Asymmetric Domino Catalysis

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Asymmetric Organocatalytic Domino Michael/Aldol Reactions: Enantioselective Synthesis of Chiral Cycloheptanones, Tetrahydrochromenones, and Polyfunctionalized Bicyclo-[3.2.1]octanes**

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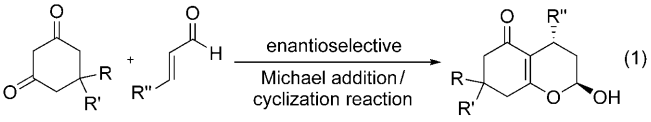
Dedicated to Professor Joachim W. Engels on the occasion of his 65th birthday

In organic synthesis the use of various carbonyl compounds is commonplace as they enable diverse C-C coupling reactions. The use of 1,2-diones is not as widespread and their reactivity has hardly been examined despite their functionality, which offers a useful starting point for additional transformations. Therefore, 1,2-diones represent a group of interesting synthetic building blocks for future study.[1]

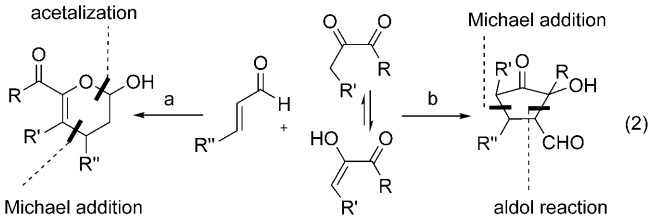
Following our recently reported development of an organocatalytic asymmetric addition/cyclization cascade using different 1,3-diketones [Eq. (1)],[2] and given the interesting synthetic possibilities provided by the 1,2-diones,[3] we decided to examine a Lewis base catalyzed reaction of α,β-unsaturated aldehydes with 1,2-diones.



(1)

In planning our investigation of the reaction, the question arose as to whether the reaction of a dione with an aldehyde is indeed analogous to our previously described Michael addition/cyclization reaction which would result in the corresponding acetals [Eq. (2), path a] or whether, after the Michael addition an intramolecular aldol reaction would occur, leading to highly substituted cyclopentanones [Eq. (2), path b].[4]

We began our investigation by examining the Lewis base catalyzed reaction of 1,2-cyclohexadione (**1a**) with the α,β-unsaturated aldehyde **2a**. Indeed, the initial experiments



(2)

showed that the use of catalytic amounts of a secondary amine enabled a reaction which resulted in the formation of the bicyclic compound **3a**. Accordingly, and in contrast to the addition/cyclization reaction that we observed in our previous work with 1,3-diketones, it was concluded that a domino Michael/aldol reaction occurred by iminium/enamine activation.[5]

On the basis of these observations we decided to develop an asymmetric version of this domino reaction.[6–8] The diarylprolinol ethers **4a–d** were used as chiral catalysts in the reaction of **1a** with cinnamylaldehyde (**2a**). Remarkably, the bicyclo[3.2.1]octane-6-carbaldehyde derivative **3a** was obtained exclusively as a single diastereomer, demonstrating the stereocontrol of four stereogenic centers, in good yields and with excellent enantioselectivities (Table 1, entries 1–3). The sterically demanding catalysts **4b** and **4c** (Table 1, entries 2 and 3) exhibited longer reaction times than the diphenylprolinol ether **4a**, which also delivered better enantioselectivities and yields (Table 1, entry 1). The unprotected diphenylprolinol **4d** also gave good selectivities, however, with reduced reactivity, possibly indicating aminal formation of the activated iminium ion (Table 1, entry 4).[9]

To optimize the reaction, we examined the use of different solvents. The new asymmetric domino Michael/aldol reaction was carried out in various solvents without notable differences in stereocontrol (Table 1, entries 5–9). Product **3a** was not formed when tetrahydrofuran (THF) or DMSO (dimethylsulfoxide) were used (Table 1, entries 10 and 11). We chose ethanol as a solvent because of the short reaction time and the better course of the reaction. Experiments run at low temperatures showed similar results to those conducted at room temperature; however, longer reaction times were required.

Under the optimized reaction conditions, the substrate scope of the domino Michael/aldol reaction was examined by

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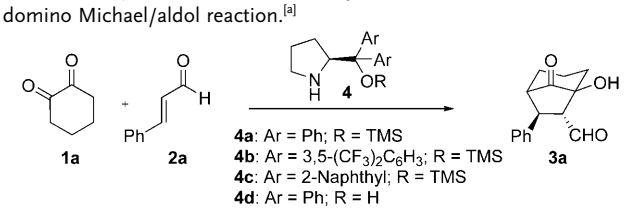
Table 1: Catalyst and solvent investigations of the enantioselective domino Michael/aldol reaction.[a]

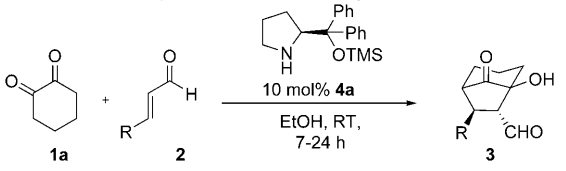


Entry[b]	Solvent	*t* [h]	Cat.	Yield [%][c]	*ee* [%][d]
1	EtOH	7	**4a**	77	96
2	EtOH	24	**4b**	66	92
3	EtOH	24	**4c**	75	94
4	EtOH	24	**4d**	53	81
5	toluene	24	**4a**	76	96
6	Et_2O	24	**4a**	76	96
7	CH_2Cl_2	24	**4a**	73	95
8	$CHCl_3$	24	**4a**	74	97
9	MeCN	40	**4a**	46	93
10	THF	72	**4a**	–	–
11	DMSO	72	**4a**	–	–

[a] TMS = trimethylsilyl. [b] Reaction conditions: 0.2 M solution of 1,2-cyclohexadione (**1a**; 1.2 equiv), aldehyde **2a** (1 equiv), and **4** (10 mol%) at RT. [c] Yield of the product isolated after chromatography. [d] Determined by HPLC analysis.

using various α,β-unsaturated aldehydes **2** (Table 2). Aromatic α,β-unsaturated aldehydes having both electron-withdrawing (Table 2, entries 2, 6, and 7) and electron-donating substituents (Table 2, entries 3–5) can effectively be used in this transformation; the substitution pattern of the arene had no influence on the enantioselectivity of the reaction (Table 2, entris 2–7). Additionally, it was possible to use both heteroaromatic (Table 2, entries 8 and 9) and aliphatic aldehydes (Table 2, entry 10) in this reaction. The ability to control the formation of four new stereogenic centers permitted the synthesis of a diverse collection of bicyclo[3.2.1]octane-6-carbaldehydes in good yields and with excellent enantioselectivities (90–98% *ee*).

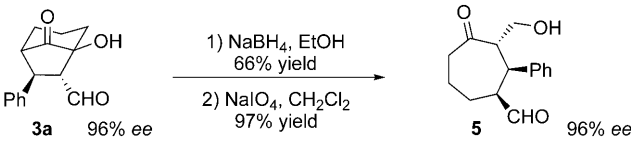
Table 2: Substrate scope of the new Michael/aldol reaction.



Entry[a]	Product	R	Yield [%][c]	*ee* [%][d]
1	**3a**	Ph	77	96
2	**3b**	4-$MeOC_6H_4$	79	95
3	**3c**	4-BrC_6H_4	80	95
4	**3d**	3-BrC_6H_4	62	96
5	**3e**	2-$NO_2C_6H_4$	66	98
6	**3f**[d]	4-$N(Me)_2C_6H_4$	60	93
7	**3g**	benzo[1,3]dioxol-5-yl	68	96
8	**3h**[e]	2-furanyl	81	95
9	**3i**[e]	2-thiophenyl	77	90
10	**3j**[e,f]	*n*-butyl	44	98

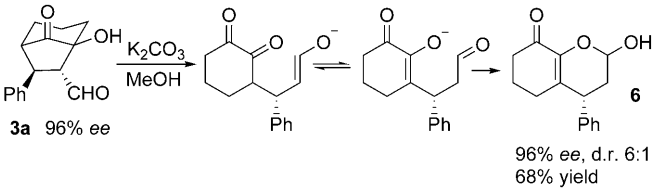
[a] Reaction conditions: 0.2 M ethanol solution, 1,2-cyclohexadione (**1a**; 1.2 equiv), aldehyde **2** (1 equiv), and **4a** (10 mol%) at RT. [b] Yield of the product isolated after chromatography. [c] Determined by HPLC analysis. [d] 20 mol% **4a** used at RT. [e] Reduced aldehyde was used for the determination of enantiomeric excess. [f] 20 mol% **4a** used at 0°C, 72 h.

The highly functionalized products **3** can be used in a variety of additional transformations. Of particular interest, are the multisubstituted chiral cycloheptanones which form the core structure of many natural products and biologically active molecules, and are not generally accessible. By using sodium borohydride in ethanol we reduced both carbonyl groups of **3a** to the corresponding alcohols, and subsequent oxidative cleavage using sodium periodate[10] provided the trisubstituted seven-membered ring **5** without loss in the enantiomeric excess (Scheme 1).



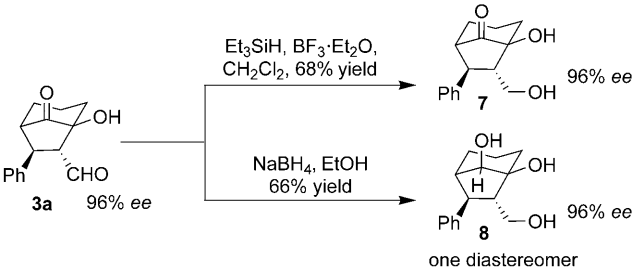
Scheme 1. The synthesis of the polysubstituted cycloheptanone **5** from the domino Michael/aldol product **3a**.

Furthermore, the bicycle **3a** can be elegantly transformed into compound **6** (Scheme 2), which in principle, could have occurred through the addition/cyclization reaction [Eq. (2a)]. The base-induced retro-aldol reaction[11] led to the opening of the diketone which was then cyclized to the hemiacetal **6**; this reaction sequence is the first example of such a retro-aldol/cyclization reaction.



Scheme 2. Retro-aldol cyclization reaction.

In addition to the double reduction of the aldehyde and ketone using sodium borohydride, the aldehyde group of compound **3a** can also be reduced selectively to the alcohol with triethylsilane and boron trifluoride etherate. Hereby, we were able to isolate diol **7** and triol **8** while maintaining the stereochemistry (Scheme 3). In the reduction that gave



Scheme 3. Single and double reduction of the bicycle **3a**.

compound **8** an additional stereocenter is stereoselectively formed, which is controlled by the conformation of adduct **3a**. The crystal structure of **8** shows that the nucleophilic attack occurs from the *Re* face of **3a** (Figure 1).[12] To determine the

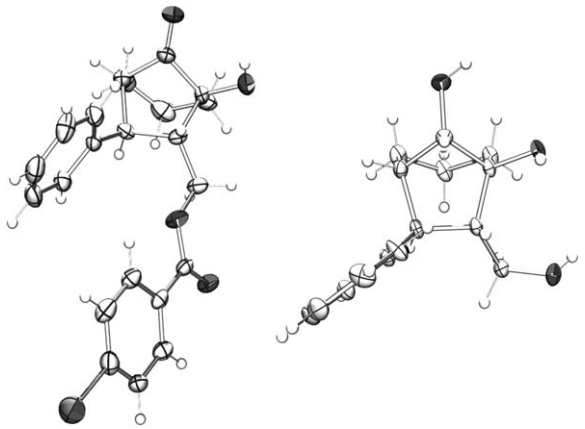
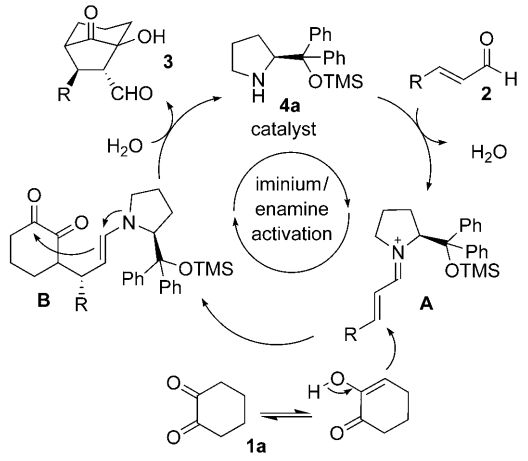


Figure 1. Molecular structure of the bicyclic triol **8** (right) and ester of **7** (left). The thermal ellipsoids are shown at the 50% probability level.

absolute configuration of the bicycle **3a** by means of X-ray crystal structure analysis, the diol **7** was esterified at the primary alcohol using 4-bromobenzoylchloride (Figure 1).[12]

With regard to the reaction mechanism of the newly developed asymmetric domino Michael/aldol reaction, we assume that the diphenylprolinol ether **4a** forms the intermediate iminium ion **A** from reaction with the α,β-unsaturated aldehyde **2** (Scheme 4).[9] A 1,4-addition then occurs



Scheme 4. Iminium/enamine activation: a proposed catalytic cycle for the asymmetric domino Michael/aldol reaction.

with the tautomeric structure of the 1,2-cyclohexadione (**1a**), resulting in the Michael adduct **B**, an activated enamine which subsequently undergoes an intramolecular aldol reaction. Hydrolysis then releases the product **3** from the catalytic cycle and the catalyst **4a** is regenerated.

In summary, we have developed a new diastereo- and enantioselective Lewis base catalyzed domino Michael/aldol reaction in which the formation of four stereogenic centers is controlled. Several α,β-unsaturated aldehydes can be used to provide access to chiral bicyclo[3.2.1]octane-6-carbaldehydes in good yields and with excellent enantioselectivities (90–98% *ee*). In addition, we described the targeted synthesis of bicyclic diols and triols, as well as introduced a new retro-aldol/cyclization reaction which enables easy access to valuable tetrahydrochromenones. Finally, our newly developed organocatalytic domino reaction allows the synthesis of chiral polysubstituted seven-membered rings that are generally difficult to synthetically access and which can be used in the future synthesis of natural products.

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[12] CCDC-725318 (**8**) and CCDC-725317 (**7**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

