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Samarium(II)-Mediated Reactions of γ,δ-Unsaturated Ketones. Cyclization and Fragmentation Processes

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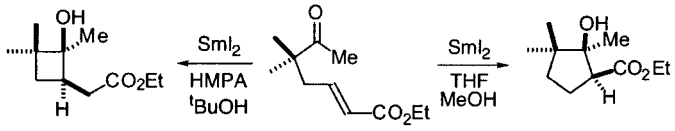
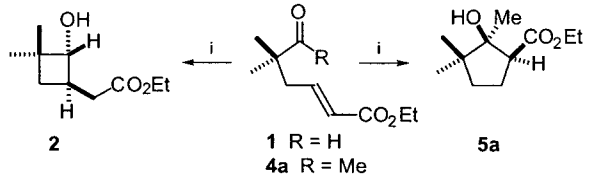
ABSTRACT



On treatment with samarium(II) iodide, γ,δ-unsaturated ketones undergo very different processes depending upon the nature of the reaction conditions. Employing samarium(II) iodide and MeOH, functionalized *syn*-cyclopentanol products are obtained stereoselectively. Mechanistic studies suggest that this cyclization occurs via a sequential reduction/intramolecular aldol reaction. With samarium(II) iodide and HMPA, products of a 4-*exo*-*trig* cyclization and of an interesting fragmentation reaction are observed.

Samarium(II) iodide continues to enjoy widespread application throughout organic synthesis.[1] We have previously reported that γ,δ-unsaturated aldehydes, such as **1**, undergo stereoselective 4-*exo*-*trig* cyclization on treatment with samarium(II) iodide to give *anti*-cyclobutanols in good yield (Scheme 1).[2,3] We have since applied our reaction in the first synthetic studies on Pestalotiopsin A.[4]

Scheme 1[a]



[a] Reagents and conditions: (i) SmI_2, THF/MeOH (4:1), 0 °C

We have sought to extend the chemistry to the cyclization of the corresponding ketones, such as methyl ketone **4a**, thus allowing the stereoselective synthesis of even more highly substituted cyclobutanols. Here we report the preliminary results of our studies into the reaction of γ,δ-unsaturated ketones with samarium(II) iodide.

As previously mentioned, treatment of γ,δ-unsaturated aldehyde **1** with samarium(II) iodide in the presence of MeOH gave *anti*-cyclobutanol **2** with complete diastereocontrol in 65% yield.[2] However, we were intrigued to find that under our standard conditions employing samarium(II) iodide in THF and MeOH (4:1), the corresponding methyl ketone **4a** gave none of the expected cyclobutanol, instead giving cyclopentanol **5a** (45%), accompanied by the acyclic reduction product **6a** (44%) (Scheme 1).

(1) For reviews on the use of samarium(II) iodide in organic synthesis, see: (a) Soderquist, J. A. *Aldrichimica Acta* **1991**, *24*, 15. (b) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29. (c) Molander, G. A. *Org. React.* **1994**, *46*, 211. (d) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307. (e) Molander, G. A.; Harris C. R. *Tetrahedron* **1998**, *54*, 3321. (f) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745. (g) Steel, P. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2727.

(2) (a) Johnston, D.; McCusker, C. M.; Procter, D. J. *Tetrahedron Lett.* **1999**, *40*, 4913. (b) Johnston, D.; McCusker, C. F.; Muir, K.; Procter, D. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 681.

(3) Prior to our work, a single example of such a cyclization had been described by Weinges: Weinges, K.; Schmidbauer, S. B.; Schick, H. *Chem. Ber.* **1994**, *127*, 1305.

(4) Johnston, D.; Francon, N.; Edmonds, D. J.; Procter, D. J. *Org. Lett.* **2001**, 2001.

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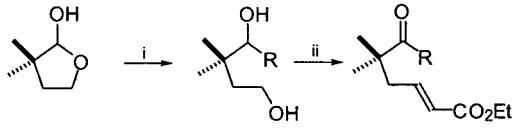
Table 1.[a]



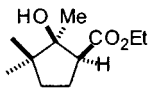
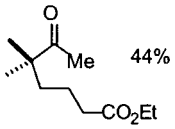
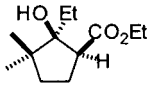
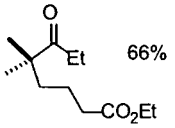
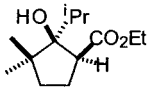
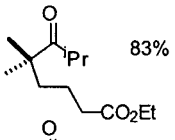
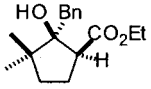
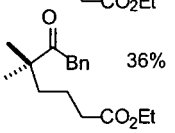
R	RM	3	4
Me	MeLi·LiBr	**3a** (74%)	**4a** (88%)
Et	EtMgCl	**3b** (45%)	**4b** (57%)
^{i}Pr	^{i}PrMgCl	**3c** (76%)	**4c** (44%)
Bn	BnMgCl	**3d** (51%)	**4d** (82%)
^{c}Pr	^{c}PrMgBr	**3e** (65%)	**4e** (53%)

[a] Reagents and conditions: (i) RM, THF, −78 °C. (ii) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78 °C then Ph_3PCHCO_2Et.

To investigate further this switch in reactivity, a series of γ,δ-unsaturated ketones was prepared. Ketone substrates **4a**−**e** were prepared from γ-butyrolactone by dimethylation, DIBALH reduction to the lactol, and subsequent ring opening of the lactol with appropriate alkylmetal reagents. Diols **3a**−**e** were obtained in the yields indicated in Table 1. One-pot Swern oxidation and Wittig reaction then gave the desired ketones **4a**−**e** in good overall yield (Table 1).

Employing methyl ketone **4a** as our test substrate, it was found that under the standard conditions used for the analogous aldehyde cyclizations, an approximately 1:1 mixture of cyclopentanol **5a** and the acyclic reduction product **6a** was obtained in 89% (Table 2). In an attempt to

Table 2.[a]

ketone		products			
4a	**5a**		45%	**6a** 	44%
4b	**5b**		33%	**6b** 	66%
4c	**5c**		trace	**6c** 	83%
4d	**5d**		17%	**6d** 	36%

[a] Typical reaction conditions: to a solution of SmI_2 (0.1 M in THF) (4 equiv) at 0 °C was added MeOH (resultant solution, 4:1 THF/MeOH), and the solution was stirred for 10 min. Ketone substrate (1 equiv) in THF (0.75 mL) was then added, and the solution was stirred at 0 °C for 1−2 h.

optimize the formation of the cyclopentanol **5a**, the quantity of proton source was reduced. This proved to be largely unsuccessful, as in line with our previous observations[2] reducing the amount of MeOH employed led to a dramatic decrease in the efficiency of the reaction and only a slight increase in the ratio of **5a** to **6a**. Cyclizations of **4b**−**d** were carried out under our standard conditions; the results are shown in Table 2**.** The proportion of cyclopentanol product obtained clearly varies according to the size of the ketone substituent (Table 2). Although the combined overall yields of **5** and **6** remained approximately constant, the product ratio decreased from 1:1 for the cyclization of **4a**, to only a trace of **5c** being observed from the cyclization of the isopropyl ketone **4c**.

In all cases, cyclopentanol products were obtained as single diastereoisomers. To ascertain the stereochemistry of the cyclization products, **5a** was reduced ($LiAlH_4$, THF, 0 °C, 80%) and the resulting diol **7** was converted to mono-*p*-nitrobenzoate **8** (*p*-$O_2NC_6H_4COCl$, pyridine, rt, 77%). X-ray crystallographic analysis of **8**[5] thus confirmed the *syn* stereochemistry of **5a**. The stereochemistry of the cyclopentanols **5b**−**d** was inferred from this observation.

Cyclopropyl ketone **4e** was prepared in order to investigate the mechanism of cyclization to form "5-*endo*-type" products. The isolation of byproducts **6** suggested that the reaction might proceed via initial conjugate reduction of the α,β-unsaturated ester,[6] protonation, and a second reduction to give an intermediate samarium(III) enolate that could either undergo cyclization via an intramolecular aldol reaction,[7] to give cyclopentanols **5**, or be protonated to give acyclic reduction products **6**. The alternative, direct 5-e*ndo* radical cyclization mechanism appeared less likely.

In the cyclization of cyclopropyl ketone **4e**, if the reaction proceeded through the generation of a ketyl-radical anion, the cyclopropinyl radical anion formed from **4e** would be expected to undergo rapid fragmentation.[8] The fragmentation of cyclopropyl ketones on treatment with samarium(II) iodide has been exploited previously in both synthetic[9] and mecha-

(5) Crystal data for **8**: $C_{16}H_{21}NO_5$, $M = 307.34$, monoclinic, space group $P21/c$, $a = 10.4932(3)$, $b = 13.0916(4)$ Å, $c = 12.2594(4)$ Å, $\beta = 111.410(1)°$, $V = 1567.9(1)$ Å^3, $T = 100$ K, $Z = 4$, $D_c = 1.302$ Mg m^{-3}, $\mu = 0.097$ mm^{-1}, $F(000) = 656$. 21, 423 reflections measured, 6788 unique ($R_{int} = 0.04$) used in refinement. R_1[4438 with $I > 2\sigma(I)$] = 0.050, $wR2$(all data) = 0.136 after adjusting 250 parameters, $|\Delta\rho| < 0.41$ e Å^{-3}. CCDC reference number 184372. Programs used: SHELX97—Programs for Crystal Structure Analysis (Release 97-2). Sheldrick, G. M. Institüt für Anorganische Chemie der Universität, Tammanstrasse 4, D-3400 Göttingen, Germany, 1998. WinGX—A Windows Program for Crystal Structure Analysis. Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837.

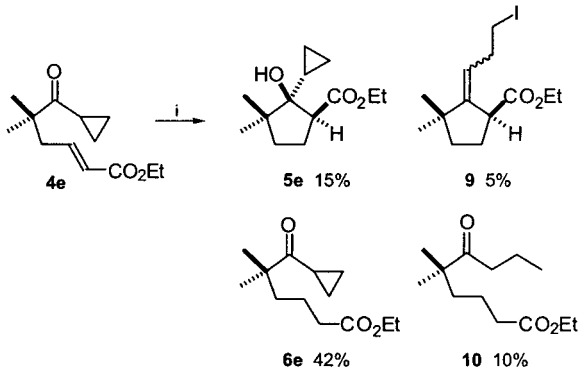
(6) The conjugate reduction of α,β-unsaturated carbonyl compounds with SmI_2 is well-precedented: (a) Inanaga, J.; Sakai, S.; Handa, Y.; Yamaguchi, M.; Yokoyama, Y. *Chem. Lett.* **1991**, 2117. (b) Cabrera, A.; Alper, H. *Tetrahedron Lett.* **1992**, *33*, 5007. (c) Fujita, Y.; Fukuzumi, S.; Otera, J. *Tetrahedron Lett.* **1997**, *38*, 2121.

(7) Cabrera has reported the cyclodimerization of α,β-unsaturated ketones, which proceeds via a similar intramolecular aldol reaction: (a) Cabrera, A.; Rosas, N.; Alvarez, C.; Sharma, P.; Toscano, A.; Salmón, M.; Arias, J. L. *Polyhedron* **1996**, *15*, 2971. (b) Cabrera, A.; Le Lagadec, R.; Sharma, P.; Arias, J. L.; Toscano, R. A.; Velasco, L.; Gaviño, R.; Alvarez, C.; Salmón, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3609.

(8) It has recently been shown that ring opening is significantly faster for radical anions derived from aliphatic cyclopropyl ketones than for the corresponding neutral cyclopropinyl radicals. Stevenson, J. P.; Jackson, W. F.; Tanko, J. M. *J. Am. Chem. Soc.* **2002**, *124*, 4271.

(9) Batey, R. A.; Motherwell, W. B. *Tetrahedron Lett.* **1991**, *32*, 6211.

Scheme 2[a]



[a] Reagents and conditions: (i) SmI_2 (0.1 M in THF), THF/MeOH (4:1), 0 °C

nistic[10] contexts. Treatment of cyclopropyl ketone **4e** with samarium(II) iodide gave **5e** (15%) and **6e** (42%) and additionally, iodide **9** (5%) and fragmented ketone **10** (10%) (Scheme 2).

The isolation of **5e**, in which the cyclopropyl group is intact, suggests that the cyclization does not proceed via a ketyl-radical anion. We believe iodide **9** arises from **5e** by cyclopropyl ring-opening and elimination. Fragmented ketone **10** appears to arise from reduction of **6e**. This experiment therefore suggests that the cyclization proceeds via a sequential reduction/intramolecular aldol mechanism.[11,12]

Changing the reaction conditions was found to dramatically alter the course of the reaction. Employing HMPA as an additive and using *t*-BuOH as a proton source, ketone **4a** underwent 4-*exo*-*trig* cyclization to give *syn*-cyclobutanol products **11** and **12** in moderate yield. No trace of cyclopentanol products was observed under these conditions.

It is clear that the switch in reaction conditions brings about a change in mechanism. SmI_2/HMPA/*t*-BuOH may promote ketyl-radical anion formation and subsequent 4-*exo*-*trig* cyclization onto the alkene, or alternatively, the formation of a dianion from the α,*β*-unsaturated ester may lead to a 4-*exo*-*trig* anionic cyclization onto the ketone. The latter may be the more plausible explanation, as the increased reactivity of the dianion in HMPA and the lower concentration of proton source would be expected to promote cyclization.

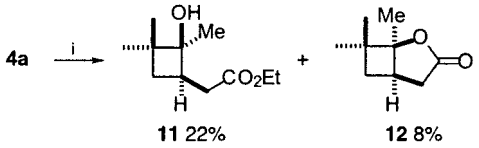
In an attempt to discover the fate of the remaining mass from the reaction shown in Scheme 3, higher molecular weight substrates **4d** and methyl ketone **13** were treated with samarium(II) iodide under identical conditions.

(10) (a) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1991**, *56*, 4112. (b) Curran, D. P.; Gu, X.; Zhang, W.; Dowd, P. *Tetrahedron* **1997**, *53*, 9023. (c) McKerlie, F.; Procter, D. J.; Wynne, G. *Chem. Commun.* **2002**, 584.

(11) Sequential conjugate reduction-aldol cyclizations using Stryker's reagent have recently been reported: Chiu, P.; Szeto, C.-P.; Geng, Z.; Cheng, K.-F. *Org. Lett.* **2001**, 1901.

(12) The *syn*-selectivity of the cyclisation is in agreement with the observed *syn*-selectivity of the processes reported by Cabrera and Chiu (refs 7 and 11, respectively).

Scheme 3[a]



[a] Reagents and conditions: (i) SmI_2 (0.1 M in THF) 3 equiv, HMPA 6 equiv, ^{t}BuOH 3 equiv, THF, 0 °C.

Interestingly, in addition to small amounts of cyclization products, **4d** gave known ketone **14** (~30%), and methyl ketone **13** gave known lactone **15** as the major products (30%) (Figure 1). These experiments suggest that either the

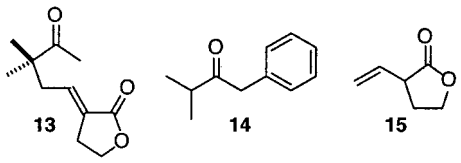


Figure 1.

ketyl-radical anion[13] or the dianion formed from the α,*β*-unsaturated ester undergoes fragmentation under these reaction conditions. A possible mechanism for the fragmentation would involve α,*β*-C−C bond cleavage in either intermediate to give a samarium(III) enolate and an extended samarium(III) enolate, which are then protonated. This fragmentation process appears to account for the low yield observed in the 4-*exo*-*trig* cyclization of **4a** (Scheme 3).

In conclusion, treatment of *γ*,*δ*-unsaturated ketones with samarium(II) iodide in the presence of MeOH results in a stereoselective cyclization to give functionalized *syn*-cyclopentanols. Mechanistic studies suggest the cyclization proceeds via a sequential reduction/intramolecular aldol process. Employing HMPA and *t*-BuOH as additives results in a dramatic switch in the reaction pathway, and products of 4-*exo*-*trig* cyclization and of fragmentation are obtained. Further investigations to increase the synthetic potential of these processes are currently underway in our laboratories.

Acknowledgment. We thank the EPSRC (T.K.H., grant GR/N02481) for financial support.

Supporting Information Available: X-ray crystal structure and crystallographic data for **8**, experimental procedures and full characterization data for compounds **3a**−**e**, **4a**−**e**, **5a**−**e**, **6a**−**e**, **7**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) For a related fragmentation, see: Haque, A.; Ghosh, S. *Chem. Commun*. **1997**, 2039. For an additional example, see ref 1b, page 47.