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α-Hydroxy Cyclopentenones from α-Diketones

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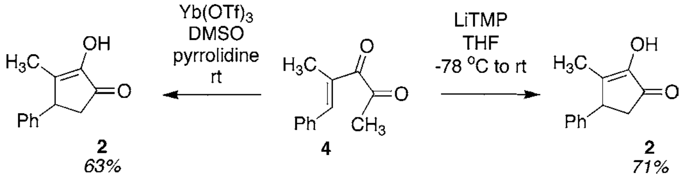
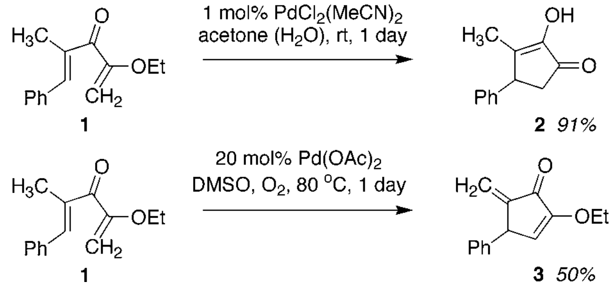
ABSTRACT



Metalloenolates derived from α,β-unsaturated α-diketones undergo cyclization to α-hydroxy cyclopentenones. This is apparently the first reported Nazarov reaction that takes place in the presence of base.

We recently described two related palladium(II)-catalyzed cyclizations of α-alkoxy dienones that led to cyclopentenones.[1] The two processes are illustrated in Scheme 1.

Scheme 1



Exposure of ketone **1** to $PdCl_2(MeCN)_2$ in wet acetone led to α-hydroxycyclopentenone **2**, whereas $Pd(OAc)_2$ in DMSO led to dienone **3** through an oxidative process. The occurrence of **2** in very small quantities in the $Pd(OAc)_2$-catalyzed reactions suggested a common mechanism involving the intermediacy of a palladium enolate. Although cyclopentenone **2**, but not dienone **3**, could also have been formed through a conventional cationic 4π electrocyclization,[2] the evidence suggested otherwise. The question we had was whether there might be additional processes operating on acyclic dienones or on closely related structures, such as α-diketone **4**, that lead to α-hydroxycyclopentenones. What follows is a preliminary account of our findings.

Scheme 2 summarizes our results. Exposure of α-diketone **4** to a small excess of lithium tetramethylpiperidide (LiTMP) in THF at −78 °C led to α-hydroxycyclopentenone **2** in 71% yield.[3] The same product is formed in 63% yield through a slower process that is catalyzed by $Yb(OTf)_3$ and other Lewis acids in the presence of an amine base.[4,5] A very rapid ring closure of **4** is catalyzed by triflic acid, leading to furanone **5** in 78% yield, whereas treatment of **4** with *tert*-butyldimethylsilyl triflate leads to silyloxyfuran **6** in 76% yield. It is possible that all four reactions are mechanistically related. Since we are most interested in carbocyclizations, these have been examined first.[6]

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(1) Bee, C.; Leclerc, E.; Tius, M. A. *Org. Lett.* **2003**, *5*, 4927−4930.

(2) For a reviews of the Nazarov reaction, see: (a) Habermas, K. L.; Denmark, S.; Jones, T. K. in *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1994; Vol. 45, pp 1−158. (b) Harmata, M. *Chemtracts* **2004**, *17*, 416−435. (c) Frontier, A.; Collison, C. *Tetrahedron* **2005**, in press. For an example of an application of the Nazarov cyclization in synthesis, see: Bender, J. A.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 7443−7444.

10.1021/ol050970x CCC: $30.25

Scheme 2

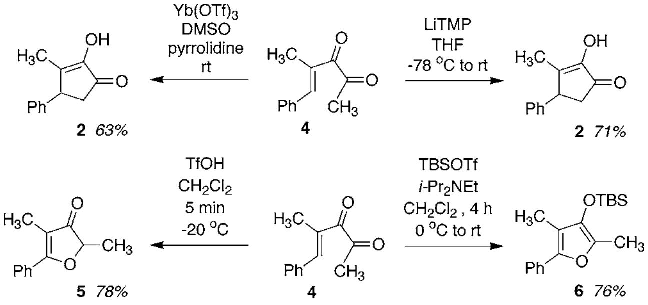
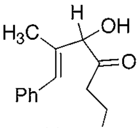


Table 1 lists our results. The α-diketone starting materials were conveniently prepared by combining the lithio anions derived from the cyanohydrin trimethylsilyl ethers of α,*β*-unsaturated aldehydes with saturated aldehydes.[7,8] The addition reaction is accompanied by migration of the trimethylsilyl group, which is cleaved hydrolytically under mild conditions to produce an α-hydroxyketone. Oxidation with IBX leads to the α-diketone.[9,10]

Amide base-catalyzed cyclizations were performed with LiTMP in THF. In the case of **4**, cyclization also took place when the α-diketone enolate was prepared with LHMDS (40% yield) or with LDA (72% yield). In the case of diketone **7**, exposure to LDA led to α-ketol **28**, presumably as a result of hydride transfer from the isopropyl group of LDA in a surprisingly efficient process. Since hydride transfer from LDA appeared to be faster than the desired cyclization in some cases, all reactions were performed with LiTMP. The cyclization generally proceeded in good yield; however, the process failed in the case of tetrasubstituted alkenes. For example, diketones **29** and **30** that lack a *β* olefinic hydrogen atom failed to undergo cyclization when exposed to LiTMP. Diketones **29** and **30** also failed to undergo cyclization under Lewis acid catalysis.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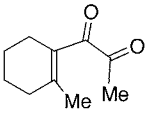
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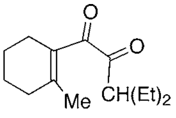
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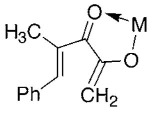
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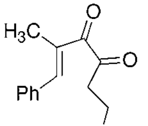
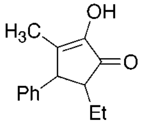
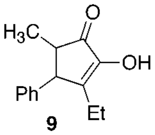
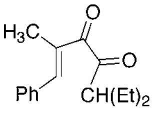
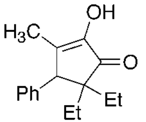
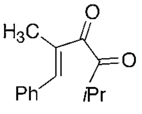
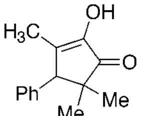
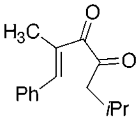
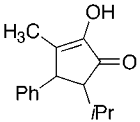
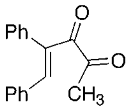
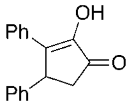
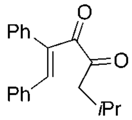
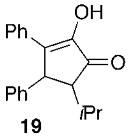
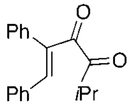
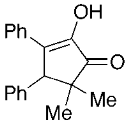
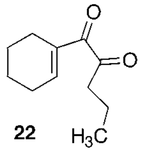
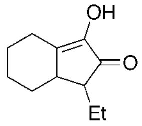
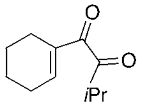
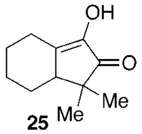
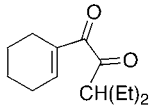
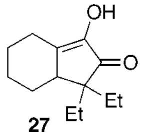
The Yb(OTf)$_3$-catalyzed reactions were performed in DMSO in the presence of pyrrolidine.[11] Although we were

Table 1. 2-Hydroxycyclopentenones[a]

α-diketone	cyclopentenone	yield
 **7**	 **8**  **9**	68%[b]; 94%[c]
 **10**	 **11**	66%; 79%
 **12**	 **13**	67%; 88%
 **14**	 **15**	d; 82%
 **16**	 **17**	d; 41%
 **18**	 **19**	d; 80%
 **20**	 **21**	d; 84%
 **22**	 **23**	70%; 70%
 **24**	 **25**	71%; 70%
 **26**	 **27**	70%; 68%

[a] The first yield refers to the LiTMP-mediated process, whereas the second refers to the process catalyzed by Yb(OTf)$_3$ and pyrrolidine. [b] The sole product of the LiTMP mediated reaction was **8**. [c] A 4/1 mixture (not separated) of **8** and **9** was formed from the Yb(OTf)$_3$-mediated reaction. [d] These reactions were not performed.

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(3) **General Procedure for the LiTMP-Mediated Cyclization.** A solution of LiTMP (0.5 M, 1.1 equiv) was prepared by the addition of *n*-BuLi to TMP in THF at 0 °C. The solution was kept at 0 °C for 0.5 h and then was cooled to −78 °C. During this time, the α-diketone was dissolved in THF (0.1 M) and allowed to stand over activated 4 Å molecular sieves for 0.5 h under nitrogen. The dry α-diketone was quickly added to the cold stirring solution of LiTMP via cannula at −78 °C. The reaction mixture was allowed to warm to room temperature over 15 min and was allowed to stir until the reaction was complete, as judged by TLC (ca. 2−24 h). The reaction mixture was cooled to 0 °C, 1 M HCl was added, and the aqueous phase was extracted with Et$_2$O. The organic phase was dried (MgSO$_4$), concentrated and purified by flash column chromatography over silica gel (5% EtOAc/hexanes) to afford the α-hydroxycyclopentenone.

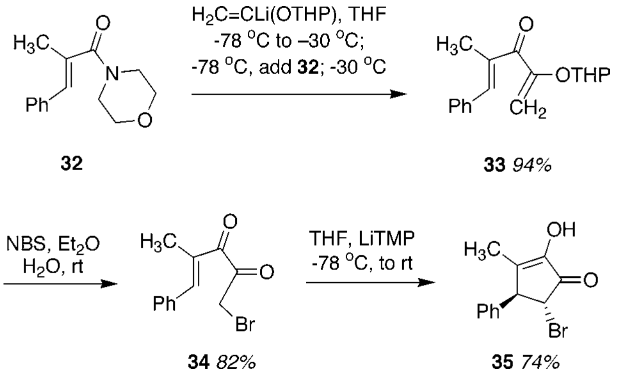
(4) Scandium triflate has been used for an asymmetric Nazarov cyclization of divinyl ketones: Liang, G.; Trauner, D. *J. Am. Chem. Soc.* **2004**, *126*, 9544−9545.

tempted to postulate an enamine intermediate, this is unlikely to be the case, since the cyclization also took place when *N*-methylpyrrolidine was used in place of pyrrolidine. The Lewis acid catalyzed process appears to take place under kinetic control. For example, diketone **7** (Table 1, entry 1) leads to a ca. 4/1 mixture of products **8** and **9**. The negligible difference in stability between these two isomers suggests that keto−enol equilibration is slow under the reaction conditions. In the case of diketone **4** (Scheme 2), $Yb(OTf)_3$ was the most effective of the Lewis acids that we screened in promoting the desired cyclization. Inferior yields of **2** were obtained from reactions catalyzed by $Cu(OTf)_2$, $Sc(OTf)_3$, $La(OTf)_3$, or $InCl_3$ (31%, 32%, 36%, or 26% yield, respectively). The same Lewis acids were screened for the cyclizations of diketone **10** (Table 1, entry 2). The yield of cyclopentenone **11** from the $Cu(OTf)_2$-, $Sc(OTf)_3$-, $La(OTf)_3$-, and $InCl_3$-catalyzed reactions was 96%, 48%, 90%, and 91%, respectively. It appears that α branching in the diketone facilitates the Lewis acid-catalyzed cyclizations.

The mechanism of the LiTMP-mediated process will be considered first, using **4** as the example. It is reasonable to assume that enolization of **4** precedes cyclization. The intramolecular Michael addition of the enolate to the enone is precluded by poor orbital overlap (this would represent a *5-endo-trig* ring closure, which is disallowed by Baldwin's Rules).[12] However, an electrocyclic process involving the internally chelated lithium enolate **31** (M = Li) cannot be ruled out. The Lewis acid-catalyzed cyclizations of the diketones may proceed through a related mechanism, whereby bidentate complexation of the metal salt by the two carbonyl oxygen atoms is followed by proton abstraction by the amine base to give enolate **31** ($M = Yb(OTf)_2$), which subsequently undergoes conrotatory ring closure. If this mechanistic hypothesis is valid, these cyclizations represent the first examples of Nazarov reactions of metalloenolates. Some years ago, in the context of allene ether Nazarov reactions we made the observation that polarization of one of the alkenes flanking the ketone carbonyl group by means of an electron-donating oxygen atom accelerates the cyclization.[13] These enolate cyclizations may represent extreme examples of the same phenomenon.[14]

If the cyclizations of α-diketones do indeed take place through the intermediacy of enolates, it is reasonable to postulate that α substitution by an electron-withdrawing group is likely to facilitate the process. The result shown in Scheme 3 lends some credence to this hypothesis. Morpholino enamide **32**[15] was treated with the α lithio anion derived from tetrahydropyranyl vinyl ether[16] to give dienone **33** in 94% yield. Exposure of an ethereal solution of **33** containing 1 mL of water to a small excess of NBS at room temperature led to bromide **34** in 82% yield following column chromatography as a labile pale yellow oil. This material underwent slow decomposition upon storage at 4 °C neat; however, in chloroform solution at room temperature over 2 days it underwent partial cyclization to bromocyclopentenone **35** *spontaneously*. Exposure of **34** to LiTMP in THF at −78 °C, followed by warming, led to **35** in 74% yield as a single (*trans*) isomer. These results suggest that the chemistry is likely to offer considerable opportunities for the synthesis of multifunctional cyclopentenones.

Scheme 3



In summary, mechanistically interesting cyclization reactions that may be categorized as Nazarov reactions have been described. If indeed these reactions represent conrotations, they are apparently the first such reactions to be described for enolates.[17] The cyclizations that lead to heterocycles **5** and **6** are likely to be part of a much larger family of heterocycle-forming electrocyclizations.

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(5) **General Procedure of the $Yb(OTf)_3$-Mediated Cyclization.** The α-diketone and $Yb(OTf)_3$ were dissolved in DMSO (0.04−0.1 M) at room temperature under nitrogen. To this solution was added pyrrolidine (1 equiv), and the reaction mixture was allowed to stir at room temperature until the reaction was judged to be complete by TLC (ca. 6−24 h). The solution was diluted with water and the aqueous phase was extracted with Et_2O. The organic phase was dried ($MgSO_4$), concentrated, and purified by flash column chromatography over silica gel (5% EtOAc/hexanes) to afford the α-hydroxycyclopentenone.

(6) Tius, M. A. *Acc. Chem. Res.* **2003**, *36*, 284−290.

(7) Yadav, J. S.; Reddy, B. V. S.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2002**, *43*, 9703−9706.

(8) (a) Hertenstein, U.; Hünig, S.; Öller, M. *Synthesis* **1976**, 416−417. (b) Fischer, K.; Hünig, S. *Chem. Ber.* **1986**, *119*, 3344−3362.

(9) Moore, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001−3003.

(10) For an alternative approach to similar compounds, see: Williams, D. R.; Robinson, L. A.; Amato, G. S.; Osterhout, M. H. *J. Org. Chem.* **1992**, *57*, 3740−3744.

(11) The reaction worked best in DMSO that had not been scrupulously dried.

(12) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734−736. (b) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736−738. (c) Baldwin, J. E.; Kruse, L. I. *J. Chem. Soc., Chem. Commun.* **1977**, 233−235. (d) Baldwin, J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, L. *J. Org. Chem.* **1977**, *42*, 3846−3852.

(13) Tius, M. A.; Kwok, C.-K.; Gu, X−q.; Zhao, C. *Synth. Commun.* **1994**, *24*, 871−885.

(14) Polarization of the alkene by electron withdrawal also accelerates the Nazarov cyclization: He, W.; Sun, X.; Frontier, A. J. *J. Am. Chem. Soc.* **2003**, *125*, 14278−14279.

(15) Harrington, P. E.; Murai, T.; Chu, C., Tius, M. A. *J. Am. Chem Soc.* **2002**, *124*, 10091−10100.

(16) Tamao, K.; Nakagawa, Y.; Arai, H.; Higuchi, N.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 3712−3714; see footnote 9.

(17) Professor David R. Williams (Indiana University) has alerted us to unpublished work from his research program that demonstrates the Nazarov reaction of an α-diketone upon exposure to $BF_3{\cdot}Et_2O$ in refluxing 1,2-dichloroethane. The vigorous conditions for cyclization are consistent with a process that proceeds through Lewis acid activation of the enol form of the diketone rather than a process involving an enolate, as we have postulated in this paper. Professor Williams' unpublished work is discussed in the following review article: Rodríguez, A.; González, E.; Ramírez, C. *Tetrahedron* **1998**, *54*, 11683−11729. See compound **164**.

Acknowledgment. We thank the National Institutes of Health (GM57873) for generous support.

Supporting Information Available: Assignment of stereochemistry for **8**, **23**, and **35**. ^{1}H and ^{13}C NMR data for **5**−**27** and **33**−**35**; spectroscopic data and reproductions of ^{1}H and ^{13}C NMR spectra for **5**−**27** and **33**−**35**. This material is available free of charge via the Internet at http://pubs.acs.org.

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