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

Kevin I. Booker-Milburn,*,† J. Leighton Jones,† Graham E. M. Sibley,† Richard Cox,‡ and Jim Meadows‡

School of Chemistry, University of Bristol, Cantock's Close, Bristol, BS8 1TS, United Kingdom, and Chemical Development, Medicines Research Centre, GlaxoSmithKline, Gunnels Wood Lane, Stevenage, Herts., SG1 2NY, United Kingdom

k.booker-milburn@bristol.ac.uk

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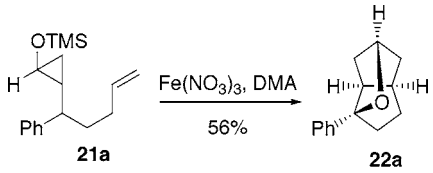
ABSTRACT

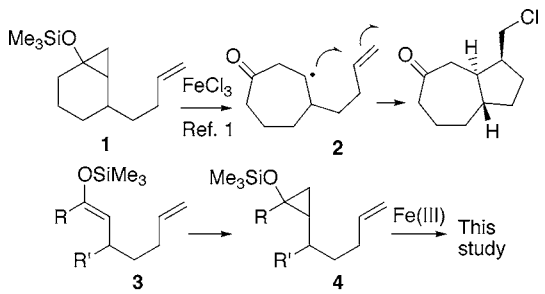


Fe(III)-mediated ring opening of cyclopropyl ethers bearing a phenyl-substituted butenyl side chain leads to the generation of β-keto radicals that undergo 5-*exo* cyclization followed by a novel cascade sequence resulting in the formation of tricyclic ethers.

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



† University of Bristol.
‡ GlaxoSmithKline.

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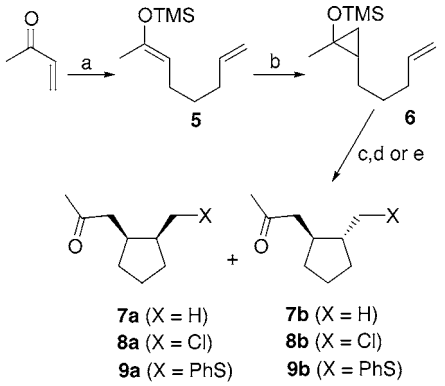
M, Aldrich) as a solvent. The reaction was complete within 20 min at 0 °C and for the first time allowed access to multigram quantities of **6**. Fe(III)-mediated ring opening/radical cyclization of **6** proceeded well using three different radical traps[2] and produced the cyclopentanes **7**−**9**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

Scheme 2 [a]

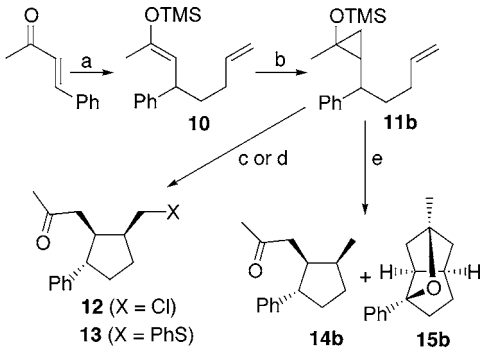


[a] Reagents and conditions: (a) 3-butenylmagnesium bromide, TMSCl, HMPA, THF, −78 °C, 86%; (b) Et_2Zn, CH_2I_2, 0 °C, 88%; (c) $Fe(NO_3)_3$, 1,4-cyclohexadiene, DMF, 2.5 h, 57% (**7a**:**7b** = 7:1); (d) $Fe(NO_3)_3$, *N*-chlorosuccinimide, DMF, 65% (**8a**:**8b** = 7:1); (e) $Fe(NO_3)_3$, PhSSPh, DMF,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

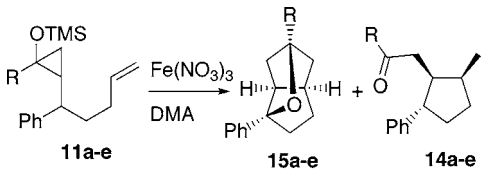
Scheme 3 [a]



[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]



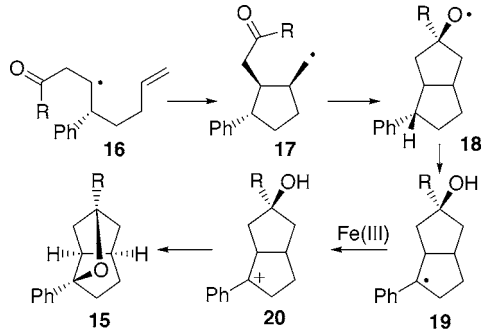
11	R	**15** (%)	**14** (%)
a	H	56	
b	Me	45	50
c	Et	40	34
d	*n*Bu	37	29
e	*i*Pr	33	23

[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$_6$H$_4$) 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.

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(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.