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Chemzymes: A New Class of Structurally Rigid Tricyclic Amphibian Organocatalyst Inspired by Natural Product

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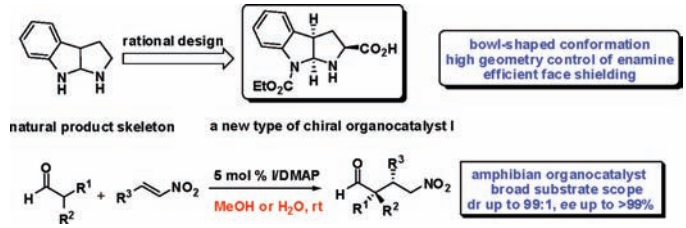
ABSTRACT



A new class of structurally rigid tricyclic amphibian chiral catalyst was rationally designed based on the hexahydropyrrolo[2,3-*b*]indole skeleton as a new type of chemzyme. This new type of chemzyme possesses a structurally rigid tricyclic skeleton and a chiral pocket which provides a well-organized chiral environment for asymmetric induction, as well as a hydrophobic pocket to enable organocatalytic reactions to proceed smoothly both in organic solvents and in water.

Designing molecular robots or chemzymes that behave like small molecules of enzymes is greatly valued as enzymatic catalysis promotes stereoselective processes with very high fidelity. Such a glorious goal was first achieved by Corey through his "CBS catalyst".[1] In this system, the two reactants are brought together and mutually activated for chemical reactions. However, the existing chemzymes work mainly in organic solvents and many of these catalysts are unstable in water unlike the actual enzymatic reactions which take place in water.[2] Therefore, the rational design of new types of molecular robots which possess a chiral pocket that could function in water is highly sought-after.

The hexahydropyrrolo[2,3-*b*]indole motif is frequently found as a key unit in many indole alkaloids with diverse biological activities that have attracted much attention from synthetic chemists (Figure 1).[3] It has been brought to our attention that the tricyclic rigid ring system with a stable bowl-shaped conformation could potentially act as a novel chiral skeleton for asymmetric catalysis and novel template for designing new chemzymes. The chiral pocket of this skeleton could serve as a catalytic site by assembling hydrophobic reactants in water and plays an important role in the function of chemzymes.

On the basis of this novel skeleton, we rationally designed chiral amino acid **I** (Figure 1). We highly anticipated that this newly designed organocatalyst **I** could function as a molecular robot or chemzyme which may accomplish the task that proline cannot. Although proline has been ascribed as a "universal catalyst" due to its widespread application

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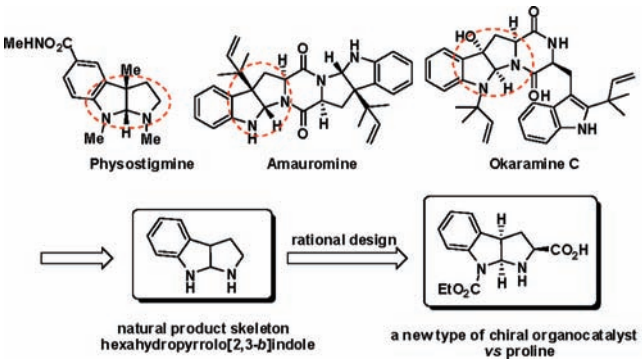
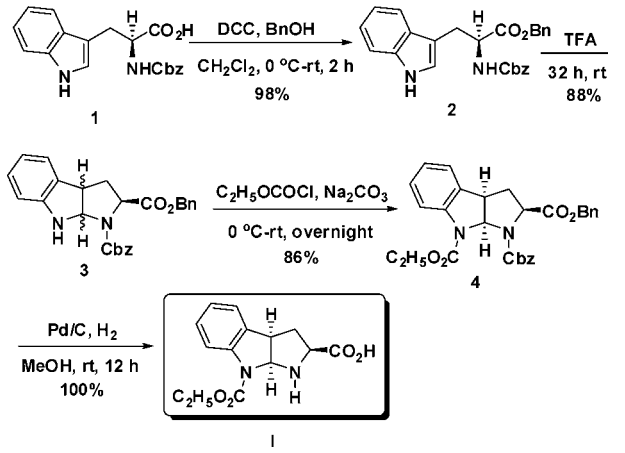


Figure 1. Rationally designed chiral amino acid catalyst **I** based on hexahydropyrrolo[2,3-*b*]indole.

in organocatalysis, it is usually not an effective catalyst in terms of yield and enantioselectivity for electrophiles that are poor hydrogen bond acceptors such as nitroalkene.[4] We also noticed that only few organocatalysts without additional assistance could work in water,[5] and among these, catalysts based on amino acids for asymmetric reactions in water is a rather special case due to their inherent involvement in enzymatic catalysis.[6] Therefore, the design and identification of novel water-compatible chiral amino acid catalysts, particularly those embedded in a new chiral skeleton is a challenging task. Herein, we report a new class of organocatalyst **I** having the hexahydropyrrolo[2,3-*b*]indole skeleton as a new type of chemzyme which works in both organic solvent and water. The efficiency of this catalyst is demonstrated in the asymmetric Michael addition of aldehydes to nitrostyrenes.

The desired catalyst **I** was easily synthesized in 4 steps from cheap commercially available Nα-carbobenzyloxy-L-tryptophan **1** on a large scale with a total yield of 74% (Scheme 1). The unique rigid tricyclic skeleton and

Scheme 1. Synthesis of Chiral Catalyst **I**



stereochemistry of **I** have been confirmed by X-ray analysis of its methyl ester derivative **II** (Figure 2).

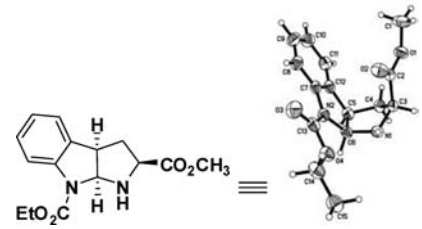
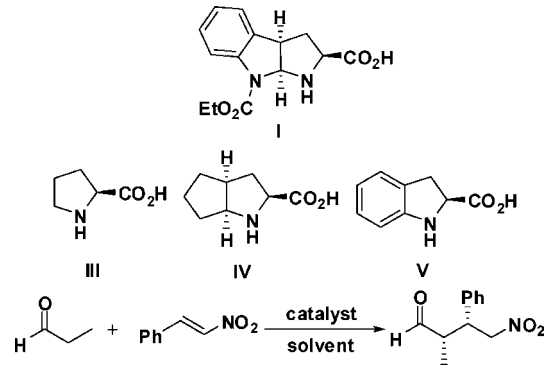


Figure 2. X-ray crystal structure of methyl ester derivative **II**.

With chiral catalyst **I** in hand, we proceeded to test our hypothesis for asymmetric catalysis. To demonstrate the efficiency of **I**, the enantioselective Michael addition of aldehydes to nitroalkenes[4b,7] was selected as the testing ground since nitroalkanes are versatile synthetic intermediates. We were delighted to find that the desired product could be obtained in 86% yield and 96% ee in the presence of 10 mol % catalyst **I** using 2 equiv of propanal at room temperature in MeOH (Table 1, entry 1). In contrast, catalysts

Table 1. Catalytic Asymmetric Michael Addition of Propanal to Nitrostyene[a]



entry	catalyst	solvent	loading (mol %)	yield (%)[b]	dr[c]	ee (%)[d]
1	**I**	MeOH	10	86	91: 9	96
2	**III**	MeOH	10	30	85:15	−20
3	**IV**	MeOH	10	<10	86:14	−20
4	**V**	MeOH	10	<10	N.D.	N.D.
5	**I**/DMAP	MeOH	5	96	91: 9	>99
6	**I**/DMAP	MeOH	2	92	75:25	>99
7	**I**/DMAP	H_2O	5	90	91:9	>99
8	**I**/DMAP	brine	10	10	86:14	96
9	**I**	H_2O	10	N.R.	N.R.	N.R.
10	**III**/DMAP	H_2O	10	N.R.	N.R.	N.R.
11	**IV**/DMAP	H_2O	10	N.R.	N.R.	N.R.
12	**V**/DMAP	H_2O	10	N.R.	N.R.	N.R.

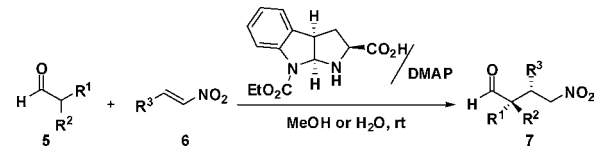
[a] Reactions were conducted with 2 equiv of aldehyde, 1 equiv of nitrostyene at room temperature in the presence of catalyst with 1:1 catalyst:DMAP. [b] Isolated yield. [c] Dr (*syn*/*anti*) was determined by chiral HPLC analysis. [d] Reported values refer to the *syn* isomer and were determined by chiral HPLC on a chiral stationary phase.

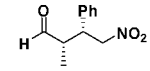
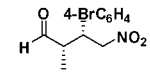
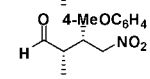
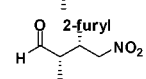
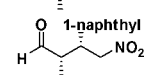
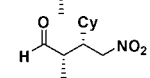
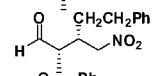
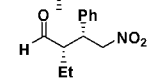
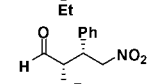
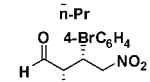
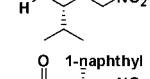
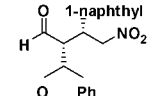
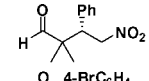
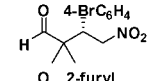
III, **IV** and **V** gave much less desirable results in MeOH (Table 1, entries 2−4). The vast differences in efficiencies

between catalyst **I** and catalysts **III**, **IV** and **V** fully *highlight the importance of this new skeleton for the success of this reaction and also demonstrate that it is proline's skeleton and not the hydrogen bonding interaction which account for its failure in this reaction*. In line with the concept of the self-assembly of organocatalysts proposed recently,[8] more than 99% ee was achieved when DMAP was added and The catalyst loading could be decreased to as low as 2 mol % (Table 1, entries 5−6). ^{1}H NMR revealed that the salt was formed rapidly and quantitatively, with significant chemical shift of all the protons. Both **I** and **I**/DMAP are soluble in water and are stable as shown by ^{1}H NMR (see Supporting Information). More importantly, the **I**/DMAP catalyst could also catalyze this reaction in water (Table 1, entry 7). Very low yield was obtained when brine was used as solvent (Table 1, entry 8). However, no reaction was observed when the reaction was carried out using either **III**/DMAP, or **IV**/DMAP, or **V**/DMAP or **I** itself in pure water (Table 1, entries 9−12).

Next, various substrates were examined and the reactions were found to exhibit broad substrate scope with regard to both the Michael acceptor and the donor (Table 2). The adducts were obtained in excellent enantioselectivity (up to >99% ee) and with good *syn* diastereoselectivity. The stereochemistry was confirmed by X-ray crystal structure of product **7b** (see Supporting Information). Both aromatic and aliphatic aldehydes, aryl- and alkyl-substituted nitroalkenes gave the desired products in good yields and excellent enantioselectivities (Table 2, entries 1−11). For the more bulky isobutyraldehyde, which was found to be a poor nucleophile giving only 68% ee using 20 mol % diarylprolinol ether catalyst alone,[7c] our catalyst afforded the product in 94−95% ee with various nitrostyrenes using 10 mol % of our catalyst (Table 2, entries 12−14). Most of the earlier reports for this reaction were carried out at 0 °C or even lower temperature with large excess of aldehyde,[7] while in our cases, only slight excess of aldehyde was employed and excellent enantioselectivity could be obtained at room temperature.

Table 2. Catalytic Asymmetric Michael Addition of Unmodified Aldehydes to Nitroalkenes[a]



entry	product		catalyst (mol %)	solvent	time (h)	yield (%)[b]	syn/anti[c]	ee (%)[d]
1		**7a**	5	MeOH	8	96	91:9	>99
				H_2O	12	90	91:9	>99
2		**7b**	5	MeOH	8	87	86:14	96
				H_2O	12	75	63:37	91
3		**7c**	5	MeOH	8	79	72:28	93
				H_2O	12	76	63:37	92
4		**7d**	5	MeOH	8	94	88:12	96
				H_2O	12	61	64:36	95
5		**7e**	5	MeOH	24	92	91:9	96
				H_2O	36	87	78:22	96
6		**7f**	10	MeOH	72	60	60:40	98
				H_2O	96	56	40:60	98
7		**7g**	10	MeOH	72	70	80:20	96
				H_2O	96	65	76:24	96
8		**7h**	5	MeOH	48	89	91:9	98
				H_2O	56	83	91:9	97
9		**7i**	5	MeOH	48	81	67:33	95
				H_2O	56	80	70:30	95
10		**7j**	10	MeOH	72	86	99:1	>99
				H_2O	96	82	98:2	>99
11		**7k**	10	MeOH	72	87	96:4	99
				H_2O	96	84	95:5	99
12		**7l**	10	MeOH	96	86	-----	95
13		**7m**	10	MeOH	96	82	-----	94
14		**7n**	10	MeOH	96	85	-----	95

[a] Reactions were conducted with 0.2 mmol nitroalkene, 0.4 mmol aldehyde at room temperature or 0.2 mmol nitroalkene, 0.8 mmol aldehyde at 60 °C (for bulky aldehydes, entries 12−14) in the presence of catalyst with 1:1 catalyst **I**:DMAP. [b] Isolated yield. [c] *Syn*/*anti* was determined by chiral HPLC analysis or by ^{1}H NMR after purification. [d] Reported values refer to the *syn* isomer and were determined by chiral HPLC on a chiral stationary phase.

Therefore, our catalytic system **I**/DMAP could be defined as "artificial enzyme", considering the high efficiency and high catalytic activity observed in both organic solvents and water.

To probe the mechanism of this reaction, different possible conformers of the enamine intermediate were subjected to DFT calculation to determine the lowest energy conforma-

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tion.[9] As expected, the ethyl carbamate group controls the geometry of the enamine to adopt the *syn* enamine conformation (Figure 3). From this conformer, we can see that at

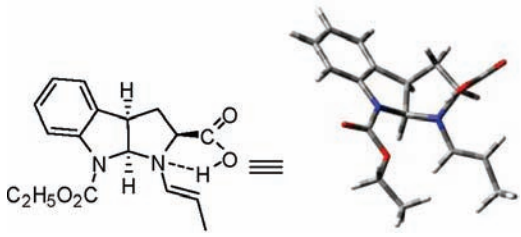

Figure 3. Most stable *syn* enamine conformation by DFT calculation.

the *Si* face of the enamine, there are several highly electronegative atoms such as O and N which could function as hydrogen bond acceptors. Therefore when the enamine is immersed into protic solvents such as methanol and water, the *Si* face is expected to develop strong hydrogen-bond networks which eventually block the attack of nitrostyrene from this side.[10] On this basis, nitrostyrene will attack the enamine from the less hindered *Re* face via transition state **4A**, where a water molecule is probably involved by forming hydrogen bonds with the CO_2H group and NO_2, which will lead to the desired (*S*,*R*) product (Figure 4).[11] The activation

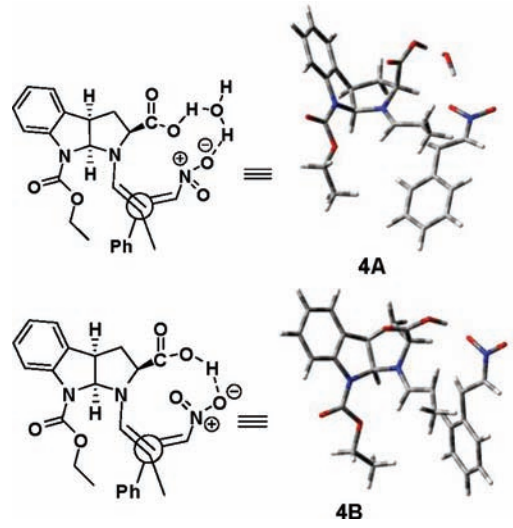

Figure 4. Lowest energy TS **4A** by DFT calculation.

energy of TS **4A** is 64.61 kJ/mol lower than that of TS **4B** without the water molecule as hydrogen-bond bridge. The whole system is stabilized by hydrogen bonds. This proposal is supported by the following experimental results: (1) methyl ester derivative **II** or phenyl ester derivative could not catalyze the reaction with or without acid additive in MeOH or H_2O, which indicate the possible activation of nitrostyrene by the carboxylic acid. (2) the reaction was much slower in aprotic solvent such as DMSO and DMF which implies that H_2O may be involved in the reaction through hydrogen-bonding interaction. Although the role of DMAP is not clear at this moment, the DMAP salt was found to improve the solubility of the catalyst and could also function as phase transfer catalyst when the reaction was carried out in water. *This structurally rigid tricyclic skeleton provides a well-organized environment for asymmetric induction as well as a hydrophobic pocket to enable this reaction to proceed smoothly in water.* For catalyst **III**, **IV** and **V**, they could not satisfy the above criteria.

In summary, a new class of structurally rigid tricyclic amphibian chiral catalyst based on the hexahydropyrrolo[2,3-*b*]indole skeleton has been developed. The special features of this catalyst include: (1) bowl-shaped conformation; (2) high geometry control of enamine and efficient face shielding; (3) involvement of a chiral pocket; (4) easy preparation in large scale; (5) **I**/DMAP catalyst has been shown to effect high yields and excellent enantioselectivities in the Michael addition of aldehydes to nitroalkenes both in organic solvents and in water with slight excess of aldehyde, low catalyst loading and broad substrate scope. These advantages render this chiral catalyst more suitable for practical use and will certainly find wide application in asymmetric synthesis. The success of this novel catalyst design will open up new perspectives in chiral catalyst or ligand design.[12] Further applications to other asymmetric reactions using this new catalyst as well as more detailed mechanistic insight are ongoing in our group.

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Supporting Information Available: Additional experiment procedures, spectrum data for reactions products and two CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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