

Iron(III)-Catalyzed Cyclization of Alkynyl Aldehyde Acetals: Experimental and Computational Studies

Tongyu Xu,^[a] Qin Yang,^[a] Dongpo Li,^[b] Jinhua Dong,^[b] Zhengkun Yu,^{*[a, c]} and Yuxue Li^{*[c]}

Abstract: FeCl₃·6H₂O- and FeBr₃-catalyzed Prins cyclization/halogenation of alkynyl aldehyde acetals has been realized with acetyl chloride or bromide as halogen source in dichloromethane to afford 2-(1-halobenzylidene or alkylidene)-substituted five-membered carbo- and heterocycles, and thus provides an alternative route for vinylic C–Cl and C–Br bond formation. Five- to eight-membered cyclic enones were

efficiently synthesized by FeCl₃·6H₂O-catalyzed intramolecular cyclization of alkynyl aldehyde acetals in acetone under mild conditions. An oxocarbenium species generated in situ is proposed to initiate the reaction, and the

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target products are formed via vinylogous carbenium cation and oxete intermediates according to DFT calculations. Intermolecular reactions of alkynes and aldehyde acetals were also investigated with 20–40 mol% FeCl₃·6H₂O catalyst, and produced α,β-unsaturated enones and chlorinated indene derivatives. The present protocol has applications in the synthesis of carbo-, oxa- and azacycles.

Introduction

Coupling reactions of alkynes with carbonyl compounds have been utilized to form carbon–carbon and carbon–heteroatom bonds.^[1–3] As masked carbonyl compounds, acetals usually act as building blocks in organic synthesis due to easy deprotection of the acetal functionality.^[4,5] Stoichiometric TiCl₄-, SnCl₄-, and Me₃SiI-based intramolecular Prins cyclization of alkynyl aldehyde acetals afforded cyclic halovinyl products.^[6,7] Recently, iron catalysis has emerged as a

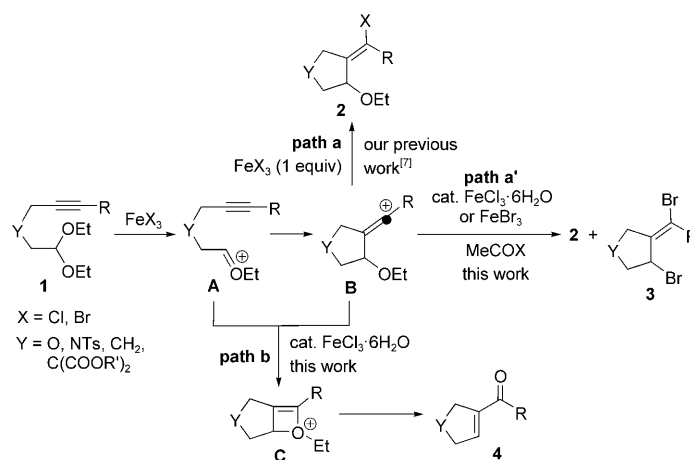
promising environmentally benign alternative to traditional transition metal catalysts.^[8–11] In this respect, FeX₃-promoted cyclization of HO- and TsHN-functionalized alkynes with aldehydes was used to prepare six-membered halogenated heterocycles and 2-halovinyl ketones.^[12] Recently, we found that stoichiometric FeCl₃ and FeBr₃ can promote Prins cyclization of alkynyl aldehyde acetals **1** at 0 °C to form five-membered halobenzylidene or alkylidene-substituted carbo- and heterocycles **2** via path a of Scheme 1.^[7] With a view to environmentally benign application of this method, a cata-

[a] T. Y. Xu, Q. Yang, Prof. Dr. Z. K. Yu
Dalian Institute of Chemical Physics, Chinese Academy of Sciences
457 Zhongshan Road, Dalian 116023 (P. R. China)
Fax: (+86) 411-8437-9227
E-mail: zkxu@dicp.ac.cn
liyuxue@mail.sioc.ac.cn

[b] D. P. Li, Prof. Dr. J. H. Dong
School of Pharmaceutical Engineering
Shenyang Pharmaceutical University
103 Wenhua Road, Shenyang, Liaoning 110016 (P. R. China)

[c] Prof. Dr. Z. K. Yu, Dr. Y. X. Li
State Key Laboratory of Organometallic Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
354 Fenglin Road, Shanghai 200032 (P. R. China)

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Scheme 1. FeX₃-promoted cyclization of alkynyl acetals.

lytic procedure using FeX_3 as catalyst and cheap and readily available halogen sources (path a') is desirable. Intrigued by the structural feature of acetals **1**, we reasonably envisioned that formal intramolecular [2+2] cycloaddition of the alkynyl and oxocarbenium moieties in intermediate **A** or nucleophilic attack of the ethoxyl oxygen atom at the vinyl carbenium carbon atom in species **B** may generate oxete **C**, leading to cyclic enone **4** through an eliminative ring-opening pathway (path b). Herein we report $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ - and FeBr_3 -catalyzed Prins cyclization/halogenation of alkynyl aldehyde diethyl acetals with acetyl chloride or bromide as halogen source, $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ -catalyzed cyclization of the same type of acetals to cyclic enones, and mechanistic studies by DFT calculations.

Results and Discussion

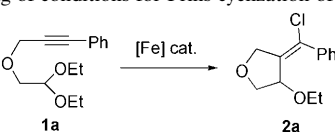
$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ and FeBr_3 -catalyzed Prins cyclization/halogenation of alkynyl aldehyde diethyl acetals **1:** In our initial study, we tried to carry out a non-metal-catalyzed reaction of acetal **1a** to prepare **2a** in dichloromethane, and found that the expected cyclization seldom occurred (Table 1, entry 1), while the reaction proceeded well in the presence of 1.0 equiv of FeCl_3 (Table 1, entry 2).^[7] On reducing the loading of FeCl_3 to a catalytic amount (e.g., 5 mol %) and using acetyl chloride (1.2 equiv) as halogen source, the reaction proceeded catalytically to form the target product **2a** in 44–59% yields at 0–40 °C (Table 1, entries 3–5). As an alternative catalyst, the cheap, nontoxic, and readily available $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ was used in the same reaction and exhibited better catalytic efficiency than FeCl_3 (Table 1, entries 6–8), affording **2a** in 83% yield at room temperature (Table 1,

entry 7). At least 10 mol % excess of acetyl chloride was necessary for the acetal substrate to reach 100% conversion (Table 1, entries 7 and 9–11). The catalyst loading affected the reaction rate and selectivity for the target product (Table 1, entries 7, 12 and 13). In THF, the reaction became complicated (Table 1, entry 14). Thus, the conditions for catalytic Prins cyclization of **1a** were optimized to 5 mol % $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ as catalyst, CH_2Cl_2 as solvent, 1.2 equiv MeCOCl as halogen source, 2 h at ambient temperature under nitrogen atmosphere.

Next, the present Prins cyclization method was extended to a variety of alkynyl aldehyde diethyl acetals under the optimal conditions (Table 2). With 5 mol % $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ as catalyst (Method A), the O-linked alkynyl acetals **1a–g** underwent the desired Prins cyclization/chlorination to afford **2a–g** in 74–87% yields (Table 2, entries 1–7). Reactions of TsN-linked alkynyl acetal substrates **1h–i** produced the target products **2h–i** in 48–81% yield (Table 2, entries 8–12), while treatment of $\text{C}(\text{COOR})_2$ -linked alkynyl acetal **1m** only generated **2m** in moderate yield (52%, Table 2, entry 13) under the stated conditions. All results are comparable with those obtained from the stoichiometric reactions of **1** with anhydrous FeCl_3 .^[7] However, treatment of **1a** with 5 mol % FeBr_3 and 1.2 equiv MeCOBr only led to an inseparable mixture. Unexpectedly, with 5 mol % FeBr_3 as catalyst and an excess of acetyl bromide (2.2 equiv) as halogen source (Method B), the reaction of **1a** afforded a dibromide product of type **3** (i.e., **3a**) in 66% yield (Table 2, entry 1). In most of the reactions carried out by Method B, dibromides **3a**, **3b**, **3d**, **3g–i**, **3k**, and **3l**, were predominantly generated with formation of the *E* isomers, and the highest yield of 89% was reached for **3g** (Table 2, entry 7). With benzoxyaryl alkyne acetal **1c** as substrate, no identifiable product could be isolated, presumably due to complicated reactions involving the BnO moiety (Table 2, entry 3). In three cases, the monobromide products of type **2** (i.e., **2e'**, **2f'** and **2j'**) were formed as the major products (Table 2, entries 5, 6, and 10). However, the reaction of $\text{C}(\text{COOEt})_2$ -linked alkynyl acetal **1m** produced cyclic enone **4m** as the isolated product (Table 2, entry 13), that is, a reaction occurs via path b of Scheme 1.

$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ -catalyzed intramolecular cyclization of alkynyl aldehyde diethyl acetals **1 to cyclic enones **4**:** Encouraged by the result obtained in entry 13 of Table 2, reactions of **1** via path b were explored. The reaction of acetal **1a** was initially carried out to screen the reaction conditions (Table 3). Treatment of **1a** with 10 mol % FeCl_3 in CH_2Cl_2 at ambient temperature afforded a 2-chlorovinyl oxacycle product of type **2**, namely **2a**, in 19% yield [Table 3, entry 1 and Eq. (1)],^[7] and $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ only showed low catalytic activity (Table 3, entry 2). However, in CH_3NO_2 solution **1a** was catalytically converted to the target product, cyclic enone **4a**, in about 60% yield with 5 mol % FeCl_3 or $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ as catalyst (Table 3, entries 3 and 4), whereas the failure of same reaction to take place in solvents such as 1,2-dichloroethane (DCE), CH_3CN , 1,4-dioxane, THF, and EtOH dem-

Table 1. Screening of conditions for Prins cyclization of **1a**.^[a]



Entry	Cat./mol %	MeCOCl [equiv]	<i>T</i> [°C]	<i>t</i> [h]	Yield ^[b] [%]
1		1.2	RT	10	<5
2	$\text{FeCl}_3/100$		0	0.5	77 ^[7]
3	$\text{FeCl}_3/5$	1.2	0	3	48
4	$\text{FeCl}_3/5$	1.2	RT	3	59
5	$\text{FeCl}_3/5$	1.2	40	0.8	44
6	$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}/5$	1.2	0	5	54
7	$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}/5$	1.2	RT	2	83
8	$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}/5$	1.2	40	0.3	48
9	$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}/5$	1.0	RT	2	65
10	$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}/5$	1.1	RT	2	71
11	$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}/5$	1.3	RT	2	81
12	$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}/3$	1.2	RT	6	77
13	$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}/10$	1.2	RT	0.7	63
14	$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}/5$	1.2 ^[c]	RT	1	— ^[d]

[a] Conditions: **1a**, 0.50 mmol; CH_2Cl_2 , 5 mL; under N_2 atmosphere. [b] Yields of isolated products. [c] THF (5 mL) as the solvent. [d] Complicated reaction.

Table 2. FeCl₃·6H₂O and FeBr₃-catalyzed cyclization of **1**.^[a]

Reaction scheme: **1** (acetal) $\xrightarrow[\text{MeCOX (X = Cl, Br)}]{[\text{Fe}] \text{ cat.}}$ **2** (chlorinated product) + **3** (brominated product, when X = Br)

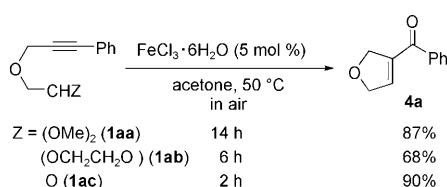
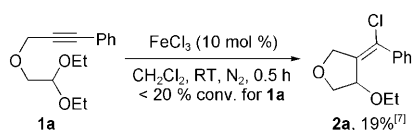
Entry	Acetal	Yield ^[b] [%]																					
		Method A	Method B																				
1																							<p>onstrates a remarkable solvent effect. Furthermore, the cyclization of 1a proceeded more efficiently in acetone at ambient temperature to give 4a in 88–93% yields, although the reaction hardly occurred at 0°C (Table 3, entries 5–8). In all cases, FeCl₃·6H₂O exhibited higher catalytic activity than anhydrous FeCl₃, presumably due to extra stabilization of the metal center by the water molecules of crystallization in FeCl₃·6H₂O and water present in acetone. Unexpectedly, 1a also efficiently underwent cyclization in acetone in air to form 4a in 93% yield at ambient temperature or 50°C (Table 3, entries 9 and 10). Trifluoroacetic acid (TFA) and hydrochloric acid promoted the reaction less efficiently (Table 3, entries 11 and 12), and PtCl₂, [Pt(cod)Cl₂] (cod = 1,5-cyclooctadiene), PdCl₂, [Rh(cod)₂]BF₄, CuCl, and [Au(PPh₃)Cl]/AgBF₄ did not initiate the same reaction under the stated conditions. However, the presence of 5 mol% CuCl₂·2H₂O led to decomposition of 1a to its parent aldehyde 1ac. For comparison, the reactions of alkynyl dimethyl and dimethylene acetals 1aa and 1ab and their parent aldehyde 1ac were investigated under the optimized conditions to form 4a in 68–90% yields at 50°C over a period of 2–14 h, that is, diethyl acetal 1a is more reactive than its analogues 1aa–ac, and 1a can undergo more efficient transformation to form the target product 4a [Eq. (2)]. The stronger electron-donating ability of the ethyl group is considered to stabilize intermediate C in Scheme 1 and favor formation of 4a.</p>

Under the optimized conditions as shown for entries 9 and 10 in Table 3, the scope of the protocol was explored (Table 4). With 5 mol% FeCl₃·6H₂O as catalyst in ace-

Table 2. (Continued)

Entry	Acetal	Yield ^[b] [%]	
		Method A	Method B
12		 (81)	 (28)
13		 (52)	 (28)

[a] Conditions: **1**, 0.50 mmol; CH₂Cl₂, 5 mL; RT, 2–5 h; under N₂ atmosphere. Method A: FeCl₃·6H₂O, 5 mol %; MeCOCl, 0.60 mmol. Method B: FeBr₃, 5 mol %; MeCOBr, 1.1 mmol; 0.5 h. [b] Yields of isolated products. [c] Complicated reaction. [d] The *E/Z* ratios were determined by ¹H NMR spectroscopy.

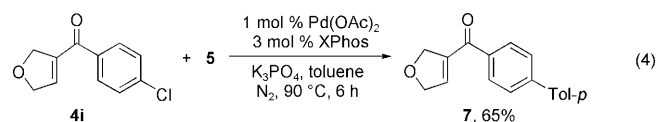
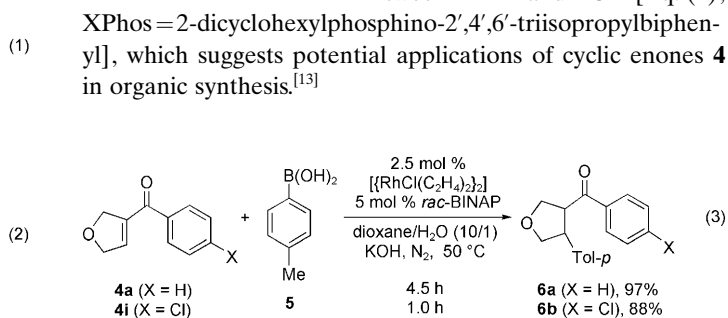
Table 3. Screening of conditions for the conversion of **1a** to cyclic enone **4a**.^[a]

Entry	Cat./mol %	Solvent	<i>T</i> [°C]	<i>t</i> [h]	Yield ^[b] [%]
1	FeCl ₃ /10	CH ₂ Cl ₂	RT	0.5	19 ^[c]
2	FeCl ₃ ·6H ₂ O/10	CH ₂ Cl ₂	RT	24	trace
3	FeCl ₃ /5	CH ₃ NO ₂	RT	1	60
4	FeCl ₃ ·6H ₂ O/5	CH ₃ NO ₂	RT	1	62
5	FeCl ₃ /5	acetone	RT	2	88
6	FeCl ₃ ·6H ₂ O/5	acetone	RT	2	93
7	FeCl ₃ ·6H ₂ O/1	acetone	RT	6	89
8	FeCl ₃ ·6H ₂ O/5	acetone	0	5	trace
9 ^[d]	FeCl₃·6H₂O/5	acetone	RT	2	93
10 ^[d]	FeCl₃·6H₂O/5	acetone	50	0.2	93
11	TFA/500	CH ₂ Cl ₂	reflux	60	72
12	37% HCl/700	H ₂ O	50	2	44

[a] Conditions: **1a**, 0.50 mmol; solvent, 5 mL; under N₂ atmosphere. [b] Yields of isolated products. [c] The product was **2a** [see Eq. (1)]. [d] Under air.

tone under air, the O-linked alkynyl acetals underwent efficient intramolecular cyclization to form five-membered cyclic enones **4a–j** in 84–99% yields (Table 4, entries 1–10). The TsN-linked acetals showed much lower reactivity, producing cyclic enones **4k** and **4l** in 45–87% yields at higher catalyst loading (20 mol %). With C(COOR)₂- or CH₂-linked acetals as substrates, target products **4m–p** were also efficiently obtained in 85–99% yield, and HO-functionalized

alkynyl acetal **1u** was converted to bicyclic enone **4q** in 70% yield. It is noteworthy that substituents such as OH, OMe, OBn, MeCO, Cl, alkenyl, and alkynyl in acetals **1** can tolerate the reaction conditions. Under Rh^I catalysis, enones **4a** and **4i** easily underwent 1,4-Michael addition with aryl boronic acid **5** [Eq. (3)]; BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl], while Pd-catalyzed Suzuki coupling occurred between **4i** and **5** [Eq. (4)]; XPhos = 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl], which suggests potential applications of cyclic enones **4** in organic synthesis.^[13]



The synthetic methodology was then applied for the synthesis of six- to eight-membered cyclic enones by extending the linker chain in the acetal substrates (Table 5). Reactions of the less reactive alkynyl acetals were carried out in DCE at 80 °C. Thus, in a fashion similar to the synthesis of five-membered cyclic enones, six-membered cyclic enones **4r–u** were obtained in 85–98% yield from their corresponding alkynyl aldehyde acetals **1v–y** (Table 5, entries 1–4). The seven-membered cyclic enones **4v–x** were prepared in 33–65% yields (Table 5, entries 5–7). The rare eight-membered cyclic enone **4y** was only obtained in 23% yield (Table 5, entry 8), while the reactions of the O- and C-linked acetals did not produce the desired eight-membered cyclic enone products.

FeCl₃·6H₂O-catalyzed intermolecular reactions of alkynes **8 and acetals **9**:** Our synthetic method was also applied to FeCl₃·6H₂O-catalyzed intermolecular reactions of alkynes **8** and acetals **9** (Table 6). Lewis acid (GaCl₃) catalyzed reaction of alkyne **8a** and 3-fluorobenzaldehyde is known to produce an α,β-unsaturated ketone of type **10** (18%) as major product and a compound of type **11** (6%) as minor product.^[2h] The strongly acidic ion-exchange resin Amberlyst-15 and Yb(OTf)₃ promoted the reactions of alkynes

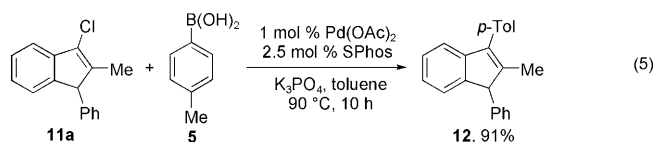
Table 4. Synthesis of five-membered cyclic enones **4a–q**.^[a]

Entry	Acetal	T [°C]	t [h]	Product (Yield ^[b] [%])	Entry	Acetal	T [°C]	t [h]	Product (Yield ^[b] [%])
1		RT	2	 4a (93)	10		50	5	 4j (89)
2		RT	0.5	 4b (94)	11		50	1.5 ^[c]	 4k (87)
3		RT	0.5	 4c (94)	12		50	24 ^[c]	 4l (45)
4		RT	0.5	 4d (92)	13		50	0.2	 4m (99)
5		RT	0.5	 4e (99)	14		50	0.2	 4n (95)
6		50	4	 4f (92)	15		50	1.5	 4o (85)
7		50	0.5	 4g (84)	16		50	0.2 ^[d]	 4p (98)
8		50	0.2	 4h (97)	17		RT	0.1	 4q (70)
9		50	0.5	 4i (99)					

[a] Conditions: **1**, 0.50 mmol; FeCl₃·6H₂O, 5 mol %; acetone, 5 mL. [b] Yields of isolated products. [c] 20 mol % FeCl₃·6H₂O, 1.5–24 h. [d] 10 mol % FeCl₃·6H₂O, 0.2 h.

with benzaldehydes to form products **10** more efficiently.^[2g,3d] In our case, by using 20 mol % FeCl₃·6H₂O in DCE at 80 °C, **8a** reacted with benzaldehyde diethyl acetal **9a** to afford the desired product **10a** (56 %) with minor formation of **11a** (24 %; Table 6, entry 1), whereas the reaction of **8a** and benzaldehyde (**9a'**) formed **10a** and **11a** in much lower yields (Table 6, entry 2), that is the aldehyde is less reactive than its diethyl acetal. However, in the presence of ethanol the same reaction of **8a** and **9a'** generated **10a** (50 %) and **11a** (23 %) more efficiently (Table 6, entry 3), which suggests that ethanol facilitates the reaction due to formation of the more reactive acetal species **9a** from **9a'** in situ. Increasing the catalyst loading to 40 mol % in toluene at 100 °C reversed the product selectivities, so that the reactions of **8a** with **9a–c** afforded **11a–c** (55–67 %) as the major products, while the reactions in DCE under the same conditions gave **11a–c** as the minor products (Table 6, entries 4–8), that is, a remarkable solvent effect is active here,

too. With aliphatic aldehyde acetals, terminal alkyne, and dialkyl alkyne as substrates, the reactions only produced enone products of type **10** (Table 6, entries 9–13). Efficient Suzuki coupling between **11a** and **5** to form **12** in 91 % yield [Eq. (5); SPhos = 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl] demonstrates potential application of products **11**.



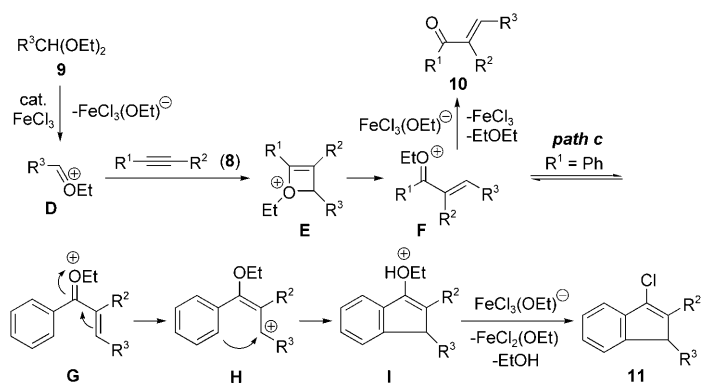
Intramolecular cyclization of **1** catalyzed by FeCl₃·6H₂O and FeBr₃ is proposed to proceed as shown in Scheme 1. A similar mechanism is proposed for the intermolecular reactions of alkynes with acetals to form enones **10** as well as **11**

Table 5. Synthesis of six- to eight-membered cyclic enones **4r–y**.^[a]

Entry	Acetal	Method	<i>t</i> [h]	Yield ^[b] [%]
1		A	0.3	 (85)
2		A	0.3	 (98)
3		A	0.2	 (98)
4		A	0.2	 (96)
5		B	2	 (33)
6		B	1.5	 (51)
7		B	2	 (65)
8		B	30	 (23)

[a] Conditions: **1**, 0.50 mmol; in air. Method A: acetone, 5 mL; 5 mol % FeCl₃·6H₂O; 50 °C. Method B: DCE, 2 mL; 20 mol % FeCl₃·6H₂O; 80 °C.
[b] Yields of isolated products.

(Scheme 2). Oxocarbenium cation **D** is initially generated by interaction of the catalyst with the acetal substrate. Species **D** is cyclized with the alkyne to form oxete **E**, which is then transformed into enone **10** via intermediate **F**. When an aryl alkyne is used, intramolecular nucleophilic attack of



Scheme 2. Proposed mechanism for the intermolecular reactions of alkynes **8** with acetals **9**.

the carbonium carbon at an aromatic CH group in tautomer **H** of species **G** forms intermediate **I**, followed by substitution with FeCl₃(OEt) anion to produce **11**. We suggest that water acts as a ligand to stabilize the catalyst during the reaction.

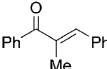
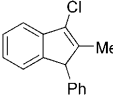
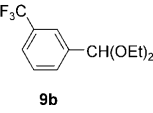
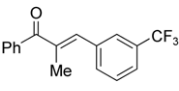
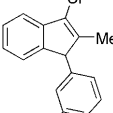
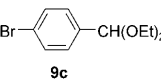
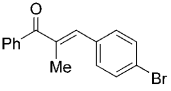
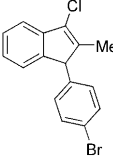
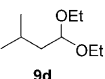
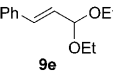
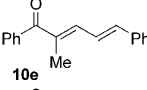
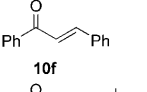
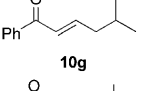
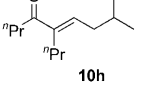
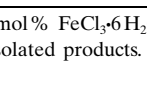
Computational studies on the reaction mechanism: To understand the reaction mechanism better, DFT^[14] studies were performed with the Gaussian 03 program suite^[15] by using the B3LYP method and the 6-311+G** basis set.^[16] The optimized structures were all checked with harmonic vibration frequency calculations, and the atomic charges were calculated by NBO analysis.^[17] The calculated reaction pathways and optimized structures are shown in Scheme 3 and Figure 1, respectively. As shown in Scheme 3, the nucleophilic attack of C4 at C1 in oxocarbenium cation **I** leads to vinyl cation **II** over a small barrier of 3.8 kcal mol⁻¹. The possible [2+2] transition state between **I** and **IV** was safely excluded by a two-dimensional relaxed potential-energy surface (PES) scan. A relaxed PES scan along C1–C5 of intermediate **I** suggests that species **III** resulting from attack of C5 at C1 does not exist (see Supporting Information for details). This is consistent with the charge distributions shown in Figure 1. It is not the positively charged C5 (+0.105) but the negatively charged C4 (−0.111) that nucleophilically attacks the positively charged C1 (+0.484). Thus, nucleophilic attack of the methoxyl oxygen atom at the carbenium carbon atom in **II** forms oxete **IV**. Ring opening of the four-membered oxacycle in **IV** via transition state **Ts-3** over a very small barrier of 1.6 kcal mol⁻¹ yields intermediate **V**, which is much more stable (40.5 kcal mol⁻¹) than intermediate **II**. However, formation of **V** must overcome a barrier of 17.2 kcal mol⁻¹ from **II** to transition state **Ts-2**. Therefore, formation of **V** is difficult at lower temperature and thus **II** is easily trapped by high concentrations of chloride anion to form product **P1**. At higher temperature and with low concentration of chloride anion, thermodynamically stable **V** is formed to produce product **P2**. Intermediate **II** acts as a branching point in this reaction. Product **P1** can be regarded as the product under kinetic control, whereas **P2** is the product under thermodynamic control. In our previous study,^[7] reactions of **1** with stoichiometric FeCl₃ afforded products of type **P1** at 0 °C, and in the presence of halogen sources such as MeCOX (X = Cl, Br) and FeX₃ as catalysts reactions of **1** also produced products **P1**. However, FeCl₃·6H₂O-catalyzed cyclization of **1** efficiently produced products of type **P2** at between room temperature and 80 °C in the absence of halogen sources. The present theoretical studies are very consistent with our observations and revealed the two reaction pathways shown in Scheme 1.

Conclusion

FeCl₃·6H₂O- and FeBr₃-catalyzed Prins cyclization/halogenation of alkynyl aldehyde acetals has been efficiently realized with acetyl chloride or bromide as the halogen source to

Table 6. FeCl₃·6H₂O-catalyzed intermolecular reactions of alkynes **8** with acetals **9**.^[a]

$$R^1-C\equiv C-R^2 + R^3-CHZ \xrightarrow[Z = (OEt)_2, O]{cat. FeCl_3 \cdot 6H_2O} R^1-C(=O)-C(R^2)=C(R^3)-Z + \text{Product 11}$$

Entry	Substrates		Method/t [h]	Yield ^[b] [%]	
	8	9		10	11
1	PhC≡CMe (8a)	PhCH(OEt) ₂ (9a)	A/4		
2	8a	PhCHO (9a')	A/24	10a (56)	11a (24)
3 ^[c]	8a	9a'	A/12	10a (35)	11a (18)
4	8a	9a	B/3	10a (50)	11a (23)
5	8a		A/6		
6	8a	9b	B/3	10b (60)	11b (27)
7	8a		A/10		
8	8a	9c	B/6	10c (55)	11c (23)
9	8a		A/2	10c (27)	11c (67)
10	8a		A/8		(67)
11	PhC≡CH (8b)	9a	A/2		(42)
12	8b	9d	A/1		(72)
13	<i>n</i> PrC≡C <i>n</i> Pr (8c)	9d	A/24		(47)
					(23)

[a] Conditions: alkyne **8**, 1.0 mmol; **9**, 1.2 mmol; in air. Method A: 20 mol% FeCl₃·6H₂O, 4 mL DCE, 80 °C. Method B: 40 mol% FeCl₃·6H₂O, 4 mL toluene, 100 °C. [b] Yields of isolated products. [c] EtOH (1.0 mmol) was added.

afford (*E*)-2-(1-halobenzylidene or alkylidene)-substituted five-membered carbo- and heterocycles and thus provide an alternative route for vinylic C–Cl and C–Br bond formation. An efficient protocol for the synthesis of five- to eight-membered cyclic enones has been developed by means of FeCl₃·6H₂O-catalyzed intramolecular cyclization of alkynyl aldehyde acetals under mild conditions. An oxocarbenium species generated in situ is proposed to initiate the reaction, and the cyclic enone product is formed via an oxete intermediate according to DFT calculations. The present meth-

odology has demonstrated its potential applications in the efficient synthesis of carbo-, oxo- and azacyclic compounds.

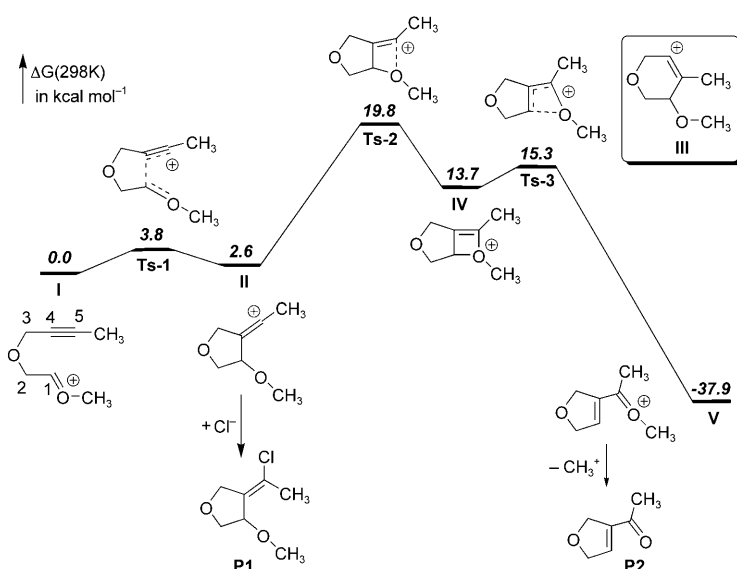
Experimental Section

General considerations: All manipulations of air- and/or moisture-sensitive compounds were carried out under nitrogen atmosphere by standard Schlenk techniques. Reaction solvents were dried and distilled prior to use by literature methods. ¹H and ¹³C{¹H} NMR spectra were recorded on a Bruker DRX-400 spectrometer, and all chemical shift values refer to δ_{TMS} = 0.00 ppm or CDCl₃ (δ(¹H) = 7.26, δ(¹³C) = 77.16 ppm). HRMS was performed on a Waters GC-TOF CA156 mass spectrometer. All melting points are uncorrected. Analytical TLC plates (Sigma-Aldrich silica gel 60_{F200}) were viewed by UV light (254 nm). Chromatographic purifications were performed on SDZF silica gel 160. FeCl₃·6H₂O was purchased from Alfa Aesar Co. Known products were identified by comparison of their NMR features with the reported data of the authentic samples.

Typical procedure for FeCl₃·6H₂O and FeBr₃-catalyzed Prins cyclization/halogenation of alkynyl aldehyde acetals **1 (synthesis of **2** and **3**):** Compound **1** (0.5 mmol) and CH₃COCl (47 mg, 0.6 mmol) were added to a suspension of FeCl₃·6H₂O (6.8 mg, 5 mol%) in CH₂Cl₂ (5 mL). The mixture was stirred at ambient temperature and monitored by TLC analysis on silica gel. When the starting acetal substrate was completely consumed, the resultant mixture was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: petroleum ether (60–90 °C)/diethyl ether 20/1) to afford the target product **2**.

Typical procedure for the synthesis of cyclic enones **4:** FeCl₃·6H₂O (6.8 mg, 5 mol%) was added to a solution of **1** (0.5 mmol) in acetone (5 mL) in air. The mixture was stirred at room tem-

perature, and monitored by TLC analysis on silica gel. When **1** was completely consumed (0.5 h), all volatile substances were evaporated from the resultant mixture under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: petroleum ether (60–90 °C)/diethyl ether 10/1) to afford the target enone product **4**. **4e**: white solid, 99% yield; m.p. 62–63 °C; ¹H NMR (400 MHz, CDCl₃, 25 °C): δ = 7.39 and 7.20 (each s, 2:1H, aromatic CH), 6.60 (t, 1H, CH), 4.99 and 4.92 (each m, 2:2H, OCH₂), 2.37 ppm (s, 6H, CH₃); ¹³C{¹H} NMR (100 MHz, CDCl₃, 25 °C): δ = 191.3 (C_q, C=O), 140.2 (C_q), 139.2 (CH), 138.3 and 138.2 (C_q), 134.4 and 126.6 (aromatic CH), 76.8 and 75.4 (OCH₂), 21.4 ppm (CH₃); HRMS calcd for C₁₂H₁₁O₂ [M–CH₃]⁺: 187.0759; found: 187.0767.



Scheme 3. Calculated reaction pathways. The geometries were fully optimized at the B3LYP/6-311+G** level. The relative free energies ΔG (298 K) are in kcal mol⁻¹.

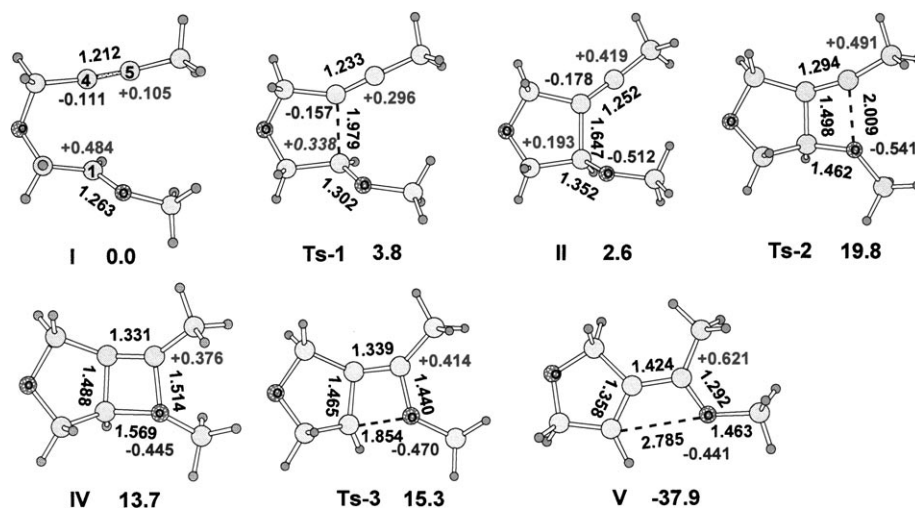


Figure 1. Optimized transition states and the intermediates with selected bond lengths [Å] and NBO charges (in italics). The geometries were fully optimized at the B3LYP/6-311+G** level. The relative free energies ΔG (298 K) are in kcal mol⁻¹.

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