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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 8705–8709

Elongation of β-hydroxyenones by cross-metathesis

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Received 7 September 2005; revised 30 September 2005; accepted 12 October 2005

Abstract—Enantioenriched aldol products derived from enones are notoriously difficult to prepare due to their sensitivity to retro-aldolisation, elimination and the requirement of a large excess of the enone donor for their preparation. However, some success has been obtained for the preparation of aldol products derived from methylvinylketone and pentenone using zinc-dinuclear catalysts or catalytic antibodies. Herein, we describe how simple first-generation hydroxyenones can be easily elongated by alkene exchange with structurally diverse olefinic partners in the presence of Ru-based metathesis catalysts allowing for the preparation of aldol products difficult to access by direct aldolisation. The data suggest that even though unprotected aldols are suitable for these cross-metathesis reactions, silyl-protected β-hydroxyenones generally afforded the desired elongated products in much higher chemical yields.

Direct catalytic asymmetric aldol reactions typically involve relatively simple ketones as donors.[1] Only limited progress has been made in catalytic enantioselective aldol reactions of enones and ynones despite the enormous synthetic potential of the corresponding multifunctional aldol products, which could be regarded as versatile building blocks. The major problems to overcome when using enones and ynones as donors, are their ability to act as powerful Michael acceptors and the tendency of the aldol products to undergo retro-aldolisations or eliminations. Thus, their use in aldol reactions is virtually unknown with the exception of two recent reports that described very elegant catalytic asymmetric aldol reactions using methyl vinyl ketone (MVK) and silyl-protected ynones in the presence of a dinuclear zinc catalyst.[2] These studies are limited to one representative enone (MVK) and two ynones used in combination with a large variety of aldehyde acceptors. Recently, we have demonstrated that the very mild nature of aldolase antibodies allows for the kinetic resolution of various racemic hydroxyenones providing the recovered aldols highly enantiomerically enriched.[3] Aldol products derived from long-chain enones could not be resolved and therefore, this biocatalytic strategy is also restricted to a limited number of substrates. Enantioenriched aldol products derived from simple enones such as MVK or pent-3-en-2-one are interesting as the existing stereogenic centre can be propagated further in a sequence of diastereoselective transformations and the double bond can be elongated upon cross-metathesis in the presence of olefinic partners.[4] In the literature, the cross-metathesis of α,β-unsaturated carbonyl derivatives has been extensively studied.[5] In contrast, to date, only two isolated examples of cross-metathesis reactions involving β-hydroxyenones have been reported in the literature (Scheme 1, Eqs. 1 and 2). These preliminary results also demonstrated that upon cross-metathesis, no epimerisation took place, allowing therefore for the formation of second-generation enantioenriched hydroxyenones.[2a,3] Herein, we report on the scope and limitation of this elongation process and on how general this transformation is to access β-hydroxyenones derived from first-generation aldol products and various readily available olefinic partners.

We prepared and studied the reactivity of four aldol products **1**–**4** formally derived from MVK or pent-3-en-2-one in combination with two conjugated aldehydes, namely, *p*-nitrobenzaldehyde and anisaldehyde. These aldol products **1**–**4**, being particularly sensitive to elimination, were selected to test the mildness of the proposed elongation procedure. Aldol products **1** and **2** derived from pent-3-en-2-one were prepared by direct aldolisation in the presence of LDA at low temperature. This strategy could not be applied for the preparation of aldol **3** as only products of decomposition were formed

Keywords: Cross-metathesis; Hydroxyenones; Aldol reaction.
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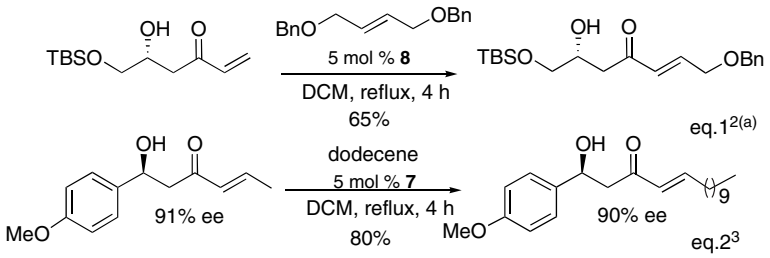
doi:10.1016/j.tetlet.2005.10.037



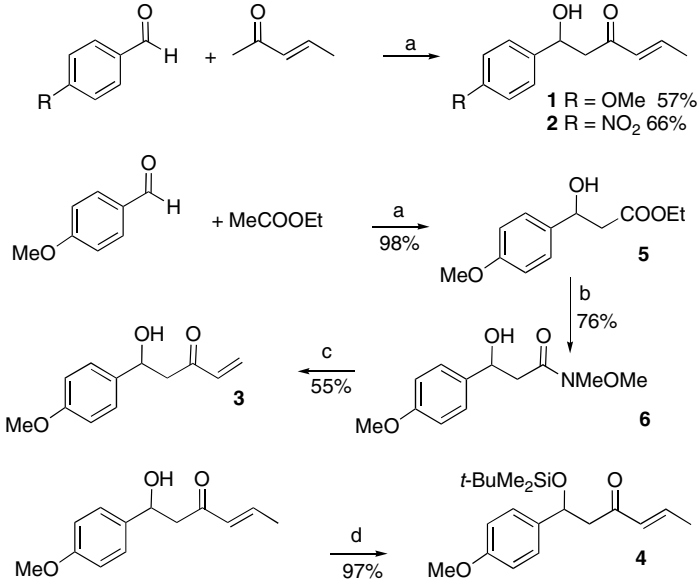
Scheme 1. Elongation of β-hydroxyenones.[2a,3]

under these conditions. The β-hydroxyenone **3** was prepared in good overall yield using a three-step sequence starting with the synthesis of β-hydroxyester **5** followed by the conversion of this ester into the corresponding Weinreb amide **6**. Treatment of the Weinreb amide **6** with an excess of vinylmagnesium bromide afforded the unsubstituted aldol product **3**, which was purified by fast filtration to avoid decomposition.

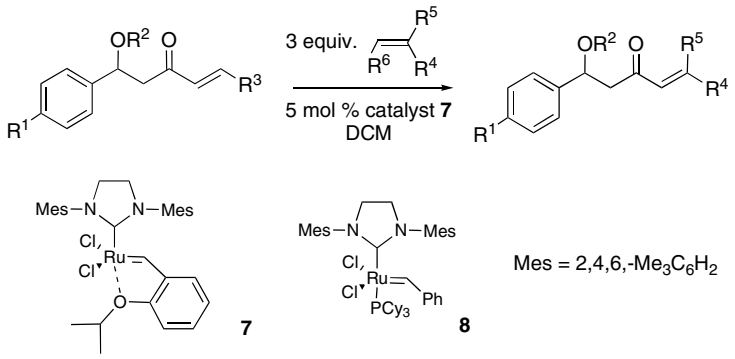
We also prepared the silyl-protected aldol product **4** to investigate to what extent the presence of the free hydroxy group was beneficial or detrimental for the cross-metathesis coupling. The direct protection of **1** was low yielding in the presence of *t*-BuMeSiCl and imidazole in DMF because the major compound formed under these conditions is the product resulting from a Michael addition of imidazole on the double bond.[6] However, the desired protected aldol **4** was obtained in 97% yield replacing imidazole with diisopropylethylamine (Scheme 2).[7]

In a preliminary study, we found that the most suitable catalyst for the cross-metathesis reaction of hydroxyenones was the Hoveyda–Grubbs catalyst **7**[8] although the second-generation Grubbs catalyst **8**[9] gave, in most cases, the desired products, albeit in lower yields. The reactions were best performed in dichloromethane at reflux or at room temperature using an excess of the olefinic partner. The use of toluene at 80 °C was not advantageous as under these conditions, products of elimination were formed in significant amounts. We therefore studied the scope and limitations of these cross-metathesis reactions using 5 mol % of the Hoveyda–Grubbs catalyst **7** in DCM using 3 equiv of the olefinic partner (Scheme 3).

Under these conditions, we examined the coupling of aldol products **1**–**4** with five representative olefinic partners, namely ethyl acrylate, methylene cyclohexane, hex-3-ene-1,6-diol, dodecene and styrene. Our results are summarised in Table 1. The data showed that for the unprotected aldol **1**, the cross-metathesis with dodecene and styrene proceeded smoothly to give the desired elongated products **9a** and **9b** in good yields (entries 1 and 2). Both products were formed and isolated as pure *E*-isomers. Methylene cyclohexane also proved to be a suitable substrate and allowed the formation of the *gem*-substituted hydroxyenone **9c** with an isolated chemical yield of 42% (entry 3). With olefins featuring electron-withdrawing groups such as ethyl acrylate, the reaction was low yielding with 24% of the desired aldol product **9d** isolated (entry 4). Similarly, the

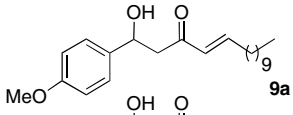
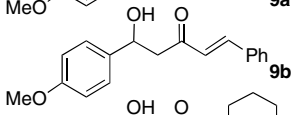
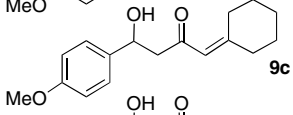
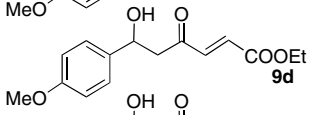
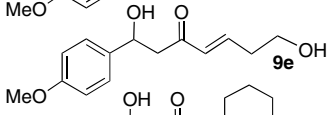
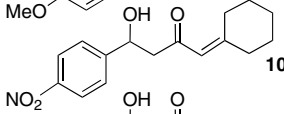
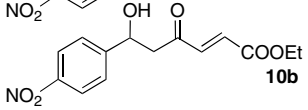
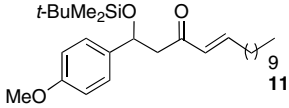
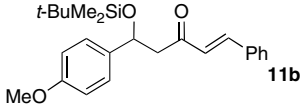
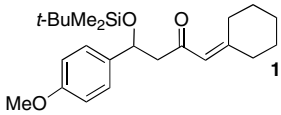
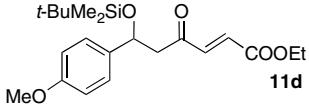
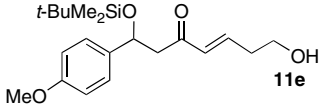


Scheme 2. Reagents and conditions: (a) LDA, THF, −78 °C, 0.5 h; (b) NH(OMe)Me, $AlMe_3$, 0 °C to rt, 3 h then 2 N HCl; (c) vinylmagnesium bromide, THF, 0 °C then NH_4Cl; (d) *t*-$BuMe_2SiCl$, *i*-$PrNEt_2$, DMF, rt, 48 h.

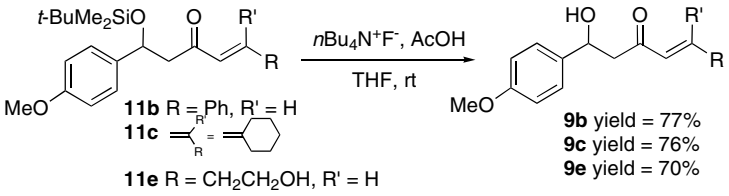


Scheme 3. Standard conditions for CM of β-hydroxyenones **1**–**4**.

Table 1. CM of aldol products **1**–**4**

Entry	Substrate, olefinic partner	Product	Yield[a] (%)
1	**1** or **3**, dodecene	 **9a**	85 from **1**[b] 76 from **3**[b]
2	**1** or **3**, styrene	 **9b**	66 from **1**[b] 70 from **3**[b]
3	**1** or **3**, methylene cyclohexane	 **9c**	42 from **1** 50 from **3**
4	**1**, ethyl acrylate	 **9d**	24
5	**1**, hex-3-ene-1,6-diol	 **9e**	24
6	**2**, methylene cyclohexane	 **10a**	55
7	**2**, ethyl acrylate	 **10b**	13
8	**4**, dodecene	 **11a**	91
9	**4**, styrene	 **11b**	80[c]
10	**4**, methylene cyclohexane	 **11c**	90
11	**4**, ethyl acrylate	 **11d**	62
12	**4**, hex-3-ene-1,6-diol	 **11e**	50

[a] Isolated yields.
[b] Reaction carried out at room temperature.
[c] % Conversion.



Scheme 4. Deprotection of aldol products **11b–c** and **11e**.

cross-coupling of **1** with the unprotected hex-3-ene-1, 6-diol was not synthetically useful as only 24% of the desired product **9e** could be recovered after column chromatography (entry 5). A similar trend of reactivity was observed for the unprotected aldol **2** derived from *para*-nitrobenzaldehyde instead of anisaldehyde, as reflected by the similar isolated yields for aldol products **10a–b** (entries 6 and 7). Aldol products **1** and **2** both possess a terminal methyl group that can potentially slow down the alkene exchange process. To test this hypothesis, we studied next the reactivity of the unprotected aldol product **3** derived from methyl vinyl ketone. In the presence of dodecene, styrene or methylene cyclohexane, all reactions proceeded smoothly to give the desired products **9a–c** with yields very similar to those obtained with aldol **1** suggesting that the cross-metathesis of terminal double bonds is not advantageous (entries 1–3). With the aim of improving the reaction yields, we investigated the reactivity of the silyl-protected aldol **4** to determine to what extent the presence of the free hydroxy group was affecting the efficiency of the cross-coupling (entries 8–12).[10]

The results revealed that for all the olefinic partners, the isolated yields of elongated products were significantly improved reaching 91% for the reactions involving unfunctionalised olefins (entries 8–10) and 62% with ethyl acrylate (entry 11). We were pleased to find that hex-3-ene-1,6-diol was a suitable olefinic partner for compound **4** as the desired elongated aldol product **11e** featuring both a silyl-protected secondary alcohol and a primary unprotected alcohol was isolated in 50% yield (entry 12). For all compounds **11a–e**, the *E*/*Z*-selectivity was excellent as no trace of the *Z*-isomer could be detected in the crude mixtures. The presence of the protected alcohol also presents the advantage of allowing for easy purification of the products. The deprotection of aldols **11a–e** was carried out using a mixture of TBAF and acetic acid in THF allowing the preparation of the free elongated aldol products **9b–c** and **9e** with chemical yields ranging from 70% to 77% (Scheme 4).[11] The purity is superior for these compounds by comparison with those obtained by direct cross-metathesis of the unprotected aldol products. This deprotection procedure is compatible with enantioenriched aldol products as previously demonstrated in our group for structurally related compounds.[12]

In summary, the CM is a highly *E*-selective and efficient transformation when applied to silyl-protected β-hydroxyenones for the preparation of aldol products that are difficult to prepare by direct aldol reactions and do not require preactivation of the pronucleophile. Indeed, in addition to the problems outlined in the introduction such as the sensitivity of β-hydroxyenones to retro-aldolisation and elimination, direct aldol reaction of enones requires the donor in excess and can therefore be applied only to readily available α,β-unsaturated ketones. The elongation process described herein circumvents these problems easily by allowing for the introduction of various substituents by a simple alkene exchange reaction carried out in the presence of a Ru-based metathesis catalyst.

Acknowledgements

The European Community is gratefully acknowledged for generous financial support to F.S. (MRTN-CT-2003-505020). We also thank Dr. Neil Hodnett who was funded by the Leverhulme Trust (F/08 341/B) for preliminary synthetic efforts on this project.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.10.037.

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