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Asymmetric Organocatalytic Four-Component Quadruple Domino Reaction Initiated by Oxa-Michael Addition of Alcohols to Acrolein

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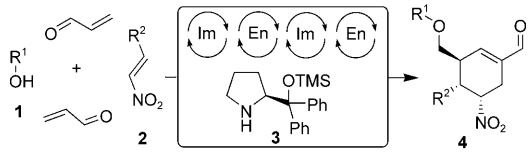
Asymmetric multicomponent cascade reaction (MCCR) catalyzed by organocatalysts is an attractive strategy and receives considerable attention as the increasing economic and ecological pressure.[1] This approach provides novel chiral complex molecules in a fast reaction via a biomimetic pathway and proceeds in a highly efficient and atom-economical manner through the formation of multiple new bonds and stereocenters in a one-pot system, which saves time and energy by avoiding purification of intermediates and the protection/deprotection of functional groups.[2] In the field, not only most two-step[3] but also many three-step MCCRs[4] have been successfully achieved using chiral secondary amines as the catalysts, which are capable of both enamine (En) and iminium (Im) catalysis in tandem sequence.[5] Recently, Kotame and co-workers[6] developed an elegant three-component quadruple domino reaction between 2-(*E*)-2-nitrovinyl)phenol and α,β-unsaturated aldehydes to produce tetrahydro-6*H*-benzo[*c*]chromenes with excellent enantioselectivity through iminium–enamine–iminium–enamine activation. However, control of more steps with more components to achieve more bond formations consecutively using chiral secondary amines through enamine and iminium activation remains an unmet challenge, because the potential reactions will proceed in an exponential amplification mode as the number of components and steps increased.

On the other hand, although the domino reactions involving the hetero-Michael addition of amines,[3i,7] thiols[3g,8] and phenols[6,9] to α,β-unsaturated aldehydes were investigated, there are no examples available for the MCCRs initiated by oxa-Michael addition of simple alcohol to α,β-unsaturated aldehyde. In addition, β-alkoxy propanal, a commercially unavailable intermediate, is usually prepared by a two-step sequence involving monoalkylation of 1,3-propanediol and subsequent Swern oxidation.[10] Few examples have been reported that the oxa-Michael addition reaction of alcohol to acrolein requires six days to provide β-alkoxy propanal in a moderate yield; in addition this methodology is limited to specific substrate alcohol such as *p*-methoxybenzyl alcohol.[11] To the best of our knowledge, one case about the asymmetric intermolecular oxa-Michael addition of simple alcohols to α,β-unsaturated aldehydes using chiral biphenyl diamine catalyst has been reported thus far,[12] in which only a moderate yield of the desired oxa-Michael adduct was obtained, mainly due to the relative weakness of O-nucleophiles, the reversibility of reaction, the affinity for acetal formation and self-aldol reaction of the oxa-Michael adduct.[13] We assumed that the side-reactions mentioned above could partially be circumvented by introducing high reactive Michael acceptors such as nitroalkenes to the reaction system for their ease to react with β-alkoxy aldehyde generated in situ by addition of simple alcohols to α,β-unsaturated aldehydes. Herein, we envisioned four-component (ABC_2) quadruple cascade reaction through iminium–enamine–iminium–enamine sequential activation initiated by oxa-Michael addition of alcohol to acrolein, as outlined in Scheme 1, to provide a straightforward protocol for the synthesis of chiral cyclic products with multiple substituents.

In this process, we found that a diphenylprolinol silyl ether[14] catalyzed the oxa-Michael/Michael/Michael/aldol



Scheme 1. Four-component quadruple cascade organocatalysis.

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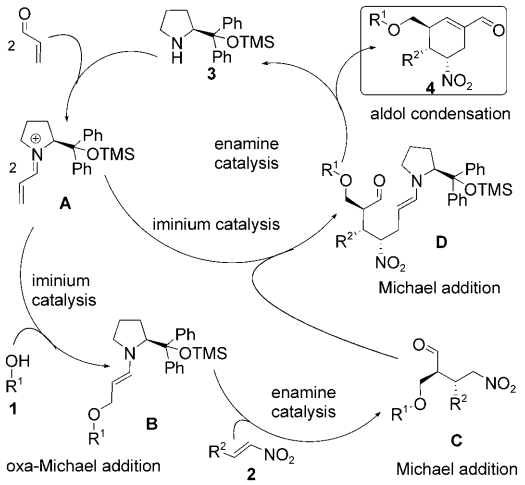
condensation reaction between simple alcohol **1**, acrolein and nitroalkene **2**; the reaction afforded highly functionalized trisubstituted cyclohexene carbaldehyde **4** with excellent stereoselectivity. As outlined in Scheme 2, in the first step, the catalyst **3** reacts with acrolein to give the iminium ion intermediate **A**. Alcohol **1**, as a hard oxygen nucleophile, selectively reacts with **A** to give enamine intermediate **B**, which then prefers to react with nitroalkene **2** to give Michael product **C**. In the third step, the nitroalkane **C** subsequently reacts with **A** to generate enamine intermediate **D**, which is unstable and easily reacts through an intramolecular aldol condensation under the reaction conditions, providing the desired trisubstituted cyclohexene carbaldehyde **4** and regenerating catalyst **3**.

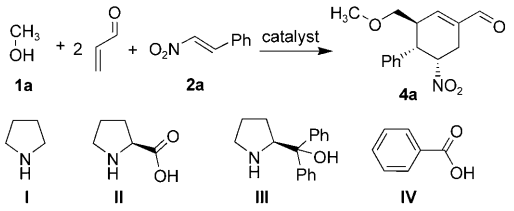


Scheme 2. Proposed mechanism for the organocatalyzed asymmetric four-component quadruple cascade reaction.

The quadruple domino reaction of methanol, acrolein and nitrostyrene was investigated first in the presence of 10 mol% of catalyst **3** in methanol at 4°C. The desired product **4a** was detected in low yield by GC-MS (Table 1, entry 1). By screening the solvents, an encouraging result was observed in that 52% yield of the adduct **4a** was isolated with excellent diastereoselectivity and an enantiopure form[15] (entry 2) after reacting methanol (4 equiv), acrolein (4 equiv) and nitrostyrene (1 equiv) in chloroform. To optimize the reaction conditions of this MCCR, other different amine catalysts such as pyrrolidine, proline and diphenylprolinol (entry 3–5) were also estimated, but no **4a** could be obtained in all cases. As expected, the reaction was significantly accelerated by adding benzoic acid, which probably promoted the formation of the iminium ion (entry 6–8). When 25 mol% of benzoic acid was used, loading of catalyst **3** could be reduced to 5 mol% and a good yield (54%) of **4a** was obtained without compromising the enantio- and diastereoselectivity (entry 8).

The generality of the MCCR initiated by oxa-Michael addition was assessed next under the reaction conditions described above. The results summarized in Table 2 show that

Table 1. Representative screening results of the MCCR.[a]



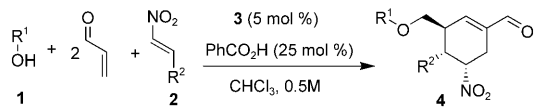
Entry	Cat. ([%])	Additive ([%])	t [h]	Yield[b] [%]	d.r.[c]	ee[d] [%]
1[e]	**3** (10)	none	84	<2	n.d.	n.d.
2	**3** (10)	none	84	52	>20:1	>99
3	**I** (30)	none	84	<5	n.d.	n.d.
4	**II** (30)	none	84	<5	n.d.	n.d.
5	**III** (30)	none	84	<5	n.d.	n.d.
6	**3** (10)	**IV** (10)	24	50	>20:1	>99
7	**3** (5)	**IV** (5)	48	51	>20:1	>99
8	**3** (5)	**IV** (25)	24	54	>20:1	>99

[a] Reactions performed with methanol (1 mmol), nitrostyrene (0.25 mmol), acrolein (1 mmol) and solvent (0.5 mL) at 4°C. [b] Isolated yield of main diastereomer. [c] Determined by ^{1}H NMR spectroscopy of the crude mixture. [d] The *ee* value for the major diastereomer determined by HPLC. [e] Methanol as the solvent.

the MCCR has broad applicability. Simple aliphatic alcohols such as ethanol, *n*-butanol, and benzyl alcohol are also reactive enough to participate, to yield the corresponding adducts in moderated to good yields (entry 1–4). Furthermore, this reaction system was also suitable for secondary alcohol (isopropanol) and for functional alcohols such as allyl alcohol, 2-chloroethanol, propargyl alcohol and 2-furanmethanol (entry 5–9). Besides alcohols, phenols can also act as O-nucleophiles. In the case of *p*-methoxyphenol, good yields of the product were obtained without addition of benzoic acid (entry 10). On the other hand, the reaction proceeds efficiently for different nitroalkenes not only with electron-rich aromatic substituents such as 3,4-methylenedioxyphenyl, but also with electron-deficient substituents such as *p*-chlorophenyl (entry 11–12). Heteroaromatic groups such as furyl are also suitable substituents (entry 13). In addition, it should be emphasized that this MCCR was also applicable to produce **4** on a larger scale. For example, the reaction between methanol, acrolein and nitrostyrene on a 10 mmol scale gave 1.49 g (54% yield) of 3-(methoxymethyl)-5-nitro-4-phenylcyclohex-1-ene carbaldehyde (**4a**) (entry 3). Foremost, in all cases, the cyclohexene carbaldehydes **4** were obtained with excellent diastereomeric and complete enantiomeric control.

In summary, we have described a novel organocatalytic four-component domino oxa-Michael/Michael/Michael/aldol condensation reaction, which can be explained as an iminium–enamine–iminium–enamine sequence, by treating alcohol, acrolein and nitroalkene. Through three intermolecular Michael and one intramolecular aldol condensation step, this quadruple cascade reaction enables the consecutive formation of four new bonds and provides an atom economic

Table 2. Scope of the MCCR.[a]



1 2 4

Entry	R^1	R^2	4	Yield[b] [%]	d.r.[c] [%]	*ee*[d] [%]
1	*n*Bu	Ph	**4b**	49	>20:1	>99
2	Et	Ph	**4c**	54	>20:1	>99
3[e]	Me	Ph	**4a**	54	>20:1	>99
4	Bn	Ph	**4d**	49	>20:1	>99
5	*i*Pr	Ph	**4e**	57	>20:1	>99
6	Allyl	Ph	**4f**	56	>20:1	>99
7	2-Cl-Et	Ph	**4g**	46	>20:1	>99
8	propargyl	Ph	**4h**	41	>20:1	>99
9	2-furan-Me	Ph	**4i**	54	>20:1	>99
10[f]	*p*-MeO-Ph	Ph	**4j**	51	>20:1	>99
11	Me	*p*-Cl-Ph	**4k**	49	>20:1	>99
12	Me	V[g]	**4l**	55	>20:1	>99
13	Me	2-furanyl	**4m**	54	>20:1	>99

[a] Reactions performed using catalyst (*S*)-**3** (0.05 mmol), benzoic acid (0.25 mmol), alcohol **1** (4 mmol), nitroalkene **2** (1 mmol), acrolein (4 mmol) in chloroform (2 mL) at 4 °C. [b] Isolated yield of main diastereomer. [c] Determined by ^{1}H NMR spectroscopy of the crude mixture. [d] The *ee* value for the major diastereomer determined by HPLC. [e] The reaction carried out on a 10 mmol scale. [f] The reaction performed with *p*-methoxy-phenol (1.5 mmol), catalyst (*S*)-**3** (10 %) without $PhCO_2H$. [g] V = 3,4-(Methylenedioxy)-Ph.

and straightforward approach to prepare the optical pure of highly functionalized trisubstituted cyclohexene carbaldehydes in good yields. Application of the oxa-Michael addition of alcohol to acrolein in other domino reactions for preparation of biologically relevant compounds is currently underway.

Experimental Section

Typical procedure: Methanol (0.162 mL, 4.0 mmol) and acrolein (224 mg, 4.0 mmol) were added to nitrostyrene (149 mg, 1.0 mmol) in choroform (2 mL). The mixture was cooled to 4 °C. Catalyst (*S*)-**3** (16 mg, 5 mol %) and benzoic acid (30 mg, 25 mol %), were added and the solution was stirred until complete conversion of the starting materials (monitored by TLC). The crude reaction mixture was directly loaded on a silica gel column, and column chromatography (ethyl acetate/petroleum ether 1:6) afford the pure product **4a** as colorless oil (149 mg, 54 %, 99 % *ee*). The enantiomers were determined by HPLC (Daicel Chirapak OD-H, flow rate 0.5 mL min^{-1}, *n*-heptane/isopropanol 90:10, 254 nm, Retention time: t_{major} = 35.4 min, and t_{minor} = 38.2 min).

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Keywords: domino reactions · Michael addition · multicomponent reactions · organocatalysis

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