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Organocatalytic asymmetric domino Michael–Henry reaction for the synthesis of substituted bicyclo[3.2.1]octan-2-ones†

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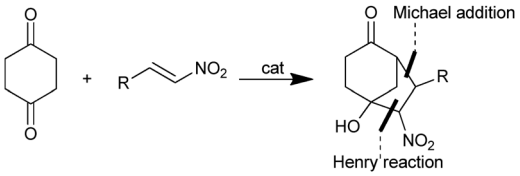
The first organocatalytic asymmetric reaction between 1,4-cyclohexanedione and nitroalkenes has been studied, affording bicyclo-[3.2.1]octane derivatives containing four continuous stereogenic centres. The products were obtained through a domino Michael–Henry process as a single diastereoisomer with excellent enantioselectivities.

In recent years, domino and cascade reactions have attracted the interest of organic chemistry researchers, as they constitute a powerful tool for the formation of several bonds in a one-step process.[1] The application of these reactions in the field of organocatalysis[2] is particularly appealing because it can lead to the formation of complex structures with high stereoselectivities, in an operationally simple and straightforward manner. Amongst the numerous strategies employed in this category,[3] domino Michael–Henry reactions[4] play a pivotal role as these reactions constitute two of the most widely used reactions in organic asymmetric synthesis.[5,6]

In line with our latest studies on the asymmetric Michael addition of ketones to nitroalkenes using bifunctional organocatalysts,[7] we became interested in the use of 1,4-cyclohexanedione as the Michael donor. Rueping *et al.* and Zhao *et al.* reported the tandem Michael–Henry reaction of 1,2-cyclohexanedione with nitroalkenes leading to bicyclo[3.2.1] octanes.[8,9] Also, Zhong and co-workers used 2,5-dioxocyclohexanecarboxylate esters with nitroolefins.[10] Bearing in mind these literature reports, we envisaged that 1,4-cyclohexanedione could be used and could undergo a similar reaction sequence to assemble a multifunctionalized bicyclo[3.2.1]octane structure [eqn (1)]. Our design plan was to use an unprecedented enamine activation of 1,4-diketones in order to obtain a skeleton which is encountered in numerous natural products and biologically active molecules,[11] and any enantioselective synthetic route to this structural motif could be of great importance.



(1)

We initiated our study by choosing as a model reaction the addition of 1,4-cyclohexanedione **1** to phenyl nitrodiene **2a** in the presence of L-proline as the chiral catalyst. The use of nitrodienes as the Michael acceptors is far less documented and it remains underdeveloped in comparison to the extensively studied nitroolefins. Indeed, proline enabled the reaction forming bicyclic compound **3a** in excellent yield but in a nearly racemic form. This result led us to the assumption that the domino Michael–Henry reaction proceeds through an enamine activation mode,[12] as opposed to the existing protocols[8,10] that suggest the formation of the enolic tautomer of the 1,2-cyclohexanedione by a cinchona-alkaloid derived catalyst. To support our hypothesis, we repeated the reaction using catalytic amounts of tertiary amines that cannot form an enamine intermediate with the dione. Thus, we tested an achiral base, such as DABCO, and a bifunctional base, like quinine, and in both cases no reaction took place. The difference in the pK_a of 1,2-cyclohexanedione in comparison to 1,4-cyclohexanedione could explain this difference in reactivity.

Based on these observations, we set out to develop an asymmetric version of this domino reaction. Several bifunctional catalysts were screened, but only the proline derived catalysts **I–III** displayed noteworthy effects on the outcome of the reaction (Table 1, entries 1–3, see ESI† for full optimization study). Catalysts **I** and **II** developed by us,[7b] bearing a thioxotetrahydropyrimidinone or a thiohydantoin ring, respectively, delivered the product in excellent enantioselectivity, but the size of the ring exhibited a tremendous impact on the activity of the catalyst (Table 1, entry 1 *vs.* 2). Catalyst **III** led to high yield

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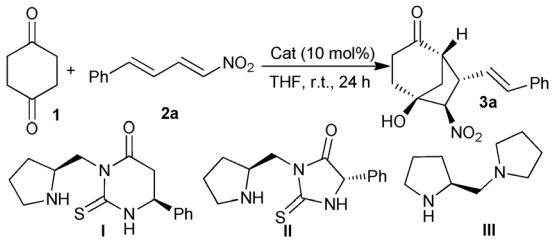
Table 1 Catalyst screening and optimization studies for the asymmetric domino Michael–Henry reaction[a]



Entry	Catalyst	Additives (10 mol%)	Yield[b] (%)	ee[c] (%)
1	**I**	4-NBA, H_2O[d]	91	96
2	**II**	4-NBA, H_2O[d]	22	90
3	**III**	—	92	75
4	**I**	4-CBA, H_2O[d]	58	89
5	**I**	4-NBA	Traces	—
6[e]	**I**	4-NBA, H_2O[d]	72	96
7[f]	**I**	4-NBA, H_2O[d]	75	96

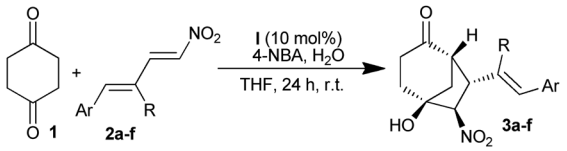
[a] Reactions were performed using **1** (0.2 mmol), **2a** (0.1 mmol) with 10 mol% of catalyst and additive in dry THF (0.25 mL) for 24 hours at r.t. [b] Isolated yield. [c] The enantiomeric excess (ee) was determined by chiral HPLC. [d] 50 μL of water were used. [e] 5 mol% of **I** was used. [f] 0.11 mmol (1.1 equiv.) of **1** was used. 4-NBA: 4-nitrobenzoic acid, 4-CBA: 4-cyanobenzoic acid.

but the selectivity dropped significantly (Table 1, entry 3). It has to be highlighted that compound **3a** was formed as a single diastereoisomer in all cases, demonstrating the excellent stereocontrol of this protocol on four continuous stereogenic centres. To optimize the reaction conditions, several solvents and additives were examined in the presence of 10 mol% of catalyst **I** (Table 1 and ESI†). Polar solvents that could solubilise efficiently the dione favoured the reaction, with THF being the optimum both in terms of yield and selectivity. On the other hand, it is well documented that a careful selection of additives can play a significant role in the activity of the catalyst.[13] Thus, 4-nitrobenzoic acid made an ideal pair with our catalyst providing the best results (Table 1, entry 1 *vs.* 4), while a controlled amount of water proved to be essential for the catalyst's turnover (Table 1, entry 1 *vs.* 5). Moreover, reducing the catalyst loading to 5 mol%, or the ratio of dione to nitrodiene to 1.1 : 1 led to decreased yields, but excellent enantioselectivity (Table 1, entries 6 and 7).

With optimal conditions in hand, the scope and limitations of our method were studied. An array of aromatic nitrodienes bearing electron-donating or electron withdrawing substituents on the phenyl ring could be well tolerated, delivering the bicyclic products **3a–e** in good to high yields and excellent enantioselectivity (Table 2, entries 2–5). Nitrodiene **2f** bearing a methyl group at the α-position with respect to the phenyl ring was also successfully employed (Table 2, entry 6).

To broaden the scope of our methodology, nitrodienes were replaced by aromatic nitroolefins as the electrophilic partner. Unfortunately, when we employed the same reaction conditions used for nitrodienes, we encountered a significant handicap with *trans*-β-nitrostyrene **4a**. The reaction rate was much slower (a reaction time of 4 days was required in order to reach completion), while simultaneously the second, intramolecular ring

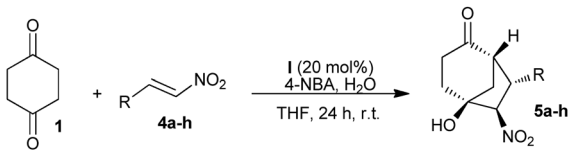
Table 2 Domino Michael–Henry reaction between dione **1** and nitrodienes **2a–f** using catalyst **I**[a]



Entry	Ar, R	Yield[b] (%)	ee[c] (%)
1	Ph, H (**2a**)	**3a**, 91	96
2	4-OMe-Ph, H (**2b**)	**3b**, 56	94
3	4-Cl-Ph, H (**2c**)	**3c**, 72	91
4	2-NO_2-Ph, H (**2d**)	**3d**, 89	86
5	4-NO_2-Ph, H (**2e**)	**3e**, 73	97
6	Ph, Me (**2f**)	**3f**, 70	95

[a] Reactions were performed using **1** (0.2 mmol), **2** (0.1 mmol) in the presence of catalyst **I** (10 mol%), 4-NBA (10 mol%) and H_2O (50 μL) in dry THF (0.25 mL) at r.t. for 24 hours. [b] Isolated yield. [c] The enantiomeric excess (ee) was determined by chiral HPLC.

Table 3 Domino Michael–Henry reaction between dione **1** and nitroolefins **4a–h** using catalyst **I**[a]



Entry	R	Yield[b] (%)	ee[c] (%)
1[d]	Ph (**4a**)	**5a**, 38	93
2	Ph (**4a**)	**5a**, 86	93
3	4-Cl-Ph (**4b**)	**5b**, 81	95
4	4-F-Ph (**4c**)	**5c**, 75	93
5	3-NO_2-Ph (**4d**)	**5d**, 80	96
6	4-NO_2-Ph (**4e**)	**5e**, 70	93
7	4-OMe-Ph (**4f**)	**5f**, 83	94
8	2-Furyl (**4g**)	**5g**, 82	91
9	2-Naphthyl (**4h**)	**5h**, 78	90

[a] Reactions were performed using **1** (0.2 mmol), **4** (0.1 mmol) in the presence of catalyst **I** (20 mol%), 4-NBA (20 mol%) and H_2O (50 μL) in dry THF (0.25 mL) at r.t. for 24 hours. [b] Isolated yield. [c] The enantiomeric excess (ee) was determined by chiral HPLC. [d] 10 mol% of catalyst **I** and 4-NBA were used.

closing step experienced difficulties in advancing (10% of the Michael adduct from the initial Michael addition of the diketone to nitrostyrene was detected in ^{1}H-NMR of the crude reaction mixture) (Table 3, entry 1). The latter was probably due to steric repulsion and/or stabilizing factors from the adjacent bulky phenyl group. To overcome this obstacle, 20 mol% of catalyst **I** was used and the desired product **5a** was delivered as a single diastereoisomer in 86% yield and 93% ee (Table 3, entry 2). Having established the optimal reaction protocol, a variety of substituted aromatic nitroolefins was investigated. Aromatic groups with electron-rich and electron-deficient substituents were successfully utilized to form the bicyclic products in high yield and with excellent ee values (Table 3, entries 3–7). In addition, nitroolefins bearing heteroaromatics as well as other aromatic groups were also well tolerated (Table 3, entries 8 and 9). It should be noted that a small percentage of the Michael adduct was observed in all cases (3–6%),

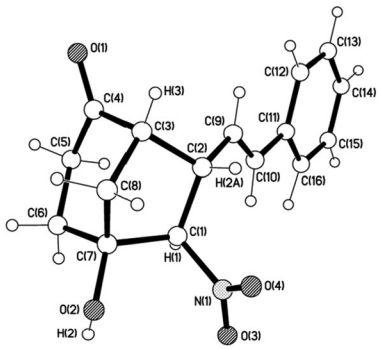


Fig. 1 X-ray structure of enantiopure **3a**.

lowering the yield of the desired product. All attempts to force the second ring closing step by adding a base in the product mixture resulted either in degradation or in the epimerization of the α-nitro carbon centre of **5a–h** (~95 : 5 dr) possibly through a retro-Henry reaction.

The absolute configuration of the products was indicated by X-ray crystallographic analysis[14] of a crystal of compound **3a** (Fig. 1). On the basis of this result, a plausible mechanistic pathway is proposed to account for the stereochemical outcome of this reaction (see ESI†).

In conclusion, we have developed an unprecedented organocatalytic asymmetric addition of 1,4-cyclohexanedione to aromatic nitrodienes and nitroolefins, leading to complex bicyclo[3.2.1]-octan-2-one derivatives containing four continuous stereogenic centres as a single diastereoisomer and with excellent enantioselectivities. The products were delivered through a domino Michael–Henry process using a proline-based bifunctional organocatalyst.

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