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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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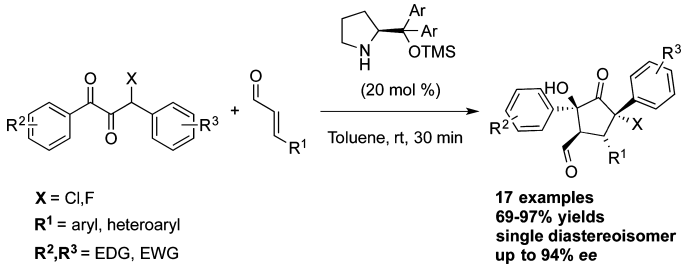
ABSTRACT



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]

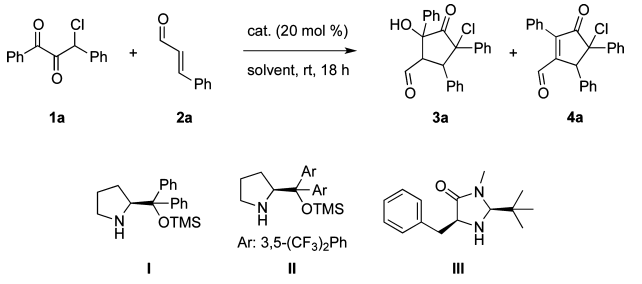
In contrast, 1,2-diones have rarely been described as pronucleophiles in organocatalytic reactions. Only the reactivity of the cyclic commercially available 1,2-cyclohexadione and 2-hydroxy-1,4-naphthoquinone has been explored. This fact is probably due to the difficulty in synthesizing new 1,2-diones. 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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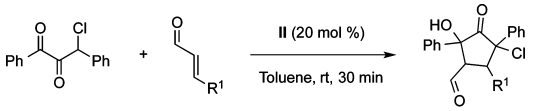
Under the optimized reaction conditions, the substrate scope of this diarylprolinol silylether catalyzed enantioselective domino Michael/aldol reaction using various α,β-unsaturated aldehydes **2** was investigated (Table 2). Aromatic α,β-unsaturated aldehydes **2b**–**h** with electron-donating (Table 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]



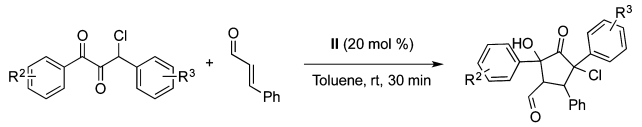
1a **2b-i** **3b-i**

entry[a]	R^1	**3**	yield[b] (%)	*dr*[c]	*ee*[d] (%)
1	*m*-$MeOC_6H_4$ (**2b**)	**3b**	83	>20:1	90
2	*p*-$MeOC_6H_4$ (**2c**)	**3c**	77	>20:1	86
3	*p*-MeC_6H_4 (**2d**)	**3d**	90	>20:1	86
4	*o*-$MeOC_6H_4$ (**2e**)	**3e**	83	>20:1	82
5	*p*-FC_6H_4 (**2f**)	**3f**	94	>20:1	90
6	*m*-BrC_6H_4 (**2g**)	**3g**	92	>20:1	88
7	*o*-BrC_6H_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]



1b-k **2a** **3j-r**

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.

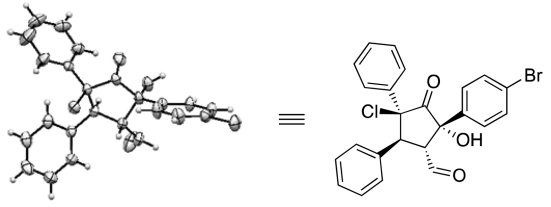
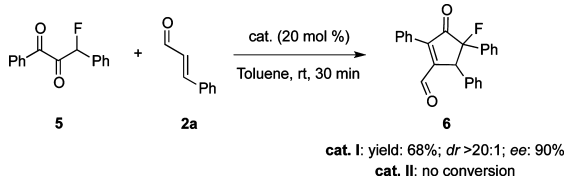


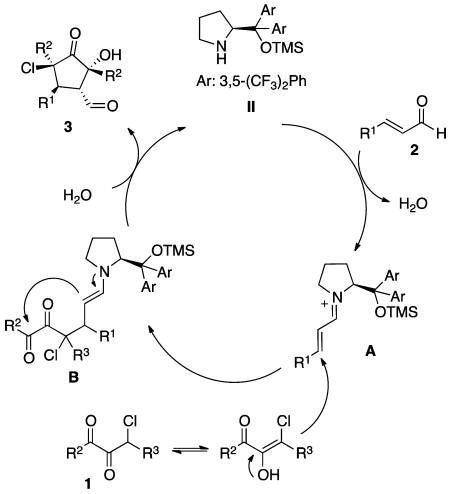
Figure 1. X-ray structure of product **3k**. Thermal ellipsoids are shown at the 50% probability level.

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.

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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.

The authors declare no competing financial interest.