Organocatalytic Asymmetric Triple Domino Reactions of Nitromethane with α,β-Unsaturated Aldehydes

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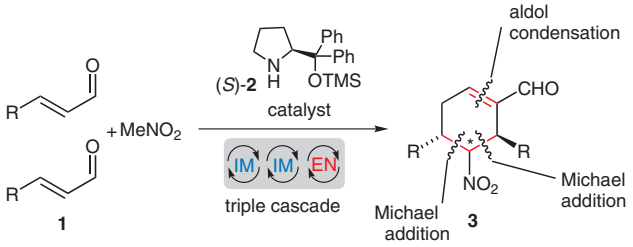
Abstract: An organocatalytic asymmetric multicomponent domino reaction employing the bulk chemical nitromethane and α,β-unsaturated aldehydes as substrates is described. The new triple cascade reaction based on two subsequent Michael additions and an intramolecular aldol condensation provides an atom-economic entry to diastereo- and enantiomerically pure 5-nitrocyclohexene carbaldehydes after flash chromatography.

Key words: domino reaction, organocatalysis, Michael addition, nitroalkane, aldol condensation

The conjugate addition of nitroalkanes to α,β-unsaturated carbonyl compounds constitutes an important carbon–carbon bond-forming reaction in organic synthesis.[1] After the pioneering work of Hanessian et al. and Corey et al. in the year 2000, many reports appeared in the literature and proved that organocatalysts such as secondary amines can promote this key reaction with high enantioselectivities.[2,3] Parallel to this development, domino reactions have gained considerable attention. This powerful tool for the construction of complex molecules in a simple operation is efficient in terms of atom and step economy, while avoiding protecting-group manipulations, one of the main drawbacks of classical synthesis.[4] For example, our group reported recently a secondary amine-catalyzed domino Michael–nitroalkane Michael–aldol condensation reaction for the stereoselective synthesis of tri- and tetrasubstituted cyclohexene carbaldehydes.[5,6] A related approach was recently reported by Jørgensen et al. using activated methylene compounds such as malonitrile, cyanoacetates, or nitro esters as nucleophiles and enals as electrophiles.[7]

To explore this field further and taking advantage of the nitroalkane specific reactivity, we envisaged the development of an organocatalytic domino nitroalkane Michael–nitroalkane Michael–aldol condensation sequence using one equivalent of nitromethane and two equivalents of α,β-unsaturated aldehydes.

We now wish to report such a triple domino reaction based on an iminium–iminium–enamine activation mode for the asymmetric synthesis of 5-nitrocyclohexene carbaldehydes **3** catalyzed by diphenylprolinol TMS ether (*S*)-**2** as organocatalyst (Scheme 1).

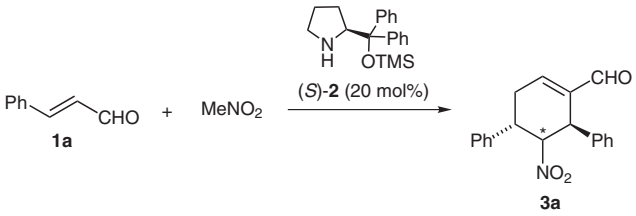


Scheme 1 Organocatalytic asymmetric multicomponent domino reaction of nitromethane with enals

We started our investigations by reacting cinnamaldehyde (**1**, R = Ph) with nitromethane in various solvents in the presence of 20 mol% of catalyst (*S*)-**2** to find out the best conditions (Table 1).

Surprisingly, toluene as solvent did not provide any conversion under the test conditions (entry 1), and the same result was obtained with THF. In ethanol the triple cas-

Table 1 Solvent Screening for the Reaction of Cinnamaldehyde with Nitromethane



Entry[a]	Solvent	Yield (%)[b]	dr[c]	ee (%)[d]
1	toluene	0	–	–
2	THF	0	–	–
3	EtOH	23	52:48	–
4	$CHCl_3$	70	65:35	>99
5[e]	$CHCl_3$	35	64:36	>99
6[f]	$CHCl_3$	65	64:36	>99

[a] All reactions were performed on a 0.5 mmol scale at r.t. for 18 h with 20 mol% of catalyst and 2.5 equiv of cinnamaldehyde.
[b] Yield of the two diastereomers after flash chromatography.
[c] Determined by GC analysis of the crude product.
[d] Determined by HPLC analysis on a chiral stationary phase; only the ee of the major diastereomer was measured.
[e] Reaction performed at 0 °C.
[f] Reaction performed with 2.2 equiv of cinnamaldehyde.

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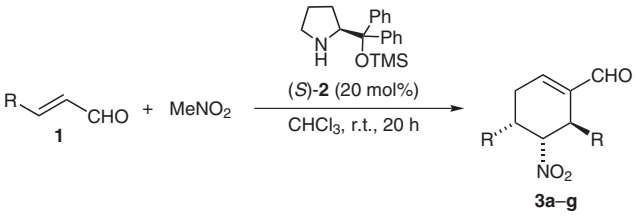
cade product was isolated in low yield and with no diastereoselectivity. Chloroform gave a dramatic improvement, and the domino product was isolated in 70% yield with a low diastereomeric ratio and a practically complete enantiomeric excess (entry 4). Despite the low diastereoselectivity, the enantiopure major diastereomer could be isolated after flash chromatography. Carrying out the reaction at low temperature (0 °C) did not improve the diastereomeric ratio, and the reaction was not complete after 18 hours (entry 5). Finally, we proved that 2.2 equivalents of cinnamaldehyde are sufficient to allow a good conversion (entry 6). In order to demonstrate the practicability of the new protocol the reaction was carried out on a 10 mmol scale without any loss of the enantiomeric purity but with a somewhat lower yield (44%). This scale-up process afforded 760 mg of the enantiopure aldehyde **3a**.

We then investigated the present reaction with respect to different α,β-unsaturated aldehydes **1** (Scheme 2). The starting enals were purchased from commercial sources or were synthesized via a Heck reaction from the corresponding aromatic halide.[8]



Scheme 2 Asymmetric synthesis of 5-nitrocyclohexene carbaldehydes **3** from nitromethane and various enals **1**

Table 2 Yields and Stereoselectivities of the Organocatalytic Triple Domino Reaction[a]

3	R	Yield (%)[b]	dr[c]	de (%)[d]	ee (%)[e]
3a	Ph	65	64:36	>98	>99
3b	2-MeOC$_6$H$_4$	57	73:27	>98	>99
3c	4-MeOC$_6$H$_4$	60	73:27	>98	>99
3d	*p*-tolyl	52	70:30	>98	>99
3e	*p*-diphenyl	40	92:8[f]	>98	>99
3f	2-naphthyl	57	78:22[f]	>98	>98
3g	5-*N*-methylindolyl	30	82:18[f]	>98	>99

[a] Reactions were performed on a 1 or 1.5 mmol scale with 20 mol% of catalyst and 2.2 equiv of cinnamaldehyde.
[b] Yield of the two diastereomers after flash chromatography.
[c] Determined by GC analysis of the crude product.
[d] Determined by NMR spectroscopy of the major diastereomer after chromatography.
[e] Determined by HPLC analysis on a chiral stationary phase, only the ee of the major diastereomer was measured.
[f] Determined by ^{1}H NMR spectroscopy of the crude product.

The results summarized in Table 2 show that this triple domino reaction can be applied with a variety of aromatic and heteroaromatic enals. Substrates similar to cinnamaldehyde gave comparable results in terms of yields and diastereoselectivity and showed virtually complete enantiomeric excesses (**3b–d**). α,β-Unsaturated aldehydes bearing bulkier aromatic substituents at the β-position led to increased diastereomic ratios while keeping the excellent enantioselectivities (**3e**,**f**). The triple cascade was also possible with enals bearing an aromatic heterocyclic substituent, although the yield was lower (**3g**). First test experiments with β-alkyl-substituted enals indicated a limitation of the protocol, and no domino product could be isolated.

The relative and absolute configuration of the cyclohexene carbaldehyde **3a** was determined as 4*S*,5*R*,6*R* by ^{1}H NMR NOE experiments and by single crystal X-ray structure analysis (Figure 1), which is in agreement with the relative topicity observed in other diphenylprolinolsilylether-catalyzed Michael additions to enals.[2]

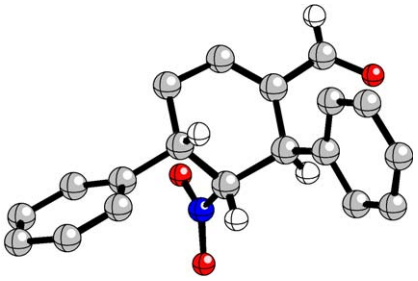
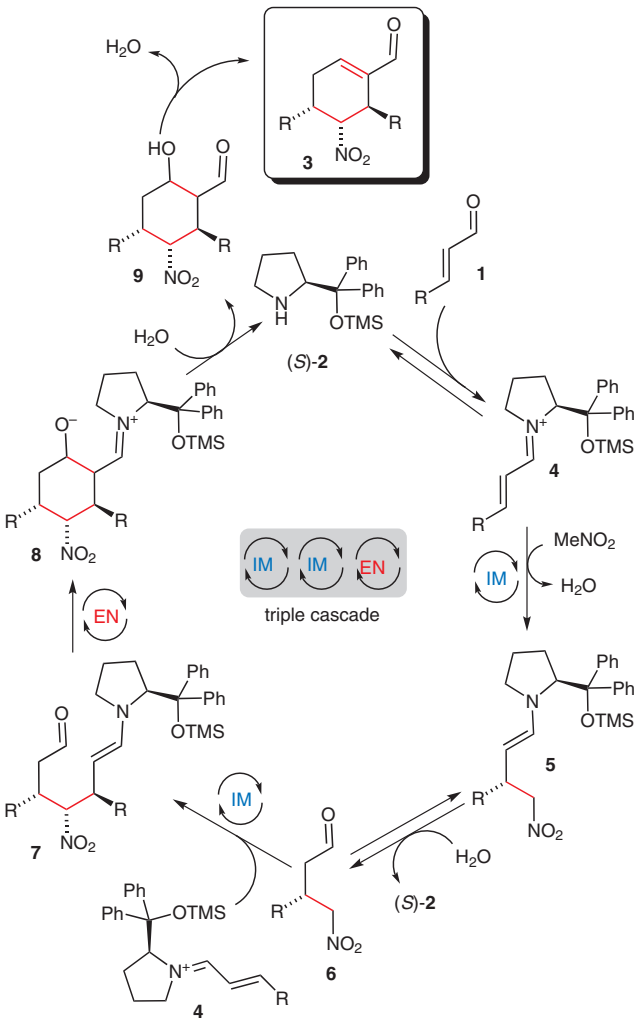


Figure 1 X-ray crystal structure of **3a**[9]

A proposal for the catalytic cycle is presented in Scheme 3. The enal **1** is first activated as the iminium ion **4** by the chiral amine catalyst (*S*)-**2**, then undergoes the first nitromethane Michael addition to afford the nitroalkane enamine **5**. Subsequent hydrolysis generates the nitroaldehyde **6** and the catalyst, which can promote a second Michael addition with another equivalent of the iminium ion **4**. The intermediate enamine **7** reacts via an intramolecular aldol cyclization to give **8**. After hydrolysis, the catalyst (*S*)-**2** is regenerated, and the intermediate alcohol **9** can dehydrate to afford the desired product **3**.

In summary, we have developed a simple and convenient organocatalytic triple domino reaction employing the bulk chemical nitromethane and α,β-unsaturated aldehydes as substrates. The triple cascade follows an iminium–iminium–enamine activation mode involving two sequential Michael additions and an intramolecular aldol condensation. After a final flash chromatography, the 5-nitrocyclohexene carbaldehydes are obtained in acceptable yields as pure stereoisomers bearing three contiguous stereocenters.[10] The method is of high atom economy with water as the simple waste product.[11]



Scheme 3 Proposed mechanism of the triple domino reaction

Acknowledgment

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(9) CCDC-743470 (**3a**) contains the supplementary crystallographic data for this paper. More data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www. ccdc.cam.ac.uk/data_request/cif.

(10) **General Procedure**
In an ordinary vial equipped with a magnetic stirring bar, the α,β-unsaturated aldehyde **1** (2.2 mmol, 2.2 equiv) was dissolved in $CHCl_3$ (1 mL). The catalyst (*S*)-**2** (0.2 mmol, 0.2 equiv) and nitromethane (1 mmol, 1 equiv) were added to the solution. The vial was sealed, and the mixture was stirred for 20 h at r.t. The crude reaction mixture was diluted in CH_2Cl_2,

washed with H_2O, and dried over $MgSO_4$. After concentration, the crude product was purified by flash chromatography (silica gel, pentane–EtOAc). All new compounds gave satisfactory spectroscopic and analytical data. As a typical example, the data of the compound **3a** are given.

(4*S*,5*R*,6*R*)-5-Nitro-4,6-diphenylcyclohex-1-ene carbaldehyde (3a, Figure 2)

Isolated as a yellow solid (202 mg, 65%). The ee (>99%) was determined by HPLC on a chiral stationary phase [Chiralcel OD; *n*-heptane–*i*-PrOH (8:2); 1.0 mL/min, t_R = 9.93 min(major), 18.25 min (minor, based on the racemic mixture)]; mp 108 °C; $[\alpha]_D^{20}$ –123 (*c* 1.1, $CHCl_3$). IR (ATR): 3060, 2807, 2718, 2323, 2115, 1684, 1653, 1547, 1494, 1450, 1410, 1366, 1247, 1162, 1078, 946 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.89 (ddd, *J* = 5.2, 5.2, 20.0 Hz, 1 H, H_3); 3.25 (dddd, *J* = 2.4, 11.2, 11.2, 20.0 Hz, 1 H, $H_{3'}$), 3.35–3.40 (m, 1 H, H_4), 4.32–4.38 (m, 1 H, H_6); 4.96 (dd, *J* = 1.9, 3.0 Hz, 1 H, H_5), 7.03–7.07 (m, 2 H, $H_{Ph\text{-}para}$), 7.22–7.38 (m, 9 H, H_{Ph} and H_2), 9.57 (s, 1 H, H_{CHO}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.0 (C_3), 37.3 (C_4), 43.2 (C_6), 91.3 (C_5), 127.3 (CH), 128.0 (CH), 128.9 (CH), 129.2 (CH), 137.9, 138.0, 138.8 (C_{Ph}, C_1), 150.4 (C_2), 191.65 (CHO). HRMS (EI): *m/z* calcd for $C_{19}H_{17}O_3N_1$: 307.1203; found: 307.1208.

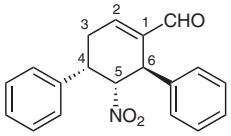

Figure 2

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