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# Bifunctional organocatalyst-catalyzed dynamic kinetic resolution of hemiketals for synthesis of chiral ketals *via* hydrogen bonding control

Meng Shan, Yongmei Yu, Mengli Sun, Shuping Yang, Mengqi Wang, Bo Zhu*, Junbiao Chang*

*State Key Laboratory of Antiviral Drugs, Pingyuan Laboratory, NMPA Key Laboratory for Research and Evaluation of Innovative Drug, School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang 453007, China*

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ABSTRACT

Herein, we report the dynamic kinetic resolution asymmetric acylation of $\gamma$-hydroxy-$\gamma$-perfluoroalkyl butenolides/phthalides catalyzed by amino acid-derived bifunctional organocatalysts, and a series of ketals were obtained in high yields (up to 95%) and excellent enantioselectivities (up to 99%). In terms of synthetic utility, the reaction can be performed on a gram scale, and the product can be converted into potential biological nucleoside analog.



Enantiomerically enriched ketal structures bearing quaternary stereocenter is highly sought-after in the field of drug discovery and development due to their prevalence in bioactive molecules and natural products [1]. Many potential drugs, such as Obtusin [2], Eudesmanolides [3], dioxole derivatives [4], Ossamycin [5], Fimbricalyxlactones [6], and Preussomerin K [7], contain this important structural unit. As one of the most attractive precursor, $\gamma$-hydroxy butenolides [8] have found widespread applications in organic synthesis, materials science, and medicinal chemistry [9]. They also serve as valuable intermediates for synthesizing complex molecules [10]. Additionally, they can be modified into five-carbon sugar analogs [11], and be made into ideal drug carriers for targeted delivery and controlled release of therapeutic agents [12]. However, asymmetric synthesis of cyclic ketal compounds with quaternary stereocenter is a challenging task due to the difficulty in controlling stereochemistry and activity during the reaction [13,14].

Dynamic kinetic resolution (DKR) [15–18], employing various catalysts including biological enzymes [19], chiral DMAPs [20,21], carbenes [22], and imidazoles [23], is an effective approach for studying the enantioselective acylation of hemiacetals. In 1995, Kellogg and Feringa demonstrated that lipase R immobilized on Hyflo Super Cell could catalyze the conversion of 5-hydroxy-5*H*-furan-2-one to acetic acid 5-oxo-2,5-dihydrofuran-2-yl ester at ambient temperature by acylation with vinyl acetate (Scheme 1a) [19]. In recent years, the iterative development of organocatalysts [24] has significantly advanced the asymmetric acylation of cyclic hemiacetals. In 2008, Yamada and coworkers reported the catalytic DKR of hemiacetal using a chiral dimethylaminopyridine (DMAP) catalyst (Scheme 1b, left) [20,21]. In 2019, Chi and coworkers developed a new catalytic DKR strategy for the asymmetric acylation of hydroxyphthalides using a chiral acyl azolium intermediate derived from a carbene catalyst (Scheme 1b, middle) [22]. Very recently, Zhang's group reported a new method for synthesizing chiral phthalidyl ester prodrugs using a chiral bicyclic imidazole organocatalyst and a continuous injection process (Scheme 1b, right) [23]. These elegant examples are mostly based on the asymmetric acylation reaction of hemiacetals with tertiary stereocenter. So far, the asymmetric acylation of hemiketal compounds containing quaternary stereocenter based on DKR remains challenges. First, the existence of steric hindrance [25] often limits the conversion of hemiketals to chiral ketals. Second, the unstable intermediate formed in this reaction can undergo external aggregation [26]. Third, hemiketal compounds bearing quaternary stereocenter have low activity and are not easily racemized [27].

Enzymes exhibit a high degree of specificity towards their substrates [28]. The successful enzymatic catalysis of DKR [19] has provided insight into our development a new strategy for the asymmetric transformation of hemiketals to chiral ketals. Based on our previous work [29,30], we hypothesize to use the enzyme-like

* Corresponding authors.
*E-mail addresses:* zbtiantang@126.com (B. Zhu), changjunbiao@zzu.edu.cn (J. Chang).

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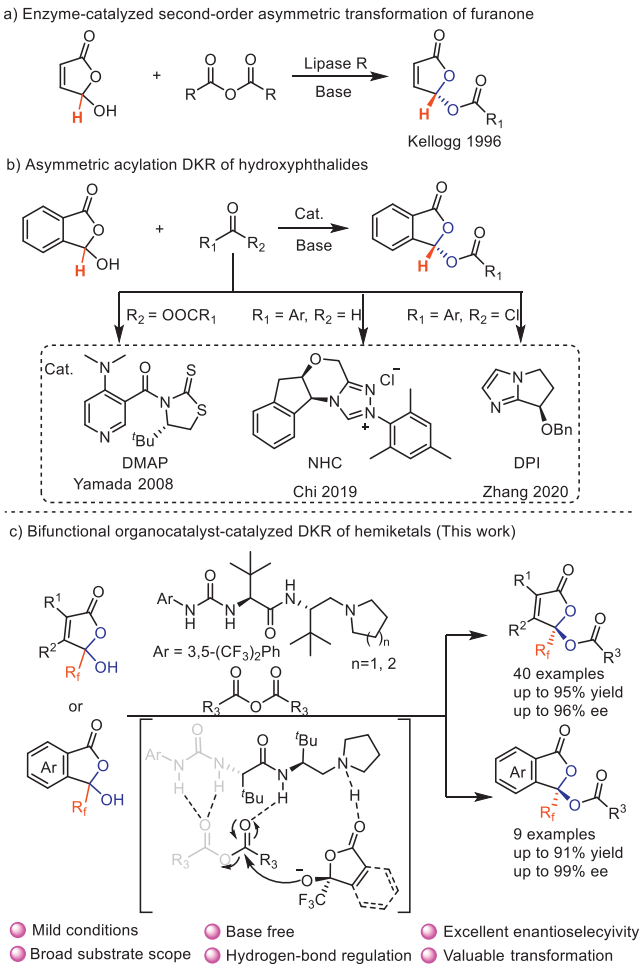
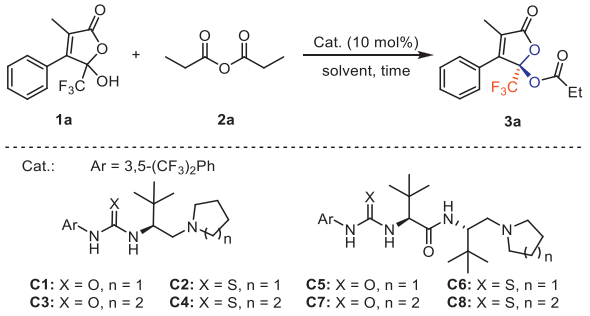



**Scheme 1.** Asymmetric DKR acylation of hemiacetals and hemiketals.

properties of amino acid-derived bifunctional organocatalyst for chiral recognition of the hemiketals. At the same time, enantiomer of the hemiketals that are difficult to recognize will undergo rapid racemization. This idea may contribute to the efficient DKR conversion of hemiketals. Rationally, we propose that the bifunctional organocatalyst first recognizes the (*S*)-enantiomer of the hemiketal through binding to the $R_3NH^+$ ammonium group and through hydrogen-bond interactions with the hemiketal substrate. Then, the rapid racemization of the unrecognized (*R*)-enantiomer facilitates smooth DKR. Therefore, we have developed a novel strategy for the DKR asymmetric acylation of $\gamma$-hydroxy-$\gamma$-perfluoroalkyl butenolides [31]/phthalides under mild conditions. The process utilizes a bifunctional organocatalyst derived from amino acids as the catalysts for substrates chiral recognition, and does not require the addition of other bases (Scheme 1c). The transformation of hemiketals into chiral ketals occurs *via* hydrogen-bond regulation.

Initially, the DKR reaction of the hemiketal **1a** with acid anhydrides **2b** was selected as the model reaction (Table 1). Preliminarily, the desired hemiketal acylation product **3a** was obtained using 10 mol% of the L-*tert*-leucine derived urea-tertiary amine bifunctional catalyst **C1** in toluene at 25 °C. Despite its moderate (63%) yield, it provided an ordinary (45%) enantioselective result (Table 1, entry 1). This result indicates that the hydrogen-bond donors and acceptor of urea and tertiary amine functional groups are suitable for the asymmetric DKR system of hemiketals, and it also confirms our speculation that bifunctional organocatalyst are capable of catalyzing such DKR reaction. Then L-*tert*-leucine-derived thiourea-tertiary amine bifunctional catalyst **C2** afforded the corresponding product **3a** in 42% yield with 21% *ee* (Table 1, entry 2). When the five-membered ring of the tertiary amine on the catalyst was replaced by a six-membered ring **C3**-**C4**, the expected yield and enantioselectivity were not obtained (entries 3 and 4). To further improve the yield and enantioselectivity, we attempted to increase the hydrogen-bond of the bifunctional organocatalyst L-*tert*-leucine-derived bifunctional organocatalyst **C5**-**C8** (entries 5–8), containing multiple hydrogen-bond donors and tertiary amine, were screened for their catalytic activity in toluene at room temperature for 96 h. It was found that the L-*tert*-leucine derived urea-tertiary amine catalyst **C7** improved both the yield and enantioselectivity (Table 1, entry 7; 72% yield, 90% *ee*). Accordingly, we selected **C7** as the catalyst to screen solvent (entries 9–13, see Supporting information for details). The solvent cyclopentyl methyl ether (CPME) provided product **3a** in 75% yield with 95% *ee* (entry 13). To further increase the yield of the reaction (entries 14–16, see Supporting information for more details), it was discovered that incorporating 5Å MS (molecular sieves) as an additive significantly improved the activity of the reaction. This resulted in the formation of **3a** in 93% yield with 94% *ee* (entry 16).

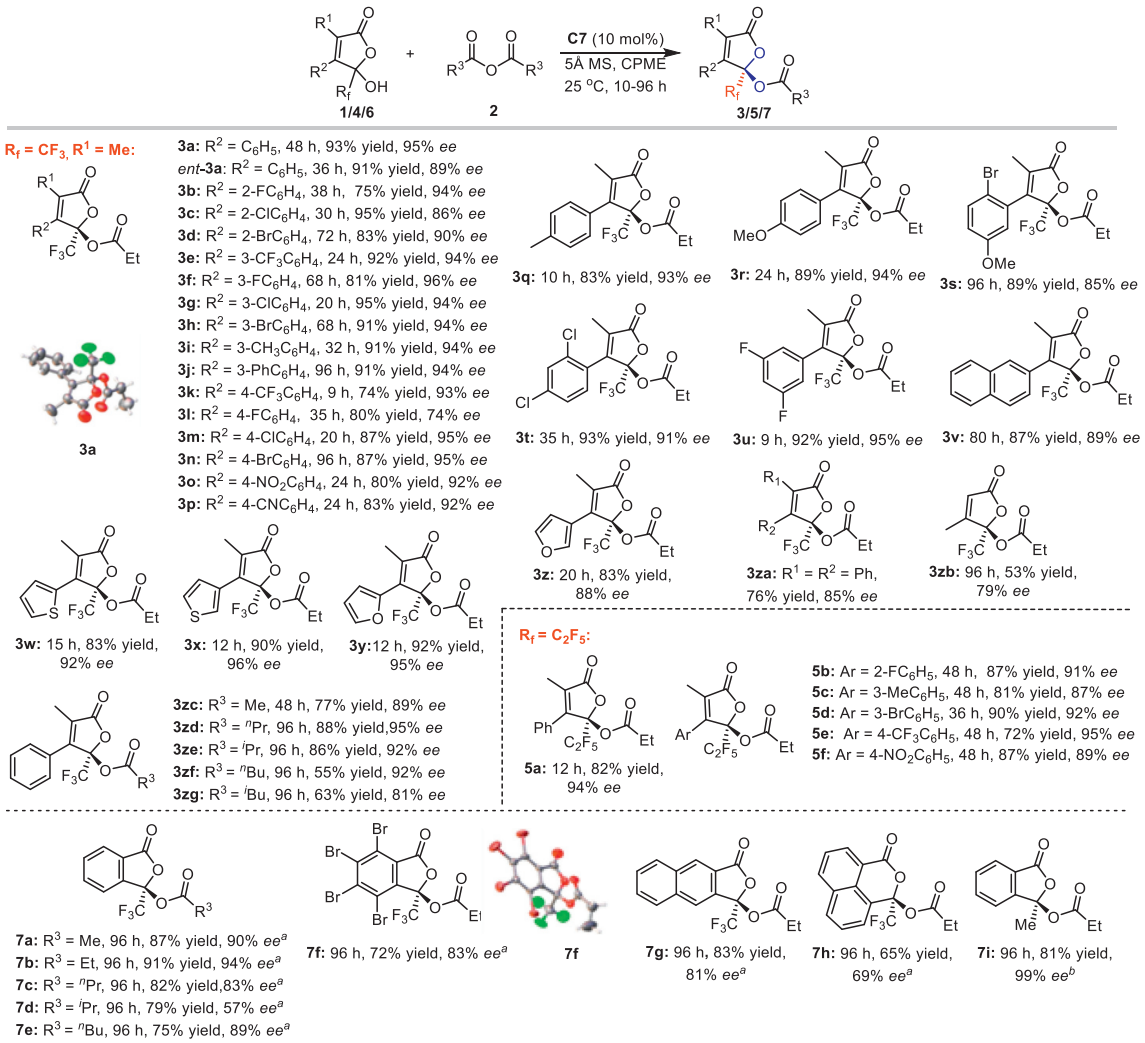
**Table 1**
Optimization of reaction conditions.[a]




| Entry | Catalyst | Solvent | Time (h)[b] | Additive | Yield (%)[c] | *ee* (%)[d] |
|---|---|---|---|---|---|---|
| 1 | **C1** | Toluene | 96 | – | 63 | 45 |
| 2 | **C2** | Toluene | 96 | – | 42 | 21 |
| 3 | **C3** | Toluene | 96 | – | 76 | 31 |
| 4 | **C4** | Toluene | 96 | – | 55 | 24 |
| 5 | **C5** | Toluene | 96 | – | 85 | 71 |
| 6 | **C6** | Toluene | 96 | – | 23 | 3 |
| 7 | **C7** | Toluene | 96 | – | 72 | 90 |
| 8 | **C8** | Toluene | 96 | – | 65 | 10 |
| 9 | **C7** | DCM | 96 | – | 53 | 74 |
| 10 | **C7** | THF | 96 | – | 48 | 74 |
| 11 | **C7** | MeCN | 96 | – | 68 | 40 |
| 12 | **C7** | $Et_2O$ | 96 | – | 32 | 91 |
| 13 | **C7** | CPME | 96 | – | 75 | 95 |
| 14 | **C7** | CPME | 48 | 3Å MS | 90 | 86 |
| 15 | **C7** | CPME | 48 | 4Å MS | 95 | 89 |
| 16 | **C7** | CPME | 48 | 5Å MS | 93 | 94 |

[a] Reaction conditions: **1a** (0.1 mmol), Cat. (0.01 mmol), **2a** (0.2 mmol), Additive (20 mg) and solvent (1.0 mL).
[b] Monitoring in different time periods.
[c] Yield of isolated product.
[d] Determined by HPLC analysis on a chiral stationary phase.

With the optimal reaction conditions in hand (Table 1, entry 16), a substrate screening was conducted to investigate the reactivity of various hemiketal **1** and acid anhydrides **2** combinations. As shown in Scheme 2, all substrates underwent smooth, resulting in the desired chiral ketal products in good yields with excellent enantioselectivities. The reaction tolerated neutral, electron-withdrawing, and electron-donating substituents at the *ortho*-, *meta*-, and *para*-positions on the aromatic ring of hemiketal **1**, affording the corresponding acylation product ketals **3a**-**3r** in 74%–95% yields with 74%–96% *ee* values. 2,5- and 3,5-disubstituted **1s**-**1u** gave the corresponding products **3s**-**3u** in 89%–93% yields

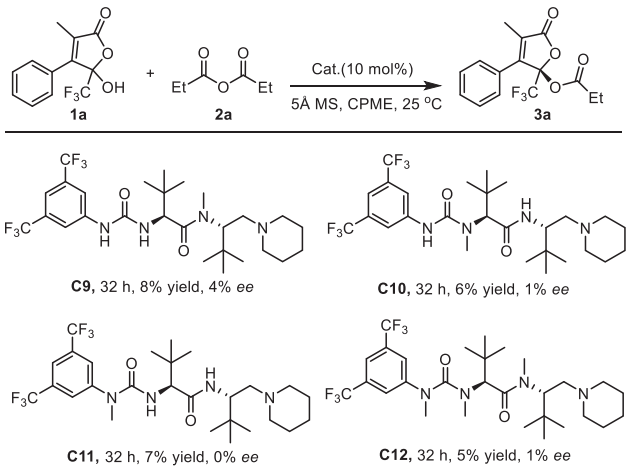



**Scheme 2.** Substrate scope of ketal products. Reaction conditions: **1** (0.1 mmol), **C7** (0.01 mmol), **2** (0.2 mmol), additive (20 mg) and solvent (1.0 mL). Yield of isolated product. Determined by HPLC analysis on a chiral stationary phase. [a] Reaction conditions: **6** (0.1 mmol), **C5** (0.01 mmol), **2** (0.2 mmol), additive (20 mg) and solvent (1.0 mL). Yield of isolated product. Determined by HPLC analysis on a chiral stationary phase. [b] **C5** (0.02 mmol), 60 °C.

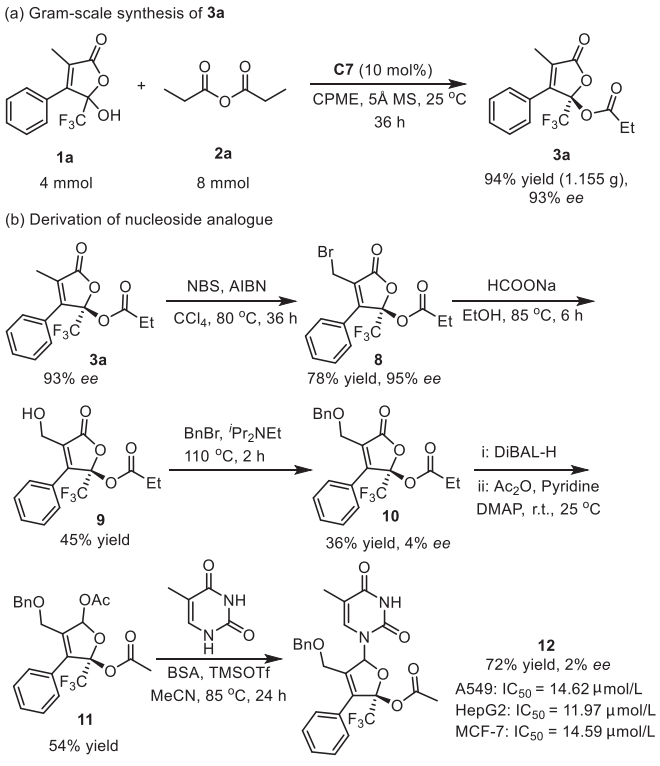
with 85%–95% *ee* values. 2-Naphthyl-substituted **1v** could afford **3v** in 87% yield with 89% *ee* within 80 h. Hemiketals bearing different thienyl and furyl substituents (2-thienyl **1w**, 3-thienyl **1x**, 2-furyl **1y** and 3-furyl **1z**) also showed good reactivities (83%–92% yields, 88%–96% *ee* values, **3w**–**3z**). Furthermore, we attempted to catalyze this reaction using the enantiomer of the catalyst under standard conditions, and successfully obtained the enantiomer of the chiral ketal *ent*-**3a** in 91% yield and 89% *ee*.

Subsequently, we investigated the substituents on the 3- or 4-position of the hemiketal moiety and found that the reaction proceeded smoothly. The product **3za**-**3zc** could still be obtained in 53%–77% yields with 79%–89% *ee*. On the other hand, acid anhydride **2** was also shown to have a broad range of applicability under standard conditions, with ketal products of **3zd**-**3zg** being obtainable in 55%–88% yields with 81%–95% *ee*. The absolute configurations of these adducts were assigned based on the crystal structure of **3a**, determined by single crystal *X*-ray diffraction analysis (CCDC: 2254748). In addition, Considering the importance of fluorine substituents in pharmaceutical chemistry [32], we also evaluated the effect of in 4-aryl-5-hydroxy-5-(pentafluoroethyl)furan-2(5*H*)-ones **4** with propionic anhydride **2a**. Subsequently, an investigation was conducted on the scope of substrate applicability. All reactions with substituents proceeded smoothly, and afforded the acylation products **5a**-**5f** in 72%–90% yields with 87%–95% *ee*. Based on previous asymmetric studies of hydroxyphthalides [20], we aim to challenge the DKR of 3-substituted hydroxyphthalides **6** to achieve asymmetric acylation reaction at the quaternary stereocenter (see Supporting information for more details). The anhydride was adjusted to acetic anhydride, propanoic anhydride, butyric anhydride, isobutyric anhydride, and *n*-valeric anhydride, respectively, and obtained the corresponding chiral products **7a**-**7e** in 75%–91% yields with 57%–94% *ee*. The results indicate that increasing the steric hindrance of the anhydride can affect the reaction activity. Changes in the substituents on the benzene ring can also lead to chiral products **7f** in 72% yields with 83% *ee*. Naphthyl group could also afford ketal product **7g** in 83% yield with 81% *ee* within 96 h. Furthermore, we attempted the DKR of a six-membered ring tetra-substituted hemiketal under standard reaction conditions, which resulted in the chiral ketal product **7h** in 65% yield with 69% *ee*. The absolute configurations of these adducts were assigned based on the crystal structure of **7f**, determined by single crystal X-ray diffraction analysis (CCDC: 2254753). Subsequent research focused on methylphenyl peptides and found that increasing temperature and using 20 mol% of **C5** resulted in 81% yield with 99% *ee*.

To further understand this reaction, we selectively performed the methylation experiment on the N–H bond and found that the catalyst **C9**-**C12** had a relatively large effect on the reaction




**Scheme 3.** The effect of hydrogen bonds in catalyst.




**Scheme 4.** Gram-scale and synthetic transformations.

(Scheme 3). The ketal **3a** was obtained in 5%–8% yield with 0–4% *ee*. It proves that the N–H bond was not only important for the activity, but also critical for the enantioselectivity. Subsequently, the reaction mixture of catalyst **C7** with hemiketals **1a** was investigated by using NMR. The analysis revealed an interaction between the pyridine nitrogen as a hydrogen bond acceptor and the hemiketal (see Supporting information for details).

$\gamma$-Hydroxy butenolides can be converted to corresponding five-carbon sugar analogues in the field of biochemistry. To further evaluate the synthetic potential of these asymmetric catalytic systems, we carried out a gram-scale synthesis using catalyst **C7** to synthesize chiral ketal **3a** from 5-hydroxy-3-methyl-4-phenyl-5-(trifluoromethyl)furan-2(5*H*)-one **1a** (4 mmol) and propionic anhydride **2b** (8 mmol). The desired product **3a** was produced in 94% yield (1.2 g) with 93% *ee* under standard conditions (Scheme 4a). Treatment of the chiral ketal **3a** with AIBN (2.0 equiv.), NBS (2.0 equiv) in $CCl_4$ at 80 °C resulted in the substitution occurring smoothly, and afforded the brominated product **8** in 78% yield with 95% *ee*. The hydrolysis of compound **8** in the presence of sodium formate successfully converted it into alcohol **9**, which could be directly benzylated to obtain the product **10** in 36% yield with 4% *ee*. Then a one-pot, two-step procedure involving selective reduction of the carbon group then yielded acetyl protected ketal **11**. Subsequent Vorbrîggen reaction with thymine furnished the nucleoside **12** in 72% yield with 2% *ee* (Scheme 4b). Nucleoside derivatives have shown significant activity in the fields of anti-tumor and anti-viral medicine [33–35]. Nucleoside analog **12** were evaluated for their cytotoxic activity against three human cancer cell lines (A549, HepG2, and MCF-7 cells) *in vitro* using the CCK-8 assay. $IC_{50}$ data analysis showed that compound **12** exhibited strong cytotoxicity against A549, HepG2, and MCF-7 cells, with $IC_{50}$ values of 14.62, 11.97, and 14.59 μmol/L, respectively. Therefore, such nucleoside analog may serve as potential anticancer agents and require further research.

In conclusion, we have established a DKR strategy for acylation reaction of hemiketals containing quaternary stereocenter through hydrogen-bond catalysis mode, and successfully achieved the transformation of hemiketals to chiral ketals. The chiral products can be applied to the synthesis of related valuable derivatives with good biological activity. This research has shown that the key to achieving such DKR reaction lies in the use of chiral bifunctional organocatalyst controlled by hydrogen-bond. Further exploration of practical synthesis of other valuable chiral building blocks is currently ongoing in our laboratory.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgments

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2024.109781.

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