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Water enables an asymmetric cross reaction of α-keto acids with α-keto esters for the synthesis of quaternary isotetronic acids†

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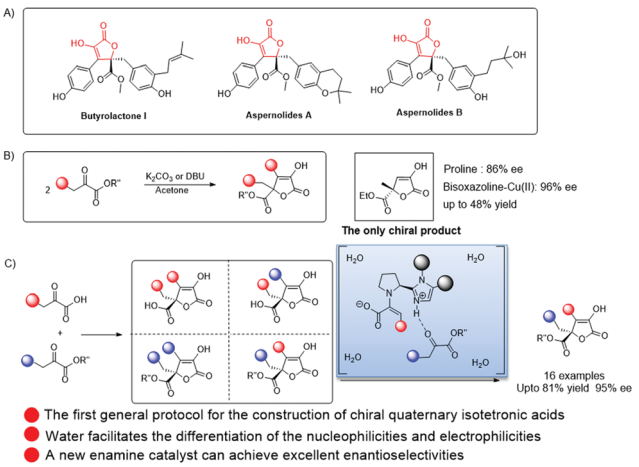
A water promoted asymmetric aldol/lactonization/enolization cascade reaction of α-keto acids and α-keto esters was developed, affording the first general protocol for the construction of chiral quaternary isotetronic acids with excellent enantioselectivity. Theoretical results indicate that intramolecular ionized enamine intermediates stabilized by water generate zwitterionic transition states in a lower activation energy and higher face selectivity, resulting in high activity and chemo- and enantioselectivity.

Isotetronic acids are a class of butenolides prevailing in numerous natural products,[1] pharmaceuticals,[2] flavouring agents and perfumes.[3] In particular, isotetronic acids with quaternary carbon centers (QC-isotetronic acids) bearing an ester moiety and an alkyl substituent exhibit excellent bioactivities.[4] For example, butyrolactone **I**,[2b] natural product isolated from *Aspergillus terreus* var. *africanus* IFO 8835 in 1977, has been found to be a specific inhibitor of cdk1/cyclin B and cdk2/cyclin A, exhibiting good antiproliferative activity against colon and pancreatic carcinoma, human lung cancer and prostatic cancer cell lines. Aspernolide **A**,[2c] isolated from the fermentation broth of a soft coral derived fungus *Aspergillus terreus* in 2009, has been proved to possess mild cytotoxicity against cancer cell lines in primary tests (Scheme 1A). Thus, the development of a general and stereoselective approach for the synthesis of this structural motif would be greatly helpful for biological studies of this type of butenolide. However, to our knowledge, such a methodology has not yet been established. So far, the QC-isotetronic acids for bioactivity studies have mainly come from isolated natural products and homo QC-isotetronic acids (only one chiral homo QC-isotetronic acid has been synthesized by the enantioselective homo-aldol reaction of pyruvates with bisoxazoline-Cu(II) or proline) (Scheme 1B).[5]



Scheme 1 (A) Representative natural QC-isotetronic acids. (B) The reported homo reaction of α-keto esters. (C) This work: polarity effect of water enables an asymmetric cross addition of α-keto acids to α-keto esters by stabilizing the ionized intermediate.

Inspired by the success of the asymmetric aldol reaction of α-keto acids with aldehydes,[6] we envisioned that QC-isotetronic acids can be accessed *via* a cross reaction of alkyl-substituted α-keto acids **1** with α-keto esters **2**. However, there has been no report on this reaction even in the racemic version, due to the fact that alkyl-substituted α-keto acids **1** and α-keto esters **2** can in principle serve as either nucleophiles or electrophiles with respect to their roles in the reaction (Scheme 1C).[7] Therefore, differentiating the nucleophilicity and electrophilicity[8] of alkyl-substituted α-keto acids and α-keto esters is the key to achieve the synthesis of QC-isotetronic acids.

Here we found that water collaborating with a new enamine[9] catalyst can differentiate the nucleophilicities and electrophilicities of alkyl substituted α-keto acids and α-keto esters (Scheme 1C). This finding encouraged us to develop a new asymmetric cross-aldol/lactonization/enolization cascade reaction, affording a wide

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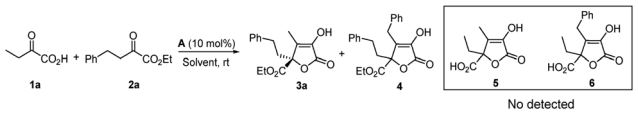
Table 1 Effect of water[a]



Entry	Solvent	Conv.[b] (%)	3a/4[b]	ee[c] (%)
1	CH_2Cl_2	8	1.5 : 1	32
2	$H_2O : CH_2Cl_2$ = 1 : 1	21	5 : 1	Nd
3	$H_2O : CH_2Cl_2$ = 2 : 1	28	6 : 1	Nd
4	$H_2O : CH_2Cl_2$ = 5 : 1	52	11 : 1	Nd
5	$H_2O : CH_2Cl_2$ = 10 : 1	64	>15 : 1	41
6	H_2O	76	>15 : 1	41
7	DMSO	<5	Nd	Nd
8	DMF	<5	Nd	Nd
9	Tol	<5	Nd	Nd
10	THF	<5	Nd	Nd

[a] Unless noted otherwise, reactions were performed with **1a** (0.3 mmol), **2a** (0.1 mmol), and **A** (10 mol%) in 0.5 mL solvent at rt for 3 days. [b] Determined by ^{1}H NMR spectroscopy of the crude mixture. [c] Determined by chiral HPLC analysis; Nd = not determined.

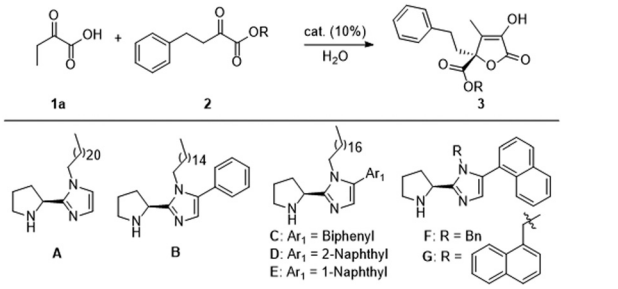
range of QC-isotetronic acids with good to excellent enantioselectivities (up to 95% ee). Moreover, water as the reaction medium[10] was demonstrated to be crucial for increasing activity and enantioselectivity. DFT calculations indicate that the high polarity of water stabilizes intramolecular ionized enamine intermediates which generate zwitterionic transition states in a lower activation energy and higher face selectivity, resulting in enhanced activity and chemo- and enantioselectivity.

We chose α-keto butyric acid **1a** and α-keto ester **2a** as the model substrates to commence our study. In view of its high efficiency in promoting the aldol reactions of α-keto acid **1a** with aldehydes, amphiphilic proline-derived imidazole **A** was first tested in the cascade reaction. The reactions were conducted at room temperature, and the results are summarized in Table 1. The reaction catalyzed by **A** in dichloromethane afforded cross QC-isotetronic acid **3a** and homo QC-isotetronic acids **4** with a ratio of about 1.5 : 1 (Table 1, entry 1), albeit plagued by a low conversion. It was surprising to find that the potential cross- and homo-aldol products **5** and **6**, which would otherwise be generated with α-keto acid **1a** as the electrophile, could not be detected. These results suggest that despite the higher loading of α-keto acid **1a** (3 molar equiv.), α-keto ester **2a** reacts as the only effective aldol acceptor in this reaction under this specific catalytic system. Given the amphiphilic nature of the secondary amine catalyst, water was subsequently examined as the co-solvent for the reaction system. The reaction in the $CH_2Cl_2 : H_2O$ = 1 : 1 mixture gave 21% conversion and the desired product **3a** was obtained with a significantly enhanced chemoselectivity (**3a/4** = 5/1). Further increasing the proportion of water led to a steady improvement in both reactivity and chemoselectivity (Table 1, entries 2–6). It was surprising to find that **3a** was found as the sole product in 76% conversion and 41% ee for the reaction carried out in pure water (Table 1, entry 6). It is worth noting that other solvents, such as DMSO, DMF, toluene and THF, could not afford the corresponding product for this cascade reaction (Table 1, entries 7–10).

The high chemoselectivity of the cascade reaction of **1a** with **2a** in water encouraged us to perform further optimizations of the reaction parameters for synthetically useful enantioselectivity. A series of new chiral pyrrolidine-imidazoles with different substituents at the 5- and/or N-position of the imidazole ring (**B–G**) were synthesized (see the ESI†). Evaluation of this type of amine catalyst in the reaction of **1a** with **2a** in water indicated that while the chemoselectivity remains high for each catalyst, the stereoselectivity of product **3** relied heavily on substituents at the 5-postion of the imidazole ring (Table 2, entries 1–5). The asymmetric reaction catalyzed by **E** bearing 1-naphthyl proceeded smoothly to give the corresponding QC-isotetronic acid with a notable improvement of the ee value up to 70% (Table 2, entry 5). A slightly enhanced result (73% ee) was obtained by using catalyst **G** with the 1-naphthylmethylene substituent on N1 of the imidazole ring (Table 2, entry 7). The effects of the ester group (COOR) in the α-keto ester **2** were then investigated. It was found that the steric bulkiness of ester groups has a significant effect on the enantioselectivity. For example, comparative enantioselectivities could be obtained for the reaction of **1a** with **2a** or **2b** as an electrophile, respectively (Table 2, entries 7 and 8). On the other hand, use of oxobutanoate **2c** bearing a bulkier *tert*-butyl group on its ester moiety led to an increase in enantioselectivity, and the corresponding cross aldol product **3c** was obtained with 91% ee without the loss of reactivity (Table 2, entries 9 and 10).

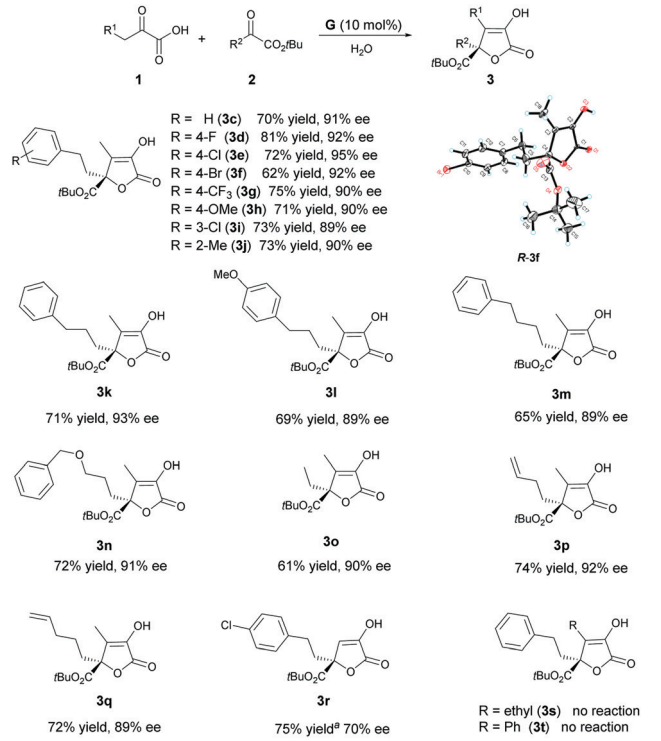
Using **G** as the catalyst, the substrate scope was then investigated with respect to both α-keto acids **1** and α-keto esters **2** (Scheme 2). Gratifyingly, all the reactions proceeded cleanly under optimized conditions, providing the corresponding QC-isotetronic acids **3** in good yields and high enantioselectivities. A series of

Table 2 Evaluation of reaction conditions[a]



Entry	R	Product	Catalyst	Conv.[b] (%)	ee[c] (%)
1	Et(**2a**)	**3a**	**A**	76	41
2	Et(**2a**)	**3a**	**B**	81	54
3[d]	Et(**2a**)	**3a**	**C**	77	63
4[d]	Et(**2a**)	**3a**	**D**	73	58
5[d]	Et(**2a**)	**3a**	**E**	70	70
6[d]	Et(**2a**)	**3a**	**F**	72	72
7[d]	Et(**2a**)	**3a**	**G**	79	73
8[d]	Me(**2b**)	**3b**	**G**	81	65
9[d]	*t*Bu(**2c**)	**3c**	**G**	78	91
10[d,e]	*t*Bu(**2c**)	**3c**	**G**	90	91
11[e,f]	*t*Bu(**2c**)	**3c**	**G**	Trace	Nd

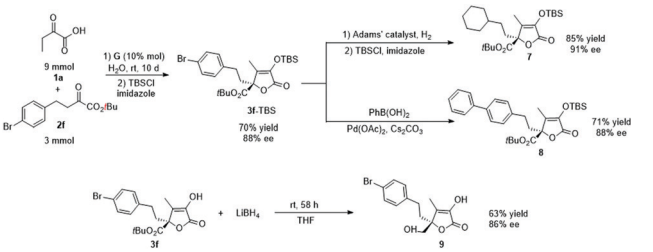
[a] Unless noted otherwise, reactions were performed with **1a** (0.3 mmol), **2a** (0.1 mmol), and cat. (10 mol%) in 0.5 mL H_2O at rt for 3 days; in all cases **3a/4** >15 : 1 as determined by crude ^{1}H NMR analysis. [b] Determined by ^{1}H NMR spectroscopy of crude mixture. [c] Determined by chiral stationary phase HPLC analysis. [d] With few drops of CH_2Cl_2 to dissolve substrates. [e] Reaction time: 5 days. [f] Using CH_2Cl_2 as solvent.



Scheme 2 Substrate scope. Unless noted otherwise, the reaction was conducted with **1** (1.2 mmol), **2** (0.4 mmol) and **G** (10 mol%) in 2 mL H_2O (100 μL CH_2Cl_2 was added to dissolve the substrates) at rt for 4–5 days. Because **3** is unstable on silica gel column chromatography, yields for all products are based on the isolated derivatives after protection by TBS, and ee values were determined by chiral stationary phase HPLC analysis (see the ESI†). [a] Reaction performed with pyruvic acid (5 mmol), **2** (1 mmol) and **G** (0.1 mmol) in H_2O (2 mL) for 10 days.

tert-butyl 2-oxo-4-aryl-substituted butanoates were investigated and the corresponding products with 62–81% yield and 89–95% ee were obtained irrespective of the electronic nature or the substitution pattern on the phenyl rings (**3c–3j**). The reaction also tolerated longer and shorter alkyl chains for the substituted α-keto esters, providing adducts **3k–n** with high enantioselectivity. Additionally, the reaction of **1a** with α-keto esters bearing a benzyl protected alcohol (**2n**) or a vinyl group (**2p–q**) also gave excellent results. Pyruvic acid was also tolerated as a nucleophile providing QC-isotetronic acid **3r** with a synthetically useful yield but with a slightly lower ee value. However, either 3-phenylpyruvic acid or 2-oxopentanoic acid could not be successfully coupled with α-keto ester **2c** under standard reaction conditions probably due to the steric hindrance (**3s–t**). The absolute configuration of **3f** was determined to be *R* by X-ray crystallographic analysis, and those of other QC-isotetronic acid products were assigned by analogy.

The synthetic utility of this method was demonstrated in several efficient transformations using **3f** as the starting material. The enantioenriched **3f** was obtained from the gram-scale reaction using the above procedure with **G** as the catalyst (Scheme 3). Treatment of **3f**-TBS with Adams' catalyst under a high pressure hydrogen atmosphere, followed by the protection with the TBS group, unexpectedly delivered the debrominated hydrogenation product **7** in high yield and without loss of enantiopurity.



Scheme 3 Synthetic transformations of **3**.

This result indicated that the ring of isotetronic acid possesses good stability. Moreover, the structural motif of isotetronic acid can also tolerate the Pd(II) catalyst, which was demonstrated by the Suzuki coupling of **3f**-TBS with phenylboronic acid, leading to the corresponding product **8** in 71% yield and 88% ee. Chiral QC-isotetronic acid linked to two different alkyl-substituted groups **9** was easily obtained by treatment of **3f** with $LiBH_4$, indicating that the present cascade reaction could be a useful platform for the synthesis of this type of compound that was otherwise difficult to access.

To improve our understanding of the mechanism and figure out the role played by water in this reaction, density functional theory (DFT) calculations for the key step-aldol reaction in the cascade reaction were carried out (see the ESI† for more details). Firstly, two plausible intermediates were obtained through the full optimization of geometries, which suggested that the intermediate with neutral form (Int-**I**) may dominate in dichloromethane and the intermediate with zwitterionic form (Int-**II**) may dominate in water. The corresponding transition states from these two intermediates were calculated. It was found that the transition state from Int-**I** had high activation barriers (TS-**I**-*R*, 31.1 kcal mol^{-1}; TS-**I**-*S*, 31.7 kcal mol^{-1}) and a relatively small energy difference (0.6 kcal mol^{-1}), which suggests that the asymmetric aldol reaction of **1a** and **2a** catalyzed by **G** in dichloromethane should have low reactivity and poor enantioselectivity. On the other hand, TS-**II** from the water-stabilized intermediate Int-**II** has lower activation energies (TS-**II**-*R*, 22.5 kcal mol^{-1}; TS-**II**-*S*, 26.8 kcal mol^{-1}). Moreover, Int-**II** prefers to attack **2a** from the *Re* face because of the steric hindrance between the ester group and imidazole ring, thus showing higher energy difference between TS-**II**-*R* and TS-**II**-*S* (4.3 kcal mol^{-1}). These calculated results suggest that the asymmetric reaction of **1a** with **2a** should exhibit higher reactivity and enantioselectivity in the presence of water which agrees well with the experimental results.

In conclusion, we discovered that a new class of bulky proline-imidazole amphiphilic organocatalysts collaborating with water shows a unique ability to differentiate the nucleophilicity between enolizable α-keto acids **1** and α-keto esters **2**. This protocol allows a new asymmetric catalytic cascade reaction of α-keto acids **1** with α-keto esters **2**, providing a fundamentally new approach towards chiral QC-isotetronic acids with excellent ees (up to 95%). DFT calculations have revealed that compared with the non-ionized transition state in dichloromethane, the zwitterionic enamine intermediate may be formed owing to the

high polarity of water. The corresponding transition state shows a lower activation energy and higher face selectivity, which may be responsible for the high activity and chemo- and enantioselectivity.

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Conflicts of interest

There are no conflicts to declare.

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