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Graphical Abstract





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Cyclization of alk-5-ynyl ketones promoted by Tf_2NH and $In(OTf)_3$: selective synthesis of 5- and 7-membered carbocycles

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ABSTRACT

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Keywords: Conia-ene reaction Cyclization Lewis acid Brønsted acid Combined use of Tf_2NH and $In(OTf)_3$ effectively promotes the cyclization of alk-5-ynyl ketones to cyclopent-1-enyl ketones at 30 °C. Single use of Tf_2NH or $In(OTf)_3$ requires heating at 50 °C for efficient cyclization. The $In(OTf)_3$ -promoted reaction of certain alk-5-ynyl ketones gives cyclohept-2-enones mainly.

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Intramolecular addition of enolizable carbons to alkenes and alkynes is valuable for the synthesis of functionalized carbocycles.1 The original reaction developed by Conia and coworkers, known as the Conia-ene reaction, requires extended heating at 300-400 °C.² Since the pioneering work, much effort has been devoted to improving the harsh reaction conditions. Some Lewis acids and transition metal catalysts have been found to effectively promote the conversion of α -alkynyl- β -ketoesters and alkynylmalonates into the corresponding Conia-ene products at lower temperatures (Scheme 1).^{3,4} However, in most cases, the known methods for the Conia-ene cyclization are not applicable to less enolizable alkynyl ketones not bearing another electronwithdrawing group at the enolizable carbon.⁵ We herein report that the use of Tf₂NH and/or In(OTf)₃ enables the cyclization of the less enolizable substrates. Double catalysis by a Brønsted acid and a mercury salt is known to be effective in the Conia-ene reaction of simple alkynyl ketones.⁶ Gold Lewis acids can also be used for this purpose.⁷ The present reaction systems are characterized by no use of the toxic or expensive metal. In addition, we disclose a novel cyclization of certain alkynyl ketones to 7-membered carbocycles with In(OTf)₃.



Scheme 1. Conia-ene reaction

Our research interest has been focused on the development of new synthetic methods utilizing In(III) catalysis.⁸ In addition,

Nakamura and coworkers have recently disclosed that In(OTf)₃ and $In(NTf_2)_3$ are effective in the Conia-ene reaction of α alkynyl- β -ketoesters.⁴ We therefore selected these indium salts as promoters, and initially examined the cyclization of alkynyl ketone 1a (Table 1). The treatment of 1a with $In(OTf)_3$ or In(NTf₂)₃ (0.2 equiv) in CH₂Cl₂ (rt, 24 h) gave no desired products (entries 1 and 2). Enolization of the ketone moiety should be crucial in promoting the Conia-ene reaction of 1a. To facilitate the enolization, we next attempted combined use of a Brønsted acid with In(OTf)₃ (entries 3-5). As a result, the reaction using Tf₂NH (1 equiv) and In(OTf)₃ (0.2 equiv) gave the cyclized product 2a in 60% yield. The formation of 2a is probably due to acid-catalyzed isomerization of β , γ -unsaturated ketone 2a'.⁹ Use of PhCF₃ as solvent and elevated temperatures improved the yield of 2a (entries 6-9). Detailed analysis of the products obtained in entry 8 revealed the formation of cyclohept-2-enone **3a**. Tf_2NH promoted the cyclization even in the absence of In(OTf)₃ although the use of In(OTf)₃ increased the reaction rate (entries 8 vs. 10). At 50 °C the Tf₂NH-promoted reaction gave 2a in a good yield (entry 11). Although the increased temperature without In(OTf)₃ gave a positive effect in this case, the reaction conditions using In(OTf)₃ at 30 °C (entry 8) were effective in suppression of side reactions and superior for efficient cyclization in other cases (vide infra). When 1a was treated with only In(OTf)₃ (0.2 equiv) in PhCF₃ at 50 °C, 2a and 3a were obtained in 52% and 16% yields, respectively (entry 12).

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Table 1. Cyclization of alkynyl ketone 1a.^a

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		InX ₃ (0. acid (1	InX ₃ (0.2 equiv) acid (1 equiv)		Me
		Ph solver	τt, 24 h	ElC2C	2a 0
entry	X in InX ₃	acid	temp (°C)	solvent	isolated yield (%)
1	OTf	none	rt	CH_2Cl_2	0
2	NTf_2	none	rt	CH_2Cl_2	0
3	OTf	CF_3CO_2H	rt	CH_2Cl_2	0
4	OTf	TfOH	rt	CH_2Cl_2	48
5	OTf	${ m Tf_2NH}$	rt	CH_2Cl_2	60
6	OTf	${ m Tf_2NH}$	rt	PhCF ₃	67
7	NTf_2	Tf_2NH	rt	PhCF ₃	65
8	OTf	Tf_2NH	30	PhCF ₃	74, 2^{b}
9	OTf	Tf_2NH	50	PhCF ₃	77
10	none	Tf ₂ NH	30	PhCF ₃	55, 23 ^c
11	none	Tf_2NH	50	PhCF ₃	74
12	OTf	none	50	PhCF ₃	52, 16 ^b

^a Conditions: 1a (0.50 mmol), InX₃ (0.10 mmol), an acid (0.50 mmol), solvent (2.5 mL). ^b Yield of 3a. ^c Recovery of 1a.



The scope of the present Conia-ene reaction was next investigated (Table 2). Alkynyl ketone 1b derived from dimethyl malonate was smoothly cyclized to cyclopentenyl ketone 2b in the presence of Tf₂NH and In(OTf)₃, at 30 °C (method A, entry 1). As in the case of 1a, 7-membered carbocycle 3b was obtained. The Tf₂NH-promoted reaction at 50 °C (method B) dropped the yield of 2b by unidentified side reactions (entry 2). Under catalysis by In(OTf)₃ at 50 °C (method C), the cyclization of 1b to 2b became less efficient by competition with the formation of **3b** (entry 3). Dimethyl-substituted alkynyl ketone 1c was efficiently converted into 2c by either method A or B (entries 4 and 5). The corresponding 7-membered product 3c was not obtained even by method C (entry 6). The reaction of methyl ketone 1d by method A formed the desired product 2d with a considerable amount of 3d (entry 7). No formation of 3d was observed by method B (entry 8). The yield of 2d, however, remained moderate due to side reactions. When the treatment of 1d was conducted with a twofold amount of Tf₂NH at 30 °C, the cyclization to 2d proceeded efficiently. On the other hand, 3d was the main product in the reaction of 1d by method C (entry 9). The reaction of 1e gave a mixture of 2e and its regioisomer 2e' (entries 10 and 11). The application of method B achieved a good combined yield with selective formation of 2e. The cyclization of 1f, bearing an internal C-C triple bond, competed with complex side reactions, and resulted in low to moderate yields of 2f (entries 12 and 13). Interestingly, the reaction of 1g, bearing a phenyl group at the sp-carbon, gave 1,2-dihydro-3H-fluorene 4 mainly (entries 14-16). o-Phenylene-tethered alkynyl ketone 1h showed high reactivity, and method C worked well for the cyclization of **1h** to **2h** (entries 17-19).¹⁰

 Table 2. Cyclization of several alkynyl ketones.^a



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17	method A	68, 82 ^e
18	method B	54
19	method C	90, 93 ^{<i>f</i>}

^{*a*} Conditions: **1** (0.50 mmol), PhCF₃ (2.5 mL), 24 h. Method A: In(OTf)₃ (0.10 mmol), Tf₂NH (0.50 mmol), 30 °C. Method B: Tf₂NH (0.50 mmol), 50 °C. Method C: In(OTf)₃ (0.10 mmol), 50 °C. ^{*b*} Determined by ¹H NMR analysis of the crude product. The substrate **1c** was recovered in 52% yield. ^{*c*} Tf₂NH (1.00 mmol), 30 °C, 48 h. ^{*d*} 80 °C, 48 h. ^{*e*} 3 h. ^{*f*} 80 °C.

The cyclization of **1a** using both Tf_2NH and $In(OTf)_3$ was faster than that using either Tf_2NH or $In(OTf)_3$ under the same conditions (Table 1). This fact suggests that the reaction mechanism involves cooperative, simultaneous activation of both the enolizable carbon and the C-C triple bond by the Brønsted and Lewis acids (Scheme 2).¹¹ Since these promoters can activate either reaction site, their correct roles in the cyclization by method A would be difficult to determine. The enolizable carbon is possibly activated by proton- or $In(OTf)_3$ -promoted enolization to **5a** or **5a'** (M = H) or by the formation of indium enolate **5a** or **5a'** (M = $In(OTf)_2$).^{4b} The activation of the C-C triple bond is likely due to coordination to $In(OTf)_3$ (**5a**)^{8c} or the subsequent formation of zuwitterionic species **5a'**.¹² Alternatively, protonation forming alkenyl cation **5a'**-H is possible for the alkyne activation.¹³



Scheme 2. Possible mechanism for cyclization of 1a

The formation of an unexpected product **4** from **1g** can be explained as follows (Scheme 3). First, upon the action of Tf_2NH or In(OTf)₃, intermediate **5g** or **5g'** was formed, and the sp-carbon bearing a phenyl group becomes more electrophilic by its cation-stabilizing effect.¹² Then the enolic carbon adds to the electrophilic carbon to form ketone **6**. The acid-catalyzed intramolecular Friedel-Crafts reaction of **6** followed by dehydration gives **4**.



Scheme 3. Possible mechanism for cyclization of 1g

As shown in entry 9 of Table 2, the $In(OTf)_3$ -promoted cyclization of 1d provided 7-membered carbocycle 3d mainly. This intriguing result induced us to explore new reaction conditions toward more selective formation of 3d. When the reaction of 1d was conducted with 1 equiv of $In(OTf)_3$ at 30 °C for 24 h, the ratio of 3d to 2d was improved but with 18% recovery of 1d (Table 3, entry 1). Elongation of the reaction time

achieved complete conversion of **1d** (entry 2). The cyclization was effectively accelerated by adding 1 equiv of MeOH and the ratio of **3d** was further improved (entry 3). To our surprise, the use of 2 equiv of MeOH preferred the formation of **2d** (entry 4). The reactions using 0.2-0.5 equiv of MeOH succeeded in efficient synthesis of **3d** (entries 5 and 6). At 10 °C the selectivity toward **3d** increased; however, the reaction rate rather decreased (entry 7).





^{*a*}Conditions: **1d** (0.50 mmol), $In(OTf)_3$ (0.50 mmol), and PhCF₃ (2.5 mL). ^{*b*}Recovery of **1d**: 18% (entry 1) and 32% (entry 7).

When alk-5-ynyl methyl ketone **1i** was treated with $In(OTf)_3$ (1 equiv) and MeOH (0.5 equiv) in PhCF₃, cyclohept-2-enone **3i** was obtained in a moderate yield (Scheme 4). The formation of cyclohept-3-enone **3i'** and cyclopetene **2i** was also observed. With 0.2 equiv of MeOH, the yield of **3i** dropped to 46%.



Scheme 4. In(OTf)₃-promoted cyclization of 1i

The cyclization to **3** is an intramolecular metathesis-type reaction between alkynes and carbonyls.^{7,8a,14} A possible mechanism involves nucleophilic addition of the terminal spcarbon to the ketone carbonyl by the aid of $In(OTf)_3$ (Scheme 5). MeOH serves for trapping the resultant zuwitterionic intermediate **7** to prevent the inverse reaction. The 1,3-rearrangement of intermediate **8** followed by elimination of MeOH forms the 7-membered carbocycle.¹⁵ The need for an equimolar amount of $In(OTf)_3$ may be due to its deactivation by coordination of the product.

Tetrahedron



Scheme 5. Possible mechanism for cyclization of 1d to 3d

In conclusion, we have developed new methods for the Coniaene reaction of alkynyl ketones. The existing methods using Lewis acids and metal catalysts are applicable to easily enolizable carbonyls such as β -ketoesters. In contrast, the present methods using Tf₂NH and In(OTf)₃ enable the Conia-ene cyclization of less enolizable alkynyl ketones at relatively low temperatures. This study has enhanced synthetic utility of the Conia-ene reaction for carbocycle construction. In addition, we have succeeded in finding a novel type of carbocyclization useful for the construction of cyclohept-2-enones. Application of the present methods to the synthesis of other carbocycles is now under further investigation.

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Supplementary Material

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Highlights:

• In(OTf)₃ and Tf₂NH cooperatively promote the Conia-ene cyclization.

- Less enolizable alk-5-ynyl ketones can be
- cyclized to cyclopent-1-enyl ketones.
- Accepter • In(OTf)₃ promotes the cyclization of alk-5-ynyl