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ARTICLE

Cycloisomerization of Enynones by Aluminum Halides: Construction of Bicyclo[3.1.0]hexanes with Introducing Halides†

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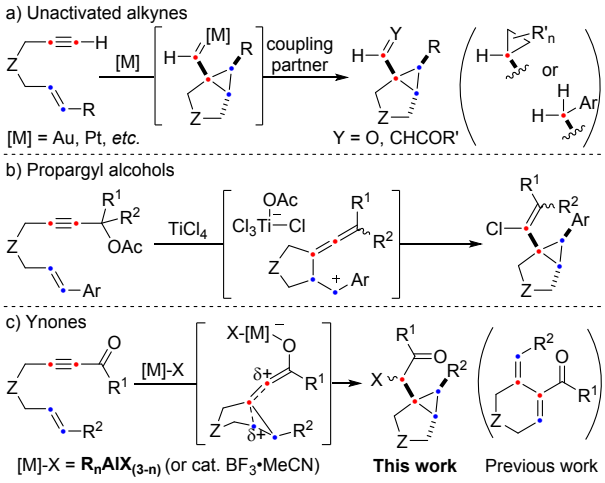
Alkyne π-bond activation by transition metal complexes has been well studied for cycloisomerization of enynes into bicyclo[3.1.0]hexanes, which can allow the introduction of carbon and oxygen functional groups concomitant with the construction of the core structures. However, the cycloisomerization of enynones through the activation of carbonyl groups into bicyclo[3.1.0]hexanes is not achieved. Herein, we report the aluminum halides-mediated cycloisomerization of 7-en-2-ynones into the halogenated bicyclo[3.1.0]hexanes.

Introduction

Cycloisomerization of enynes provides a variety of cyclic compounds via multiple bond cleavage and formation. Since these processes are generally induced by alkyne π-bond activation, transition metal catalysts have been well studied for the selective construction of these cyclic products.[1] Among them, cycloisomerization of 1,6-enynes with introduction of functional groups[2] and with hydrogen migration[3] has been developed for the synthesis of bicyclo[3.1.0]hexanes (Scheme 1a), which are important core structures found in many biologically active compounds.[4] However, although the methods based on the activation of acyloxy (Scheme 1b)[2i] or hydroxy groups[2g,3d] of propargyl alcohol derivatives have been reported, the cycloisomerization of enynones through the activation of carbonyl groups into bicyclo[3.1.0]hexanes is not achieved.

Other known approaches to bicyclo[3.1.0]hexanes from enynes include the methods triggered by the oxidative addition of Pd to propargylic esters or vinyl halides,[5] by the insertion of alkynes into metal-carbon or metal-heteroatom bonds,[6] by the formation of metallacycles[7] or carbenes,[8] and by metathesis with metal carbene complexes,[9] in addition to radical cyclization.[10] Nevertheless, the method with the introduction of halogens is limited to the $TiCl_4$-mediated cycloisomerization of O-acetyl enynols (Scheme 1b),[2i] although there are some methods using substrates such as alkene-tethered ynals,[8h,i] ynones,[8j] ynoates[6e-g,7g,8j] and ynamides.[2f,6e,f,8j]



Scheme 1. Cycloisomerization of enynes into bicyclo[3.1.0]hexanes.

Recently, as an extension of our research on metathesis-type reactions between alkynes and heteroenes catalyzed by σ-electrophilic acids,[11a-d] we have reported catalytic cycloisomerization of 7-en-2-ynones into six-membered cyclic dienes using BF_3·MeCN (Scheme 1c).[11e] This reaction proceeds via the activation of the carbonyl group by BF_3 followed by the generation of a zwitterionic intermediate, in which the secondary carbocation of a cyclohexane ring is partially stabilized by π-electrons of the allene moiety. Therefore, we expected the selection of proper metal halides would lead to the formation of halogenated bicyclo[3.1.0]hexanes via the intramolecular addition of halides to allene centers of the zwitterionic intermediates. Herein, we describe the aluminum

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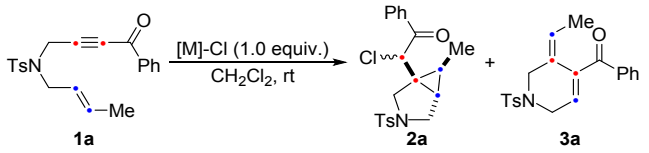
halides-mediated cycloisomerization of 7-en-2-ynones into the halogenated bicyclo[3.1.0]hexanes (Scheme 1c).

Results and discussion

Initially, metal chlorides were evaluated for the formation of chlorinated bicyclo[3.1.0]hexane **2a** from 7-en-2-ynone **1a** in CH_2Cl_2 (Table 1). In the course of investigating the cycloisomerization of 7-en-2-ynones into the *endo*-type dienes in our previous work,[11e] we found out that the desired product **2a** was formed in 33% yield by the treatment of **1a** with $AlCl_3$ (0.2 equiv.) at room temperature for 24 h (entry 1). Thus, the addition of TMSCl (TMS = trimethylsilyl, 2 equiv.) with the catalytic amount of $AlCl_3$ (0.2 equiv.) was attempted and unfortunately the similar result was obtained (**2a**: 36%, entry 2). On the other hand, when the amount of $AlCl_3$ was increased up to 1 equiv., the yield of **2a** was improved up to 78% yield (entry 3). Furthermore, although the use of the other metal chlorides resulted in the quantitative recovery of **1a** (entry 4) or lower yield of **2a** (entries 5-8), $EtAlCl_2$ and Et_2AlCl were more effective (entries 9 and 10). In particular, the use of Et_2AlCl afforded **2a** in excellent yield (94%) without the detection of cyclic dienes **3a** (entry 10). Note that other solvents such as dichloroethane, $CHCl_3$, CCl_4, CH_2Br_2, toluene, $MeNO_2$, MeCN and THF did not give good results (See Table S1 in ESI).

Table 1. Screening of metal halides.

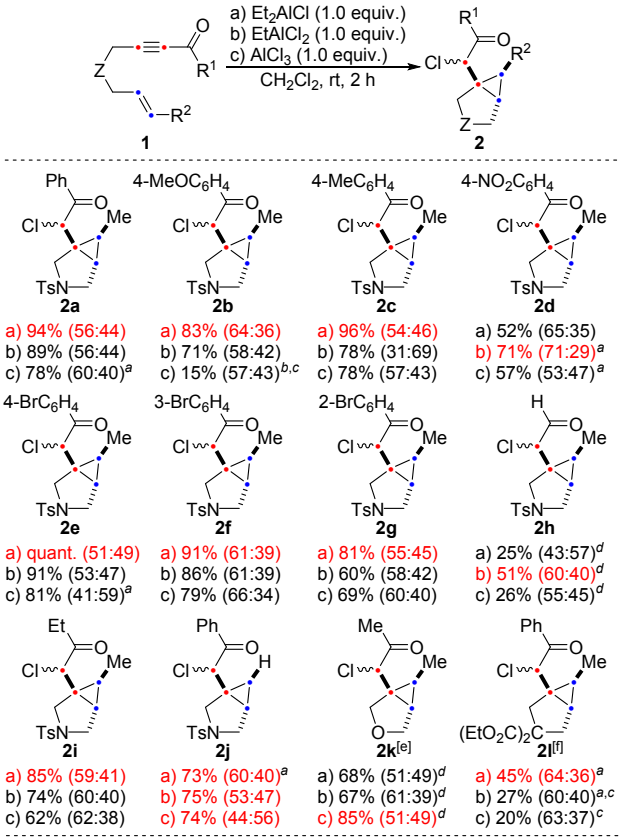


1a 2a 3a

entry	[M]-Cl	time (h)	**2a** (%)	dr[a]	**3a** (%)
1	$AlCl_3$[b]	24	33	62:38	trace
2	$AlCl_3$[b,c]	24	36	59:41	trace
3	$AlCl_3$	4	78	60:40	trace
4	$InCl_3$	24	0[d]	-	0
5	BCl_3	0.5	59	56:44	ND[e]
6	$SnCl_4$	4	50	64:36	trace
7	$TiCl_4$	4	54	47:53	trace
8	$FeCl_3$	24	36	ND[e]	15
9	$EtAlCl_2$	2	89	56:44	trace
10	Et_2AlCl	2	94	56:44	0

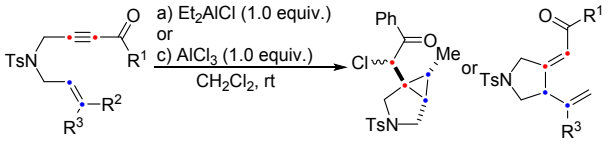
[a] Diastereomeric ratio. [b] 0.2 equiv. [c] Addtive: TMSCl (2 equiv.) [d] Recovery of **1a**: 99%. [e] Not determined.

Next, we examined the cycloisomerization of various 7-en-2-ynones **1** using Et_2AlCl (method a), $EtAlCl_2$ (method b) and $AlCl_3$ (method c) in CH_2Cl_2 at room temperature (Scheme 2). Similar to the phenyl ynone **1a**, other aryl ynones **1b**, **1c**, **1e-g** and ethyl ynone **1i** were treated with Et_2AlCl for 2 h giving rise to the corresponding chlorinated bicyclo[3.1.0]hexanes **2b**, **2c**, **2e-g** and **2i** in high yields (81%-quant.). These transformations using $AlCl_3$ tended to afford complex mixture and thus relatively mild Et_2AlCl would be effective on these reactions. On the other hand, in cases of nitrophenyl ketone **2d** and aldehyde **2h**, $EtAlCl_2$ gave good results likely due to a decrease in the Et ligand involved in reduction of carbonyl groups.[12] Actually, in the Et_2AlCl-mediated reactions of **1d** and **1h**, the reduced products of **2d** and **2h** were observed. Although ene adducts **4m** and **4n** were obtained from prenyl derivative **1m** and ynoate **1n** in 75% and 78% yields, respectively (Scheme 3), *Z*-alkene *Z*-**1a** gave the corresponding product *cis*-**2a** in 61% yield (Scheme 3) and allyl derivative **1j** were smoothly converted into the desired product **2j** in 73-75% yields in all cases with $Et_nAlCl_{(3-n)}$ (Scheme 2). Furthermore, the present method using $AlCl_3$ or Et_2AlCl could be applied to the synthesis of cyclic ether **2k** (85% by method c) and carbocycle **2l** (45% by method a).[13]



[a] Time: 4 h. [b] Time: 8 h. [c] Yields were determined by ^{1}H NMR analysis using an internal standard. [d] Time: 1 h. [e] **1k**: *E*:*Z* = 82:18. [f] **1l**: *E*:*Z* = 83:17.

Scheme 2. Cycloisomerization of **1** into **2**.



Z-**1a** (R^1 = Ph, R^2 = H, R^3 = Me) **a)** (1 h) *cis*-**2a**: 61%[a] -

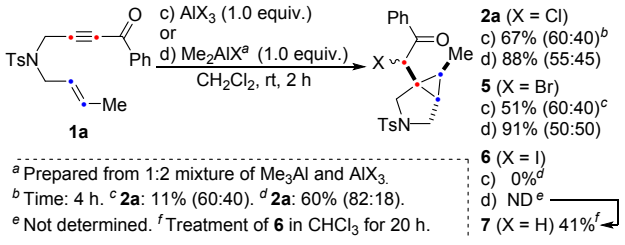
1m (R^1 = Ph, R^2 = R^3 = Me) **a)** (1 h) - **4m**: 75%[b]

1n (R^1 = OMe, R^2 = Me, R^3 = H) **c)** (24 h) - **4n**: 78%[c]

[a] Diastereomeric ratio = 65:35. [b] *Z*:*E* = 90:10. [c] *Z*-isomer only.

Scheme 3. Cycloisomerization of *Z*-**1a**, **1m** and **1n**.

Unfortunately, the use of AlF_3 resulted in the quantitative recovery of **1a**, and $AlBr_3$ and AlI_3 in CH_2Cl_2 brought about the production of the chlorinated product **2a** as a byproduct or as a main product (Scheme 4). The production of **2a** is probably due to the generation of aluminum chloride by the halogen exchange between AlX_3 and CH_2Cl_2 solvent.[14] Whereas, by using Me_2AlX (X = Cl, Br, I) *in situ* generated from Me_3Al (0.67 equiv.) and AlX_3 (0.33 equiv.),[15] the brominated **5** (91%) and the iodinated **6** (the yield was not determined) were produced as well as **2a** (88%) even in CH_2Cl_2. Notably, the iodinated **6** was smoothly converted into the hydrogenated **7** in organic solvents such as $CHCl_3$ and MeCN,[16] and thus was obtained as **7** in 41% yield after the exposure to $CHCl_3$ at rt for 20 h. It should be mentioned that the stereochemistries of products **2a** and *cis*-**2a** were determined by single crystal X-ray analysis (for **2a**)[17] or NOESY spectra analysis (for *cis*-**2a**, see ESI) and these products were found to be obtained as a mixture of epimers having the different stereogenic center on *α*-position of carbonyl groups. Furthermore, considering the configuration of **2a**, those of other products **2b**-**2l** and **5** were determined.



Scheme 4. Cycloisomerization of **1a** into **2a**, **5** or **6**.

As described above, in contrast to BF_3·MeCN giving six-membered cyclic diene **3**,[11e] aluminum halides led to the selective formation of bicyclo[3.1.0]hexanes **2a-l** from 7-en-2-ynones **1a-l**. To obtain mechanistic insight, we conducted DFT calculations on the $AlCl_3$-promoted cycloisomerization of 7-en-2-ynone **1k**. As shown in Figure 1, the $AlCl_3$-**1k** complex **INT1a** undergoes C2–C4 bond formation via **TS1a** to give **INT2a** with a small activation energy (8.7 kcal/mol). Considering the elongated C2–C3 bond distance (1.64 Å) and the near-linearity (173.2º) of the allenyl moiety, **INT2a** would be a zwitterionic intermediate, in which the secondary carbocation at the C3 position is partially stabilized by the C1–C2 double bond. **INT2a** is the bifurcating intermediate for bicyclo[3.1.0]hexane and cyclic diene products. In the case of cyclic diene product, C1–C3 bond formation with C1–C2 π-bond cleavage (**INT3a'**) followed by C2–C4 π-bond formation with C3–C4 bond cleavage and an electron donation of the enolate anion to C3 cation center give rise to the $AlCl_3$-**3k** complex **INT4a'** with a high stabilization energy (45.3 kcal/mol). Notably, **INT2a**, **TS2a'**, **INT3a'** and **TS3a'** are present as nonclassical structures between homoallyl, cyclopropylcarbinyl and cyclobutyl cations and such a delocalized cation species has been recognized as a reactive intermediate in various types of cycloisomerization of enynes.[1,18]

On the other hand, the positively charged C1 carbon in **INT2a** undergoes chlorination by $AlCl_3$ associating with the enolate moiety to produce **INT3a** with 3.9 kcal/mol of an activation energy, which is lower than that of **TS2a'** by 2.6 kcal/mol. Thus, the formation of the bicyclo[3.1.0]hexanes is favored kinetically in this system. This is because a Cl ligand of $AlCl_3$ is located in a direction near-vertical to sp-like C1 carbon (93.3º, Figure 2). According to DFT calculations on the BF_3-promoted skeletal rearrangement of **1k**, the zwitterionic analog **INT2b** (C2–C3:

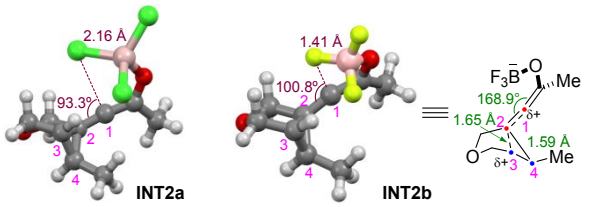


Figure 2. Conformations of **INT2a** and **INT2b** in $AlCl_3$- or BF_3-promoted reactions of **1k** calculated by M062X/6-31+G*.

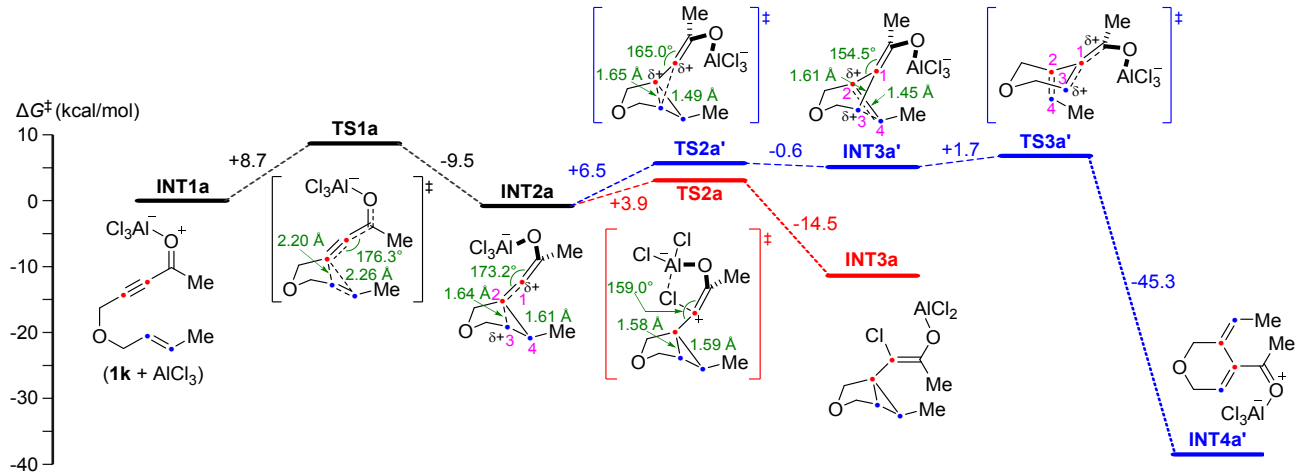
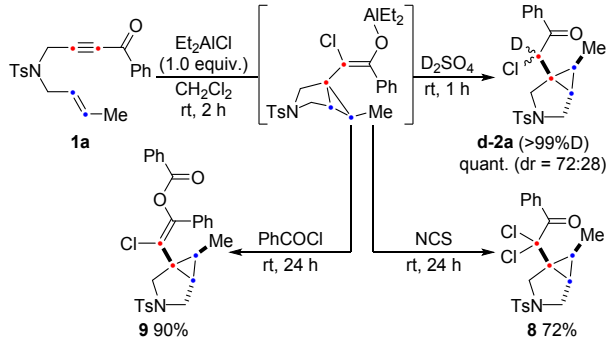


Figure 1. DFT calculations on $AlCl_3$-promoted conversion of **1k** into cyclic diene and into bicyclo[3.1.0]hexane at the M062X/6-31+G* level.

1.65 Å, C1-centered angle: 168.9º, Figure 2) is a reactive intermediate for cyclic diene **3k**.[11e] However, the B–F bond distance (**INT2b**: 1.41 Å) is much shorter than the Al–Cl bond distance (**INT2a**: 2.16 Å) and thereby the corresponding F ligand of BF_3 is deviated from the direction vertical to sp-like C1 carbon (100.8º, Figure 2). Consequently, BF_3·MeCN would lead to the formation of cyclic diene **3**. These calculated results are consistent with the experimental observations.

In order to better understand the involvement of aluminum enolate intermediate such as **INT3a**, we carried out deuterium labeling experiments using **1a** (Scheme 5). Consequently, after **1a** was treated with Et_2AlCl at rt for 2 h, the exposure of the reaction mixture to D_2SO_4 was found to afford the deuterated product **d-2a** (>99%D) quantitatively. This result supports the involvement of aluminum enolate intermediate.[19] In addition, the use of *N*-chlorosuccinimide (NCS) and benzoyl chloride instead of D_2SO_4 afforded dichloro product **8** and enol benzoate **9**[19a] in 72% and 90% yields, respectively.



Scheme 5. Quenching of aluminum enolate with electrophiles.

Conclusions

In conclusion, we have developed a synthetic method of halogenated bicyclo[3.1.0]hexanes by aluminum halides-mediated cycloisomerization of 7-en-2-ynones. This work represents the first report of selective formation of bicyclo[3.1.0]hexanes from enynones through the activation of carbonyl groups. Since aluminum halides gave different products from those obtained by using BF_3 as a homologous element halide,[11e] we believe that our findings would open a new window on cycloisomerization based on the activation of carbonyl groups as well as a powerful procedure for accessing bicyclo[3.1.0]hexanes. Furthermore, on the basis of DFT calculations and experimental data, we proposed a reaction mechanism involving the branching zwitterionic intermediate (**INT2a**), and concluded that different bond lengths between group 13 elements and halogens lead to cycloisomerization into different products. Studies on other cycloisomerization of n-en-2-ynones are underway.

Experimental

Representative procedure for cycloisomerization of 1a into 2a.
To a solution of enynone **1a** (147.0 mg, 0.4 mmol) in CH_2Cl_2 (2 mL) was added Et_2AlCl (1.0 M in hexane solution, 0.4 mL, 0.4 mmol) at 0 ºC. After being stirred at room temperature for 2 h, the reaction mixture was quenched with sat. $NaHCO_3$ and sat. Rochelle salt, and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to dryness. The residue was purified by MPLC (hexane:AcOEt = 88:12) to give **2a** (151.7 mg, 94%) as an epimeric mixture (56:44).

Author Contributions

Conceptualization, A.S.; data curation, all; formal analysis, all; funding acquisition, A.S. and M.U.; investigation, D.S., A.T. and Y.W.; methodology, D.S. and A.S.; project administration, A.S.; resources, A.S. and M.U.; supervision, A.S. and M.U.; validation, D.S. and A.T.; visualization, D.S. and A.T.; writing—original draft preparation, A.S.; writing—review and editing, A.T., K.M., M.U. and A.S.

Conflicts of interest

There are no conflicts to declare.

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17 CCDC 2210449 (for major epimer) and CCDC 2210451 (for minor epimer) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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