

Iron-Catalyzed Redox Radical
Cyclizations of 1,6-Dienes and Enynes

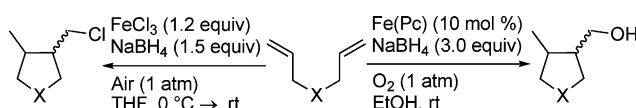
Tsuyoshi Taniguchi, Naoya Goto, Asami Nishibata, and Hiroyuki Ishibashi*

*School of Pharmaceutical Sciences, Institute of Medical, Pharmaceutical and Health
Sciences, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan*

isibashi@p.kanazawa-u.ac.jp

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ABSTRACT



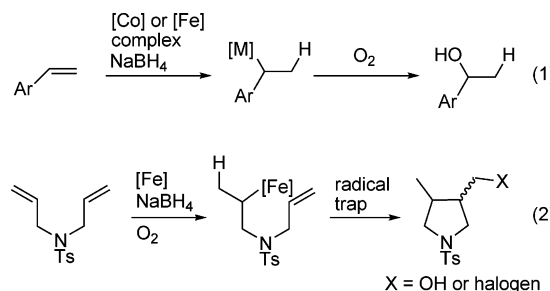
Treatment of 1,6-dienes and enynes with FeCl_3 or Fe(Pc) in the presence of NaBH_4 and air or O_2 causes radical cyclization to give five-membered carbo or heterocyclic compounds, into which a halogen atom or hydroxyl group was introduced.

Radical cyclizations have been powerful tools for the construction of cyclic systems in synthetic chemistry.¹ Radical reactions have generally been performed by treatment of alkyl or aryl halides or chalcogenides with a hydrogen donor such as Bu_3SnH in the presence of a radical initiator such as AIBN [azobis(isobutyronitrile)].

There are, however, some disadvantages due to the use of toxic reagents and the difficulty in product purification. Therefore, tin-free radical reactions have been developed in recent years.²

Interest has recently been shown in iron as a low-toxicity and inexpensive substitute for rare metals such as palladium, and many efficient iron-catalyzed reactions have been reported.³ In 1984, Okamoto reported the hydration of styrenes using cobalt or iron complexes and NaBH_4 under air (Scheme 1, eq 1).^{4–6} Quite recently, Beller and co-workers reported the synthesis of oximes from styrenes using a catalytic amount of iron phthalocyanine [Fe(Pc)] in the

Scheme 1. Cobalt- or Iron-Catalyzed Oxygenation of Olefins



presence of NaBH_4 ,⁷ and Boger and co-workers reported the hydration of trisubstituted olefins of vinblastine and β -citronellol using excess iron salts and NaBH_4 under air.⁸ A radical mechanism has been proposed for these reactions.^{4,5,8} Nevertheless, an application of these methods using iron compounds and NaBH_4 to radical cyclizations has never been explored.⁹ Herein, we report iron-catalyzed redox

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(2) For selected recent examples, see: (a) Schaffner, A.-P.; Darmency, V.; Renaud, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 5847. (b) Medeiros, M. R.; Schacherer, L. N.; Spiegel, D. A.; Wood, J. L. *Org. Lett.* **2007**, *9*, 4427. (c) Smith, D. M.; Pulling, M. E.; Norton, J. R. *J. Am. Chem. Soc.* **2007**, *129*, 770. (d) Gansäuer, A.; Fan, C.-A.; Piester, F. *J. Am. Chem. Soc.* **2008**, *130*, 6916. (e) Ueng, S.-H.; Makhlof Brahmi, M.; Derat, E.; Fensterbank, L.; Lacôte, E.; Malacria, M.; Curran, D. P. *J. Am. Chem. Soc.* **2008**, *130*, 10082. (f) Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2008**, *10*, 3279. (g) Akindele, T.; Yamada, K.; Tomioka, K. *Acc. Chem. Res.* **2009**, *42*, 345. (h) Friestad, G. K.; Banerjee, K. *Org. Lett.* **2009**, *11*, 1095.

(3) For reviews, see: (a) *Iron Catalysis in Organic Chemistry*; Plietker, B., Ed.; Wiley-VCH: Weinheim, 2008. (b) Bolm, C.; Legros, J.; Le Pailh, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217. (c) Fürstner, A.; Martin, R. *Chem. Lett.* **2005**, *34*, 624. (d) Correa, A.; Mancheño, O. G.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108. (e) Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3317. (f) Sherry, B. D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500. (g) Correa, A.; García Mancheño, O.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108. (h) Fürstner, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 1364.

(4) Okamoto, T.; Oka, S. *J. Org. Chem.* **1984**, *49*, 1589.

Table 1. Iron-Catalyzed Radical Cyclization of **1a**

entry	[Fe] (equiv)	[BH ₄] [−] (equiv)	solvent	gas	temp (°C)	time (h)	yield (%) ^{a,b}	
							2a	3a
1	FeCl ₃ (1.2)	NaBH ₄ (1.5)	THF	Air	0 → rt	0.5	68	17
2	FeCl ₃ (1.2)	NaBH ₄ (1.5)	THF	N ₂	0 → rt	0.5	18	3
3	FeCl ₃ (1.2)	NaBH ₄ (1.5)	THF	Air	−45	4	48	28
4	FeCl ₃ (1.2)	NaBH ₄ (1.5)	THF	O ₂	−45	2	4	54
5	FeCl ₃ (1.2)	LiBH ₄ (1.5)	THF	O ₂	−45	5	18	55
6	FeCl ₃ (1.2)	NaBH ₄ (1.5)	THF	O ₂	−78 → rt	2	15	58
7	Fe(NO ₃) ₃ (1.2)	NaBH ₄ (1.5)	THF	O ₂	−78 → rt	2		44
8	Fe(Pc) (0.1)	NaBH ₄ (3.0)	THF	O ₂	rt	1		
9	Fe(Pc) (0.1)	NaBH ₄ (3.0)	EtOH	O ₂	rt	3		65

^a Yield of isolated products. ^b Diastereomer ratio was determined by ¹H NMR analysis.

radical cyclizations of 1,6-dienes using NaBH₄ (Scheme 1, eq 2).¹⁰

Treatment of 1,6-diene **1a** with 1.2 equiv of FeCl₃ and NaBH₄ (1.5 equiv) in THF (0.1 M) under air at room temperature gave chlorinated cyclization product **2a** (68%) along with a small amount of hydroxy cyclization product **3a** (17%) (Table 1, entry 1).^{11,12} When Et₂O, MeCN, or MeOH was used as a solvent, very lower yield of product was observed. The change of concentration of a substrate

(0.01–0.5 M) and the use of excess reagents also gave no improved result. The reaction under N₂ atmosphere instead of air resulted in a significant lower yield of products. (Table 1, entry 2). At the lower reaction temperature, the increased quantity of hydroxy product **3a** was observed (Table 1, entry 3). It was found that FeCl₃-mediated reaction under O₂ atmosphere in lower temperature gave **3a** as the major product (Table 1, entries 4–6). The use of LiBH₄ instead of NaBH₄ gave a similar result (Table 1, entry 5). The use of Fe(NO₃)₃ instead of FeCl₃ gave only **3a** (Table 1, entry 7). When a catalytic amount of iron phthalocyanine [Fe(Pc)] was used in EtOH under O₂ atmosphere at room temperature, only **3a** was obtained in good yield (Table 1, entry 9). Fe(Pc) showed catalytic activity, whereas FeCl₃ showed no catalytic activity.¹³ Therefore, we concluded that FeCl₃/NaBH₄ in THF under air gives chlorinated cyclization product **2a** and that Fe(Pc) (cat.)/NaBH₄ in EtOH under O₂ atmosphere affords hydroxy cyclization product **3a**.

Next, radical cyclizations of several 1,6-dienes **1b–g** using FeCl₃ (method A) and Fe(Pc) (method B) were examined (Table 2). The precursor **1b** bearing a prenyl group gave chlorinated cyclization product **2b** by method A, whereas no cyclization product was obtained by method B (Table 2, entries 2). Since the hydrated product of the trisubstituted olefin of **1b** was detected, the trisubstituted olefin might be more reactive than the terminal olefin in the condition using method B. Reactions of precursors **1c** and **1d** bearing a cyclohexene group or 2-methylallyl group gave chlorinated products **2c**, **2c'** and **2d**, **2d'** by method A and hydroxy

(5) Co- or Mn-catalyzed hydration reactions of olefins using O₂ and silanes have been reported by Mukaiyama and co-workers; see: (a) Mukaiyama, T.; Isayama, S.; Inoki, S.; Kato, K.; Yamada, T.; Takai, T. *Chem. Lett.* **1989**, 449. (b) Inoki, S.; Kato, K.; Takai, T.; Isayama, S.; Yamada, T.; Mukaiyama, T. *Chem. Lett.* **1989**, 515. (c) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 1071. (d) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 569. (e) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 573. (f) Kato, K.; Yamada, T.; Takai, T.; Inoki, S.; Isayama, S. *Bull. Chem. Soc. Jpn.* **1990**, 63, 179. (g) Isayama, S. *Bull. Chem. Soc. Jpn.* **1990**, 63, 1305.

(6) Recently, Carreira and co-workers have reported the cobalt-catalyzed functionalization of inactive alkenes; see: (a) Waser, J.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, 127, 8294. (b) Waser, J.; González-Gómez, J. C.; Nambu, H.; Huber, P.; Carreira, E. M. *Org. Lett.* **2005**, 7, 4249. (c) Waser, J.; Gaspar, B.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2006**, 128, 11693. (d) Gaspar, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, 46, 4519. (e) Gaspar, B.; Waser, J.; Carreira, E. M. *Synthesis* **2007**, 3839. (f) Gaspar, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, 47, 5758.

(7) Prateetongkum, S.; Jovel, I.; Jackstell, R.; Vogl, N.; Weckbecker, C.; Beller, M. *Chem. Commun.* **2009**, 1990.

(8) Ishikawa, H.; Colby, D. A.; Seto, S.; Va, P.; Tam, A.; Kakei, H.; Rayl, T. J.; Hwang, I.; Boger, D. L. *J. Am. Chem. Soc.* **2009**, 131, 4904.

(9) For examples of iron-mediated radical cyclizations, see: (a) Cabri, W.; Borghi, D.; Arlandini, E.; Sbraletta, P.; Bedeschi, A. *Tetrahedron* **1993**, 49, 6837. (b) Booker-Milburn, K. I.; Thompson, D. F. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2315. (c) Booker-Milburn, K. I.; Barker, A.; Brailsford, W.; Cox, B.; Mansley, T. E. *Tetrahedron* **1998**, 54, 15321. (d) Jahn, P.; Hartmann, P. *Chem. Commun.* **1998**, 209. (e) Bach, T.; Schlummer, B.; Harms, K. *Chem. Commun.* **2000**, 287. (f) Booker-Milburn, K. I.; Jones, J. L.; Sibley, G. E. M.; Cox, R.; Meadows, J. *Org. Lett.* **2003**, 5, 1107.

(10) For selected recent examples of radical cyclizations of 1,6-dienes, see: (a) Ueda, M.; Miyabe, H.; Nishimura, A.; Miyata, O.; Takemoto, Y.; Naito, T. *Org. Lett.* **2003**, 5, 3835. (b) Schmidt, B.; Pohler, M.; Costisella, B. *J. Org. Chem.* **2004**, 69, 1421. (c) James, P.; Schenk, K.; Landais, Y. *J. Org. Chem.* **2006**, 71, 3630. (d) Hirai, T.; Han, L.-B. *Org. Lett.* **2007**, 9, 53. (e) Mantrand, N.; Renaud, P. *Tetrahedron* **2008**, 64, 11860. (f) Sánchez, E. M.; Arteaga, J. F.; Domingo, V.; Quílez del Moral, J. F.; Mar Herrador, M.; Barrero, A. F. *Tetrahedron* **2008**, 64, 5111.

(11) *cis*-Isomers for **2a** and **3a** were assumed to be major products, since radical cyclizations of 1,6-dienes generally afforded *cis* products; see: Tripp, J. C.; Schiesser, C. H.; Curran, D. P. *J. Am. Chem. Soc.* **2006**, 127, 5518.

(12) In the reaction of **1a**, simple hydrochlorinated or hydrated product of olefin was also detected by NMR analysis of the crude product.

(13) It has been reported that the reaction of FeCl₃ with LiBH₄ or NaBH₄ gives iron(II) borohydride [Fe(BH₄)₂]; see: (a) Schaeffer, G. W.; Roscoe, J. S.; Stewart, A. C. *J. Am. Chem. Soc.* **1956**, 78, 729. (b) Glavee, G. N.; Klabunde, K. J.; Sorensen, C. M.; Hadjipanyis, G. C. *Inorg. Chem.* **1995**, 34, 28.

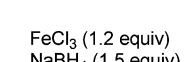
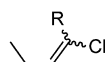
Table 2. Iron-Catalyzed Radical Cyclization of Various 1,6-Dienes

FeCl_3 (1.2 equiv) NaBH_4 (1.5 equiv) Air (1 atm) THF, 0 °C → rt method A		Fe(Pc) (10 mol %) NaBH_4 (3.0 equiv) O_2 (1 atm) EtOH, rt method B	
entry	1	method A ^{a,b}	method B ^{a,b}
1		 0.5 h 69% (75:25)	 3 h 63% (75:25)
2		 1.5 h 54% (80:20)	—
3		 1 h 32% (50:50)	 2 h 57% (3c:3c' = 88:12)
4		 0.5 h 63% (2d:2d' = 85:15)	 1 h 68%
5		 1 h 49% (90:10)	 4 h 11% (90:10)
6		 1.5 h 74% (70:30)	 3 h 81% (70:30)
7		 0.5 h 76% ^c (75:25)	 1 h 61% (75:25)

^a Yield of isolated products. ^b Ratio was determined by ¹H NMR analysis. ^c Determined by ¹H NMR analysis of a crude product.

products **3c**, **3c'**, and **3d** by method B, respectively (Table 2, entries 3 and 4). In terms of the reactions of these unsymmetrical 1,6-dienes, chemoselectivity in functionalization of olefins was observed. Dimethyl malonate derivative **1e** gave chlorinated product **2e** in moderate yield (method A), but hydroxy product **3e** was obtained in very low yield (method B) (Table 2, entry 5). It was assumed that the low yield of **3e** was due to the instability of ester moieties under the reaction conditions.¹⁴ This consideration was supported

Table 3. Iron-Catalyzed Radical Cyclization of Eneynes **4a–d**

					
4a-d		method A		5a-d	
entry	R		time (h)	yield (%) ^a	ratio ^b
1	Ph	a	4.5	43	85:15
2	TMS	b	1	53	75:25
3	TBS	c	0.5	65	75:25
4	TIPS	d	1	57	60:40

^a Yield of isolated products. ^b Ratio was determined by ¹H NMR analysis.

by the fact that bis-sulfone derivative **1f** gave chlorinated product **2f** and hydroxy product **3f** in excellent yields (Table 2, entry 6). The reaction of diallyl ether (**1g**) also gave chlorinated product **2g** and hydroxy product **3g** in good yields, respectively (Table 2, entry 7). The cyclization reactions of several enyne compounds were also examined.^{15–17} As shown in Table 3, treatment of enyne compounds **4a–d** bearing phenyl or silyl groups on alkyne with FeCl_3 and NaBH_4 under air resulted in 5-*exo-dig* cyclization to give vinyl chlorides **5a–d** in moderate yields, respectively.^{18,19}

A brominated or iodinated cyclization compound was also accessible by using appropriate radical trapping reagents. Treatment of **1a** with FeBr_3 and NaBH_4 under air gave brominated cyclization product **6a** (Scheme 2, eq 1), and the addition of excess diiodoethane to the mixture of $\text{FeCl}_3/\text{NaBH}_4$ gave iodinated cyclization product **7a** (Scheme 2, eq 2).

A plausible mechanism for the reaction is shown in Scheme 3. Reaction of 1,6-diene **1a** may be initiated by generation of σ -alkyliron(III) complex **8**. Fe–C bond cleavage of complex **8** by O_2 followed by cyclization of the resultant radical intermediate **9** gives the new radical **10**. When FeCl_3 is employed as an iron source, the addition of

(14) When Et_3SiH was used as a hydride source, no reaction occurred.

(15) For a recent review of catalytic enyne cyclizations, see: Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268.

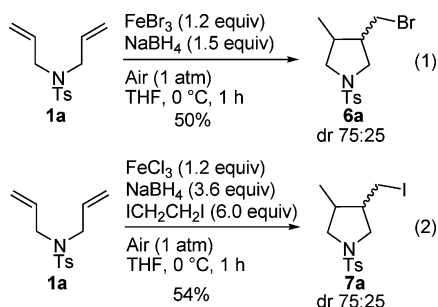
(16) Indium-mediated reductive radical cyclizations of enynes have been reported; see: (a) Takami, K.; Mikami, S.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2003**, *68*, 6627. (b) Miura, K.; Fujisawa, N.; Hosomi, A. *J. Org. Chem.* **2004**, *69*, 2427. (c) Hayashi, N.; Shibata, I.; Baba, A. *Org. Lett.* **2004**, *6*, 4981. (d) Hayashi, N.; Shibata, I.; Baba, A. *Org. Lett.* **2005**, *7*, 3093.

(17) Quite recently, the iron-catalyzed reductive cyclization of 1,6-enynes and diynes has been reported; see: (a) Sylvester, K. T.; Chirik, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 8772.

(18) For recent examples of the synthesis of vinyl halides using iron catalyst, see: (a) Miranda, P. O.; Díaz, D. D.; Padrón, J. I.; Bermejo, J.; Martín, V. S. *Org. Lett.* **2003**, *11*, 1979. (b) Miranda, P. O.; Díaz, D. D.; Padrón, J. I.; Ramírez, M. A.; Martín, V. S. *J. Org. Chem.* **2005**, *70*, 57. (c) Carballo, R. M.; Ramírez, M. A.; Rodríguez, M. L.; Martín, V. S.; Padrón, J. I. *Org. Lett.* **2006**, *8*, 3837. (d) Miranda, P. O.; Carballo, R. M.; Martín, V. S.; Padrón, J. I. *Org. Lett.* **2009**, *11*, 357. (e) Xu, T.; Yu, Z.; Wang, L. *Org. Lett.* **2009**, *11*, 2113. (f) Cantagrel, G.; Carné-Carnavalet, B.; Meyer, C.; Cossy, J. *Org. Lett.* **2009**, *11*, 4262.

(19) The reaction of enyne substrates using method B gave a complex mixture of products.

Scheme 2. Introduction of Bromine and Iodine Atoms

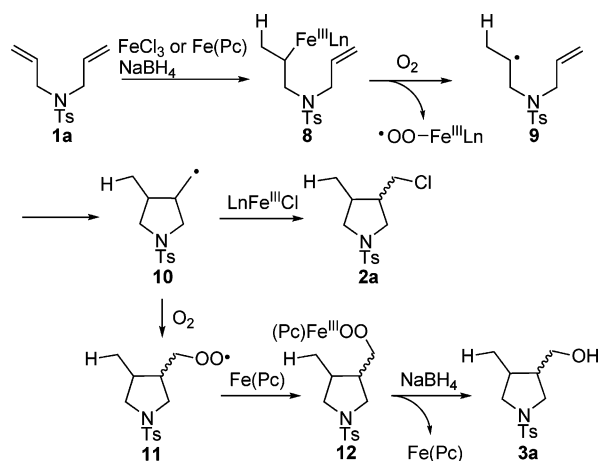


a chlorine atom to the radical **10** gives chlorinated product **2a**.⁹ On the other hand, in the case of using a catalytic Fe(Pc), the radical **10** was trapped by O₂ to give peroxide radical **11**. Formation of Fe(Pc)-peroxide complex **12** followed by reduction by NaBH₄ gives hydroxy product **3a**.²⁰

In summary, we have developed efficient iron-catalyzed redox radical cyclizations of 1,6-dienes to give functionalized cyclic compounds. The present reaction system consists of inexpensive and environmentally friendly reagents, and the experimental procedure is simple and safe. Further studies directed toward application of these iron-catalyzed redox radical cyclizations to the reactions of various precursors are currently underway in our laboratory.

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Scheme 3. Plausible Mechanism



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Supporting Information Available: Experimental detail and spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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