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Authors: Jian Cao, Ran Fang, Jin-Yu Liu, Hong Lu, Yong-Chun Luo, and Peng-Fei Xu

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Organocatalytic Regiodivergent C–C Bond Cleavage of Cyclopropenones: A Highly Efficient Cascade Approach to Enantiopure Heterocyclic Frameworks

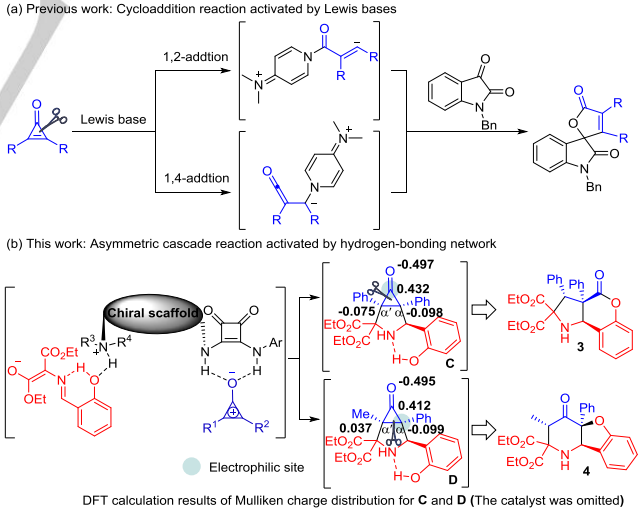
Jian Cao, Ran Fang, Jin-Yu Liu, Hong Lu, Yong-Chun Luo and Peng-Fei Xu*

Abstract: Here we report a highly efficient cascade approach combining a cycloaddition reaction with a regioselective strain-release process to afford diverse heterocyclic frameworks via bifunctional catalysis. The cooperation of hydrogen-bonding network activation and regiodivergent strain-assisted effect is the key to promoting this complex chemical transformation, leading to the generation of two different ring systems in high yields with excellent stereoselectivities. The reaction proceeded by a mechanism involving a “spring-loaded” intermediate with switchable C–C bond cleavages achieved by controllable ring-strain release. This reaction was also amenable to gram scale synthesis with only 0.1 mol % catalyst loading.

C–C bond cleavage, which has attracted much attention from and also challenged organic chemists for decades,[1] is of significant synthetic value for chemical conversions. Among the basic strategies for facilitating C–C bond cleavage, the most typical one is to release the potential energy stored in strained three- or four-membered ring compounds to form more stable intermediates or products.[2] In 1955, strain release was proved to be responsible for the enhanced oxidation of steroidal secondary alcohols.[3] Since then, many outstanding works about strain release have been reported,[4] which proved that simple and rapid, click-like access[5a] to new connections could be achieved by harnessing the strained bonds properly.[5b]

Since the first synthesis of cyclopropenones by Breslow[6a,6b] and Vol'pin,[6c,6d] numerous research efforts have been paid on exploring the synthetic value,[7a] the properties[7b-d] and the applications[7e-j] of this fascinating class of compounds. There even was a vivid description for this kind of chemical compounds: having a simple appearance outside, yet full of wonder inside, cyclopropenone seems like a miniature carved ivory altarpiece in a Chinese curio box.[8] As far as we know, cyclopropenones have been utilized as useful building blocks in transition metal catalysis,[9a-g] organocatalysis[9h,9i] and cycloaddition reactions.[9j,9k] These molecules could also be used as catalysts[9l-o] or for bioorthogonal chemistries.[9p] With regard to organocatalysis reactions, the ring-opening and C–C bond activation process of cyclopropenones was resulted from either 1,2-addition or 1,4-addition by Lewis bases, which yielded nucleophilic intermediates and facilitated the subsequent formal [3+2] cycloaddition reations (**Scheme 1a**).[9h,9i]

Cyclopropenones are ideal candidates for C−C bond cleavage methodologies because of their considerable ring strain, polarized nature and aromaticity,[10] and these small unsaturated rings could be potentially activated by the acidic protons of squaramide to generate an electrophilic transition state that has not been reported in the previous literature.[11] Such a transition state would have a tendency to react with *o*-hydroxy aromatic aldimines activated by hydrogen-bonding network due to the reduced HOMO–LUMO gap and activation energy (**Scheme 1b**).[12] More interestingly, the different chiral intermediates generated from the [3+2] cycloaddition can act as “spring-loaded” reagents with strain energy,[13] which could show strain-assisted effect[14] and induce nucleophilic attack of phenol group at different electrophilic sites (either the carbonyl carbon or α-site of the carbonyl group). To test our hypothesis, two different computational models were established to calculate the feasibility of switchable regioselectivity. As expected, different substituents changed the polarization of the bonds and two different ring-opening pathways involving either intermediate **C** or intermediate **D** (**Scheme 1b**) could be predicted. Therefore, we envisioned that the cleavage precursors (intermediate **C** and **D**) could provide strong driving power and accurate steric site recognition for the reactions with switchable regioselectivity.



Scheme 1. Distinct Modes for the Activation of Cyclopropenones.

The study was initiated by testing the model reaction of *o*-hydroxy aromatic aldimine (**1a**) and 2,3-diphenylcycloprop-2-enone (**2a**) in the presence of a bifunctional organocatalyst in CH_2Cl_2 (1 mL) at 30 °C (**Table 1**). First, several bifunctional catalysts were screened to evaluate their catalytic performance. To our delight, product **3aa** was successfully obtained in moderate to good yield with excellent selectivity when catalysts

[*] Dr. J. Cao, Prof. R. Fang, Dr. J.-Y. Liu, Dr. H. Lu, Prof. Y.-C. Luo, Prof. Dr. P.-F. Xu
State Key Laboratory of Applied Organic Chemistry
College of Chemistry and Chemical Engineering
Lanzhou University
Lanzhou 730000 (P.R. China)
Fax: (+86) 931-8915557
E-mail: xupf@lzu.edu.cn

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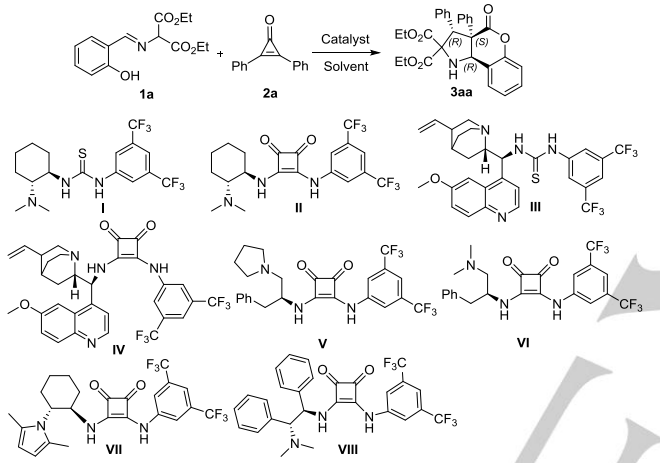
I–VII were used (entries 1–7). The structure of **3aa** was unambiguously determined by X-ray crystallographic analysis.[15a] Among these bifunctional organocatalysts, bifunctional squaramide **IV** was identified as the optimal one (entries 4). Subsequently, screening of solvents revealed that mesitylene was the optimal solvent, and 99% yield, >20:1 d.r. and >99% ee were obtained from the reaction with mesitylene as the solvent (entries 9–14). Then the experiments with lower catalytic loadings were carried out and the results showed that excellent yields and stereoselectivites could be obtained even in the presence of 1 mol % catalyst **IV** (entries 15–17). However, using 0.5 mol % catalyst **IV** in 1 mL mesitylene led to an obvious decrease of the yield (entry 18). Finally, the optimal reaction conditions were determined by further tests as follows: 0.5 mL mesitylene, 0.5 mol % catalyst and ambient temperature (entries 19-21).

Table 1. Optimization of the Reaction Conditions[a]

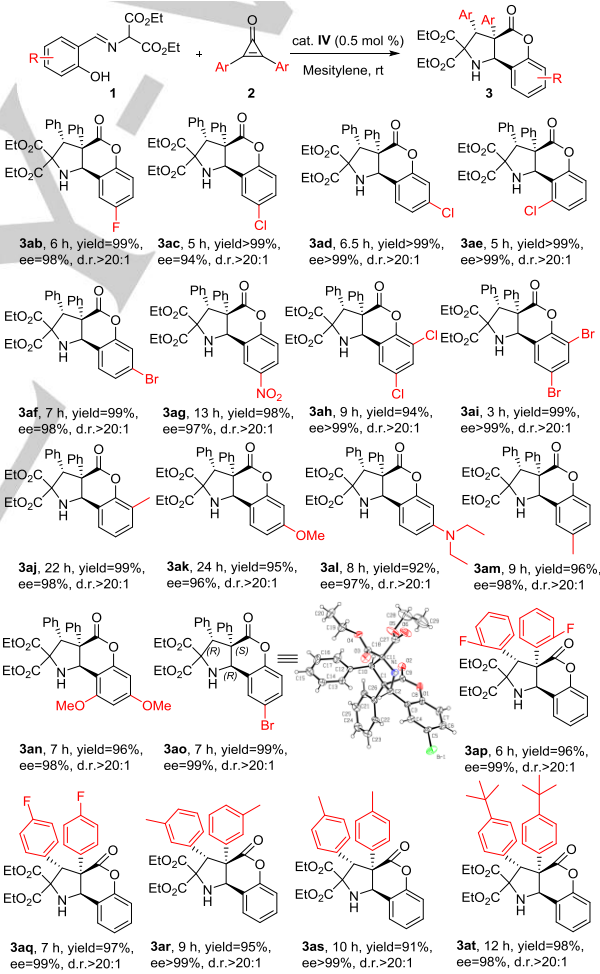


entry	cat.	solvent	time	Yield[b]	d.r.[c]	ee[d]
1	**I**	CH_2Cl_2	72 h	52%	>20:1	-94%
2	**II**	CH_2Cl_2	5 h	68%	>20:1	-89%
3	**III**	CH_2Cl_2	5 h	74%	>20:1	96%
4	**IV**	CH_2Cl_2	5.5 h	62%	>20:1	98%
5	**V**	CH_2Cl_2	70 h	89%	>20:1	87%
6	**VI**	CH_2Cl_2	72 h	87%	>20:1	73%
7	**VII**	CH_2Cl_2	72 h	94%	>20:1	-91%
8	**VIII**	CH_2Cl_2	72 h	trace	n.d.	n.d.
9	**IV**	DCE	5.5 h	76%	>20:1	98%
10	**IV**	CH_3CN	24 h	98%	>20:1	94%
11	**IV**	THF	22 h	95%	>20:1	98%
12	**IV**	toulene	5 h	81%	>20:1	98%
13	**IV**	xylene	3 h	95%	>20:1	>99%
14	**IV**	mesitylene	0.6 h	99%	>20:1	>99%
15[e]	**IV**	mesitylene	1.2 h	99%	>20:1	>99%
16[f]	**IV**	mesitylene	1.5 h	99%	>20:1	>99%
17[g]	**IV**	mesitylene	2 h	99%	>20:1	>99%
18[h]	**IV**	mesitylene	72 h	90%	>20:1	>99%
19[h,i]	**IV**	mesitylene	12 h	99%	>20:1	>99%
20[h,i,j]	**IV**	mesitylene	6 h	99%	>20:1	>99%
21[h,i,j,k]	**IV**	mesitylene	6 h	99%	>20:1	>99%

[a]Conditions: Reactions performed with **1a** (0.1 mmol), **2a** (0.1 mmol), catalyst (20 mol %) in the indicated solvent (1 mL) at 30 °C. [b] Isolated yield. [c] Determined by NMR analysis of the combined mixture. [d] Determined by HPLC analysis using a chiral stationary phase. [e] 10 mol % organocatalyst was used. [f] 5 mol % organocatalyst was used. [g] 1 mol % organocatalyst was used. [h] 0.5 mol % organocatalyst was used. [i] 0.5 mL solvent was used. [j] 0.12 mmol **1a** was used. [k] Reaction performed at ambient temperature.

Under the optimized conditions, the substrate scope was then investigated. As shown in **Table 2**, in all cases, the products were obtained as a single diastereomer in high yields with excellent stereoselectivities. The electronic and steric properties of substrates **1** had no obvious effects on the yields and stereoselectivities albeit with slight influences on the reaction times. With different cyclopropenones **2**, excellent results were generally obtained. The absolute configuration of **3ao** was determined by X-ray crystallographic analysis.[15b] The same absolute configuration was assigned to all the products.

Table 2. Substrate Scope of the Cascade Reactions of the *o*-Hydroxy Aromatic Aldimines **1** with Cyclopropenones **2**[a,b]



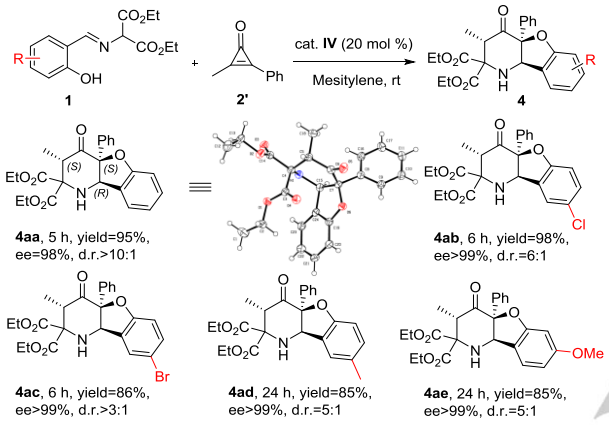
[a] Reaction conditions: **1** (0.12 mmol, 1.2 equiv), **2** (0.1 mmol, 1.0 equiv), **IV** (0.5 mol %) in mesitylene (0.5 mL) at ambient temperature. [b] Isolated yields.

As illustrated in **Scheme 1b**, the intermediate obtained from the cycloaddition has multiple electrophilic sites. Thus, the α-site of the carbonyl group can be an alternative reactive site with suitable substituents. Using methylphenylcyclopropenone **2'** as

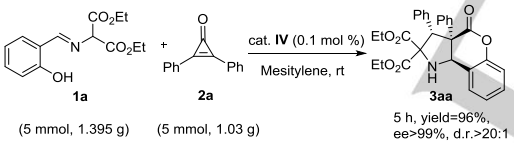
the substrate, a completely different cyclization product **4aa** was delivered in high yield with excellent diastereoselectivity (>10:1 d.r.) and enantioselectivity (98% ee) under the optimized reaction conditions (**Table 3**). And different *o*-hydroxy aromatic aldimines **1** were well tolerated. The absolute configuration of the product **4aa** was determined by using X-ray crystallographic analysis.[15c]

To further verify the practicality of this organocatalytic cascade reaction, a gram-scale asymmetric synthesis of **3aa** with lower catalyst loading (0.1 mol %) was carried out (**Scheme 2**). High efficiency and excellent selectivity were maintained in the large scale reaction, further proving the synthetic value of this reaction.

Table 3. Substrate Scope of the Cascade Reactions of the *o*-Hydroxy Aromatic Aldimines[a,b]



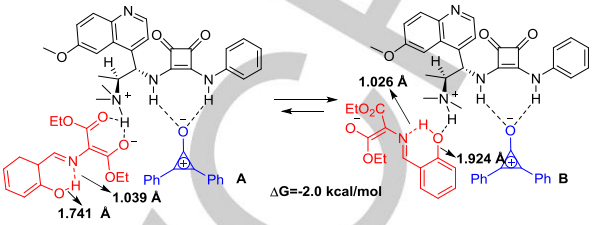
[a]Reaction conditions: **1** (0.1 mmol, 1 equiv), **2a** (0.1 mmol, 1 equiv), **IV** (20 mol %) in mesitylene (0.5 mL) at ambient temperature. [b] Isolated yields.



Scheme 2. Gram-Scale Synthesis of **3aa** with 0.1 mol % Catalyst Loading

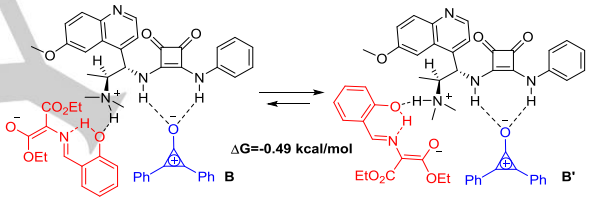
DFT calculations were carried out to investigate the possible interactions between the catalyst and substrates/intermediates. We conducted a reasonable simplification of the squaramide structure (see Supporting Information) since such simplification could decrease the computational costs but ensure an almost identical simulation of the experiments[16] (calculation result of ee value of product **3aa** employing **IV'** was >99%, consistent with experimental results).

DFT calculations revealed the existence of the intramolecular hydrogen-bonding between the nitrogen atom of imine and the hydrogen atom of the phenol group (N···H = 1.039 Å, O···H = 1.741 Å for configuration **A** and N···H = 1.026 Å, O···H = 1.924 Å for configuration **B**, **Scheme 3**). And the hydrogen-bonding interaction between squaramide and the *o*-hydroxyl group (configuration **B**) was more favorable (2 kcal/mol) than the interaction between squaramide and the enolized carbethoxy group (configuration **A**). In addition, DFT calculations indicated that a proton was transferred from the *o*-hydroxy group to imine in complexe **B** (the bond length of N···H was reduced compared with that of complexe **A**), which implied an enhanced kinetics control by the catalyst. DFT calculations suggested that the hydrogen-bonding network could not only stabilize the reaction intermediate, but also activates the imine within substrate **1** synergistically,[17] compared to that of aldimines without *o*-hydroxy.[18]



Scheme 3. DFT Studies of Catalyst-Substrate Coordination

Next, a conformational study of catalyst-substrate complexes was carried out by DFT calculations to determine the zero potential energy surface of Gibbs free energy. As showed in **Scheme 4**, complex **B'** was the preferential conformation over complex **B** in steric orientation with a slightly reduced relative energy.



Scheme 4. DFT Studies of Catalyst-Substrate Complex Conformation

Regarding the Gibbs free energy of catalyst-substrates complexe **B'** as the zero potential energy surface, we studied the energetic profile of this cascade reaction by DFT calculations (**Figure 1**). Obviously, the stereochemistry of the reaction was determined by the face selectivity (namely complexes **B** and **B'**), while the regioselectivity was determined by the selective strain-release (namely different C–C bond cleavages). First, by comparing two possible approaches to key intermediates (**C** and **C'**), it became clear that the [3+2] cycloaddition starting from catalyst-substrate complex **B** was strongly favored, in view of the considerably higher activation energy required for the formation of transition state **TS-I'** (ΔΔG = 5.4 kcal/mol). Calculation results illustrated that the excellent enantioselectivity observed in experiments was the results of overwhelming superiority of preferential intermediate **C** over intermediate **C'**. For the succedent regioselectivity, there were also two possible ring closure pathways, the annulation at the carbonyl (**C1**) group which would produce the lactonization product **3** and, alternatively, the annulation at α-site of the carbonyl (**C2**) group, leading to the formation of the dihydrobenzofuran product **4**. The predicted regioselectivity has been proved by experiments. As shown in **Scheme 1b**, regiodiversity was due to the different C–C bond cleavages caused by diverse electronic effects.

In conclusion, we have developed a highly efficient cascade strategy to access enantiopure heterocyclic frameworks with switchable regioselectivity. The key to success was the combination of hydrogen-bonding network activation with regiodivergent strain-assisted effect, which promoted the whole catalytic efficiency significantly. Hydrogen-bonding network activation involved a promoted proton transfer from *o*-hydroxy group to imine to generate a more reactive and thermodynamically stable transition state, which was anchored on the catalyst through the formation of a hydrogen-bonding network. The regiodivergent strain-assisted effect provided the selective strain-release to control the reaction regioselectivity. A rational mechanistic study based on DFT and experimental results indicated that selective strain-release was the result of diverse polarization caused by electronic effects. Intramolecular hydrogen-bonding, coordination modes, enantioselectivity and regioselectivity have also been studied by DFT calculations. A gram-scale synthesis further proved the potential utility of this methodology.

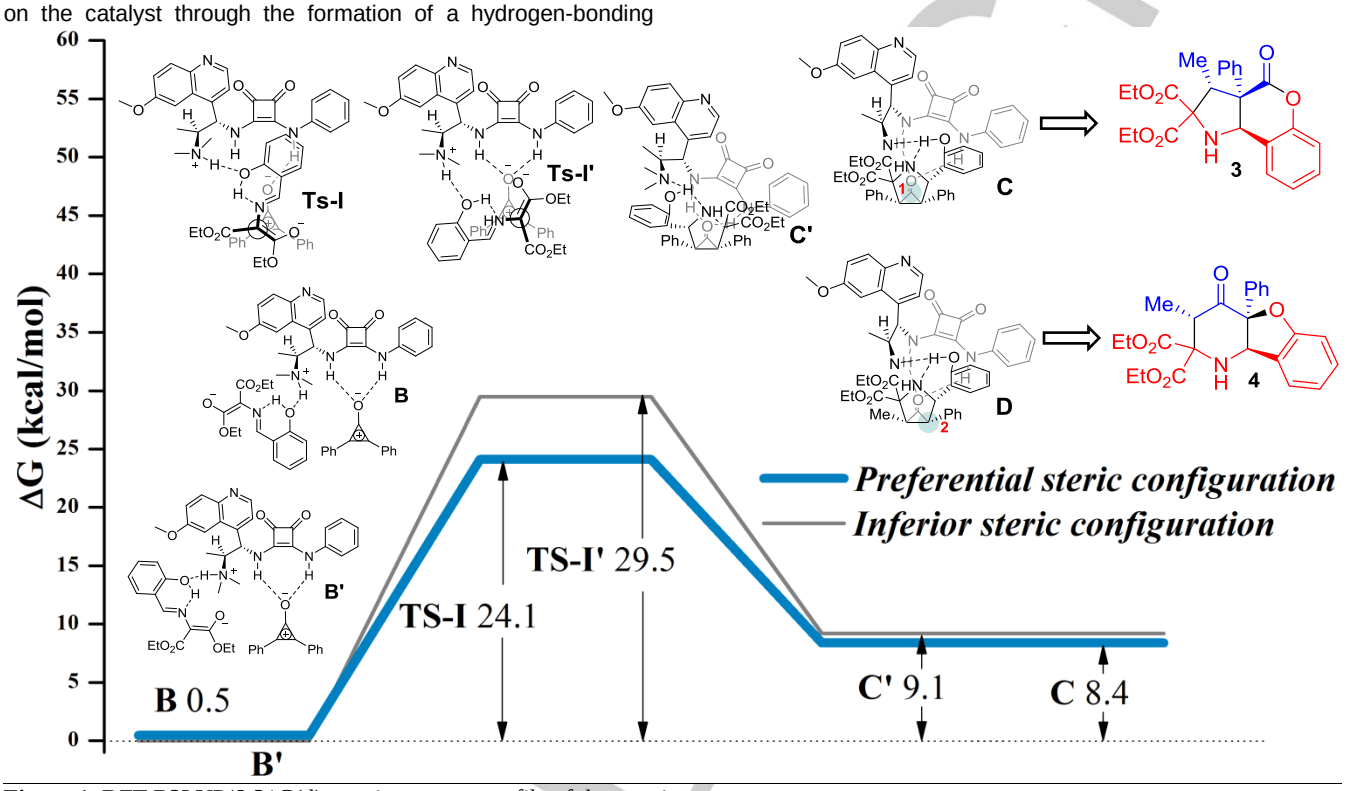


Figure 1. DFT B3LYP/6-31G(d) reaction energy profile of the reaction system.

Acknowledgements

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Keywords: strain-release • spring-loaded • switchable regioselectivity • DFT calculations

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[15] a) CCDC 1821440 (**3aa**) contains the supplementary crystallographic data for this paper; b) CCDC 1821441 (**3ao**) contains the supplementary crystallographic data for this paper; c) CCDC 1821439 (**4aa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

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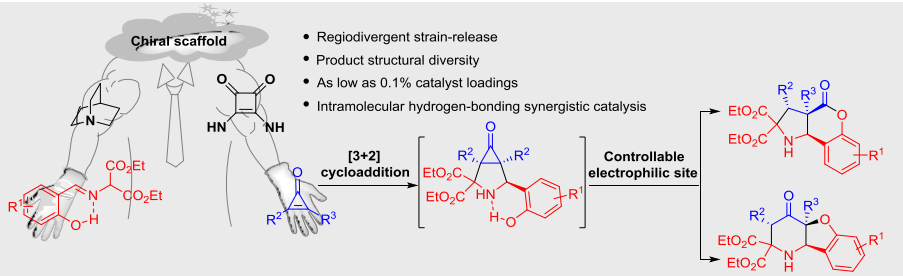

*Jian Cao, Ran Fang, Jin-Yu Liu, Hong Lu, Yong-Chun Luo and Peng-Fei Xu**

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Organocatalytic Regiodivergent C–C Bond Cleavage of Cyclopropenones: A Highly Efficient Cascade Approach to Enantiopure Heterocyclic Frameworks

Here, we describe a strain-release reaction with switchable regioselectivity. A rational mechanistic study based on DFT and experimental results indicated that selective strain-release was the result of changed polarization caused by electronic effects.