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

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ARTICLE TYPE

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

Michail Tsakos,[a] Mark R. J. Elsegood[b] and Christoforos G. Kokotos*[a]

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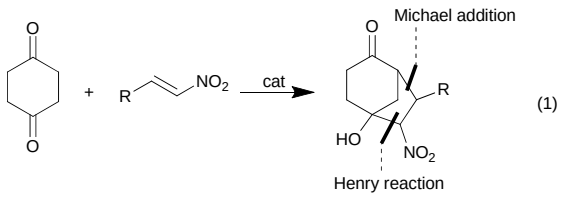
The first organocatalytic asymmetric reaction between 1,4-cyclohexanedione and nitroalkenes have been studied, affording bicyclo[3.2.1]octane derivatives containing four continuous stereogenic centres. The products were obtained through a domino Michael-Henry process as a single diastereoisomer with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

In recent years, domino and cascade reactions have attracted the interest of organic chemistry research, 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 reaction[4] plays 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 utilizing 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.[8,9] The only example utilising a modified tricarbonyl 1,4-diketone has been reported by Zhong and co-workers.[10] Bearing in mind these literature reports, we envisaged that 1,4-cyclohexanedione could be used for the first time in a such a reaction and could also undergo a similar reaction sequence to assemble a multifunctionalized bicyclo[3.2.1]octane structure [Eq. (1)]. This unprecedented methodology would lead to 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.

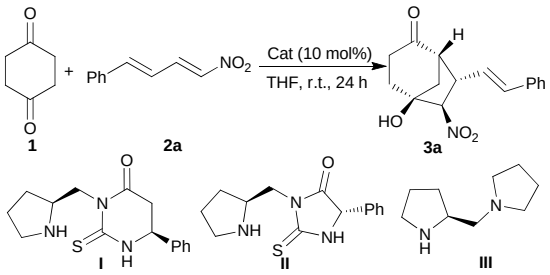


(1)

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 acceptor is considered much more challenging[7d, 7e] and it remains underdeveloped in comparison to the extensively studied nitrostyrenes. Indeed, proline enabled the reaction forming the 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 dione by a cinchona-alkaloid derived catalyst. To support our hypothesis, we repeated the reaction using catalytic amounts of tertiary amine bases that cannot form an enamine intermediate with the dione. Thus, we tested an achiral base, such as DABCO, and a bifunctional base, such as quinine, and in both cases no reaction took place.

Based on these observations, we set out to develop an

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

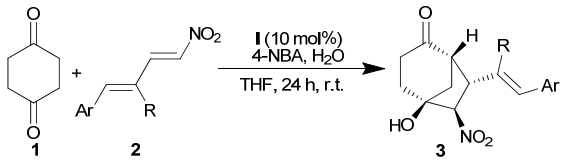
[a] Reactions were performed using **1** (0.2 mmol) and **2a** (0.1 mmol) with 10 mol% of catalyst and additive in dry THF (0.25 mL) for 24 hours at room temperature. [b] Isolated yield. [c] The enantiomeric excess (*ee*) was determined by chiral HPLC. [d] 50 μL of water were used. [e] 5 mol% of catalyst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

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 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 proper pKa value for maximum result (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, albeit the excellent enantioselectivity was maintained (Table 1, entries 6 and 7).

With optimal conditions in hand, the scope and limitations of our method was 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 nitrostyrenes as the electrophilic partner. Unfortunately, when we employed the same reaction conditions

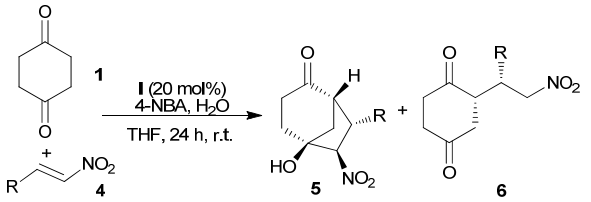
Table 2 Domino Michael-Henry reaction between dione **1** and nitrodienes **2** utilizing catalyst **I**.[a]



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) and **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 room temperature 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 nitrostyrenes **4** utilizing 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-Napthyl (**4h**)	**5h**, 78	90

[a] Reactions were performed using **1** (0.2 mmol) and **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 room temperature 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.

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 closing, step experienced difficulties in advancing, thus leading to the formation of intermediate **6a** in 10% yield (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 nitrostyrenes 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, nitrostyrenes bearing heteroaromatic as well as other aromatic groups were also well tolerated (Table 3, entries 8, 9). It should be noticed that a small percentage of the Michael adduct **6** was observed in all cases, lowering the yield of the desired product. All attempts to force the second ring closing step on **6** by adding a base in the product mixture resulted in the epimerization of the α-nitro carbon centre of **5** and subsequently retro-Henry degradation. The products were separated by FC chromatography.

The absolute configuration of the products was indicated by X-ray crystallographic analysis[14] of a crystal of compound **3a** (Figure 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 nitrostyrenes, leading to complex

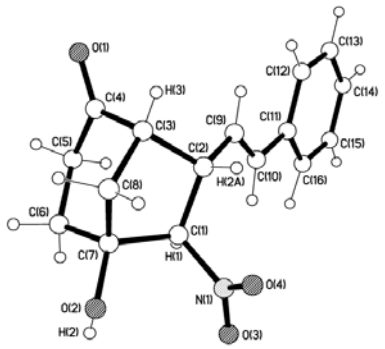


Fig. 1 X-Ray structure of enantiopure **3a**.

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 utilizing a proline-based bifunctional organocatalyst.

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[a] *Laboratory of Organic Chemistry, Department of Chemistry, University of Athens, Panepistimiopolis 15771, Athens, Greece. Fax: +30 210 7274761; Tel: +30 210 7274281; E-mail: ckokotos@chem.uoa.gr*

[b] *Loughborough University, Loughborough, LE11 3TU, UK. Fax: +44 1509 223925; Tel: +44 1509 228751; E-mail:m.r.j.elsegood@lboro.ac.uk*

† Electronic Supplementary Information (ESI) available: [Full optimization studies, proposed mechanism, characterization of the products, NMR, HPLC and crystallographic data]. See DOI: 10.1039/b000000x/

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14. X-ray data for **3a**. $C_{16}H_{17}NO_4$, M = 278.30, colourless block, 0.70 × 0.21 × 0.17 mm^3, orthorhombic, $P2_12_12$, a = 10.3329(10), b = 19.6202(19), c = 7.1804(7) Å, V = 1455.7(2) Å^3, Z = 4, μ(Mo-Kα) = 0.10 mm^{-1}, T = 150K, 17114 reflections measured on a Bruker APEX 2 CCD diffractometer, 4410 unique, R_{int} = 0.033, $R_1[F^2>2\sigma(F^2)]$ = 0.041, wR_2 (all data) = 0.107, Flack x = –0.6(4); not reliably determined, but gives an indication. H atoms freely refined. CCDC 916313 contains 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.