Fused-Ring Systems

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Acid-Catalyzed Intramolecular [2+2] Cycloaddition of Ene-allenones: Facile Access to Bicyclo[*n*.2.0] Frameworks**

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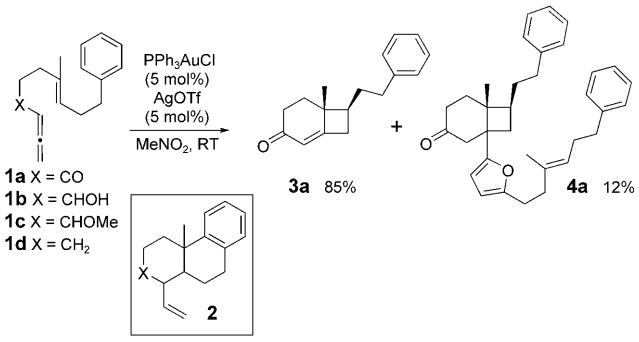
The fused cyclobutane fragment is a key motif found in many biologically important natural products, such as sterpurene and illudene derivatives.[1] Among the strategies, the [2+2]-cycloaddition reaction stands out as one of the most versatile methods for the construction of such fused systems.[2] A noteworthy class of this reaction is the intramolecular version, involving an allene and an alkene in a single molecule, which enables the stereocontrolled construction of complex polycyclic compounds containing methylenecyclobutane frameworks.[3] Photochemical and thermal [2+2] cycloadditions between allenes and alkenes have been extensively investigated.[4] However, most of the reported procedures involve the use of activated alkenes and suffer from many limitations including harsh reaction conditions and narrow substrate scope.

Furthermore, selective [2+2]-cycloaddition reactions involving the distal allenic double bond remain a contemporary challenge to synthetic chemists. Snider and co-workers[5] and Hoffmann et al.[6] independently reported Lewis acid catalyzed [2+2] cycloadditions of allenic esters under mild conditions. However, the efficiencies and substrate scopes were limited in both cases. Although the [2+2] cycloadditions of allenyl sulfones by Padwa et al. demonstrated that the regioselectivity could be controlled by using different substrates,[7] the sulfonyl group must be removed for further elaboration and the regioselectivity may be inconsistent in complex molecules.[4d] Recently, difluoroallenes,[8] β-lactam-tethered allenes,[9] diyne-diallenes,[10] and allenynes[11] have also been employed as substrates to overcome such drawbacks. Unfortunately, many of these reactions involved high-temperature conditions that would limit their use in the synthesis of complex molecules. Intramolecular [2+2] cycloadditions of ene-allenones, such as **1a**, which would offer a convenient access to the carbon bicyclo[*n*.2.0] framework with an α,β-unsaturated ketone fragment, have remained unexplored, possibly due to the facile cycloisomerization and dimerization of allenones that take place in the presence of Lewis acids or transition metals.[12] Herein, we describe a highly efficient acid-catalyzed intramolecular [2+2] cycloaddition between the distal allenic double bond and unactivated alkene moieties, with excellent chemo-, regio-, and diastereoselectivities under very mild reaction conditions.

In the course of our efforts toward the development of cationic polyene cyclization,[13] we became interested in an alternative initiating model by activation of C–C double bonds with carbophilic transition metals.[14] Very recently, Gagné and co-workers[15] and Fürstner and Morency[16] reported gold(I)-complex-catalyzed ene-allene and enyne cycloisomerizations, respectively. Both transformations were presumed to involve a carbocationic mechanism. Inspired by their work and considering the parallels in the reactivity of allenes and alkynes toward metal-mediated nucleophilic additions,[17] we hypothesized that allenes could also be used as the "head" to initiate cationic polyene cyclization by using a gold(I) complex as the carbophilic π-acid catalyst. Surprisingly, when **1a** was treated with 5 mol% of Ph_3PAuCl and silver trifluoromethanesulfonate (AgOTf) in 0.1M $MeNO_2$, only the [2+2]-cycloaddition product **3a** was obtained, as a single diastereomer, accompanied by a small amount of dimer **4a** (Scheme 1). No trace of the cationic polyene cyclization product **2** was observed. The structure of **3a** was confirmed by an X-ray diffraction study of the ester derivative (see the Supporting Information).[18]



Scheme 1. Preliminary study of the [2+2]-cycloaddition reaction.

Further optimization of the conditions demonstrated that this reaction is sensitive to solvent, as well as to the catalyst used (Table 1). Generally, polar solvents gave **3a** as the major product, whereas nonpolar solvents provided mainly cycloisomerization product **5a** (Table 1, entries 1–7). Interestingly, we did not observe the coexistence of **3a** and **5a** in any of these cases, but rather a single diastereomer of dimer **4a** accompanied by **3a** or **5a**. To our delight, the formation of cycloisomerization product **5a** and dimer **4a** could be sup-

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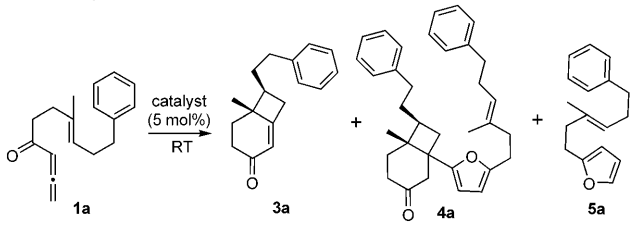
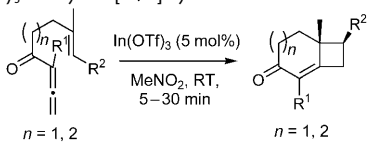
Table 1: Optimization studies.[a]

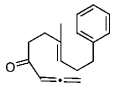
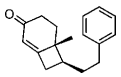
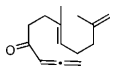
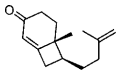
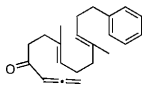
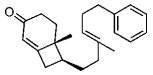
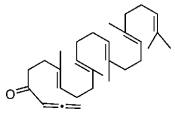
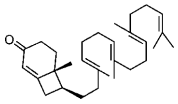
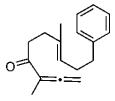
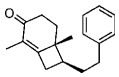
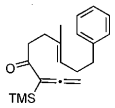
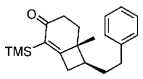
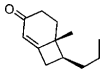
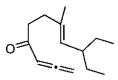
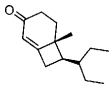
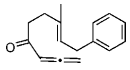
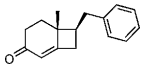
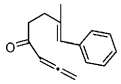
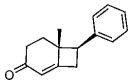
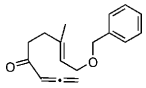
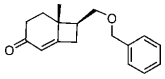
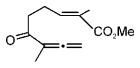
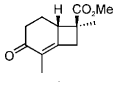
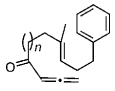
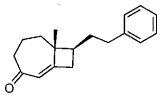


Entry	Solvent	Catalyst	Yield [%][b]	Ratio (**3a**/**4a**/**5a**)[c]
1	THF	$AuClPPh_3/AgOTf$	84	0:5:95
2	$CHCl_3$	$AuClPPh_3/AgOTf$	65/32	0:50:50
3	toluene	$AuClPPh_3/AgOTf$	44/45	0:33:67
4	CH_2Cl_2	$AuClPPh_3/AgOTf$	45/44	67:33:0
5	$(CH_2Cl)_2$	$AuClPPh_3/AgOTf$	70	86:14:0
6	MeCN	$AuClPPh_3/AgOTf$	40/40	68:32:0
7	$MeNO_2$	$AuClPPh_3/AgOTf$	85	94:6:0
8	$MeNO_2$	AgOTf	88	>99:1:0
9	$MeNO_2$	$In(OTf)_3$	94	>99:1:0
10	$MeNO_2$	$InBr_3$	84	>99:1:0
11	$MeNO_2$	$InCl_3$	90	>99:1:0
12	$MeNO_2$	$Cu(OTf)_2$	81	>99:1:0
13	$MeNO_2$	$BF_3{\cdot}Et_2O$	79	>99:1:0
14	$MeNO_2$	$TiCl_4$	92	>99:1:0
15	$MeNO_2$	$SnCl_4$	88	>99:1:0
16	$MeNO_2$	TfOH	82	>99:1:0
17	$MeNO_2$	HCl (4 N)	71	>99:1:0
18	$MeNO_2$	CF_3CO_2H	79	>99:1:0
19	$MeNO_2$	*p*-TSA·H_2O	80	>99:1:0

[a] Reactions were carried out on a 0.2 mmol scale with 0.1 M substrate. THF: tetrahydrofuran; *p*-TSA: toluene-4-sulfonic acid. [b] Yield of major product after isolation. [c] The ratio was determined by ^1H NMR analysis of the crude product mixture.

Table 2: $In(OTf)_3$-catalyzed [2+2] cycloadditions.[a]



Entry	Substrate		Product[b]		Yield [%][c]
1		**1a**		**3a**	94
2		**7**		**20**	83
3		**8**		**21**	81
4		**9**		**22**	76
5		**10**		**23**	80
6		**11**		**24**	85
7		**12**		**25**	89
8		**13**		**26**	95
9		**14**		**27**	70
10		**15**		**28**	85
11		**16**		**29**	91
12		**17**		**30**	70
13[d]		**18**		**31**	76
14		**19** (*n*=2)		**32**	82

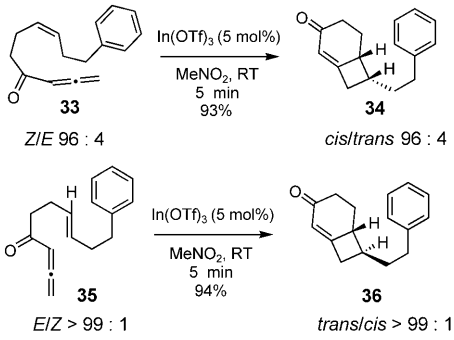
[a] Reactions were carried out on a 0.2 mmol scale with 0.1 M substrate. [b] Single diastereomer (as determined by ^1H and ^{13}C NMR analysis). [c] Yield of isolated product. [d] The reaction time was 16 h.

pressed by using common Lewis acids as the catalyst (Table 1, entries 8–15). For example, 5 mol% of AgOTf alone is efficient enough to offer **3a** in 88% yield by suppressing the cycloisomerization (Table 1, entry 8). A series of Lewis and Brønsted acids were examined and all of them catalyzed the reaction smoothly to give the [2+2]-cycloaddition product exclusively in good to excellent yields (Table 1, entries 8–19). Finally, the use of 5 mol% of $In(OTf)_3$ in $MeNO_2$ was identified as the best conditions in terms of economy, practicality, selectivity, and yield of **3a** (Table 1, entry 9).

Various substrates were prepared to test the generality of the acid-catalyzed intramolecular [2+2] cycloaddition of ene-allenones under the optimal conditions, and the results are summarized in Table 2. The intramolecular [2+2]-cycloaddition reactions proceeded readily for all of the tested ene-allenones to give the strained bicyclo[*n*.2.0] frameworks in good to excellent yields and with excellent diastereoselectivities. Variation in the tail length had little effect on the reaction efficiency (Table 2, entries 3, 4, and 12). Interestingly, ene-allenones possessing an α substituent at the allenone motif gave the [2+2]-cycloaddition products in good yields (Table 2, entries 5 and 6). With both α,β-unsaturated ketone and vinylsilane fragments concurrently, adduct **24** is rendered more versatile for further modification (Table 2, entry 6).[19] The most promising case is the intramolecular [2+2] cycloaddition of ene-allenone **17**, which constructed the core structure of sterpurene and illudene derivatives[1] in one operation. Notably, the [2+2] cycloaddition went smoothly to furnish the bicyclo[4.2.0] framework in good yield, albeit with a longer reaction time required, when an electron-withdrawing group was introduced to the alkene motif (Table 2, entry 13). In addition, the

bicyclo[5.2.0] framework **32** could also be obtained with good yield and excellent diastereoselectivity (Table 2, entry 14).

To probe the mechanism of this [2+2]-cycloaddition reaction, the stereospecificity and steric effects on the alkene motif were examined. Substrates **33** and **35** were designed and treated under the standard conditions (Scheme 2). Both **33** and **35**, in the absence of the methyl

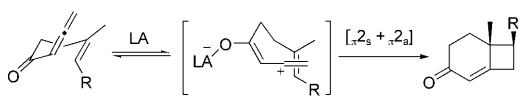


Scheme 2. Investigation of stereospecificity and steric effects of the [2+2] cycloaddition.

group on the alkene motif, were transformed smoothly to give [2+2]-cycloaddition products **34** and **36** with excellent yields and diastereoselectivities, which suggested that the methyl group has no significant effect on the efficiency of the [2+2] cycloadditions. Another interesting observation is that the *cis* and *trans* products were obtained exclusively from the *Z* and *E* alkenes, respectively, which demonstrated that this is a stereospecific process.

Although stepwise mechanisms have been proposed in some Lewis acid catalyzed [2+2] cycloadditions,[2i,7,8,20] the debate between a concerted or a stepwise mechanism for [2+2] cycloaddition is still ongoing.[7b,21] We have not detected any cationic intermediate in this reaction.[22] Considering the similar behaviors of allenic esters and allenones in the presence of Lewis acids, we believe that the mechanism proposed for the [2+2] cycloaddition of allenic esters[5,6] could also be used to rationalize the intramolecular [2+2] cycloaddition of ene-allenones. So far, our experimental results[23] support the idea that this reaction may prefer a $[_{\pi}2_s+_{\pi}2_a]$ concerted mechanism, which involves the vinyl-cation resonance structure,[19a,24] as shown in Scheme 3. However, the stepwise mechanism cannot be excluded at this stage.

In summary, we have developed the first acid-catalyzed selective intramolecular [2+2] cycloaddition between the less activated distal allenic double bond and the unactivated alkene of ene-allenones. The cycloaddition reactions provide facile access to strained carbon bicyclo[*n*.2.0] frameworks under very mild reaction conditions with high yields and excellent diastereoselectivities. The excellent regioselectivities demonstrate that it is feasible to perform reactions selectively at the distal allenic double bond of the ene-allenones. The mild reaction conditions, excellent yields and diastereoselectivities, easy functionalization of the product, and the simplicity of the reaction procedure make this method attractive for the synthesis of complex molecules. The development of the asymmetric version and the application of this methodology to the total synthesis of natural products are ongoing in our laboratory.



Scheme 3. Proposed mechanism (LA: Lewis acid).

Experimental Section

General procedure for the Lewis acid catalyzed intramolecular [2+2] cycloaddition of ene-allenones: Ene-allenone (0.2 mmol) was added slowly to a mixture of Lewis acid (5 mol%) and nitromethane (2 mL), and the reaction mixture was stirred at room temperature. The reaction was monitored by TLC analysis until the ene-allenone was consumed completely. The reaction was quenched by adding saturated $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted with Et_2O (3×5 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed under vacuum, and the crude residue was purified by silica gel column chromatography to give the desired products.

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