Heterocycles

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Enantioselective Organocatalytic Multicomponent Synthesis of 2,6-Diazabicyclo[2.2.2]octanones**

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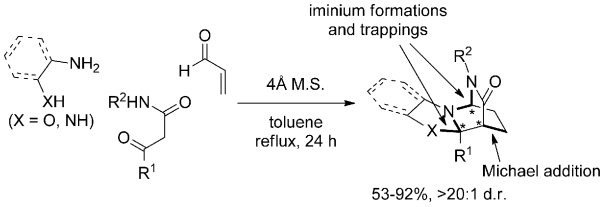
Multicomponent reactions consist of the combination of at least three different partners in a domino sequence which occurs without any modification of the reaction conditions.[1] They represent powerful multiple bond-forming transformations for the fast construction of complex structures which are not easily synthesized by traditional stepwise strategies.[2] With the increased focus on the preparation of enantiopure compounds, recent efforts have been directed towards the development of enantioselective multicomponent reactions.[3] However, the potential interference of the third reactant during the enantioselective combination of the two other reaction partners adds complexity when compared to enantioselective two-component processes. Pioneering work by Enders and co-workers illustrated how a prolinol derivative can be used to control the chemo- and enantioselective assembly of three different reaction partners.[4] Since then, organocatalysts, which have high functional-group tolerance and operate under mild reaction conditions, have appeared as the most suitable tools for promoting enantioselective multicomponent reactions.[5]

During the course of our studies directed towards the development of multicomponent reactions from 1,3-dicarbonyls to access highly elaborated polycyclic molecules,[6] the highest level of complexity was reached in 2005, when our group reported the Michael addition initiated three-component reaction of β-ketoamides, acrolein, and an amine functionalized with a pendant nucleophile. The three starting materials were combined in refluxing toluene in the presence of 4 Å molecular sieves to afford the structurally complex 2,6-diazabicyclo[2.2.2]octanone (2,6-DABCO) core in good yield [Eq. (1); M.S. = molecular sieves].[7] Noteworthy is that five new bonds[8] were created during this Michael addition/



(1)

double iminium trapping sequence and three stereocenters were installed with complete diastereoselectivity, with the production of two molecules of water as the only by-product. Later, we showed that replacing toluene by an ionic liquid could broaden the scope of the reaction.[9]

However, to valorize these original structures, it would be helpful to obtain them under enantioenriched form. The main challenge to develop a catalytic enantioselective synthesis of 2,6-DABCOs is to find reaction conditions which are suitable both for the enantioselective Michael addition of a β-ketoamide with an enal and for the subsequent iminium trappings. The enantioselective Michael addition of 1,3-dicarbonyls is arguably one of the most studied organocatalytic transformations.[10] However, the use of this elemental step as the enantiodetermining one in multicomponent sequences still remains scarce in the literature.[11]

We report herein our efforts towards the development of an enantioselective synthesis of 2,6-DABCOs under bifunctional organocatalysis.[12,13] This also constitutes a proof of concept that very complex transformations are amenable to enantioselective control by hydrogen-bonding activation, even in the presence of substrates containing acidic hydrogen atoms. The targeted bridged pentacyclic scaffolds[14] were obtained in excellent chemical yields along with high enantio- and diastereoselectivities by assembling three simple polyfunctionalized starting materials in a very chemoselective manner while creating very efficiently a large number of new bonds and stereogenic centers.

Based on our preceding studies on the enantioselective Michael addition of β-ketoamides to α,β-unsaturated carbonyl derivatives,[15] we started our investigations by mixing the *N*-tosyl-β-ketoamide **1a**, 2-aminophenol (**2a**), and acrolein (**3**) in the presence of bifunctional Takemoto catalyst (*R*,*R*)-**4** and crushed 4 Å molecular sieves in dry toluene at room temperature (Table 1, entry 1). Pleasingly, the expected DABCO **5a** was formed as the only product and isolated in 74% yield with 14:1 d.r. and an encouraging 87:13 e.r. X-ray diffraction analyses of the product allowed the determination

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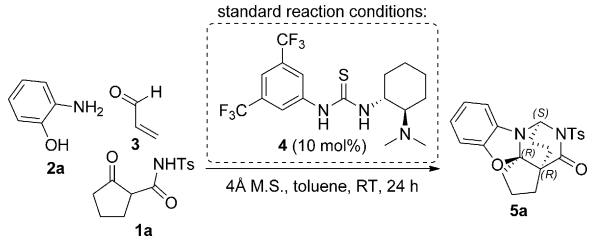
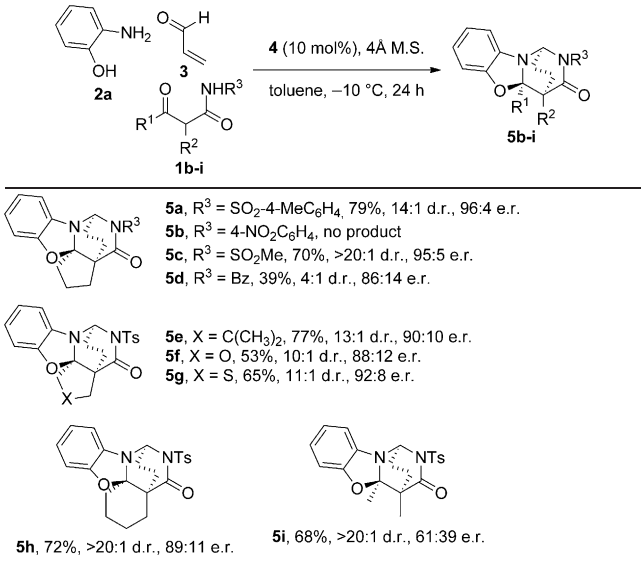
Table 1: Optimization of reaction conditions.



Entry	Variation of the standard reaction conditions[a]	Yield[b]	e.r.[c]
1	none	74%	87:13
2	−10°C	79%	96:4
3	−30°C	72%	96:4
4	−10°C, no 4 Å molecular sieves	66%	83:17

[a] Standard conditions: *N*-tosyl-β-ketoamide **1a** (0.2 mmol, 1 equiv), 2-aminophenol (**2a**; 0.3 mmol, 1.5 equiv), acrolein (**3**; 0.4 mmol, 2 equiv) catalyst **4** (20 μmol, 10 mol%), and 4 Å molecular sieves (200 mg) were mixed in dry toluene (6 mL) at RT for 24 h. [b] Yield of the analytically pure 2,6-DABCO **5a**, obtained as a 14:1 mixture of equilibrating diastereomers. [c] Determined by HPLC analysis using a chiral stationary phase. Ts = 4-toluenesulfonyl.

Table 2: Scope of β-ketoamides.



The yields are those for the isolated products. The d.r. values were determined by 1 H NMR analysis of the crude reaction mixture; the e.r. values were determined by HPLC analysis on a chiral stationary phase. Bz = benzoyl.

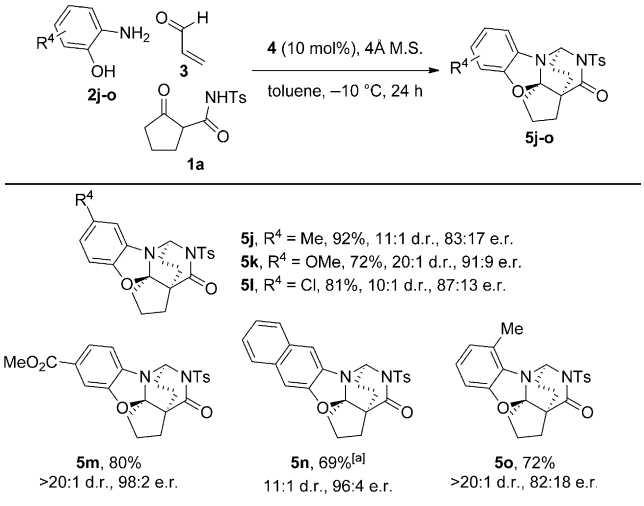
of both the absolute and the relative configurations of the three stereogenic centers,[16,17] including the two contiguous tetrasubstituted ones.[18] Other reaction parameters were evaluated,[17] but the enantioselectivity could not be improved and the diastereomeric ratio remained unchanged, which probably reflects the relative stabilities of the diastereomers. This latter observation could be explained by the fact that both diastereomers are in equilibrium at room temperature.[17] Reducing the reaction temperature to −10°C could increase the enantiomeric ratio to 96:4 (Table 1, entry 2) but a further decrease to −30°C was not beneficial (entry 3). The removal of the dehydrating agent only slightly reduced the yield of the reaction but severely impeded the enantioselectivity (entry 4).

With these optimized reaction conditions in hand, the scope and limitations of the transformation were investigated, at first by modifying the structure of the β-ketoamide (Table 2).[19] A strongly electron-withdrawing group on the nitrogen atom of the amide was necessary to allow the formation of the 2,6-DABCO unit: for example, no product was obtained with a 4-nitrophenyl substituent whereas **5c**, bearing a methanesulfonyl group, was formed in good yield and high stereoselectivity. An *N*-benzoyl-β-ketoamide could also afford the expected 2,6-DABCO **5d**, but in significantly lower yield and stereoselectivity.

With the tosyl substituent as the best activating group, variations on the other positions of the β-ketoamide were performed. Other five-membered rings, including oxa- and thia-heterocycles provided the corresponding products **5e**–**g** with good enantioselectivities. The six-membered carbocycle was equally efficient, thus leading to **5h** with comparable yield and stereoselectivity, while the 2,6-DABCO **5i**, originating from an acyclic β-ketoamide, was obtained with the same very high diastereoselectivity but with a lower enantiomeric ratio.

Electronically diversified 2-aminophenols **2j**–**o** could be used as substrates in the enantioselective synthesis of 2,6-DABCOs (Table 3). Both electron-donating and electron-withdrawing groups were tolerated at the 4-position to yield the compounds **5j**–**l** with a small decrease in the enantiomeric excess. At this point of the study, further catalyst screening was conducted on the reaction leading to the product **5l** but none of the tested catalysts could improve the enantioselectivity of the reaction.[17] Besides this, sequential experiments were conducted to understand the origin of this erosion of the enantioselectivity, and it seems to originate from the rever-

Table 3: Scope of aminophenols.

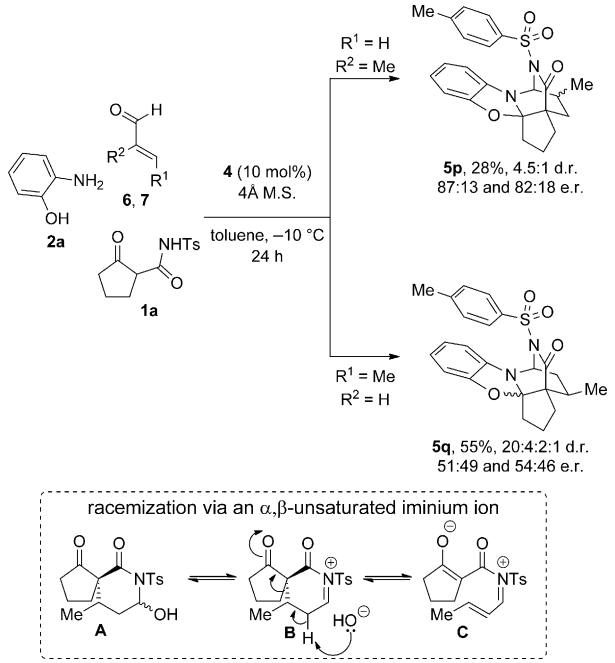


[a] Reaction time: 48 h. The yields are those for the isolated products. The d.r. values were determined by 1 H NMR analysis of the crude reaction mixture; the e.r. values were determined by HPLC analysis on a chiral stationary phase.

sibility of several steps of the sequence.[17] Theoretical studies will be pursued to try to shed light on this phenomenon.

The products **5m** and **5n**, containing an ester function and a naphthyl group, were obtained with excellent enantiomeric ratios of 98:2 and 96:4, respectively. Substitution *ortho* to the amine was also tolerated, thus resulting only in a slight alteration of the enantioselectivity in **5o**. Preliminary studies with other bis-nucleophiles such as 2-aminobenzyl alcohol, *ortho*-phenylene diamine, or anthranilic acid, used under the standard reaction conditions have failed to provide the expected DABCOs in meaningful yields (usually $<20\%$), further attesting of the complexity of carrying out this multicomponent reaction in an enantioselective way.[17]

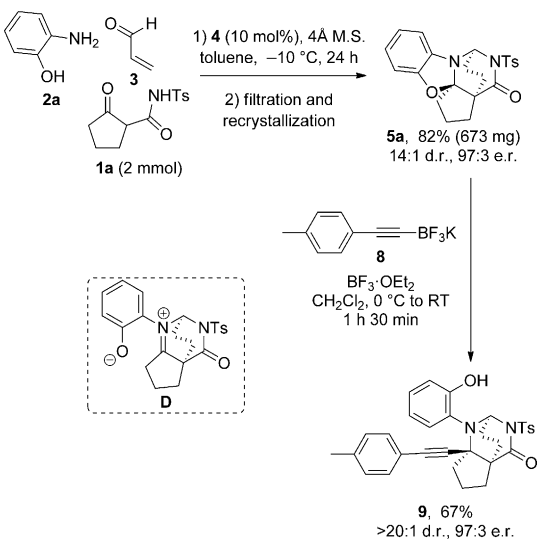
Attempts to vary the third coupling partner proved rather disappointing (Scheme 1). When acrolein was replaced by methacrolein (**6**), fair enantioselectivity was observed for the



Scheme 1. Reactions with crotonaldehyde and methacrolein.

2,6-DABCO **5p** but at the cost of a low yield. In contrast, with crotonaldehyde (**7**), the 2,6-DABCO **5q** was obtained with encouraging yield and diastereoselectivity, but surprisingly as a virtually racemic product. As presented in our preliminary work on the conjugate addition of β-ketoamides to α,β-unsaturated carbonyl compounds,[15] the Michael adduct readily cyclizes to give the hemiaminal **A**. Its dehydration can afford the iminium ion **B**, for which a racemization pathway via a retro-Michael and uncatalyzed intramolecular Michael addition sequence can be envisaged. For both electronic and steric reasons, the presence of the methyl group presumably increases the propensity to form the α,β-unsaturated iminium ion **C**, thus accounting for the absence of enantioselectivity of the reaction when crotonaldehyde is used as the enal coupling partner.

To demonstrate the applicability of our method, we carried out the synthesis of **5a** on a synthetically useful



Scheme 2. Preparative-scale reaction and postfunctionalization of the 2,6-DABCOs.

scale (Scheme 2). Pleasingly, high yield and stereoselectivities were preserved and the product was isolated without the need to purify it by flash chromatography.

In addition to this, the 2,6-DABCO unit could serve as a platform for further elaboration. Its treatment with a Lewis acid such as $BF_3{\cdot}OEt_2$ enabled the opening of the *N*,*O*-aminal and the regeneration of the iminium ion **D** which could be trapped with external nucleophiles. With the potassium alkynyltrifluoroborate **8**,[20] the product **9** was formed in 67% yield. Interestingly, no erosion of the enantiomeric excess was observed and the newly created tetrasubstituted center, adjacent to the previously existing one, was forged with complete diastereoselectivity. This postfunctionalization illustrates the potential of our method to generate enantioenriched bridged polycyclic scaffolds which could hardly be assembled by stepwise synthesis.

In summary, we developed an enantioselective organocatalytic multicomponent reaction which combines a β-ketoamide, acrolein, and an aminophenol in a well-defined manner to afford a functionalized 2,6-diazabicyclo-[2.2.2]octanone (2,6-DABCO) core. This complex and original structure was assembled in high yield and good stereoselectivities. Our future studies will focus on the understanding of the reaction mechanism using computational studies, and on increasing the value of the 2,6-DABCO scaffold. Moreover, the present transformation is one of the first multicomponent reactions including the Michael addition of a 1,3-dicarbonyl as the enantiodetermining step and it should pave the way for other related processes.

Experimental Section

Crushed 4 Å molecular sieves (200 mg) were placed in a 25 mL reaction flask equipped with a septum. Air was evacuated under high vacuum and the reaction flask heated by means of a heat gun. After cooling to room temperature, the reaction flask was filled with argon. This operation was repeated a second time. (*R*,*R*)-TUC **4** (8.3 mg,

20.0 μmol, 0.1 equiv), the β-ketoamide **1a–k** (0.200 mmol, 1 equiv), and the aminophenol **2a,j–o** (0.300 mmol, 1.5 equiv) were introduced to the reaction flask, which was once again flushed with argon. Dry toluene (6 mL) was added and the reaction flask was cooled to −10 °C. After 10 min, the enal **3**, **6**, or **7** (0.400 mmol, 2 equiv) was added by syringe and the reaction mixture was stirred at −10 °C for 24 h. It was then filtered through a short pad of silica gel (2 cm) which was washed with EtOAc (50 mL). Concentration under reduced pressure afforded a solid that was purified by flash column chromatography on silica gel (CH_2Cl_2/EtOAc) to provide the pure 2,6-DABCOs **5a–q** (NMR spectra and HPLC profiles generally showed small amounts of the epimer resulting from the equilibrium of the *N*,*O*-aminal).

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