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Carbene-Catalyzed Intramolecular Cyclization to Access Inherently Chiral Saddle-Shaped Lactones: Achiral Bases Alternate Product Chirality

Liwen Wei,[⊥] Yuhang Chen,[⊥] Qinglong Zhou,[⊥] Zhikang Wei,[⊥] Ting Tu, Shichao Ren, Yonggui Robin Chi,* Xinglong Zhang,* and Xing Yang*

Cite This: https://doi.org/10.1021/jacs.5c05380

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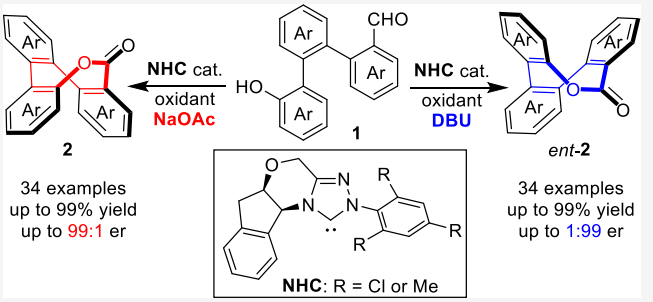
ABSTRACT: Enantiodivergent synthesis using a single catalyst or catalysts with the same chiral scaffold has evolved as a particularly attractive tool to access both enantiomers of chiral molecules. Progress in this field mainly comes from the enantiodivergent construction of central chirality as well as axial chirality. We report herein a carbene-catalyzed base-controlled enantiodivergent synthesis of saddle-shaped eight-membered lactones with inherent chirality. With the use of the same carbene catalyst or the carbene catalysts with the same chiral scaffold, both enantiomers of the inherently chiral eight-membered lactones could be obtained under different base conditions in high yields with good to excellent enantioselectivities. The resulting inherently chiral eight-membered lactones allow further stereospecific derivatizations and exhibit notable antibacterial activity. Preliminary DFT calculations unraveled the origins of this base-controlled enantiodivergent process.



INTRODUCTION

It has been well demonstrated that a pair of enantiomers can differentially affect physiological processes,[1] and the development of efficient methods to obtain both enantiomers of chiral molecules is one of the fundamental tasks in organic synthesis and medicinal chemistry.[2] Compared to the conventional method of using both enantiomers of a chiral catalyst, enantiodivergent synthesis using a single catalyst or ligand scaffold has evolved as a particularly attractive tool.[3] A lot of tunable parameters such as achiral residues or ligand substituents,[4ab−c] additives,[4def−g] temperature,[4h] solvent,[4ijkl−m] reaction time,[4n] and others[4o−pqrstuvwxyz] have been recognized to give unusual opposite enantio-control and enable enantiodivergence. Generally, the scope of chiral molecules in enantiodivergent synthesis has mostly been limited to central chirality,[4] with recent advancements in axial chirality.[5] In contrast, the enantiodivergent synthesis and application of chiral molecules with other types of chiral elements remain scarce and highly desirable.

Inherent chirality, first used by Böhmer et al. to define the isomerism in calixarene frameworks,[6] is different from conventional central, axial, planar, helical chirality, etc.[7] Inherently chiral molecules play an important role in chiral sensing and asymmetric synthesis[8] due to their unique and rigid chiral scaffold, which thus pique the interests of chemists in the enantioselective synthesis of such type of chiral compounds. In addition to the asymmetric synthesis of inherently chiral macromolecules such as calix[4]arenes as reported by McKervey,[9a] Wang and Tong,[9bc−d] Cai,[9e] Yang,[9f] Chen,[9g] and Liu[9hi−j] and prism-like cages as reported by Wang,[9k] dominant research has focused on the synthesis of inherently chiral molecules with medium-sized ring systems (Figure 1a).[10,11] For example, Shibata,[10a] Liu,[10b,c] and Zhu[10d] reported the enantioselective synthesis of 7-membered rings with inherent chirality, respectively. Moreover, enantioselective synthesis of inherently chiral 8-membered cyclic compounds has received great attention, since Shibata and co-workers reported the first catalytic enantioselective synthesis of chiral eight-membered tetraphenylenes through Rh-catalyzed cycloadditions of two triynes.[11a] For example, the Zhu group[11b,c] and Yang group[11d,e] accomplished the highly enantioselective synthesis of saddle-shaped aza analogues of tetraphenylene. In 2024, the asymmetric synthesis of saddle-shaped eight-membered oxa-analogues through high-order annulations was reported by the Yan group[11f] and Jiang group,[11g] respectively. In addition, Liao disclosed the enantioselective synthesis of chiral eight-membered lactones via an axial-to-inherent chirality conversion strategy (Figure 1b).[11h]

Received: March 29, 2025
Revised: June 11, 2025
Accepted: June 13, 2025
Published: June 19, 2025

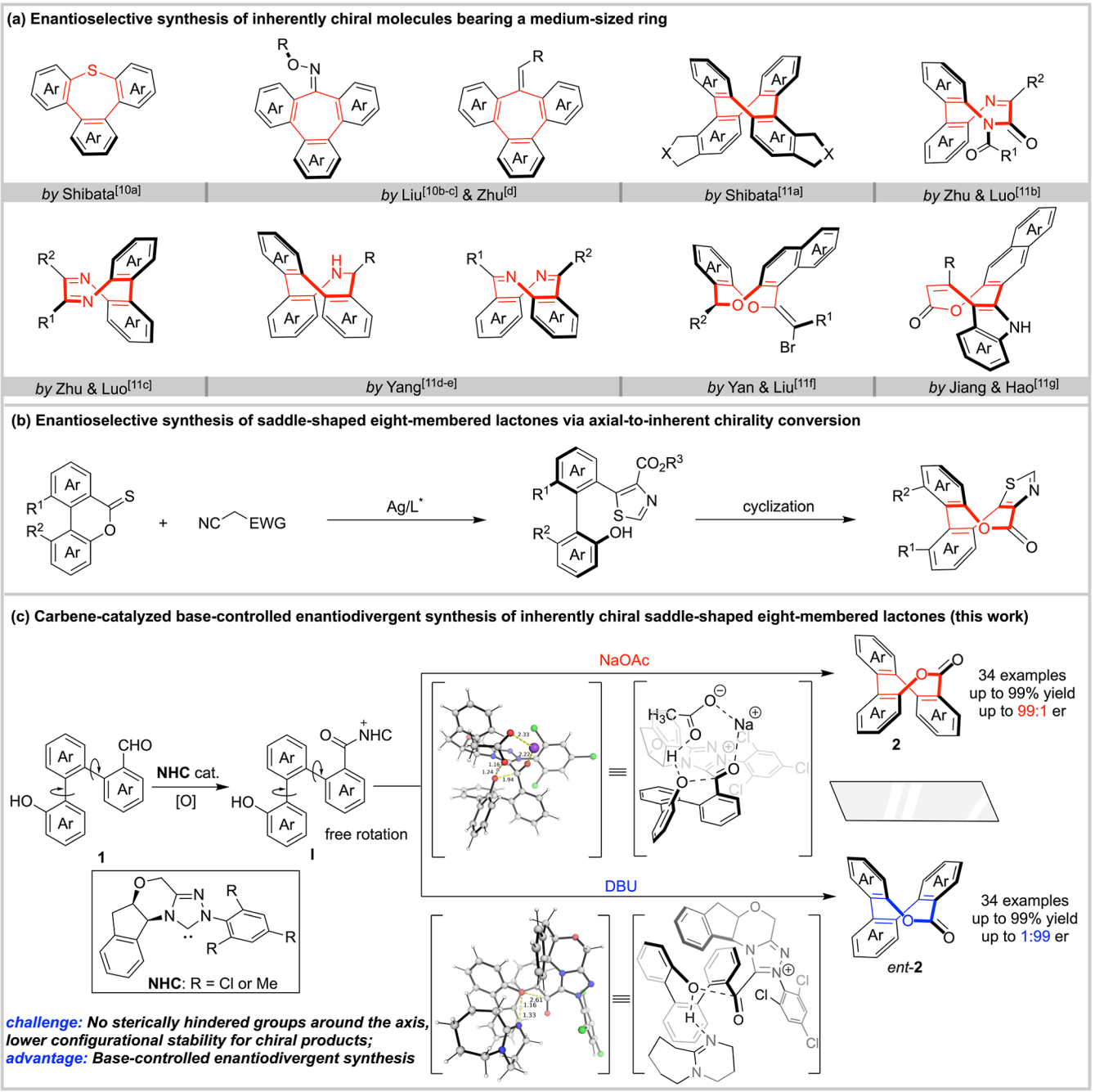


Figure 1. Background introduction and our strategy for synthesizing inherently chiral saddle-shaped eight-membered lactones.

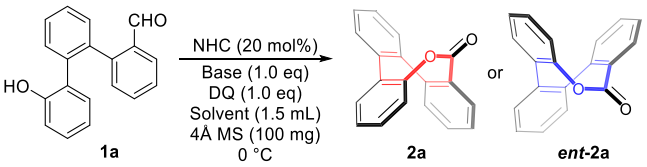
Following our ongoing interest in the catalytic asymmetric construction of medium-sized ring systems,[12ab−c] herein we reported a carbene[13]-catalyzed base-controlled enantiodivergent synthesis of inherently chiral saddle-shaped eight-membered lactones **2** via an intramolecular esterification of the triaryl aldehydes **1** (Figure 1c). With the use of the same carbene catalyst or the carbene catalysts with the same chiral scaffold, both enantiomers of the inherently chiral eight-membered lactones could be accessed in high yields with good to excellent enantioselectivities. Compared to Liao's[11h] work, the inherently chiral products **2** obtained in our work have a lower rotational barrier, since there is no substituted group around the axis for each aryl of products **2** or triaryl aldehydes **1**. In addition, the free rotation of triaryl aldehydes **1** allows for the formation of multiple configurations in the transition states for the cyclization step; therefore, the enantioselectivity is likely to be controlled by other conditions, such as bases. In this work, DFT calculations demonstrated that NaOAc and DBU have dramatically different interactions with an acyl azolium intermediate **I** in the transition state of the cyclization step and thus achieved enantiodivergent synthesis of the chiral products **2**.

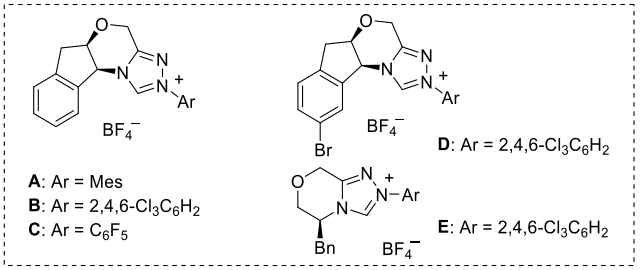
RESULTS AND DISCUSSION

We initiated our studies using **1a** as the model substrates with tetra-*tert*-butyldiphenyl-quinone (DQ)[14] as an oxidant to search for suitable conditions, with key results summarized in Table 1. The aminoindanol-derived precatalyst bearing an *N*-mesityl substituent (**A**)[15] resulted in the formation of a trace

https://doi.org/10.1021/jacs.5c05380
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Table 1. Optimization of the Reaction Conditions[a]





entry	NHC	base	solvent	yield [%][b]	er[c]
1	**A**	NaOAc	DCM	trace	
2	**B**	NaOAc	DCM	99	97:3
3	**C**	NaOAc	DCM	99	94:6
4	**D**	NaOAc	DCM	99	97:3
5	**E**	NaOAc	DCM	91	81:19
6	**B**	DBU	DCM	91	16:84
7	**B**	DIPEA	DCM	54	23:77
8	**B**	LiOH	DCM	99	21:79
9	**B**	DMAP	DCM	90	93:7
10	**B**	Cs_2CO_3	DCM	80	47:53
11	**B**	DABCO	DCM	40	83:17
12[d]	**B**	DBU	DCM	70	17:83
13[e]	**B**	DBU	DCM	60	26:74
14[f]	**B**	DBU	DCM	99	7:93
15	**A**	DBU	DCM	99	3:97
16	**A**	DBU	DMF	99	3:97

[a]Reaction conditions: **1a** (0.1 mmol), base (1.0 equiv), NHC·HBF_4 (20 mol %), 4Å MS (100 mg), and DQ (1.0 equiv) in solvent (1.5 mL) at 0 °C. [b]Isolated yield. [c]Enantiomeric ratio of **2a** was determined via HPLC on a chiral stationary phase. [d]DBU (0.5 equiv). [e]DBU (5.0 equiv). [f]0.5 equiv of 4-Nitrophenylboronic acid and 0.5 equiv of Bismuth(III) trifluoromethanesulfonate were used.

amount of the desired product **2a** (Table 1, entry 1). Gratifyingly, replacing the *N*-mesityl unit of **A** with an electron-deficient trichlorophenyl group (to get catalyst **B**)[16] gave the product in a dramatically improved yield (99% yield) and equally excellent er value (entry 2). When the precatalyst (**C**)[17] with a more electron-deficient *N*-pentafluorophenyl substitute was examined, the desired product was isolated in lower enantioselectivity (entry 3). The introduction of a bromine atom (**D**)[18] on the Indane moiety gave the product **2a** in comparable results as catalyst **B** (entry 4). The phenylalanine-derived catalyst **E** provided only moderate enantioselectivity (entry 5). Surprisingly, screening of bases (entries 6−11) revealed that the bases have a dramatic effect on the enantiocontrol. For example, the use of the strong base 1,8-diazabicyclo[5.4.0]undec-7-en (DBU) gave the opposite enantiomeric ratio (entry 6). Variation of the amount of DBU did not lead to improved results (entries 12−13). Subsequently, by evaluating the effects of typical additives, such as triflate salts, phenylboronic acid, we were able to achieve an optimal reaction condition with NHC **B** as the catalyst and DBU as the base when the reaction was performed at 0 °C in DCM for 24 h, leading to the desired product (*ent*)-**2a** with 99% isolated yield and an excellent enantioselectivity (7:93 er, entry 14). Furthermore, the use of carbene catalyst **A**, with the same chiral scaffold as carbene catalyst **B**, afforded the product (*ent*)-**2** in 99% yield and 3:97 er (entry 15). The replacement of solvent DCM with DMF gave the same results in terms of the yield or enantioselectivity (entry 16).

With acceptable optimized reaction conditions in hand (Table 1, entries 2 and 14−16), we next investigated the scope of the NHC-catalyzed base-controlled enantiodivergent cyclization reaction and the results are shown in Scheme 1. We first investigated the effect of various R^1 substituents on the reaction. For aldehyde moieties with aromatic rings bearing electron-donating groups (such as Me and MeO) or electron-withdrawing groups (such as F and Cl), all the reactions proceeded smoothly to generate both enantiomers of the desired products (**2a−2i**) in acceptable to excellent yields (82−99% yields for the **2a−2i** and 76−99% yields for (*ent*)-**2a−2i**) and enantiomeric ratios (91:9−97:3 er for the **2a−2i** and 10:90−4:96 er for (*ent*)-**2a−2i**). Aldehyde moieties bearing 1,3-benzodioxole also worked efficiently as well, affording the corresponding product **2j** with good outcomes (88% yield and 95:5 er for the **2j**, and 95% yield and 7:93 er for the (*ent*)-**2j**). Next, a series of R^2 groups on the benzene ring were examined (**2k−2q**). A variety of substituents at different positions of the aromatic ring were well tolerated, generating the corresponding products **2k−2q** (81−99% yields and 90:10 er for the **2k−2q**, and 82−99% yields and 10:90−6:94 er for (*ent*)-**2k−2q**). The absolute configuration of **2q** was confirmed by X-ray analysis.[19] Furthermore, we examined the influence of the R^3 group for the reaction (**2r−2v**). By introducing a methyl group at the 3-position of the benzene ring, product **2r** could be isolated in high yields (90% yield for the **2r** and 94% yield for (*ent*)-**2r**) and good enantioselectivities (96:4 er for the **2r** and 9:91 er for (*ent*)-**2r**). Substituents with different electronic properties at the 4-position of the benzene ring were all amenable in this reaction, giving the product in high yields with excellent enantioselectivities (**2s−2v**). Substrates with a fused aromatic ring underwent this reaction smoothly to form the corresponding products **2w** and **2x**, and the latter showed a better enantioselectivity than the former. Introducing two substituents on different benzene rings almost has no effect on the reaction (**2y−2ag**). Notably, substrates with a highly symmetric structure also can be used in this reaction, leading to the formation of both enantiomers of C_2-symmetric chiral product **2ah** in moderate to good yields and good to excellent enantioselectivities (40% yield and 94:6 er for the **2ah**, and 81% yield and 1:99 er for (*ent*)-**2ah**).

To understand the molecular origins underpinning the base-controlled enantiodivergence, we performed DFT studies at the SMD(DCM)-M06-2X/def2-TZVP//M06-2X/def2-SVP level of theory to understand the enantiodetermining step (see Supporting Information). Conformational sampling of the acyl azolium intermediate (see Supporting Information) indicates that the rotation about the C−C axial bonds is facile, allowing different conformations to easily interconvert and exist in a thermal equilibrium. With detailed conformational sampling, we located the lowest barrier transition states (TSs) leading to **2a** and (*ent*)-**2a** under NaOAc and a DBU base (Figures 2 and 3). The transition state occurs as the base performs deprotonation of the hydroxyl group on the phenol group, allowing the phenoxide oxygen to attack the carbonyl carbon of the acyl azolium intermediate to affect the ring closure.

https://doi.org/10.1021/jacs.5c05380
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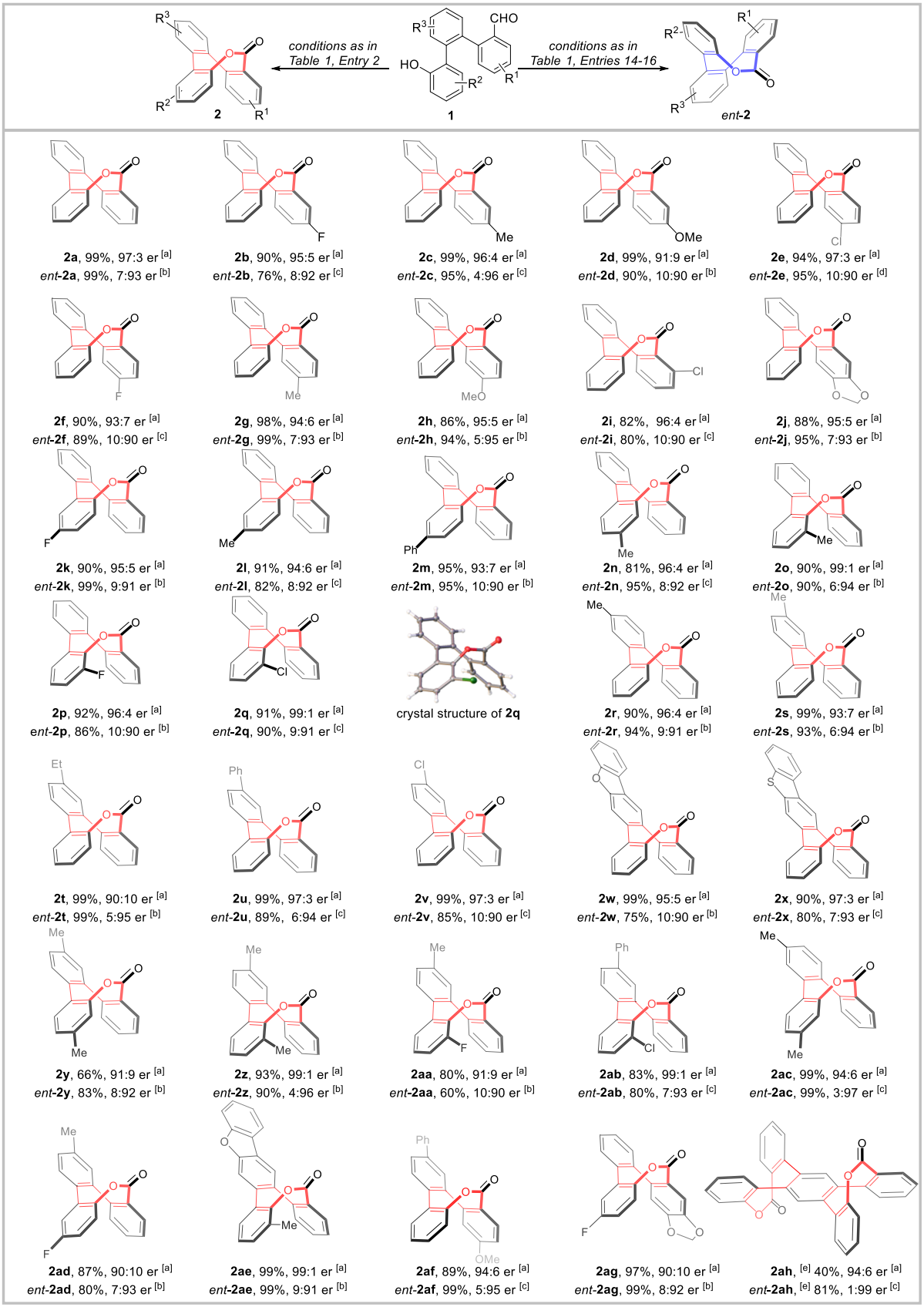
Scheme 1. [a] Reaction Conditions as Stated in Table 1, Entry 2; [b] Reaction Conditions as Stated in Table 1, Entry 14; [c] Reaction Conditions as Stated in Table 1, Entry 15; [d] Reaction Conditions as Stated in Table 1, Entry 16; [e] Single Diastereoisomer



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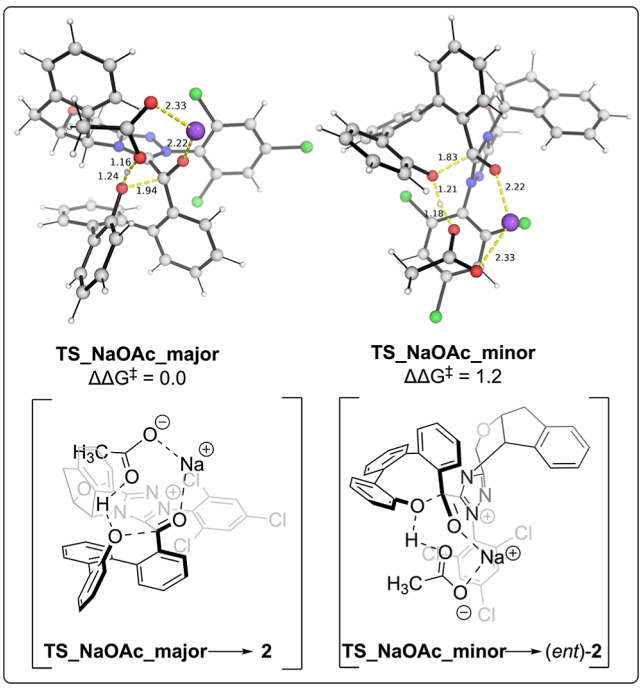

Figure 2. DFT-optimized transition state structures leading to the major and minor products under the NaOAc base. Key bond distances are given in Å.

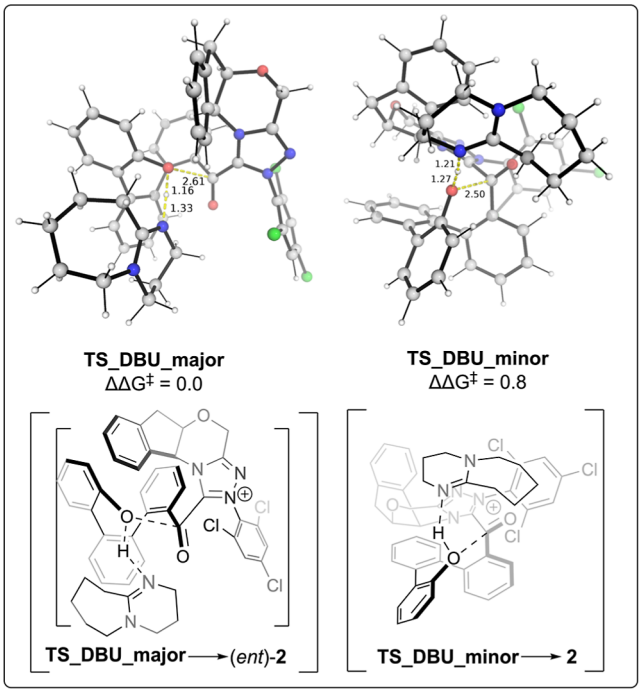

Figure 3. DFT-optimized transition state structures leading to the major and minor products under the DBU base. Key bond distances are given in Å.

Under the NaOAc base, the TS leading to the major product **2a**, **TS_NaOAc_major**, is lower than the TS leading to the minor product (*ent*)-**2a**, **TS_NaOAc_minor**, by 1.2 kcal/mol (Figure 2). This translates to an er ratio of 90:10 using a simple transition state theory, in reasonably good agreement with the experimentally observed er ratio of 97:3. The analysis of frontier molecular orbital (HOMO and LUMO) non-covalent interaction (NCI) plots (see Supporting Information, Figure S3) suggests that the FMOs are similar for both cases and that **TS_NaOAc_major** may benefit from more favorable noncovalent interactions, making the barrier lower than **TS_NaOAc_minor**. This has been confirmed by distortion interaction analysis, which shows that although the distortion energy is 1.0 kcal/mol higher in **TS_NaOAc_major**, the interaction energy is more favorable, by 2.9 kcal/mol than in **TS_NaOAc_minor** (Table S6).

Under the DBU base, on the other hand, the lowest barrier TS structure leading to the major product (*ent*)-**2a**, via **TS_DBU_major**, is lower than the TS leading to the minor product **2a**, **TS_DBU_minor**, by 0.8 kcal/mol (Figure 3). This translates to an er ratio of 81:19, in good agreement with the experimentally observed er ratio of 84:16 (Table 1, entry 6). The FMOs are similar for both cases (Supporting Information, Figure S5). Distortion interaction analysis suggests that **TS_DBU_major** benefits from a lower distortion energy (by 14.5 kcal/mol) although it has a less favorable interaction energy (by 13.9 kcal/mol) (Table S6). We note that the differences in the noncovalent interaction network in the presence of different bases contribute to the divergent enantioselectivity.

To demonstrate the practicality of our method, we first conducted the desymmetrization reaction of compound **3** in the presence of 10 mol % of NHC precatalyst **A**, which efficiently yielded the eight-membered lactone **4** in 99% yield with a 1:99 er. Product **4** was found to be highly resistant to racemization (no racemization observed at 140 °C in mesitylene for 4 h), with a computed rotational barrier of 34.9 kcal/mol (Supporting Information, Figure S7). The product **4** was amenable in various transformations (Scheme 2a). For instance, the aldehyde group of **4** can react with 1,3-ethanedithiol under acidic conditions to give product **5** in a high yield and enantioselectivity. The Wittig reaction of **4** using the stable ester-bearing ylide resulted in the formation of the target olefin derivative **6** in 99% yield, 3.4:1 E:Z ratio, and 1:99 er. Condensation of the aldehyde group with NH_2OH generated oxime **7** in 75% yield and 1:99 er. Oxidation of the aldehyde group could produce chiral carboxylic acid **8** in good yields. The palladium-catalyzed C−H olefination could afford product **9** in 80% yield and 1:99 er. Reduction of **4** in DCM with HBpin afforded product **10** in 90% yield with retention of the product er value. Alkenes derived from bioactive molecules, such as Cholesterol, can react with lactone **4** to offer the corresponding product **11** in moderate to high yields with high stereoselectivity. Product **2a** can achieve the conversion from inherent chirality to central chirality (**13**) through a sequence of Tebbe olefination, followed by Pd-catalyzed hydrogenation.

Inspired by the diverse biological activities of lactones, we initiated preliminary investigations into the antimicrobial properties of our products to develop potent antibacterial agrochemicals for crop protection (Scheme 2b). Most evaluated compounds demonstrated significant inhibitory activity against *Xanthomonas oryzae pv oryzae (Xoo)*, the causative agent of bacterial leaf blight (BLB) disease, which poses a substantial risk to rice cultivation. Specifically, the enantio-enriched eight-membered lactone (*ent*)-**2c** exhibited a remarkable rate of 69.82% against *Xoo* at a concentration of 50 μg/mL, exceeding the positive controls, thiodiazole-copper (**TC**) and bismerthiazol (**BT**). Additionally, the synthesized lactone products demonstrated notable inhibitory effectiveness against *Xanthomonas axonopodis pv citri (Xac)*, a bacterium

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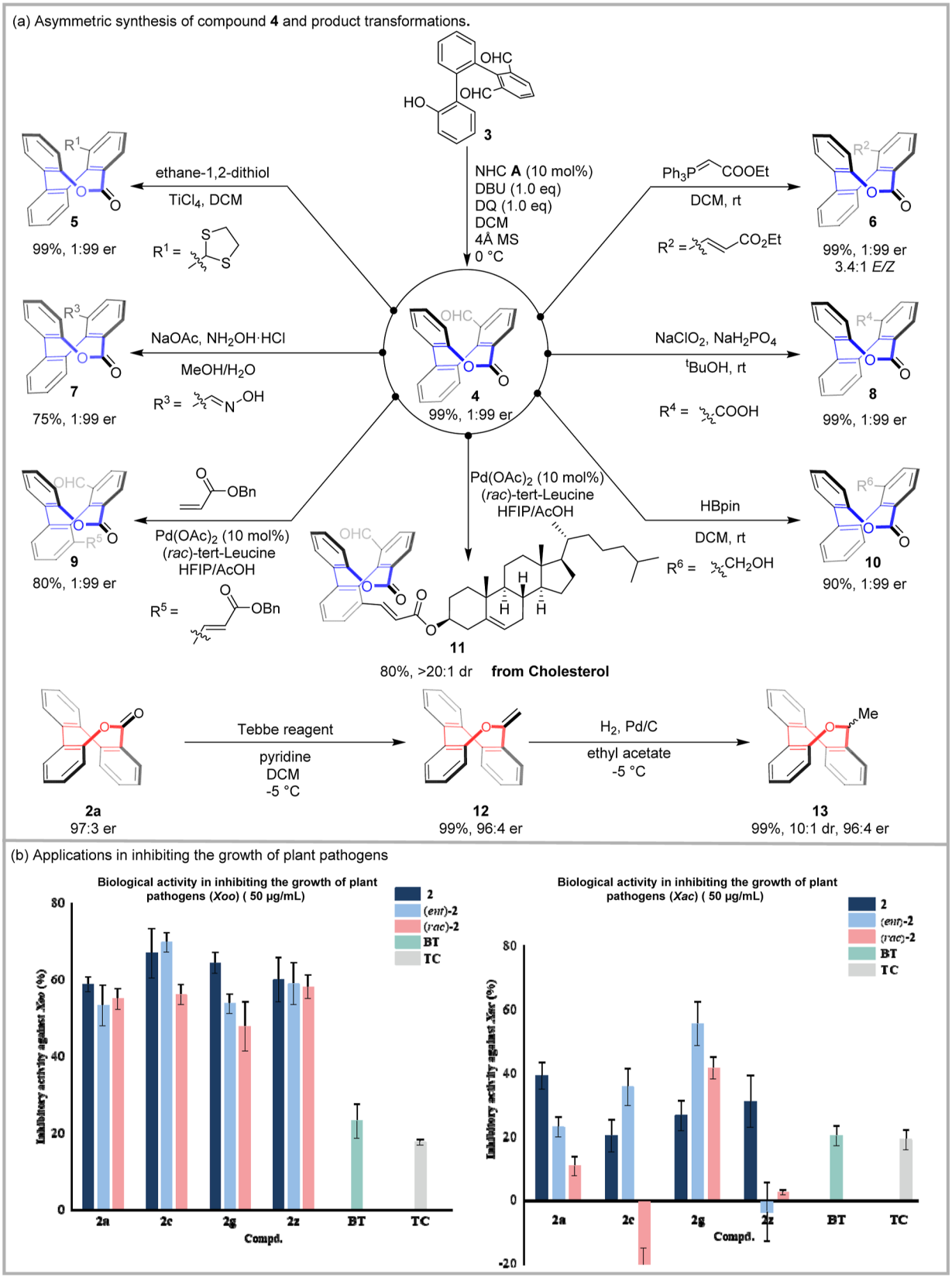
Scheme 2. Synthetic Applications and Biological Activity Test



responsible for inducing lesions on plant surfaces, which can lead to plant necrosis. In this context, compound (*ent*)-**2g** exhibited an inhibitory activity of 55.63%, significantly exceeding that of the positive controls, which exhibited activities of 19.04% for **TC** and 20.34% for **BT**. In contrast, (*rac*)-**2c** and (*ent*)-**2z** exhibited lower antibacterial activities. This suggests that the inherent chiralities of the lactone structures are likely to play a significant role in their biological

https://doi.org/10.1021/jacs.5c05380
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

efficacy. Notably, 14 chiral products synthesized via our methodology demonstrated markedly superior antibacterial activities, establishing them as promising candidates for the development of novel pesticide formulations.

CONCLUSIONS

In summary, we have developed a carbene-catalyzed enantiodivergent intramolecular cyclization reaction for the synthesis of saddle-shaped, eight-membered lactones with inherent chirality. Both enantiomers of the inherently chiral eight-membered lactones could be obtained in high yields with good to excellent enantioselectivities by switching the bases in the presence of the same carbene catalyst or the carbene catalysts with the same chiral scaffold. Further stereospecific transformations and an antibacterial activity test of the inherently chiral eight-membered lactone products demonstrated the synthetic utility of this method. Preliminary DFT calculations indicated that the bases have dramatically different interactions with the acyl azolium intermediate in the transition state of the cyclization step, thus effecting the enantiodivergent synthesis of the chiral products.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.5c05380.

Experimental procedures and spectral data for all new compounds (PDF)

Accession Codes

Deposition Number 2413315 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structure service.

AUTHOR INFORMATION

Corresponding Authors

Yonggui Robin Chi − *State Key Laboratory of Green Pesticide, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Guiyang 550025, China; School of Chemistry, Chemical Engineering, and Biotechnology, Nanyang Technological University, Singapore 637371, Singapore;* orcid.org/0000-0003-0573-257X; Email: robinchi@ntu.edu.sg

Xinglong Zhang − *Department of Chemistry, The Chinese University of Hong Kong, Shatin, Hong Kong 999077, P. R. China;* orcid.org/0000-0003-1698-692X; Email: xinglong.zhang@cuhk.edu.hk

Xing Yang − *Key Laboratory of Chemical Biology and Traditional Chinese Medicine (Ministry of Educational of China), Key Laboratory of the Assembly and Application of Organic Functional Molecules of Hunan Province, College of Chemistry and Chemical Engineering, Hunan Normal University, Changsha 410081, P. R. China;* orcid.org/0009-0002-3031-6746; Email: xingyang@hunnu.edu.cn

Authors

Liwen Wei − *Key Laboratory of Chemical Biology and Traditional Chinese Medicine (Ministry of Educational of China), Key Laboratory of the Assembly and Application of Organic Functional Molecules of Hunan Province, College of Chemistry and Chemical Engineering, Hunan Normal University, Changsha 410081, P. R. China*

Yuhang Chen − *Key Laboratory of Chemical Biology and Traditional Chinese Medicine (Ministry of Educational of China), Key Laboratory of the Assembly and Application of Organic Functional Molecules of Hunan Province, College of Chemistry and Chemical Engineering, Hunan Normal University, Changsha 410081, P. R. China*

Qinglong Zhou − *Key Laboratory of Chemical Biology and Traditional Chinese Medicine (Ministry of Educational of China), Key Laboratory of the Assembly and Application of Organic Functional Molecules of Hunan Province, College of Chemistry and Chemical Engineering, Hunan Normal University, Changsha 410081, P. R. China*

Zhikang Wei − *Key Laboratory of Chemical Biology and Traditional Chinese Medicine (Ministry of Educational of China), Key Laboratory of the Assembly and Application of Organic Functional Molecules of Hunan Province, College of Chemistry and Chemical Engineering, Hunan Normal University, Changsha 410081, P. R. China*

Ting Tu − *State Key Laboratory of Green Pesticide, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Guiyang 550025, China*

Shichao Ren − *State Key Laboratory of Green Pesticide, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Guiyang 550025, China;* orcid.org/0000-0003-4248-6021

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.5c05380

Author Contributions

⊥L.W., Y.C., Q.Z., and Z.W. contributed equally.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We acknowledge the National Natural Science Foundation of China (22201071, 22371058), Natural Science Foundation of Hunan Province (2023JJ10027), Scientific Research Fund of Hunan Provincial Education Department (22A0048), and Science and Technology Planning Project of Hunan Province (2018TP1017). X.Z. acknowledges the funding support from the Chinese University of Hong Kong (CUHK) under the Vice-Chancellor Early Career Professorship Scheme Research Startup Fund (Project Code 4933634) and Research Startup Matching Support (Project Code 5501779).

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