Angewandte Chemie

DOI: 10.1002/anie.200604479

Multicomponent Reactions

A New Approach for an Organocatalytic Multicomponent Domino Asymmetric Reaction**

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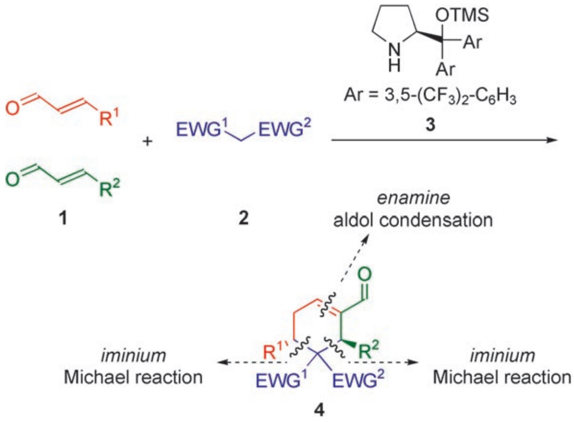
The field of asymmetric catalysis has recently been complemented with organocatalysis—a rapidly expanding and new important field in organic chemistry.[1] A central role in organocatalysis is played by chiral secondary amines which can activate carbonyl compounds, either by enamine or iminium intermediates.[1–3] These types of activation have been exploited to functionalize aldehydes and ketones with electrophiles and α,β-unsaturated compounds with nucleophiles.[1–3]

One of the challenges in organocatalysis is to implement various reaction concepts in a multicomponent domino reaction to achieve multibond formation in one operation. This strategy is atom economical, it avoids the need of protecting groups and isolation of intermediates, and as its goal resembles nature in its highly selective sequential transformations.[4] Recently, combinations of enamine–iminium ion activations in asymmetric organocatalytic domino and multicomponent reactions have been developed to achieve the enantioselective consecutive formation of two bonds in a stereoselective fashion.[5] This result paved the way for the sequential creation of three bonds that was recently reported by Enders et al.; they described a highly enantioselective combination of enamine–iminium–enamine catalysis for a triple cascade reaction of aldehydes, α,β-unsaturated aldehydes, and nitroalkenes to afford cyclohexene derivatives.[6]

Herein, we disclose a new approach for an enantioselective concurrent multicomponent domino organocatalytic reaction: a sequential iminium–iminium–enamine catalysis, which enables the consecutive formation of three new carbon–carbon bonds and provides, for a large number of reagents, enantiopure products through reaction of α,β-unsaturated aldehydes **1** with activated methylene compounds **2** by using (*S*)-2-[bis(3,5-bistrifluoromethylphenyl)-trimethylsilanyloxymethyl]pyrrolidine (**3**) as the catalyst[2b–f,3c,d,h] (Scheme 1). The high stereoselectivities obtained in this multicomponent domino organocatalytic reaction rely on the sequential activation of α,β-unsaturated aldehydes **1** by catalyst **3** leading to iminium–enamine intermediates in which the efficient shielding of the chiral fragment in **3** provides the high diastereo- and enantioselectivity.



Scheme 1. Multicomponent domino organocatalytic asymmetric reaction.

The stereoselective multicomponent domino organocatalytic formation of cyclohex-1-ene-carbaldehyde derivatives **4** can be explained by iminium–iminium–enamine sequential activation of the α,β-unsaturated aldehydes by catalyst **3** as outlined in Figure 1. In the first step (Cycle I), aldehyde **1**

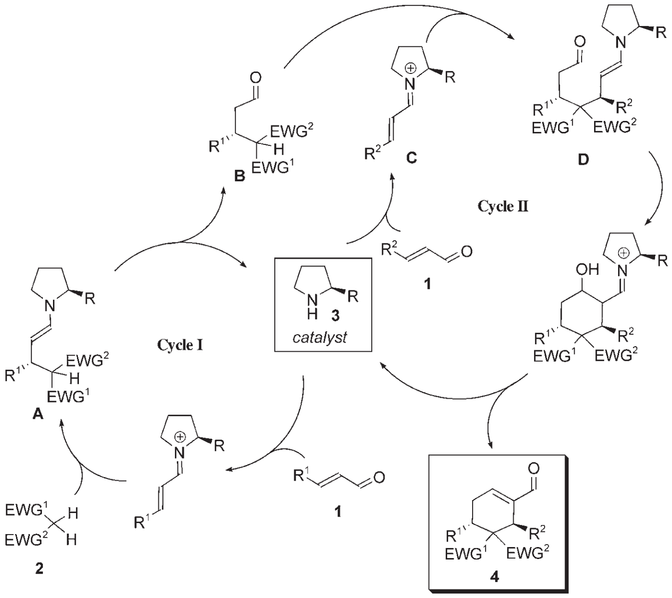


Figure 1. Proposed mechanism for the organocatalyzed asymmetric multicomponent domino reaction.

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[**] This work was made possible by a grant from the Danish National Research Foundation. Thanks are expressed to Dr. Jacob Overgaard for performing X-ray analysis.

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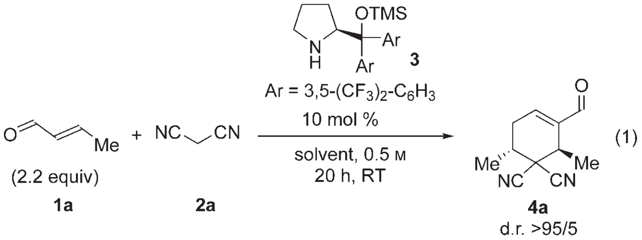
reacts with catalyst **3** to give the iminium ion intermediate. Malononitrile, or another activated methylene compound (see below) **2**, reacts as a nucleophile with this intermediate to give **A**, which is followed by hydrolysis of the resulting enamine to yield compound **B** with regeneration of the catalyst. Then, catalyst **3** re-enters the second cycle (Cycle II) to form iminium intermediate **C**, which subsequently reacts with **B** to generate an additional stereocenter (if EWG^1 = EWG^2) in intermediate **D**. At this stage, the final product, cyclohex-1-ene-carbaldehyde derivative **4**, which has up to three stereocenters (if EWG^1 $\neq$ EWG^2), is formed from the enamine intermediate that mediates the ring-closure reaction by an intramolecular aldol reaction, followed by elimination of water.

We started our investigation by reacting crotonaldehyde (**1a**) with malononitrile (**2a**) in the presence of catalyst **3** (10 mol %) [Eq. (1) and Table 1]. To our delight, by performing the reaction in CH_2Cl_2 as the solvent, we were able to isolate desired product **4a** in 50 % yield as a single diastereoisomer and in an enantiopure form (Table 1, entry 1). In attempts to improve the yield, we screened several solvents and reaction conditions; whereas in some solvents such as alcohols, H_2O, Et_2O, and acetone no product was formed, we were pleased to find that with respect to CH_2Cl_2, toluene and $CHCl_3$ led to higher yields while maintaining the optimal stereocontrol of the reaction course (Table 1, entries 7–11).

Table 1: Representative screening results for the reaction of crotonaldehyde (**1a**) with malononitrile (**2a**) by using **3** as the catalyst.[a]



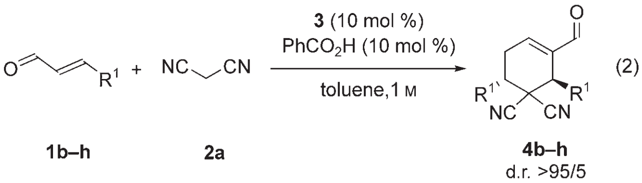
Entry	Solvent	Conversion [%]	Yield [%][b]	*ee* [%][c]
1	CH_2Cl_2	> 98	50	> 99
2	EtOH	–	–	–
3	H_2O	–	–	–
4	Et_2O	–	–	–
5	acetone	–	–	–
6	AcOEt	95	57	> 99
7	toluene	> 98	72	> 99
8	$CHCl_3$	> 98	74	> 99
9[d]	toluene	> 98	78	> 99
10[d]	$CHCl_3$	> 98	67	> 99
11[d,e]	toluene	> 98	89	> 99
12[d–f]	toluene	> 98	90	> 99[g]
13[d,e,h]	toluene	> 98	90	> 99

[a] All reactions were performed on a 0.3-mmol scale with $PhCO_2H$ (10 mol%) as the additive with the use of 0.6 mL of solvent. In all cases only one diastereoisomer was identified (by GC and ^1H NMR analysis of the crude reaction). TMS = trimethylsilyl. [b] Product isolated by flash chromatography. [c] Determined by chiral HPLC (see the Supporting Information). [d] 0.3 mL of solvent was used. [e] 3 equiv of α,β-unsaturated aldehyde **1a** were used. [f] The (*R*) enantiomer of catalyst **3** was used. [g] The opposite enantiomer was obtained. [h] 5 mol% of catalyst **3** was used.

As expected, the opposite enantiomer of the catalyst furnished the desired product with the same enantioselectivity and opposite configuration (Table 1, entry 12). It should also be noted that the reaction can be performed with only 5 mol % of catalyst **3** to provide isolated product **4a** in 90 % yield without affecting the enantioselectivity (Table 1, entry 13).

We then investigated the present reaction with respect to α,β-unsaturated aldehydes **1b–h** ($R^1 = R^2$ in Scheme 1) as electrophiles with malononitrile **2a** catalyzed by **3** (10 mol %) and in the presence of benzoic acid as an additive (10 mol %) [Eq. (2), Table 2].

Table 2: Reaction of various α,β-unsaturated aldehydes **1b–h** with malononitrile (**2a**).[a]



Entry	Aldehyde		Product	Yield [%][b]	*ee* [%][c]
1	Et	**1b**	**4b**	89	98
2	*i*Pr	**1c**	**4c**	68	> 99
3	$CH_3CH{=}CH$	**1d**	**4d**	80	97
4	Ph	**1e**	**4e**	77	> 99
5	*p*-Cl-C_6H_4	**1f**	**4f**	54 (65[d])	> 99 (> 99[d])
6	2-furyl	**1g**	**4g**	57	98
7	2-thiophene	**1h**	**4h**	66	97

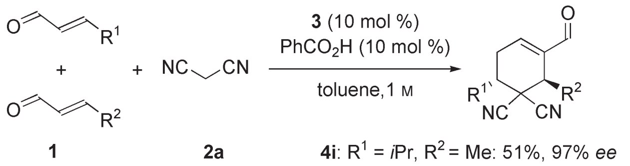
[a] Malononitrile (**2a**) (0.3 mmol) was added to a mixture of catalyst **3** (0.03 mmol, 10 mol%), $PhCO_2H$ (10 mol%), and α,β-unsaturated aldehyde **1** (0.9 mmol, 3 equiv) in toluene (0.3 mL). The product was isolated after 1–48 h (see the Supporting Information). In all cases only one diastereoisomer was identified (by GC and ^1H NMR analysis of the crude reaction). [b] Product isolated by flash chromatography. [c] Determined by chiral HPLC (see the Supporting Information). [d] 20 mol% of **3** and $PhCO_2H$ were used.

As shown in Table 2, the domino reaction proceeds well for both aliphatic and aromatic aldehydes and provides almost enantiopure products. For alkyl α,β-unsaturated aldehydes **1b–d** having both unbranched, branched, and unsaturated substituents, the yields of **4b–d** are in the range 68–89 % and only one diastereoisomer with 97– > 99 % *ee* was obtained (Table 2, entries 1–3). In terms of diastereo- and enantioselectivity, aromatic and heteroaromatic substituents also gave only one diastereomer with enantioselectivities in the range 97–99 % *ee*; however, the yields of products **4e–h** are slightly lower (Table 2, entries 4–7) relative to those of the aliphatic α,β-unsaturated aldehydes.

On the basis of the mechanism outlined in Figure 1, we decided to investigate the reaction further: ^1H NMR spectroscopic studies showed the formation of monoadduct **A** and the subsequent formation of product **4** without any other intermediates. This result indicates that the enamine-mediated ring-closure probably takes place when the catalyst is still attached to adduct **D** (i.e. no hydrolysis of intermediate **D** occurs).

We therefore questioned whether it would be possible to generate **4** having two different R groups (i.e. the reaction of two different α,β-unsaturated aldehydes). To accomplish this task, we reasoned that the first α,β-unsaturated aldehyde, **1** leading to **B**, needed to be unreactive enough in Cycle II so that Cycle I would be complete prior to the beginning of the formation of adduct **D**. This way, the second α,β-unsaturated aldehyde could be subsequently added and enter Cycle II together with **B**. The products obtained will thus be differently substituted (R^1 and R^2) cyclohex-1-ene-carbaldehyde derivatives **4**. The reason for choosing isopropyl acrolein was to have a sterically hindered product formed in Cycle I, which would react very slowly in Cycle II.

This reasoning was then applied as proof-of-principle and the results support our blueprint. It was shown that it is possible to control the reaction sequence with regard to the α,β-unsaturated aldehydes. Interestingly, the sequence can be applied to both aliphatic and aromatic aldehydes providing **4i** and **4j**, respectively, as exclusively one regioisomer and one diastereoisomer formed with excellent enantiomeric excess (Scheme 2).



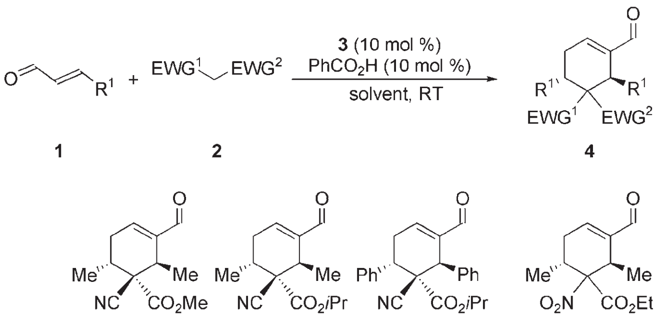
4i: R^1 = *i*Pr, R^2 = Me: 51%, 97% *ee*
4j: R^1 = *i*Pr, R^2 = Ph: 52%, >99% *ee*

Scheme 2. Organocatalytic domino reactions with two different α,β-unsaturated aldehydes.

We then questioned whether it would be possible to extend the presented multicomponent domino transformation to other activated methylene compounds. In particular, nucleophiles having two different electron-withdrawing groups might be interesting, as a quaternary stereocenter would be generated.[7]

As outlined in Scheme 3, the approach was fruitful with cyanoacetates as the nucleophiles and provided products **4k–m** in excellent enantiomeric excess and good to very good diastereomeric ratio. The results show that better diastereocontrol is obtained by increasing the size of the ester group (compare **4k** and **4l**).[8] Thus, by treating isopropyl cyanoacetate with crotonaldehyde (**1a**), product **4l** was obtained in 99% *ee* and 90/10 d.r., whereas cinnamic aldehyde (**1e**) worked better in terms of yield and diastereocontrol, which led to product **4m** with >99% *ee*, >98/<2 d.r., and 53% yield.

Interestingly, these compounds could give access to both of the isomers at the fully substituted carbon atom of quaternary α-amino acid derivatives[9] by choosing the appropriate sequence of reactions.[10]



	4k	4l	4m	4n[a]
yield:	47 %	40 %	53 %	46 %
d.r.:	86/14	90/10	>98/<2	60/40
ee:	98 %	99 %	>99 %	98 %/>99 %

[a] 20 mol % of **3** and 10 mol % of DABCO were used

Scheme 3. Reaction of α,β-unsaturated aldehydes **1a** or **1e** with activated methylene compounds.

Another way to access potential precursors of α-amino acids is through the reaction of nitromalonates; the reaction between **1a** and ethyl nitroacetate was successful and expected product **4n** was obtained in excellent enantiomeric excess. Even though the diastereocontrol is moderate, the possibility of separating the two diastereoisomers by flash chromatography renders the approach appealing as it gives access—once again—to the two isomers of quaternary α-amino acids. The major isomer of **4n** has the nitro group and the methyl substituent in the 6-position *syn* to each other. Notably, although Cycle II is sluggish, it was possible to improve the reactivity of the system by changing the additive: by swapping the usual acidic additive to a basic one (DABCO: 1,4-diazabicyclo[2.2.2]octane)[11] the reaction proceeded smoothly without a decrease in either the enantioselectivity or the diastereoselectivity. Noteworthy is that a chiral secondary amine and a tertiary amine can successfully cooperate without interfering with each other.

The absolute configuration of the addition product was assigned by single-crystal X-ray analysis of 3-formyl-2,6-di-2-thienylcyclohex-3-ene-1,1-dicarbonitrile (**4h**) as shown in Figure 2.[12] The structure led to the (2*S*,6*R*) assignment of the formed chiral centers, which indicates that the addition takes place from below—the *Re*-face[13]—in the two intermediates in Cycles I and II in Figure 1.

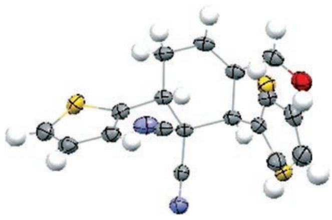


Figure 2. X-ray structure of 3-formyl-2,6-di-2-thienylcyclohex-3-ene-1,1-dicarbonitrile (**4h**). C gray, H white, N blue, O red, S yellow.

In conclusion, we have developed a new organocatalytic multicomponent domino asymmetric approach, which can be viewed as an iminium–iminium–enamine sequence, by treating α,β-unsaturated aldehydes with activated methylene compounds. The reaction proceeds in good to high yields for the malononitrile and only one, nearly enantiopure diastereomer is formed. This concept has been extended to also work well for the combination of different aldehydes and for other activated methylene compounds, such as cyanoacetates and nitro esters.

Experimental Section

In an ordinary vial equipped with a magnetic stirring bar, **2** (0.3 mmol) was added to a mixture of catalyst **3** (0.03 mmol, 10 mol%), benzoic acid (0.03 mmol, 10 mol%), and α,β-unsaturated aldehyde **1** (0.9 mmol) in toluene (0.3 mL). The stirring was maintained at room temperature until completion of the reaction. The crude reaction mixture was directly charged on silica gel and subjected to flash chromatography (FC).

Example: (2*S*,6*R*)-3-Formyl-2,6-dimethyl-cyclohex-3-ene-1,1-dicarbonitrile (**4a**) was isolated after 1 h by FC (CH_2Cl_2/Et_2O 98:2) in 89% yield. $[\alpha]_D^{20} = -78$ ($c = 1.0$, CH_2Cl_2, > 99% *ee*). The *ee* value was determined by HPLC analysis on a Daicel Chiralcel OJ column, hex/*i*PrOH 90:10, flow rate = 1.0 mL min^{-1}, $\tau = 18.8$ min (minor) and $\tau = 26.8$ min (major), 220 nm. GC–MS: *m/z* 188. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.44$ (s, 1H), 6.82 (dd, $J = 4.7$, 2.5 Hz, 1H), 3.39 (q, $J = 7.2$ Hz, 1H), 2.71 (m, 1H), 2.46–2.26 (m, 2H), 1.41 (d, $J = 6.4$ Hz, 3H), 1.34 ppm (d, $J = 7.2$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 191.2$, 147.2, 140.2, 114.1, 113.6, 41.9, 34.8, 31.3, 30.3, 17.6, 16.6 ppm.

Received: November 1, 2006

Keywords: aldehydes · asymmetry · domino reactions · multicomponent reactions · organocatalysis

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[11] Other conditions and additives (e.g. *o*-NO_2PhCO_2H, *m*-NO_2PhCO_2H, Et_3N, Hünig's base) were tested but all gave inferior results.

[12] CCDC 627399 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

[13] Please note that the assignment of the face changes for the alkyl substituted α,β-unsaturated compounds.