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

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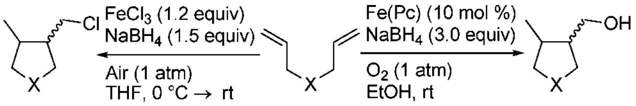
ABSTRACT



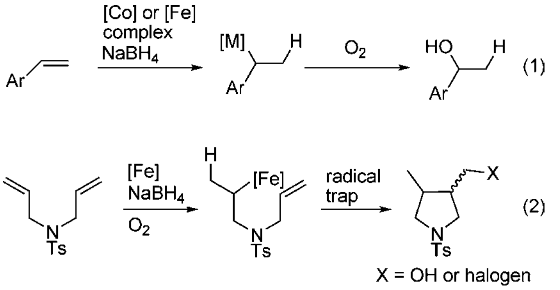
Treatment of 1,6-dienes and enynes with $FeCl_3$ or Fe(Pc) in the presence of $NaBH_4$ and air or O_2 causes radical cyclization to give five-membered carbo or heterocyclic compounds, into which a halogen atom or hydroxyl group was introduced.

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 phtalocyanine [Fe(Pc)] in the presence of $NaBH_4$,[7] and Boger and co-workers reported the hydration of trisubstitute 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

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



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(1) For reviews, see: (a) Renaud, P.; Sibi, M. P. *Radical in Organic Synthesis*; Wiley-VCH: Weinheim, 2001. (b) Gansäuer, A., Ed.; *Topics Current Chemistry; Radicals in Synthesis I and II*; Springer: Berlin; 2006; Vols. *263* and *264*.

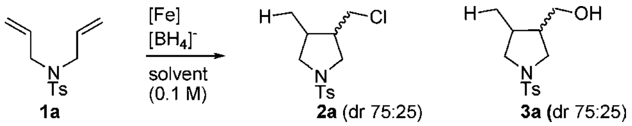
(2) For selected recent examples, see: (a) Schaffner, A.-P.; Darmency, V.; Renaud, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 5847. (b) Medeiros, M. R.; Schacherer, L. N.; Spiegel, D. A.; Wood, J. L. *Org. Lett.* **2007**, *9*, 4427. (c) Smith, D. M.; Pulling, M. E.; Norton, J. R. *J. Am. Chem. Soc.* **2007**, *129*, 770. (d) Gansäuer, A.; Fan, C.-A.; Piestert, F. *J. Am. Chem. Soc.* **2008**, *130*, 6916. (e) Ueng, S.-H.; Makhlouf 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 Paih, 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**, *47*, 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.

10.1021/ol902562j

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



entry	[Fe] (equiv)	$[BH_4]^-$ (equiv)	solvent	gas	temp (°C)	time (h)	yield (%)[a,b] **2a**	yield (%)[a,b] **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 $NaBH_4$ (Scheme 1, eq 2).[10]

Treatment of 1,6-diene **1a** with 1.2 equiv of $FeCl_3$ and $NaBH_4$ (1.5 equiv) in THF (0.1 M) under air at room temperature gave chlorinated cyclization product **2a** (68%) along with a small amout of hydroxy cyclization product **3a** (17%) (Table 1, entry 1).[11,12] When Et_2O, 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 N_2 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 $FeCl_3$-mediated reaction under O_2 atmosphere in lower temperature gave **3a** as the major product (Table 1, entries 4−6). The use of $LiBH_4$ instead of $NaBH_4$ gave a similar result (Table 1, entry 5). The use of $Fe(NO_3)_3$ instead of $FeCl_3$ gave only **3a** (Table 1, entry 7). When a catalytic amount of iron phtalocyanine [Fe(Pc)] was used in EtOH under O_2 atmosphere at room temperature, only **3a** was obtained in good yield (Table 1, entry 9). Fe(Pc) showed catalytic activity, whereas $FeCl_3$ showed no catalytic activity.[13] Therefore, we concluded that $FeCl_3/NaBH_4$ in THF under air gives chlorinated cyclization product **2a** and that Fe(Pc) (cat.)/$NaBH_4$ in EtOH under O_2 atmosphere affords hydroxy cyclization product **3a**.

Next, radical cyclizations of several 1,6-dienes **1b**−**g** using $FeCl_3$ (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 trisubsutituted olefin of **1b** was detected, the trisubsutituted 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

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(5) Co- or Mn-catalyzed hydration reactions of olefins using O_2 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) Prateeptongkum, 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.

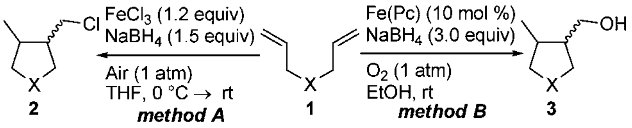
(10) For selected recent examples of radical cyclizations of 1,6-dienes, see: (a) Ueda, M.; Miyabe, H.; Nishimura, A.; Miyata, O.; Takemoto, Y.; Naito, T. *Org. Lett.* **2003**, *5*, 3835. (b) Schmidt, B.; Pohler, M.; Costisella, B. *J. Org. Chem.* **2004**, *69*, 1421. (c) James, P.; Schenk, K.; Landais, 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.

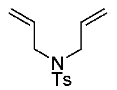
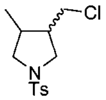
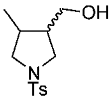
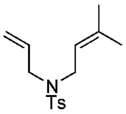
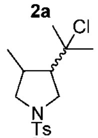
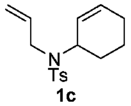
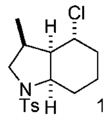
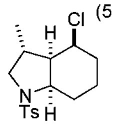
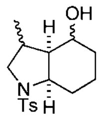
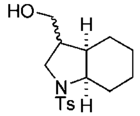
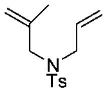
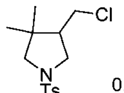
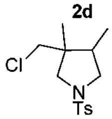
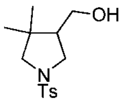
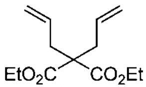
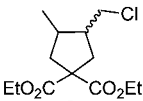
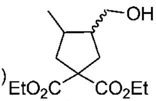
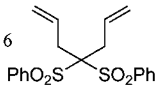
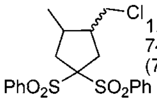
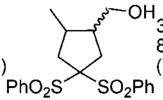
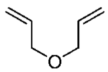
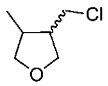
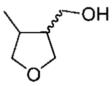
(11) *cis*-Isomers for **2a** and **3a** were assumed to be major products, since radical cyclizations of 1,6-dienes generally afforded *cis* products; see: Tripp, J. C.; Schiesser, C. H.; Curran, D. P. *J. Am. Chem. Soc.* **2006**, *127*, 5518.

(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 $FeCl_3$ with $LiBH_4$ or $NaBH_4$ gives iron(II) borohydride $[Fe(BH_4)_2]$; 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.; Hadjipanayis, G. C. *Inorg. Chem.* **1995**, *34*, 28.

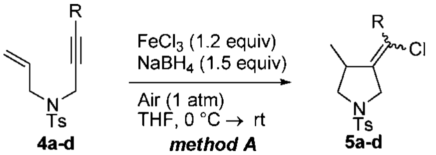
Table 2. Iron-Catalyzed Radical Cyclization of Various 1,6-Dienes



entry	1	method A[a,b]	method B[a,b]
1	 **1a**	 **2a** 0.5 h 69% (75:25)	 **3a** 3 h 63% (75:25)
2	 **1b**	 **2b** 1.5 h 54% (80:20)	—
3	 **1c**	 **2c**  **2c′** 1 h 32% (50:50)	 **3c** (34:33:33)  **3c′** (single isomer) 2 h 57% (**3c**:**3c′** = 88:12)
4	 **1d**	 **2d**  **2d′** 0.5 h 63% (**2d**:**2d′** = 85:15)	 **3d** 1 h 68%
5	 **1e**	 **2e** 1 h 49% (90:10)	 **3e** 4 h 11% (90:10)
6	 **1f**	 **2f** 1.5 h 74% (70:30)	 **3f** 3 h 81% (70:30)
7	 **1g**	 **2g** 0.5 h 76%[c] (75:25)	 **3g** 1 h 61% (75:25)

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

Table 3. Iron-Catalyzed Radical Cyclization of Eneynes **4a**−**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 ^{1}H NMR analysis.

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 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 eneyne compounds were also examined.[15−17] As shown in Table 3, treatment of eneyne 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 FeCl$_3$/NaBH$_4$ gave iodinated cyclization prouduct **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

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(14) When Et$_3$SiH 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.

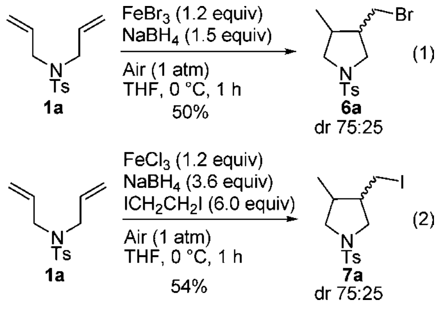
(16) Indium-madiated reductive radical cyclizations of enynes have been reported; see: (a) Takami, K.; Mikami, S.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2003**, *68*, 6627. (b) Miura, K.; Fujisawa, N.; Hosomi, A. *J. Org. Chem.* **2004**, *69*, 2427. (c) Hayashi, N.; Shibata, I.; 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.; Diaz, 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.; Martin, 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.

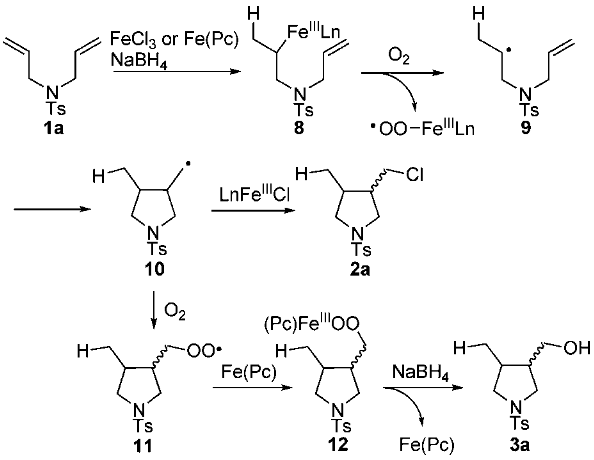
Scheme 2. Introduction of Bromine and Iodine Atoms



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 O_2 to give peroxide radical **11**. Formation of Fe(Pc)-peroxide complex **12** followed by reduction by $NaBH_4$ 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.

Scheme 3. Plausible Mechanism



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Supporting Information Available: Expermental 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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