferred to a small separatory funnel with 3 mL of ethyl acetate. After removing the organic layer, the aqueous layer was washed three times with 1 mL portions of ethyl acetate. Pooled organic layers were then dried over magnesium sulfate, filtered, and concentrated to yield 11.0 mg of a light yellow oil (>95% pure by NMR analysis, 62% yield): IR (thin film) 2982 (w), 1777 (s), 1735 (s), 1437 (w), 1391 (w), 1376 (w), 1271 (m), 1259 (m), 1215 (m), 1172 (w), 1119 (m), 1088 (w), 1018 (w), 1001(w), 965 (w), 929 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 3.20 (dd, J = 9.7, 8.6 Hz, 1H), 3.09 (dd, J = 17.8, 9.7 Hz, 1H), 2.71 (dd, J = 17.8, 8.6 Hz, 1H), 1.61 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 170.4, 52.6, 50.6, 32.0, 29.9, 28.7, 23.5; HRMS (ESI+) calcd for $C_8H_{14}NO_3^+$ $[M + H]^+$ 172.0974, found 172.0979.

cis-Methyl 4-Bromo-2,2-dimethyl-3-oxocyclobutanecarboxylate (***27***). Pyridinium perbromide (0.126 g, 0.394 mmol, 1.0 equiv) was added to **12** (51.4 mg, 0.394 mmol) in 0.66 mL of anhydrous ethyl acetate under inert atmosphere. After 48 h of stirring at 23 °C, the turbid yellow reaction mixture was diluted with 4 mL of hexanes, dried over magnesium sulfate, filtered, and then concentrated by rotary evaporation to afford 74.0 mg of a light orange oil (>96% pure by ^{1}H NMR analysis, 96% yield, exclusively the *cis*-diastereomer by NOE experiments): IR (thin film) 2957 (w), 2931 (w), 2871 (w), 1797 (s), 1735 (s), 1461 (w), 1437 (w), 1386 (w), 1354 (w), 1260 (m), 1212 (m), 1177 (w), 1093 (w), 1053 (w), 978 (w), 849 (w); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43 (d, J = 7.9 Hz, 1H), 3.82 (s, 3H), 3.11 (d, J = 7.9 Hz, 1H), 1.44 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.4, 169.8, 62.5, 52.7, 52.0, 46.3, 24.1, 18.9; LRMS (ESI+) calcd for $C_8H_{12}BrO_3^+$ $[M + H]^+$ 234.9970, found 235.0201.

Dimethyltrans-3,3-Dimethylcyclopropane-1,2-dicarboxylate (***28***). A flame-dried 2 dram (7.4 mL) vial equipped with a stir bar was charged with a solution of cyclobutanone **27** (9.1 mg, 0.039 mmol, 1 equiv) in 0.30 mL of methanol and cooled to 0 °C. Sodium methoxide (10.7 μL of a 30% solution in methanol, 0.0580 mmol, 1.5 equiv) was then added dropwise by syringe. The reaction was stirred for 1 h at 0 °C and quenched with 1.0 mL of a saturated solution of ammonium chloride. The resulting mixture was diluted with water (5 mL) and in a separatory funnel, and the aqueous layer was washed with three 6 mL volumes of Et_2O. Combined organic layers were dried over magnesium sulfate, filtered, and concentrated to an oil (>98% yield). Spectroscopic data for this material matched that reported in the literature.[27]

2,2 -Dimethyl-3-(1-octenyl)-cyclobutanone (***30***)

Representative Procedure for Catalytic [2 + 2] Cycloaddition with a Non-Carbonyl-Substituted Alkene. In a glovebox, a flame-dried 2 dram (7.4 mL) vial equipped with a small stir bar was charged in succession with *trans*-1,3-decadiene (190 mg, 1.0 mmol, 1.0 equiv), 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine (136 mg, 1.0 mmol), and zinc(II) triflate (91.0 mg, 0.250 mmol, 0.25 equiv). After sealing the vial with a rubber septum and removing it from the glovebox, 1.0 mL of CH_2Cl_2 was added under positive nitrogen pressure in a fume hood, dissolving the reactants and forming a light yellow homogeneous solution. The vial was then sealed with a Teflon-lined screw cap and stirred for 18 h at 23 °C. Then, 0.5 mL of 10:1 THF−H_2O was added to the solution to hydrolyze the iminium salt of the product. After 1 h of stirring, the mixture was diluted with 3 mL of CH_2Cl_2 and dried over magnesium sulfate. Vacuum filtration and concentration delivered a yellow oil that showed >98% conversion to product (based on the lack of detectable signals corresponding to **19**). Purification was achieved by silica gel chromatography in 25:1 hexanes/ethyl acetate (TLC R_f = 0.33). Concentration of fractions yielded 177 mg of a colorless oil (85% yield): IR (thin film) 2958 (m), 2924 (s), 2856 (m), 1778 (s), 1461 (m), 1379 (w), 1363 (w), 1161 (w), 1062 (m), 968 (m), 757 (m), 733 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.55−5.43 (m, 2H), 3.12 (dd, J = 17.4, 9.1 Hz, 1H), 2.94 (dd, J = 17.6, 7.8 Hz, 1H), 2.67−2.61 (m, 1H), 2.06−2.02 (m, 2H), 1.39−1.22 (m, 8H), 1.17 (s, 3H), 1.02 (s, 3H), 0.87 (t, J = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.8, 133.3, 128.4, 63.1, 47.9, 39.2, 32.7, 31.8, 29.5, 28.9, 23.0, 22.8, 18.5, 14.2; HRMS (ESI+) calcd for $C_{14}H_{25}O^+$ $[M + H]^+$ 209.1905, found 209.1907.

Fused Bicyclobutanone ***29***:. IR (thin film) 2930 (m), 2859 (w), 1763 (s), 1450 (m), 1367 (w), 1313 (w), 1161 (w), 1012 (m), 971 (w), 916 (w), 904 (w), 834 (w); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.53−3.46 (m, 1H), 2.12−2.05 (m, 1H), 1.94−1.87 (m, 1H), 1.86−1.78 (m, 1H), 1.57−1.37 (m, 3H), 1.29 (s, 3H), 1.19−1.05 (m, 3H), 1.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.2, 61.0, 52.5, 34.4, 26.4, 24.5, 22.29, 22.28, 20.5, 16.9; HRMS (ESI+) calcd for $C_{10}H_{17}O^+$ $[M + H]^+$ 153.1279, found 153.1240.

2,2-Dimethyl-3-phenylcyclobutanone (***31***):. IR (thin film) 2961 (w), 2924 (w), 2864 (w), 1775 (s), 1497 (w), 1460 (w), 1380 (w), 1364 (w), 1261 (w), 1159 (w), 1068 (m), 1031 (w), 985 (w), 943 (w), 909 (w), 848 (w), 801 (w), 764 (m), 733 (w), 700 (s), 650 (w), 568 (w); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (dd, J = 7.6, 7.3 Hz, 2H), 7.29−7.24 (m, 1H), 7.20 (d, J = 7.3 Hz, 2H), 3.47 (dd, J = 16.4, 8.3 Hz, 1H), 3.41 (dd, J = 16.6, 8.3 Hz, 1H), 3.29 (dd, J = 16.1, 8.3 Hz, 1H), 1.36 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.7, 139.0, 128.5, 127.7, 126.8, 63.8, 46.0, 41.6, 23.6, 19.0; HRMS (ESI+) calcd for $C_{12}H_{15}O^+$ $[M + H]^+$ 175.1123, found 175.1137.

2,2-Dimethyl-3-(p-methoxyphenyl)cyclobutanone (***32***):. IR (thin film) 2960 (w), 2926 (w), 2865 (w), 2837 (w), 1775 (s), 1612 (w), 1583 (w), 1513 (s), 1461 (w), 1443 (w), 1422 (w), 1381 (w), 1363 (w), 1302 (w), 1248 (s), 1180 (w), 1160 (m), 1035 (w), 1066 (m), 826 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, J = 8.3 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 3.81 (s, 3H), 3.40 (dd, J = 15.5, 7.7 Hz, 1H), 3.35 (dd, J = 15.9, 7.6 Hz, 1H), 3.27 (dd, J = 15.5, 8.2 Hz, 1H), 1.33 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.1, 158.5, 131.1, 128.7, 114.0, 63.7, 55.4, 46.4, 40.9, 23.6, 19.0; LRMS (ESI+) calcd for $C_{13}H_{17}O_2^+$ $[M + H]^+$ 205.1229, found 205.1239.

2,2-Dimethyl-3-(p-nitrophenyl)cyclobutanone (***33***):. mp = 78−82 °C; IR (thin film) 2963 (w), 2927 (w), 2866 (w), 1775 (s), 1599 (m), 1514 (s), 1496 (w), 1461 (w), 1382 (w), 1343 (s), 1293 (w), 1262 (w), 1184 (w), 1060 (w), 1139 (w), 1110 (w), 1066 (w), 1014 (w), 988 (w), 942 (w), 866 (w), 853 (m), 759 (m), 713 (w), 698 (w); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, J = 8.1 Hz, 2H), 7.36 (d, J = 8.6 Hz, 2H), 3.54−3.45 (m, 2H), 1.40 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.6, 147.0, 147.0, 128.6, 123.9, 64.8, 46.2, 41.8, 23.7, 19.1; HRMS (ESI+) calcd for $C_{12}H_{14}NO_3^+$ $[M + H]^+$ 220.0974, found 220.0972.

■ ASSOCIATED CONTENT

Supporting Information. Copies of ^{1}H and ^{13}C NMR spectra for all compounds; 1- and 2-D NOESY spectra for **27**; CIF files for **18** and **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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