OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

The Quinary Catalyst−Substrate Complex Induced Construction of Spiro-Bridged or Cagelike Polyheterocyclic Compounds via a Substrate-Controlled Cascade Process

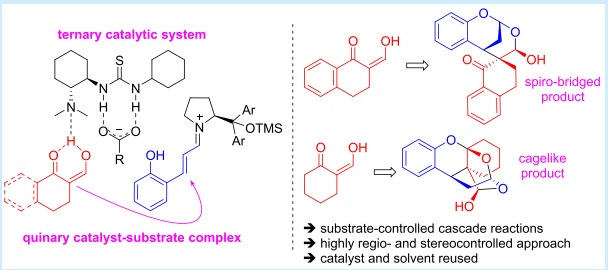
Chen Wang,[†] Ying-Han Chen,[†] Hui-Chun Wu,[†] Cong Wang,*[,†] and Yan-Kai Liu*[,†,‡]

[†]Key Laboratory of Marine Drugs, Chinese Ministry of Education, School of Medicine and Pharmacy, Ocean University of China, Qingdao 266003, China

[‡]Laboratory for Marine Drugs and Bioproducts of Qingdao National Laboratory for Marine Science and Technology, Qingdao 266003, China

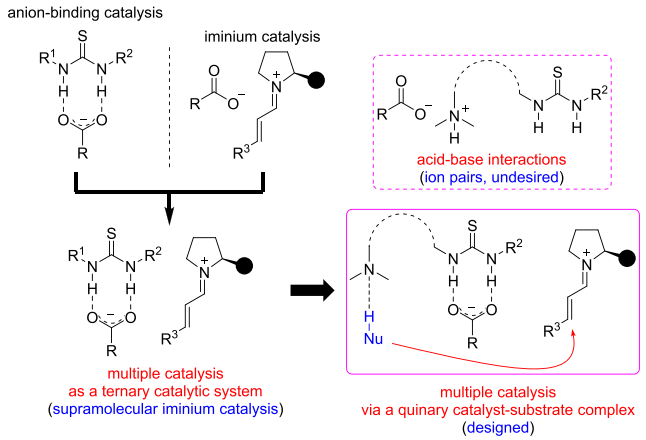
Supporting Information

ABSTRACT: The asymmetric organocatalytic cascade reaction of cyclic β-oxo aldehydes to 2-hydroxycinnamaldehydes is developed. The bifunctional tertiary amine−thiourea catalyst was used in a rationally designed multiple catalysis where the asymmetric iminium catalysis and thiourea anion-binding catalysis were combined by carboxylate anion as a ternary catalytic system to form a quinary catalyst−substrate complex, providing an efficient protocol for the construction of enantioenriched spiro-bridged or cagelike polyheterocyclic compounds. The reuse of catalysts was also successfully realized.



The coplanar carboxylate anion, which topology allows for a bidentate binding with thiourea catalyst, has been applied with particular success in chiral thiourea-induced anion-binding catalysis (Scheme 1).[1] Meanwhile, the carboxylate anion is also crucial for iminium ion activation. Generally, the active iminium ion species existed as a tight ion pair with the carboxylate anion in the reaction solution (Scheme 1), which should be responsible for the observed reactivity and high levels of stereoselectivity in iminium catalysis.[2]

Scheme 1. Motivation and Design



Multiple catalysis is evolving as an attractive direction in asymmetric organocatalysis in the past decade,[3] where two distinct chiral organocatalysts are generally brought together as a binary catalytic system, mostly via chiral ion pairs, to provide facile and efficient protocols for the quick construction of biologically interesting chiral complex molecules.

However, although both asymmetric iminium catalysis and thiourea anion-binding catalysis involved the carboxylate anion species, the integration of these two catalytic activations into a multiple catalysis fashion connected by the carboxylate anion has been much less developed, despite the combined ternary catalytic system could potentially improve the activity of the whole catalytic system.

Indeed, the development of such multiple catalysis has been considered to be a challenging task, and there are only a few relatively simple examples reported on this concept by Xu and co-workers, which is also called supramolecular iminium catalysis (Scheme 1).[4] However, only monofunctional hydrogen-bond donor catalysts could be used in this underdeveloped concept, while the bifunctional tertiary amine−thiourea catalysts, which could activate electrophile and nucleophile simultaneously,[5] are not applicable to this supramolecular iminium catalysis. This could be mainly attributed to the competitive acid−base interactions between the acid cocatalyst and the tertiary amine moiety of the bifunctional catalyst (Scheme 1),[6] which could potentially decrease the catalytic reactivity of the basic tertiary amine on the nucleophile (Nu-H). Accordingly, we proposed that, by judicious choice of the substrates bearing different acidic or basic sites to finely balance the interactions between the substrates and the

Received: July 9, 2019

DOI: 10.1021/acs.orglett.9b02375
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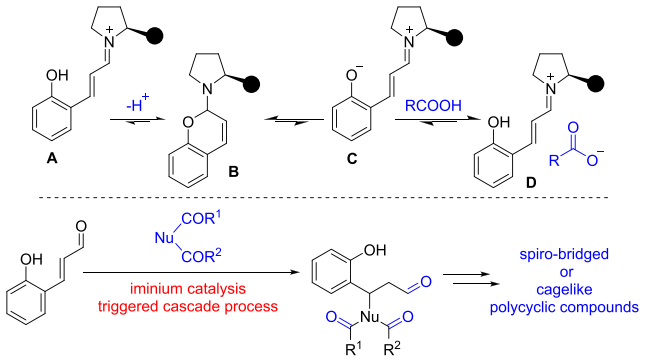
catalysts, the challenging issue mentioned above might be addressed toward the application of bifunctional tertiary amine−thiourea catalysts in multiple catalysis (Scheme 1), which could potentially provide new opportunities for asymmetric organocatalysis.

When 2-hydroxycinnamaldehydes were involved in asymmetric iminium catalysis (Scheme 2, top),[7] the formed

Scheme 2. Reactivity Analysis and Our Design Plan



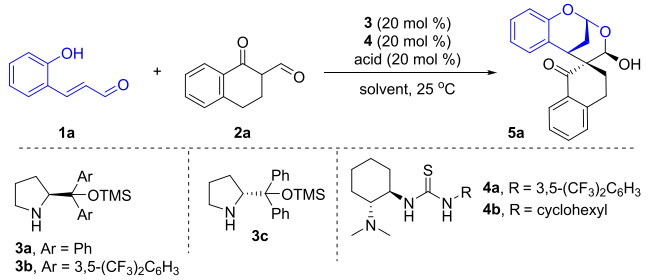
iminium ion intermediate **A** would quickly transform into the relatively stable aminal **B** and potentially in equilibrium with the zwitterionic intermediate **C**, which could be used as oxygen nucleophiles in oxa-Michael reactions under basic conditions.[8] It was surmised that, in the presence of carboxylic acid (RCOOH), the phenoxide anion in zwitterion **C** would be protonated to afford the iminium/carboxylate ion pair **D**. On the basis of this point, 2-hydroxycinnamaldehydes seemed particularly suitable for supramolecular iminium catalysis.

The asymmetric construction of heterocyclic compounds containing a spiro-bridged or cagelike ring system represents an important challenge in organic synthesis, and these skeletons may function as useful intermediates in the synthesis of medically important and biologically active agents.[9] Therefore, the development of efficient asymmetric catalytic methods for the preparation of enantioenriched spiro-bridged or cagelike polyheterocyclic compounds has attracted considerable attention.[10] We recently found that, due to their structural characteristics, 2-hydroxycinnamaldehydes have the specific advantage of constructing bridged polyheterocyclic scaffolds through the asymmetric iminium catalysis triggered reaction sequence.[11] Inspired by these successes, we wondered whether such a synthetic strategy could be expanded to the preparation of chiral spiro-bridged or cagelike ring systems by racting with active carbonyl-containing nucleophiles (R^1CO-Nu-COR^2; Scheme 2, bottom).[12] However, this is undoubtedly a challenging task, since there are several active carbonyl groups with similar reactivity in the formed intermedicates, which made the control of regioselectivity to be a stringent issue. To address this issue, a new activation model for both regio- and stereocontrol is required.

As a continuation of our efforts on developing asymmetric organocatalytic cascade reactions to construct acetal-containing polyheterocyclic compounds,[13] herein we report the development of a novel multiple catalysis, where the bifunctional tertiary amine−thiourea catalyst was successfully used for the first time in a ternary supramolecular iminium catalysis to activate nucleophiles and electrophiles simultaneously, and the final quinary catalyst-substrate complex provided a highly regio- and stereoselective asymmetric protocol, which could directly convert cyclic β-oxo aldehydes and 2-hydroxycinnamaldehydes into chiral spiro-bridged and cagelike polyheterocyclic compounds bearing polyacetal moieties.

To probe the feasibility of our hypothesis, the model reaction of benzofused cyclic β-oxo aldehyde **2a** and 2-hydroxycinnamaldehyde **1a** was first investigated under the classical conditions of asymmetric iminium catalysis. As shown in Table 1 (see the Supporting Information for full

Table 1. Optimization of the Reaction Conditions[a]



entry	3/4	acid	solvent	time (h)	yield[b] (%)	ee[c] (%)
1	**3a**/−	BA	toluene	46	52	48
2	**3a**/**4a**	BA	toluene	12	57	70
3	**3a**/**4a**		toluene	14	45	17
4	**3c**/**4a**	BA	toluene	14	58	43
6	**3b**/−	BA	toluene	>120	54	65
7	**3b**/**4a**	BA	toluene	17	64	90
8	**3b**/Et_3N	BA	toluene	>72	43	90
9	**3b**/**4a**	BA	toluene	24	65	94
10	**3b**/**4b**	BA	toluene	15	70	94
11	**3b**/**4b**	BA	DCE	12	74	94
12	**3b**/**4b**	NBL	DCE	49	68	89
13[d]	**3b**/**4b**	BA	DCE	28	84	99
14[e]	**3b**/**4b**	BA	DCE	>72		

[a]Unless otherwise noted, reactions were performed with **1a** (0.10 mmol) and **2a** (0.12 mmol) in toluene (0.2 mL) in the presence of **3** (20 mol %), **4** (20 mol %), and acid (20 mol %) at 25 °C. Solvent (1.0 mL) was used for entries 9−14. [b]Isolated yield. [c]Determined by using a chiral HPLC stationary phase. [d]At 0 °C. [e]The simple cinnamaldehyde was used instead of **1a**. TMS = trimethylsilyl, DCE = 1,2-dichloroethane, NBL = *N*-Boc-L-*tert*-leucine.

optimization studies), when the diphenylprolinol silyl ether **3a** was used as the catalyst and PhCOOH (BA) as the cocatalyst in toluene at 25 °C, the asymmetric Michael addition-triggered cascade reaction, which involved double hemiacetal formations, showed complete regiocontrol, and the desired spiro-bridged polycyclic hemiacetal product **5a** was isolated as the sole product bearing four chiral centers including an all-carbon quaternary stereocenter in 52% yield with moderate enantioselectivity (48% ee) as a single diastereoisomer, and no other isomers were observed (entry 1). As expected, the introduction of a bifunctional tertiary amine−thiourea catalyst **4a** to activate the nucleophile cyclic β-oxo aldehyde **1a** could considerably increase the enantioselectivity, and the reaction was also completed in a shorter reaction time (entry 2). Not surprisingly, much lower enantioselectivity was obtained in the absence of acid cocatalyst (entry 3). By comparison, there appeared a mismatch between the chirality of the bifunctional catalyst and the aminocatalyst, leading to worse result (entry 4 vs entry

DOI: 10.1021/acs.orglett.9b02375
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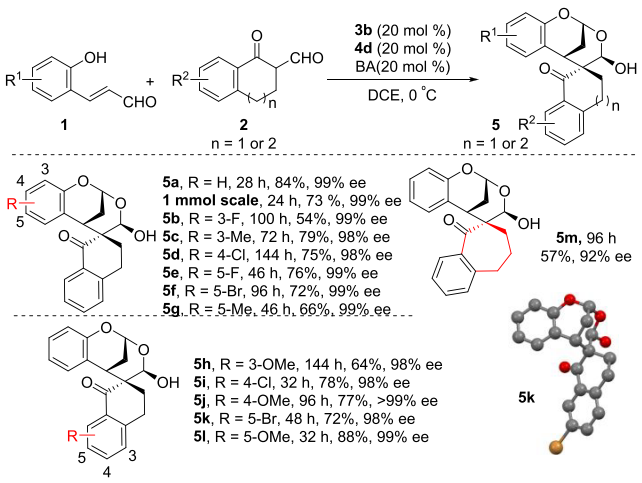
2). Noteworthy, together these results suggest that a ternary supramolecular iminium catalysis was involved in the reaction process to form a quinary catalyst−substrate complex, and the carboxylate anion, which was used to connect both asymmetric iminium catalysis and chiral thiourea anion-binding catalysis, played a crucial role in the reactivity and selectivity of the reaction. Encouraged by these promising results, we tested the use of more bulky prolinol ether **3b** for the reaction. The process proceeded much slower (>120 h) with slightly higher enantioselectivity (entry 6 vs entry 1). As might be expected, a much shorter reaction time was observed together with a much better enantioselectivity under the multiple catalysis conditions (entry 7 vs entry 6). While using Et_3N instead of bifunctional catalyst **4a**, much longer reaction time (>72 h) was required, leading to an incomplete reaction in 43% isolated yield of **5a** (entry 8 vs entry 7). Although slightly longer reaction time was observed, reaction under dilute conditions gave better enantioselectivity in similar good yield (entry 9 vs entry 7). Subsequently, it was found that the cyclohexyl-substituted bifunctional catalyst **4b** furnished the product in higher yield even after shorter reaction time (entry 10). Furthermore, dichloroethane (DCE) proved to be a better solvent, giving shorter reaction time while maintaining good enantioselectivity (entry 11). No better results were obtained with the *N*-Boc amino acid derived from L-*tert*-leucine (entry 12).[14] To our delight, decreasing the temperature to 0 °C led to complete stereocontrol, giving **5a** in good isolated yield (83%) with excellent enantioselectivity and diastereoselectivity (entry 13, 99% ee, dr >20:1). Noteworthy, no reaction occurred when we replaced the 2-hydroxycinnamaldehyde **1a** by simple cinnamaldehyde (entry 14, see the SI for details).

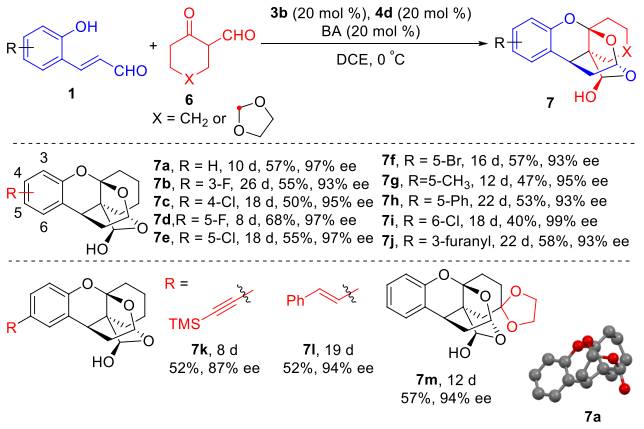
With the optimized conditions in hand (Table 1, entry 13), we next investigated the substrate scope of the highly regio- and stereocontrolled cascade reactions between 2-hydroxycinnamaldehydes **1** and benzofused cyclic *β*-oxo aldehydes **2**. As summarized in Scheme 3, substituents with different electronic properties at various positions on the aryl ring of both **1** and **2** have little effect on the reactivity and stereoselectivity, and the reactions proceeded smoothly, providing structurally complex spiro-bridged hemiacetal products **5a**–**l** in moderate to good yields (54–88%) with excellent enantioselectivities (98–99% ee) all as a single diastereoisomer. Furthermore, the substrate **2** bearing a seven-membered ring was also applicable to this reaction (**5m**). Furthermore, similar good results of product **5a** were obtained when running the reaction on a 1 mmol scale.

Scheme 3. Scope of the Preparation of Spiro-Bridged Products 5



However, to our surprise, the reaction of 2-hydroxycinnamaldehydes **1** and aliphatic cyclic *β*-oxo aldehydes **6** under the optimized conditions did not provide spiro-bridged hemiacetal products **5** but instead gave the structurally more complex cagelike polycyclic hemiacetal products **7** via a completely different cascade process from the preparation of spiro-bridged products **5**, where the phenolic hydroxyl first attacked the ketone carbonyl group instead of the aldehyde carbonyl group. It should be noted that the obtained cagelike polyacetal products contained five stereogenic centers including a quaternary all-carbon chiral center and a quaternary ketal chiral center. Next, we further explored the scope of this reaction with respect to the aliphatic substrates **6**. As shown in Scheme 4, regardless of the electronic nature and positions of

Scheme 4. Scope of the Preparation of Spiro-Bridged Products 7



substituents on the aromatic ring of 2-hydroxycinnamaldehydes **1**, the reaction proceeded smoothly to deliver chiral cagelike products **7a**–**i** in moderate yields with good to excellent enantioselectivities (up to 99% ee). Notably, substrates **1** bearing different functional groups, such as alkyne, alkene and furanyl groups can also be applied in this cascade reaction (**7j**–**l**). Moreover, a ketal-bearing substrate **6** was proved to be reactive, affording the desired product **7m** with reasonable yield and good enantioselectivity.

Due to the poor reactivity of aliphatic cyclic *β*-oxo aldehydes **6** (compared to benzofused **2**) under our established reaction conditions, longer reaction times (8–26 days) were required to achieve full conversion for the formation of the cagelike products **7** involving one C−C bond and three C−O bonds formations in a highly enantioselective cascade process. To overcome these limitations, we have studied the possibility of recycling and reuse of the catalyst. However, we have tried but failed to recover the catalysts directly from the original homogeneous reaction system. It is found that the reaction was performed under diluted conditions, and we thus anticipated that it might be possible to reuse the catalysts in situ. To this end, the reaction between **1a** (0.1 mmol) and **6a** (0.12 mmol) was carried out with 100 mol % catalysts loading (**3c**, **4f**, and BA). When substrate **6a** was completely consumed, fresh **1a** and **6a** was added to the reaction mixture and no workup was needed. This procedure was repeated five times, where the

DOI: 10.1021/acs.orglett.9b02375
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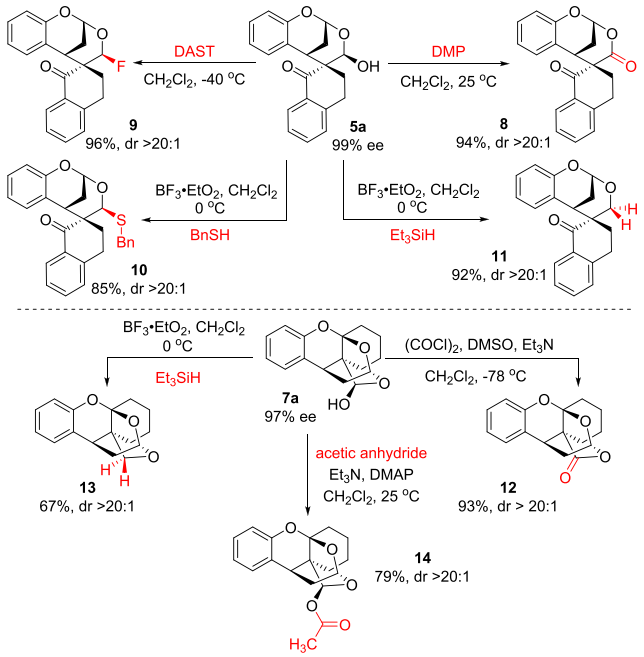
catalyst loading would be equivalent to 20 mol %, and the desired product **7a** was finally obtained in 47% yield (an average of five runs) with good stereoselectivity (91% ee, dr >20:1). But, most remarkably, the average reaction time for each run was only 4 d (compared to 10 d, when the catalyst loading was 20 mol %).

In order to demonstrate the utility of these obtained spiro-bridged and cagelike polycyclic hemiacetal products, several useful transformations were applied for further functionalization of spiro-bridged **5a** and cagelike **7a** (Scheme 5). We

Scheme 5. Useful Transformations



submitted **5a** and **7a** to Dess–Martin periodinane (DMP) oxidation and Swern oxidation, respectively, and the corresponding lactone products **8** and **12** were furnished in high yields. Upon reduction with $BF_3{\cdot}OEt_2/Et_3SiH$, the spiro-bridged polycyclic acetal **11** was obtained in 92% yield, while the cagelike acetal **13** in 67% yield. The deoxyfluorination of **5a** using diethylaminosulfur trifluoride (DAST) delivered fluorinated spiro-bridged acetal **9** with excellent diastereocontrol, while the dehydroxylation of **5a** in the presence of $BF_3{\cdot}OEt_2$ followed by the nucleophilic addition of benzyl mercaptan to the formed oxocarbenium ion led to the O,S-acetal **10** in 85% yield with high level of diastereoselectivity. Finally, treatment of **7a** with triethylamine (TEA) and acetic anhydride (Ac_2O) in the presence of 4-dimethylaminopyridine (DMAP, 10 mol %) in CH_2Cl_2 at 25 °C gave the acetylated product **14** in good yield.

The absolute configuration of spiro-bridged product **5k** (CCDC 1911882) and the relative configuration of cagelike product **7a** (CCDC 1911881) was determined by X-ray crystallography (see Scheme 3 for **5k** and Scheme 4 for **7a**; the H atoms are omitted for clarity), while the absolute configuration of cagelike polycyclic product **7a** was assigned by means of TD-DFT calculations of the electronic circular dichroism (ECD) spectra. The stereochemistry of the remaining products **5** and **7** was assigned analogously. Additionally, the relative stereochemistry of diastereoisomers **9** and **10** was confirmed by NOE experiments (see the Supporting Information for details).

In summary, we have achieved the application of a bifunctional tertiary amine–thiourea catalyst for the first time to activate active carbonyl-containing nucleophiles in multiple catalysis, where the asymmetric iminium catalysis and chiral thiourea anion-binding catalysis were combined by carboxylate anion as ternary supramolecular iminium catalysis to form a quinary catalyst–substrate complex, providing a highly regio- and stereoselective asymmetric protocol that directly converted cyclic β-oxo aldehydes and 2-hydroxycinnamaldehydes into chiral spiro-bridged and cagelike polyheterocyclic compounds. It should be noted that the asymmetric organocatalytic cascade processes proceeded by two different, substrate-controlled reaction pathways, leading to structurally diverse acetal-containing products bearing spiro-bridged and cagelike ring system, respectively. Further investigations on the applications of this novel quinary catalyst–substrate complex for the development of synthetic useful scaffolds are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02375.

Detailed optimization, complete experimental procedures, spectroscopic data for all new compounds, X-ray data, and proposed reaction mechanism for the formation of compounds **5** and **7** (PDF)

Accession Codes

CCDC 1911881–1911882 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: liuyankai@ouc.edu.cn.
*E-mail: wangcong@ouc.edu.cn.

ORCID

Yan-Kai Liu: 0000-0002-6559-2348

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the NSFC-Shandong Joint Fund for Marine Science Research Centers (No. U1606403), the National Science and Technology Major Project for Significant New Drugs Development (No. 2018ZX09735004), and the Scientific and Technological Innovation Project financially supported by Qingdao National Laboratory for Marine Science and Technology (No. 2015ASKJ02-06).

■ REFERENCES

(1) For selected reviews, see: (a) Zhang, Z.; Schreiner, P. R. (Thio)urea Organocatalysis—What Can be Learnt from Anion Recognition? *Chem. Soc. Rev.* **2009**, *38*, 1187. (b) Brak, K.;

DOI: 10.1021/acs.orglett.9b02375
Org. Lett. XXXX, XXX, XXX–XXX

Jacobsen, E. N. Asymmetric Ion-Pairing Catalysis. *Angew. Chem., Int. Ed.* **2013**, *52*, 534. (c) Mahlau, M.; List, B. Asymmetric Counteranion-Directed Catalysis: Concept, Definition, and Applications. *Angew. Chem., Int. Ed.* **2013**, *52*, 518.

(2) For selected reviews, see: (a) Erkkilä, A.; Majander, I.; Pihko, P. M. Iminium Catalysis. *Chem. Rev.* **2007**, *107*, 5416. (b) Moyano, A.; Rios, R. Asymmetric Organocatalytic Cyclization and Cycloaddition Reactions. *Chem. Rev.* **2011**, *111*, 4703. (c) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, Ł.; Jørgensen, K. A. The Diarylprolinol Silyl Ether System: A General Organocatalyst. *Acc. Chem. Res.* **2012**, *45*, 248. (d) Donslund, B. S.; Johansen, T. K.; Poulsen, P. H.; Halskov, K. S.; Jørgensen, K. A. The Diarylprolinol Silyl Ethers: Ten Years After. *Angew. Chem., Int. Ed.* **2015**, *54*, 13860. (e) Hong, L.; Sun, W.; Yang, D.; Li, G.; Wang, R. Additive Effects on Asymmetric Catalysis. *Chem. Rev.* **2016**, *116*, 4006. (f) Chauhan, P.; Mahajan, S.; Enders, D. Achieving Molecular Complexity via Stereoselective Multiple Domino Reactions Promoted by a Secondary Amine Organocatalyst. *Acc. Chem. Res.* **2017**, *50*, 2809. (g) Zou, Y.-Q.; Hörmann, F. M.; Bach, T. Iminium and Enamine Catalysis in Enantioselective Photochemical Reactions. *Chem. Soc. Rev.* **2018**, *47*, 278.

(3) For selected reviews, see: (a) Shao, Z.; Zhang, H. Combining Transition Metal Catalysis and Organocatalysis: A Broad New Concept for Catalysis. *Chem. Soc. Rev.* **2009**, *38*, 2745. (b) Rueping, M.; Koenigs, R. M.; Atodiresei, I. Unifying Metal and Brønsted Acid Catalysis—Concepts, Mechanisms, and Classifications. *Chem. - Eur. J.* **2010**, *16*, 9350. (c) Zhong, C.; Shi, X. When Organocatalysis Meets Transition-Metal Catalysis. *Eur. J. Org. Chem.* **2010**, *2010*, 2999. (d) Piovesana, S.; Scarpino Schietroma, D. M.; Bella, M. Multiple Catalysis with Two Chiral Units: An Additional Dimension for Asymmetric Synthesis. *Angew. Chem., Int. Ed.* **2011**, *50*, 6216. (e) Allen, A. E.; MacMillan, D. W. C. Synergistic Catalysis: A Powerful Synthetic Strategy for New Reaction Development. *Chem. Sci.* **2012**, *3*, 633. (f) Brière, J.-F.; Oudeyer, S.; Dalla, V.; Levacher, V. Recent Advances in Cooperative Ion Pairing in Asymmetric Organocatalysis. *Chem. Soc. Rev.* **2012**, *41*, 1696.

(4) (a) Wang, Y.; Yu, T.-Y.; Zhang, H.-B.; Luo, Y.-C.; Xu, P.-F. Hydrogen-Bond-Mediated Supramolecular Iminium Ion Catalysis. *Angew. Chem., Int. Ed.* **2012**, *51*, 12339. (b) Gu, Y.; Wang, Y.; Yu, T.-Y.; Liang, Y.-M.; Xu, P.-F. Rationally Designed Multifunctional Supramolecular Iminium Catalysis: Direct Vinylogous Michael Addition of Unmodified Linear Dienol Substrates. *Angew. Chem., Int. Ed.* **2014**, *53*, 14128. (c) Jia, Z.-L.; Wang, Y.; Xu, G.-Q.; Xu, P.-F. Kinetic Resolution via Supramolecular Iminium Catalysis: Multiactivation Enables the Asymmetric Synthesis of β-Aryl Substituted Aldehydes and Densely Functionalized Cyclohexanes. *Chem. Commun.* **2017**, *53*, 4938.

(5) For selected reviews, see: (a) Connon, S. J. Asymmetric Catalysis with Bifunctional Cinchona Alkaloid-Based Urea and Thiourea Organocatalysts. *Chem. Commun.* **2008**, 2499. (b) Takemoto, Y. Development of Chiral Thiourea Catalysts and Its Application to Asymmetric Catalytic Reactions. *Chem. Pharm. Bull.* **2010**, *58*, 593. (c) Siau, W.-Y.; Wang, J. Asymmetric Organocatalytic Reactions by Bifunctional Amine-Thioureas. *Catal. Sci. Technol.* **2011**, *1*, 1298. For leading references on the application of bifunctional tertiary amine—thiourea catalysts, see: (d) Okino, T.; Hoashi, Y.; Takemoto, Y. Enantioselective Michael Reaction of Malonates to Nitroolefins Catalyzed by Bifunctional Organocatalysts. *J. Am. Chem. Soc.* **2003**, *125*, 12672. (e) McCooey, S. H.; Connon, S. J. Urea- and Thiourea-Substituted Cinchona Alkaloid Derivatives as Highly Efficient Bifunctional Organocatalysts for the Asymmetric Addition of Malonate to Nitroalkenes: Inversion of Configuration at C9 Dramatically Improves Catalyst Performance. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367. (f) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. Highly Enantioselective Conjugate Addition of Nitromethane to Chalcones Using Bifunctional Cinchona Organocatalysts. *Org. Lett.* **2005**, *7*, 1967. (g) Ye, J.; Dixon, D. J.; Hynes, P. S. Enantioselective Organocatalytic Michael Addition of Malonate Esters to Nitro Olefins Using Bifunctional Cinchonine Derivatives. *Chem. Commun.* **2005**, 4481.

(6) Singh, R. P.; Foxman, B. M.; Deng, L. Asymmetric Vinylogous Aldol Reaction of Silyloxy Furans with a Chiral Organic Salt. *J. Am. Chem. Soc.* **2010**, *132*, 9558.

(7) (a) Cabrera, S.; Reyes, E.; Alemán, J.; Milelli, A.; Kobbelgaard, S.; Jørgensen, K. A. Organocatalytic Asymmetric Synthesis of α,α-Disubstituted α-Amino Acids and Derivatives. *J. Am. Chem. Soc.* **2008**, *130*, 12031. (b) Lee, Y.; Seo, S. W.; Kim, S.-G. Highly Enantioselective Conjugate Addition−Cyclization Cascade Reaction of Malonates with o-Hydroxycinnamaldehydes: Asymmetric Synthesis of 4-Substituted Chromanols. *Adv. Synth. Catal.* **2011**, *353*, 2671. (c) Choi, K.-S.; Kim, S.-G. Asymmetric Organocatalytic Michael Addition−Cyclization Cascade Reaction of Nitroalkanes with *o*-Hydroxycinnamaldehydes. *Eur. J. Org. Chem.* **2012**, *2012*, 1119. (d) Kim, Y. S.; Kim, S. M.; Wang, B.; Companyó, X.; Li, J.; Moyano, A.; Im, S.; Tošner, Z.; Yang, J. W.; Rios, R. Expanding the Scope of the Organocatalytic Addition of Fluorobis(phenylsulfonyl)methane to Enals: Enantioselective Cascade Synthesis of Fluoroindane and Fluorochromanol Derivatives. *Adv. Synth. Catal.* **2014**, *356*, 437. (e) Ackrill, T. D.; Sparkes, H. A.; Willis, C. L. Synthesis of Diarylheptanoid Scaffolds Inspired by Calyxins I and J. *Org. Lett.* **2015**, *17*, 3884. (f) Maity, R.; Pan, S. C. Organocatalytic Asymmetric Michael/Hemiacetalization/Acyl Transfer Reaction of α-Nitroketones with *o*-Hydroxycinnamaldehydes: Synthesis of 2,4-Disubstituted Chromans. *Org. Biomol. Chem.* **2018**, *16*, 1598.

(8) (a) Zu, L.; Zhang, S.; Xie, H.; Wang, W. Catalytic Asymmetric oxa-Michael−Michael Cascade for Facile Construction of Chiral Chromans via an Aminal Intermediate. *Org. Lett.* **2009**, *11*, 1627. (b) Ramachary, D. B.; Shiva Prasad, M.; Vijaya Laxmi, S.; Madhavachary, R. Asymmetric Synthesis of Drug-Like Spiro-[chroman-3,3′-indolin]-2′-ones through Aminal-Catalysis. *Org. Biomol. Chem.* **2014**, *12*, 574.

(9) (a) Mossa, J. S.; Cassady, J. M.; Antoun, M. D.; Byrn, S. R.; McKenzie, A. T.; Kozlowski, J. F.; Main, P.; Saudin, A. Hypoglycemic Diterpenoid, with A Novel 6,7-Seco-Labdane Carbon Skeleton, from Cluytia Richardiana. *J. Org. Chem.* **1985**, *50*, 916. (b) Teponno, R. B.; Tapondjou, A. L.; Ju-Jung, H.; Nam, J.-H.; Tane, P.; Park, H.-J. Three New Clerodane Diterpenoids from the Bulbils of Dioscorea bulbifera L. var. sativa. *Helv. Chim. Acta* **2007**, *90*, 1599. (c) Lin, S.; Zhang, Y.; Liu, M.; Yang, S.; Gan, M.; Zi, J.; Song, W.; Fan, X.; Wang, S.; Liu, Y.; Yang, Y.; Chen, X.; Guo, Y.; Wang, W.; Shi, J. Abietane and C20-Norabietane Diterpenes from the Stem Bark of Fraxinus sieboldiana and Their Biological Activities. *J. Nat. Prod.* **2010**, *73*, 1914. (d) Fang, X.; Di, Y. T.; Zhang, Y.; Xu, Z. P.; Lu, Y.; Chen, Q. Q.; Zheng, Q. T.; Hao, X. J. Unprecedented Quassinoids with Promising Biological Activity from Harrisonia perforata. *Angew. Chem., Int. Ed.* **2015**, *54*, 5592. (e) Guo, B.; Onakpa, M. M.; Huang, X.-J.; Santarsiero, B. D.; Chen, W.-L.; Zhao, M.; Zhang, X.-Q.; Swanson, S. M.; Burdette, J. E.; Che, C.-T. Di-nor- and 17-nor-pimaranes from Icacina Trichantha. *J. Nat. Prod.* **2016**, *79*, 1815.

(10) (a) Eiden, F.; Gmeiner, P. Synthese Anellierter Oxabenzomorphane. *Arch. Pharm.* **1986**, *319*, 431. (b) Winkler, J. D.; Doherty, E. M. The First Total Synthesis of (±)-Saudin. *J. Am. Chem. Soc.* **1999**, *121*, 7425. (c) Mehta, G.; Islam, K. An Eventful Synthetic Approach towards the Biologically Potent Natural Product Ottelione A: Enantio-, Regio- And Stereoselective Construction of the Bicyclic Core. *Synlett* **2000**, 1473. (d) Boeckman, R. K.; del Rosario Rico Ferreira, M.; Mitchell, L. H.; Shao, P. An Enantioselective Total Synthesis of (+)- and (−)-Saudin. Determination of the Absolute Configuration. *J. Am. Chem. Soc.* **2002**, *124*, 190. (e) Cheng, H.; Zeng, F.-H.; Yang, X.; Meng, Y.-J.; Xu, L.; Wang, F.-P. Collective Total Syntheses of Atisane-Type Diterpenes and Atisine-Type Diterpenoid Alkaloids: (±)-Spiramilactone B, (±)-Spiraminol, (±)-Dihydroajaconine, and (±)-Spiramines C and D. *Angew. Chem., Int. Ed.* **2016**, *55*, 392.

(11) (a) You, Z.-H.; Chen, Y.-H.; Tang, Y.; Liu, Y.-K. Organocatalytic Asymmetric Synthesis of Spiro-Bridged and Spiro-Fused Heterocyclic Compounds Containing Chromane, Indole, and Oxindole Moieties. *Org. Lett.* **2018**, *20*, 6682. (b) Lv, X.-J.; Chen, Y.-H.; Liu, Y.-K. Two Competitive but Switchable Organocatalytic

DOI: 10.1021/acs.orglett.9b02375
Org. Lett. XXXX, XXX, XXX−XXX

Cascade Reaction Pathways: The Diversified Synthesis of Chiral Acetal-Containing Bridged Cyclic Compounds. *Org. Lett.* **2019**, *21*, 190.

(12) (a) Yao, W.; Pan, L.; Wu, Y.; Ma, C. Asymmetric Synthesis of Spiro-3,4-dihydropyrans via a Domino Organocatalytic Sequence. *Org. Lett.* **2010**, *12*, 2422. (b) Hong, B.-C.; Kotame, P.; Lee, G.-H. Asymmetric Synthesis of 3,4-Dihydrocoumarin Motif with an All-Carbon Quaternary Stereocenter via a Michael−Acetalization Sequence with Bifunctional Amine-thiourea Organocatalysts. *Org. Lett.* **2011**, *13*, 5758. (c) Sternativo, S.; Calandriello, A.; Costantino, F.; Testaferri, L.; Tiecco, M.; Marini, F. A Highly Enantioselective One-Pot Synthesis of Spirolactones by an Organocatalyzed Michael Addition/Cyclization Sequence. *Angew. Chem., Int. Ed.* **2011**, *50*, 9382. (d) Wang, X.; Yao, W.; Yao, Z.; Ma, C. Bifuctional Amino-Squaramides Catalyzed Asymmetric Spiroannulation Cascades with Aliphatic β,γ-Unsaturated α-Keto Esters: Controlling an Aldehyde Enolate. *J. Org. Chem.* **2012**, *77*, 2959. (e) Vishwanath, M.; Vinayagam, P.; Gajulapalli, V. P. R.; Kesavan, V. Asymmetric Organocatalytic Assembly of Oxindoles Fused with Spiro-3,4-dihydropyrans with Three Contiguous Stereocenters Consisting of Vicinal Quaternary Centers. *Asian J. Org. Chem.* **2016**, *5*, 613. (f) Zhang, Z.-P.; Chen, L.; Li, X.; Cheng, J.-P. Organocatalytic Asymmetric Sequential 1,6-Addition/Acetalization of 1-Oxotetralin-2-carbaldehyde to *ortho*-Hydroxyphenyl-Substituted *para*-Quinone Methides for Synthesis of Spiro-3,4-dihydrocoumarins. *J. Org. Chem.* **2018**, *83*, 2714.

(13) (a) Sun, X.-L.; Chen, Y.-H.; Zhu, D.-Y.; Zhang, Y.; Liu, Y.-K. Substrate-Controlled, One-Pot Synthesis: Access to Chiral Chroman-2-one and Polycyclic Derivatives. *Org. Lett.* **2016**, *18*, 864. (b) Li, J.-Y.; Yu, K.-W.; Xie, C.-C.; Liu, Y.-K. Lactols in An Asymmetric Aldol-Desymmetrization Sequence: Access to Tetrahydro-4*H*-Furo[2,3-*b*]Ppyran-2-One and Tetrahydro-4*H*-Furo[2,3-*b*]Furan-2-One Derivatives. *Org. Biomol. Chem.* **2017**, *15*, 1407. (c) Liu, C.; Liu, Y.-K. Asymmetric Organocatalytic One-Pot, Two-Step Sequential Process to Synthesize Chiral Acetal-Containing Polycyclic Derivatives from Cyclic Hemiacetals and Enones. *J. Org. Chem.* **2017**, *82*, 10450. (d) Zhao, W.-W.; Liu, Y.-K. Enantio- and Diastereoselective Synthesis of Tetrahydrofuro[2,3-*b*]Furan-2(3*H*)-One Derivatives and Related Oxygen Heterocycles via An Asymmetric Organocatalytic Cascade Process. *Org. Chem. Front.* **2017**, *4*, 2358. (e) Pei, J.-P.; Chen, Y.-H.; Liu, Y.-K. Asymmetric Organocatalytic Sequential Reaction of Structurally Complex Cyclic Hemiacetals and Functionalized Nitro-Olefins to Synthesize Diverse Heterocycles. *Org. Lett.* **2018**, *20*, 3609. (f) Wu, X.-N.; You, Z.-H.; Liu, Y.-K. Different Hybridized Oxygen Atoms Controlled Chemoselective Formation of Oxocarbenium Ions: Synthesis of Chiral Heterocyclic Compounds. *Org. Biomol. Chem.* **2018**, *16*, 6507. (g) Lv, X.-J.; Zhao, W.-W.; Chen, Y.-H.; Wan, S.-B.; Liu, Y.-K. Organocatalytic asymmetric Synthesis of both *cis*- and *trans*-Configured Pyrano[2,3-*b*]Chromenes via Different Dehydration Pathways. *Org. Chem. Front.* **2019**, *6*, 1972.

(14) (a) De Vincentiis, F.; Bencivenni, G.; Pesciaioli, F.; Mazzanti, A.; Bartoli, G.; Galzerano, P.; Melchiorre, P. Asymmetric Catalytic Aziridination of Cyclic Enones. *Chem. - Asian J.* **2010**, *5*, 1652. (b) Tian, X.; Liu, Y.; Melchiorre, P. Aminocatalytic Enantioselective 1,6-Additions of Alkyl Thiols to Cyclic Dienones: Vinylogous Iminium Ion Activation. *Angew. Chem., Int. Ed.* **2012**, *51*, 6439.

DOI: 10.1021/acs.orglett.9b02375
Org. Lett. XXXX, XXX, XXX−XXX