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New Fe(III)-Mediated Radical Cascade Reactions of Cyclopropyl Silyl Ethers

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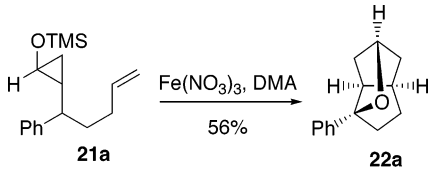
ABSTRACT

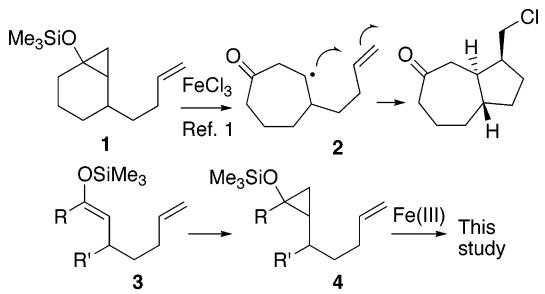


Fe(III)-mediated ring opening of cyclopropyl ethers bearing a phenyl-substituted butenyl side chain leads to the generation of β-keto radicals that undergo 5-*exo* cyclization followed by a novel cascade sequence resulting in the formation of tricyclic ethers.

Previously we have reported that both cyclopropylsilyl ethers[1] (e.g., **1**) and cyclopropanone ketene-acetals[2] undergo Fe(III)-mediated tandem ring opening/cyclization to yield mono- and bicyclic products.[3] The reaction is thought to proceed by initial oxidative ring cleavage to give β-carbonyl radicals (e.g., **2**) that then undergo 5-*exo* cyclization to the products. In the case of cyclopropylsilyl ethers, we had previously discounted cyclization studies of simple variants such as **4** because of problems encountered with the cyclopropanation of acyclic enol-ethers **3**. However, recent observations in our laboratory with cyclopropanation led us to reinvestigate acylic-enol ethers, and herein we describe the unexpected reactions of these cyclopropanes on treatment with Fe(III) salts (Scheme 1).

Treatment of MVK with 3-butenylmagnesium chloride under our previously developed conditions gave the enol ether **5** in 86% yield. Previously, we[1] had found that the best conditions for the selective cyclopropanation of silyl enol-ethers in the presence of alkenes were those described by Furukawa (Et_2Zn, CH_2I_2, Et_2O).[4] Unfortunately, these conditions were unsuccessful for related acyclic-enol ethers we investigated in the past (very slow, incomplete reactions). Use of the more reactive conditions described by Denmark[5] resulted in biscyclopropanation. Recently, we found that the use of Et_2Zn/CH_2I_2 in toluene[6] dramatically accelerated the rate of cyclopropanation of cyclic enol-ethers. Following on from these results, we found that **5** could be cyclopropanated in 88% yield by using *only* the hexane present in Et_2Zn (1

Scheme 1. Fe(III)-Mediated Cyclopropane Ring-Opening Radical Cylization Reactions



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(1) Booker-Milburn, K. I.; Thompson, D. F. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2315.
(2) Booker-Milburn, K. I.; Barker, A.; Brailsford, W.; Cox, B.; Mansley, T. E. *Tetrahedron* **1998**, *54*, 15321.
(3) Independent studies by Narasaka and co-workers showed that Mn-(III) could be used to effect similar transformations with cyclopropanols: Iwasawa, N.; Funahashi, M.; Hayakawa, S.; Ikeno, T.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 85.

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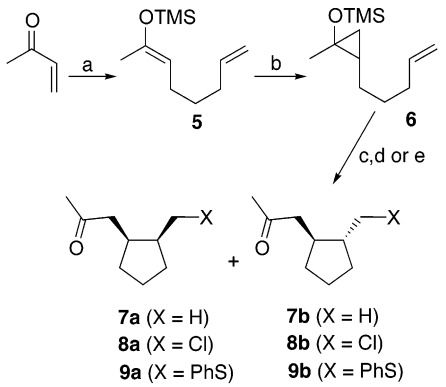
M, Aldrich) as a solvent. The reaction was complete within 20 min at 0 °C and for the first time allowed access to multigram quantities of **6**. Fe(III)-mediated ring opening/radical cyclization of **6** proceeded well using three different radical traps[2] and produced the cyclopentanes **7**−**9** as 7:1 mixtures of cis:trans isomers (Scheme 2).

Scheme 2 [a]

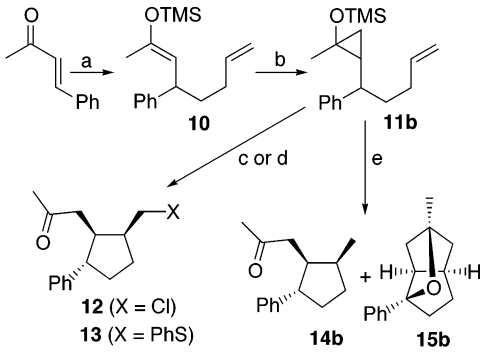


[a] Reagents and conditions: (a) 3-butenylmagnesium bromide, TMSCl, HMPA, THF, −78 °C, 86%; (b) Et_2Zn, CH_2I_2, 0 °C, 88%; (c) $Fe(NO_3)_3$, 1,4-cyclohexadiene, DMF, 2.5 h, 57% (**7a**:**7b** = 7:1); (d) $Fe(NO_3)_3$, *N*-chlorosuccinimide, DMF, 65% (**8a**:**8b** = 7:1); (e) $Fe(NO_3)_3$, PhSSPh, DMF, 60% (**9a**:**9b** = 7:1).

We then sought to explore the stereochemical influence of a substituent in the cyclization as we had done previously for cyclopropanone acetals.[2] The phenyl-substituted enol-ether **10** was synthesized and cyclopropanated as before to yield the cyclization substrate **11b** (R = Me) in high overall yield. Fe(III)-mediated cyclization using either NCS or PhSSPh as radical traps furnished the cyclized products **12** (sole product) and **13** in reasonable yield, with minor amounts (9:1) of another diastereomer of **13** obtained. The relative stereochemistry of **13** was obtained by X-ray crystallography of the corresponding 2,4-dinitrophenylhydrazone.[7] To our surprise, however, when **11b** was treated with $Fe(NO_3)_3$ and 1,4-cyclohexadiene as a H-atom donor, the expected cyclization product **14b** was formed along with a very unusual tricyclic ether product **15b** (Scheme 3).

We then sought to probe the scope of this likely cascade-type sequence by synthesizing a range of substituted cyclopropylsilyl ethers bearing a phenyl group in the side chain. All the cyclopropanes **11a**−**e** were synthesized from known enones by the conjugate addition−cyclopropanation sequence used above. Initially, we sought to increase the proportion of **15b** by slowing down the rate of hydrogen atom abstraction from radical intermediates leading to **14b**. Surprisingly, carrying out the reaction *without* 1,4-cyclohexadiene made little difference in the ratios of **14b** and **15b**,

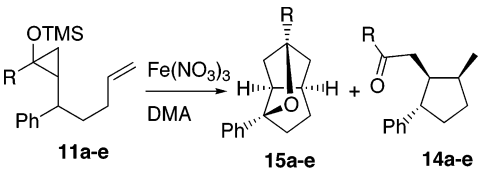
Scheme 3 [a]



[a] Reagents and conditions: (a) 3-butenylmagnesium bromide, TMSCl, HMPA, THF, −78 °C, 84%; (b) Et_2Zn, CH_2I_2, 0 °C, 91%; (c) $Fe(NO_3)_3$, *N*-chlorosuccinimide, DMF, 50% **12**; (d) $Fe(NO_3)_3$, PhSSPh, DMF, 58% **13** (9:1 with minor diastereoisomer); (e) $Fe(NO_3)_3$, 1,4-cyclohexadiene, DMF, 60% **14b** (9:1 with minor diastereoisomer) and 31% **15b**.

suggesting that termination to **14b** was caused by hydrogen atom abstraction from DMF. Repeating the reaction in dimethylacetamide (DMA) improved matters somewhat, and the ratio of **14b**:**15b** was almost 1:1. These optimized conditions were then used for the other cyclopropanes described in Table 1. Cyclization of **11a** (R = H) gave only

Table 1. [a]



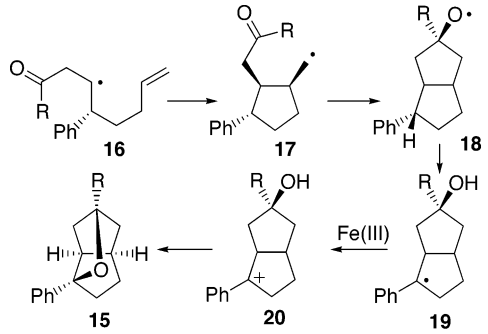
11	R	15 (%)	14 (%)
a	H	56	
b	Me	45	50
c	Et	40	34
d	*n*Bu	37	29
e	*i*Pr	33	23

[a] Other minor diastereomers were formed in ratios of 9:1, 5:1, and 3:1 for compounds **11b**, **11c**, and **11d**,**e**, respectively. The stereochemistry not assigned.

the tricyclic ether **15a**. Interestingly, the relative size of the R group was found to have a significant effect on both the yield and the stereochemistry of the products. As the size of R increased, the yield of **15** decreased. This was matched by a decrease in the observed stereoselectivity of the monocyclization products **14c**−**e**. Only the major isomers of **14b**−**e** have been depicted, as it was not possible to assign the relative stereochemistry of the minor products. Attempts to synthesize phenyl derivatives of **11** (R = Ph and *p*$MeOC_6H_4$) were unsuccessful as the corresponding enol-ethers failed to undergo cyclopropanation.

(4) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53.
(5) Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6974.
(6) Jenkins, H. Unpublished results.
(7) See Supporting Information.

Scheme 4. Mechanism of Tricyclic Ether **15** Formation



The formation of **15** is the result of a previously unreported radical cascade process, the mechanism of which is proposed in Scheme 4. It is likely that on oxidation of **11** with Fe(III), the β-keto radical **16** is formed and undergoes 5-*exo* cyclization to the cyclopentylmethyl radical **17**. This then undergoes two different termination pathways. First, hydrogen atom abstraction from the solvent leads to the observed cyclopentanes **14a**−**e**. Obviously, that process is relatively slow and the radical is able to undergo a second 5-*exo* cyclization onto the newly formed ketone carbonyl, resulting in the alkoxyl radical **18**.[8] If the stereochemistry of **18** is as shown, it would then undergo a facile 1,5 H-atom abstraction leading to the formation of the benzylic radical **19**. We believe that this radical then undergoes oxidation to the cation **20** by electron transfer to the ferric nitrate [Fe(III)→Fe(II)]. Finally, this cation undergoes ionic ring closure to form the tricyclic ether product. It would appear that the larger R groups affect the cis selectivity of the cyclization of **16** to **17**, and presumably therefore a diastereomer of **17** is generated that cannot undergo cyclization to **18**. This would account for the lower stereoselectivity observed with the monocyclized products **14c**−**e**.

In summary, access to previously unobtainable cyclopropylsilyl ethers has uncovered a novel Fe(III)-mediated oxidative radical cascade process resulting in the formation of complex tricyclic ethers.

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Supporting Information Available: Experimental procedures and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0341703

(8) (a) Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1989**, *111*, 2674. (b) For an annulation sequence involving abstraction/cyclization reactions of cyclopropylamines, see: Ha, J. D.; Lee, J.; Blackstock, S. C.; Cha, J. K. *J. Org. Chem.* **1998**, *63*, 8510.