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Stereoselective Formation of Fully Substituted Ketone Enolates

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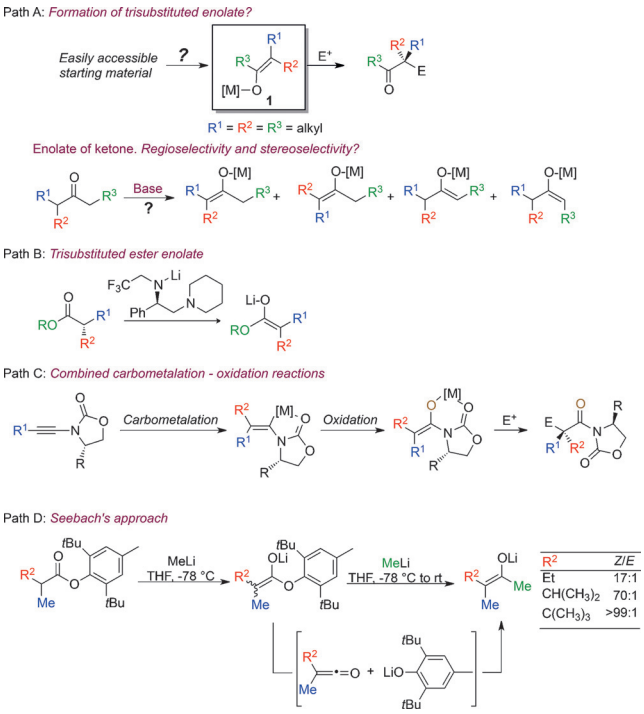
Abstract: *The application of stereochemically defined acyclic fully substituted enolates of ketones to the enantioselective synthesis of quaternary carbon stereocenters would be highly valuable. Herein, we describe an approach leading to the formation of several new stereogenic centers through a combined metalation–addition of a carbonyl–carbamoyl transfer to reveal in situ stereodefined α,α-disubstituted enolates of ketone as a single stereoisomer. This approach could produce a series of aldol and Mannich products from enol carbamate with excellent diastereomeric ratios.*

The carbonyl group is one of the most versatile and broadly utilized functional groups in organic synthesis.[1] The success of this widely employed starting material results from its multiple reactivities. Reactions proceed either at the electrophilic carbon or nucleophilic oxygen center of the carbonyl group, or alternatively at the adjacent C–H position by removing an acidic hydrogen. In the latter case, an enolate for carbon–carbon and carbon–heteroatom bonds formation is generated. Taking into consideration the significance of enolates as valuable intermediates in asymmetric organic synthesis,[2] one can evaluate the consequence of developing efficient methods to the direct access of α,α-disubstituted metal enolates **1** as a route to the formation of challenging quaternary carbon stereocenters (Scheme 1, Path A).[3] Indeed, one structural element that invariably increases the difficulty of a chemical synthesis is the presence of quaternary carbon stereocenters in the target molecule.[4] The impediment to synthesis presented by such centers arises from the steric congestion imposed by the four attached carbons. If such stereocenters could be prepared in a single-pot operation through the formation of several C–C bonds from common and easily accessible starting materials, it would surely find numerous applications in organic synthesis.[5,6] However, the generation of a stereodefined fully substituted enolate precursor as a single isomer in acyclic systems is not a trivial task, especially for ketone enolates, and therefore all the enolization reactions leading to stereodefined α,α-disubstituted enolates were restricted to esters and amides. For instance, α,α-acyclic disubstituted esters require a perfect conformational control for the abstraction of the α-hydrogen,[3] and this control can only be achieved by deprotonation of diastereomerically pure α,α-acyclic dialkylated amides,[7] enantiomerically pure α,α-acyclic dialkylated esters with chiral bases (Scheme 1, Path B),[8] or through conjugate additions.[9]



Scheme 1. Formation of fully substituted enolates.

As we have been involved over the last few years in the development of synthetic strategies leading to the creation of several carbon–carbon bonds in acyclic systems and a single-pot operation, including the formation of quaternary carbon stereocenters,[5,10] we reported a direct access to the formation of α,α-disubstituted enolates of amides by carbocupration of ynamides followed by selective oxidation of the resulting alkenyl cuprates species (Scheme 1, Path C).[11,12] Despite all these efforts, the stereoselective formation of α,α-disubstituted enolate of ketones is still very challenging and remains in its complete infancy, as the regioselectivity and the *E*/*Z*-selectivity of the enolization need to be concomitantly controlled (Scheme 1, Path A).[3] The only report to date for the stereoselective preparation of a fully substituted ketone

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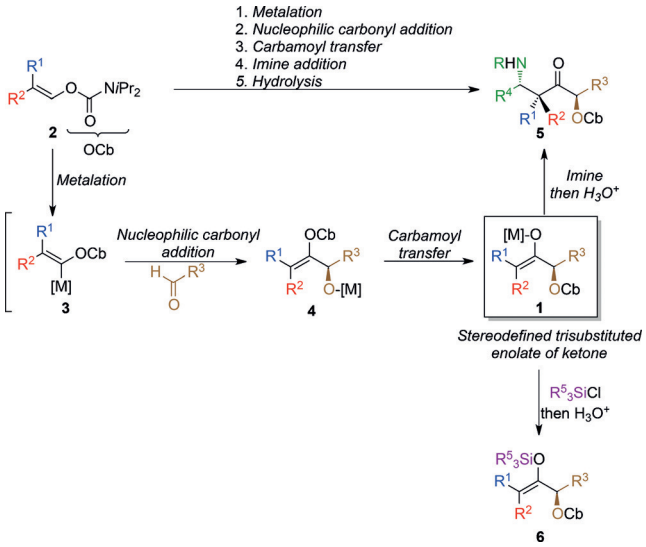
enolate originates from Seebach and co-workers through the in situ generation and trapping of ketene intermediates.[13] It was proposed that ketene or ketene-like intermediate species, produced by elimination reaction from BHT ester lithium enolates, were trapped by methyllithium to lead to the diastereoselective formation of ketone enolates (Scheme 1, Path D). The *Z*/*E* ratio improved with increased differences in steric bulk between the two substituents on the ketene intermediate, with methyllithium reacting from the less sterically encumbered stereoface.[13]

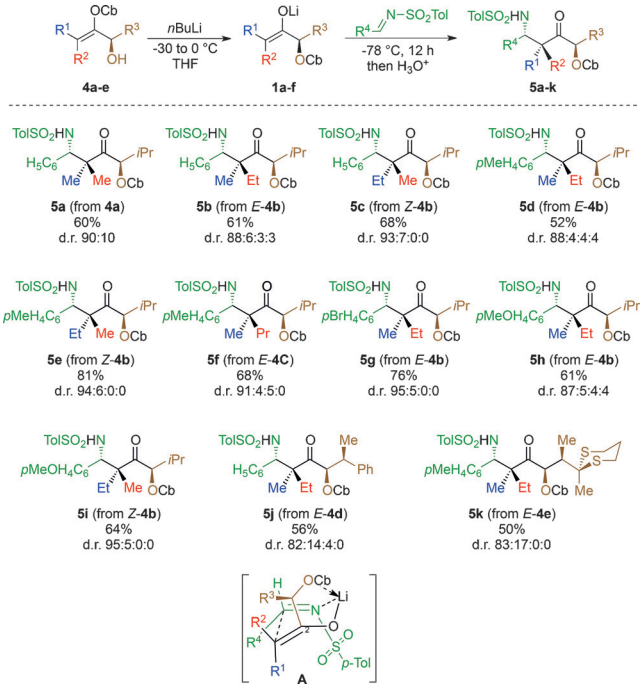
In our on-going efforts to develop strategies that could answer challenging problems while improving efficiency in synthesis,[14,15] we report herein an approach for the preparation of a single regioisomer (kinetic versus thermodynamic) as well as a single stereoisomer (*E* versus *Z*) of stereodefined fully substituted ketone enolates, such as **1** ($R^1 \neq R^2 \neq R^3 =$ alkyl), in a single-pot operation from simple starting materials. This approach, which does not start by classical enolization processes, presents the additional advantage of creating several carbon–carbon bonds in a single-pot operation as well as more than one stereogenic centers, including the quaternary carbon stereocenter (Scheme 2).[5,15]



Scheme 2. Proposed strategy.

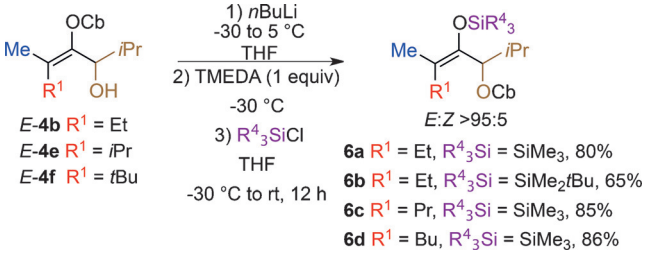
The reaction sequence that could rapidly construct stereodefined α,α-disubstituted ketone enolate **1** should start from simple enol carbamate derivatives **2** (Scheme 2), easily accessible from carbocupration of O-alkynyl carbamate.[16] The latter being easily prepared from 2,2,2-tribromoethyl carbamate by simple treatment with LDA.[17] The process would then begin through a selective metalation of **2** leading to α-metalated enol carbamate **3** with retention of the stereochemistry of the initial double bond.[18] Then, the addition of a carbonyl compound should lead to the formation of the stereodefined allylic alcoholate **4** that would undergo a carbamoyl transfer to reveal the expected fully substituted ketone enolates **1**. Such carbamoyl transfers have already been described by Hoppe[19] for the transformation of thioenol carbamates, Snieckus[20] and Percy[21] as a route to acyl anion equivalents, and more recently by Clayden[22] for N–C aryl migration. It should be emphasized that enolate **1** would never be formed through enolization reactions of the parent ketone. Additionally, if one adds an aldehyde possessing an existing stereocenter in the α-position of the carbonyl group, the diastereoselectivity should easily be controlled by the Felkin–Anh–Eisenstein model.[23] The stereochemistry of enolate **1** is therefore defined by the stereoselectivity of the starting enol carbamate **2**, and analysis of the stereochemistry of the product **6**, resulting from the trapping of the ketone enolate with silyl chloride, should confirm the formation of a unique stereoisomer of **1**. On the other hand, the addition of various imines to **1** would lead, after hydrolysis, to Mannich-type products **5** with the concomitant creation of two stereogenic centers in the acyclic system, including the quaternary carbon stereocenter, from simple alkenes **2**. Although this proposed approach is appealing, to obtain high chemical yield in decent diastereoisomeric ratio requires complete control of all of the elementary steps. Our initial challenge was therefore to study the formation and reactivity of fully substituted ketones enolates **1** from allylic alcohols **4**. The simple deprotonation of allylic alcohol **4a**, possessing two identical substituents on the alkenyl group ($R^1 = R^2 =$ Me, Scheme 3), with *n*-BuLi in THF induced, by raising the temperature of the reaction mixture from −30 to 0 °C, the migration of the carbamoyl group to generate in situ and quantitatively the enolate **1a**. Addition of tosyl imine gave the Mannich-type adduct **5a** in 60% yield with a 1–4 diastereomeric ratio of 9:1, representing the diastereofacial choice in the Mannich reaction.[11,24]

When the nature of the two alkyl groups is different (*E*-**4b**, R^1 = Me, R^2 = Et, Scheme 3), the combined carbamoyl



Scheme 3. Formation of α,α-disubstituted ketone enolates from allylic alcohols.

transfer–Mannich reaction proceeds smoothly to give the amino ketone **5b** possessing three stereogenic centers, including the quaternary carbon stereocenter, in a good overall yield with a diastereomeric ratio of 88:6:3:3. To get information on the stereochemistry of the in situ formed stereodefined ketone enolates **1**, various intermediates were trapped with silyl chloride. A single geometrical isomer was obtained for all of silyl enol ethers **6a–d** (Scheme 4; the

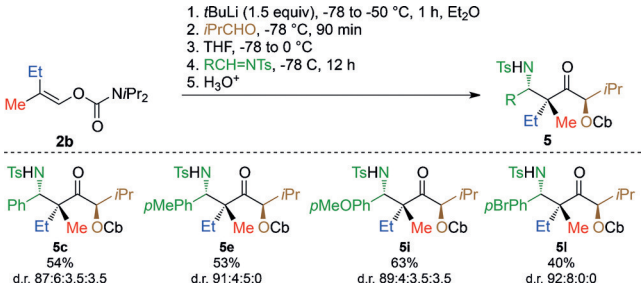


Scheme 4. Formation of stereodefined trisubstituted silyl enol ethers.

stereochemistry was confirmed from NOE analysis on **6a**,**b**, see the Supporting Information), supporting the formation of a single isomer of the fully substituted ketone enolates **1**. To obtain further mechanistic insight and to prepare, at will, both diastereoisomers at the quaternary carbon stereocenter, we then permuted the nature of the alkyl groups R^1 and R^2 and performed the same combined carbamoyl transfer–Mannich reaction on *Z*-**4b** (R^1 = Et, R^2 = Me, Scheme 3). The opposite diastereoisomer **5c** was obtained in excellent diastereoisomeric ratio and yield (Scheme 3), and the relative configuration of the major diastereoisomer was determined by X-ray crystallographic analysis (Supporting Information).[25] The stereochemistry of the major isomer could be rationalized by a Zimmerman–Traxler transition state **A** in which the *i*Pr group shields one face in the chelated six-membered ring[26] and the imine approaches the enolate anti to this bulky group, with its R^3 substituent occupying a pseudo-equatorial position to avoid 1,3-diaxial steric interactions with the substituent in C_2 (Scheme 3).[27] It is interesting to note that the larger the R^1 substituent, the higher the diastereoisomeric ratio (compare **5b** and **5c**, **5d** and **5e**, **5h** and **5i**). Moreover, all of the major diastereoisomers could be purified by simple column chromatography and be obtained diastereoisomerically pure. Various aromatic imines (Scheme 3, formation of **5a**,**d**,**g**,**h**) could be used successfully in this reaction in good to excellent diastereomeric ratios.

One approach to further increase the complexity of the formed linear products **5** would be to start from allylic alcohols *syn*-*E*-**4d**,**e** possessing an extra stereogenic center through the Felkin–Anh–Eisenstein model for the addition of metalated enol carbamate **3** to chiral aldehydes (R^3 = CH(Me)Ph for *syn*-*E*-**4d**, and R^3 = CH(Me)-CMe(SCH_2CH_2)$_2$[28] for *syn*-*E*-**4e**) as unique diastereoisomers. When these two substrates were treated with BuLi and then imine, the stereodefined tetrads **5j**,**k** were obtained in moderate yields but with good diastereoselectivities (Scheme 3).

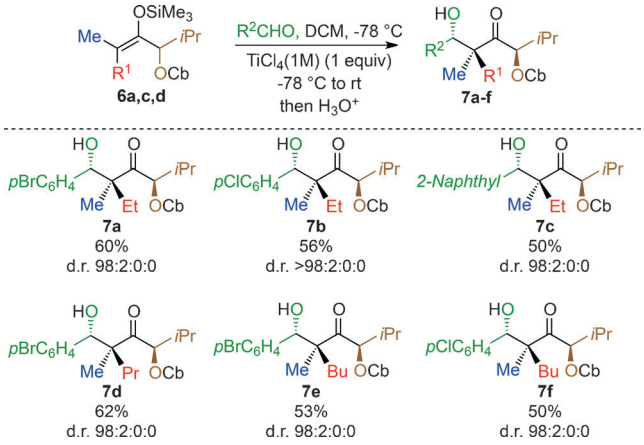
Having in hand an easy approach to prepare stereodefined fully substituted ketone lithium enolate **1** as single isomer from allylic alcohols through the carbamoyl transfer, we then decided to further improve the efficiency of our approach by directly transforming enol carbamate **2** into the Mannich products **5** in a single-pot operation.[15] The sequence of metalation–carbonyl addition–carbamoyl transfer–Mannich reactions was tested on **2b** with various imines and, in all cases, the expected products **5** possessing three stereogenic centers were obtained in good yields and diastereoselectivities directly from the alkene **2b** (Scheme 5).



Scheme 5. One-pot transformation of enol carbamates into Mannich products.

Additionally, the fully substituted silyl enol ethers **6a–d** previously prepared as a single stereoisomer by silylation of enolate **1** (Scheme 4) could also represent ideal candidates for the Mukaiyama aldol reaction giving access to β-hydroxy alcohols possessing a quaternary stereocenter α to the carbonyl groups.[28] Therefore, the Mukaiyama aldol reaction was tested by addition of one equivalent of $TiCl_4$ at low temperature with various aldehydes and to our delight the reaction proceeded smoothly to give the desired aldol products **7a–f** with the formation of a quaternary stereocenter in moderate yields but outstanding diastereoisomeric ratios (Scheme 6).[29,30] The configuration of the aldol products was determined by X-ray analyses of **7a**,**c** (Supporting Information).[25]

In conclusion, the sequence of metalation of enol carbamate, carbonyl addition, followed by a carbamoyl transfer allows an easy and unique access to fully substituted



Scheme 6. Application of the Mukaiyama aldol reaction.

enolates of ketones as single regio- and stereoisomers. The enolate **1** can react with a large variety of imines to provide the Mannich-type products **5** with very good diastereoselectivities, but can also serve as precursors of stereodefined fully substituted silyl enol ethers **6** as single isomers. To illustrate the reactivity of such silyl enol ethers **6**, the Mukaiyama reaction has been performed with various aromatic aldehydes to provide the expected aldol products **7** in outstanding diastereoselectivities. This study shows that alternative approaches to the preparation of quaternary carbon stereocenter may provide easy and efficient access to the formation of stereodefined α,α-substituted enolates of ketones in which several bonds and stereogenic centers are created in a single-pot operation. Owing to its flexibility, this approach will surely find a large number of applications for the transformation of vinyl carbamate into stereodefined fully substituted enolates.

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[30] The aldol reaction directly from lithium enolate **1** suffers from the retro-aldol reaction. Different transformations are ongoing and will be reported in due course.

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