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Diastereodivergent synthesis of 4-oxocyclohexanecarbaldehydes by using the modularly designed organocatalysts upon switching on their iminium catalysis†

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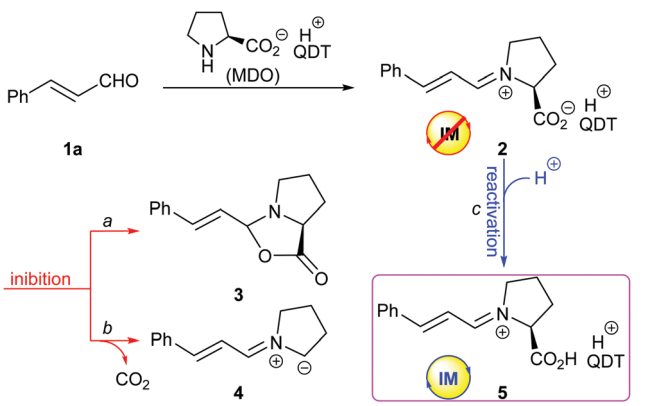
The cinchona thiourea moiety in the self-assembled modularly designed organocatalysts (MDOs) switches off the iminium catalysis of these catalysts. In this study, it was found that the inhibited iminium catalysis could be switched on by using an appropriate weak acid and that, once the iminium catalysis was switched on, these catalysts could be applied for the highly stereoselective and diastereodivergent synthesis of 4-oxocyclohexanecarbaldehydes *via* a domino reaction between ketones and α,β-unsaturated aldehydes.

In a living cell, numerous reactions occur simultaneously. To ensure that all these reactions are not interfering with each other, the enzymes that catalyze these reactions are often regulated by feedback loops or triggers in order to allow them to proceed with exact spatial and temporal control.[1] Simple chemical systems that mimic the enzyme reactivities, which are reversibly switchable, have been actively pursued by chemists in the past decades with the goals of understanding the fundamental questions regarding enzyme activation and developing synthetically useful catalysts inspired by the enzymes.[1] In the past two decades, an exponential growth has been witnessed in the amine-mediated organocatalysis *via* the iminium and/or the enamine mechanisms.[2] Nonetheless, amine-based switchable organocatalytic systems are still very limited.[3]

In the past a few years, our group has developed the modular designed organocatalysts (MDOs),[4a] which are self-assembled from amino acids and cinchona alkaloid thiourea derivatives [such as quinidine thiourea (QDT)] in the reaction media, for various asymmetric enamine-mediated reactions, including diastereodivergent catalysis.[4] Formation of MDO greatly enhances the reactivity and stereoselectivity of L-proline in enamine catalysis.[4] However, when we tried to apply these catalysts in activating an α,β-unsaturated aldehyde *via* the iminium catalysis, we had not much success. After careful examination of the reported mechanism of proline catalysis,[5] we realized that the formation of MDO promoted two pathways that could inhibit its iminium catalysis (Scheme 1, pathways a and b), since the deprotonation of the L-proline by QDT will make the iminium intermediate **2** more prone to the formation of the parasitic intermediate **3**[5] and the 1,3-dipolar intermediate **4**.[5b,6] Thus, while QDT activates the enamine catalysis of L-proline, it switches off the iminium catalysis simultaneously. Since protonation of the iminium intermediate **2** (pathway c) should make it less prone to the formation of intermediate **3** and **4**, we hypothesized that an acid that is strong enough to protonate iminium intermediate **2**, but weak enough to keep the self-assembled MDO intact should behave as an activator to switch on the iminium catalysis of the MDO.[7] Herein we report that the iminium catalysis mode of the MDOs can indeed be switched on by adding an acid[7] and that we are able to conduct a diastereodivergent catalysis for a domino Mannich



Scheme 1 Potential pathways that switch off the MDO iminium catalysis by QDT (**9e**) and proposed switch-on.

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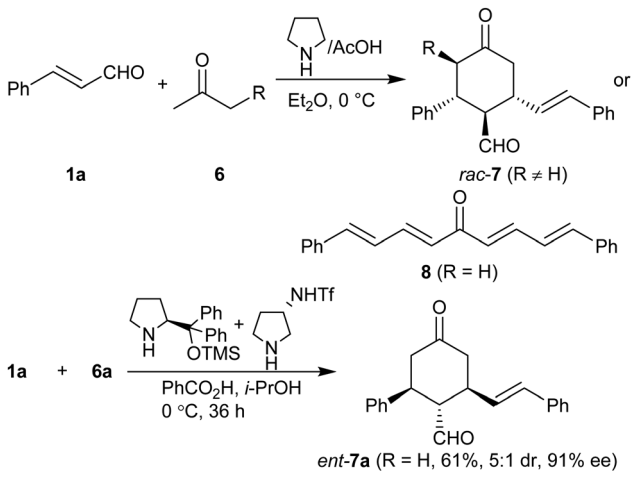
condensation/Michael/Michael reaction of ketones and α, β-unsaturated aldehydes[8,9] and obtained both diastereomers of the desired 4-oxocyclohexanecarbaldehydes.

Despite the advances in organocatalysis, the organocatalytic asymmetric Michael addition of ketones or aldehydes to α, β-unsaturated aldehydes *via* the enamine/iminium catalysis remains a challenging task,[8,9] and only a few examples are available.[8,10] In 2013, Kong and coworkers reported a pyrrolidine-catalyzed domino reaction between ketones **6** and cinnamaldehydes (such as **1a**), which yields the racemic cyclohexanecarbaldehydes **7** in low to mediocre yields (Scheme 2, upper equation).[8a] Unfortunately, an asymmetric version of this reaction was not possible because the chiral amine catalysts tried failed to catalyze this reaction.[8a] Moreover, the reaction between acetone (**6a**, R = H) and **1a** yielded the condensation product **8** instead (Scheme 2).[8a] We adopted this reaction as a model reaction to test our hypothesis since this domino reaction would require the simultaneous enamine and iminium activations. It should be pointed out that, while this manuscript was under preparation, Appayee and coworkers reported an enantioselective synthesis of this diastereomer (*ent*-**7a**)[10] using a two-catalyst system similar to those of Hayashi's, which was reported to work through an enolate/iminium activation[9] (Scheme 2, lower equation). In comparison, as our results shown below, we were able to obtain both diastereomers in high stereoselectivities using the reactivated MDOs.

As usual, cinchona alkaloid derivatives (**9**) and amino acid derivatives (**10**) were adopted to form the MDOs. Some weak acids (**11**) were adopted as the activator to switch on the iminium catalysis. Some representative examples of these compounds are collected in Fig. 1 and the representative results of catalyst screening and reaction condition optimizations are collected in Table 1 (For detailed catalyst screening and optimizations, please see Section S3 of the ESI†).

As the results in Table 1 show, when the MDO formed from **9a**/**10a** was employed without the addition of any acid, no formation the expected product was observed. Instead, a 60% yield of the mono-condensation product **12** was obtained (entry 1).[11]



Scheme 2 Organocatalyzed domino reaction between **1a** and **6**.

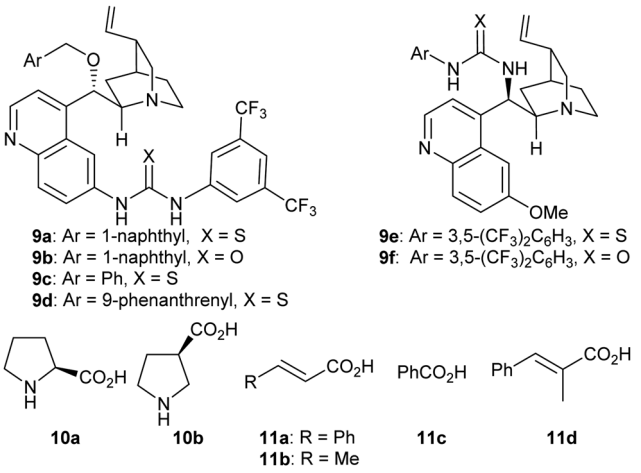
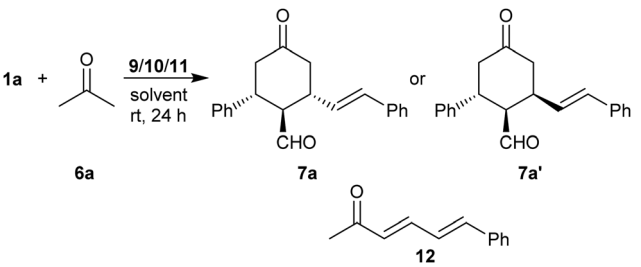


Fig. 1 Structure of selected precatalyst modules and acids used in this study.

Table 1 Selected results of catalyst screening and reaction condition optimizations[a]



Entry	9	10	11	Yield[b] (%)	dr[c] (**7a**/**7a**′)	ee[d] (%)
1	**9a**	**10a**	—	0[e]	—	—
2	**9a**	**10a**	**11a**	77	75 : 25	95
3	**9a**	—	**11a**	0	—	—
4	—	**10a**	**11a**	0[f]	—	—
5	**9b**	**10a**	**11a**	70	91 : 9	39
6	**9c**	**10a**	**11a**	70	71 : 29	54
7	**9d**	**10a**	**11a**	65	63 : 37	86
8	**9e**	**10a**	**11a**	83	8 : 92	>99
9	**9f**	**10a**	**11a**	60	32 : 68	40
10	**9a**	**10b**	**11a**	51	70 : 30	37
11	**9a**	**10a**	**11b**	67	76 : 24	72
12	**9a**	**10a**	**11c**	42	70 : 30	71
13	**9a**	**10a**	**11d**	50	70 : 30	90
14[g]	**9a**	**10a**	**11a**	86	84 : 16	97
15[gh]	**9a**	**10a**	**11a**	90	90 : 10	>99
16[i]	**9e**	**10a**	**11a**	91	6 : 94	>99
17[j]	**9a**	**10a**	**11a**	Trace	—	—

[a] Unless otherwise indicated, all reactions were carried out with **1a** (0.10 mmol), **6a** (0.10 mL), the precatalyst modules **9** and **10** (0.010 mmol each, 10 mol%), and the acid cocatalyst **11** (0.010 mmol, 10 mol%) in dry toluene (1.0 mL) at room temperature for 24 h. [b] Yield of the isolated product after column chromatography. [c] Determined by ^{1}H NMR analysis of the crude product. [d] Determined by HPLC analysis for the major diastereomer. [e] The condensation product **12** was obtained in 60% yield. [f] Product **12** was obtained in 29% yield. [g] EtOH was used as the solvent. [h] Carried out at −5 °C. [i] Carried out with 0.5 mL toluene at 0 °C. [j] Water was used as solvent.

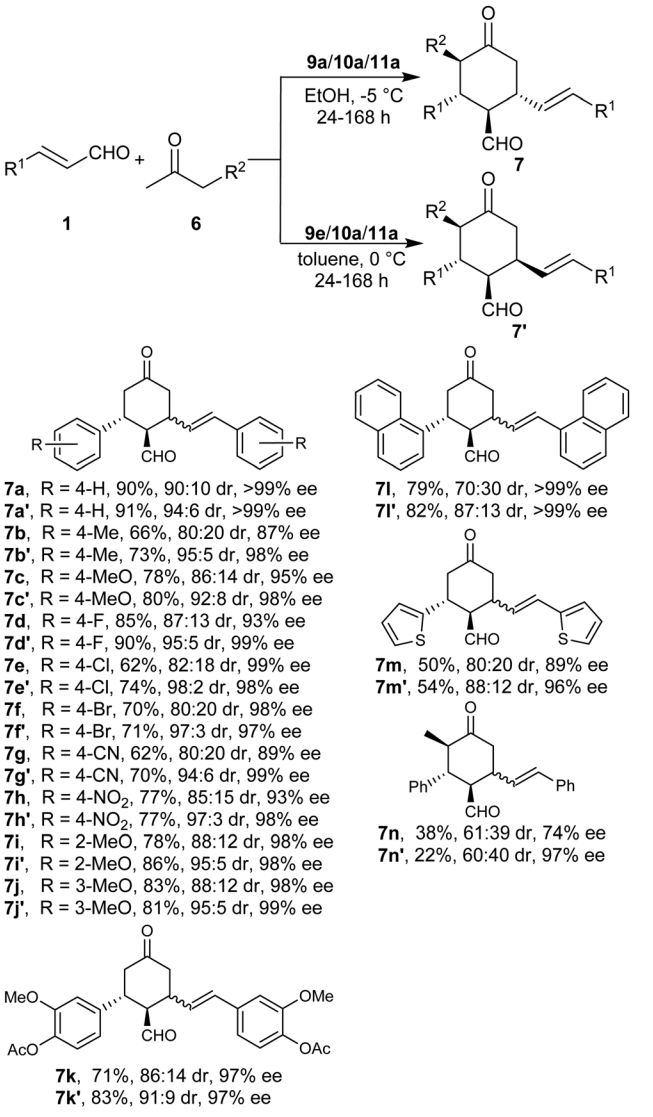
However, when a weak acid such as *trans*-cinnamic acid (**11a**) was employed together with **9a**/**10a**, the desired domino product **7a** was obtained in 77% yield with a dr of 75 : 25 and ee value of

95% (entry 2). These results clear demonstrate that a weak acid like **11a** is required to switch on the iminium catalysis for the Michael addition step. In addition, the combination of the MDO and **11a** yielded very decent stereoselectivities for **7a**, which indicates this weak acid doesn't affect the self-assembly of the MDO. The results of the other control reactions reveal that all three components of this catalytic system are required to achieve the desired domino reaction (entries 3 and 4). Further screening of different cinchona derivatives against L-proline (**10a**) (entries 5–9) revealed that, while the MDO of **9a**/**10a** yielded the best results for diastereomer **7a** (entry 2), the MDO of **9e**/**10a** produced high dr and ee values for the other diastereomer **7a′** (entry 8). On the other hand, screening of the other amino acids against **9a** showed that, except for amino acid **10b** (entry 10), which gave a much inferior results than L-proline, all the other amino acids were not reactive at all (Section S3 of the ESI†). Finally, the acid was screened (entries 11–13), and the results indicate that *trans*-cinnamic acid (**11a**) is the best in terms of stereoselectivities (entry 2). Next the solvent and reaction temperature were further optimized (please see Section S3 of the ESI† for details). In summary, for obtaining diastereomer **7a**, the use of **9a**/**10a**/**11a** in EtOH at −5 °C gives the best results (entry 15). For obtaining the other diastereomer **7a′**, the best outcome was obtained by using **9e**/**10a**/**11a** in toluene at 0 °C (entry 16). While protic solvent EtOH is a good solvent for these reactions, especially for obtaining diastereomer **7a**, a similar reaction conducted in water failed to yield the desired product (entry 17).

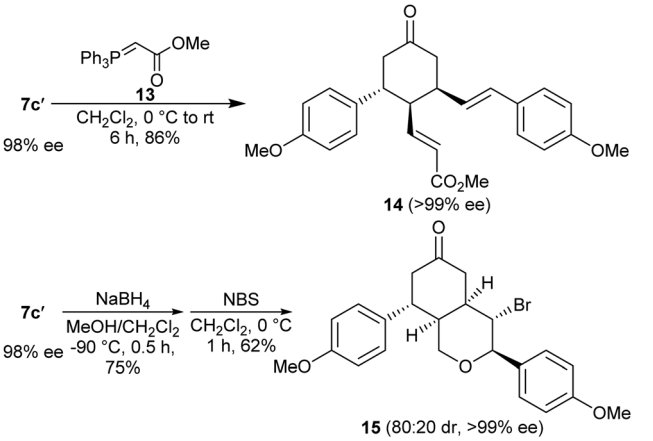
Once the reaction conditions were optimized, the scope of this domino reaction was then established for both catalytic systems to obtain either one of the two product diastereomers (Scheme 3). As the results in Scheme 3 show, both catalytic systems have very similar substrate tolerance, while catalyst system **9e**/**10a**/**11a** normally produces slightly higher stereoselectivities for product 7′ than **9a**/**10a**/**11a** does for diastereomer **7**. In terms of the cinnamaldehydes used, the substituent on the phenyl has almost no influence on the reactions, except for slight lower product yields were normally obtained for substituted cinnamaldehydes. 1-Naphthyl and 2-thiophenyl-substituted enals also worked well for both catalytic systems (Scheme 3). Nonetheless, crotonaldehyde (an alkyl-substituted aldehyde) gave a complex mixture of products (data not shown). In addition, both reactions are very sensitive toward the ketone substrate. For example, when 2-butanone was applied in this reaction, the yield and diastereoselectivities of **7n** and **7n′** were much worse (Scheme 3), while the other ketones (2- and 3-pentanones, and 4-phenylbutan-2-one) we tried all failed to give the desired product. This is most likely due to steric reasons.

The absolute stereochemistry of the diastereomeric products was determined by the X-ray crystallographic analysis of compounds **7c** and **7h′** (please see Section S4 of the ESI†).[12]

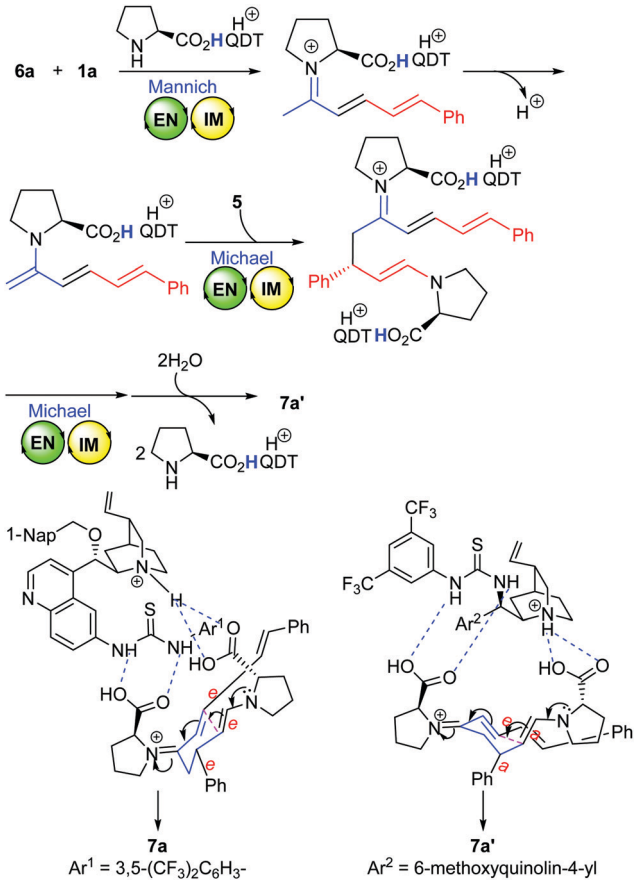
To show the utility of this method, we conducted some derivatizations of reaction product **7c′**. As shown in Scheme 4, the selective reaction of the aldehyde group of **7c′** with phosphorane **13** gave product **14** in 86% yield with complete retention of the stereochemistry. Moreover, a selective reduction of



Scheme 3 Substrate scope study.



Scheme 4 Derivatizations of the reaction product **7c′**.



Scheme 5 Proposed reaction mechanism and favored transition states.

the aldehyde group in **7c′** was achieved with $NaBH_4$ at −90 °C, and an ensuing reaction of the alcohol product with NBS in CH_2Cl_2 at 0 °C yielded the octahydro-6*H*-isochromen-6-one derivative **15** in a good diastereoselectivity (80 : 20) with complete retention of the stereochemistry.

In order to understand the reaction mechanism, we conducted some control experiments (please see Section S5 of the ESI†). Based on the results of these control experiments, we propose a domino Mannich condensation[13]/Michael/Michael reaction mechanism for the observed catalysis (Scheme 5). From the structural difference of these two diastereomers, it is evident that the diastereodivergence is created in the last-step intramolecular Michael reaction. The two proline moieties and the cinchona thiourea are most likely assembled with each other through hydrogen bonding in the transition state of this step. To account for the observed diastereodivergence in the product, two different favored transition states (Scheme 5, bottom structures) are proposed for this step on the basis of our previous study of the MDO enamine catalysis[4d] and a computational study[14] of the MDO catalysis.

In summary, we have demonstrated that the iminium catalysis mode of the MDOs inhibited by the cinchona alkaloid thiourea component of the MDOs is switchable and can be easily restored by using an appropriate acid. After the iminium catalysis mode is switched on, these catalysts can be used for catalyzing a domino Mannich condensation/Michael/Michael reaction between ketones and α,β-unsaturated aldehydes and achieving a highly stereoselective and diastereodivergent synthesis of 4-oxocyclohexanecarbaldehydes.

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Conflicts of interest

There are no conflicts to declare.

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