ORGANIC
LETTERS

2013
Vol. 15, No. 9
2172–2175

# Highly Diastereo- and Enantioselective Organocatalytic Domino Michael/Aldol Reaction of Acyclic 3-Halogeno-1,2-Diones to α,*β*-Unsaturated Aldehydes

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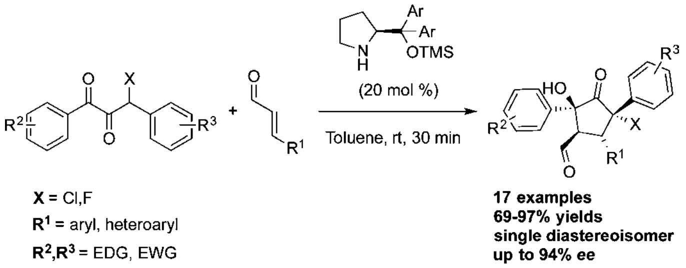
**Received March 16, 2013**

## ABSTRACT



**The first organocatalytic diastereo- and enantioselective domino Michael/aldol reaction of 3-halogeno-1,2-diones to α,*β*-unsaturated aldehydes has been achieved. This transformation tolerates a large variety of electronically different substituents on both reactive partners and allows the synthesis of challenging cyclopentanone derivatives with four contiguous stereogenic centers in excellent diastereoselectivities (>20:1 dr) as well as good yields (69−97%), and enantioselectivities (up to 94% *ee*).**

The formation of C−C bonds with a limited number of steps is one of the most important challenges in organic synthesis.[1] For this purpose, organocatalytic cascade or domino reactions represent a particularly powerful tool for accessing versatile chiral building blocks with functional and molecular diversity in an atom-economical manner.[2,3]

1,2-Dicarbonyl compounds are very attractive scaffolds due to their diverse number of reactive centers.[4] They have two nucleophilic and two electrophilic potentially reactive sites.[5] Thanks to their functional complexity, 1,2-dicarbonyl compounds represent very interesting pronucleophiles for organocatalytic cascade or domino reactions.[6]

Recently, this type of compound has been widely utilized in asymmetric organocatalytic transformations.[7−9]

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The development of different activation modes, increasing their nucleophilicity instead of competitive useless self-condensation, has become a very attractive challenge.[10]

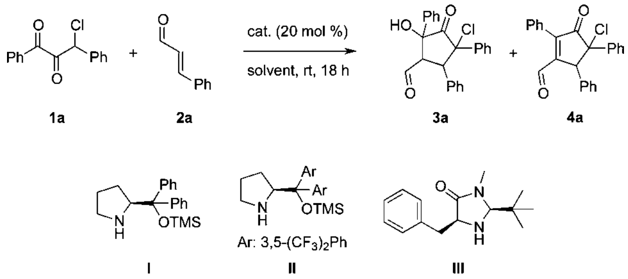
In contrast, 1,2-diones have rarely been described as pronucleophiles in organocatalytic reactions. Only the reactivity of the cyclic commercially available 1,2-cyclohexadione and 2-hydroxy-1,4-naphthoquinone has been explored. This fact is probably due to the difficulty in synthesizing new 1,2-diones. Rueping et al. reported successively the first domino Michael/acetalization C–O heterocyclization sequence of 2-hydroxy-1,4-naphthoquinone[11] and the domino Michael/aldol reaction of 1,2-cyclohexadione[12] with α,*β*-unsaturated aldehydes catalyzed by the Hayashi–Jørgensen catalyst forming respectively chiral 1,4-pyranonaphthoquinones and bicyclo(3,2,1)octane-6-carbaldehydes. Furthermore, other Michael acceptors, such as nitroolefins,[13] arylidenemanonitriles,[14] and α,*β*-unsaturated pyruvates,[15] have been also reported as a replacement for α,*β*-unsaturated aldehydes catalyzed by a bifunctional Bronsted acid/base catalyst affording similar bicyclic structures.

Herein, we describe the first organocatalytic domino Michael/aldol reaction of acyclic 3-halogeno-1,2-diones with α,*β*-unsaturated aldehydes to form cyclopentanones with four contiguous stereogenic centers. Activation of position 3 by the halogen atom could increase the nucleophilicity of these 1,2-dicarbonyls at the expense of the electrophilic sites. Higher flexibility and molecular complexity could also be obtained by the use of acyclic 1,2-diones.

We began our investigations by examining the organocatalytic reaction of 3-chloro-1,2-dione **1a** with cinnamaldehyde **2a** in toluene catalyzed by the Hayashi–Jørgensen catalyst **I**.[16] Degradation of the reactive mixture was observed with a catalyst loading of 20 mol % (Table 1, entry 1). But with 10 mol % of the same catalyst **I**, products **3a** and **4a** were formed in a ratio of 6:1 (Table 1, entry 2). Product **4a** corresponds to the dehydrated derivative of **3a**. Remarkably, product **3a** was obtained exclusively as a single diastereoisomer, indicating the perfect stereocontrol of four contiguous stereogenic centers, with a good yield and enantioselectivity. The other diarylprolinol silylether catalyst **II**[16] was also tested in this reaction; only product **3a** was observed with a perfect diastereoselectivity ( > 20:1 *dr*) as well as excellent yield (91%) and enantioselectivity (91% *ee*). But when the catalyst loading was decreased to 10 mol %, the reactivity and stereocontrol of the reaction were reduced (Table 1, entries 3 and 4). In the same manner, the use of the Macmillan type catalyst **III**[16] showed a dramatic drop in the diastereoselectivity (Table 1, entry 5).

After this first optimization, we decided to examine the influence of different solvents. The new asymmetric domino Michael/aldol reaction was carried out in various solvents without any improvements in terms of reactivity and selectivity (Table 1, entries 6–11). Experimentation at low temperature showed the formation of products **3a** and **4a** in a ratio of 5:1 and the diastereoselectivity was reduced (Table 1, entry 12). NMR monitored investigations indicated that the reaction was finished after 30 min, and product **3a** was obtained with the same diastereoselectivity ( > 20:1 *dr*), a better yield (97%), and a similar enantioselectivity (88% *ee*) (Table 1, entry 13).

**Table 1.** Optimization of the Reaction Conditions[a]



| entry[a] | cat. | solvent | **3a:4a**[b] | yield[c] (%) | *dr*[b] | *ee*[d] (%) |
|---|---|---|---|---|---|---|
| 1[e] | **I** | toluene | – | – | – | – |
| 2[f] | **I** | toluene | 6:1 | 70 | >20:1 | 87 |
| 3 | **II** | toluene | >20:1 | 91 | >20:1 | 91 |
| 4[f] | **II** | toluene | >20:1 | 83[g] | 9:1 | 89[g] |
| 5 | **III** | toluene | >20:1 | 86[h] | 5:1 | – |
| 6 | **II** | MeOH | >20:1 | 53 | >20:1 | 84 |
| 7 | **II** | $CH_2Cl_2$ | >20:1 | 80 | >20:1 | 88 |
| 8 | **II** | EtOAc | >20:1 | 74 | >20:1 | 90 |
| 9 | **II** | MeCN | 3:1 | 53 | >20:1 | 80 |
| 10 | **II** | DMF | >20:1 | 78 | >20:1 | 87 |
| 11 | **II** | $CHCl_3$ | >20:1 | 77 | >20:1 | 53 |
| 12[i] | **II** | toluene | 5:1 | 83[h] | 4:1 | – |
| 13[j] | **II** | toluene | >20:1 | 97 | >20:1 | 88 |

[a] 1,2-Dione (0.1 mmol), cinnamaldehyde (0.5 mmol), solvent (0.2 mL). [b] Ratio determined by $^1$H NMR of the crude reaction mixture for product **3a**. [c] Isolated yield for product **3a**. [d] Determined by chiral SFC for product **3a**. [e] Degradation of the reactive mixture was observed. [f] 10 mol % of the catalyst was used. [g] Determined for the major diastereoisomer. [h] Determined for the mixture of the two diastereoisomers. [i] Reaction was performed at 0 °C. [j] Reaction was performed with 1,2-dione (0.1 mmol), cinnamaldehyde (0.2 mmol) in toluene (0.2 mL) at room temperature for 30 min.

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(8) For the utilization of 1,2-ketoamides as pronucleophiles in organocatalytic reactions: Baslé, O.; Raimondi, W.; Sanchez Duque, M. M.; Bonne, D.; Constantieux, T.; Rodriguez, J. *Org. Lett.* **2010**, *12*, 5246.

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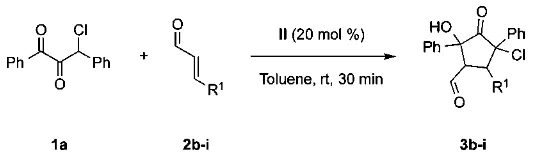
Under the optimized reaction conditions, the substrate scope of this diarylprolinol silylether catalyzed enantioselective domino Michael/aldol reaction using various α,*β*-unsaturated aldehydes **2** was investigated (Table 2). Aromatic α,*β*-unsaturated aldehydes **2b**–**h** with electron-donating (Table 2, entries 1–4) and electron-withdrawing (Table 2, entries 5–7) substituents were involved successfully in the reaction. Various new cyclopentanones with four contiguous stereogenic centers were synthesized in good yields (77–94%) and enantioselectivities (82–90% *ee*). The diastereoselectivity was also perfectly controlled in the same manner (> 20:1 *dr*). Additionally, a heteroaromatic α,*β*-unsaturated aldehyde could be also involved in this transformation (Table 2, entry 8). Finally, less reactive *trans*-2-pentenal was used, and almost no reaction occurred.

**Table 2.** Organocatalytic Domino Michael/Aldol Reactions of 3-Chloro-1,3-diphenylpropane-1,2-dione (**1a**) and α,*β*-Unsaturated Aldehydes Catalyzed by the Catalyst **II**[a]

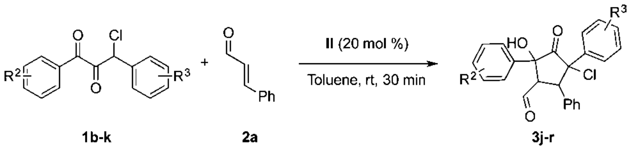


| entry[a] | $R^1$ | 3 | yield[b] (%) | *dr*[c] | *ee*[d] (%) |
|---|---|---|---|---|---|
| 1 | *m*-MeOC$_6$H$_4$ (**2b**) | **3b** | 83 | >20:1 | 90 |
| 2 | *p*-MeOC$_6$H$_4$ (**2c**) | **3c** | 77 | >20:1 | 86 |
| 3 | *p*-MeC$_6$H$_4$ (**2d**) | **3d** | 90 | >20:1 | 86 |
| 4 | *o*-MeOC$_6$H$_4$ (**2e**) | **3e** | 83 | >20:1 | 82 |
| 5 | *p*-FC$_6$H$_4$ (**2f**) | **3f** | 94 | >20:1 | 90 |
| 6 | *m*-BrC$_6$H$_4$ (**2g**) | **3g** | 92 | >20:1 | 88 |
| 7 | *o*-BrC$_6$H$_4$ (**2h**) | **3h** | 85 | >20:1 | 83 |
| 8 | 2-furanyl (**2i**) | **3i** | 81 | >20:1 | 82 |

[a] Reaction was performed with 1,2-dione (0.2 mmol) and α,*β*-unsaturated aldehyde (0.4 mmol) in toluene (0.2 mL). [b] Isolated yield. [c] Determined by $^1$H NMR of the crude reaction mixture. [d] Determined by chiral SFC.

After the first application of this new methodology, we decided to apply the same optimized conditions to various 3-chloro-1,2-diones **1b**–**k** with electron-withdrawing and -donating substituents on the aryl moiety in position 1. Products were obtained with excellent diastereoselectivities (> 20:1 *dr*), good yields (80–95%), and enantioselectivities (88–94% *ee*) (Table 3, entries 1–4). Other 3-chloro-1,3-diphenylpropane-1,2-diones with electron-donating and -withdrawing substituents on the aryl moiety in position 3 were also employed successfully in the new transformation. A diverse set of new cyclopentanones with four contiguous stereogenic centers was isolated in good yields (69–95%) and enantioselectivities (77–91% *ee*). Only one diastereoisomer was still observed (> 20:1 *dr*) (Table 3, entries 5–8). It is interesting to note that whatever the electronic properties of the substituent in the *ortho* position, no reactivity was observed (Table 3, entries 9 and 10). This lack of reactivity is probably due to the steric hindrance of the substituents.

**Table 3.** Organocatalytic Domino Michael/Aldol Reactions of 3-Chloro-1,3-diphenylpropane-1,2-diones and Cinnamaldehyde (**2a**) Catalyzed by the Catalyst **II**[a]



| entry[a] | R$^2$, R$^3$ | 1 | 3 | yield (%)[b] | *dr*[c] | *ee* (%)[d] |
|---|---|---|---|---|---|---|
| 1 | R$^2$ = *o*-Cl-, R$^3$ = H | **1b** | **3j** | 80 | >20:1 | 94 |
| 2 | R$^2$ = *p*-Br-, R$^3$ = H | **1c** | **3k** | 85 | >20:1 | 89 |
| 3 | R$^2$ = *p*-MeO-, R$^3$ = H | **1d** | **3l** | 95 | >20:1 | 90 |
| 4 | R$^2$ = *m*-Me-, R$^3$ = H | **1e** | **3m** | 95 | >20:1 | 88 |
| 5 | R$^2$ = R$^3$ = *p*-Cl- | **1f** | **3n** | 75 | >20:1 | 91 |
| 6 | R$^2$ = H, R$^3$ = *m*-MeO- | **1g** | **3o** | 95 | >20:1 | 90 |
| 7 | R$^2$ = H, R$^3$ = *p*-Me- | **1h** | **3p** | 80 | >20:1 | 90 |
| 8 | R$^2$ = H, R$^3$ = *p*-NO$_2$- | **1i** | **3q** | 69 | >20:1 | 77 |
| 9[e] | R$^2$ = H, R$^3$ = *o*-Br- | **1j** | **3r** | – | – | – |
| 10[e] | R$^2$ = H, R$^3$ = *o*-Me- | **1k** | **3s** | – | – | – |

[a] Reaction was performed with 1,2-dione (0.2 mmol) and α,*β*-unsaturated aldehyde (0.4 mmol) in toluene (0.2 mL). [b] Isolated yield. [c] Determined by $^1$H NMR of the crude reaction mixture. [d] Determined by chiral SFC. [e] No conversion was observed. Starting materials were recovered.

The absolue configuration of product **3k** was determined by X-ray crystallographic analysis (Figure 1; see the Supporting Information). The stereochemistry of these new cyclopentanones with four contiguous stereogenic centers was then established.

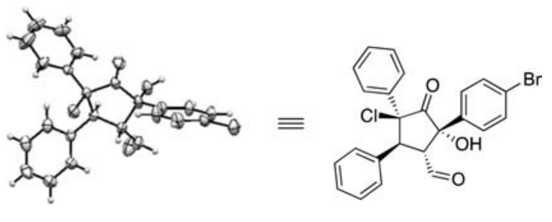
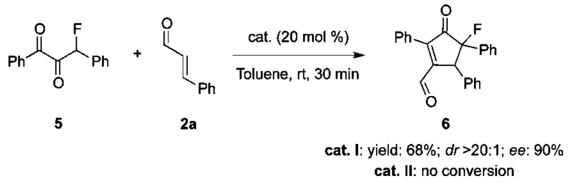


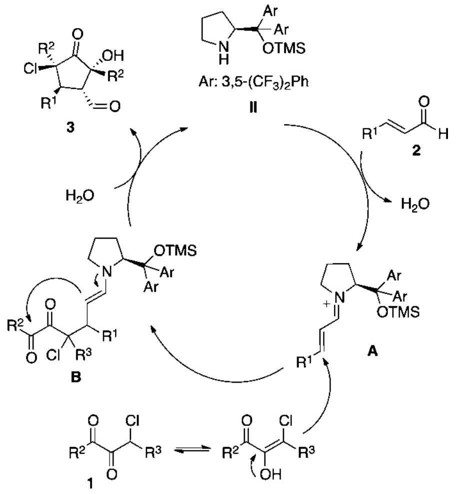
**Figure 1.** X-ray structure of product **3k**. Thermal ellipsoids are shown at the 50% probability level.

In order to study other modes of activation of 1,2-diones, we decided to test 3-fluoro-1,3-diphenylpropane-1,2-dione **5** in the reaction (Scheme 1).

**Scheme 1.** Reaction of 3-Fluoro-1,3-diphenylpropane-1,2-dione (**5**) and Cinnamaldehyde (**2a**)



**Scheme 2.** Proposed Catalytic Cycle for the Organocatalytic Domino Michael/Aldol Reaction



Unlike chloro derivatives, 3-fluoro-1,3-diphenylpropane-1,2-dione **5** did not react with cinnamaldehyde **2a** in the presence of catalyst **II**. But with catalyst **I**, a new cyclopentenone with two contiguous stereogenic centers, **6**, was synthesized after 30 min in an excellent diastereoselectivity (> 20:1 dr) as well as good yield (68%) and enantioselectivity (90% *ee*). The formation of the corresponding hydrated compound was not observed (Scheme 1).

In the present transformation, we assume that diaryl prolinol silylether catalyst **II** forms the reactive imminium intermediate **A** with the α,*β*-unsaturated aldehyde **2**. Then, a 1,4-addition occurs with the enol form of the acyclic 1,2-diketone **1**, forming the Michael adduct **B**. This enamine intermediate **B** achieves the intramolecular aldol reaction. After hydrolysis, product **3** is obtained and the catalyst **II** is regenerated (Scheme 2).

In conclusion, we described a new highly diastereo- and enantioselective organocatalyzed domino Michael/aldol reaction in which the formation of four contiguous stereogenic centers was controlled. Several acyclic 3-chloro-1,2-diones and α,*β*-unsaturated aldehydes could be used providing an access to challenging chiral cyclopentanones in excellent diastereoselectivities as well as good yields and enantioselectivities. In addition, the reactivity of 3-fluoro-1,2-dione was also evaluated in the transformation. New chiral cyclopentenone was obtained with the same excellent diastereoselectivity, in a good yield and enantioselectivity. The expansion of the scope and synthetic applications of this reaction constitute our future investigations.

**Acknowledgment.** This research was supported by the Swiss National Research Foundation (Grant No. 200020_144344) and COST action CM905 "Organocatalysis" (SER Contract No. C11.0080).

**Supporting Information Available.** Experimental procedures, NMR spectra, and chiral separations for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.