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Highly Enantioselective Inverse-Electron-Demand Hetero-Diels–Alder Reactions Catalyzed by Modularly Designed Organocatalysts

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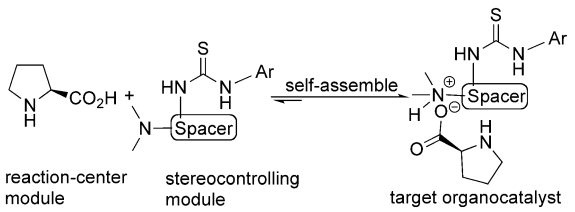
With the exponential developments of organocatalytic methods in recent years, organocatalysis has now been established as a very powerful tool for the synthesis of functional molecules.[1] Most recently, there was considerable interest in applying self-assembled organocatalysts in catalytic reactions.[2] Compared to conventional organocatalysts, the structure of self-assembled organocatalysts is easy to modify and optimize due to the fact that synthesis is not involved in the final catalyst formation step. Moreover, it is very convenient to build a large catalyst library of these self-assembled organocatalysts for high-throughput screenings.[2,3] Several self-assembled organocatalysts have been reported since the seminal work of Clarke and co-workers;[2a] nonetheless, the reactions catalyzed by these catalysts are still very limited. Most of the reported catalytic systems can only catalyze Michael and/or aldol reactions through the enamine mechanism.[2,3]

In 2008, we developed the modularly designed organocatalysts (MDOs) through the self-assembly of amino acids and cinchona alkaloids through ionic interactions (Scheme 1).[4a] Previously we demonstrated that these



Scheme 1. Formation of MDOs through self-assembly.

MDOs are very efficient catalysts for Michael and aldol reactions.[4] Formation of MDOs from these precatalyst modules has been confirmed by our previous ^{1}H NMR spectroscopic study[4a] and a recent HRMS study[2m] of the self-assembled organocatalyst. Nevertheless, these studies were not able to reveal how these two precatalyst modules are assembled in the final self-assembled catalyst. Herein we wish to disclose our recent finding that novel MDOs self-assembled from proline derivatives and cinchona alkaloid derived thioureas are also highly efficient catalysts for inverse-electron-demand hetero-Diels–Alder reactions.[5] Our new results not only demonstrated that forming an MDO may dramatically improve the catalytic activity and asymmetric induction of those poor catalysts, such as proline, so that these readily available but otherwise useless catalysts may be still applied in this important reaction, but also reveals the most likely structure for these self-assembled catalysts through a new NOESY study of the MDO.

Previously, Jørgensen,[5a] Ma,[5c] and our group[5b] have reported that pyrolidine derivatives are good catalysts for the hetero-Diels–Alder reactions between aldehydes and electron-deficient enones. In the presence of silica gel or an acid, these catalysts catalyze the desired reaction through an enamine intermediate.[5a–c] We envisioned that MDOs of proline derivatives should serve the same purpose since these catalysts are known to form enamines with aldehydes.[4a] To test our hypothesis, an electron-poor enone **3a** and propanal (**4a**) were adopted as the model substrates for screening the MDOs self-assembled from the selected catalyst modules (Figure 1). The most interesting results of the screening are summarized in Table 1.[6]

As the results in Table 1 show, when L-proline (**1a**) and quinidine thiourea **2a** (10 mol% loading each) were used as the catalyst in toluene at RT, the reaction generated a mixture of the aldol product **5a** and the desired hetero-Diels–Alder product **6a** in a ratio of about 1:4 with over 90% conversion of **3a** after 3 h (Table 1, entry 1). Prolonging the reaction time to 5 h led to almost exclusive formation of **6a** (entry 2), which was isolated in 92% yield. It should be pointed out that, unlike those pyrolidine-derived organocatalysts,[5a–c] no silica gel or acid is necessary for the MDO to achieve an efficient conversion of the substrates. As expected for this type of compound,[5a–c] **6a** was obtained as a mixture of two anomers (ratio 80:20).[7] To facilitate the determination of the enantiomeric excess (*ee*) value, product **6a** was oxidized with pyridinium chlorochromate (PCC) to give the dihydropyranone derivative **7a** as a single *trans* diastereomer in 90% *ee* (entry 2), which should be very useful in organic synthesis.[8] Increasing the loading of aldehyde **4a** slows down the formation of **6a**, but does not affect the product *ee* value (entries 3 and 4). These results indicate that the aldol reaction is reversible under the reaction con-

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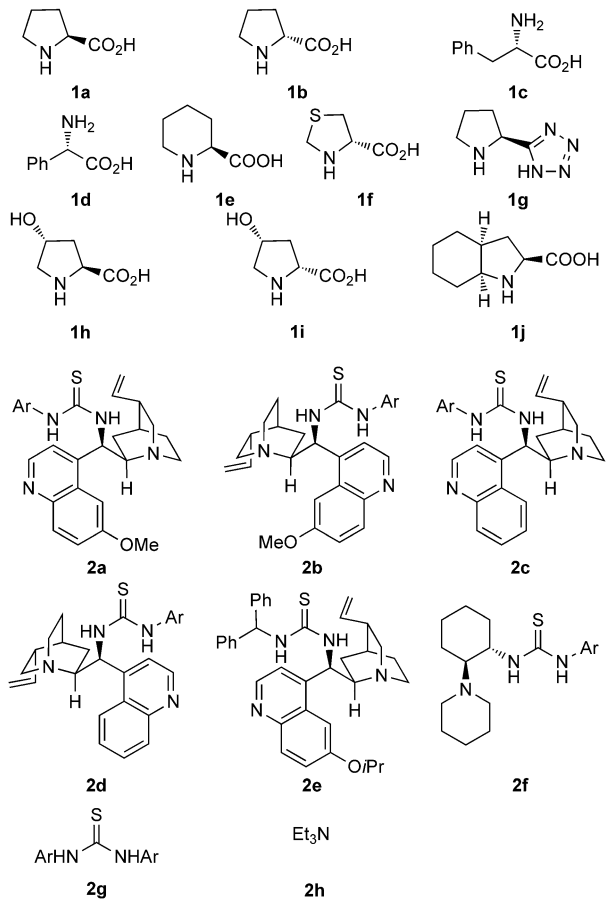
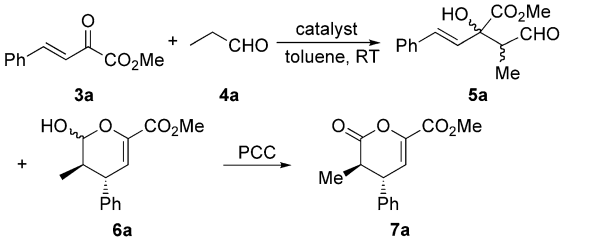


Figure 1. Structure of the catalyst modules used in the asymmetric hetero-Diels–Alder reaction (Ar = $(3,5\text{-}CF_3)_2C_6H_4$–).

ditions and that the hetero-Diels–Alder product is thermodynamically more stable. In contrast, when L-proline (entry 5) or **2a** (entry 6) were used alone, low conversion of **3a** and almost no formation of **6a** were observed. These results clearly demonstrate that the MDOs of **1a** and **2a** are much superior to the individual precatalyst modules. To further clarify the role of quinidine thiourea **2a** in this reaction, the reactions were also attempted with the mixtures of **1a** and an achiral thiourea **2g** as well as **1a** and triethylamine (**2h**) as the catalysts (entries 7 and 8). Again poor results were obtained in both cases. Thus, the concurrent presence of a base and a thiourea moiety in **2a** is crucial for the observed reactivity and enantioselectivity. These data lend further support to the formation of an MDO under the reaction conditions. Next other amino acids were screened as the reaction-center module in this reaction with **2a** as the stereocontrolling module. The MDO of D-proline (**1b**) and **2a** yield the opposite enantiomer in 90% yield and 88% *ee* (entry 9). In contrast, the MDOs of **2a** with primary amino acids **1c** and **1d**, L-pipecolic acid (**1e**), and proline derivatives **1f–i** all showed very poor reactivities (Table S1 in the Supporting Information). Nonetheless, (2*S*,3a*S*,7a*S*)-octahydro-1*H*-indole-2-carboxylic acid (OHIC, **1j**)[9] was identified as a slightly better reaction-center module than L-proline.

Table 1. Catalyst screening for the MDO-catalyzed hetero-Diels–Alder reaction[a]



Entry	Modules [mol%]	*t* [h]	**3a**/**5a**/**6a**[b]	**6a** [%][c]	*ee* [%][d]
1	**1a**/**2a** (10:10)	3	06:19:75	nd[e]	–
2	**1a**/**2a** (10:10)	5	02:02:96	92	90
3[f]	**1a**/**2a** (10:10)	5	03:20:77	75	90
4[g]	**1a**/**2a** (10:10)	5	03:25:72	70	90
5	**1a** (10)	5	94:05:01	nd	–
6	**2a** (10)	5	93:06:01	nd	–
7	**1a**/**2g** (10:10)	5	80:11:09	nd	–
8	**1a**/**2h** (10:20)	5	76:04:20	18	38
9	**1b**/**2a** (10:10)	5		90	88[h]
10	**1j**/**2a** (10:10)	2		91	94
11	**1j**/**2b** (10:10)	3		89	94
12	**1j**/**2c** (10:10)	2		91	94
13	**1j**/**2d** (10:10)	4		90	94
14	**1j**/**2e**(10:10)	3		88	94
15	**1j**/**2f** (10:10)	5		91	94
16	**1j**/**2a** (5:5)	5		91	94
17	**1j**/**2a** (3:3)	24		89	94

[a] Unless otherwise indicated, all reactions were carried out with **3a** (0.20 mmol), **4a** (0.24 mmol, 1.2 equiv), and the specified catalyst modules in toluene at room temperature (ca. 25 °C). Upon the completion of the reaction (monitored by TLC analysis and ^{1}H NMR spectroscopy), the product **6a** was isolated (anomeric ratio 80:20) and subjected to oxidation by PCC to **7a** to facilitate the *ee* value determination. [b] The ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Yield of the isolated compound **6a** after column chromatography. [d] Determined by HPLC analysis on the oxidative product **7a** by using a ChiralPakIB column. Only a single *trans* diastereomer was observed for compound **7a** according to ^{1}H NMR spectroscopy and HPLC analysis. Absolute configuration of the major enantiomer was assigned by comparing the observed optical rotation value with the literature data. [e] Not determined. [f] 2.0 equiv **4a** were used. [g] 5.0 equiv **4a** were used. [h] The opposite enantiomer was obtained as the major product.

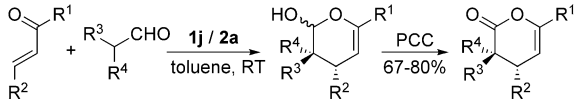
The reaction gave the desired product **6a** in 91% yield and 94% *ee* in just 2 h (entry 10).[10] Further screening of other cinchona alkaloid thioureas (**2b–e**) and Takemoto thiourea **2f** as the stereocontrolling modules reveals that all these modules led to similar product yields and identical product *ee* values with **2j** as the reaction-center module (entries 11–15), except that a few of these modules took a slightly longer time to complete the reaction.

The reaction conditions were further optimized with the MDO of **1j** and **2a**. Normal organic solvents were found to have only minimal influences on the asymmetric induction, except that poor results were obtained with a very polar solvent DMF (Table S1 in the Supporting Information). When the reaction was carried out at 0 °C, the reaction proceeded much slower, while there was no improvement on the product *ee* value (Table S1 in the Supporting Information). It was also found that reducing the precatalyst loading to 5 mol% each did not affect the reactivity and asymmetric

induction of this MDO (entry 16). However, further dropping the loading to 3 mol% each slowed down the desired reaction, although there was no effect on the asymmetric induction (entry 17). The ratio of these two modules was found to have some influence on the reaction: Slightly lower product *ee* values were observed with a 2:1 loading of **2a** and **1j** (Table S1 in the Supporting Information).

Once the reaction conditions were optimized, the scope of this MDO-catalyzed hetero-Diels–Alder reaction was evaluated and the results are summarized in Table 2. As the data in Table 2 show, besides propanal (Table 2, entry 1), various aldehydes, including long-chain and branched aldehydes, were found to be excellent substrates for this reaction (entries 2–6), except for phenylacetaldehyde, with which the opposite enantiomer[11] was obtained with a poor *ee* value of 35% (entry 7). This was most likely due to electronic effects,[12] since high *ee* values were obtained for the products of the more sterically hindered isovaleraldehyde (entry 5) and isobutyraldehyde (entry 6). Upon moving the phenyl group further away from the reaction center, such as in hydrocinnamaldehyde, the high reactivity and enantioselectivity of this reaction was restored (95% yield and 95% *ee*, entry 4). The ester alkyl group of the β,γ-unsaturated α-ketoesters has almost no influence on either the reactivity or enantioselectivity (entries 4, 8, and 9). Similarly, the substituent on the phenyl ring of the enones has minimal effects on the reactivity and the asymmetric induction of this reaction (entries 1 and 10–14), except that the 4-methoxyphenyl-substituted enone is less reactive (entry 10). Excellent results were also achieved for a γ-alkyl β,γ-unsaturated α-ketoester (entry 11). Besides β,γ-unsaturated α-ketoesters, β,γ-unsaturated α-ketophosphonates may also applied in this reaction[5b,9c] if a slightly higher loading of the precatalyst modules (10 mol% each) was used. Again high yields and enantioselectivities were obtained (entries 17–21).

Table 2. Substrate scope of the MDO-catalyzed hetero-Diels–Alder reaction.[a]

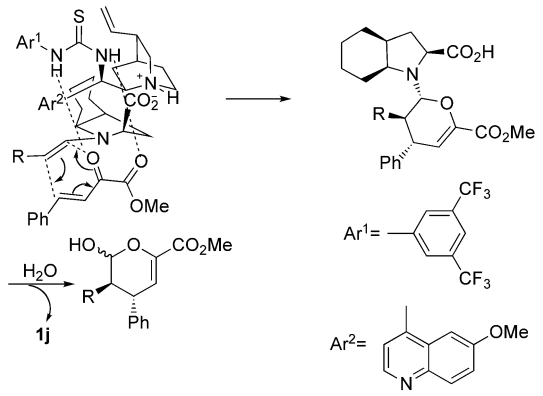


3 4 6 7

Entry	$R^1/R^2/R^3/R^4$	6/7	*t* [h]	Yield[b] [%]	ar[c]	*ee*[d] [%]
1	CO_2Me/Ph/Me/H	**a**	5	91	80:20	94
2	CO_2Me/Ph/*n*Pr/H	**b**	6	91	90:10	93
3	CO_2Me/Ph/$nC_{10}H_{21}$/H	**c**	6	90	87:13	94
4	CO_2Me/Ph/Bn/H	**d**	6	95	91:09	95
5	CO_2Me/Ph/*i*Pr/H	**e**	48	72	76:24	93
6	CO_2Me/Ph/Me/Me	**f**	48	51	85:15	91
7	CO_2Me/Ph/Ph/H	**g**	5	64	64:36	35[e]
8	CO_2Et/Ph/Bn/H	**h**	6	92	91:09	95
9	CO_2iPr/Ph/Bn/H	**i**	6	93	90:10	96
10	CO_2Me/4-$OMeC_6H_4$/Bn/H	**j**	24	88	85:15	94
11	CO_2Me/4-MeC_6H_4/Bn/H	**k**	5	90	86:14	91
12	CO_2Me/4-$CF_3C_6H_4$/Bn/H	**l**	5	92	88:12	94
13	CO_2Me/4-ClC_6H_4/Bn/H	**m**	6	91	88:12	92
14	CO_2Me/2-ClC_6H_4/Bn/H	**n**	6	96	82:18	92
15	CO_2Et/Me/Bn/H	**o**	4	94	79:21	98
16	$P(O)(OMe)_2$/Me/Me/H	**p**[f]	8	93	62:38	85
17	$P(O)(OEt)_2$/Me/Me/H	**q**[f]	5	95	67:33	94
18	$P(O)(Oi$Pr$)_2$/Me/Me/H	**r**[f]	4	92	66:34	92
19	$P(O)(OEt)_2$/Me/*n*Pr/H	**s**[f]	5	99	70:30	93
20	$P(O)(OEt)_2$/Me/*i*Pr/H	**t**[f]	24	82	56:44	86
21	$P(O)(OEt)_2$/Me/$nC_{10}H_{21}$/H	**u**[f]	2	97	66:34	94

[a] Unless otherwise indicated, all reactions were carried out with enone **3** (0.20 mmol) and aldehyde **4** (0.24 mmol) by using the catalyst modules **1j** (0.010 mmol, 5 mmol%) and **2a** (0.010 mmol, 5 mmol%) at room temperature in toluene. [b] Yield of the isolated product **6** after column chromatography. [c] Anomeric ratio as determined by ^{1}H NMR spectroscopic analysis of the crude **6**. [d] Determined by HPLC analysis of the oxidized product **7** (67–80% yield). Only a single diastereomer was obtained after the oxidation according to the ^{1}H NMR spectra of the crude product. [e] The opposite enantiomer is obtained as the major product in this case. [f] The loading of the catalyst modules (**1j** and **2a**) was 10 mmol% each.

As aforementioned, although previous studies have confirmed the formation of MDO from the precatalyst modules, such as L-proline (**1a**) and quinidine thiourea (**2a**),[2m,4a] they were not able to reveal the possible structure of the MDO. To find out how these two precatalyst modules are self-assembled in the MDO, we conducted a NOESY study of the MDO of **1a**/**2a**. On the basis of these new results (Figures S2–S4 in the Supporting Information), a more plausible structure of the MDO is proposed (Figure S5 in the Supporting Information), in which **1a** sits right under the quinuclidine ring of **2a**, with its amine group facing the front and its carboxylic acid group forming an ammonium salt with **2a**. On the other hand, the absolute configuration of the hetero-Diels–Alder products **6** was assigned as 4*S*,5*R* by comparing the measured optical rotation data of compounds **7d** and **7e** with the reported values.[5a] Except for compound **7g**,[11] the absolute configuration of the other compounds was similarly assigned according to the reaction mechanism. On the basis of the product stereochemistry and the proposed MDO structure, a plausible transition state is proposed. As shown in Scheme 2, the aldehyde reacts with the OHIC moiety of the MDO to form an *E* enamine. Simultaneously, the thiourea moiety of the MDO forms hydrogen bonds with the enone and directs the enone to approach enamine from the front. The attack of the enone onto the *Re* face of the enamine in an *endo* fashion[5a] leads to the formation of the observed (4*S*,5*R*)-product after hydrolysis.



Scheme 2. Proposed transition state of the MDO-catalyzed hetero-Diels–Alder reaction.

In summary, we have developed a highly enantioselective hetero-Diels–Alder reaction of electron-deficient enones and aldehydes by using MDOs. The reactivity and stereoselectivity of proline derivatives may be dramatically improved through the formation of MDOs. A new NOESY study also reveals the most likely structure for these self-assembled catalysts.

Experimental Section

General procedure: (2*S*,3a*S*,7a*S*)-Octahydro-1*H*-indole-2-carboxylic acid (OHIC, **1j**) (1.7 mg, 0.010 mmol, 5 mol%) and quinidine thiourea **2a** (5.9 mg, 0.010 mmol, 5 mol%) were added to a stirred solution of propanal (**4a**) (13.9 mg, 0.24 mmol) in toluene (0.5 mL) at room temperature. After the mixture had been stirred for 10 min, a solution of β,γ-unsaturated-α-ketoester **3a** (0.20 mmol) in toluene (0.5 mL) was added and the stirring was continued at RT (for β,γ-unsaturated α-ketophosphonate substrates (0.10 mmol), propanal **4a** (29.0 mg, 0.50 mmol) was used with 10 mol% of the two catalyst modules in toluene (0.1 mL)). The progress of the reaction was monitored by TLC analysis. Upon completion, the crude reaction mixture was transferred to a silica gel column and eluted with a 15–20% ethyl acetate/hexane mixture. After the evaporation of the solvent, the product **6a** was obtained as a colorless gummy liquid (45.1 mg, 0.18 mmol, 91% yield). It was then oxidized by PCC (196.1 mg, 0.91 mmol) in CH_2Cl_2 (1.0 mL) at RT for 48 h to the corresponding lactone **7a**. Product **7a** was again purified by flash column chromatography (32.3 mg, 0.13 mmol, 71% yield) and its *ee* value was determined to be 94% by HPLC analysis by using a ChiralPak IB column.

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Keywords: aldehydes · Diels–Alder reaction · ketoesters · ketophosphonate · organocatalsis

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[6] For more details, please see the Supporting Information.

[7] Although the possibility of a tandem Michael-acetalization reaction cannot be ruled out for the formation of the final product, we never observed the expected Michael product in the ^{1}H NMR spectra during the reaction.

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[9] OHIC (**1j**) has never been used as a catalyst in hetero-Diels–Alder reactions; for its application in Michael reactions, see: a) J.-W. Xie, L. Yue, D. Xue, X.-L. Ma, Y.-C. Chen, Y. Wu, J. Zhu, J.-G. Deng, *Chem. Commun.* **2006**, 1563; b) R.-S. Luo, J. Weng, H.-B. Ai, G. Lu, A. S. C. Chan, *Adv. Synth. Catal.* **2009**, *351*, 2449; c) D. Roca-Lopez, P. Merino, F. J. Sayago, C. Cativiela, R. P. Herrera, *Synlett* **2011**, 249; for its application in aldol reactions, see: d) X. Tang, B. Liegault, J.-L. Renaud, C. Bruneau, *Tetrahedron: Asymmetry* **2006**, *17*, 2187.

[10] Control experiments conducted with **1j** alone as the catalyst gave no conversion of the substrate. For details, please see the Supporting Information.

[11] The absolute stereochemistry of compound **7g** was determined by comparing the measured optical rotation data with those reported in: D. Belmessieri, L. C. Morrill, C. Simal, A. M. Z. Slawin, A. D. Smith, *J. Am. Chem. Soc.* **2011**, *133*, 2714.

[12] A similar phenomenon was also observed in the hetero-Diels–Alder reaction of β,γ-unsaturated α-ketophosphonate, see ref. [5b].

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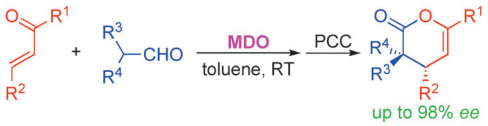

MDO rocks! Proline and (2*S*,3a*S*,7a*S*)-octahydro-1*H*-indole-2-carboxylic acid are both poor catalysts for the inverse-electron-demand hetero-Diels–Alder reactions between aldehydes and electron-deficient enones. However, forming modularly designed organocatalysts (MDOs) through their self-assembly with cinchona alkaloid-derived thioureas can dramatically improve the efficiency of these unfunctional catalysts (see scheme; PCC = pyridinium chlorochromate).

Synthetic Methods

*D. Sinha, S. Perera, J. C.-G. Zhao** ..... ▮▮▮▮–▮▮▮▮

Highly Enantioselective Inverse-Electron-Demand Hetero-Diels–Alder Reactions Catalyzed by Modularly Designed Organocatalysts