ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 8325–8327

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Highly diastereo- and enantioselective one-pot Michael–Aldol reactions of α,β-unsaturated aldehydes with imidazole derivatives†

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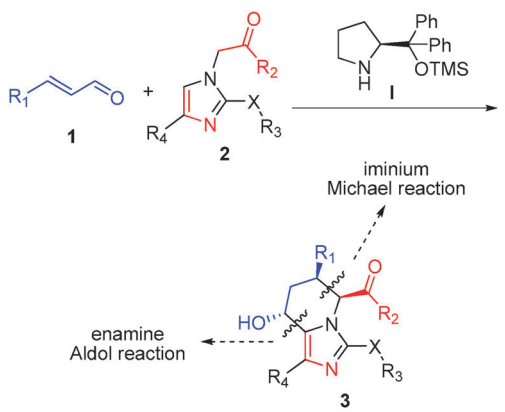
Received 20th April 2011, Accepted 2nd June 2011
DOI: 10.1039/c1cc12300a

Highly diastereo- and enantioselective one-pot Michael–Aldol reactions of α,β-unsaturated aldehydes with imidazole derivatives have been developed. The cascade reactions products could be obtained with three stereocenters in high yields and excellent diastereo- and enantioselectivities.

Recently, heterocyclic compounds have drawn special attention because of their biological activities. As one of the most important kind of heteroaromatic compounds, imidazole derivatives have exhibited considerable biological activities such as anti-inflammatory, antifungal, antiallergic, antileishmanial and analgesic activities.[1] Notably, they are also useful precursors to N-heterocyclic carbenes (NHC), which serve as powerful ligands in various transition-metal complexes.[2] Furthermore, in the field of organocatalysis, chiral imidazole derivatives have been proven to be wonderful organocatalysts in the enantioselective kinetic resolutions.[3] However, *to the best of our knowledge*, the research on imidazole derivative in cascade organocatalytic reactions has been rare. Therefore, the use of imidazole derivative in cascade organocatalytic reaction with the formation of multiple stereocenters in excellent diastereo- and enantioselectivity remains a challenging task. Up to now, the field of organocatalysis has been developing rapidly.[4] One of the challenges in organocatalysis is to devise novel and significant cascade reactions and implement them in one pot with excellent diastereo- and enantioselectivities.[5] Gratifyingly, organic chemists have developed many kinds of organocatalysts to overcome this difficulty. Of those developed organocatalysts, diarylprolinol silyl ether,[6] which was originally developed by Jørgensen[7] and Hayashi,[8] has been recognized as a powerful one. Among the developed strategy, the iminium-enamine catalysis is the most employed method in asymmetric organocatalytic domino reactions involving α,β-unsaturated aldehydes,[9] which displays widely application prospect in the future.

We are interested in devising and searching for the novel and interesting nucleophiles, which could exhibit high reactivities in the cascade organocatalytic reactions to afford the complex compounds in excellent stereoselective manner and simple one-pot operation. Herein, we designed a new class of nucleophilic imidazole derivatives **2**, which contain two nucleophilic points in the molecules. We considered that the carbon atom of substituted acetophenone is more acidic and nucleophilic than the carbon atom of imidazole ring, which could attack the α, β-unsaturated aldehydes **1** firstly. As showed in Scheme 1, the Michael–Aldol reaction is composed of iminium Michael reaction and enamine aldol reaction. It should be noted that this enamine aldol reaction mechanism differed from the reported studies. Imidazole could also be regarded as an enamine. Once the first step finished, the imidazole ring could take part in the cascade reaction spontaneously without secondary amine catalyst. The high stereoselectivities of the domino organocatalytic reaction was mainly determined by the activation of α, β-unsaturated aldehydes **1** by catalyst **I**, which provided the efficient shielding of the fragment in the catalytic process.

To explore the possibility of the proposed cascade Michael–Aldol process, we started our investigations by reacting cinnamaldehyde **1a** with imidazole derivative **2a** in the presence of catalyst **I** in dichloromethane. To our delight, by performing the cascade reaction in dichloromethane, we were able to obtain 54% of conversion with 10 : 1 dr and 95% ee in the presence of catalyst **I** (Table 1, entry 1). Screening of the catalysts showed that they exhibited significantly different catalytic activities. Using catalysts **II** and **III** would result in poor conversions



Scheme 1 One-pot, domino and organocatalytic Michael–Aldol reactions.

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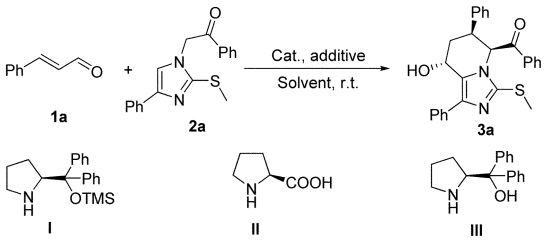
† Electronic supplementary information (ESI) available: Experimental procedures and characterization of the Michael addition products. CCDC 805085. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc12300a

Table 1 Optimization of the reaction conditions for the one-pot, domino and organocatalytic Michael–Aldol reaction[a]



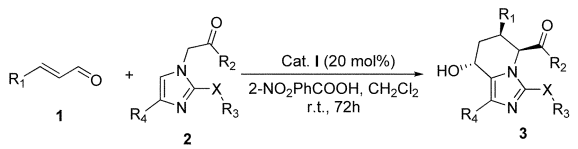
Entry	Additive	Solvent	Cat.	Conv.[b](%)	dr[b]	ee[c](%)
1	None	CH_2Cl_2	**I**	54	10:1	95
2	None	CH_2Cl_2	**II**	13	nd	nd
3	None	CH_2Cl_2	**III**	25	nd	nd
4	LiOAc	CH_2Cl_2	**I**	78	30:1	93
5	PhCOOLi	CH_2Cl_2	**I**	79	30:1	96
6	TFA	CH_2Cl_2	**I**	85	30:1	95
7	TsOH	CH_2Cl_2	**I**	84	30:1	93
8	PhCOOH	CH_2Cl_2	**I**	90	30:1	96
9	2-OMePhCOOH	CH_2Cl_2	**I**	93	30:1	96
10	4-ClPhCOOH	CH_2Cl_2	**I**	92	30:1	92
11	2-NO_2PhCOOH	CH_2Cl_2	**I**	>99	30:1	98
12	2-NO_2PhCOOH	THF	**I**	87	30:1	96
13	2-NO_2PhCOOH	Toluene	**I**	96	30:1	95
14	2-NO_2PhCOOH	CH_3CN	**I**	89	30:1	94
15	2-NO_2PhCOOH	EtOAc	**I**	91	30:1	93
16	2-NO_2PhCOOH	DMF	**I**	84	30:1	90
17	2-NO_2PhCOOH	MeOH	**I**	82	30:1	91

[a] Unless otherwise noticed, all reactions were carried out with **1a** (0.10 mmol), **2a** (0.15 mmol), catalyst (20 mol%) and additive (20 mol%) in CH_2Cl_2 (0.3 mL) at room temperature for 72 h. [b] Determined by the crude ^{1}H NMR. [c] Determined by chiral HPLC.

(Table 1, entries 2–3). Having identified catalyst **I** as the best catalyst, we attempted to improve the conversion through introducing different additives to the cascade Michael–Aldol reaction. To our delight, the conversion would increase to 78–79% in the presence of lithium acetate and lithium benzoate (Table 1, entries 4–5). Further investigations revealed that the **I**-catalyzed cascade reaction was more sensitive to an additive acid, which could be attributed to the convenient formation of iminium in the acidic environment. For instance, in a strong acid such as TFA, up to 85% of conversion with 30 : 1 dr and 95% ee were obtained (Table 1, entry 6). Similar results were observed in the presence of 4-methylbenzenesulfonic acid (Table 1, entry 7). We were pleased to find that the conversion would increase to 90% in the presence of benzoic acid with dr and ee maintained (Table 1, entry 8). Further screenings indicated that benzoic acid analogues which contained the substituent groups on the benzene ring were more suitable for this cascade reaction. When 2-methoxybenzoic acid and 4-chlorobenzoic acid were employed, the reaction conversion would be improved to 93% and 92% without sacrificing dr and ee (Table 1, entries 9–10). It should be noted that the best results (>99% conversion, 30 : 1 dr, 98% ee) were obtained when 2-nitrobenzoic acid was used as the additive (Table 1, entry 11). An investigation of the effects of the reaction medium led to the selection of dichloromethane as the ideal solvent for the cascade Michael–Aldol reaction. Slightly inferior results were obtained in other solvents (Table 1, entries 12–17). Notably, 82% conversion with excellent dr and ee were still observed even in the protonic solvents such as MeOH (Table 1, entry 17).

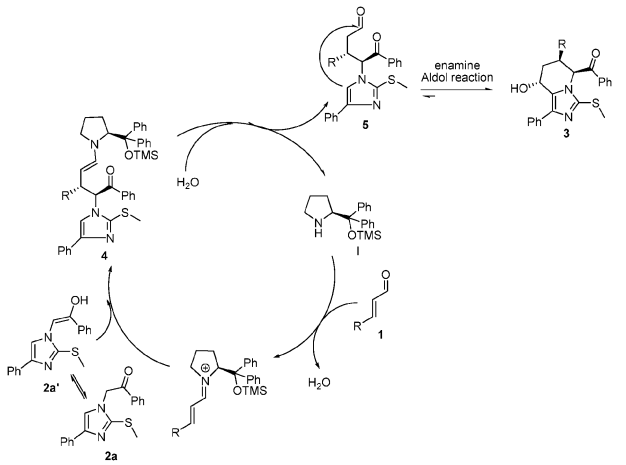
With the best reaction conditions in hand (20 mol% of **I**, 20 mol% of 2-NO_2PhCOOH in CH_2Cl_2), the one-pot, domino and organocatalytic Michael–Aldol processes between a variety of α,β-unsaturated aldehydes **1** and imidazole derivatives **2** were next investigated.‡ The results were summarized in Table 2. In general, the domino Michael–Aldol processes took place efficiently in high yields (65–95%) with good to excellent enantioselectivities (87–>99%) and excellent dr values (6 : 1–30 : 1). The reactions were applicable to α,β-unsaturated aldehydes **1**, which bear both aryl and alkyl groups with imidazole derivatives **2a** (Table 2, entries 1–11). Aromatic α,β-unsaturated aldehydes, regardless of electron-rich, electron-deficient groups on *o*-, *m*-, *p*-position of benzene ring, took part in this cascade process in excellent results (Table 2, entries 1–9, 76–95% yields, 98–>99% ee, 6 : 1–30 : 1 dr). For less reactive alkyl α,β-unsaturated aldehydes, a slightly inferior results were obtained (Table 2, entries 10–11, 65–67% yields, 87–95% ee, 30 : 1 dr). Furthermore, excellent results were also independent of the structural variations of imidazole derivatives **2**. Substrates **2b–2d**, bearing various substituent groups on R_2, reacted with cinnamaldehyde **1a** in high efficiency (Table 2, entries 12–14, 83–86% yields, 92–99% ee, 10 : 1–30 : 1 dr). When S-methyl was replaced with S-benzyl (R_3 = Bn), the dr would decrease to 13 : 1 with good yield and enantioselectivity (Table 2, entry 15). To our delight, when the substrate **2f** (R_2 = R_4 = *n*-Pr) was employed, excellent

Table 2 One-pot, domino and organocatalytic Michael–Aldol reactions between α,β-unsaturated aldehydes and imidazole derivatives[a]



Entry	R_1	R_2	R_3	R_4	X	Yield[b] (%)	dr[c]	ee[d] (%)
1	C_6H_5	C_6H_5, **2a**	Me	C_6H_5	S	89, **3a**	30:1	98
2	2-$OMeC_6H_4$	C_6H_5, **2a**	Me	C_6H_5	S	85, **3b**	30:1	>99
3	4-$OMeC_6H_4$	C_6H_5, **2a**	Me	C_6H_5	S	82, **3c**	13:1	98
4	3-MeC_6H_4	C_6H_5, **2a**	Me	C_6H_5	S	95, **3d**	30:1	98
5	4-MeC_6H_4	C_6H_5, **2a**	Me	C_6H_5	S	85, **3e**	16:1	98
6	4-ClC_6H_4	C_6H_5, **2a**	Me	C_6H_5	S	78, **3f**	10:1	99
7	3-ClC_6H_4	C_6H_5, **2a**	Me	C_6H_5	S	76, **3g**	6:1	98
8	4-BrC_6H_4	C_6H_5, **2a**	Me	C_6H_5	S	85, **3h**	30:1	>99
9	4-FC_6H_4	C_6H_5, **2a**	Me	C_6H_5	S	84, **3i**	30:1	98
10	Et	C_6H_5, **2a**	Me	C_6H_5	S	65, **3j**	30:1	95
11	Me	C_6H_5, **2a**	Me	C_6H_5	S	67, **3k**	30:1	87
12	C_6H_5	4-$CF_3C_6H_4$, **2b**	Me	C_6H_5	S	83, **3l**	30:1	98
13	C_6H_5	4-BrC_6H_4, **2c**	Me	C_6H_5	S	86, **3m**	30:1	92
14	C_6H_5	4-$OMeC_6H_4$, **2d**	Me	C_6H_5	S	85, **3n**	10:1	99
15	C_6H_5	C_6H_5, **2e**	Bn	C_6H_5	S	82, **3o**	13:1	98
16	C_6H_5	*n*-Pr, **2f**	Me	*n*-Pr	S	74, **3p**	30:1	>99
17	C_6H_5	C_6H_5, **2g**	Me	C_6H_5	O	87, **3q**	30:1	98
18	2-$OMeC_6H_4$	C_6H_5, **2g**	Me	C_6H_5	O	80, **3r**	30:1	99
19	4-MeC_6H_4	C_6H_5, **2g**	Me	C_6H_5	O	82, **3s**	30:1	99
20	4-ClC_6H_4	C_6H_5, **2g**	Me	C_6H_5	O	84, **3t**	30:1	99
21	4-BrC_6H_4	C_6H_5, **2g**	Me	C_6H_5	O	82, **3u**	20:1	>99

[a] Unless otherwise noticed, all reactions were carried out with α, β-unsaturated aldehydes **1** (0.30 mmol), imidazole derivatives **2** (0.45 mmol), catalyst **I** (0.06 mmol), 2-NO_2PhCOOH (0.06 mmol) in CH_2Cl_2 (0.9 mL) under room temperature for 72 h. [b] Isolated yield. [c] Determined by the crude ^{1}H NMR. [d] Determined by chiral HPLC.



Scheme 2 Assuming process of the asymmetric Michael–Aldol reaction.

ee and dr with high yield were also obtained (Table 2, entry 16, 74% yield, 99% ee, 30 : 1 dr). Substrate **2g**, in which S was replaced with O (X = O), reacted with α,β-unsaturated aldehydes smoothly to give the cascade products in excellent results (Table 2, entries 17–21, 80–84% yields, 99–>99% ee, 20 : 1–30 : 1 dr). In order to determine the absolute configuration of the cascade products, enantiopure **3h** containing the bromine atom was fortunately obtained. The absolute configuration of the product **3h** was determined to be (5*S*,6*S*,8*R*) based on X-ray crystal structure analysis (see supporting information†).[10]

The domino organocatalytic formation of products **3** could be explained by activation of α,β-unsaturated aldehyde **1** by catalyst **I**. As illustrated in Scheme 2, α,β-unsaturated aldehyde **1** reacted with catalyst **I** to give the iminium intermediate. The imidazole derivative **2a** could isomerize to its enol form **2a′**. Then the Michael reaction took place between imidazole derivative **2a′** with iminium intermediate to give the Michael adduct **4**, which released the catalyst **I** to afford the compound **5** in excellent enantioselectivity. The final enamine Aldol reaction proceeded spontaneously on the formation of intermediates **5** to give the cascade products **3** with excellent diastereo- and enantioselectivities. In this cycle, excellent diastereo- and enantioselectivities were obtained because of the efficient shielding of the fragment in catalyst **I** in the first step.

In summary, we have developed a novel and simple organocatalytic domino Michael–Aldol reaction between α,β-unsaturated aldehyde and imidazole derivative employing iminium-enamine catalysis. This process could provide the products with three stereocenters in one pot in high yields with excellent diastereo- and enantioselectivities (up to >99% ee, 30 : 1 dr). A broad substrate scope has been successfully employed in this process, including aromatic and alkyl α,β-unsaturated aldehydes **1** and various imidazole derivatives **2**. Further researches on this field are undergoing within our group.

This work was supported by the National Natural Science Foundation of China (20902018), the Innovation Program of Shanghai Municipal Education Commission (11ZZ56), the Shanghai Pujiang Program (08PJ1403300), and the Fundamental Research Funds for the Central Universities.

Notes and references

‡ General procedure for cascade one-pot Michael–Aldol reactions: To a solution of CH_2Cl_2 (0.9 mL) were added α,β-unsaturated aldehydes **1** (0.30 mmol), imidazole derivatives **2** (0.45 mmol), catalyst **I** (0.06 mmol) and 2-NO_2PhCOOH (0.06 mmol). The reaction mixture was stirred at room temperature for 72 h and then the solvent was removed under vacuum. The residue was purified by silica gel chromatography to yield the desired product.

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10 The crystallographic data of **3h** for this paper has been deposited in the Cambridge Structural Database, Cambridge Crystallographic Data Centre, Cambridge CB2 1EZ, United Kingdom (CSD reference no. 805085).