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Facile Synthesis of Azaspirocycles via Iron Trichloride-Promoted Cyclization/Chlorination of Cyclic 8-Aryl-5-aza-5-tosyl-2-en-7-yn-1-ols

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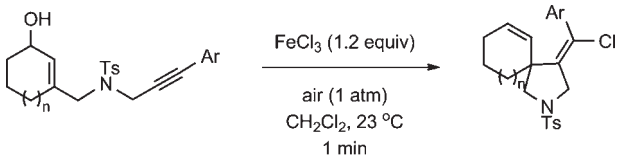
ABSTRACT



A simple and efficient $FeCl_3$-promoted cyclization/chlorination of cyclic tosylamine-tethered 8-aryl-2-en-7-yn-1-ols was observed. The reaction proceeded instantaneously at 23 °C in air to afford (*Z*)-4-(arylchloromethylene)-substituted azaspirocycles in good to excellent yields. This transformation can also be applied to the synthesis of spirocarbocyclic analogues from cyclic 8-aryl-2-en-7-yn-1-ols and $FeCl_3$.

Azaspirocycles are important synthetic building blocks in alkaloid chemistry because such ring skeletons are present in many naturally occurring substances of biological properties.[1] Many synthetic methods, as the key step, have been developed in pursuit of these structures, including the platinum(II)-catalyzed intramolecular cyclization of cyclic enesulfoamides bearing an alkyne tether,[2a] the ene-type cyclization of cyclic nitrogen-tethered 1,7-enynes catalyzed by the cationic palladium complex,[2b] the samarium(II)-mediated cyclization of unsaturated ketolactams,[2c] the intramolecular radical cyclization of cyclic enamines carrying an alkylbromide,[2d] the palladium-catalyzed transformation of 3,4-dihydro-2-pyridinones carrying a (2-bromophenyl)ethyl substituent,[2e] the ytterbium-catalyzed intramolecular hydroamination of alkenes,[2f] the zirconium-catalyzed cyclization of diallylamines,[2g] and the 1,3-dipolar cycloaddition reactions of azomethine ylides with olefins and acetylenes.[2h–j] Recently, iron complexes have emerged as inexpensive and low-toxicity substitutes for precious metals allowing numerous synthetic transformations of unsaturated systems into useful structure motifs.[3] Although iron(0)-ate complex-catalyzed cycloisomerization of enynes with cyclic alkenes via an Alder-ene reaction affording fused bicycles,[4] iron-catalyzed redox radical cyclization of 1,6-dienes and enynes producing five-membered carbo- or

(1) (a) Yang, L.; Morriello, G.; Prendergast, K.; Cheng, K.; Jacks, T.; Chan, W. S.; Schleim, K. D.; Smith, R. G.; Patchett, A. A. *Biorg. Med. Chem. Lett.* **1998**, *8*, 107. (b) Ma, Z.; Chu, D. T. W.; Cooper, C. S.; Li, Q.; Fung, A. K. L.; Wang, S.; Shen, L. L.; Flamm, R. K.; Nilius, A. M.; Alder, J. D.; Meulbroek, J. A.; Or, Y. S. *J. Med. Chem.* **1999**, *42*, 4202. (c) Makovec, F.; Peris, W.; Revel, L.; Giovanetti, R.; Mennuni, L.; Rovati, L. C. *J. Med. Chem.* **1992**, *35*, 28. (d) Dake, G. *Tetrahedron* **2006**, *62*, 3467. (e) Li, M; Dixon, D. J. *Org. Lett.* **2010**, *12*, 3784.

(2) (a) Harrison, T. J.; Patrick, B. O.; Dake, G. R. *Org. Lett.* **2007**, *9*, 367. (b) Hatano, M.; Mikami, K. *J. Am. Chem. Soc.* **2003**, *125*, 4704. (c) Guazzelli, G.; Duffy, L. A.; Procter, D. J. *Org. Lett.* **2008**, *10*, 4291. (d) Aurrecoechea, J. M.; Coy, C. A.; Patiño, O. J. *J. Org. Chem.* **2008**, *73*, 5194. (e) Satyanarayana, G.; Maier, M. E. *J. Org. Chem.* **2008**, *73*, 5410. (f) Riegert, d.; Collin, J.; Meddour, A.; Schulz, E.; Trifonov, A. *J. Org. Chem.* **2006**, *71*, 2514–2517. (g) Yamaura, Y.; Hyakutake, M.; Mori, M. *J. Am. Chem. Soc.* **1997**, *119*, 7615. (h) Sureshbabu, A. R.; Raghunathan, R.; Satiskumar, B. K. *Tetrahedron Lett.* **2009**, *50*, 2818. (i) Prasad, T. A. A.; Vithiya, B. S. M.; Ignacimuthu, S. *Pharma Chem.* **2011**, *3*, 293. (j) Subramaniyan, G.; Raghunathan, R *Tetrahedron* **2001**, *57*, 2909.

(3) (a) Correa, A.; Mancheño, O. G.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108. (b) Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3317. (c) Fürstner, A.; Martin, R.; Krause, H.; Seidel, G.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 8773. (d) Fürstner, A.; Martin, R. *Chem. Lett.* **2005**, *34*, 624. (e) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217. (f) Sherry, B. D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500. (g) Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 5858. (h) Volla, C. M. R.; Vogel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 1305. (i) Lu, Z.; Chai, G.; Ma, S. *J. Am. Chem. Soc.* **2007**, *129*, 14546. (j) Langlotz, B. K.; Wadepohl, H.; Gade, L. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 4670. (k) Shaikh, N. S.; Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 2497.

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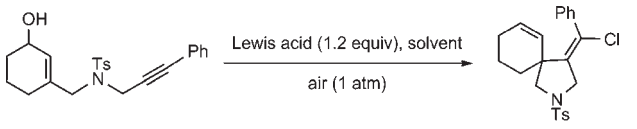
heterocycles,[5] $FeCl_3$-promoted coupling of alkynes and aldehydes giving 1,5-dihalo-1,4-dienes,[6] and ironhalide-promoted cyclization/halogenation of alkynyl diethyl acetals generating arylhalomethylene-substituted five-membered cycles have been reported,[7] a general iron trichloride-promoted intramolecular cyclization of tosylamine-tethered 8-aryl-2-en-7-yn-1-ols to produce azaspirocycles has yet to be developed. We have now demonstrated that $FeCl_3$ can be applied toward the stereospecific synthesis of (*Z*)-4-(arylchloromethylene)-substituted azaspirocycles by treatment of cyclic 8-aryl-5-aza-5-tosyl-2-en-7-yn-1-ols with 1.2 equiv of $FeCl_3$. In this transformation, activation of the hydroxyl group of the enynols by $FeCl_3$ followed by a subsequent *anti*-addition of the allylic group and a chloride ion across the alkyne gave the azaspirocycles. Moreover, the $FeCl_3$-promoted cyclization/chlorination can be extended to the synthesis of carbospirocyclic analogues from cyclic 8-aryl-2-en-7-yn-1-ols.

Table 1. Optimizing the Reaction Conditions



1a **2a**

entry	Lewis acid	solvent	temp (°C)	time	yield (%)
1	$FeCl_3$	CH_2Cl_2	23	1 min	83
2	$FeCl_3$	CH_2Cl_2	0	3 min	72
3	$AlCl_3$	CH_2Cl_2	23	1 min	67[a]
4	$TiCl_4$	CH_2Cl_2	23	0.5 h	17[b]
5	$SnCl_4$	CH_2Cl_2	23	0.5 h	27
6	$ZnCl_2$	CH_2Cl_2	23	48 h	0
7	$Fe(NO_3)_3 \cdot 9H_2O$	CH_2Cl_2	23	48 h	0
8	$FeCl_3$	DCE	23	1 min	74
9	$FeCl_3$	DBE	23	2 h	72
10	$FeCl_3$	THF	23	26 h	23
11	$FeCl_3$	CH_3CN	23		0

[a] *Z*/*E* = 6:1 (determined by 400 MHz ^{1}H NMR analysis of the crude reaction mixture). [b] *Z*/*E* = 13:1 (determined by 400 MHz ^{1}H NMR analysis of the crude reaction mixture).

The requisite cyclic 8-aryl-5-aza-5-tosyl-2-en-7-yn-1-ols **1** were prepared starting from addition of lithiated dimethylsufide to 3-isobutoxycyclohex-2-en-1-one in THF at room temperature to generate 3-((methylthio)methyl)cyclohex-2-en-1-one. Treatment of the resultant thioether with methyl iodide in CH_2Cl_2 at reflux afforded 3-(iodomethyl)-cyclohexe-2-en-1-one. Reaction of the corresponding arylpropagylsulfonamide with 3-(iodomethyl)cyclohexe-2-en-1-one in acetone at room temperature followed by reduction of the resulting enones with $NaBH_4$ in MeOH at 0 °C provided **1** in 43% overall yields.[8] The reaction conditions were optimized for the cyclization/chlorination of the parent compound **1a** as shown in Table 1. The reaction of **1a** with 1.2 equiv of $FeCl_3$ in CH_2Cl_2 at 23 °C under an atmosphere of nitrogen took place rapidly to produce 4-(chloro(phenyl)-methylene)-2-tosyl-2-azaspiro[4.5]dec-6-ene (**2a**) with (*Z*)-configuration in 84% isolated yield. The (*Z*)-configuration of **2a** was confirmed by X-ray diffraction analysis. If in the air, the reaction also proceeded instantaneously at 23 °C and afforded **2a** in 83% yield (Table 1, entry 1). Thus, the following screening of the reaction conditions was conducted in the air. Lowering the temperature to 0 °C increased the reaction time to 3 min and allowed for the isolation of **2a** in 72% yield (Table 1, entry 2). Moreover, the reaction of **1a** with 1.2 equiv of $FeBr_3$ in CH_2Cl_2 at 23 °C produced a 74% yield of the bromine-incorporated spiropyrrolidine **3** (Figure 1). The use of $AlCl_3$ in CH_2Cl_2 at 23 °C decreased the yield of **2a** to 67% (Table 1, entry 3) and **2a** was formed as a mixture of *Z*- and *E*-isomers in a ratio of 6:1. Of other Lewis acids tested, $TiCl_4$ and $SnCl_4$ were less efficient and provided **2a** in 17[9] and 27% isolated yields, respectively (Table 1, entries 4 and 5), whereas $ZnCl_2$ and $Fe(NO_3)_3 \cdot 9H_2O$ were completely ineffectively even after prolonged reaction at 23 °C (Table 1, entries 6 and 7). In the presence of $FeCl_3$, the use of 1,2-dichloroethane (DCE) and 1,2-dibromoethane (DBE) as solvents gave yields comparable with CH_2Cl_2 (Table 1, entries 8 and 9). On the other hand, the more coordinating solvent, such as THF, required extended reaction time (26 h) at 23 °C, and the desired **2a** was isolated in 23% yield (Table 1, entry 10). Moreover, no desired product was observed when CH_3CN was used (Table 1, entry 11). Thus, the use of $FeCl_3$ (1.2 equiv) in CH_2Cl_2 at 23 °C in the air was found to be efficient and was chosen as the standard reaction conditions. Transition metals, such as platinum,[10] rhodium,[11] and palladium,[12] are well-known catalysts of choice for synthesis of pyrrolidine ring skeletons from enynes. However, these protocols required longer reaction times (3−24 h) and higher reaction temperatures (70−100 °C). Furthermore, cycloisomerization of compound **1a** using 5 mol % of $PPh_3AuCl/AgOTf$ in CH_2Cl_2 at 40 °C under nitrogen for 15 min produced azaspiro[4.5]decenone **4** (Figure 1) in 67% yield as a mixture of two diastereomers.[8a] The current approach for the construction of azaspirocyclic ring systems is achieved without the use of complex catalysts or removable of air and moisture, only requiring 1.2 equiv of $FeCl_3$ in CH_2Cl_2 at room temperature in the air for 1 min.

With the optimal reaction conditions, we next examined the substrate scope of the $FeCl_3$-promoted transformation.

(4) (a) Fürstner, A.; Martin, R.; Majima, K. *J. Am. Chem. Soc.* **2005**, *127*, 12236. (b) Fürstner, A.; Majima, K.; Martín, R.; Krause, H.; Kattnig, E.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 1992.

(5) Taniguchi, T.; Goto, N.; Nishibata, A.; Ishibashi, H. *Org. Lett.* **2010**, *12*, 112.

(6) Miranda, P. O.; Díaz, D. D.; Padrón, J. I.; Ramírez, M. A.; Martín, V. S. *J. Org. Chem.* **2005**, *70*, 57–62.

(7) Xu, T.; Yu, Z.; Wang, L. *Org. Lett.* **2009**, *11*, 2113.

(8) (a) Yeh, M. C. P.; Pai, H. F.; Hsiow, C. Y.; Wang, Y. R. *Organometallics* **2010**, *29*, 160. (b) Lin, M. N.; Wu, S. H.; Yeh, M. C. P. *Adv. Synth. Catal.* **2011**, *353*, 3290.

(9) A mixture of *Z*- and *E*-isomers was formed in a ratio of 13:1.

(10) (a) Miura, T.; Shimada, M.; Murakami, M. *J. Am. Chem. Soc.* **2005**, *127*, 1094. (b) Matsuda, T.; Kadowaki, S.; Murakami, M. *Helv. Chim. Acta* **2006**, *89*, 1672.

(11) (a) Tong, X.; Li, D.; Zhang, Z.; Zhang, X. *J. Am. Chem. Soc.* **2004**, *126*, 7601. (b) Wang, J.; Tong, X.; Xie, X.; Zhang, Z. *Org. Lett.* **2010**, *12*, 5370.

(12) Hatano, M.; Mikami, K. *Org. Biomol. Chem.* **2003**, *1*, 3871.

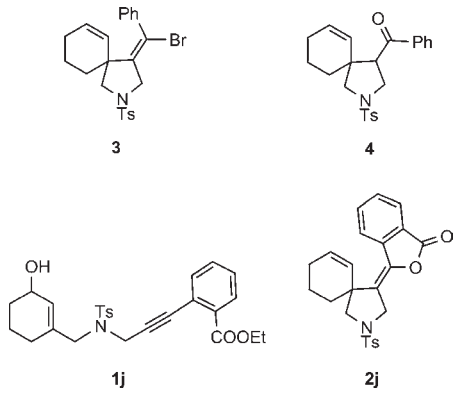
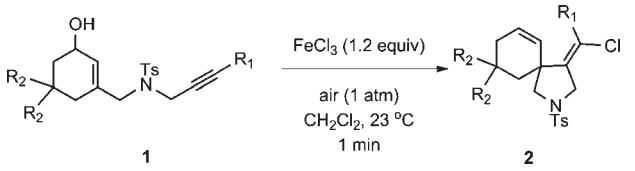


Figure 1. Structures of **3**, **4**, **1j**, and **2j**.

Results of the cyclization/chlorination of cyclic 8-aryl-5-aza-5-tosyl-2-en-7-yn-1-ols **1a**–**g** to produce (*Z*)-4-(aryl-chloromethylene)-substituted spiro[4.5]pyrrolidines **2a**–**g** are listed in Table 2. Both electron-neutral and electron-deficient arenes at the alkyne terminus were proven to be good substrates under the standard reaction conditions, as the yields of desired spiropyrrolidines **2a**–**g** ranged from 80 to 97% (Table 2, entries 1–7). In all cases, the (*E*)-products were not detected on 400 MHz ^{1}H NMR spectra of crude mixtures. It is worth mentioning that $FeCl_3$-mediated intermolecular coupling reactions of benzylic alcohols and arylalkynes afforded alkenyl chlorides as a mixture of *E*- and *Z*-isomers, and no reaction took place when arylalkynes bearing a nitro group were used.[13] However, compound **1c** containing a nitro group at the *para* position of the phenyl ring produced the corresponding spiropyrrodine **2c** in 83% yield (Table 2, entry 3). In addition, a bromine atom on the phenyl ring, for example, **1f**, did not inhibit the activity of $FeCl_3$, as evidenced by the good yield of **2f** (90% yield, Table 2, entry 6). A double substituted methyl group at the C-5 position of the cyclohexenol ring, for example, **1g**, achieved the highest yield (Table 2, entry 7). However, substrate **1h** containing an methoxy group at the C-4 position of the phenyl ring inhibited the activity of $FeCl_3$, and the reaction failed to give any desired products. A mixture of unidentified products was formed. Unfortunately, the reaction of the substrate with a terminal alkyne, for example, **1i**, resulted in decomposition of the starting substrate. Interestingly, substrate **1j** (Figure 1), bearing an *o*-carbethoxyphenyl substituent on the alkyne, reacted smoothly with $FeCl_3$ to afford azaspirocyclic lactone **2j** (Figure 1) in 80% isolated yield.

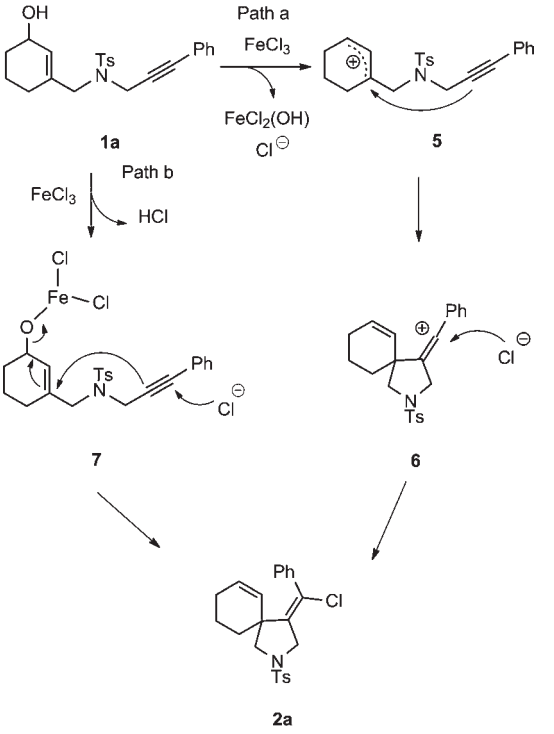
Stepwise (path a) and concerted (path b) pathways are speculated in Scheme 1. Detachment of the hydroxyl group

Table 2. $FeCl_3$-Promoted Cyclization/Chlorination of Various Cyclic 8-Aryl-5-aza-5-tosyl-2-en-7-yn-1-ols



entry	substrate	R_1	R_2	product	yield (%)
1	**1a**	phenyl	H	**2a**	83
2	**1b**	4-methylphenyl	H	**2b**	80
3	**1c**	4-nitrophenyl	H	**2c**	83
4	**1d**	3-carbethoxyphenyl	H	**2d**	89
5	**1e**	4-phenylphenyl	H	**2e**	89
6	**1f**	4-bromophenyl	H	**2f**	90
7	**1g**	phenyl	CH_3	**2g**	97
8	**1h**	4-methoxyphenyl	H		
9	**1i**	H	H		

Scheme 1. Plausible Mechanism



of **1a** by $FeCl_3$ led to the allylic carbonium **5** (path a). Attack of the alkyne at the allylic carbon generated the vinylic cation **6**.[14] The vinylic cation may be stabilized by delocalization of the positive charge through the adjacent C–C double bond. Trapping of **6** with a chloride ion from the less hindered side produced the spiropyrrolidine **2a** with *Z* selectivity. However, from the observed good yield in the cyclization/chlorination of a strong electron-deficient nitro-substituted substrate **1c** (Table 1, entry 3), it could be suggested that no vinylic cation was formed in

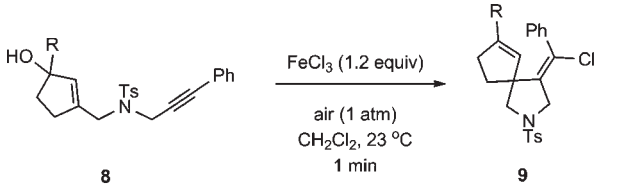
(13) (a) Liu, Z.; Wang, J.; Han, J.; Zhao, Y.; Zhou, B. *Tetrahedon Lett.* **2009**, *50*, 1240. (b) Biswas, S.; Maiti, S.; Jana, U. *Eur. J. Org. Chem.* **2009**, *14*, 2354. (c) Liu, Z.; Wang, J.; Zhao, Y.; Zhou, B. *Adv. Synth. Catal.* **2009**, *351*, 371.

(14) (a) Jin, T.; Uchiyama, J.; Himuro, M.; Yamamoto, Y. *Tetrahedron Lett.* **2011**, *52*, 2069. (b) Jin, T.; Himuro, M.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 5893. (c) Jin, T.; Himuro, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **2010**, *132*, 5590.

this reaction. A concerted reaction pathway is suggested (path b, Scheme 1). Substrate **1a** was activated by $FeCl_3$ to form an iron intermediate **7** and HCl. A subsequent *anti*-addition of the allylic group and a chloride ion (from the less hindered side) across the alkyne produced the spiropyrrolidine derivative **2a** with *Z* selectivity. In the case of **1j** (Figure 1), *anti*-addition of the carbethoxy group and the allylic group across the alkyne gave the azaspirocyclic lactone **2j** (Figure 1).

The chemistry can be applied to the synthesis of (*Z*)-4-(arylchloromethylene)-2-tosyl-2-azaspiro[4.4]non-6-ene derivatives from five-membered ring substrates. Thus, treatment of cyclic 8-aryl-5-aza-5-tosyl-2-en-7-yn-1-ols **8a** and **8b** with 1.2 molar equiv of $FeCl_3$ using the standard reaction conditions (CH_2Cl_2, 23 °C, 1 min, air) afforded spiropyrrolidines **9a** (84%) and **9b** (64%), respectively (Scheme 2). Moreover, the chemistry is general for synthesis of the carbospirocyclic analogues. Aliphatic carbon linked cyclic 8-aryl-2-en-7-yn-1-ols **10a**–**f** were prepared starting from addition of the corresponding 5-lithio-1-arylpent-1-yne to 3-methoxycyclohex-2-en-1-one followed by reduction of the resulting enones with $NaBH_4$ in MeOH to afford cyclic enynols **10a**–**f** in good overall yields. Substrates **10a**–**f** reacted with 1.2 equiv of $FeCl_3$ efficiently to generate chlorinated carbospirocycles **11a**–**f** in 58–86% yields under the standard reaction conditions (Scheme 3).

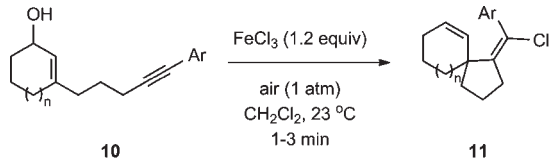
Scheme 2. $FeCl_3$-Promoted Cylization/Chlorination of **8**



8 **9**

a : R = H, 84%
b : R = Ph, 64%

Scheme 3. $FeCl_3$-Promoted Cylization/Chlorination of **10**



10 **11**

a : n = 1, Ar = phenyl 86%
b : n = 1, Ar = 4-phenylphenyl 58%
c : n = 1, Ar = 4-methylphenyl 63%
d : n = 1, Ar = 4-bromophenyl 76%
e : n = 1, Ar = 3-carbethoxyphenyl 86%
f : n = 0, Ar = phenyl 81%

In summary, we have developed an efficient and convenient method for the synthesis of (*Z*)-4-(arylchloromethylene)-substituted spiropyrrolidines from cyclic 8-aryl-5-tosyl-5-aza-2-en-7-yn-1-ols and nontoxic and inexpensive iron trichloride. The reaction has many advantages: they are virtually instantaneous, even in the presence of air, the required $FeCl_3$ loading is 1.2 molar equiv, no extra ligand is necessary, and the yields are good to excellent. This $FeCl_3$-promoted cyclization/chlorination can be applied to the formation of carbospirocycles. The easy formation of spirocycles in an efficient way under mild reaction conditions may have further applications.

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Supporting Information Available. Experimental details, analytical data, copies of NMR spectra, and X-ray crystallographic information files for compounds **2a**, **2c**, **9a**, **11b**, **11c**, and **11d**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.