ORGANIC LETTERS

2012
Vol. 14, No. 7
1830–1833

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

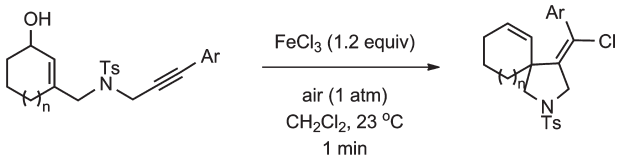
Ming-Chang P. Yeh,* Cheng-Wei Fang, and Hsin-Hui Lin

Department of Chemistry, National Taiwan Normal University, 88 Ding-Jou Road, Section 4, Taipei 11677, Taiwan, Republic of China

cheyeh@ntnu.edu.tw

Received February 22, 2012

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.

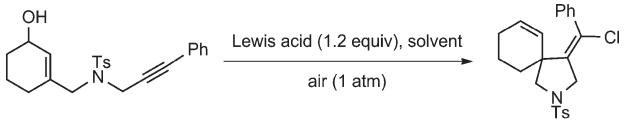
(2) (a) Harrison, T. J.; Patrick, B. O.; Dake, G. R. *Org. Lett.* **2007**, *9*, 367. (b) Hatano, M.; Mikami, K. *J. Am. Chem. Soc.* **2003**, *125*, 4704. (c) Guazzelli, G.; Duffy, L. A.; Procter, D. J. *Org. Lett.* **2008**, *10*, 4291. (d) Aurrecoechea, J. M.; Coy, C. A.; Patiño, O. J. *J. Org. Chem.* **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.

10.1021/ol300434m
Published on Web 03/28/2012

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.

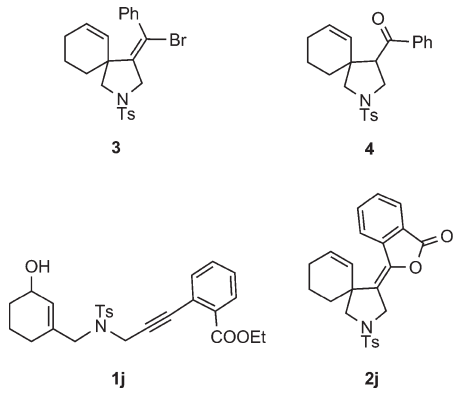
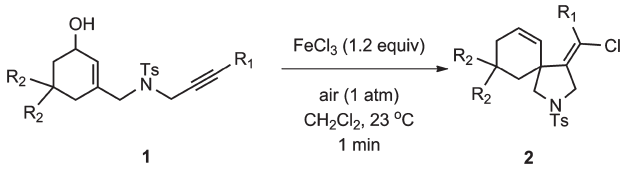


Figure 1. Structures of **3**, **4**, **1j**, and **2j**.

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.

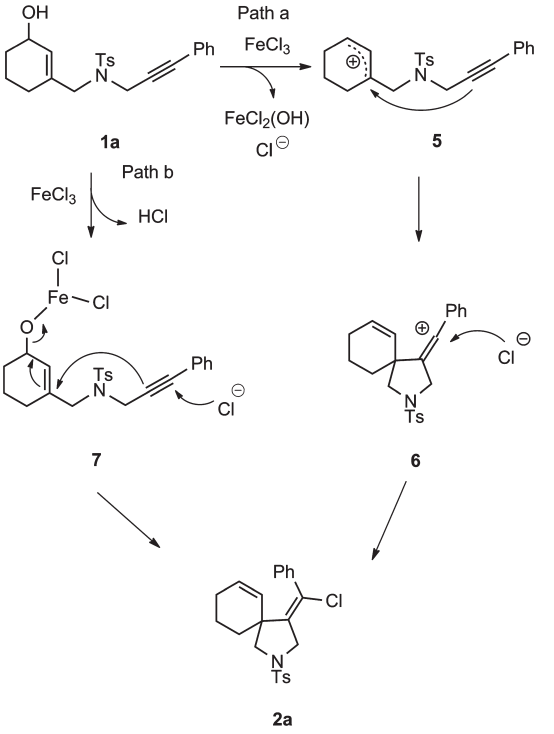
Stepwise (path a) and concerted (path b) pathways are speculated in Scheme 1. Detachment of the hydroxyl group

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

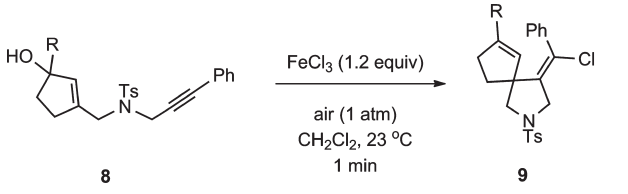
(13) (a) Liu, Z.; Wang, J.; Han, J.; Zhao, Y.; Zhou, B. *Tetrahedon Lett*. **2009**, *50*, 1240. (b) Biswas, S.; Maiti, S.; Jana, U. *Eur. J. Org. Chem*. **2009**, *14*, 2354. (c) Liu, Z.; Wang, J.; Zhao, Y.; Zhou, B. *Adv. Synth. Catal*. **2009**, *351*, 371.

(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).

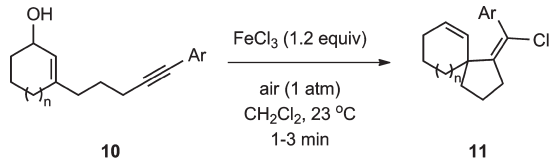
Scheme 2. $FeCl_3$-Promoted Cylization/Chlorination of **8**



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.

Acknowledgment. This research was supported by grants from the National Science Council (NSC 98-2119-M-003-004-MY3, NSC 98-2119-M-003-001-MY2) and National Taiwan Normal University.

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.