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Switching between Novel Samarium(II)-Mediated Cyclizations by a Simple Change in Alcohol Cosolvent

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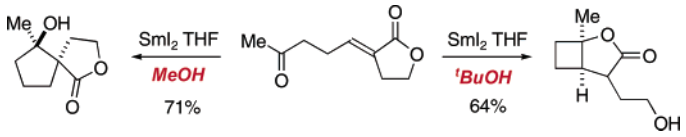
ABSTRACT



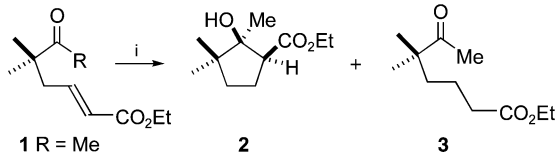
γ,δ-Unsaturated ketones undergo two very different stereoselective cyclization reactions mediated by samarium(II) iodide depending upon the alcohol cosolvent used in the reaction. Switching between an unprecedented aldol spirocyclization and a novel cyclobutanol-forming process can be achieved simply by changing the alcohol cosolvent from methanol to *tert*-butyl alcohol.

It is well appreciated that the outcome of many samarium(II) iodide[1] reactions can be influenced by the use of additives and cosolvents.[2] Common examples of the use of additives include the addition of HMPA or DMPU to increase the reduction potential of the reagent and the use of alcohol cosolvents to quench intermediate anions in reactions.[2] In general, however, the role of additives in samarium(II)-mediated organic reactions is still poorly understood. In this Letter we report how a simple class of unsaturated ketones can be directed down either of two distinct, stereoselective reaction pathways, simply by the choice of the alcohol cosolvent under otherwise identical reaction conditions.

We have previously described the stereoselective synthesis of cyclobutanols using a Sm(II)-mediated 4-*exo*-trig cyclization of aldehydes,[3] and have applied the process in target synthesis.[4] During these studies we have noted the important role played by the alcohol cosolvent in achieving a satisfactory reaction outcome.[3,4c]

We have recently reported that on treatment with SmI_2 in THF and MeOH, γ,δ-unsaturated ketones **1** give a mixture of *syn*-cyclopentanols and acyclic conjugate reduction products such as **2** and **3**, respectively.[5]

Scheme 1[a]



1 R = Me **2** **3**

[a] Reagents and conditions: (i) SmI_2, THF−MeOH (4:1), 0 °C, 89%, **2**:**3**, 1:1.

In addition, we have shown that cyclopentanols such as **2** are formed by a sequential conjugate reduction/intramolecular aldol reaction.[5] Although not immediately of synthetic value, the formation of *syn*-cyclopentanols such as **2** prompted us to examine the Sm(II)-mediated cyclizations of γ,δ-unsaturated ketones more closely. At the outset of our investigation, we were delighted to find that unsaturated lactone substrate

(1) For reviews on the use of samarium(II) iodide in organic synthesis: (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) Kagan, H.; Namy, J. L. *Lanthanides: Chemistry and Use in Organic Synthesis*; Kobayashi, S., Ed.; Springer: New York, 1999.

(3) (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.

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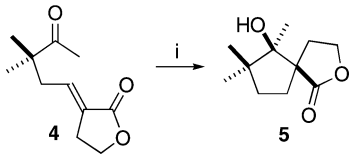
Scheme 2[a]



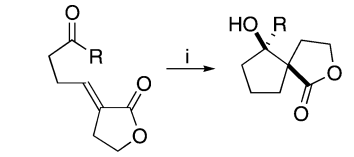
[a] Reagents and conditions: (i) SmI_2, THF−MeOH (4:1), 0 °C, 63%.

4 underwent cyclization to give *syn*-spirocycle **5** in 63% yield (Scheme 2).

X-ray crystallographic analysis confirmed the syn stereochemistry of **5**.[6] Thus, in the spirocyclization of **4**, two stereocenters are formed, including one quaternary center, with complete stereocontrol. In addition, the carbon−carbon bond-forming step occurs with relative efficiency despite acute steric congestion around the reacting centers.

A range of simpler substrates, lacking the gem-dimethyl group, were prepared to probe the generality of the spirocyclization process. Thus, substrates **6**−**10** were conveniently prepared from tetrahydrofuran-2-ol by ring opening with an alkylmetal reagent and one-pot Swern oxidation/Wittig reaction with (1-butyrolactonylidine)triphenylphosphorane, in line with our previously reported route.[5] On exposure to our standard conditions, ketones **6**−**10** underwent smooth cyclization to give the corresponding spirocyclic cyclopentanols **11**[7] and **12**−**15** in moderate to good yield (Scheme 3).

Scheme 3[a]



R= Me	**6**	**11** 71%
R= Et	**7**	**12** 60%
R= ^{i}Pr	**8**	**13** 48%
R= Bn	**9**	**14** 68%
R= ^{c}Pr	**10**	**15** 49%

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

X-ray crystallographic analysis of **15**[6] again confirmed the syn stereoselectivity of the spirocyclization process.

To investigate the facile conjugate reduction/aldol spirocyclization sequence further, we sought to modify the unsaturated lactone moiety present in the cyclization substrates. Lactone phosphonate **16** was prepared from δ-valerolactone using the method of Weimer,[8] while lactam phosphonate **17** was prepared from *N*-benzylpyrrolidinone using a modified literature procedure (Figure 1).[9]

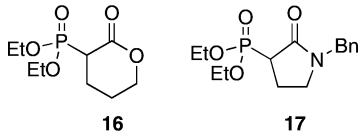
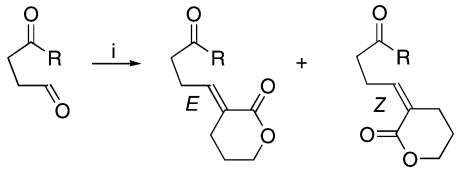


Figure 1.

Treatment of keto aldehydes **18**−**20** with lactone phosphonate **16** gave isomeric mixtures of keto-olefins **21**−**23** in moderate yield (Scheme 4). The stereoselectivity of olefinations with **16** was found to depend markedly on the reaction conditions employed and the substrate. Similarly, treatment of keto aldehyde **18** with lactam phosphonate **17** gave lactam cyclization substrate **24***E*/*Z* in moderate yield (Scheme 5).

Scheme 4[a]

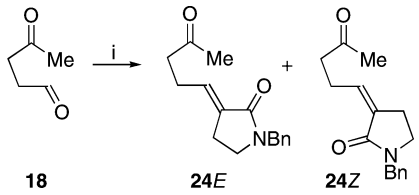


R= Me	**18**	**21***E* : **21***Z*, 16% : 39%
R= Et	**19**	**22***E* : **22***Z*, 41% : 16%
R= Bn	**20**	**23***E* : **23***Z*, 46% : 0%

[a] Reagents and conditions: (i) **16**, K_2CO_3, 18-C-6, THF, rt, 16 h.

On treatment with SmI_2 in THF and MeOH, **21***E* underwent efficient cyclization to give methyl ester **25**, the product of spirocyclization followed by opening of the lactone ring with MeOH (Scheme 6). Interestingly, the cyclization of **21***Z* and mixtures of **21***E* and **21***Z* gave identical results.[10]

Scheme 5[a]



[a] Reagents and conditions: (i) **17**, KHMDS (0.5 M in toluene), 18-C-6, THF, −78 °C to room temperature, 18 h, **24***E* 53% and **24***Z* 16%.

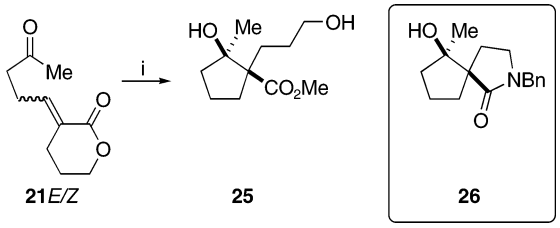
(4) (a) Johnston, D.; Francon, N.; Edmonds, D. J.; Procter, D. J. *Org. Lett.* **2001**, *3*, 2001. (b) Johnston, D.; Couché, E.; Edmonds, D. J.; Muir, K.; Procter, D. J. *Org. Biomol. Chem.* **2003**, 328. (c) Edmonds, D. J.; Muir, K. W.; Procter, D. J. *J. Org. Chem.* **2003**, *68*, 3190.

(5) Hutton, T. K.; Muir, K.; Procter, D. J. *Org. Lett.* **2002**, *4*, 2345.

(6) See Supporting Information for X-ray crystal structures and crystallographic data.

(7) Molander, G. A.; Etter, J. B.; Zinke, P. W. *J. Am. Chem. Soc.* **1987**, *109*, 453.

Scheme 6[a]

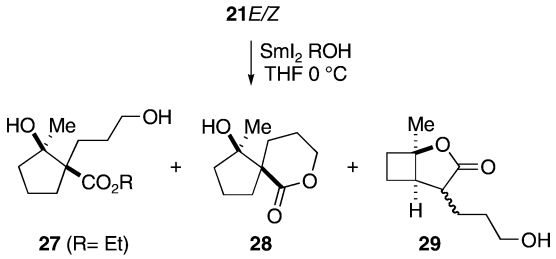


[a] Reagents and conditions: (i) SmI_2, THF−MeOH (4:1), 0 °C, 81%.

Unfortunately, the cyclization of lactam substrate **24***E* gave the spirocycle **26** in low yield (~10%).

In an attempt to prevent the lactone ring-opening by the cosolvent in the cyclization of **21**, we investigated the use of less nucleophilic cosolvents in the SmI_2-mediated cyclization. To our surprise, the use of EtOH as a cosolvent gave three products: ethyl ester **27**, spirocycle **28**, and cyclobutane product **29** (Scheme 7). Using propan-2-ol as a cosolvent gave mostly **29** with a small amount of spirocycle **28**. Interestingly, the use of *t*-BuOH completed the switch from five-membered ring formation to four-membered ring formation and **29** was obtained as the sole product (Scheme 7).

Scheme 7

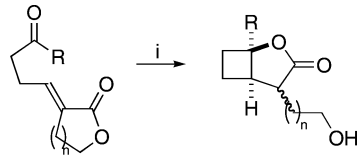


R= Et,	41%	12%	10%
R= ^{i}Pr,	—	10%	75%
R= ^{t}Bu,	—	—	66%

Thus, simply by changing the cosolvent from MeOH to *t*-BuOH, the SmI_2-mediated cyclization of **21** switches between five-membered ring and four-membered ring formation.

We were eager to see if the same dramatic switch to the formation of four-membered ring products would be observed when *t*-BuOH was employed in the cyclizations of other related substrates. On treatment with SmI_2 in THF and *t*-BuOH, substrates **6**, **7**, **8**, **22***E/Z*, and **23***E/Z* all underwent cyclization to give cyclobutanol-derived products *as the sole cyclized products* in moderate yield (Scheme 8). The structure of **30** was confirmed by conversion to the corresponding *p*-nitrobenzoate **35**, fractional recrystallization, and X-ray crystallographic analysis on a single diastereoisomer.[6]

Scheme 8[a]

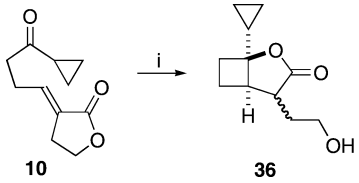


R= Me, n= 1	**6**	**30** 64%
R= Et, n= 1	**7**	**31** 31%
R= ^{i}Pr, n=1	**8**	**32** 54%
R= Et, n= 2	**22**	**33** 50%
R= Bn, n= 2	**23**	**34** 34%

[a] Reagents and conditions: (i) SmI_2, THF−^{t}BuOH (4:1), 0 °C.

The cyclization of cyclopropyl ketone substrate **10** in *t*-BuOH was carried out to investigate the mechanism of the four-membered ring-forming reaction. In substrate **10**, the cyclopropyl ring acts as a mechanistic probe for the formation of a ketyl radical anion from the ketone carbonyl group.[11] Treatment of **10** with SmI_2 in THF and *t*-BuOH gave **36** in which the cyclopropyl ring was intact, thus suggesting cyclization to give **36** does not proceed via formation of a ketyl radical anion (Scheme 9). When taken in conjunction with our previous observations,[5,10] we believe the mechanistic switch observed on changing the cosolvent from MeOH to *t*-BuOH can be best explained from the mechanistic outline shown in Scheme 10.

Scheme 9[a]



[a] Reagents and conditions: (i) SmI_2, THF−^{t}BuOH (4:1), 0 °C, 70%.

Reduction of the α,*β*-unsaturated moiety gives radical anion **37**. In MeOH, the *β*-anion is protonated rapidly, whereas in *t*-BuOH, the rate of protonation is sufficiently slow to allow cyclization to give cyclobutanol products. In both processes, Sm(III)-enolates are then formed by a second reduction. In the MeOH pathway, the enolate then undergoes aldol cyclization to give *syn*-cyclopentanols.[12]

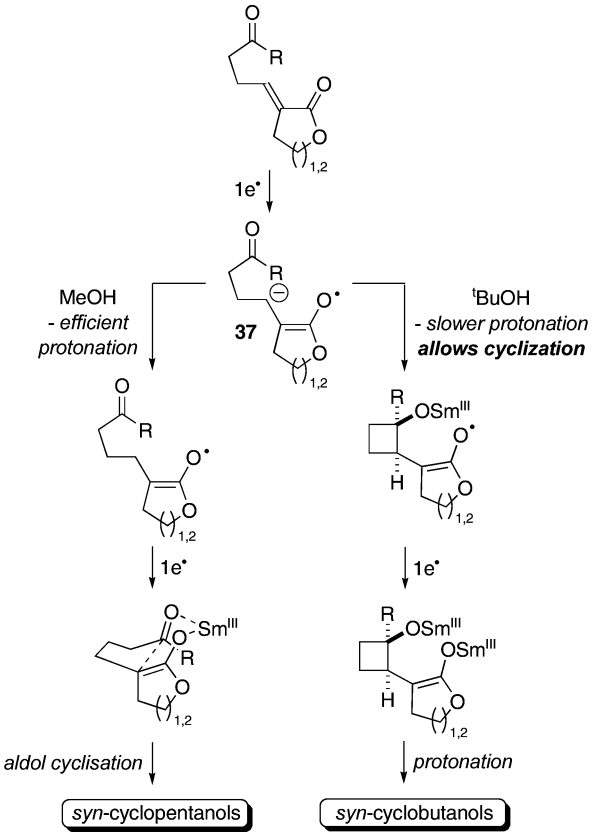
(8) Jackson, J. A.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1989**, *54*, 4750.

(9) Tay, M. K.; About-Jaudet, E.; Collignon, N.; Savignac, P. *Tetrahedron* **1989**, *45*, 4415.

(10) This again suggests that the cyclization proceeds via sequential conjugate reduction/aldol cyclization as the stereochemical outcome and the efficiency of ketyl-olefin cyclizations generally depends on the initial olefin geometry: (a) Enholm, E. J.; Trivellas, A. *Tetrahedron Lett.* **1989**, *30*, 1063. (b) Enholm, E. J.; Trivellas, A. *J. Am. Chem. Soc.* **1989**, *111*, 6463. (c) Enholm, E. J.; Satici, H.; Trivellas, A. *J. Org. Chem.* **1989**, *54*, 5841. See also ref 4.

(11) Stevenson, J. P.; Jackson, W. F.; Tanko, J. M. *J. Am. Chem. Soc.* **2002**, *124*, 4271.

Scheme 10

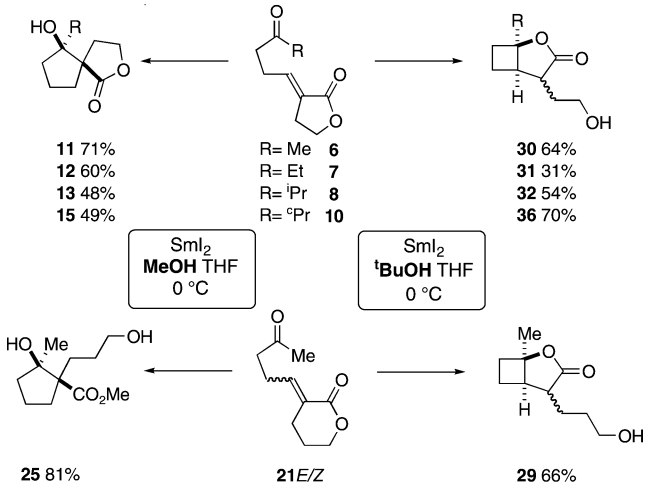


In summary, γ,δ-unsaturated ketones undergo two very different, stereoselective cyclization reactions mediated by samarium(II) iodide depending upon the alcohol cosolvent used in the reaction. Clean switching between an unprecedented aldol spirocyclization and a stereoselective cyclobutanol-forming process can be achieved simply by changing the alcohol cosolvent from MeOH to *t*-BuOH.

(12) Alternatively, divergence may result from differing rates of protonation of a dianion intermediate formed after two-electron reduction.

Under either set of conditions, none of the alternative cyclization product was isolated. The dramatic switch in the reaction outcome is summarized in Scheme 11 for five substrates. Partitioning between the two reaction pathways may result from the differing rates of protonation of a radical anion intermediate.

Scheme 11



Acknowledgment. We thank the EPSRC (T.K.H., Grant GR/N02481) for financial support. We thank Kenny McDougall and Lisa Sloan for carrying out the cyclizations of **9** (to give **14**) and **10** (to give **15**), respectively.

Supporting Information Available: Experimental procedures and data for all new compounds, as well as ^{1}H and ^{13}C NMR spectra and X-ray structures and crystallographic data for **5**, **15**, and **35**. This material is available free of charge via the Internet at http://pubs.acs.org.

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