Reductive cleavage of 2-methyleneoxetanes with lithium and 4,4′-di-*tert*-butylbiphenyl

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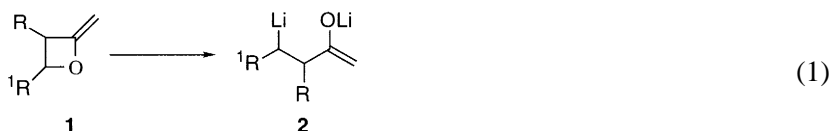
Abstract

3,3-Dimethyl-2-methylene-4-phenyloxetane (**5**) undergoes reductive cleavage with lithium and 4,4′-di-*tert*-butylbiphenyl (DTBB) to give an intermediate dianion, which reacts regioselectively with aldehydes and ketones to give aldol adducts in modest yields. Alternatively, the enolate can be trapped with TMSCl to give the corresponding silyl enol ether. © 2000 Elsevier Science Ltd. All rights reserved.
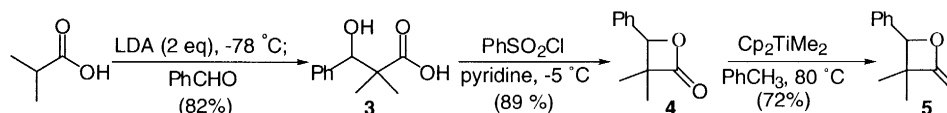
The lithium/arene-promoted cleavage of carbon–heteroatom bonds has proved highly flexible for the creation of functionalized organolithium reagents. For example, using lithium and 4,4′-di-*tert*-butylbiphenyl (DTBB), alkyl or vinyl halides undergo reduction in the presence of a number of functional groups.[1] Yus and co-workers have extended this methodology to promote reductive cleavage of a number of other carbon–heteroatom bonds in acyclic systems.[2] It is in the reductive cleavage of heterocyclic systems, however, that this sequence has found widest application. Following an initial paper by Bartmann,[3] this work was further developed by Cohen et al. who reported on the reductive ring opening of oxiranes[4] and oxetanes[5] to give the acyclic carbanions which could be trapped with electrophiles. Subsequently, 4-, 5- and 6-membered nitrogen,[6,7] oxygen,[8–12] and sulfur[13,14] heterocycles have been shown to undergo similar ring-openings.

Our interest in this work was prompted by our recent investigations of the synthesis and reactivity of 2-methyleneoxetanes **1**.[15] We were optimistic that, given the precedent for the ring opening of oxetanes, **1** would undergo ring opening to give the dianion **2** (Eq. (1)). The alkyl and enolate anions of **2** might be expected to have different reactivities and, hence, lead to useful bis-functionalization.
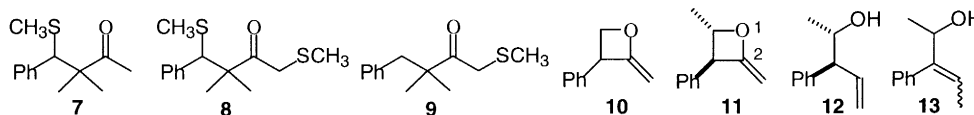

$$\tag{1}$$

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Based on the observation in several of the prior studies that an aryl group adjacent to the heteroatom regioselectively promotes cleavage of that carbon–heteroatom bond,[3,5,7,9–12] 3,3-dimethyl-2-methylene-4-phenyloxetane (**5**), prepared as shown in Scheme 1, was chosen as the substrate.[16,17] When **5** was exposed to the standard arene-catalyzed ring opening conditions (excess lithium, catalytic DTBB), followed by quenching with water, the ketone **6a** was isolated in excellent (86%) yield, indicating successful cleavage of the oxetane ring. Encouraged by the efficient reductive cleavage of **5**, we switched to other electrophiles (Eq. (2) and Table 1).[18] Trapping the enolate anion with cyclohexanone provided the β-hydroxy ketone **6b** in modest yield. Reaction with 1 equivalent of pivalaldehyde or acetaldehyde proved equally successful. However, in these cases, the intermediate β-hydroxy ketones were not isolated but underwent spontaneous elimination to give the α,β-unsaturated ketones **6c** and **6e**. An attempt to increase the yield using excess pivalaldehyde (2 equiv.) provided **6c** in only 22% yield, along with the acylated diol **6d**, which was isolated as a single diastereomer. The latter presumably arose from a Tischenko reduction.[19] The enolate could also be trapped with TMSCl to give the silyl enol ether **6f** which was not further purified, but whose clean formation was evident from the ¹H NMR spectrum of the reaction mixture. Reaction with methyl iodide gave, in poor yield, a mixture of mono and dimethyl adducts **6g** and **6h** arising from alkylation of the enolate anion. Products arising from addition of methyllithium, formed from the metal/lithium exchange of methyl iodide, to **6g** and **6h** were evident in the NMR spectrum of the crude reaction mixture but were not characterized.
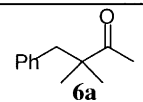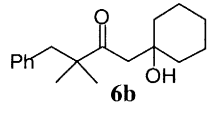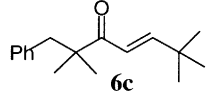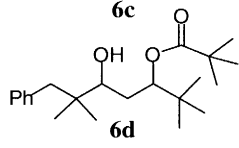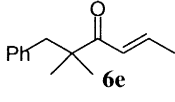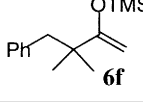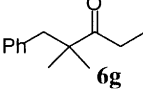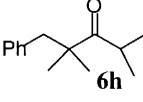

Scheme 1.

Although it seemed likely that the dianion was being generated, no evidence of electrophile trapping by the, presumably, more reactive benzylic anion was observed. Steric hindrance might have been a problem, or, since the solution was stirred for 2 h prior to the addition of the electrophile, the benzyl anion could have abstracted a proton from THF. A D₂O study was inconclusive as, based on ¹H NMR, deuterium incorporation was observed only at the enolate carbon (triplet, 2.1 ppm, 70% D incorporation). However, when a dianion solution, which had been stirred for 1 h at rt, was treated with (CH₃)₂S₂ (2 equiv.) at −78°C and immediately worked up, the sole products were **6a** and **7** in a 1:0.7 molar ratio, respectively. When a dianion solution was left for 3 h at rt, treated with (CH₃)₂S₂ (3 equiv.) at −78°C, then allowed to stir at rt for several hours prior to quenching, **7**, **8** and **9** were formed in a 0.1:0.8:1 ratio. These results confirm the presence of a reactive benzylic anion. Further, they demonstrate that proton abstraction at the benzylic position is occurring during the room temperature stirring. If the dianion solution was cooled to −78°C immediately after the solution became green (1 min after oxetane addition), treated with (CH₃)₂S₂ (3 equiv.) and left at −78°C for 1 h prior to quenching, **7** was the main product observed by ¹H NMR.

Having established that reductive cleavage of 2-methyleneoxetanes was feasible, we wanted to ascertain functional group requirements for successful opening. Other compounds examined included 2-methylene-3-phenyloxetane (**10**),[15a] and *trans*-4-methyl-2-methylene-3-phenyloxetane (**11**).[17] The result with **10** was unexpected and is described in the communication following this one. When 2-methyleneoxetane **11** was subjected to the standard reducing conditions, no green color resulted, even

$$\text{5} \quad \xrightarrow[\text{electrophile}]{\text{Li, DTBB}} \quad \textbf{6} \tag{2}$$

Table 1

Electrophile	Product	% Yield
Water	**6a**	86
Cyclohexanone	**6b**	48
Pivalaldehyde (1 equiv)	**6c**	45
Pivalaldehyde (2 equiv)	**6c** **6d**	22 18
Acetaldehyde (1 equiv)	**6e**	43
TMSCl	**6f**	100*
methyl iodide	**6g** **6h**	17 (1:1)

*Based on ^{1}H NMR

when the suspension was warmed to rt and allowed to stir overnight. Ultimately, most of the starting material disappeared; however, ^{1}H NMR of the crude reaction mixture showed a mixture of products. The only two isolated compounds, as an inseparable mixture (25% yield), were alkenes **12**[20] and **13**. This result suggests that for the formation of **12** and **13** reductive cleavage occurred at the O1–C2 bond to give, initially, a vinyl radical/oxyanion. We are investigating other 4-substituted (non-phenyl) 2-methyleneoxetanes to determine if the reversal in regioselectivity is general. In addition, we are altering the reaction conditions to see if it is possible to trap the benzylic anion in a regioselective fashion, followed by capture of the less reactive enolate anion.

Acknowledgements

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17. 2-Methyleneoxetanes **5** and **11** were prepared by the procedure described in Ref. 15a. All new compounds have been fully characterized.

18. 3,3-Dimethyl-1-cyclohexyl-1-ol-4-phenyl-2-butanone (**6b**): 3,3-Dimethyl-4-phenyl-2-methyleneoxetane (**5**) (50 mg, 0.28 mmol) in dry THF (2 mL) was added to a cooled ($-78°$C) suspension under N_2 of Li powder (30 mg, 4.30 mmol) and a catalytic amount of DTTB (8.00 mg, 0.028 mmol) in dry THF (1 mL). The resulting deep green suspension was stirred for 2 h at rt. The reaction mixture was cooled ($-78°$C), and cyclohexanone (0.16 mL, 1.49 mmol) in THF (5 mL) was added dropwise. The reaction mixture was stirred at $-78°$C for 1 h, followed by quenching with H_2O (5 mL). The mixture was then extracted with Et_2O (3×10 mL). The organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo. Purification by flash chromatography on silica gel (dry loaded CH_2Cl_2) (petroleum ether:EtOAc, 90:10) yielded a colorless oil (76 mg, 48%): IR ($CHCl_3$): 3300, 2900, 1760, 780 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08–7.28 (m, 5H), 2.81 (s, 2H), 2.58 (s, 2H), 1.21–1.73 (m, 10H), 1.12 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.5, 137.4, 130.4, 128.0, 126.5, 70.5, 48.9, 47.3, 45.3, 37.5, 25.7, 24.2, 23.9, 21.8; anal. calcd for $C_{18}H_{26}O_2$: C, 78.78; H, 9.56. Found: C, 78.52; H, 9.68.

19. For examples of tandem aldol–Tischenko reactions, see: Bodnar, P. M.; Shaw, J. T.; Woerpel, K. A. *J. Org. Chem.* **1997**, *62*, 5674–5675, and references cited therein.

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