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Expanding the scope of the asymmetric anti-aldol addition of chiral *N*-amino cyclic carbamate hydrazones

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ABSTRACT

An asymmetric *anti*-aldol addition process of ketone-derived donors that is not limited by the structure of the ketone is described. This is achieved by merging the enantioselective α,α-bisalkylation of *N*-amino cyclic carbamate (ACC) hydrazones with the asymmetric *anti*-aldol addition of ACC hydrazones. The products of this process are obtained with essentially perfect stereoselectivity. Using this procedure it is possible to gain access to ketone-based *anti*-aldol addition products that are inaccessible in a controlled sense via direct aldol methods.

The asymmetric *anti*-aldol addition of ketone donors is an important synthetic transformation.[1] Remarkably, despite this, and in contrast to its *syn*-counterpart,[2] no general way of conducting the *anti*-aldol addition of ketone donors is available that is not limited by the structure of the ketone that can be used.[1] We recently described two new methods for the asymmetric α-functionalization of ketones through the use of *N*-amino cyclic carbamate (ACC) hydrazones, namely ACC α,α-bisalkyation[3] and ACC *anti*-aldol addition[4] (Scheme 1). In what follows, we demonstrate that by merging these two methods, the limitations associated with current ketone-based aldol reaction regarding the structure of the ketone that may be used can be overcome. Consequently, access to ketone-based aldol addition products that have previously been inaccessible in a controlled manner via direct aldol methods becomes possible.

Over the years, a few *anti*-selective aldol additions have been reported.[5] In the early 1990s, Heathcock and Patterson independently developed highly effective *anti*-selective methods for certain chiral, nonracemic α-, and β-substituted ketones.[6] More recently, some achiral ketones have been shown to undergo *anti*-aldol additions in the presence of organocatalysts.[7] Unfortunately, the latter transformations are also inherently limited with regard to the structure of the ketone that may be used. Specifically, only ketones for which regioselectivity of deprotonation is not a factor (e.g., symmetrical ketones, aryl alkyl ketones, etc.) are viable substrates. Previous attempts to use chiral auxiliaries for ketone-based aldol additions have met with variable success.[8] Given the importance of the *anti*-selective ketone aldol addition, the ability to conduct it in a manner that is independent of the structure of the ketone is extremely desirable.

As mentioned, we have developed an approach to the enantioselective α,α-bisalkylation of ketones via chiral *N*-amino cyclic carbamate (ACC) hydrazones[3] (Scheme 1a).[9] This method has several desirable attributes. For instance, the auxiliaries are both easily introduced into and removed from ketones, with nearly quantitative recovery. Deprotonation is rapid and alkylation proceeds with excellent regio- and stereoselectivity, as well as yield. Given these traits, we were curious about the possibility of extending the use of this alkylation method to the aldol addition. Our investigations along these lines led to the development of an unusual, thermodynamically controlled *anti*-aldol addition reaction.[4] In that study, the symmetrical ketone, 3-pentanone, was used to prepare the hydrazone substrate (**3**), which was then combined with a variety of aldehydes to produce, following in situ benzylation and then auxiliary removal, the corresponding *anti*-aldol products (**4**) as a single stereoisomer (Scheme 1b). To further probe this method, we wanted to investigate the possibility of extending it to the synthesis of even more structurally challenging *anti*-aldol products. In particular, we wished to access aldol products that, structurally, would correspond to those obtained by the regiocontrolled addition of nonsymmetrical ketones having both α- and α′-protons (e.g., 3-hexanone) to aldehydes. Despite the considerable effort that has been devoted to the study of aldol chemistry over the years, no such method has yet been reported to achieve this.

In order to access these more structurally complex compounds, we planned to use a modified version of our enantioselective ACC α,α-bisalkylation method (Scheme 1a).[3] In that method, complex

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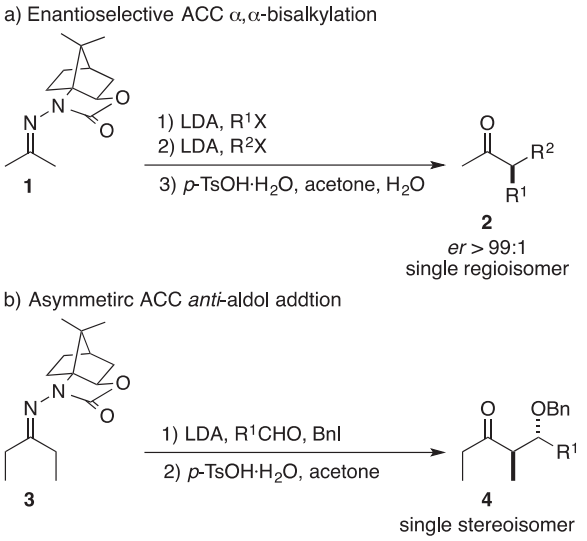
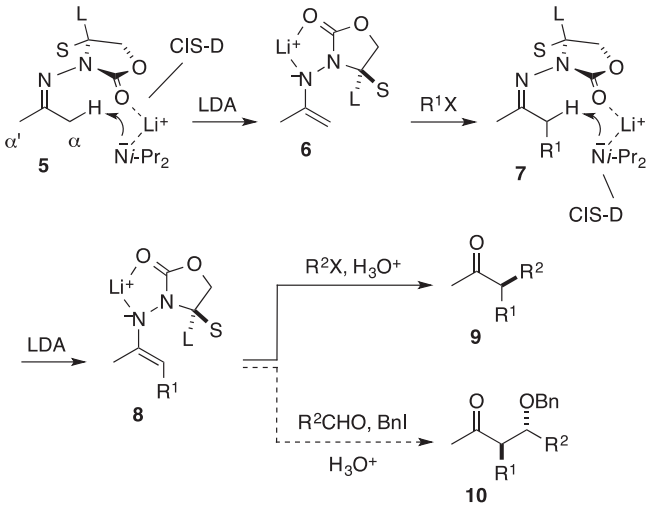


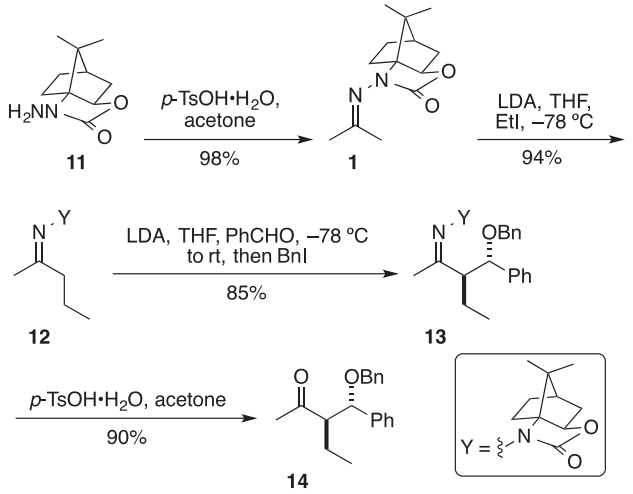
Scheme 1. Reagents and conditions: (a) enantioselective ACC α,α-bisalkylation; (b) Asymmetric ACC *anti*-aldol addition.

induced-*syn* deprotonation (CIS-D) is used to direct removal of the proton on the same side of the carbon–nitrogen double bond as the ACC auxiliary (Scheme 2, **5** → **6**). Alkylation of the resulting configurationally stable azaenolate (**6**) then gives exclusively the α-alkylated product (**7**). Repetition of this process provides the α,α-bisalkylated hydrazone having a new stereogenic center at the α-position. Auxiliary removal then gives the desired α,α-bisalkylated ketone enantiomer (**9**). If our recently developed aldol addition reaction[4] could be used in place of the second alkylation step, then it should be possible to gain access to the more structurally challenging *anti*-aldol structures desired (**8** → **10**).

To test this process, hydrazone **1** was prepared by the condensation of ACC auxiliary **11** and acetone. Treatment of **1** with LDA at −78 °C, followed by ethyl iodide gave compound **12** as a single double bond diastereomer.[3,10] With this nonsymmetrical hydrazone **12** in hand, we were able to try the *anti*-aldol addition process. Thus, **12** was treated with LDA at −78 °C, benzaldehyde was then added, the cold bath was removed and the mixture was stirred for 2 h, at which point benzyl iodide was added. As hoped, this one-pot process gave rise to the O-benzylated *anti*-addition



Scheme 2. Asymmetric ACC α,α-bisalkylation and proposed asymmetric ACC alkylation/*anti*-aldol addition via complex induced *syn*-deprotonation (CIS-D).

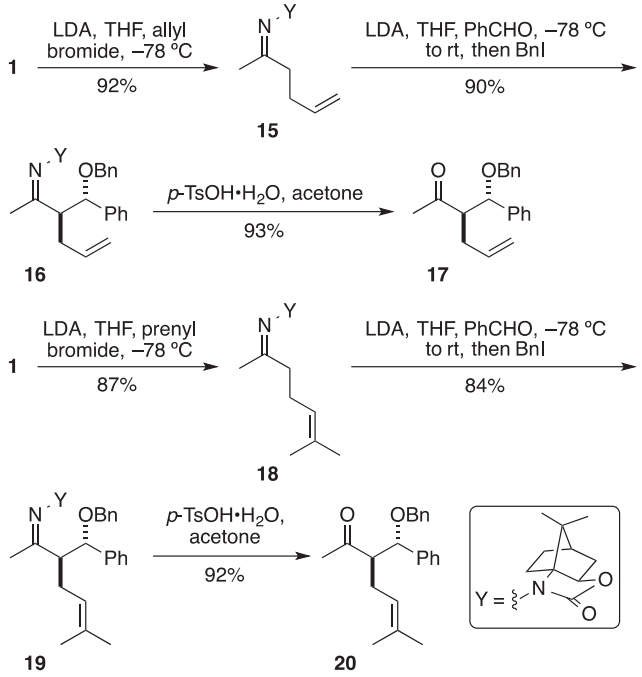


Scheme 3. Synthesis of nonsymmetrical ketone-based *anti*-aldol product **14**.

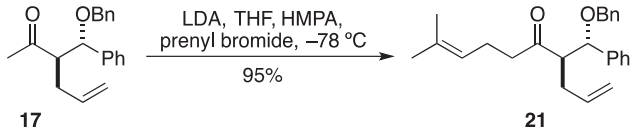
product **13** in excellent yield, and as a single stereoisomer. Auxiliary removal was achieved in excellent yield by treatment with *p*-TsOH·H_2O in acetone, and occurred without epimerization to give β-benzyloxy ketone **14** (see Scheme 3).

In a similar way, the allyl- and prenyl-containing *anti*-aldol products (**17** and **20**, respectively) were obtained in very good overall yield (Scheme 4).[11] In each case, the alkylation step proceeded to give a single regioisomer (**15** and **18**, respectively), and the aldol process produced a single β-benzyloxy ketone stereoisomer (**17** and **20**, respectively).

Given the expansive body of literature addressing the chemical manipulation of ketones, the methyl ketones (cf. **14**, **17**, **20**) obtained from this process are poised for further elaboration in numerous synthetically useful ways. For example, simple alkylation at the α′-position could be used to provide additional structural diversity. To demonstrate this, methyl ketone **17** was



Scheme 4. Synthesis of nonsymmetrical ketone-based *anti*-aldol products **17** and **20**.



17 21

Scheme 5. Prenylation of methyl ketone **17**.

treated with LDA followed by prenyl bromide, which provided compound **21** in excellent yield (Scheme 5). Addition of HMPA to the reaction mixture after deprotonation with LDA but before the addition of prenyl bromide was necessary to achieve a high yield of product. Significantly, a compound such as **21** could not be accessed in a stereo- or regiocontrolled manner via conventional ketone-based aldol additions.

In conclusion, we have developed an asymmetric *anti*-aldol addition of ketone-derived donors to aldehydes through the use of ACC hydrazones. Unlike other *anti*-selective asymmetric ketone-based aldol reactions, the present transformation is not limited by the structure of the ketone that can be used. As such, it enables the preparation of unsymmetrical ketone aldol products that would be very challenging or impossible to prepare in a controlled manner using established methods.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.140.

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10. Synthesis of **12** via condensation of 2-pentanone and the ACC auxiliary (**11**) is possible but would be expected to lead preferentially to the undesired (*E*)-diastereomer, which cannot be used for the intended regiocontrolled aldol addition.
11. See the Supplementary data for details.