Desymmetrizing asymmetric ring expansion: stereoselective synthesis of 7-membered cyclic β-keto carbonyl compounds with an α-hydrogen†

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Ring expansion of symmetrically substituted cyclohexanones with *N*-α-diazoacetyl camphorsultam was devised as a stereoselective pathway to the functionalized 7-membered cyclic β-keto carbonyls having a kinetically stabilized α-hydrogen.

Asymmetric synthesis of *acyclic* β-keto carbonyl compounds having an α-hydrogen was introduced a quarter of a century ago by Evans and co-workers, capitalizing on the ability of a bulky chiral ligand to kinetically stabilize the enantiomerically enriched α-carbon established in the Claisen condensation of acyl halides and imide enolates (Fig. 1, eq 1).[1] Recently, an acid-catalyzed reaction of aldehydes and α-substituted α-diazocarbonyl compounds bearing a camphorsultam was developed in our laboratory as a new tool to achieve this goal (eq 2).[2–4] However, with regard to the preparation of their *cyclic* counterparts, there has been no general approach to realizing this objective.[5] This is probably due to the difficulty of directly applying the existing intermolecular methods to an intramolecular variant giving cyclic β-keto carbonyl compounds with a kinetically stabilized α-hydrogen, as well as the foreseeable difficulty of introducing additional functionalities stereoselectively in the ring system.

As a reliable method for the preparation of racemic cyclic β-keto esters having an α-hydrogen, acid-mediated ring expansion of cyclic ketones with α-diazoacetates has been exploited for nearly half a century.[6,7] It can be envisaged that replacement of the ester functionality of α-diazoacetates with a chiral bulky carbonyl substituent in this reaction system would meet the criteria for the asymmetric construction of cyclic β-keto carbonyl compounds having an α-hydrogen (eq 3). We report herein an investigation in this perspective, which culminated in the discovery of a novel and reliable tactic for the asymmetric construction of seven-membered β-keto carbonyl compounds having a kinetically stabilized α-hydrogen and additional stereocenters.

At the beginning of this research, asymmetric ring expansion of cycloalkanones having a varying number of carbon atoms was examined using α-diazocarbonyl compound (+)-**1** to validate our hypothesis (Scheme 1). We opted for the use of (+)-camphorsultam as an ideal chiral auxiliary, shielding one prochiral face of the diazo carbon efficiently and imposing a high kinetic barrier for the epimerization of thus-generated chiral α-carbon on the basis of our previous study.[2] Using a

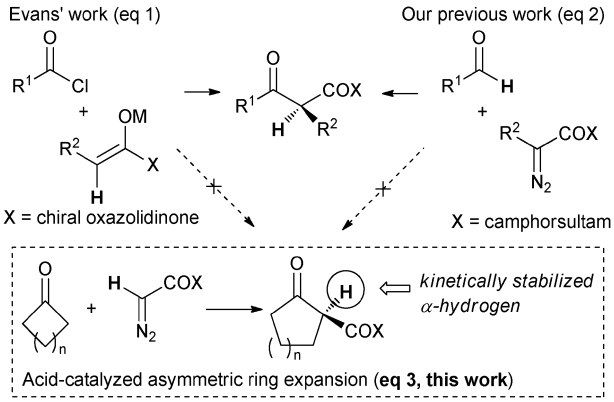
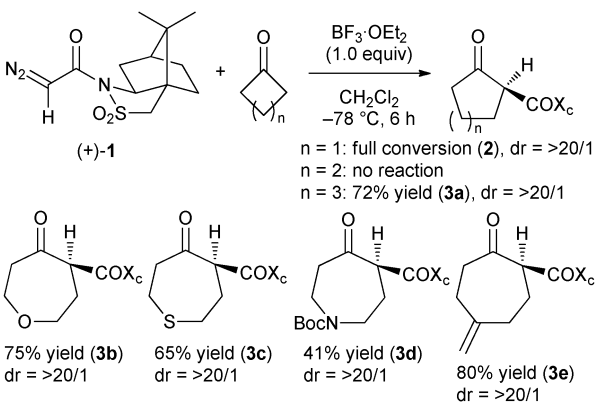


Fig. 1 Acid-catalyzed asymmetric ring expansion.

stoichiometric amount of $BF_3{\cdot}Et_2O$ as an inexpensive and benign Lewis acid at −78 °C, cyclobutanone and cyclohexanone could be successfully converted to the expected ring-expanded products **2** and **3a** with >20/1 dr as determined by the ^1H NMR of the crude mixture,[8] whereas cyclopentanone remained intact. In the case of thus-obtained 5-membered cyclic β-keto carbonyl compound **2**, a considerable loss of dr was observed during the purification using silica gel column chromatography by the epimerization of the α-chiral center. On the other hand, the stereocenter at the α-carbon of 7-membered ring **3a** was stable enough to be isolated without any epimerization,[9] and could only be epimerized by treating this material with a strong base like 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU).[10] The remarkably high stereoselectivity of this ring expansion was confirmed by determining the ee value to be 98% after the reductive detachment of the chiral auxiliary.[11] Furthermore, this asymmetric ring expansion of cyclohexanone could also be extended to its 4-oxa-, 4-thia-,



Scheme 1 Asymmetric ring expansion of cycloalkanones.

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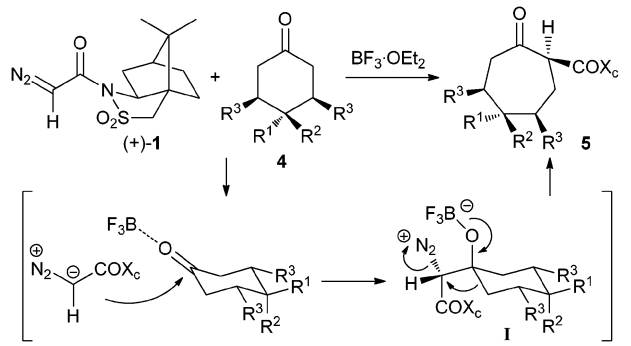


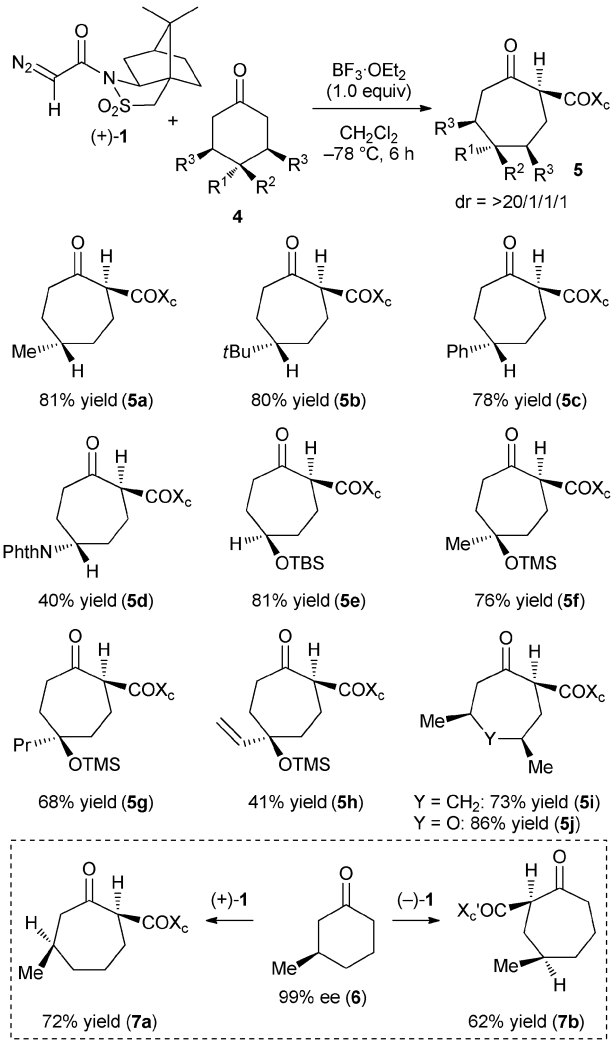
Scheme 2 Schematic representation of desymmetrizing asymmetric ring expansion of substituted cyclohexanones.

4-aza- and 4-exo-methylene analogs without difficulty, giving **3b**, **3c**, **3d** and **3e** in good yields and excellent selectivities.

The observed high stereoselectivity and robustness of the thus-generated α-chiral center then prompted us to merge this foundation and our recent discovery on the stereochemical prediction model of ring-expansions using symmetrically substituted cyclohexanones and α-substituted α-diazoacetates.[12] According to this model, it is assumed that the use of symmetrically substituted cyclohexanones **4** with (+)-**1** would initially form the intermediate **I** *via* the equatorial attack of (+)-**1** while the chiral auxiliary shields one prochiral face of the diazo carbon (Scheme 2).[13] From this intermediate orienting the bulky carbonyl moiety in an axial fashion to reduce the steric repulsion, migration of the alkyl group occurs through the inversion of the chiral center at the diazonium carbon. As such, symmetrically substituted cyclohexanones would be converted to homologated chiral cycloheptanones **5** with a kinetically stabilized α-hydrogen, while desymmetrizing residual substituents to create additional stereogenic centers.

To prove the validity of this principle, the asymmetric ring expansion of 4-methylcyclohexanone using (+)-**1** was implemented under identical reaction conditions as above (Scheme 3). Consequently, the expected cycloheptanone **5a** bearing methyl and the carbonyl groups in a *trans* relationship was obtained as a single diastereomer in 81% yield. Prompted by this result, we then examined other cyclohexanones bearing *t*-butyl, phenyl, and *N*-phthalimido groups as 4-substituent. In all cases, this desymmetrizing asymmetric ring expansion proceeded with high stereoselectivities, giving **5b**, **5c** and **5d**, respectively. In contrast to these 4-substituents which are oriented in an equatorial position of the cyclohexanone, a 4-siloxy moiety is known to be in an axial position.[14] Due to this fact, the ring expansion of 4-(*tert*-butyldimethylsiloxy)-cyclohexanone with (+)-**1** furnished the product **5e**, projecting the carbonyl and siloxy groups in a *cis* fashion. By building on this dichotomy, cyclohexanones having both alkyl and siloxy groups as 4-substituents could be stereoselectively converted to **5f**, **5g** and **5h**, incorporating chiral tertiary alcohol in the 7-membered ring. Furthermore, the same strategy could be applied to *cis*-3,5-dimethylcyclohexanone and its oxa-analogue to give seven-membered rings **5i** and **5j** having 1,3,5-tertiary-tertiary-tertiary stereogenic centers in an expected stereochemistry.

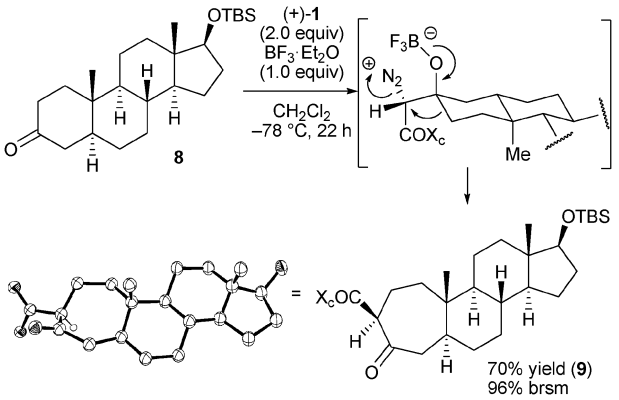
Since the state-of-the-art asymmetric catalysis provides us with facile access to a variety of almost enantiomerically pure



Scheme 3 Desymmetrizing asymmetric ring expansion of cyclohexanones.

3-substituted cyclohexanones,[15] we looked into the application of our asymmetric ring expansion to one such compound (*R*)-3-methylcylohexanone **6** (Scheme 3, in dashed rectangle). In accordance with the mechanistic model in Scheme 2, the ring expansion with (+)-**1** led to the stereoselective formation of the cycloheptanone **7a**. On the other hand, use of the antipode (−)-**1** gave rise to the regioisomeric product **7b** exclusively. It should be noted that the simple ring expansion of **6** with ethyl diazoacetate resulted in a mixture of four isomers composed of two regioisomers derived from nonselective ring expansion and two diastereomers stemming from the labile chirality at the α-carbon.

The regio- and stereoselective nature of this ring expansion with regard to chiral nonracemic cyclohexanones further prompted us to employ a chiral polycyclic system which has a cyclohexanone moiety harnessed in a chair conformation. In this context, TBS-protected dihydrotestosterone **8** was subjected to the conditions optimized for this specific reaction, giving the ring-expanded product **9** as a single isomer in 70% yield (Scheme 4). The nearly quantitative recovery of the unreacted substrate indicated clean conversion (96% yield based on recovered starting material). As polycyclic systems

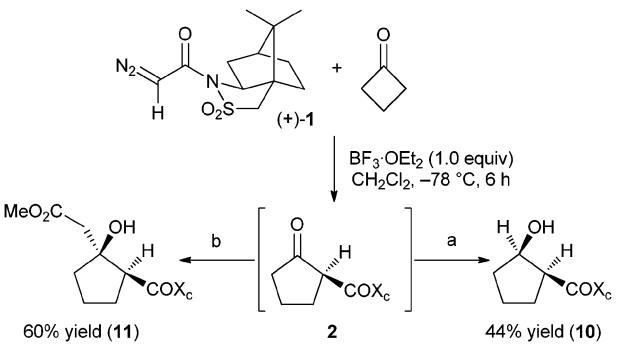


Scheme 4 Ring expansion of TBSO-dihydrotestosterone with (+)-**1**. ORTEP diagram of **9** drawn at 50% thermal ellipsoids with H atoms, TBS group, camphorsultam and a solvent molecule omitted for clarity.

having a 7-membered ring are abundant in nature, this strategy would provide a new, appealing tool in the arsenal of 7-membered ring constructions applicable in a complex setting.[16]

Finally, we re-investigated the ring expansion of cyclobutanone briefly in an attempt to pave a new way to functionalized chiral cyclopentanes (Scheme 5). As the generated α-stereocenter eroded during purification, we decided to trap the ring-expanded product **2** with a nucleophilic reagent sequentially in one pot. To this end, the reaction solution containing **2** was directly treated with $NaBH_4$ to give *cis*-cyclopentanol **10** in 44% yield (unoptimized). By taking advantage of the Lewis acidic reaction conditions, a one-pot ring expansion/Mukaiyama aldol reaction sequence was also implemented to generate the cyclopentanol **11** bearing a tertiary alcohol moiety in moderate yield as an essentially single isomer.

In summary, we have demonstrated herein the viability of acid-catalyzed ring expansion using *N*-α-diazoacetyl camphorsultam **1** as a means to afford cyclic β-keto carbonyl compounds with a kinetically stabilized α-hydrogen stereoselectively. Combination of this finding with our stereochemical prediction model of ring-expansions using symmetrically substituted cyclohexanones led to the establishment of a reliable system, providing rigorously



Scheme 5 One-pot asymmetric ring expansion/functionalization of cyclobutanone. Reaction conditions: (a) $NaBH_4$ (3 equiv.), MeOH, −78 °C, 18 h; (b) $H_2C{=}C(OMe)OTBS$ (2 equiv.), −20 °C, 16 h.

functionalized 7-membered ring systems in almost enantiomerically pure form. This strategy could be further extended to regio- and stereoselective ring expansion of chiral nonracemic cyclohexanones.

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9 The stereochemistries of **3a**, **5a**, **5e**, **5f**, **5i**, **7a**, **7b** and **10** were unambiguously determined by X-ray crystallographic analysis. See ESI† for details.
10 Treatment of **3a** with 1 equiv. of DBU in CH_2Cl_2 at 0 °C for 4 h led to the predominant formation of the opposite diastereomer (dr = 1 : 4.6).
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