

A Branched Domino Reaction: Asymmetric Organocatalytic Two-Component Four-Step Synthesis of Polyfunctionalized Cyclohexene Derivatives**

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Traditionally, domino reactions are defined as processes of two or more bond-forming reactions, in which the subsequent transformation takes place at the functionalities obtained in the former transformation under identical reaction conditions.^[1,2] In linear domino reactions, the progress of the former step will always affect that of the next steps (Figure 1 a). Among the domino/cascade reactions, organocata-

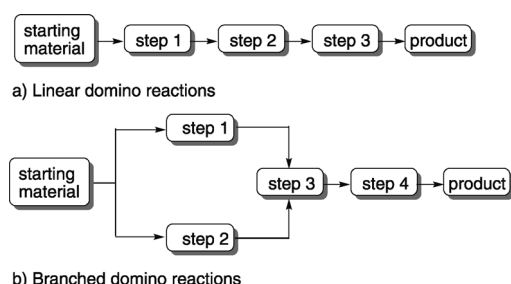
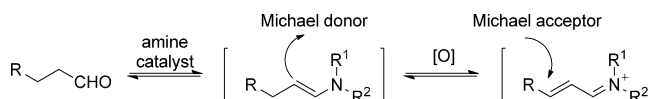


Figure 1. General sequences of linear and branched domino reactions.

lytic enantioselective reactions^[3] have been developed at a remarkable pace after the revitalization of the field of organocatalysis.^[4,5] However, we planned to develop another kind of domino reaction, which we call a “branched domino reaction” (Figure 1 b). In this domino sequence, the starting material can be used in two parallel reactions at the same time under identical conditions to generate two intermediates, which will then act as reactants in the next reaction step to form the desired product. In this version, the progress of the first step will have no effect on the second step, and higher overall yields could be achieved. This will enable the efficient synthesis of complex molecules from a few simple starting materials in an ecologically and economically manner.

In 2011, Wang and co-workers^[6] and Hayashi et al.^[7] independently reported the diphenylprolinol trimethylsilyl ether (**I**)^[8] catalyzed enantioselective β -functionalization of aldehydes through oxidation of enamines, formed from the amine catalyst and aldehydes, to iminium ions. In this

“oxidative enamine catalysis”, *o*-iodoxybenzoic acid (IBX) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) were used as the oxidants for converting the enamines to iminium ions in the presence of the amine catalyst, which facilitated the further nucleophilic addition to afford the β -functionalized products. Shortly after, Rueping and co-workers^[9] reported an enantioselective oxidative domino reaction, in which an allylic alcohol was oxidized in situ to an aldehyde by MnO_2 , followed by the tandem cyclopropanation and 1,4-addition reactions with high yields and enantioselectivities. Very recently, Jang and co-workers presented a combination of a copper complex and a chiral amine for the transformation of allylic alcohols to enantiomerically enriched β -functionalized aldehydes. In this sequence, the allylic alcohols were oxidized to aldehydes followed by the formation of iminium intermediates.^[10] We wondered whether both the enamine and iminium salt intermediates derived from the aldehyde and catalyst could be simultaneously applied in the same cascade reaction, which means that two parallel reactions starting from the aldehyde occur at the same time during the transformation process (Scheme 1).



Scheme 1. The generation of both a Michael donor and Michael acceptor from the same aldehyde.

Herein we report the use of an aldehyde as both nucleophile and electrophile in such a branched domino reaction for the formation of six-membered-ring derivatives through oxidative enamine catalysis (Scheme 2).

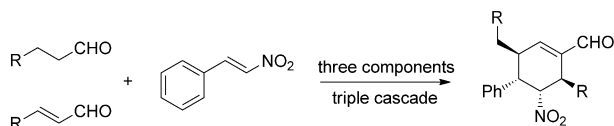
First, we needed to figure out whether the enamine generated from aldehyde and amine catalyst could act as nucleophile in the presence of an oxidant such as IBX. We carried out the reaction of dihydrocinnamaldehyde (**2a**; 1.2 equiv) and nitrostyrene (**1a**; 1.0 equiv) in the presence of (*R*)-**I** (10 mol %) and IBX (1.0 equiv). To our delight, the nucleophilic addition product could be obtained in good yield,^[8b,11] indicating that the Michael addition is possible in the presence of IBX. Based on contributions from our group^[12] and others^[13–15] regarding organocatalyzed enantioselective three-component domino reactions leading to polysubstituted cyclohexene derivatives, we continued our study with the reaction of nitrostyrene (**1a**) and dihydrocinnamaldehyde (**2a**) in the presence of catalyst (*R*)-**I** and oxidant for the formation of the cyclohexenyl ring system (Scheme 2). In this study, 3.0 equivalents of dihydrocinna-

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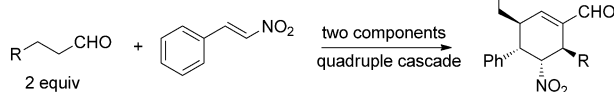
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Previous work

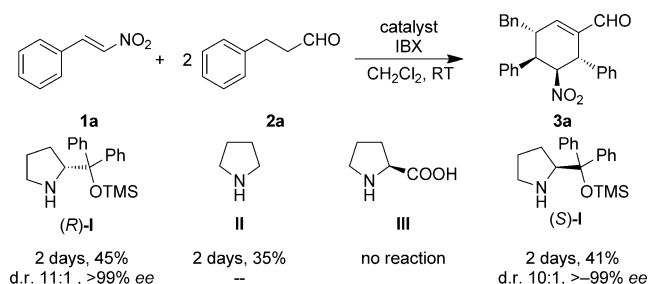


This work



Scheme 2. Amine-catalyzed cascade reactions for the enantioselective synthesis of cyclohexene derivatives.

maldehyde were used to facilitate the further oxidative enamine catalysis. Interestingly, the cyclohexene derivative was detected by NMR spectroscopy and LC-MS of the crude after completion of the reaction, and further purification by column chromatography afforded compound **3a** in moderate yields. Some other chiral and achiral amines were also tested in this reaction. Pyrrolidine (**II**) could promote the reaction and gave the desired cascade product in 35 % yield, and the use of the enantiomeric catalyst (*S*)-**I** resulted in the enantiomer of **3a**. However, almost no reaction occurred when (*S*)-proline was used. Thus, the catalysts (*R*)-**I** and (*S*)-**I** were found to be the best (Scheme 3).



Scheme 3. Investigation of different amine catalysts.

Next, we focused on the improvement of the diastereoselectivity and yield of this reaction (Table 1). We first evaluated the effect of different oxidants during the enamine/iminium catalysis cascade process. Reagents such as *m*-chloroperbenzoic acid (*m*-CPBA), *t*BuOOH, H₂O₂, DDQ and PCC were not effective at all for this reaction (Table 1, entries 2–5 and 7) and MnO₂ only gave a low yield (Table 1, entry 6), while IBX was proven to be the best oxidant. Further investigations showed that 1.5 equivalents of IBX led to the best result (see the Supporting Information). Then the solvent effect of this reaction was studied. The cascade reaction proceeded smoothly in all solvents listed in Table 1 and the desired product could be obtained with moderate to good yield as well as good enantioselectivity except in *n*-hexane (Table 1, entry 13). This may be a result of the poor solubility, however, the diastereoselectivity was sensitive to the solvents. Of those tested, CHCl₃ was found to give the highest diastereoselectivity. Further optimization of the catalytic loading and reaction concentration showed that the best result could be achieved in the presence of 1.5 equivalents of

Table 1: The effects of different oxidants and solvents on the domino reaction.^[a]

Entry	Oxidant	Solvent	Yield [%] ^[b]	d.r. ^[c]	ee [%] ^[d]
1	IBX	CHCl ₃	55	> 20:1	> 99
2	<i>m</i> -CPBA	CHCl ₃	n.r. ^[e]		
3	<i>t</i> BuOOH	CHCl ₃	n.r. ^[e]		
4	H ₂ O ₂	CHCl ₃	n.r. ^[e]		
5	DDQ	CHCl ₃	n.r. ^[e]		
6	MnO ₂	CHCl ₃	12	n.d. ^[f]	n.d. ^[f]
7	PCC	CHCl ₃	n.r. ^[e]		
8	IBX	CH ₂ Cl ₂	55	12:1	> 99
9	IBX	toluene	56	8:1	99
10	IBX	benzene	60	10:1	99
11	IBX	EtOAc	38	3:1	91
12	IBX	THF	45	2:1	93
13	IBX	<i>n</i> -hexane	21	3:1	–

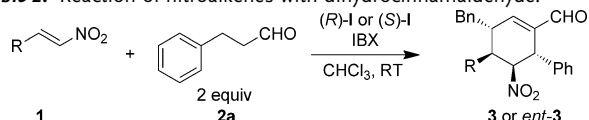
[a] Reactions were carried out with **1** (0.2 mmol), **2** (0.6 mmol), oxidant (0.3 mmol), and catalyst (*R*)-**I** (0.01 mmol) in different solvents (0.1 M) at RT. [b] Yield of isolated **3a**. [c] Determined by ¹H NMR spectroscopy and HPLC analysis (on a chiral stationary phase) of the crude product. [d] Determined by HPLC analysis on a chiral stationary phase. [e] n.r.: no reaction. [f] n.d.: not determined.

IBX with 5 mol % of catalyst (*R*)-**I** or (*S*)-**I** in 0.1 M CHCl₃ at room temperature.

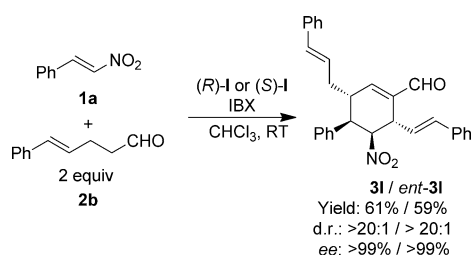
Under the optimized reaction conditions, we next tested the utility of this approach for the branched domino reaction through oxidative enamine/iminium catalysis with a range of nitroalkenes (Table 2). All reactions proceeded well and provided the desired products in moderate to good yields, with virtually complete enantioselectivities and good to excellent diastereoselectivities. The diastereomeric ratio of the products was affected by the positions and electronic properties of the substituents on the aromatic ring of the nitroolefins. For those with electron-donating groups (*para*, *meta*, or *ortho*; Table 2, entries 2–5), lower diastereomeric ratios were obtained. On the other hand, higher ratios could be achieved when the nitroolefins with electron-withdrawing groups were used. However, the yields and enantioselectivities of this reaction were not sensitive to the electronic properties, and excellent *ee* values were obtained for all cases. The use of a nitroolefin derived from a heteroaromatic aldehyde (Table 2, entry 11) also provided the cyclized product with similar yield and selectivity. Furthermore, when the dihydrocinnamaldehyde was changed to (*E*)-5-phenylpent-4-enal (**2b**), the corresponding cyclohexenyl product **3l** was also formed with excellent stereoselectivity (Scheme 4). As expected, the enantiomer of catalyst **I** promoted the oxidative enamine/iminium catalysis as well and led to the corresponding enantiomers with virtually the same results.

The two-component cascade reaction was also carried out on a gram scale. 20 mmol of **1a** were reacted with 3.0 equivalents of **2a** in the presence of 5 mol % of (*R*)-**I** and 1.5 equivalents of IBX in CHCl₃, and the desired product was obtained in 67 % yield and with excellent diastereo-

Table 2: Reaction of nitroalkenes with dihydrocinnamaldehyde.^[a]

					
Entry	R	Cat.	Yield [%] ^[b]	d.r. ^[c]	ee [%] ^[d]
1	Ph	(R)-I (S)-I	3 a , 58 <i>ent-3 a</i> , 60	> 20:1 > 20:1	> 99 > 99
2	3-MeOC ₆ H ₄	(R)-I (S)-I	3 b , 58 <i>ent-3 b</i> , 55	12:1 10:1	> 99 > 99
3	4-MeOC ₆ H ₄	(R)-I (S)-I	3 c , 51 <i>ent-3 c</i> , 54	10:1 9:1	> 99 > 99
4	3,4-(MeO) ₂ C ₆ H ₃	(R)-I (S)-I	3 d , 48 <i>ent-3 d</i> , 45	9:1 8:1	> 99 > 99
5	3,4-OCH ₂ OC ₆ H ₃	(R)-I (S)-I	3 e , 45 <i>ent-3 e</i> , 49	> 20:1 > 20:1	> 99 > 99
6	1-naphthyl	(R)-I (S)-I	3 f , 59 <i>ent-3 f</i> , 55	> 20:1 > 20:1	> 99 > 99
7	4-FC ₆ H ₄	(R)-I (S)-I	3 g , 48 <i>ent-3 g</i> , 50	10:1 9:1	> 99 > 99
8	4-ClC ₆ H ₄	(R)-I (S)-I	3 h , 60 <i>ent-3 h</i> , 58	> 20:1 > 20:1	> 99 > 99
9	2-ClC ₆ H ₄	(R)-I (S)-I	3 i , 62 <i>ent-3 i</i> , 65	14:1 13:1	99 98
10	4-NO ₂ C ₆ H ₄	(R)-I (S)-I	3 j , 45 <i>ent-3 j</i> , 49	> 20:1 > 20:1	> 99 > 99
11	1-Boc-indolyl ^[e]	(R)-I (S)-I	3 k , 48 <i>ent-3 k</i> , 51	> 20:1 > 20:1	95 > 99

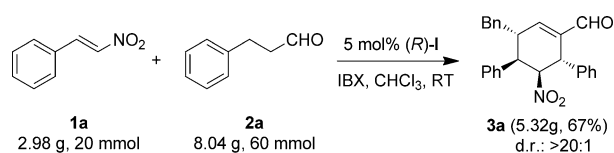
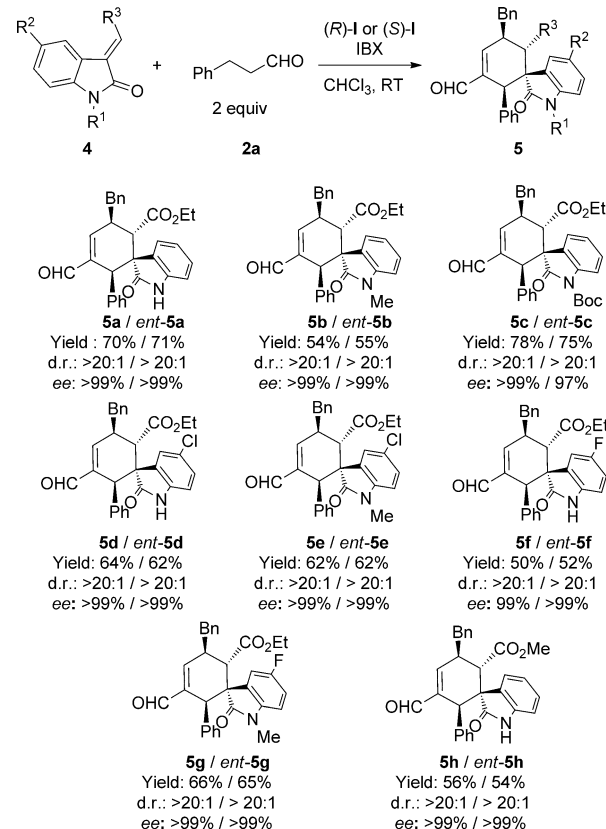
[a] Reactions were carried out with **1** (0.5 mmol), **2 a** (1.5 mmol), oxidant (0.75 mmol), and catalyst (R)-I or (S)-I (0.025 mmol) in CHCl₃ (0.1 M) at room temperature. [b] Yield of the isolated products **3**. [c, d] See Table 1. [e] Boc = *tert*-butoxycarbonyl


Scheme 4. The reaction of nitrostyrene with (*E*)-5-phenylpent-4-enal.

enantioselectivity. Thus, this reaction might be suitable for scale up and large-scale chemical production (Scheme 5).

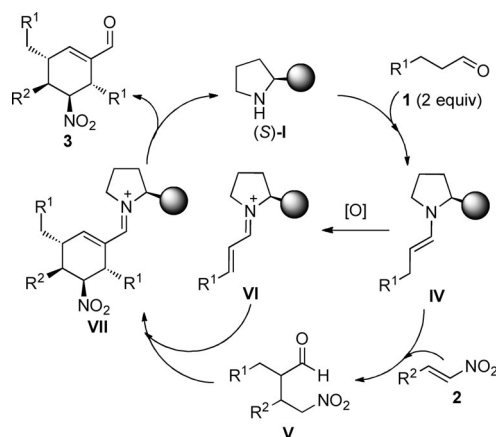
Next, we investigated the reactions of aldehyde **2 a** with 2-(2-oxindolin-3-ylidene)acetate derivatives **4 a–h** instead of nitroolefins to afford oxindole-derived spirocyclic compounds **5** (Scheme 6). All substrates **4** reacted well with **2 a** under the same conditions to give the corresponding spiro products **5 a–h** in good yields and with excellent diastereo- and enantioselectivities. All products listed were fully characterized, and the absolute configuration of compound **5 b** was confirmed by X-ray crystallography (see the Supporting Information).^[13b,16]

Our results, together with the proposed mechanisms by Wang^[6] and co-workers and Hayashi^[7] et al. suggest that aldehyde **1** first reacts with amine catalyst **I** to form an enamine intermediate **IV**, which performs a Michael addition with nitroalkene **2**, leading to adduct **V**. Simultaneously,


Scheme 5. The gram-scale reaction.

Scheme 6. The substrate scope of the reaction of aldehyde **2** with 2-(2-oxindolin-3-ylidene)acetate derivatives **4** to form the spiro compounds **5**.

enamine **IV** is oxidized to the corresponding iminium ion **VI**, which reacts as a Michael acceptor with **V** to form intermediate **VII** through aldol condensation. Finally, hydrolysis leads to cyclohexene product **3** and release of the catalyst (Scheme 7).

In conclusion, we have developed a two-component four-step branched domino reaction of polyfunctionalized cyclohexene derivatives through an asymmetric organocatalytic cascade of a Michael addition with parallel oxidation, a second Michael addition and a final aldol condensation, in which both the enamine nucleophile and the iminium electrophile are derived from the same aldehyde. The desired products could be obtained in moderate to good yields, with good to excellent diastereoselectivities and excellent enantioselectivities. Especially for spirocyclic products, excellent results were observed, and the parallel oxidation step did not have a negative effect on the cascade. The novel branched domino reaction reported here makes use of mild reaction



Scheme 7. Proposed catalytic cycle of the branched domino reaction through oxidative enamine catalysis.

conditions and only two cheap starting materials, and will thus be useful in pharmaceutical research and diversity-oriented synthesis.

Experimental Section

General procedure: IBX (210 mg, 0.75 mmol, 1.5 equiv) was added to a solution of nitroalkene (0.5 mmol, 1.0 equiv) and catalyst (*R*)-**I** or (*S*)-**I** (8.2 mg, 0.025 mmol, 5 mol%) in CHCl_3 (5.0 mL), and the resulting mixture was stirred at room temperature for 2 min followed by addition of the aldehyde (1.5 mmol, 3.0 equiv). The reaction was stirred for another 2–3 d until conversion of the nitroolefin was complete (monitored by thin-layer chromatography). The reaction mixture was directly purified by flash column chromatography (SiO_2 , diethyl ether/pentane 1:4–1:1) to afford the desired product as a colorless solid.

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- [16] CCDC 911581 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.