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Stoichiometric and catalytic reductive aldol cyclizations of alkynediones induced by Stryker's reagent†

Pauline Chiu* and Sze Kar Leung

Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong, P. R. China. E-mail: pchiu@hku.hk; Fax: +852 2857 1586; Tel: +852 2859 8949

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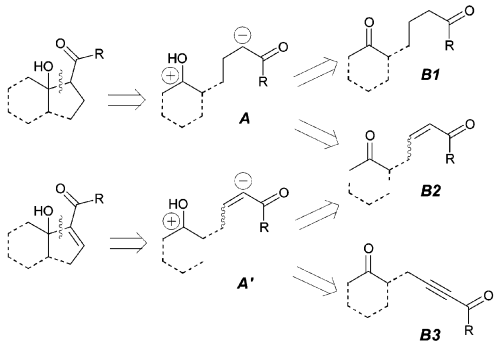
Conjugate reduction of alkynones by stoichiometric $[(Ph_3P)CuH]_6$ or catalytic $[(Ph_3P)CuH]_6$ and polymethylhydrosiloxane proceeds to cyclization by an aldol reaction with tethered ketones to generate β-hydroxyenones with good diastereoselectivity.

The β-hydroxyketone structure is a classical motif produced by the aldol reaction, one of the most used carbon–carbon bond forming reactions in synthetic organic chemistry (Scheme 1).[1] Retrosynthetically, the nucleophilic synthon *A* may be obtained from the parent ketone *B1*, which yields the enolate by deprotonation, or from a conjugated ketone such as *B2*, which is a latent enolate revealed upon conjugate reduction. The latter approach is especially advantageous over traditional base-induced aldol reactions in the regioselective formation of enolates in unsymmetrical ketones, or intramolecular aldol reactions of substrates with multiple carbonyl groups. Recently, efforts in this area resulted in the development of new stoichiometric and catalytic reductive aldol reactions using enones as precursors.[2,3]

From a β-hydroxyenone target structure, a similar aldol-type disconnection could be made (Scheme 1). The enolate synthon *A′* in this case cannot be readily generated by deprotonation. Nevertheless, the precursor could still be conjugated ketone *B2*, which is able to serve as the enolate equivalent of *A′ via* a Baylis–Hillman reaction.[4] There has been a sustained interest in this useful transformation, although typically it is still a very slow reaction and is further retarded by additional substituents in the alkenone as well as using ketones as electrophiles. Synthon *A′* may also be retroanalyzed to alkynone *B3*, which can yield an allenoate upon conjugate reduction. Herein, we report that stoichiometric Stryker's reagent $[(Ph_3P)CuH]_6$ **1**[5] is able to induce the conjugate reduction-tandem intramolecular aldol reaction of alkynones to realize the latter disconnection. Furthermore, the catalytic version of this reaction represents the first examples of non-radical, reductive aldol reactions catalyzed by complexes of copper.[6]

To investigate this reaction, alkynedione **2a** was synthesized and treated with a stoichiometric amount of **1** (Table 1, entry 1.1). The reaction proceeded rapidly even at −40 °C and was complete in 15 minutes to afford a 67% yield of cyclized aldol products **3a** and **4a**.‡



Scheme 1 Retrosynthetic analysis of β-hydroxyketones.

The use of silanes as a stoichiometric reductant to regenerate copper hydride has been amply demonstrated.[7] This reducing system has been exploited to accomplish copper-catalyzed reductions of a variety of activated olefins. Thus a reductive aldol reaction catalytic in **1** was deemed possible through the use of silanes as the stoichiometric reductant. Alkynedione **2a** was accordingly subjected to reaction with 10 mol% of **1** and a stoichiometric amount of PMHS (polymethylhydrosiloxane). Gratifyingly, this catalytic reductive reaction proceeded efficiently to furnish the same aldol products **3a** and **4a** in 97% combined yield (Table 1, entry 1.2). In both the stoichiometric and catalytic reductions, the major product was *cis*-fused β-hydroxybicycloalkenone **3a** from the mono-reductive aldol cyclization of **2a**, obtained as a single diastereomer.[8]

To examine the scope of the reaction, alkynedione systems **2b–f** were synthesized and subjected to reductive aldol cyclizations using stoichiometric and catalytic amounts of **1** (Table 1). Generally, reductive cyclizations to form five-membered rings were complete within one hour (Table 1, entries 1–3), while six-membered ring cyclizations required slightly longer times (Table 1, entries 4–6). In all cases, the major products obtained were the β-hydroxycycloalkenones **3b–f** from the mono-reductive aldol cyclization of the substrates. The *cis*-fused products were the sole or major diastereomeric products in all systems examined.[8]

The minor products obtained were derived from an apparent over-reduction. For instance, hydroxyketone **4a** was also isolated along with **3a** in the reductive aldol cyclization of **2a** (Table 1, entry 1.1, 1.2). The over-reduction yields ranged from 6–39%, and proceeded with varied diastereoselectivities. Whereas **4f** was obtained as the sole diastereomer, **4a** was obtained as a 9 : 1 mixture of epimers. In the reductions of **2b** and **2c**, the corresponding over-reduced products were enones **5b** and **5c**. Similar minor products were obtained in the catalytic reductive aldol reaction, including the over-reduced ketones **4**, dehydrated products **5**, as well as enones **6** from 1,4-reduction without cyclization. For example, in the catalytic reduction of **2b**, alkenedione **6b** (Fig. 1) was isolated exclusively as the (*E*)-diastereomer along with **3b** (Table 1, entry 2.3). It is possible to drive the reaction to exhaustive reduction in some cases. Either by resubjecting **3b** to the reduction, or reacting **2b** with excess **1** over prolonged reaction times, **5b** was isolated as the major product in 73 and 56% yields respectively.[9]

Although conjugated alkenoates underwent reductive aldol cyclizations with tethered ketones,[3] under a variety of reaction conditions using stoichiometric or catalytic **1**, the analogous alkynyl esters such as **7** (Fig. 1) did not undergo reductive aldol cyclization, and yielded only simple reduction products upon workup.

Notably, the present reductive aldol methodology provides β-hydroxycycloalkenone products which are complementary to those obtained efficiently from intramolecular Baylis–Hillman reactions. Whereas β-substituted alkenones and ketones make poor Michael receptors and electrophiles respectively for the Baylis–Hillman reaction, the reductive aldol cyclizations of the related

† Electronic supplementary information (ESI) available: experimental procedures and characterization for **2a–f**, **3a–f**, **4a–b,d–f**, **5b–c**, **6b,f**; ^{1}H and ^{13}C nmr spectra, ORTEP diagrams of **3b** and 2,4-DNPH-**3c**. See http://www.rsc.org/suppdata/cc/b4/b407842j/

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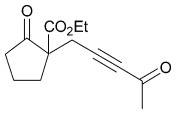
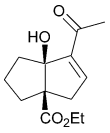
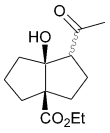
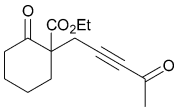
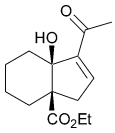
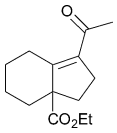
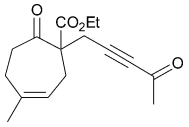
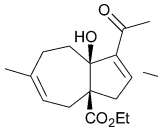
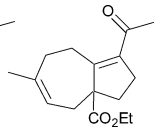
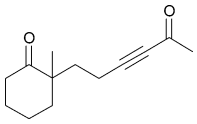
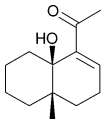
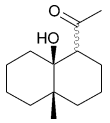
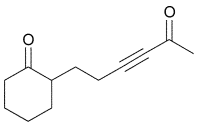
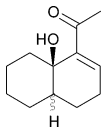
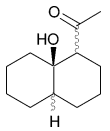
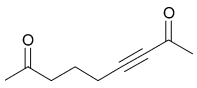
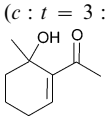
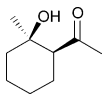
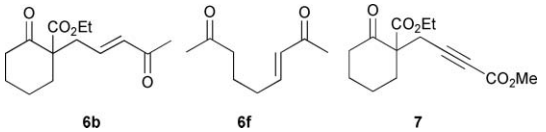
Table 1 Reductive aldol cyclizations induced by **1**

Entry	Substrate	T/°C (t/h)	Product/yield[a] (%)	
				
	2a		**3a**	**4a**
1.1		−40 (0.25)[b]	54	13
1.2		−40 (0.5)[c]	58	39
				
	2b		**3b**[d]	**5b**
2.1		−40 (1)[b]	48	16
2.2		25 (0.25)[b]	60	23
2.3		−40 (0.25)[c]	56	0[e]
				
	2c		**3c**[d]	**5c**
3.1		−40 (1)[b]	48	16
3.2		−40 (0.25)[c]	65	6
				
	2d		**3d**	**4d**
4.1		−40 (4)[b]	53	16
4.2		−40 (2.5)[c]	56	25
				
	2e		**3e**	**4e**
5.1		−40 (1.5)[b]	62 (c : t = 4 : 1)	14
5.2		−40 (0.5)[c]	53 (c : t = 3 : 1)	28
				
	2f		**3f**	**4f**
6.1		−40 (1.5)[b]	62	14
6.2		−40 (3)[c]	46	0[f]

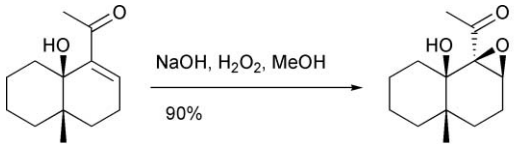
[a] Isolated yields. [b] Stoichiometric (1.5 equiv.) **1**, PhMe. [c] Catalytic (10 mol%) **1**, 2 equiv. PMHS, PhMe. [d] Structures of **3b** and 2,4-DNPH-**3c** derivative were elucidated by X-ray crystallography. [e] **6b** also isolated in 16% yield (Fig. 1). [f] **6f** also isolated in 24% yield (Fig. 1).



6b **6f** **7**

Fig. 1

alkynones mediated by **1** occur at low temperatures and mild conditions within hours. Significantly, six-membered ring formations occur readily as do five-membered ring annulations. The β-hydroxy-alkenone products thus obtained are highly functionalized synthetic intermediates that are amenable to further derivatization. For example, decalenone **3d** undergoes epoxidation to give oxirane **8** exclusively as one diastereomer with four contiguous stereocentres in high yield (eqn. 1).



3d **8** (1)

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Notes and references

‡ *Crystal data for* **3b**: $C_{14}H_{20}O_4$, M = 252.30, triclinic, a = 7.3680(15), b = 9.1860(18), c = 10.640(2) Å, V = 683.7(2) Å^3, T = 301 K, space group $P\bar{1}$, Z = 2, μ(Mo–Kα) = 0.089 mm^{-1}, 3246 reflections measured, 1933 unique (R_{int} = 0.0234). Final $R1$ = 0.0743, $wR2$ = 0.1917 (all data). *Crystal data for* 2,4-DNPH-**3c**: $C_{22}H_{26}N_4O_7$, M = 458.47, triclinic, a = 7.460(2), b = 8.609(2), c = 18.302(4) Å, V = 1140.9(4) Å^3, T = 301 K, space group $P\bar{1}$, Z = 2, μ(Mo–Kα) = 0.101 mm^{-1}, 5057 reflections measured, 3078 unique (R_{int} = 0.0194). Final $R1$ = 0.0767, $wR2$ = 0.1912 (all data). CCDC 240837 and 240836. See http://www.rsc.org/suppdata/cc/b4/b407842j/ for crystallographic data in .cif or other electronic format.

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8 The structures of all products were elucidated by 1-D and 2-D nmr spectroscopy and/or X-ray crystallographic analyses.
9 The over-reduced products could be derived from a second, *in situ* reduction of aldolates of **4**, or an *in situ* reductive cyclization of 1,4-reduction products such as alkenediones **6b** or **6f**.[3] Experiments are being done to elucidate the details of the mechanism.