Asymmetric Catalysis

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The Synthesis of Chiral Isotetronic Acids with Amphiphilic Imidazole/Pyrrolidine Catalysts Assembled in Oil-in-Water Emulsion Droplets**

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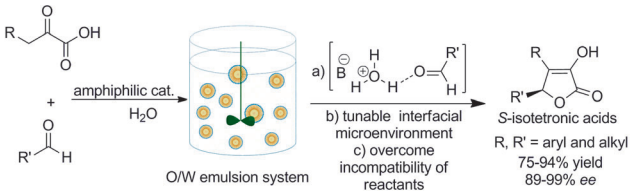
Isotetronic acids are important five-membered lactones, which have been isolated from a variety of natural sources.[1] This structural motif was found in a number of bioactive natural products, including compounds with antiumor[2a,b] and aldose reductase inhibitory[2c,d] activities. Functionalized isotetronic acids are also significant for the synthesis of natural products.[3] Many synthetic strategies have been devised to achieve the synthesis of this type of compound.[4] However, so far there have been only a few asymmetric methods reported to obtain enantiomerically enriched isotetronic acids, and most of these approaches relied heavily on the ex-chiral pool or chiral auxiliaries[5] to control the stereoselectivities. Bisoxazoline/copper(II) and proline have been utilized as a catalyst to realize the enantioselective homo-aldol reaction of pyruvates.[6] In 2007, an elegant asymmetric organocatalytic cascade reaction of α-ketoacids to aldehydes, thus providing a straightforward and atom economical entry to chiral isotetronic acids, was developed by Landais and coworkers.[7] However, this method is still plagued by drawbacks of relatively low efficiency and limited scope. Thus, the development of catalytic protocols for efficient synthesis of enantiomerically enriched isotetronic acids remains a distinct challenge.

Emulsions are thermodynamically unstable two-phase mixtures of oil, water, and surfactants, and are usually used as reaction media to overcome the reactant incompatibility problem.[8] Indeed, emulsion droplets, which have a uniform microenvironment, were found to act as a nano-macroreactor to induce the regioselectivities of organic reactions[9] and accelerate the reaction rates.[10] The importance of the isotetronic acids structural motif coupled with our ongoing interest in developing catalytic emulsion systems[11] prompted our investigation into the cascade reaction of α-ketoacids with aldehydes in an oil-in-water (O/W) emulsion system. Firstly, we anticipated that the strong acidity of the hydrated ion generated from an α-ketoacid in water would accelerate the proton transfer to the aldehyde and increase the reactivity.[12] Secondly, an emulsion system can supply a much larger interfacial area and overcome the incompatibility between α-ketoacids in water with aldehydes. Importantly, the tunable emulsion droplets on the nano- to macroscale could supply a different interfacial microenvironment[13] for the reaction and might exhibit some special effect to improve the stereoselectivity (Scheme 1).



Scheme 1. Asymmetric catalytic cascade reaction for synthesis of enantiopure isotetronic acids. 'emulsion catalysis strategy'

Herein, we report a new amphiphilic proline-derived imidazole organocatalyst, which forms an emulsion system in the reaction mixture through self-assembly. This catalytic system can promote a high yielding and enantioselective (up to 99% *ee*) cascade reaction of α-ketoacids with aldehydes using water as the solvent for the synthesis of isotetronic acids, and the state of the emulsions are essential for the high activity and enantioselectivity. Furthermore, based on a direct fluorescence image of the reaction system, we found that catalyst molecules are mainly distributed on the surface of the emulsion droplets.

With the concept of adjusting an interfacial microenvironment of emulsion droplets, through changing the amphiphilicity of the catalyst in mind, a series of proline-based organocatalysts[14] having a bezoimidazole motif (**1**; for structure see Table 1) bearing hydrophobic alkyl chains with different lengths were designed and synthesized by a three- or four-step reaction sequence (see the Supporting Information). In terms of the stronger basicity of imidazole, a series of pyrolidine/imidazole organocatalysts (**2**) were also synthesized with different synthetic routes from **1** (see the Supporting Information).

With these catalysts in hand, we began our investigation on the asymmetric reaction of α-ketobutyric acid (**3a**) to benzaldehyde (**4a**) in water[15] by using a 10 mol% catalyst loading at room temperature. As can be seen from the results summarized in Table 1, the catalyst **1a** displayed low activity and poor enantioselectivity (entry 1). We were glad to find that catalysts **1b**–**e**, bearing hydrophobic alkyl chains with different lengths, exhibited higher reactivities and the conversion was as high as 79% after 12 hours (entries 2–5). It is

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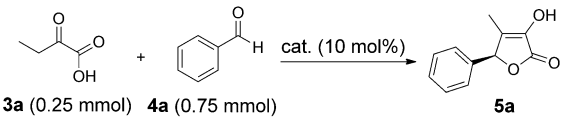
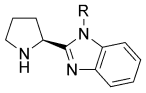
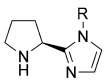
Table 1: The cascade reaction of **3a** and **4a** catalyzed by **1** and **2**.[a]



3a (0.25 mmol) **4a** (0.75 mmol) **5a**



1a: R=H
1b: R=*n*-C_4H_9
1c: R=*n*-C_8H_{17}
1d: R=*n*-$C_{12}H_{25}$
1e: R=*n*-$C_{16}H_{33}$



2a: R=H
2b: R=*n*-C_4H_9
2c: R=*n*-C_8H_{17}
2d: R=*n*-$C_{12}H_{25}$
2e: R=*n*-$C_{16}H_{33}$
2f: R=*n*-$C_{18}H_{37}$
2g: R=*n*-$C_{22}H_{45}$

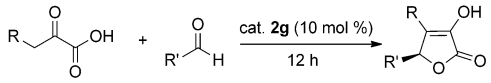
Entry	Catalyst	*t* [h]	Conversion [%][b]	*ee* [%][c]
1	**1a**	12	20	30
2	**1b**	12	49	29
3	**1c**	12	55	27
4	**1d**	12	61	2
5	**1e**	12	79	60
6	**2a**	144	8	64
7	**2b**	12	7	41
8	**2c**	12	81	89
9	**2d**	12	76	89
10	**2e**	12	86	85
11	**2f**	12	86	94
12	**2g**	12	91	95
13	**2g**	24	95	94
14[d]	**2g**	12	77	97
15[e]	**2g**	12	65	98
16	**2g**[f]	12	77	96
17	**2g**[g]	12	52	95

[a] Unless otherwise noted, the reaction was conducted with 0.75 mmol of benzaldehyde and 0.25 mmol of α-ketobutyric acid in 0.5 mL water at 25 °C. [b] Conversion was determined by ^{1}H NMR spectroscopy. [c] The *ee* value was determined by HPLC analysis (see the Supporting Information). [d] Reaction performed at 15 °C. [e] 5 °C. [f] Reaction performed using 5 mol% of **2g**. [g] 1 mol% of **2g**.

worth noting that the reaction systems catalyzed by **1c–e** are in metastable emulsion states. The obviously different enantioselectivities achieved by **1c–e** implied that the catalysts bearing hydrophobic tails of different lengths might supply a different microenvironment on the surface of the emulsion droplets for the reactions and strongly affect the stereoselectivity. The primary results encouraged us to test the series of catalyst **2a–g**, having an imidazole motif, for the title reaction. The reaction was sluggish using **2a**, as only 8% substrate conversion was achieved after six days, however the corresponding product was obtained with moderate enantioselectivity (entry 6). The catalyst **2b** having a C_4 hydrophobic tail also displayed unsatisfactory reactivity and enantioselectivity (entry 7). Gratifyingly, the amphiphilic catalyst **2c** carrying a C_8 alkyl chain exhibited good catalytic performance, thus affording an 81% conversion and 89% *ee* in 12 hours (entry 8). Furthermore, an O/W emulsion emerged in the reaction system after the reactants and the catalyst were added and stirred in water. Encouraged by this result, the catalysts with longer alkyl side chains (**2d–g**) were also investigated in the reaction of **3a** and **4a**. In these cases, the emulsions were always formed in the reaction systems and the reactions proceeded smoothly. To our great delight, the asymmetric reaction catalyzed by **2f** bearing a C_{18} alkyl chain proceeded rapidly to give the corresponding isotetronic acid with a notable improvement of the *ee* value of up to 94% (entry 11). A further enhanced result (91% conversion, 95% *ee*) was obtained by using the catalyst **2g** having an even longer alkyl chain (C_{22}, entry 12). By prolonging the reaction time to 24 hours, **2g** afforded a conversion of 95% and enantioselectivity of 94% (entry 13). By lowering the reaction temperature to 5 °C, the **2g**-catalyzed reaction of **3a** to **4a** generated the corresponding product in 98% *ee* (entry 15). To further explore the efficiency of the catalyst **2g**, the model reaction was carried out with a reduced catalyst loading (1 mol%), thereby affording **5a** with a 52% conversion with the enantioselectivity as high as 95% (entry 17).

After optimizing the reaction conditions, we explored the generality of the catalytic emulsion system for the asymmetric cascade reaction. We were pleased to find that the high efficiency of **2g** could be extended to the reaction of α-ketoacids with different aldehydes under emulsion conditions. As listed in Table 2, variation of the substituent at different positions of the phenyl moiety of the aldehyde has little impact on the enantioselectivity of the reaction (entries 1–3). Various substituted benzaldehydes (**4e–i**) reacted with α-ketobutyric acid using the catalyst **2g**, and all show high enantioselectivities (95–99% *ee*; entries 5–9). Moreover, the reaction of α-ketobutyric acid with thiophene-2-carbaldehyde also provides **5j** with satisfactory results (entry 10). To our delight, aliphatic aldehydes were also amenable to the reaction protocol, thus giving rise to desired products with

Table 2: The cascade reaction of **3** and **4** catalyzed by **2g**.[a]



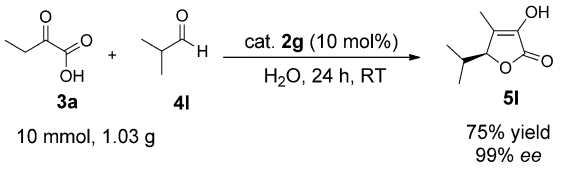
3 (1.0 mmol) **4** (3.0 mmol) **5**

Entry	R	R′	Yield [%][b]	*ee* [%][c]
1	Me	Ph	86	95 (**5a**)
2[e]	Me	2-ClC_6H_4	91	97 (**5b**)
3	Me	3-ClC_6H_4	80	98 (**5c**)
4[e]	Me	4-ClC_6H_4	83	95 (**5d**)
5[e,f]	Me	4-BrC_6H_4	85	96 (**5e**)
6	Me	4-FC_6H_4	86	95 (**5f**)
7	Me	4-$CF_3C_6H_4$	92	97 (**5g**)
8[e]	Me	4-$NO_2C_6H_4$	94	98 (**5h**)
9[f]	Me	4-$CH_3C_6H_4$	94	95[d] (**5i**)
10[f]	Me	2-thiophenyl	83	93 (**5j**)
11[f]	Me	cyclohexyl	75	98 (**5k**)
12[f]	Me	*i*Pr	82	99 (**5l**)
13	Et	3-ClC_6H_4	87	89(**5m**)
14	Et	4-$CF_3C_6H_4$	90	95 (**5n**)
15[f]	Ph	*i*Pr	82	93 (**5o**)

[a] Unless noted otherwise, the reaction was conducted with 3 mmol of **4** and 1.0 mmol of **3** in 2 mL water at 25 °C. [b] Yield of product isolated after the one-step protection by *t*$BuMe_2SiCl$ (see the Supporting Information), because **5** is unstable to column chromatography and results in a loss of yield. [c] The *ee* value was determined by HPLC analysis (see the Supporting Information). [d] Absolute configuration of **5i** was determined to be *S*; for details, see the Supporting Information. [e] 5 mmol $CHCl_3$ were added to dissolve the solid aldehydes. [f] Reaction time: 24 h.

enantioselectivities up to 99% *ee* (entries 11 and 12). Notably, the reaction could also be realized by using different donors. For examples, both α-ketopentanoic acid and α-ketophenylpropanoic acid could be employed in the reaction, to provide the products **5n** and **5o**, respectively, with high yields and *ee* values (entries 13–15).

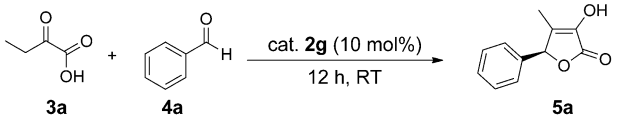
To demonstrate the synthetic potential of the method, the reaction of **3a** and **4l** was carried out on a gram scale in water under optimized reaction conditions with **2g**. The corresponding product **5l**, a food flavoring agent,[1e] was obtained in 75% yield and with 99% *ee* (Scheme 2).



Scheme 2. Asymmetric catalytic synthesis of food flavoring agent on the gram scale using an emulsion catalyst.

To determine the role water plays in the reaction, control experiments were performed for the reactions of **3a** and **4a** with **2g** using dry chloroform as the solvent or solvent-free conditions. Both cases gave much lower reactivities and enantioselectivities compared to using water as the solvent, thus suggesting that hydrated ions generated from α-ketoacid in water is crucial for both the reactivity and stereoselectivity of the reaction. To further study the effect of water, the reactions were performed using chloroform with small amount of water (5 equiv to **3a**). The fact that the enantioselectivity is significantly improved suggests that water plays an important role in inducing enantioselectivity. As increasing the proportion of water, emulsion state can be formed and the activity and stereoselectivity are enhanced significantly. The reactions using methanol or a methanol/water mixture as solvents were also performed (Scheme 3 and see Table S1 in the Supporting Information). Similarly, the highest reactivity and stereoselectivity were provided in the emulsion state.

To confirm that the reaction takes place on the surface of the emulsion droplets, the catalysts **2a** and **2g** in the reaction solution were imaged by fluorescence spectroscopy (see the Supporting Information). As shown in Figure 1, the catalyst



anhydrous $CHCl_3$	(homogeneous)	18% conv.	75% *ee*
$CHCl_3$ + H_2O (5.0 equiv)		30% conv.	89% *ee*
H_2O + $CHCl_3$ (5.0 equiv)	(emulsion)	72% conv.	92% *ee*
MeOH	(homogeneous)	9% conv.	90% *ee*
H_2O + MeOH (5.0 equiv)	(emulsion)	88% conv.	96% *ee*
H_2O	(emulsion)	91% conv.	95% *ee*
neat conditions		42% conv.	67% *ee*

Scheme 3. The cascade reaction of **3a** and **4a** catalyzed by **2g** in different solvents.

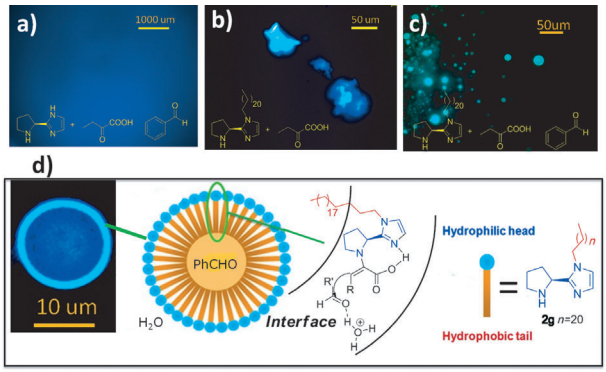


Figure 1. Fluorescence microscope images of a) reaction mixtures of **4a** (0.75 mmol) and **3a** (0.25 mmol) in 2 mL H_2O with 0.025 mmol **2a**, b) **2g** (0.025 mmol) combined with α-ketobutyric acid **3a** (0.25 mmol) dispersed in water, c) **4a** (0.75 mmol) added to system b). d) Enlarged images of emulsion droplets and the emulsion reaction model.

2a in combination with α-ketobutyric acid (**3a**) is water-soluble, and the stained aqueous phase is observed in the reaction medium. In contrast to **2a**, **2g** in combination with **3a** generated an ion pair which can be dispersed in water in an aggregated state at the micron scale (Figure 1b). When benzaldehyde was added into the above mixture and stirred for a few minutes, the emulsion was formed and bright-blue, circular-shaped fluorescent domains, emitted from amphiphilic catalyst **2g**, are clearly detected by fluorescence microscopy, thus indicating that the catalyst is mainly distributed at the interface of the emulsion droplets. Accordingly, it is proposed that the active sites of this asymmetric reaction might be on the surface of emulsion droplets (Figures 1c–d).

In terms of the control experiment and fluorescence imaging of the emulsion droplet, a possible reaction model is proposed. As shown in Figure 1d, at the surface of emulsion droplets the nucleophile α-ketoacid was activated by the amphiphilic catalyst through enamine formation[16] and acid–base interactions,[17] while the interfacial hydrated ion generated from α-ketoacids in water activated the aldehyde electrophile. Presumably, the microenvironment of the emulsion droplets allows a more efficient activation of the electrophile by the aqueous phase, while exposing the reactive ends of the amine catalyst to the aqueous phase. This leads to an effectively higher concentration of the reactants, which could explain the observed improvements in both yield as well as the enantioselectivity of the reactions.

In summary, we have synthesized a class of novel amphiphilic organocatalysts for the cascade reaction of α-ketoacids to aldehydes using water as the solvent. Under the optimized reaction conditions, various functionalized isotetronic acids were obtained with high yields (up to 94%) and excellent *ee* values (up to 99%). Both water and emulsion states were found to be crucial for achieving the high reactivity and stereoselectivity. It was also determined that the catalyst molecules are distributed mainly on the surface of the emulsion droplets according to the direct fluorescence image of the reaction system.

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