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Synthetic Methods

Metal-Triflate-Catalyzed Synthesis of Polycyclic Tertiary Alcohols by Cyclization of γ-Allenic Ketones**

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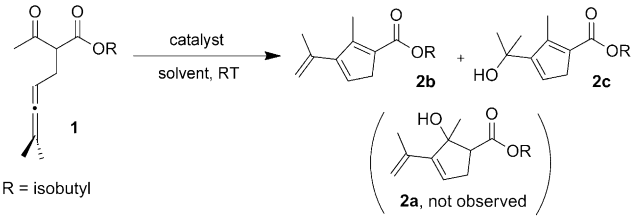
Abstract: *It has been established that bismuth(III) triflate catalyzes the cyclization of γ-allenic ketones under mild reaction conditions. This reaction allows the selective formation of polycyclic tertiary alcohols from cyclic ketone derivatives. The resulting dienols can engage in stereoselective cycloadditions to efficiently afford complex polycyclic systems.*

Complex polycyclic molecules have always fascinated organic chemists, and their rapid, reliable, and efficient synthesis constitutes a motivating challenge to accept. Cycloisomerization reactions are undoubtedly powerful and provide a sustainable means to generate molecular complexity with good control of selectivity.[1] In this context, the intramolecular carbonyl-ene reaction represents a very useful tool for the efficient formation of substituted cyclohexanols,[2] and has been widely used in natural product synthesis. Because of the relatively high energetic barrier, carbonyl-ene processes often require high temperatures or the employment of Lewis acids, usually in excess (Prins reaction). Despite its reliability, this reaction presents some important limitations, such as the difficulty in forming five-membered rings because of the higher cyclization energy requirement induced by geometric factors. In addition, ketones are intrinsically much poorer enophiles than aldehydes in these reactions. Cyclizations involving ketone derivatives have been reported[3] and include highly activated ketones such as trifluoromethylketones[4] or α-ketoesters.[5]

The cyclization of carbonyl-allene compounds has been mainly studied under thermal,[6] radical,[7] and transition-metal-catalyzed[8] processes. Herein we present our results concerning the metal-triflate-catalyzed cyclization of γ-allenic ketones. We anticipated that allenes could be used as ene components to bias the geometric cyclization for the formation of five-membered rings. Moreover, the higher reactivity of allenes, as compared to alkenes, should allow the reaction with ketones to proceed under mild reaction conditions.

We first used the acyclic β-ketoester **1** bearing a pendant trisubstituted allene as a model and assessed its reactivity towards various metal triflate catalysts in nitromethane (Table 1, entries 1–4). A rapid screening highlighted non-expensive bismuth(III) triflate[9,10] as a very active catalyst at low loading with the total conversion of **1** occurring at −20 °C. Switching solvents from nitromethane to CH_2Cl_2 considerably slowed down the reaction rate and led to the isolation of the cyclopentadienes **2b** and **2c** in good yield (88 %) at room temperature by using only 1 mol % of bismuth(III) triflate (entry 5). The formation of **2b** could arise from the elusive ene product **2a** undergoing an elimination reaction. Hydration of compound **2b** could lead to the tertiary alcohol **2c**.

Table 1: Metal-triflate-catalyzed cyclization of methyl ketone **1**.[a]



Entry	Catalyst (mol %)	Solvent	*t* [h]	Yield [%][b]
1	$Al(OTf)_3$ (5)	CH_3NO_2	0.5	54
2	$Fe(OTf)_3$ (5)	CH_3NO_2	3	62
3	$Cu(OTf)_2$ (5)	CH_3NO_2	3	52
4	$Bi(OTf)_3$ (5)	CH_3NO_2	12	59[c]
5	$Bi(OTf)_3$ (1)	CH_2Cl_2	0.5	88
6	$Bi(OTf)_3$ (1)	toluene	0.5	31
7	HOTf (1)	CH_2Cl_2	0.5	20

[a] Reaction conditions: allenic ketone **1** (0.2–1 mmol) in solvent (0.1 M) and catalyst (1–5 mol %) stirred at room temperature, unless otherwise stated [b] Combined yield of the isolated products **2b** and **2c**. [c] The reaction was conducted at −20 °C.

To prevent the elimination of the alcohol in **2a**, a reaction which is possibly favored by the position of OH group β to the ester, the reactivity of the allenic cyclohexanone derivative **3** was examined (Scheme 1). In the presence of 1 mol % of $Bi(OTf)_3$, the bicyclic triene isomers **4a** and **4b** were predominantly produced in 40 % yield (Scheme 1). Remarkably, the related cyclopentanone derivative **5a** behaved differently under the same mild reaction conditions. Elimination of the tertiary alcohol did not occur and the substituted *cis*-diquinane **6a** was obtained in 85 % yield as a single diastereoisomer.

The selectivity in favor of the bicyclic tertiary alcohol seemed to be quite general for allene-derived cyclopenta-

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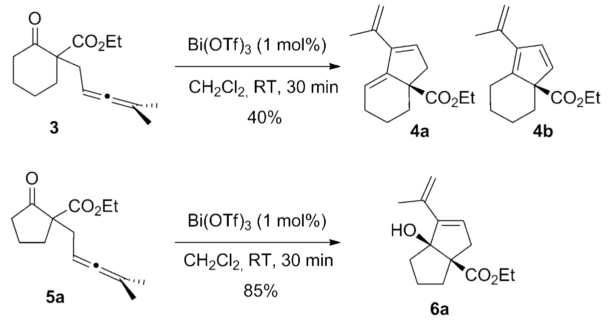
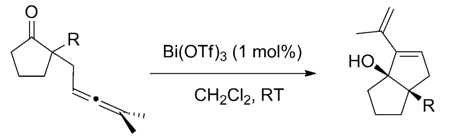
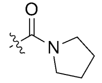
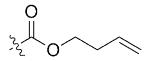


Scheme 1. Reactivity of cyclic allenic ketones.

nones bearing diverse functional groups (Table 2). For instance, **5b** and the nitrile-containing precursor **5c** cyclized smoothly to afford the desired bicyclic products **6b** (84 %) and **6c** (47 %), respectively (Table 2, entries 2 and 3). The allenic substrate **5d**, having a more elaborate ester group featuring an additional terminal olefin, was chemoselectively cyclized with a very good yield of 83 %. Although low conversion was observed with the allenic ketone **5e**, this cycloisomerization reaction was not restricted to β-carboxylic acid derivatives. Indeed, the reaction also took place with the substrates **5f** and **5g** bearing a methyl and phenyl group, respectively (entries 6 and 7), to afford the corresponding tertiary alcohols with good yields.

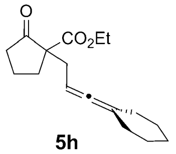
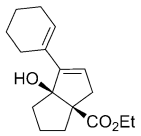
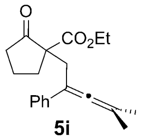
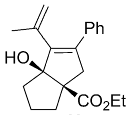
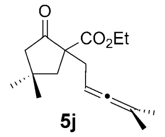
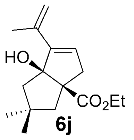
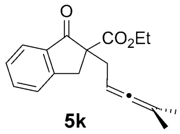
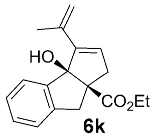
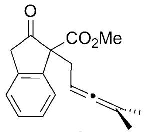
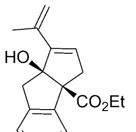
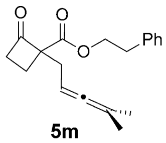
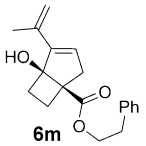
Table 2: Bismuth(III)-catalyzed cycloisomerization of allenic ketones.[a]



Entry	Substrate	R	*t*	Product	Yield [%][b]
1	**5a**	CO_2Et	30 min	**6a**	85
2	**5b**		24 h	**6b**	84[c]
3	**5c**	CN	3 days	**6c**	47[d]
4	**5d**		30 min	**6d**	83
5	**5e**	H	1 day	**6e**	–
6	**5f**	Me	10 min	**6f**	50[e]
7	**5g**	Ph	10 min	**6g**	75[e]

[a] Reaction conditions: allenic ketone **5** (0.2–1 mmol) in CH_2Cl_2 (0.1 M) and $Bi(OTf)_3$ (1 mol %) were stirred at room temperature. [b] Yield of isolated product. [c] A 1.4:1 isomer ratio was obtained. [d] 5 mol % of catalyst was used. [e] Traces of diene isomers were also observed.

Table 3: Bismuth(III)-catalyzed cyclization of γ-allenic ketones.[a]

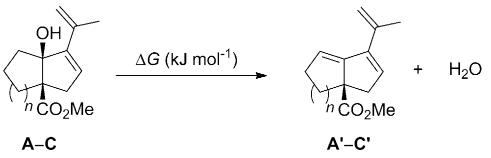
Entry	Substrate	*t*	Product	Yield [%][b]
1	 **5h**	15 min	 **6h**	86
2	 **5i**	2 h	 **6i**	87[c]
3	 **5j**	8 h	 **6j**	63[d]
4	 **5k**	2 h	 **6k**	40 (52)[e]
5	 **5l**	5 min	 **6l**	96
6	 **5m**	5 min	 **6m**	98

[a] Reaction conditions as in Table 2. [b] Yield of isolated product. [c] The reaction was conducted in toluene. [d] 5 mol % of catalyst was used. [e] Yield based on the recovered starting material.

These results point out that pentacyclic β-ketoesters are particularly suitable substrates for the intramolecular carbonyl ene reaction with allenes. Therefore, a study involving the modification of the cyclopentanone core and of the allene substitution was undertaken to explore the reaction scope (Table 3). The cyclohexyl derivative **5h** was efficiently transformed into the polycyclic alcohol **6h** (entry 1). Although 1,3-disubstituted allenes were not compatible with these catalytic conditions, the fully substituted allene **5i**, bearing an internal phenyl group, was satisfactorily cyclized into **6i**. It was observed that **6i** was more prone to elimination than previous pentacyclic substrates. However, we were able to limit the formation of this undesired by-product by conducting the reaction in toluene instead of CH_2Cl_2, and the tertiary alcohol was isolated with 87 % yield (entry 2). Interestingly, the hindered cyclopentanone **5j**, having a gem-dimethyl group, also reacted at room temperature under the standard reaction conditions to afford the highly substituted alcohol **6j** (entry 3). Surprisingly, the less-reactive 1-indanone derivative **5k** could also be cyclized in the presence of 1 mol % of bismuth(III) triflate, and led to the allylic/benzylic alcohol **6k** in 40 % yield upon isolation (entry 4). In addition, the 2-indanone derivative **5l** proved to be a particularly appropriate substrate for this metal-catalyzed cycloisomerization, thus leading efficiently to the polycylic alcohol **6l** in almost quantitative yield (entry 5). The allenic compound **5m**, having a strained cyclobutanone moiety,[11] was also cleanly transformed into the bicyclo[3.2.0]heptene **6m** within a very short reaction time and a nearly quantitative yield (entry 6).

A remarkable effect of the ring size of the starting cyclic ketone on the product selectivity was observed (see Scheme 1). This reactivity difference might be attributed to the higher strain of the cyclopentane and cyclobutane rings, and would thus slow down the elimination process. To confirm this hypothesis, we performed DFT calculations[12] to evaluate the Gibbs free energies corresponding to the elimination processes for bicyclic systems with different ring sizes. As shown in Table 4, dehydration is a highly endergonic process for the bicyclic alcohol **A** which contains a four-membered ring (entry 1, $\Delta G = +53.7$ kJ mol^{-1}). The reaction becomes energetically favored for the analogous alcohol **B** which contains a five-membered ring and has a dehydration energy of -20.5 kJ mol^{-1} (entry 2). As expected, the elimination is highly favored in the case of the six-membered ring substrate **C** with a calculated energy of -50.7 kJ mol^{-1} (entry 3). The trend observed from these calculations is in good agreement with the experimental results and can explain the propensity of the non-isolable hydrindenol derivative **C** to easily eliminate in Lewis acid media.

Table 4: Calculated Gibbs free energies for the alcohol elimination.[a]

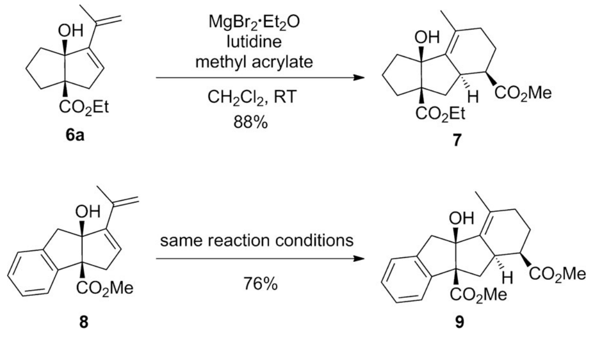


Entry	Substrate	n	ΔG [kJ mol^{-1}]	Product
1	**A**	0	$+53.7$	**A′**
2	**B**	1	-20.5	**B′**
3	**C**	2	-50.7	**C′**

[a] DFT calculations were performed at the B3LYP6-31+G(d,p) level of theory. The effects of dichloromethane as solvent were taken into account by using the polarizable continuum model (PCM).

Finally, we were interested in further synthetic applications and the dienol products were used in subsequent selective cycloadditions to attain more complex polycyclic structures. We were able to successfully perform highly diastereoselective Diels–Alder reactions by reacting the prepared bicyclic systems with methyl acrylate in the presence of $MgBr_2$ and lutidine at room temperature (Scheme 2).[13] This methodology afforded the cycloaddition adducts **7** and **9** from conjugated the 1,3-dienes **6a** and **8**, respectively, as single regio- and diastereoisomers.[14] No conversions were detected in the absence of lutidine, and could indicate that a possible hydroxy-directed[15] mechanism is involved. This procedure constitutes a straightforward route to complex polycyclic systems with a controlled stereochemistry.

In conclusion we have reported on the metal-triflate-catalyzed cycloisomerization of γ-allenic ketones. This carbonyl-ene reaction was efficiently performed under mild reaction conditions by using only 1 mol% of the nontoxic, relatively cheap, and easily recyclable bismuth(III) triflate.[10a] The resulting acid-sensitive diene-containing tertiary alcohols were successfully isolated from substrates featuring four- and five-membered cyclic ketones. This methodology provides access to original and highly functionalized bicyclic alcohols from readily available starting materials. Some preliminary DFT calculations were performed to rationalize the remarkable effect of the substrate ring size on the reaction outcome. We confirmed that the elimination of the tertiary alcohol from the final product was thermodynamically favored for cyclopentenes fused to a cyclohexane ring. We showed that the bicyclic dienol products successfully engaged in highly selective Diels–Alder reactions, thus leading to more complex polycyclic systems with complete control of the relative stereochemistry of the four stereogenic centers.



Scheme 2. Diastereoselective transformation of diene products.

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[14] The relative stereochemistry of **9** was confirmed by X-ray diffraction (see the Supporting Information).

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