A Mild and Efficient Bisaldolization of Ketones and its Application towards Spirocyclic 1,3-Dioxanes and Novel 1,3,5-Trioxocanes

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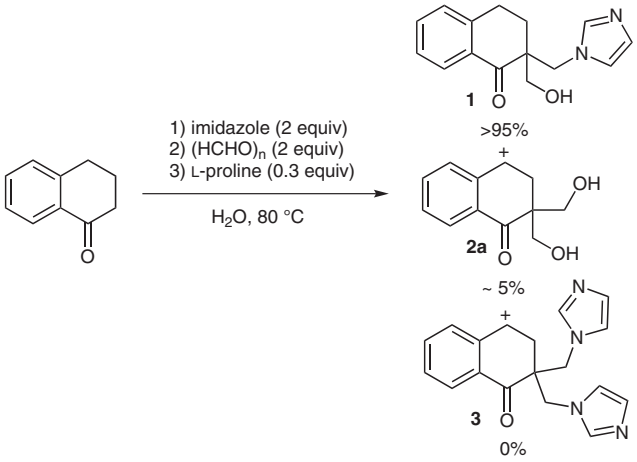
Abstract: Bisaldolization of aryl alkyl ketones as well as cyclic ketones with paraformaldehyde in the presence of a catalytic amount of L-proline and low concentration of aqueous sodium hydroxide has been developed in excellent yields. Further, these bisaldols are elaborated to the corresponding spirocyclic dioxanes and novel spirocyclic trioxocanes in the presence of *p*-toluene sulfonic acid. The structures and preferred conformations of these eight-membered spirocyclic 1,3,5-trioxocanes are discussed.

Key words: aqueous media, bisaldol, Mannich adduct, Mannich-aldol, L-proline, spirocylic dioxane, trioxocane

Bisaldol (1,3-diol) units are frequently found in complex polyol architectures (which are raw material for lubricants, surface coatings, and synthetic resins) of natural products and have attracted a great deal of attention from synthetic organic chemists.[1] Mostly 1,3-diol units are the key substrates for the synthesis of dendrimers (drug carriers) and crown-ethers.[2] The traditional production methods of these bisaldols use strong alkali and several anion-exchange resin catalysts.[3] These methods create mixture of products (aldol, cross-aldol, and acroleins) along with the required product.[4]

Cordova and co-workers have demonstrated the L-proline-catalyzed direct stereoselective aldol reaction between ketone and formaldehyde, which have triggered a broad interest in organocatalysis.[5] However, there is no report of bisaldolization under similar reaction conditions. Ibrahem et al. have introduced the first enantioselective three-component Mannich reaction of ketone, formaldehyde, and amine using L-proline as catalyst.[6] Later, Erkkila et al. and Wei Wang and co-workers used a similar type of strategy for synthesis of α,β-unsaturated aldehydes and ketones, respectively.[7] Based on this, we have reported the Mannich adducts and Mannich–aldol products of unsubstituted azoles using L-proline as a catalyst for the first time.[8]

In connection with this study and our continued interest on azole-based compounds,[9] we conducted an initial reaction of ketone (1.0.equiv), paraformaldehyde (2.0 equiv), and L-proline (0.3 equiv) with excess of imidazole (2.0 equiv). The reaction proceeded smoothly to furnish the Mannich–aldol-type compound **1** (ca. 93–95%) along with small amount of bisaldol product **2a**, but no bis-Mannich adduct **3** was observed (Scheme 1). This observation is consistent with the previous report that the unsubstituted azoles cannot form iminium ions with aldehydes,[10] so the Mannich adduct of imidazole, such as compound **1** (Scheme 1), is likely to form by a mechanism that proceeds first through aldol reaction with paraformaldehyde, then elimination to generate *exo*-enone and subsequent conjugate addition of the azole.



Scheme 1 Mannich adducts of azoles with excess of imidazole

Herein, we report a very efficient L-proline and aqueous NaOH-catalyzed bisaldol reaction of aryl alkyl and cyclic ketones in water.[11] The use of water makes it an easy handling and attractive alternative for large-scale production of bisaldols. We also report the elaboration of these bisaldols into corresponding spirocyclic 1,3-dioxanes **9–16a** and novel spirocyclic 1,3,5-trioxocanes **10b–16b**.

We next performed the above reaction (Scheme 1) using more than 2.0 equivalents of imidazole and observed that the bisaldol product **2a** also increased up to certain extent (5–7%). Hence, we anticipated that bisaldol formation is favored by increasing the basicity of the reaction medium. This presumption was confirmed by carrying out the reaction of tetralone (1.0 equiv), paraformaldehyde (4.0 equiv), and L-proline (40.0 mole%) in aqueous 0.2 M NaOH (instead of imidazole) at ambient temperature to furnish exclusively the bisaldol product in excellent yields (Table 1, **2a**). Consequently, by increasing the molar ratio of aqueous NaOH (>0.2 M), several products were found in the reaction mixture (from TLC observation). Howev-

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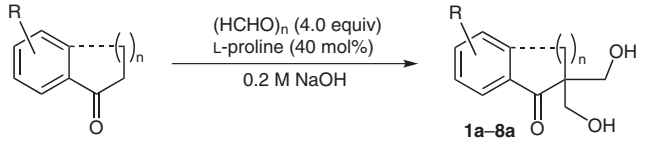
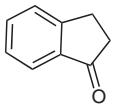
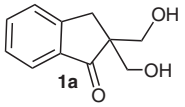
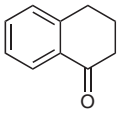
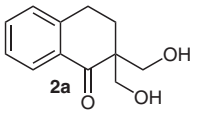
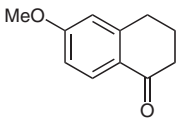
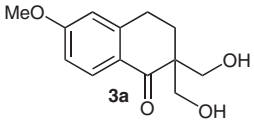
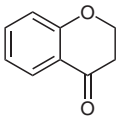
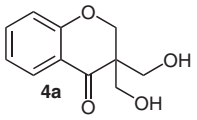
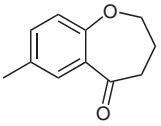
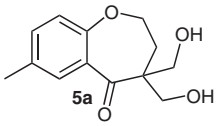
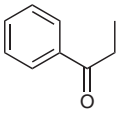
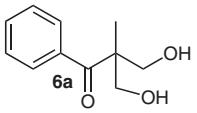
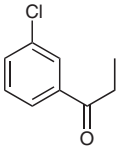
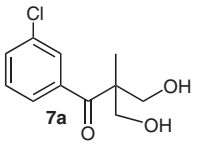
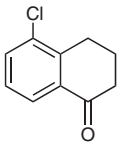
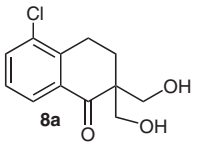
Table 1 L-Proline and Aqueous NaOH-Promoted Bisaldol Reaction of Ketones with Paraformaldehyde[a]



Entry	Ketone	Product[b]	Time (h)	Yield (%)[c]	mp (°C)
1			5	88	83
2			4	96	98
3			4.5	95	106
4			4	97	78
5			4	98	84
6			6.5	87	oil
7			6	89	90
8			3.5	89	93

[a] For general synthetic procedure see References and Notes section.
[b] Products identified by ^{1}H NMR and ^{13}C NMR spectroscopy.
[c] Isolated yields.

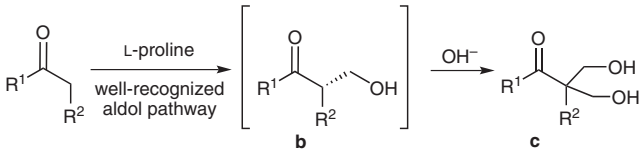
er, in the absence of L-proline the ketone was not consumed, and the formation of bisaldol adduct was not observed.

Encouraged by the results obtained in the above reaction and in order to show the generality and scope of this new protocol, a wide variety of cyclic and aryl alkyl ketones were evaluated and the results are summarized in Table 1. These ketones reacted efficiently with paraformaldehyde to afford the desired products in high yields (**1a**–**8a**).

Further, instead of L-proline different amines were also examined in bisaldolization using the same reaction conditions. However, in the presence of secondary amines like pyrrolidine or morpholine the Mannich product of these amines were obtained in major amount (total amine involved in the reaction)[12] with only traces of the desired bisaldol product. Thus, the best results for bisaldolization were obtained with L-proline as catalyst.

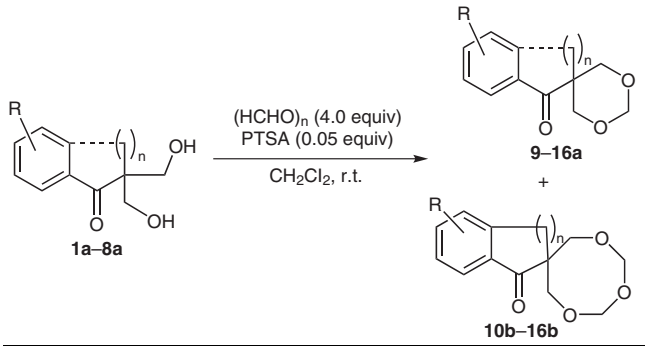
We speculate that the above reaction proceeds through an L-proline-catalyzed aldol formation[13] and subsequent generation of enol in the presence of alkali followed by conjugate addition of formaldehyde to furnish the bisaldol. To confirm this, we performed the reaction of a

ketone with paraformaldehyde and L-proline in the absence of NaOH. The only product isolated was the monoaldol **b**. On addition of 0.2 M aqueous NaOH, the reaction proceeded very fast to completion and furnished the desired bisaldol **c** (Scheme 2).



Scheme 2

Table 2 Transformation of Bisaldols to Corresponding Spirocyclic Compounds[a]



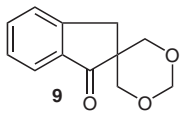
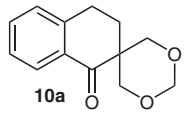
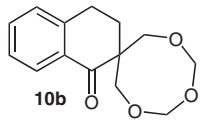
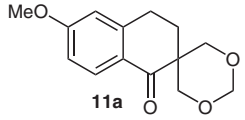
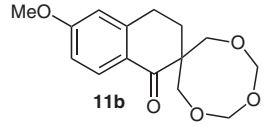
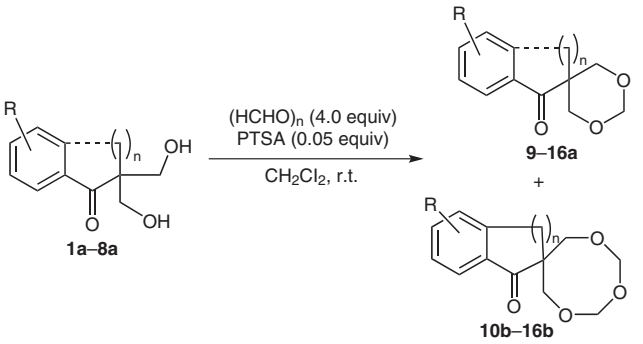
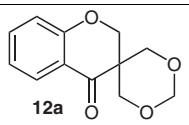
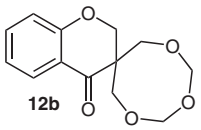
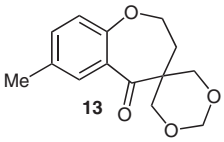
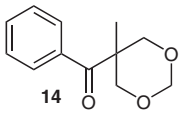
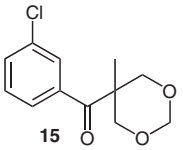
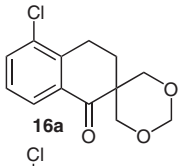
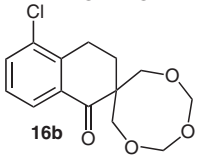
Entry	Product[b]	Time (h)	mp (°C)	Yield (%)[c,d]
1	 **9**	12	82	99
2	 **10a**  **10b**	11	47 oil	100 (45:55)
3	 **11a**  **11b**	11.5	101 oil	100 (35:65)

Table 2 Transformation of Bisaldols to Corresponding Spirocyclic Compounds[a] (continued)



Entry	Product[b]	Time (h)	mp (°C)	Yield (%)[c,d]
4	 **12a**  **12b**	12	oil 62	97 (46:51)
5	 **13**	9	88	100
6	 **14**	8	102	98
7	 **15**	8.5	128	96
8	 **16a**  **16b**	10.5	oil 134	100 (44:56)

[a] For general synthetic procedure see References and Notes section.
[b] Corresponding bisaldols are the starting materials.
[c] Isolated yields.
[d] Both spirocyclic 1,3-dioxane and 1,3,5-trioxocanes mentioned in specified ratios.

We further elaborated these bisaldols into spirocyclic ring systems. Thus, a reaction between bisaldol **2a** with paraformaldehyde and catalytic amount of PTSA[14] in CH_2Cl_2 at room temperature resulted in the expected six-

membered spirocyclic 1,3-dioxane **10a** along with unexpected eight-membered spirocyclic 1,3,5-trioxocane **10b** in almost equal amounts. Bisaldols **1a**–**8a**[15] were used to furnish the corresponding spirocyclic compounds **9**–**16b**,[16] and the results are summarized in Table 2. It can be seen from Table 2 that all the bisaldols **1a**–**8a** reacted to provide corresponding 1,3-dioxanes **9**–**16a**. Interestingly, it can also be seen that only chromanone and tetralone derived bisaldols **2a**, **3a**, **4a**, and **8a** reacted to provide the corresponding 1,3,5-trioxocanes **10b**, **11b**, **12b**, and **16b**, respectively.

To the best of our knowledge no report concerning spirocyclic 1,3,5-trioxocanes exist. However, limited number of literature is available regarding 1,2,4-, 1,3,5-, and 1,3,6-trioxocanes.[17] Based on earlier reports we hypothesized that the large molecules like the spirotrioxocanes are unstable under extreme (high temperature, pressure, and microwave-assisted) conditions.[18] However, the reactions performed at ambient temperature and mild conditions have permitted us to the isolate and characterize these novel compounds.[19]

The structure and conformation of spirocyclic trioxocanes was deduced from the ^{1}H NMR, ^{13}C NMR, and 2D NMR data. The conformational flexibility could lead to two conformers **I** and **II** in which the eight-membered trioxocane ring is stable in crown shape (Figure 1). This was confirmed by the 2D NOESY cross peaks between H-2/H-8 and H-2/H-4 of all the same pole protons (like H-2, the H-4, H-6, and H-8 are also correlating). The energy-minimized structure **III** also supported the same fact.

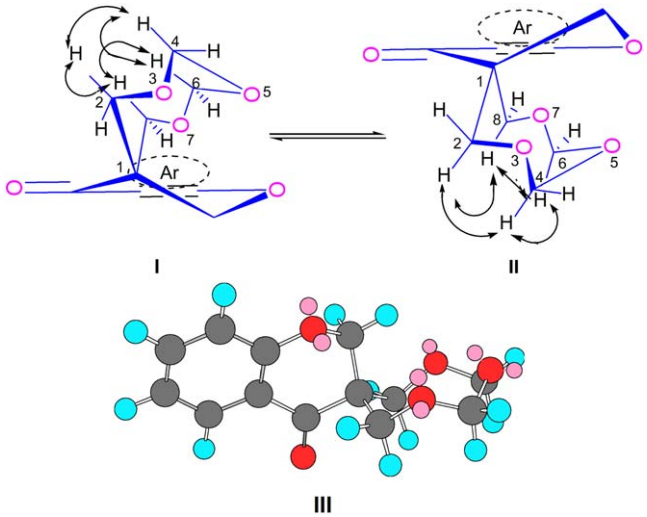


Figure 1 Characteristic NOE and energy-minimized structure of **12b** was optimized from MM and MD simulations

In summary, we have developed a very efficient and mild reaction for synthesizing bisaldols from cyclic and aryl alkyl ketones and converted them into spirocyclic 1,3-dioxanes and novel spirocyclic 1,3,5-trioxocanes. Further elaboration of this transformation and its synthetic applications are ongoing in our laboratory.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(15) **General Procedure for the Preparation of Bisaldols 1a–8a (e.g., 2a)**
A solution of a-tetralone (1.0 mmol), paraformaldehyde (4.0 mmol), and L-proline (40 mol%) in H_2O (0.5 mL) was stirred at r.t. for 34 h. To this added 0.53 M NaOH (0.3 mL) solution slowly. After completion of the reaction (monitored by TLC) the reaction mixture was extracted with EtOAc (3 × 4 mL). The combined organic extracts were washed with distilled H_2O (5 × 3 mL), dried over Na_2SO_4, and removal of the solvent under reduced pressure furnished the crude product, which was filtered through SiO_2 column (EtOAc–hexane = 1:2, v/v) to give **2a** (96%) as a white solid; mp 98–99 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.98 (t, *J* = 6.4 Hz, 2 H), 3.01 (t, *J* = 6.4 Hz, 2 H), 3.62 (br s, 2 H), 3.71–3.95 (dd, *J* = 11.3 Hz, 4 H), 6.69 (m, 2 H), 6.84 (d, *J* = 8.8 Hz, 1 H), 7.97 (d,

J = 8.8 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.9, 26.4, 51.2, 64 (2 C), 126.8, 127.6, 128.9, 131.6, 134.1, 143.8, 203.1. ESI-MS: *m/z* (%) = 207 (100) $[M + 1]^+$.

(16) **General Procedure for the Preparation of 9–16b (e.g., 10a,b)**
A mixture of 2,2-bishydroxymethyl-3,4-dihydro-2*H*-naphthalen-1-one (**2a**, 1.0 mmol), paraformaldehyde (4.0 mmol), and catalytic amount of PTSA (0.05 equiv) in CH_2Cl_2 (6 mL) was stirred at ambient temperature for 11 h. After completion of reaction (monitored by TLC), the reaction mixture was filtered through sintered funnel. The filtrate was washed with 1% aq $NaHCO_3$ solution (2 × 2 mL), followed by H_2O (3 × 2 mL), and dried over anhyd Na_2SO_4. Removal of the solvent under vacuum afforded the crude mixture of corresponding spirocyclic 1,3-dioxane **10a** and 1,3,5-trioxocane **10b** in quantitative amount. The above mixture was subjected to Florisil column (EtOAc–hexane = 1:20, v/v) to give pure products (**10a** and **10b** in a 1:1.2 ratio). Compound **10a**: mp 46–47 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ= 2.92 (t, J = 6.9 Hz, 2 H), 3.66 (d, J = 11.6 Hz, 2 H), 3.98–4.07 (dd, J = 11.6 Hz, 2 H), 4.69 (d, J = 5.8 Hz, 2 H), 5.24 (d, J = 5.8 Hz, 2 H), 7.18 (m, 1 H), 7.31 (m, 2 H), 7.63 (d, J = 6.4 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.8, 27.5, 45.9, 70.6 (2 C), 94.3, 126.8, 127.7, 128.9, 131.7, 133.9, 143.2, 198.1. IR (KBr): 3222, 2361, 1708, 1221, 1165, 762, 667 cm^{-1}. ESI-MS: *m/z* (%) = 219 (77) $[M + 1]^+$.
Compound **10b**: oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.26 (t, J = 6.4 Hz, 2 H), 3.04 (t, J = 6.4 Hz, 2 H), 3.82–4.21 (dd, J = 12.0 Hz, 4 H), 4.8 (d, J = 6.7 Hz, 2 H), 4.96 (d, J = 6.4 Hz, 2 H), 7.34 (m, 2 H), 7.52 (m, 1 H), 8.03 (d, J = 7.8 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.8 (2 C), 28.7, 29.6, 49.6, 69.9, 95.9, 126.7, 127.8, 128.7, 131.4, 133.5, 143.2, 199.4. IR (neat): 3027, 2367, 1709, 1217, 1161, 767 cm^{-1}. ESI-MS: *m/z* (%) = 249 (100) $[M + 1]^+$.

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(19) Experimental procedures, characterization and 1D, 2D NMR spectra are available as supplementary data.