Letter

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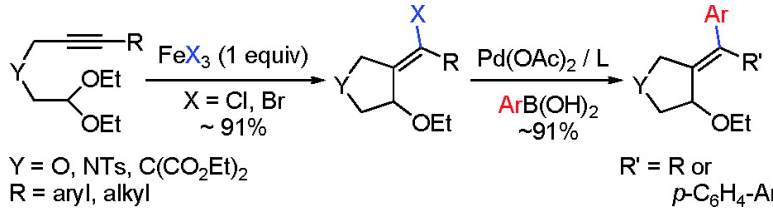

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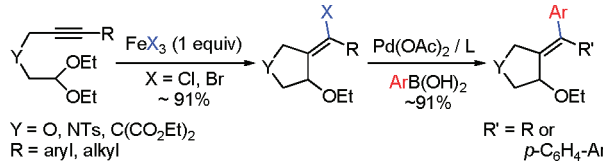
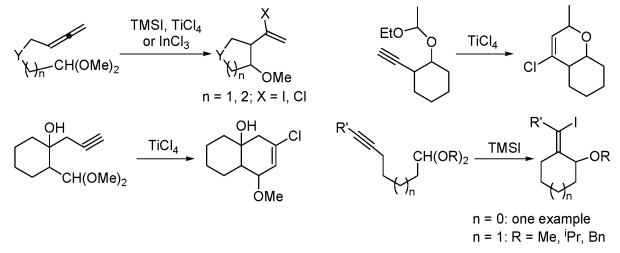
ABSTRACT



$FeCl_3$- and $FeBr_3$-promoted cyclization/halogenation of alkynyl diethyl acetals has been efficiently realized, selectively affording (*E*)-2-(1-halobenzylidene or alkylidene)-substituted five-membered carbo- and heterocycles which were then efficiently transformed to vinylarenes by Suzuki coupling. The present protocol has provided a new alternative route to vinylic C−Cl and C−Br bond formation.

Acetal functional groups are usually used to protect carbonyls in organic synthesis,[1,2] and acetal derivatives have exhibited versatile chemistry in carbon−carbon bond formation due to easy deprotection and transformation of the acetal functions by acid catalysis.[3,4] Lewis acid-promoted carbon−carbon bond-forming cyclization of alkenyl-aldehyde acetals is well-known (Scheme 1).[5] $TiBr_4$-promoted reactions of alkenyl-aldehyde acetals with silyl enol ethers formed five-membered rings.[6] $SnCl_4$- and $TiCl_4$-catalyzed acetal-initiated polyene cyclization produced terpenoids.[7] Benzaldehyde acetal was used in BCl_3-involved organocatalysis.[8] Allenyl-aldehyde dimethyl acetals reacted with iodotrimethylsilane TMSI, $TiCl_4$, or $InCl_3$ to afford 2-(1-halovinyl)cycloalkyl methyl ethers.[9] $TiCl_4$-promoted cyclization of ethynylcyclo-hexanol acetals[10] and β-hydroxy alkynyl acetals[11] generated chloro-hydropyrans and 1-chlorocyclohexenes, respectively. TMSI-

Scheme 1. Lewis Acid Promoted C−C Bond-Forming Cyclization/Halogenation of Acetals (LA ≥ 1.0 equiv)



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(3) For selected recent reports on the reactions of acetals, see: (a) Ratnikov, M. O.; Tumanov, V. V.; Smit, W. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9739. (b) Umebayashi, N.; Hamashima, Y.; Hashizume, D.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4196. (c) Zhao, Y.-J.; Loh, T.-P. *Org. Lett.* **2008**, *10*, 2143.

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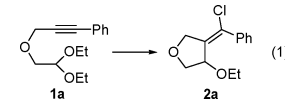
induced cyclization of 6-alkynyl acetals formed iodobenzylidene cyclohexyl methyl ethers.[12] $SnCl_4$-initiated ring-enlarging cyclopentene annulation was realized with silyl ether alkynyl-aldehyde dimethyl acetals.[13] Recently, iron salts have emerged as alternative and promising catalysts for a wide range of organic transformations due to their advantages such as low cost, nontoxicity, good stability, and easy manner to handle.[14−18] FeX_3 (X = Cl, Br)-catalyzed Prins-type cyclization between homopropargylic alcohol and aldehydes formed 2-alkyl-4-halo-5,6-dihydro-*2H*-pyrans,[19a] and FeX_3-promoted coupling of alkynes and aldehydes afforded 1,5-dihalo-1,4-dienes.[19b] Noniron Lewis acid-catalyzed cyclization of alkynes and aldehydes or alkynyl carbonyls have also been documented.[20] Intrigued by the versatile interactions of Lewis acids with acetals, we envisioned that the reactions of $FeCl_3$ with acetals might generate active species which can initiate new reactions. Herein, we report $FeCl_3$- and $FeBr_3$-promoted cyclization/halogenation of alkynyl diethyl acetals to form (*E*)-2-(l-halobenzylidene or alkylidene)-substituted five-membered carbo- and heterocycles.

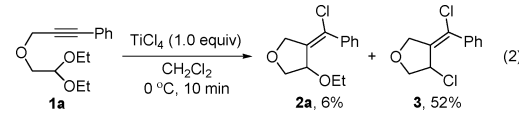
In our initial studies, the reaction of alkynyl acetal **1a** was chosen to screen the reaction conditions (Table 1). Treatment of **1a** with 10 mol % $FeCl_3$ in CH_2Cl_2 at ambient temperature for 0.5 h afforded the desired product **2a** in <19% yield (entry 1) with a low conversion of **1a**. Increasing the amount of $FeCl_3$ to 0.33 equiv (total chlorine ~1.0 equiv), the same reaction formed **2a** with (*E*)-configuration in 60% isolated yield with incomplete conversion of **1a** within 30 min (entry 2), suggesting that the second and/or third chlorides in the promoter took part in the reaction. A trace amount of isomeric **2a** (<5%), presumably the six-membered product of Martín-type,[19] was detected by GC-MS analysis (see Supporting Information), but it was not successfully isolated. Further increasing the amount of $FeCl_3$ enhanced the formation of **2a** (entries 5−10). It was found that the 1:1 molar ratio reaction of **1a** with $FeCl_3$ proceeded more efficiently at 0 °C than at other temperatures, reaching a 77% yield for **2a**. The reaction also worked well in toluene (entry 11) but less efficiently in THF and water (entries 12 and 13).

Table 1. Screening of the Reaction Conditions[a]



entry	cat./equiv	solvent	temp	time (h)	yield (%)[b]
1	$FeCl_3$/0.10	CH_2Cl_2	rt	0.5	<19[c]
2	$FeCl_3$/0.33	CH_2Cl_2	rt	0.5	60
3	$FeCl_3$/0.33	CH_2Cl_2	reflux	0.5	59
4	$FeCl_3$/0.33	CH_2Cl_2	0	0.5	54
5	$FeCl_3$/0.50	CH_2Cl_2	rt	0.5	66
6	$FeCl_3$/0.50	CH_2Cl_2	0	0.5	68
7	$FeCl_3$/0.70	CH_2Cl_2	0	0.5	74
8	$FeCl_3$/1.00	CH_2Cl_2	rt	0.5	73
9	$FeCl_3$/1.00	CH_2Cl_2	reflux	0.5	50
10	**$FeCl_3$/1.00**	**CH_2Cl_2**	**0**	**0.5**	**77**
11	$FeCl_3$/1.00	toluene	0	0.5	67
12	$FeCl_3$/1.00	THF	0	5	20
13	$FeCl_3$/1.00	H_2O	rt	0.5	<1[c]
14	$CuCl_2{\cdot}2H_2O$/1.00	CH_2Cl_2	rt	12	
15	$FeCl_2$/1.00	CH_2Cl_2	reflux	12	
16	$TiCl_4$/1.00	CH_2Cl_2	0	0.2	6[d]
17	$SnCl_4$/1.00	CH_2Cl_2	0	0.5	52

[a] Conditions: **1a**, 0.5 mmol; solvent, 5 mL. [b] Isolated yields of **2a**. [c] Determined by GC analysis. [d] See eq 2.



$CuCl_2{\cdot}2H_2O$ and $FeCl_2$ did not initiate the reaction (entries 14 and 15). Unexpectedly, treatment of **1a** with $TiCl_4$ (1.0 equiv) afforded **2a** (6%) and the dichloro product **3** (52%) within 10 min (entry 16 and eq 2). However, the reaction of **1a** with $SnCl_4$ (1.0 equiv) exclusively gave **2a** as the product (52% yield, entry 17). Thus, the reaction conditions were optimized to: **1a** (0.5 mmol), $FeCl_3$ (1.0 equiv), CH_2Cl_2 as the solvent, 0 °C/0.5 h under a nitrogen atmosphere.

The reactions of $FeCl_3$ and $FeBr_3$ with other alkynyl acetals were then carried out to define the protocol generality (Table 2). In all the cases, the (*Z*)-products were not isolated in a measurable amount. With *O*-linked alkynyl acetals as the substrates, the reactions produced the (*E*)-products **2a**−**i** in 61−91% yields (entries 1−9). Substituents on the aryl group of the alkynyl moiety did not obviously affect formation of the desired products (entries 1−8), but an adjacent 2-substituent such as 2-methoxy lessened generation of the product such as **2i** (entry 9). Increasing the steric hindrance of the linker chain dramatically decreased the reaction efficiency (entry 10) or made the reaction complicated (entry 11). Benzoyl alkynyl acetal (**1l**) also underwent a complicated

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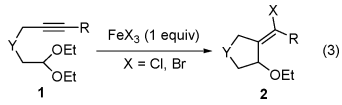
Table 2. FeX_3-Promoted Cyclization/Halogenation of **1**[a]

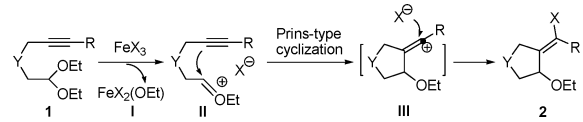


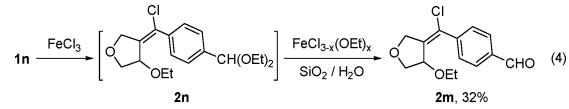
entry	substrate	yield (%)[b]	entry	substrate	yield (%)[b]
1	**1a**	**2a** (77)	13	**1m**	**2m** (54)
2	**1b**	**2b** (78)	14	**1n**	**2m** (32)
3	**1c**	**2c** (82)	15	**1o**	**2o** (77)
4	**1d**	**2d** (91)	16	**1p**	**2p** (45)
5[c]	**1e**	**2e** (76)	17	**1q**	**2q** (78)
6	**1f**	**2f** (76)	18	**1r**	**2r** (78)
7	**1g**	**2g** (75)	19	**1s**	**2s** (0)
8	**1h**	**2h** (75)	20	**1t**	**2t** (71)
9	**1i**	**2i** (61)	21[f]	**1a**	**2aa** (73)
10	**1j**	**2j** (18)	22[f]	**1p**	**2pp** (50)
11	**1k**	**2k** (-)[d]	23[f]	**1q**	**2qq** (90)
12[e]	**1l**	**2l** (-)[d]	24[f]	**1t**	**2tt** (75)

[a] Conditions: **1a**, 0.5 mmol; $FeCl_3$, 0.5 mmol; CH_2Cl_2, 5 mL; 0 °C, 10−30 min. [b] Isolated yields in parentheses. [c] rt, 2 h. [d] Complicated. [e] rt, 12 h. [f] $FeBr_3$ (0.5 mmol) instead of $FeCl_3$ was used.

reaction (entry 12). When acetal **1m** was used as the substrate, the desired product **2m** was obtained in 54% yield with the formyl group unchanged (entry 13). Unexpectedly, the reaction of diacetal **1n** also yielded **2m** as the product (32%, entry 14), revealing that the desired product **2n** may be initially formed and then deprotected to **2m** (eq 4). Tosyl-*N*-linked alkynyl acetals (**1o**−**r**) underwent the same type of reactions, affording the desired products **2o**−**r** in 45−78% yields (entries 15−18). It should be noted that the reaction of alkyl-terminated alkynyl acetal **1p** proceeded less efficiently than those of its methyl and aryl analogues **1o**, **1q**, and **1r**. Somehow, benzyl-*N*-linked alkynyl acetal **1s** did not show any reactivity (entry 19). The reaction of aliphatic carbon-linked alkynyl acetal **1t** formed **2t** in 71% yield (entry 20). In the same fashion as using $FeCl_3$ as the promoter, $FeBr_3$-promoted reactions of **1a**, **1p**, **1q**, and **1t** produced bromine-incorporated products **2aa**, **2pp**, **2qq**, and **2tt** in 50−90% yields (entries 21−24). It is noteworthy that $FeCl_3$-promoted reactions of terminal alkynyl acetals or substrates with an additional methylene linker only formed complicated mixtures from which no desired products were successfully isolated.

Scheme 2. Proposed Mechanism





Although an oxocarbenium ion intermediate has never been isolated from Lewis acid promoted reactions of acetals,[6−10,12] a plausible mechanism for $FeCl_3$- and $FeBr_3$-promoted cyclization/halogenation of alkynyl diethyl acetals **1** is proposed in Scheme 2 based on Denmark et al.'s work.[5c,d] $FeCl_3$ abstracts an ethoxy moiety from **1** to form species $FeCl_2(OEt)$ (**I**), oxocarbenium ion **II**, and a chloride anion. A Prins-type cyclization[6] occurs through intramolecular nucleophilic attack of the acetylenic moiety to the cationic carbon atom of **II**, followed by trapping the resultant vinyl cation **III** by the chloride anion, yielding the desired product **2**. Products **2** were fully characterized, and their (*E*)-configuration was further confirmed by the NOESY experiments of **2f** and **2q** (see Supporting Information) and X-ray crystallographic structural determination of **2o** (Figure 1). The high or exclusive (*E*)-stereoselectivity for **2** is attributed to the steric hindrance from the ethoxy moiety and the ring strain of the newly formed five-membered cyclic systems. Martín's reactions of FeX_3-catalyzed homopropargylic alcohol (a terminal alkyne) with aldehydes usually gave the six-membered ring products, and only in one case a type **2** product was obtained.[19a] Aliphatic,[21a−c] vinylic,[19,21d] and aromatic[21e] C−Cl bond-forming reactions have played an important role in organic synthesis. Thus, our work provides an alternative route to five-membered rings with a vinylic C−Cl or C−Br bond from internal alkynyl acetals.

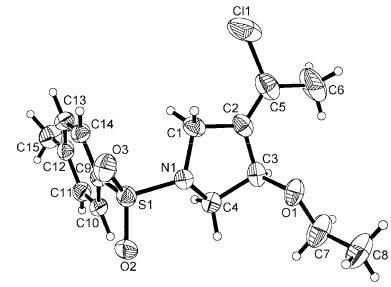
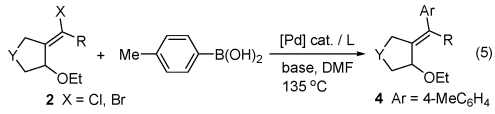


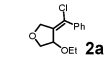
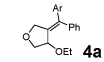
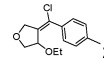
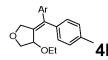
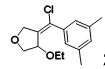
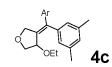
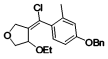
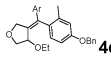
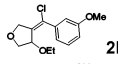
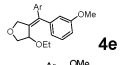
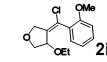
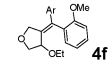
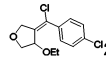
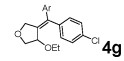
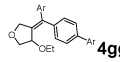
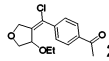
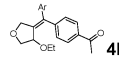
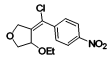
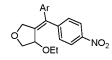
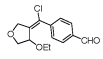
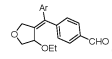
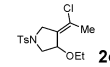
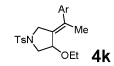
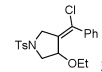
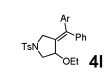
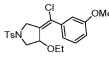
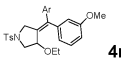
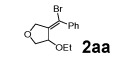
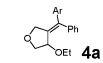
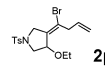
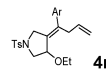
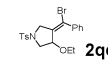
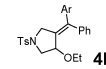
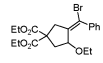
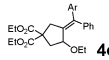
Figure 1. Molecular structure of compound **2o**.

Table 3. Palladium-Catalyzed Coupling of **2**[a]



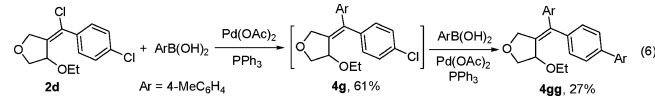
2 X = Cl, Br

4 Ar = 4-MeC$_6$H$_4$

entry	substrate	method	time (h)	product	yield (%)[b]
1	 **2a**	A	12	 **4a**	90
2	 **2b**	A	8	 **4b**	87
3	 **2c**	A	12	 **4c**	84
4	 **2g**	A	12	 **4d**	90[c]
5	 **2h**	A	12	 **4e**	91
6	 **2i**	A	12	 **4f**	62
7	 **2d**	A	12	 **4g**  **4gg**	61 27
8	 **2e**	A	24	 **4h**	27
9	 **2f**	B	2	 **4i**	24
10	 **2m**	B	2	 **4j**	16
11	 **2o**	A	24	 **4k**	62
12	 **2q**	B	12	 **4l**	71
13	 **2r**	B	12	 **4m**	28
14	 **2aa**	A	12	 **4a**	78
15	 **2pp**	B	2	 **4n**	26
16	 **2qq**	B	12	 **4l**	79
17	 **2tt**	B	24	 **4o**	71

[a] Conditions: **2**, 0.3 mmol; *p*-tolylboronic acid, 1.5 equiv; Cs_2CO_3, 2.0 equiv; DMF, 1 mL; 5.0 mol % $Pd(OAc)_2$; 135 °C. (A) 20 mol % PPh_3; (B) 5 mol % XantPhos. [b] Isolated yields. [c] *Z*/*E* = 4:1 by ^{1}H NMR.

Next, arylation of **2** with *p*-tolylboronic acid was tried in DMF at 135 °C by using $Pd(OAc)_2/PPh_3$ or XantPhos as the catalyst in the presence of Cs_2CO_3 base (Table 3 and eq 5). The Suzuki coupling reactions of **2a**−**c** and **2g**−**i** proceeded efficiently affording the desired products **4a**−**f** in 62−91% isolated yields (entries 1−6). When the dichloro substrate, i.e., **2d** bearing both vinylic and aromatic C−Cl bonds, was applied, its reaction produced the desired product **4g** (61%) as well as the double-arylation product **4gg** (27%) (entry 7). It is obvious that **4gg** was generated from **4g** under the palladium catalysis conditions (eq 6). An electron-withdrawing substituent on the aryl group of **2** decreased the reactivity of the substrates such as **2e**, **2f**, and **2m** and led to inefficient formation of the desired products (entries 8−10). It



2d Ar = 4-MeC$_6$H$_4$ **4g**, 61% **4gg**, 27%

is noteworthy that **2f** and **2m** did not undergo the coupling reactions in the presence of PPh_3, while the same reactions occurred to form **4i** and **4j** in 24% and 16% yields with XantPhos as the ligand (entries 9 and 10), respectively. Substrate **2j** is thermally unstable and thus could not be applied in the coupling reaction. The tosyl-*N*-heterocyclic substrates exhibited much lower reactivity than their *O*-heterocyclic analogues. Thus, the reactions of **2o** and **2q** afforded the desired products **4k** and **4l** in 62−71% yields (entries 11 and 12), but the reaction of **2r** only gave **4m** in 28% yield (entry 13). Compounds **2p** and **2t** showed no reactivity, but the bromide substrates **2aa**, **2qq**, and **2tt** underwent the coupling reactions as efficiently as their chloride analogues (entries 14, 16, and 17). Compound **2pp** also demonstrated a low reactivity (entry 15). As alternatives to the vinylic C−Cl substrates, the bromide analogues of type **2** have shown promising applications in vinylic C−C bond formation.[22]

In conclusion, $FeCl_3$- and $FeBr_3$-promoted cyclization/halogenation of alkynyl diethyl acetals has been efficiently realized, selectively affording (*E*)-2-(1-halobenzylidene or alkylidene)-substituted five-membered carbo- and heterocycles. The present protocol has provided a new alternative route to vinylic C−Cl and C−Br bond formation.

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Supporting Information Available: Experimental details, analytical data, copies of NMR spectra, and X-ray crystallographic data for **2o**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) (a) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461. (b) Chrovian, C. C.; Knapp-Reed, B.; Montgomery, J. *Org. Lett.* **2008**, *10*, 811. (c) Ng, S.-S.; Ho, C.-Y.; Schleicher, K. D.; Jamison, T. F. *Pure Appl. Chem.* **2008**, *80*, 929.