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Titanium(IV) chloride-mediated intramolecular ring enlargement of methylenecyclopropanes with propargylic esters: a concise synthesis of bicyclo[4.2.0]oct-5-ene derivatives

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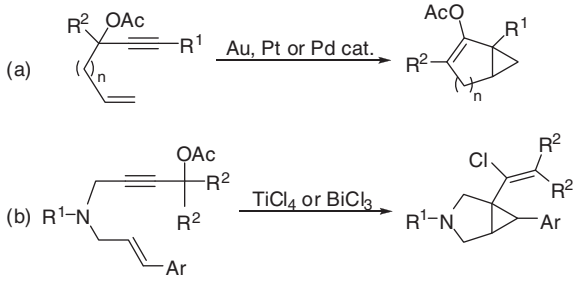
ABSTRACT

Titanium(IV) chloride-mediated intramolecular ring enlargement of methylenecyclopropanes with propargylic esters has been described in this context, affording the corresponding chlorinated bicyclo[4.2.0]oct-5-ene derivatives in moderate to good yields under mild conditions. The *E*- and *Z*-methylenecyclopropanes could all be converted to the corresponding bicyclo[4.2.0]oct-5-enes with moderate to high diastereoselectivities.

In recent years, propargylic esters have received extensive attention as a special class of alkynes for their rich reactivities and easy availabilities. Many transition-metal-catalysts, such as gold,[1] platinum,[2] palladium,[3] ruthenium,[4] and rhodium,[5] have been identified as effective promoters in their transformations to a variety of valuable substances. To the best of our knowledge, examples using other metal catalysts in their transformations are rare. One notable example is the use of metal halide such as $FeCl_3$, CuCl, or $TiCl_4$ as Lewis acid in nucleophilic displacement reactions of propargylic esters under mild conditions, affording the corresponding α-substituted propargylic compounds in good yields.[6] However, using these inexpensive metal halides to produce structurally complex molecules is relatively limited.

Carbocyclization of enynes is a powerful method in organic synthesis to access carbo- or heterobicyclic rings which are important structural motifs found in many natural and pharmaceutical materials. Gold, platinum, or palladium-catalyzed intramolecular cycloisomerization of propargylic esters is an efficient route to synthesize a variety of bicyclo[*n*.1.0]enol esters in good yields (Scheme 1a).[7] More recently, we have found that titanium(IV) chloride and bismuth(III) chloride can serve as effective promoters to achieve the synthesis of chlorinated 3-azabicyclo[3.1.0]hexanes from the corresponding easily available propargylic esters under mild conditions (Scheme 1b).[8] These intriguing results promote us to examine other novel intramolecular carbocyclization processes to access other interesting bicyclic ring skeletons. Herein, we wish to report an efficient route to accomplish the synthesis of bicyclo[4.2.0]oct-5-ene derivatives which have been only synthesized upon heating allenes at high temperature in dioxane or DMF through thermal-induced intramolecular [2+2] cycloaddition reactions.[9]

Initially, we examined the carbocyclization of *E*-**1a** using $TiCl_4$ as a Lewis acid promoter in various solvents such as toluene, chloroform, perchloromethane, 1,2-dichloroethane, and dichloromethane, and found that the corresponding chlorinated cycloisomerization product **2a** was formed in 56% yield along with 10:1 diastereoselec-



Scheme 1. (a) The Rautenstrauch cyclopropanation catalyzed by Au, Pt, or Pd catalysts. (b) Carbocyclization of enynes mediated by $TiCl_4$ or $BiCl_3$.

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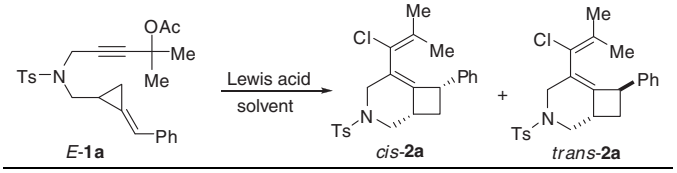
Table 1
Optimization of the reaction conditions



E-**1a** *cis*-**2a** *trans*-**2a**

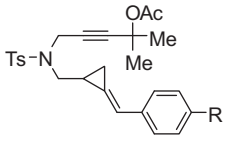
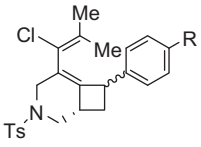
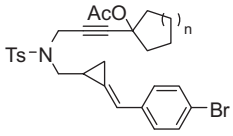
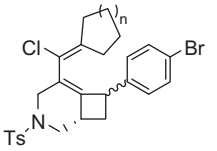
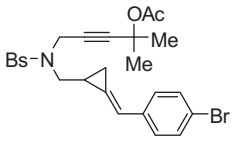
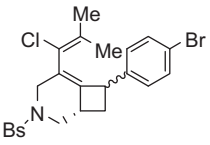
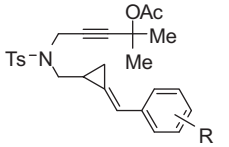
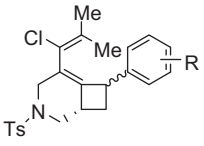
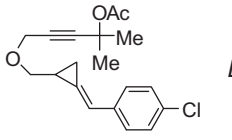
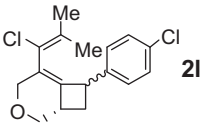
Entry[a]	Lewis acid (equiv)	Solvent	*T* [°C]	Yield[b] (*cis*:*trans*)
1	$TiCl_4$ (1.2)	Toluene	rt	Complex
2	$TiCl_4$ (1.2)	$CHCl_3$	rt	Complex
3	$TiCl_4$ (1.2)	CCl_4	rt	42% (2:1)
4	$TiCl_4$ (1.2)	$ClCH_2CH_2Cl$	rt	28% (2:1)
5	$TiCl_4$ (1.2)	CH_2Cl_2	rt	56% (10:1)
6[c]	$TiCl_4$ (1.2)	CH_2Cl_2	rt	47% (4:1)
7	$TiCl_4$ (0.8)	CH_2Cl_2	rt	45% (3:1)
8	$TiCl_4$ (1.5)	CH_2Cl_2	rt	27% (5:1)
9[d]	$TiCl_4$ (1.1)	CH_2Cl_2	0	37% (3:1)
10[e]	$TiCl_4$ (1.1)	CH_2Cl_2	-20	25% (2:1)
11[f]	$TiCl_4$ (2.0)	CH_2Cl_2	rt	61% (3:1)
12	$TiCl_3$ (O^iPr) (2.0)	CH_2Cl_2	rt	Complex
13	$TiCl_3$ (OTf) (1.2)	CH_2Cl_2	rt	21% (2:1)

[a] [*E*-**1a**] = 0.10 M, <10 min.
[b] The diastereomeric ratio was determined by ^1H NMR spectroscopic data of the isolated product.
[c] [*E*-**1a**] = 0.05 M.
[d] 3 h.
[e] 6 h.
[f] *E*-**1a** (0.20 M in CH_2Cl_2) was added to the solution of $TiCl_4$ (0.40 M in CH_2Cl_2) using a syringe pump over 2 h.

tivity (*cis*:*trans*) in dichloromethane at room temperature within 10 min (Table 1, entries 1–5). Decreasing the concentration of *E*-**1a** from 0.10 to 0.05 M did not improve the reaction outcome (Table 1, entry 6). Upon changing the employed amount of $TiCl_4$ to 0.80 or 1.50 equiv, **2a** were obtained in 45% and 27% yields, respectively, under otherwise identical conditions (Table 1, entries 7 and 8). Further optimization of the reaction conditions revealed that decreasing the reaction temperature to 0 and −20 °C did not give **2a** in higher yield (Table 1, entries 9 and 10). By slow addition of the substrate *E*-**1a** to the solution of 2.0 equiv $TiCl_4$ in dichloromethane with a syringe pump, **2a** was obtained in 61% yield after 2 h along with 3:1 diastereoselectivity (*cis*:*trans*) (Table 1, entry 11). Other titanium(IV) Lewis acids were not suitable promoters in this reaction (Table 1, entries 12 and 13).

Next, with the optimized conditions in hand, we investigated the substrate scope of this $TiCl_4$-mediated carbocyclization with various methylenecyclopropanes *E*-**1b**–*E*-**1k** in the synthesis of 3-azabicyclo[4.2.0]oct-5-enes and the results are summarized in Table 2. As can be seen from Table 2, as for substrates *E*-**1b**, *E*-**1c**, and *E*-**1h**–*E*-**1k** bearing electron-withdrawing groups (chloride or bromide) on their benzene rings, the reactions proceeded smoothly to give the desired products **2b**, **2c**, and **2h**–**2k** in 44–62% yields at room temperature along with moderate diastereoselectivities (25 °C) (Table 2, entries 1, 2, and 7–10). The stereochemistry of 3-azabicyclo[4.2.0]oct-5-ene has been unequivocally confirmed by X-ray diffraction of the representative product *cis*-**2h**. Its ORTEP drawing is indicated in Figure 1 and the corresponding CIF data have been presented in the Supplementary data. However, introducing electron-donating groups (methyl or methoxy group) at their aryl units, such as substrates *E*-**1d** and *E*-**1e**, afforded the corresponding products in poor yields, presumably due to the electronic effect (Table 2, entries 3 and 4). For the cycloalkyl group substituted propargylic esters *E*-**1f** and *E*-**1g**, the corresponding products **2f** and **2g** were obtained in 40% and 39% yields with

Table 2
$TiCl_4$-mediated synthesis of **2** from *E*-**1**

Entry[a]	Substrate		Product			Yield[b] (*cis*:*trans*)
1		*E*-**1b**, R = Cl		**2b**	48% (3:1)	48% (3:1)
2						62% (4:1)
3		*E*-**1c**, R = Br		**2c**	62% (4:1)	30% (5:1)
4		*E*-**1d**, R = Me		**2d**	30% (5:1)	15% (>20:1)
		E-**1e**, R = OMe		**2e**	15% (>20:1)	
5		*E*-**1f**, n = 1		**2f**	40% (>20:1)	40% (>20:1)
6		*E*-**1g**, n = 2		**2g**	39% (5:1)	39% (5:1)
7		*E*-**1h**		**2h**	52% (3:1)	52% (3:1)
8		*E*-**1i**, R = 2-Cl		**2i**	44% (3:1)	44% (3:1)
9						54% (3:1)
10		*E*-**1j**, R = 3-Cl		**2j**	54% (3:1)	50% (3:1)
		E-**1k**, R = 2,3-Cl_2		**2k**	50% (3:1)	
11[c]		*E*-**1l**		**2l**	0	0

[a] [**1**] = 0.10 M, 1.2 equiv $TiCl_4$, rt, 10 min.
[b] The diastereomeric ratio was determined by ^1H NMR spectroscopic data of the isolated product.
[c] Decomposed.

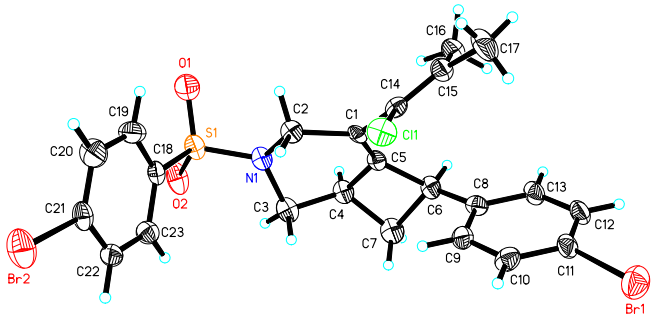
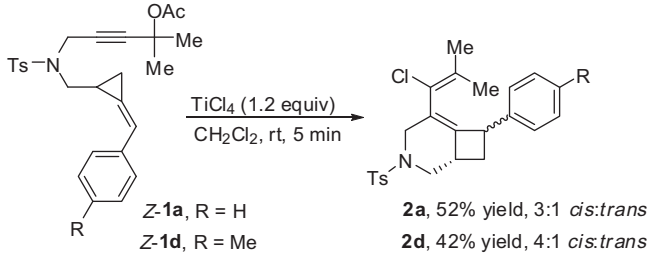


Figure 1. ORTEP drawing of *cis*-**2h**.

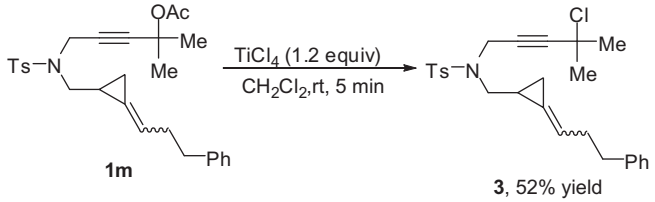
excellent diastereoselectivities, respectively (Table 2, entries 5 and 6). Moreover, *ortho*- or *meta*-substitution on the aromatic ring did not significantly interfere with the reaction outcomes (Table 2, entries 8–10). Other substrate such as *E*-**1l** tethered by an oxygen atom was also tested under the standard conditions, but none of the corresponding product **2l** was observed (Table 2, entries 11).

To gain more insight into this $TiCl_4$-mediated transformation of **1** to **2**, we investigated the stereochemical course of ring enlargement of methylenecyclopropanes (MCPs) using *Z*-**1a** and *Z*-**1d** as the substrates under the standard conditions and found that the products **2a** and **2d** having the same diastereoselectivities as those described in Table 2 were obtained in 52% and 42% yields, respectively (Scheme 2). Substrate **1m** having an alkyl group substituted methylenecyclopropane was also tested in this reaction, but the corresponding nucleophilic displacement product **3** was afforded in 52% yield without the formation of 3-azabicyclo[4.2.0]oct-5-ene under the standard conditions (Scheme 3).

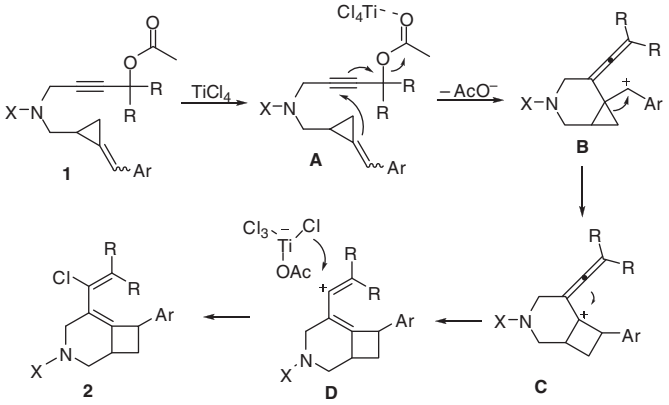
Based on the above investigations, we proposed a plausible reaction mechanism for this $TiCl_4$-mediated carbocyclization in Scheme 4. Coordination of the ester group to $TiCl_4$ gives intermediate **A**.[10] The nucleophilic intramolecular addition of the pendant methylenecyclopropane to the alkyne moiety along with the release of acyloxy group affords carbocation **B**, which contains a vinylidene moiety.[11] Subsequently, carbocationic intermediate **B** undergoes intramolecular ring enlargement of cyclopropane[12] via 1,2-carbon migration[13] gives intermediate **C** which can give vinyl cationic intermediate **D** through isomerization. Then chloride ion is transferred to vinyl cation from the in situ generated metal complex, affording the corresponding chlorinated bicyclo[4.2.0]oct-5-ene **2**.[14] It should be noted that carbocation **B** could be stabilized by the neighboring aryl unit which can serve as a driving force for this transformation. While alkyl group substituted methylenecyclopropane could not afford the stabilized intermediate **B**, only producing the corresponding chlorinated nucleophilic displacement compound **3**. Moreover, as can be seen from Scheme 4, *E*- and *Z*-methylenecyclopropanes give the same benzylic cation **B** under identical conditions. This can explain why the same products could be formed using *Z*-**1a** and *E*-**1a** as the substrates.



Scheme 2. The transformation of *Z*-**1**.



Scheme 3. The transformation of **1m**.



Scheme 4. A plausible reaction mechanism.

In conclusion, we have explored a novel synthetic route to access nitrogen-containing heterocycles by means of $TiCl_4$-mediated carbocyclization of enyne derivatives under mild conditions. The corresponding chlorinated bicyclo[4.2.0]oct-5-ene derivatives **2** could be afforded by the intramolecular ring enlargement of monoarylmethylenecyclopropanes with propargylic esters along with moderate to high diastereoselectivities. In the cases of enyne derivatives **1** having electron-deficient aromatic ring within MCP moiety, the corresponding chlorinated bicyclo[4.2.0]oct-5-enes were obtained in moderate to good yields whether they are *E*- and *Z*-monoarylmethylenecyclopropanes. On the basis of the above results, we believe that $TiCl_4$ could be one of the choices being used to mediate the cyclization of enyne derivatives for the construction of various heterocycles as well. Further investigation on the mechanistic insights and the extension of this procedure to the synthesis of other heterocycles are ongoing in our laboratory.

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Supplementary data

Supplementary data associated (general procedures and spectral data) with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.124.

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