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A base-promoted deprotection of 1,3-dioxolanes to ketones

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ABSTRACT

An effective deprotection methodology of dioxolanes was developed, affording moderate to excellent yield via a LTMP-promoted reaction in THF, which displays admirable chemoselectivity in the presence of dimethylketal, 1,3-dioxane, 1,3-dithiane, or other acid-sensitive protective groups.

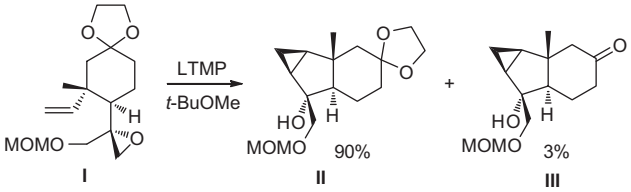
Acetals and ketals are commonly used protective groups for carbonyl compounds in organic synthesis. Accordingly, there are many solutions for the conversion of acetals and ketals into carbonyl compounds, mostly by acidic hydrolysis or acid-catalyzed exchange with acetone;[1] however, such conditions are incompatible with acid-labile functional groups (–OTBS, –OMOM etc.) within the same molecule. To solve this problem, milder reagents[2] were utilized for the deprotection of acetals and ketals, including the application of a catalytic amount of transition metal or Lewis acid reagents,[3] silicon reagents,[4] iodine reagents,[5] and others.[6] A solution under basic condition with TESOTf-2,6-lutidine or TESOTf-2,4,6-collidine for deprotection of acetals in dichloromethane followed by aqueous workup has been reported as well.[7] However, the development of a novel and potentially chemoselective deprotection method with base is still strongly desirable.

Interestingly, in the course of our total synthesis of (±)-chloranthalactone A,[8] treatment of compound **I** with lithium 2,2,6,6-tetramethylpiperidide[9] (LTMP) not only generated the 3/5/6 tricyclic compound **II** in 90% yield smoothly, but also provided ketone **III** in 3% yield (Scheme 1). Considering the successful cleavage of 1,3-dioxolane in this particular condition albeit in relatively low yield, we anticipate that it may afford a novel method to deprotect 1,3-dioxolane of ketones.

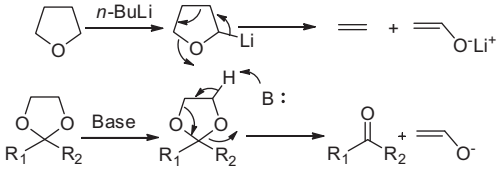
It is well known that when *n*-BuLi is stored in tetrahydrofuran, THF may undergo metallation at the α-position; the formed anion can then break down through a fragmentation process to generate ethylene and enolate of acetaldehyde (Scheme 2).[10]

Accordingly, we envisaged that 1,3-dioxolanes might go through the similar mechanism with base, and generate the enolate of acetaldehyde and ketones (Scheme 2). Herein we would like to report our results on this LTMP-promoted reaction.

Initial studies were focused on the deprotection of 1,3-dioxolane of α-tetralone (**1a**) with various bases which play a very crucial role in this reaction (Table 1, entries 1–8). No reactions took place for the application of LiHMDS, KHMDS, and *t*-BuOK at 0 °C or even room temperature. As for *n*-BuLi, ketone **2a** was generated in 28% yield, along with compound **3** in 60% yield, which was generated by *n*-BuLi attacking on the generated ketone **2a**. Other com-



Scheme 1.



Scheme 2.

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† These authors contributed equally to this work.

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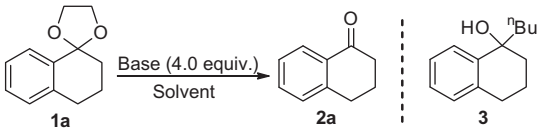
Table 1
Optimization of the reaction conditions[a]



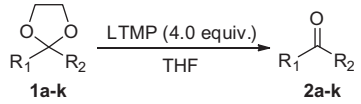
Entry	Solvent	Base	Temperature	Yield of **2a**[b]
1	THF	LiHMDS	0 °C to rt	NR[c]
2	THF	KHMDS	0 °C to rt	NR
3	THF	*t*-BuOK	0 °C to rt	NR
4	THF	*n*-BuLi	0 °C	28%
5	THF	LDA	0 °C to rt	61%
6	THF	*s*-BuLi	0 °C	60%
7	THF	*t*-BuLi	0 °C	68%
8	THF	LTMP	0 °C	76%
9	1,4-Dioxane	LTMP	0 °C to rt	NR
10	DME	LTMP	0 °C to rt	NR
11	*t*-BuOMe	LTMP	0 °C to rt	42%
12	Et_2O	LTMP	0 °C to rt	17%
13	Toluene	LTMP	0 °C to rt	Trace
14	DMF	LTMP	0 °C	0%
15	THF	LTMP	−20 °C	91%
16	THF	LTMP	−40 °C	28% brsm[d]

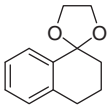
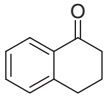
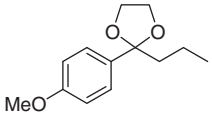
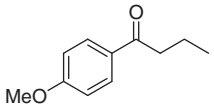
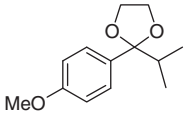
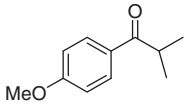
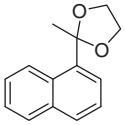
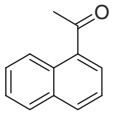
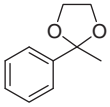
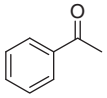
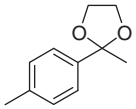
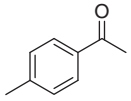
[a] Unless otherwise specified, the reaction was carried out with **1a** (0.5 mmol) and the corresponding base (2.0 mmol) in solvent (5 mL) under argon atmosphere and was monitored by TLC to ensure complete conversion.
[b] Isolated yields.
[c] NR = no reaction.
[d] The starting material was recovered in 39% yield. brsm = based on the recovered starting material.

mon bases such as LDA, *s*-BuLi, and *t*-BuLi were effective and afforded better yields (Table 1, entries 5, 6, 7). To our delight, LTMP in THF can provide the deprotected product in the most satisfactory yield (76%, Table 1, entry 8). So LTMP was selected as the optimum base for this particular reaction. We next examined the effect of solvent and noticed that no reaction occurred in dioxane or diglyme at 0 °C or even at room temperature, and inferior yields were obtained in *tert*-butyl methyl ether (42%) or diethyl ether (17%). Trace product was obtained in toluene even after the reaction was warmed from 0 °C to room temperature for a long time. A complex mixture of products was gained in DMF, without ketone **2a** being detected. The temperature plays a very important role for the cleavage of dioxolanes with LTMP since the best yield (91%) of α-tetralone (**2a**) can be achieved at −20 °C. It is worth noting that the reaction activity is too low at −40 °C with **2a** obtained in only 28% yield based on the recovered starting material. Thus the following reaction conditions were chosen as the optimal: 0.5 mmol of 1,3-dioxolanes and 2.0 mmol of LTMP in 5 mL THF at −20 °C or a higher temperature under argon atmosphere.

Next the scope of this reaction was further investigated and the temperature was screened again for different substrates to ensure the best transformation. As shown in Table 2, both the aromatic and the aliphatic dioxolanes are applicable in this methodology. Linear substrates **1a**–**1d** and cyclic substrates **1j**–**1k** pleasingly provided the desired products **2a**–**2d** and **2j**–**2k** in satisfying yields (Table 2, entries 1–4 and entries 10–11). Furthermore, the reaction was also successful for compounds **1e**–**1i**. Substituted aromatic dioxolanes with both electron-donating and electron-withdrawing groups at the para positions, produced the corresponding products

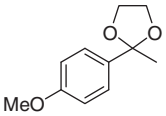
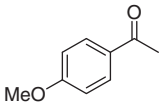
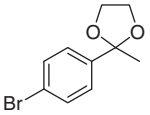
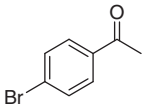
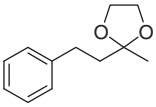
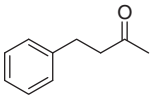
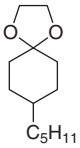
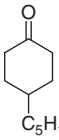
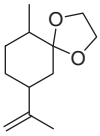
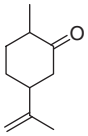
Table 2
Deprotection of 1,3-dioxolane of ketones[a]



Entry	Starting materials[b]		Temperature	Product **2**		Yield of **2**[c]
1		**1a**	−20 °C		**2a**	91%
2		**1b**	−20 °C		**2b**	86%
3		**1c**	0 °C - rt		**2c**	80%
4		**1d**	0 °C - rt		**2d**	70%
5		**1e**	0 °C - rt		**2e**	63%
6		**1f**	−20 °C - 0 °C		**2f**	65%

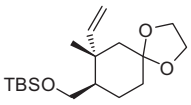
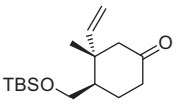
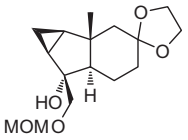
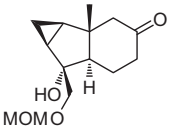
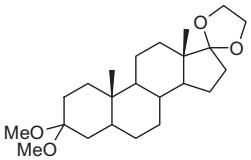
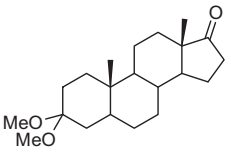
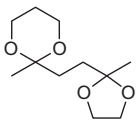
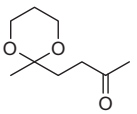
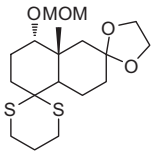
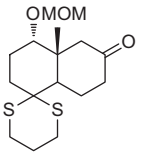
(*continued on next page*)

Table 2 (*continued*)

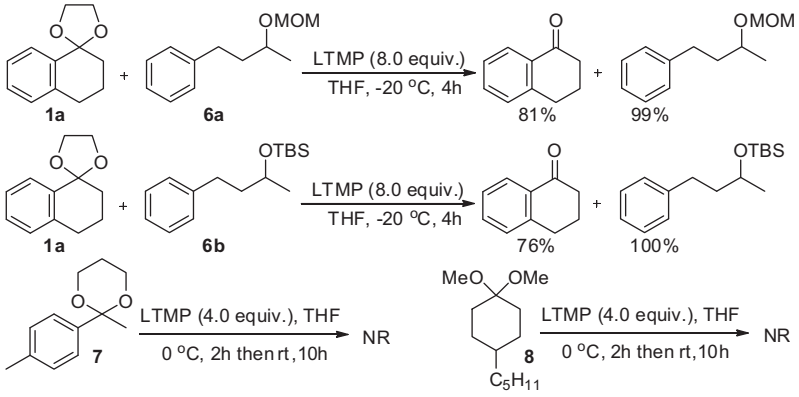
Entry	Starting materials[b]		Temperature	Product **2**		Yield of **2**[c]
7		**1g**	0 °C - rt		**2g**	66%
8		**1h**	−20 °C		**2h**	63%
9		**1i**	0 °C		**2i**	65%
10		**1j**	−20 °C - rt		**2j**	74%
11		**1k**	−20 °C - rt		**2k**	85%

[a] Unless otherwise specified, the reaction was carried out with **1** (0.5 mmol) and LTMP (2.0 mmol) in THF (5 mL) under argon atmosphere and was monitored by TLC to ensure complete conversion. The reaction time is not more than 16 h (see Supplementary data).
[b] All starting materials were prepared in the presence of trialkyl orthoformate and a catalytic amount of tetrabutylammonium tribromide (TBATB) in ethylene glycol.
[c] Isolated yields.

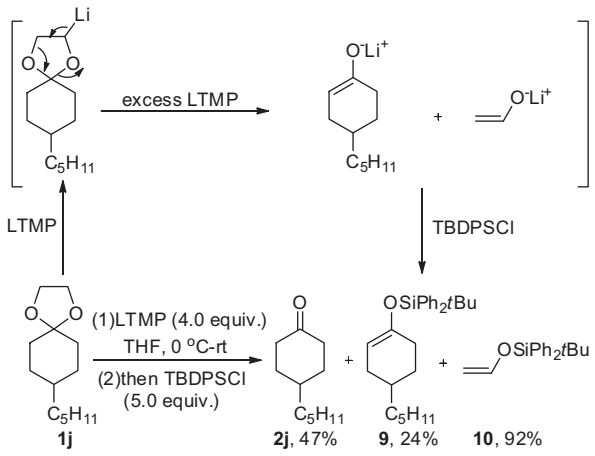
Table 3
Chemoselective deprotection of dioxolanes in the presence of acid-sensitive protective groups or 1,3-dithiane of ketal[a]

Entry	Starting materials		Temperature	Product **5**		Yield of **5**[b]
1		**4a**	0 °C - rt		**5a**	77%
2		**4b**[c]	0 °C - rt		**5b**	85%
3		**4c**	0 °C - rt		**5c**	78%
4		**4d**	0 °C - rt		**5d**	67%
5		**4e**	0 °C - rt		**5e**	75%

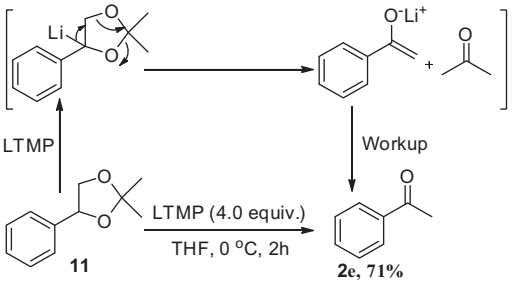
[a] Unless otherwise specified, the reaction was carried out with **4** (0.5 mmol) and LTMP (2.0 mmol) in THF (5 mL) under argon atmosphere and was monitored by TLC to ensure complete conversion. The reaction time is not more than 16 h (see Supplementary data).
[b] Isolated yields.
[c] The reaction was carried out with **4b** (0.5 mmol) and LTMP (3.0 mmol) in THF (5 mL) under argon atmosphere.



Scheme 3.



Scheme 4.



Scheme 5.

in similar results (Table 2, entries 5–8), illustrating that electronic factor is not pivotal for this reaction. Accordingly compound **1i** without typical electronic contribution also provided a similar result as compounds **1e**–**1h** (Table 2, entry 9). However, the methodology failed to give the desired products when it was applied to dioxolanes from aldehydes or conjugated ketones.

More importantly, this methodology displays excellent chemoselectivity in the presence of acid-sensitive protective groups as illustrated in Table 3. Compounds **4a**–**4b** with protected hydroxyl groups in the molecule were examined and transformed to the deprotected ketals **5a**–**5b** smoothly (Table 3, entries 1–2). Other examples were shown for the smoothly chemoselective deprotection of 1,3-dioxolane in the presence of 1,3-dioxane or dimethylketal or 1,3-dithiane (Table 3, entries 3–5).

To illustrate the generality of this chemoselectivity, control experiments were conducted. When an equimolar mixture of dioxolane of α-tetralone **1a** and 4-phenyl-2-butanol protected by the *tert*-butyldimethylsilyl (TBS) or methoxymethyl (MOM) (**6a**–**6b**) was treated with LTMP, compound **1a** was chemoselectively deprotected over compounds **6** (Scheme 3). The preferential deprotection of 1,3-dioxolanes over 1,3-dioxanes and dimethylketal was also elucidated. When 1,3-dioxane (**7**) or dimethylketal (**8**) was treated with LTMP in THF at 0 °C for 2 h and then at room temperature for 10 h, no reaction occurred in the end (Scheme 3).

To have insightful information on the reaction mechanism, a trapping experiment was executed. Thus exposure of **1j** to LTMP in THF furnished the enolate of ketone and acetaldehyde through a fragmentation process, which were trapped with TBDPSCl to afford compounds **9** and **10** along with compound **2j** (Scheme 4). The observation of compound **2j** could be ascribed to the inefficient silylation of lithium enolate of **2j** by TBDPSCl.[11]

Interestingly, when compound **11** was treated with LTMP in THF, **2e** was obtained in 71% yield. The formation of compound **2e** could be rationalized with the mechanism in Scheme 5. Other than the unfunctionalized 1,3-dioxolanes, the stabilizing effect of aromatic ring on carbanion makes the benzyl position deprotonated more facilely. The mechanistic pathway herein compensates that illustrated in Scheme 3, altogether elucidating the reason why dimethylketal and dioxane are inert under the same basic condition.

In summary, we have developed an effective deprotection methodology of dioxolanes derived from ketones, showing significant chemoselectivity in the presence of acid-sensitive protected hydroxyls and other ketals. We believe it could get wide application in organic synthesis.

Acknowledgments

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Supplementary data

Supplementary data (characterization data for new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.037.

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9. 2,2,6,6-Tetramethylpiperidide can be easily obtained from commercial suppliers at price 80$per 250 g in China.
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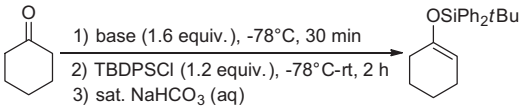
11. Model reactions with cyclohexone were tested, proving that the counterion of the enolate is crucial for this silyl trapping:



entry	base	yield
a	LTMP	24% (40% cyclohexone recovered)
b	LHMDS	23% (43% cyclohexone recovered)
c	KHMDS	94%