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A New Catalytic Prins Cyclization Leading to Oxa- and Azacycles

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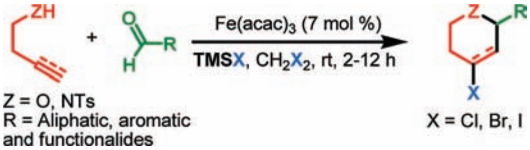
ABSTRACT



A new Prins cyclization process that builds up one carbon−carbon bond, one heteroatom-carbon bond, and one halogen-carbon bond, (in an oxa- and azacycle) relies on an iron catalyst system formed from Fe(acac)$_3$ and trimethylsilyl halide. The method displays a broad substrate scope and is economical, environmentally friendly, and experimentally simple. This catalytic method permits the construction of chloro, bromo and iodo heterocycles, by the suitable combination of iron(III) source, the corresponding trimethylsilyl halide and the solvent, in high yields.

The six membered ring heterocycles of nitrogen and oxygen are structural motifs of particular interest in synthetic and medicinal chemistry, as they are present in a large number of bioactive compounds.[1] Among existing methodologies, the Prins cyclization has emerged as a powerful tool in the synthesis of this type of heterocycles.[2]

Typically, the Prins cyclization requires the use of stoichiometric amounts of a Lewis acid and mixed acetals as starting materials, being used in the production of a large number of organic compounds.[3] On the other hand, there has been an increasing demand for environmentally friendly and sustainable chemical processes.[4] This inspired us to develop alkyne-Prins and aza-alkyne-Prins cyclizations using stoichiometric iron (III) halides as the promoter, generating in situ the acetal intermediates leading to the corresponding halo-heterocycles.[5] These methods are distinguished by the low cost, readily availability of components, and environmentally benign character of the iron salts used, in combination with the high reaction rates observed and mild condi-

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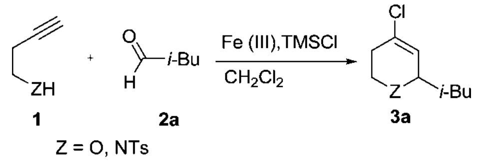
10.1021/ol802593u CCC: \$40.75

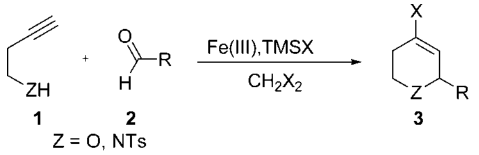
Table 1. Iron-Catalyzed Alkyne-Prins Cyclization of Homopropargylic Derivatives (**1**) with Isovaleraldehyde (**2a**)[a]



entry	Z	$FeCl_3$ (mol %)	$Fe(acac)_3$ (mol %)[b]	TMSCl (equiv)	yield (%)[c]
1	O or NTs	0	0	1.0	0
2	O	10	0	0.5	70
3	O	10	0	1.0	88
4	O	10	0	1.2	90
5	O	7	0	1.2	90
6	O	5	0	1.2	80
7	O	0	10	1.2	85
8	O	0	7	1.2	90
9	O	0	5	1.2	78
10	NTs	10	0	1.0	70
11	NTs	10	0	1.0	80[d]
12	NTs	0	10	1.0	50[e]
13	NTs	0	7.5	1.5	80[d]

[a] Reaction conditions: **1** (1.0 equiv), **2** (1.0 equiv), [Fe] (0.07 equiv), TMSCl (1.2 equiv), CH_2Cl_2, rt, 2−12 h. [b] acac = acetylacetonate. [c] Yield of the pure product after silica-gel chromatography. [d] 1.5 equiv of **2**. [e] Conversion of 80%.

Table 2. Iron-Catalyzed Construction of Chloro and Bromo Heterocycles



entry	Z	X	R	TMSCL (equiv)	yield (%)[a]
1	O or NTs	Cl	*i*-Bu	1.0	0[b]
2	O or NTs	Br	*i*-Bu	1.0	0[b]
3	O	Cl	*i*-Bu	1.2	90[c]
4	NTs	Cl	*i*-Bu	1.5	80[c]
5	NTs	Cl	*c*-C_6H_{11}	1.5	79[c]
6	NTs	Cl	Bn	1.5	65[c]
7	NTs	Br	*i*-Bu	1.5	87[c]
8	NTs	Br	*c*-C_6H_{11}	1.5	81[c]
9	NTs	Br	Bn	1.5	88[c]
10	O	Cl	$CH_2{=}CH(CH_2)_2$-	1.0	30[d]
11	O	Cl	$AcO(CH_2)_3$-	1.0	37[d]
12	NTs	Cl	Bn	1.5	70[d]
13	NTs	Br	*i*-Bu	1.5	85[d]
14	O	Br	*i*-Bu	1.0	85[d]

[a] Yield of the pure product after silica-gel chromatography. [b] Control experiment without iron source. [c] $FeCl_3$ (0.07 equiv) as iron source. [d] $Fe(acac)_3$ (0.07 equiv) as iron source.

tions. Encouraged by these results, we have made considerable efforts to replace stoichiometric methods by catalytic processes, being the halide source our first concern.

It has been reported that silicon is one of the most oxyphilic elements, and it has been used as additive in several catalytic process.[6] On the other hand, Baba and co-workers reported that a combination of $InCl_3$ and chlorotrimethylsilane (TMSCl) acts a catalyst for the Sakurai-Hosomi reaction.[7] More recently, Loh et al. have reported the synthesis of 4-halo tetrahydropyran rings using trimethylsilyl halides as additives and indium salts as catalyst.[8] Herein, we report the first iron-catalyzed Prins- and aza-Prins cyclizations. The catalytic system, which is obtained by combining readily available iron salts with trimethylsilyl halides,[9] is widely applicable and promotes the construction of substituted six membered oxa- and aza-cycles.

As a model study for the optimization of the reaction conditions, we first chose the alkyne-Prins cyclization of homopropargyl derivatives (**1**) and isovaleraldehyde (**2a**) to give the unsaturated six membered ring heterocycles **3a**. We tested tetrabutylammonium chloride and TMSCl as the halide source in the presence of catalytic $FeCl_3$ (10 mol %) in CH_2Cl_2 at room tempereature and found, that the Prins cyclization was possible only with TMSCl providing the desired product **3a** in good yield (Table 1, entry 2). Control experiments confirmed that in the absence of the iron salts no product was obtained (Table 1, entry 1).[10] We found that using 1.2 equivalents of TMSCl it was possible to obtain better yields (Table 1, compare entries 2, 3 and 4). When only 0.5 equivalents of TMSCl were used, **3a** was formed in lower yield (Table 1, entry 2), and no significant improvement was observed with 1.5 equivalents. With respect to the catalyst loading, 7 mol % of the iron salt was found to be optimal. The use of 5 mol% of the iron salt furnished **3a** with lower yield (80%, Table 1, entry 6). After these good results, $Fe(acac)_3$ was chosen for further investigations as it is less hygroscopic and easier to handle than $FeCl_3$. Interestingly, the related iron species was as efficient as $FeCl_3$ (Table 1, entries 7, 8 and 9).[11]

Encouraged by these results, we next investigated the scope of the process regarding the aldehyde type. We tested aliphatic and aromatic aldehydes under the optimized reaction conditions, using homopropargyl derivatives (**1**) as unsatur-

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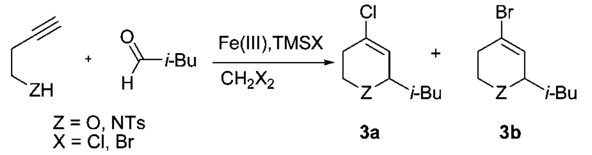
(10) Using a catalytic amount of $FeCl_3$ (0.1 equiv), we obtained the corresponding acetal as a single product in good yield (80%). See ref 5.

(11) When this cyclization was performed, using $Fe(acac)_3$ and isovaleraldehyde, in the presence of air and moisture the target product was obtained in a remarkable 70% yield.

Table 3. Halogen Exchange with Halogenated Solvents in the Oxa- and Aza-alkyne Prins Cyclization[a]

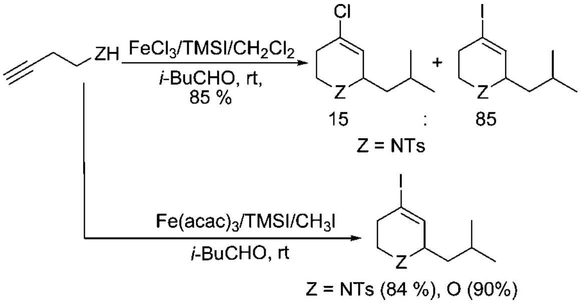


entry	Z	solvent/ TMSX	$FeBr_3$ 3a:3b	$FeCl_3$ 3a:3b	$Fe(acac)_3$ 3a:3b
1	O	CH_2Cl_2 TMSCl	80:20[b]	100:0	100:0
2	O	CH_2Cl_2 TMSBr	25:75	25:75	20:80
3	O	CH_2Br_2 TMSBr	0:100	0:100	0:100
4	O	CH_2Br_2 TMSCl	30:70	35:65	40:60
5	NTs	CH_2Cl_2 TMSCl	85:15	100:0	100:0
6	NTs	CH_2Br_2 TMSCl	30:70	40:60	40:60

[a] Determined by ^1H NMR. [b] Ratio **3a:3b**, 85:15 at 0°

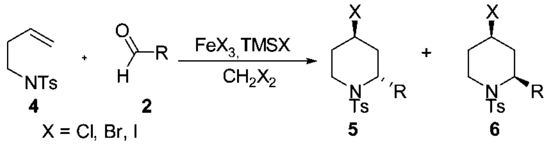
ated compounds. In general, the corresponding heterocycles (**3**) were obtained in high yields under the previously optimized conditions. The current iron-catalyst system efficiently promoted the alkyne-Prins cyclization with different types of aldehydes, in both the oxa- and aza- version (30−90% yield, Table 2, entries 3−14). Importantly, the iron catalyst also proved to be efficient in the cyclization process of more challenging aldehydes bearing functional groups such as double bonds and acetates, but with lower yield (Table 2, entries 10 and 11).[12] Furthermore, the method permits the construction of bromo heterocycles by using TMSBr as additive (Table 2, entries 7, 8, 9, 13, and 14).

Scheme 1. Synthesis of Iodo-Substituted 6-Membered Heterocycles



A halide exchange with halogenated solvents, using stoichiometric amounts of iron(III) halides as promoters, in oxa- and aza-alkyne Prins cyclizations have been observed. The process is specific for alkynes, since during the Prins cyclization using both homoallyl *N*-tosyl amines and homoallyl alcohols, the halide participation from the halogenated solvent was absent.[5,5,13] As shown in Table 3, we tested the halogen exchange with halogenated solvents in the current iron-catalyst process. In general, dibromomethane was more reactive than dichloromethane and gave the corresponding dihydropyran (Table 3, entries 1−4) and tetrahydropyridine (Table 3, entries 5 and 6) products with higher halide exchange. This halide exchange ranged between 25% for CH_2Cl_2 (Table 3, entry 2) and 65% for CH_2Br_2 (Table 3, entry 4). Surprisingly, the combination $FeCl_3$/TMSBr/CH_2Br_2 led exclusively to the bromotetrahydropyran (Table 3, entry 3). The catalytic system using $Fe(acac)_3$ as iron source, and the same halogen in TMSX and CH_2X_2 avoided the halogen exchange to give the desired product (Table 3, entries 1, 3 and 5).

Table 4. Iron-Catalyzed Aza-Prins Cyclization of Homoallyl Tosyl Amines[a]



entry	X	FeX_3 [mol %]	$Fe(acac)_3$ [mol %]	R	5:6[b]	yield (%)
1	Cl	10	0	*i*-Bu	94:6	95
2	Cl	10	0	*c*-C_6H_{11}	95:5	92
3	Cl	10	0	Bn	84:16	80
4	Br	10	0	*i*-Bu	95:5	95
5	Br	10	0	*c*-C_6H_{11}	94:6	98
6	Br	10	0	Bn	83:17	86
7	Cl	0	7.5	*i*-Bu	95:5	≥99
8	Cl	0	7.5	Bn	83:17	≥99
9	Br	0	7.5	*i*-Bu	94:6	≥99
10	Cl	0	7.5	$CH_2{=}CH(CH_2)_2$-	95:5	85
11	Cl	0	7.5	$BnO(CH_2)_2$-	95:5	85
12	Cl	0	7.5	$TBSO(CH_2)_7$-	95:5	71[c]
13	Cl	0	7.5	$AcO(CH_2)_3$-		0
14	I	0	7.5	*i*-Bu	95:5	92[d]

[a] Reaction conditions: **4** (1. 0 equiv), **2** (1.5 equiv), [Fe] (0.1 or 0.07 equiv), TMSCl (1.5 equiv), CH_2Cl_2, rt, 2−12 h. [b] Determinated by ^1H NMR. [c] 30% protected as TBS and 41% as alcohol. [d] CH_3I was used as solvent.

This catalytic method also permits the construction of iodo heterocycles, presumably via the in situ generation of the unstable and noncommercial available FeI_3.[14] The optimal solvent for this reaction should be methylene iodide (CH_2I_2) since the use of CH_2Cl_2 leads to a mixture of products. To our delight methyl iodide (CH_3I) could be used as the solvent with excellent results, and thus, avoids the use of CH_2I_2 which has a higher boiling point (181 °C) that complicates the workup (Scheme 1).[15]

The conditions for the iron-catalyzed alkyne-Prins cyclization can also be applied to homoallyl *N*-tosyl amines and homoallyl alcohols as unsaturated heteroatomic species (Table 4 and Table 5, respectively). With *N*-(but-3-enyl)-4-methylbenzenesulfonamide, the iron sources, $FeCl_3$ and $Fe(acac)_3$ catalyzed the cyclization and afforded in both cases

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(12) The reaction does not work with other functional groups as benzyl, THP, or TBS.

(13) Miranda, P. O.; Carballo, R. M.; Ramírez, M. A.; Martín, V. S.; Padrón, J. I. *Arkivoc* **2007**, *iv*, 331–334.

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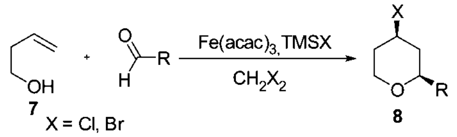
Table 5. Iron-Catalyzed Prins Cyclization of Homoallyl Alcohols[a]

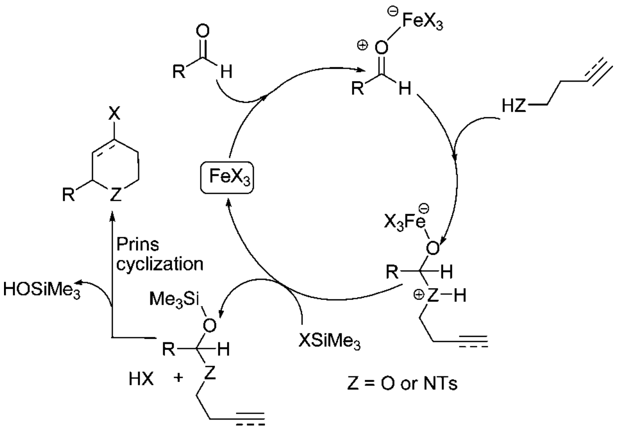


entry	X	R	yield (%)
1	Br	*i*-Bu	88
2	Br	*p*-NO_2Ph	78
3	Cl	$CH_2{=}CH(CH_2)_2$-	70
4	Cl	$AcO(CH_2)_3$-	60
5	Cl	$TBSO(CH_2)_7$-	71[b]
6	Cl	$BnO(CH_2)_2$-	86

[a] Reaction conditions: **7** (1. 0 equiv), **2** (1.0 equiv), [Fe] (0.07 equiv), TMSCl (1.0 equiv), CH_2Cl_2, rt, 2−12 h. [b] 30% protected as TBS and 41% as alcohol

trans-4-halo-2-alkyl tosylpiperidine **5** as the major product in very good yield (Table 4).[5] The aza-Prins cyclization works well with either aliphatic or aromatic aldehydes. The catalysts loadings, 10 mol% of $FeCl_3$ and 7.5 mol% of $Fe(acac)_3$ were found to be optimal (Table 4). The tolerance of functional groups at the aldehyde such as alkene, benzyloxy (BnO) and *tert*-butydimethyllsilyloxy (TBSO), with $Fe(acac)_3$ as the iron source, to the described protocol is remarkable, and much higher than in the alkyne-Prins cyclization (Table 4, entries 10, 11 and 12, respectively). Surprisingly, the benzyl group was stable under the catalytic conditions (Table 4, entry 11).[16] As before the use of $Fe(acac)_3$ as the iron source, with a 7 mol% as catalyst loading led the Prins cyclization of homoallyl alcohol (**7**) with several aldehydes (Table 5). Consistent with the previous results, the cyclization works very well with a wide range of aldehydes; aliphatics, aromatics and functionalides (Table 5). An advantage of the catalytic process, with respect to stoichiometric version, is the tolerance of aldehydes functionalized with double bonds, acetates, or benzyl groups (Table 5, entries 3, 4 and 6).

Scheme 2. Plausible Mechanism for the Iron-Catalyzed Construction of Oxa- and Azacycles Through the Prins Cyclization



The tentative catalytic cycle is depicted in Scheme 2. We reasoned that a plausible catalytic cycle could be readily initiated via an activation of the aldehyde with the iron salt.[17] Its reaction with the corresponding unsaturated nucleophilic species would lead to the acetal precursor.[18] The very high stability of the accumulating iron oxide or nitrogen counterpart, and the fact that the iron salt is the only source of halide, constitute the thermodynamic sink which drives the conversion but demands the use of stochoichiometric or excess amount of iron (III) salts.

Therefore an indirect way to complete a catalytic cycle was devised relying on a ligand exchange between the iron complex and a chlorosilane, regenerating the iron (III) halide due to the more oxyphilic character of the silicon.

In summary, we have developed a novel iron-catalyzed Prins cyclization of γ,δ-unsaturated (alkyne and alkene) amines and alcohols with different substituted aldehydes. The key finding for this protocol is the catalytic effect of a combination of readily available and inexpensive iron source (FeX_3 or $Fe(acac)_3$) and TMSCl. This catalytic method also permits the construction of chloro, bromo and iodo heterocycles by the suitable combination of iron(III) source, the corresponding trimethylsilyl halide and the solvent. Overall, this process builds up one carbon−carbon bond, one heteroatom-carbon bond, one halogen-carbon bond, and a ring in a regioselective and efficient manner. Our results expand the application of iron salts as promising cost-efficient catalysts in organic synthesis. In addition, the asymmetric version, the use of secondary homoallylic and homopropargylic alchohols, and the synthetic application to more structurally complex products are under development and the results will be reported in due course.

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Supporting Information Available: ^1H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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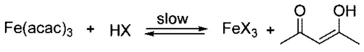
(16) The utilization of stoichiometric ferric chloride in CH_2Cl_2 at room temperature is a suitable method to achieve debenzylations. See: Padrón, J. I.; Vázquez, J. T. *Tetrahedron Asymmetry* **1995**, *6*, 857–858.

(17) It should be emphasized that the storage of R_3SiX generate traces of free acid HX by hydrolysis: Dilman, A. D.; Ioffe, S. L *Chem. Rev.* **2003**, *103*, 733–772. On the other hand, in the presence of free acid HX, $Fe(acac)_3$ is hydrolyzed to the corresponding iron (III) halide: Miller, D. D.; Van Campen, D *Am. J. Clin. Nutr.* **1979**, *32*, 2354–2361.



(18) With 0.1 equiv of $FeCl_3$, the corresponding acetal was isolated only when Z is oxygen.