ACS Catalysis

pubs.acs.org/acscatalysis Research Article

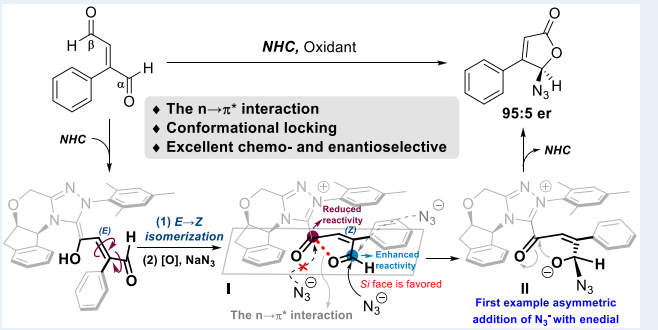
Carbene-Catalyzed Addition/Lactonization of Azides and Enedials

Xuyang Liang,[§] Qingyun Wang,[§] Pengcheng Zheng,* and Yonggui Robin Chi*

Cite This: *ACS Catal.* 2025, 15, 18750−18757 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: The azide moiety, as a bioactive structural unit, is found in a wide range of drugs and pharmaceutical compounds. Currently, the predominant method for synthesizing azide-containing chiral molecules involves S_N2-type reactions. Therefore, developing diverse and efficient methodologies for the synthesis of chiral azide-containing molecules is of great significance. However, the direct addition of azide anions to aryl aldehydes and ketones remains difficult and typically requires strong Brønsted acid catalysts to proceed. Moreover, achieving high enantioselectivity in such addition reactions via asymmetric catalysis remains a challenge. Herein, we report an N-heterocyclic carbene (NHC)-catalyzed strategy for the asymmetric synthesis of chiral azide-containing lactones. The reaction between enedials and sodium azide proceeds with chemo- and enantioselectivity, affording optically enriched azide-containing lactones. These azide-containing lactones can be further converted into various functional molecules, and their antibacterial activities are also investigated. In addition, density functional theory (DFT) calculations, along with noncovalent interaction (NCI) and natural bond orbital (NBO) analyses, demonstrate that the chemo- and enantioselectivity of the azide anion can be effectively modulated by the $n\rightarrow\pi^*$ interactions involving the acylazolium intermediate. These findings may enrich the synthetic strategies of chiral azide-containing compounds.



KEYWORDS: *N-heterocyclic carbenes, organocatalysis, addition of azide anion, chiral azide-containing lactone, antibacterial activity*

INTRODUCTION

The azide moiety is widely present in various bioactive molecules and pharmaceuticals.[1−6] For example, Azvudine and Zidovudine are antiviral drugs used in the treatment of HIV,[7−9] while Azidocillin has been reported as an antibiotic for respiratory tract infections.[9,10] Currently, the incorporation of azide groups into functional molecules is predominantly achieved through S_N2-type reactions (Figure 1a).[9,11] The development of novel methodologies for azide group installation is highly desirable, as it can greatly expand the structural diversity of azide-containing compounds.[12] It is generally recognized that the nucleophilic addition of azide anions to aldehydes can be easily realized to afford the corresponding α-azido alcohols. However, it is not an easy task.[13,14] For instance, in the Schmidt reaction, stoichiometric amounts of strong Brønsted acids (e.g., H_2SO_4 and TfOH) are required to activate aldehydes toward reaction with azide anions, forming α-azido alcohol intermediates.[15,16] These intermediates are typically unstable and rapidly undergo rearrangement to form nitriles. In 2010, Banert and co-workers[14] investigated the equilibrium constants (K) for reactions between aldehydes and hydrazoic acid. Their results revealed low K values for aryl aldehydes, indicating that such additions are highly unfavorable and have long been overlooked in synthetic chemistry (Figure 1b). Furthermore, achieving the asymmetric addition of azide anions to aldehydes remains a significant challenge.

Herein, we present a novel strategy for the N-heterocyclic carbene (NHC)-catalyzed asymmetric nucleophilic addition of azide anions to aldehyde/ketone groups, enabling the synthesis of enantioenriched azide-containing lactones. In this reaction, sodium azide worked as an azide anion source. The enedial substrate **1a** reacts with the NHC catalyst; during this process, the *E*-isomer enedial undergoes $E\rightarrow Z$ isomerization to afford a *Z*-isomer Breslow intermediate. Moreover, an intramolecular hydrogen bond is formed in the *Z*-isomer Breslow intermediate, which can largely stabilize the structure.[17] An external oxidant is required to generate the corresponding acylazolium intermediate **I**.[18−20] Subsequently, the azide anion undergoes a stereoselective addition to the *Si* face of the remaining aldehyde moiety, affording azido alcohol intermediate **II** with a high optical purity. Finally, intramolecular lactonization of intermediate **II** furnishes the desired azide-containing lactone product **3a** (Figure 1c).

Received: September 5, 2025
Revised: October 18, 2025
Accepted: October 20, 2025
Published: October 29, 2025

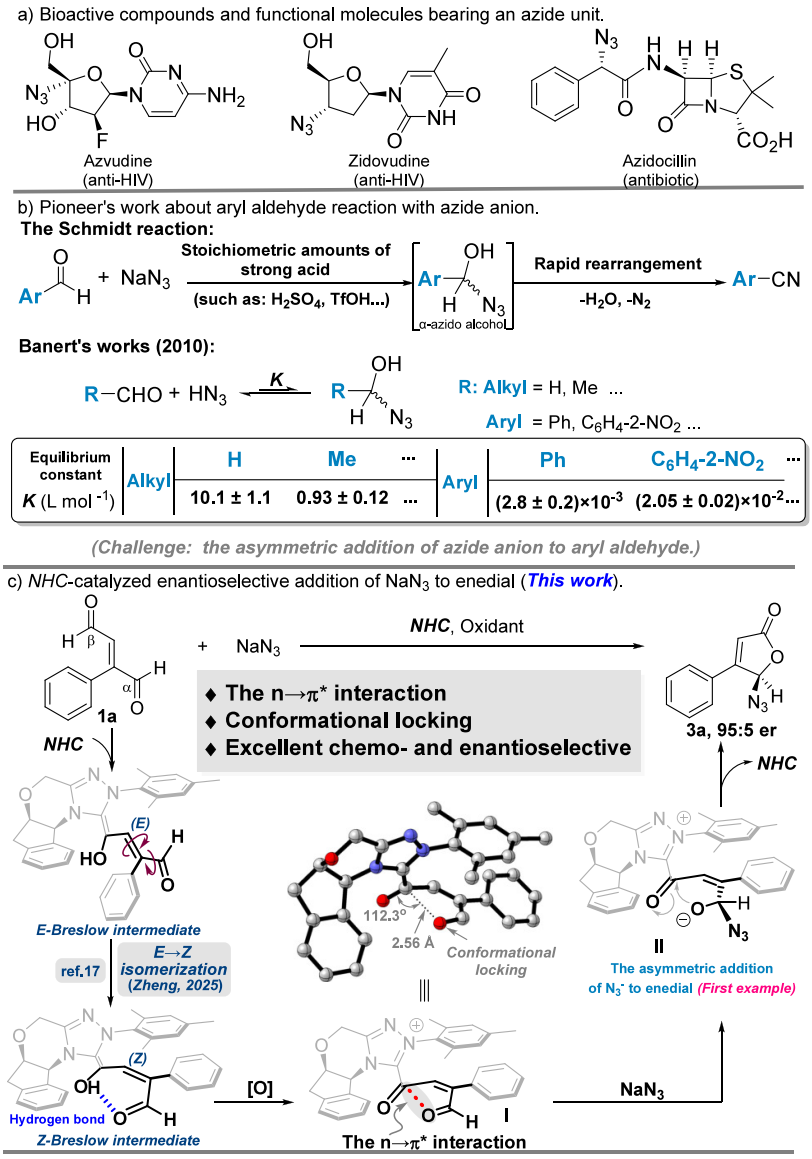


Figure 1. (a) Azide-containing functional molecules; (b) Pioneer's work; (c) strategy for synthesizing azide-containing lactone via $n\rightarrow\pi^*$ interaction.

To the best of our knowledge, achieving asymmetric addition to aldehydes without any steric or electronic directing groups, such as steric hindrance or weak interactions to lock the carbonyl conformation, remains extremely challenging. Inspired by our previous work, we have demonstrated that certain noncovalent interactions, such as silicon-tetrahedral bonding,[21] chalcogen bonding,[22] and pnictogen bonding,[23] can effectively lock the conformation of isomeric intermediates. These interactions, when combined with NHC catalysis, have enabled the construction of heteroatom-stereogenic molecules bearing stereogenic centers on P, S, or Si atoms. In this work, the acylazolium intermediate **I** may involve an intramolecular $n\rightarrow\pi^*$ interaction, in which the carbonyl oxygen of the aldehyde moiety donates a lone pair to the electron-deficient carbon of the acylazolium group.[24] This interaction is proposed to lock the conformation of the aldehyde moiety and thereby facilitate the enantioselective nucleophilic addition of the azide anion in the presence of the NHC catalyst (Figure 1c). In recent years, the significance of $n\rightarrow\pi^*$ interactions has been increasingly recognized,[25−33] and this type of noncovalent interaction has attracted growing attention in the field of organocatalysis.[34−41]

METHODS

General Procedure for the Catalytic Reactions. To a dry 4.0 mL vial equipped with a magnetic stir bar were added **1a** (0.10 mmol), **2a** (0.50 mmol), pre-**NHC-A** (0.02 mmol), and DQ (0.10 mmol). The anhydrous tetrahydrofuran (2.0 mL) and 4 Å MS (100 mg) were added, and the solution was sealed. The reaction mixture was stirred at 45 °C for 12 h. Then the mixture was directly concentrated under reduced pressure to afford a crude product. The crude product was purified via column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1) to afford the desired product **3a**.

General Procedure for the Scale-Up Catalytic Reactions. To a 100.0 mL overdried round-bottom flask equipped with a magnetic stir bar were added **1a** (6.24 mmol, 1g), **2a** (31.22 mmol, 2.03 g), pre-**NHC-A** (1.25 mmol, 0.52 g), and DQ (0.1 mmol, 2.55 g). The flask was then sealed before adding tetrahydrofuran (60.0 mL). The reaction

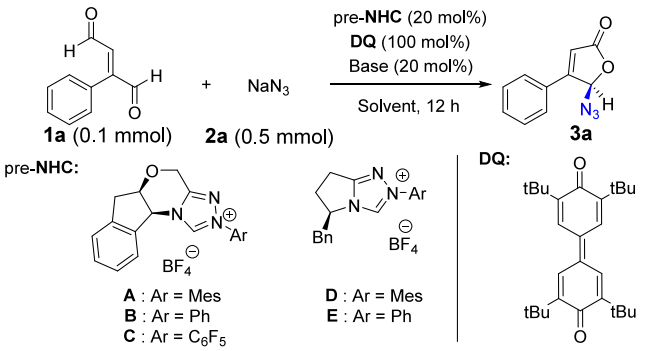
https://doi.org/10.1021/acscatal.5c06307
ACS Catal. 2025, 15, 18750−18757

mixture was stirred at 45 °C for 24 h. Then the mixture was directly concentrated under reduced pressure to afford a crude product. The crude product was purified via column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1) to afford the desired product **3a** in 49% yield.

RESULTS AND DISCUSSION

To explore suitable conditions for the above design, enedial (**1a**) was chosen as the model substrate and NaN_3 as the nucleophile for condition screening. The key results are summarized in Table 1. To our delight, the desired chiral

Table 1. Optimization of Reaction Conditions[a]



entry	pre-**NHC**	base	solvent	yield [%][b]	er[c]
1	**A**	TEA	THF	53	87:13
2	**B**	TEA	THF	30	79:21
3	**C**	TEA	THF	trace	53:47
4	**D**	TEA	THF	20	68:32
5	**E**	TEA	THF	trace	56:44
6	**A**	K_2CO_3	THF	34	89:11
7	**A**	*t*-BuOK	THF	16	83:17
8	**A**	NaOMe	THF	26	87:13
9	**A**	DABCO	THF	trace	73:27
10	**A**	TEA	EA	26	90:10
11	**A**	TEA	Toluene	14	84:16
12	**A**	TEA	DCM	23	88:12
13	**A**	TEA	MeCN	34	64:36
14[d]	**A**		THF	53	87:13
15[e]	**A**		THF	54	95:5
16[f]	**A**		THF	63	95:5

[a]Unless otherwise specified, the reactions were conducted with **1a** (0.10 mmol), **2a** (0.50 mmol), pre-**NHC**s (0.02 mmol), **DQ** (0.1 mmol), solvents (2.00 mL), and 4Å MS (100.00 mg) at 25 °C for 12 h. [b]Isolated yield of **3a**. [c]The er values were determined via HPLC on chiral stationary phase. [d]Without base. [e]$MgCl_2$ (0.02 mmol) as an additive. [f]45 °C as the reaction temperature.

product **3a** was obtained in 53% yield and 87:13 er value when the reaction was carried out with pre-**NHC-A** as a catalyst in THF at 25 °C for 12 h, with DQ as an oxidant. The effects of different pre-**NHC** (-**B**, -**C**, -**D**, -**E**, Table 1, entries 2−5) were also investigated; the yields and er values did not show a positive improvement. Then, various bases were subsequently evaluated. Compared with organic bases, the yields dropped a lot via using inorganic bases (Table 1, entries 6−9). Furthermore, the effect of solvent was also examined; THF was found to be a suitable solvent (Table 1, entries 10−13). When excess NaN_3 was employed as the base and nucleophile, the yield and er value showed no significant improvement (Table 1, entry 14). To our surprise, when $MgCl_2$ was introduced as the additive, the er value of product **3a** could be obtained in excellent enantioselectivity (95:5 er) with moderate yield (54%). The $MgCl_2$ as a Lewis acid may coordinate the carbonyl group of substrate **1a** to improve the selectivity (Table 1, entry 15).[42,43] For the sake of improving the yield, the optimal reaction result was afforded when 45 °C was the reaction temperature; the isolated yield of product **3a** was provided in 63% with excellent enantioselectivity (95:5 er) (Table 1, entry 16).

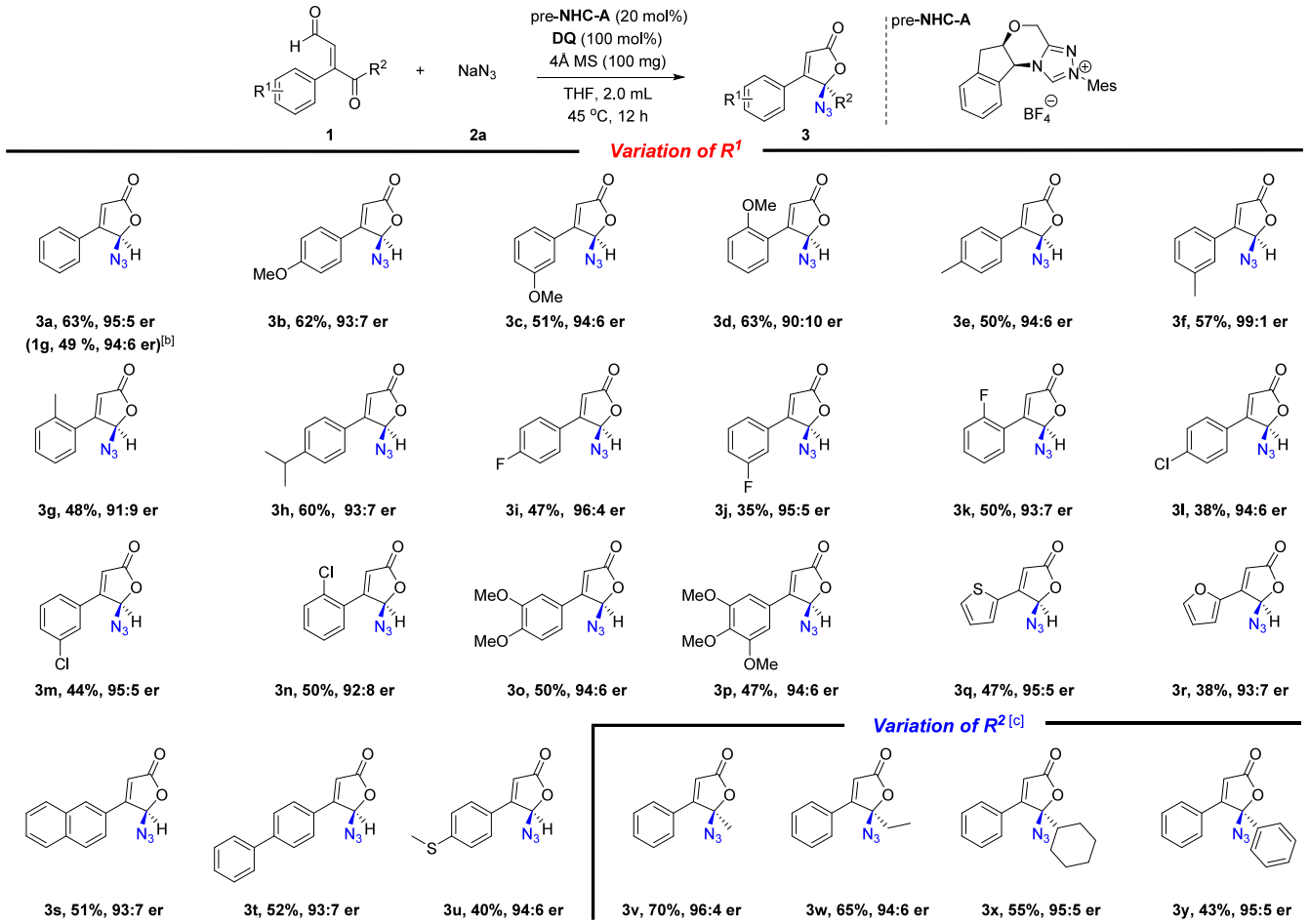
Having an acceptable condition after screening the reactive factor, the generality of the reaction was then estimated (Scheme 1). First, when the electron-donating substituents were installed on each (para-, meta-, and ortho-) position of the benzene ring in the enedial, the corresponding products exhibited moderate to good yields with high optical purities (**3a**−**3h**, **3o**, **3p**, and **3u**). The catalytic approach could also be carried out smoothly on a 1.00 g scale with the desired product **3a** in acceptable yield and excellent enantioselectivity (49%, 94:6 er). It was worth noting that the yields could be gradually decreased under these current catalytic conditions, when the electron-withdrawing substituents were installed on the same position of the benzene ring. The optical purities were basically unchanged (**3i**−**3n**, **3q**, and **3r**). Furthermore, when the benzene ring of the enedial was switched to the 2-naphthyl or 4-biphenyl group, the corresponding products **3s** and **3t** were afforded in moderate yields and excellent er values. Meanwhile, the compound **1** also showed good tolerance to various substitution patterns (R^2 group) and was investigated. Pleasingly, the products could be obtained with alkyl substituents (methyl, ethyl, and cyclohexyl), giving the target products in good yields with excellent enantioselectivities (**3v**−**3x**). Changing the alkyl substituents to the aromatic substituent such as benzene allowed the reaction to proceed smoothly with moderate yield and brilliant optical purity (43%, 95:5 er, **3y**).

With our convenient method to access chiral azide-containing lactones, further transformations of product **3v** were carried out through simple protocols, and the functional molecules are shown in Scheme 2. For instance, chiral azide **3v** could be further transformed to a chiral phosphoramide **4a** with 62% yield and 96:4 er value by using triethyl phosphite. The synthetic strategy could be used to design functional molecules.[44,45] In addition, the classic click reaction[46,47] could also be performed well; the enantioenriched product **4b** could be easily afforded in 91% yield and 96:4 er value. The alkynyl-containing drugs (norethindrone and propyzamide) readily transformed chiral triazole products **4c** and **4d** (CCDC: 2401908) in excellent yield and er value under $CuSO_4$ and sodium ascorbate conditions. The absolute configurations of the azide-containing lactones were established by X-ray crystallographic analysis of derivative **4d**.

To understand the mechanism of the catalytic reaction, some control experiments were carried out (Scheme 3). Based on the model reaction conditions, two additional experiments were performed (w/o pre-**NHC-A**, w/o pre-**NHC-A** & DQ). After 12 h, no desired product **3a** can be detected by crude ^1H NMR (see SI), and substrate **1a** still remained. The results suggested that the nucleophilic addition of azide anion to the aldehyde moiety of enedial was kinetically unfavorable without NHC catalysis. Furthermore, the influence of catalyst loading and product inhibition was investigated. The experimental results revealed that low catalyst loading for the reaction was adverse, and the presence of the product **3a** had no effect on

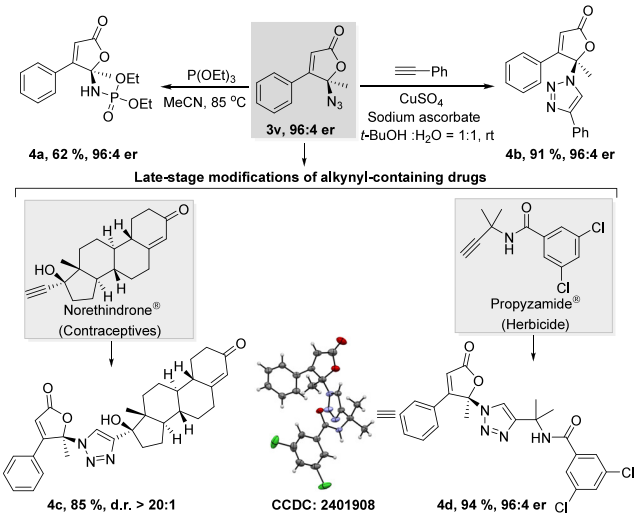
https://doi.org/10.1021/acscatal.5c06307
ACS Catal. 2025, 15, 18750−18757

Scheme 1. Substrate Scope[a]

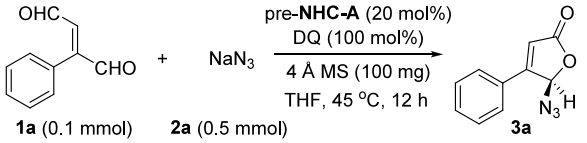


[a]Reaction conditions as stated in Table 1, entry 16, yields were isolated yields after purification by column chromatography, er values were determined *via* HPLC on a chiral stationary phase. [b]The reaction was carried out at 1.00 g-scale based on **1a** (6.24 mmol), 0.20 mmol pre-**NHC-A**, reaction time was 24 h. [c]1,4-dioxane as a solvent.

Scheme 2. Synthetic Transformations of 3v



Scheme 3. Control Experiments for Mechanistic Studies



Conditions	**3a** (Yield %) [a]
1. w/o pre-**NHC-A**	0%
2. w/o pre-**NHC-A** and DQ	0%

[a] detected by crude ^{1}H NMR.

either yield or *ee* value (see theSupporting Information). Meanwhile, the nonlinear effect was also characterized: a linear relationship between the *ee* value of product **3a** and the *ee* value of the **NHC-A** catalyst, indicating that a single catalyst was involved in the enantiodetermining transition state (see the Supporting Information).

In the year, we had reported the substrate **1a** as *E*-form formed the Breslow intermediate with the NHC catalyst, which could achieve the *E*→*Z* isomerization under mild conditions.[17,48] Furthermore, additional DFT calculations were performed to investigate the influence of the $n\rightarrow\pi^*$ interaction in intermediate **I**. First, noncovalent interaction (NCI) analysis revealed an attractive interaction between the α-aldehyde group and the NHC-bound acylazolium moiety (Figure 2a).

https://doi.org/10.1021/acscatal.5c06307
ACS Catal. 2025, 15, 18750−18757

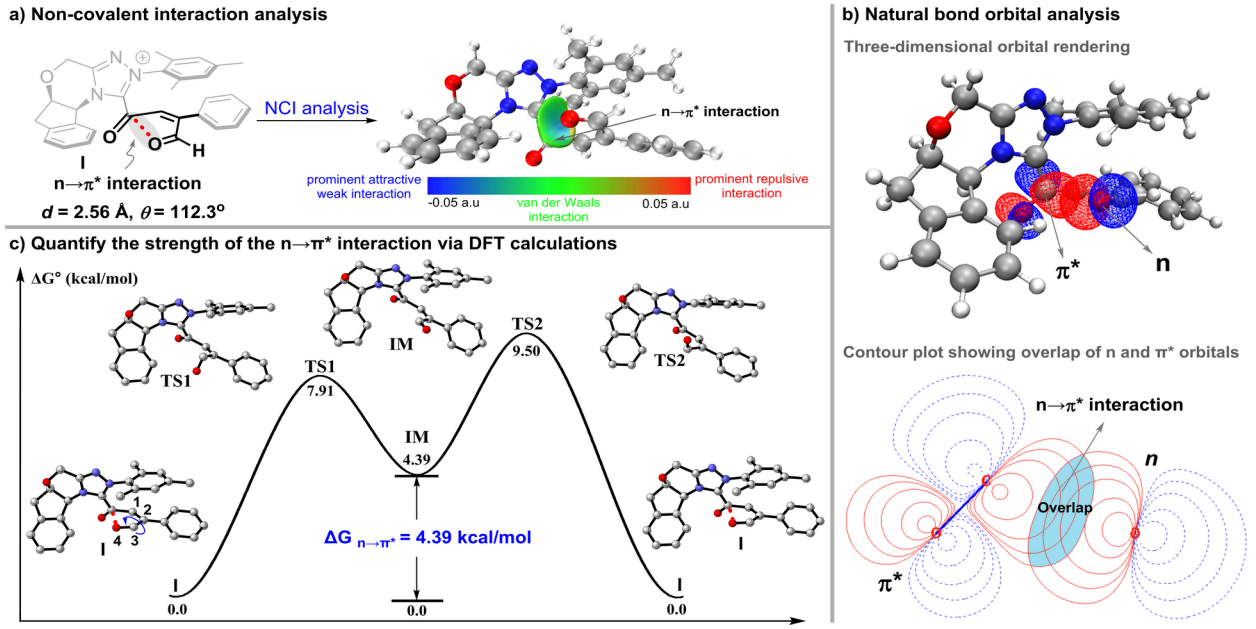


Figure 2. (a) Noncovalent interaction analysis of intermediate **I**; (b) natural bond orbital analysis; and (c) quantification of the strength of the $n\rightarrow\pi^*$ interaction. All the theoretical calculated results are computed at the SMD (THF)-M06−2X-D3/def2-TZVPP// SMD (THF)-M06−2X-D3/def2-SVP level of theory and are quoted in kcal/mol.

The results indicated that the α-aldehyde group interacted with the NHC-bound acylazolium moiety. Natural bond orbital (NBO) analysis further supported this hypothesis by showing orbital overlap between the lone pair electrons of the oxygen atom in the α-aldehyde and the π^* orbital of the acylazolium carbonyl (Figure 2b). The highly polarized acylazolium moiety promoted the lone-pair electrons of the α-aldehyde to fill into the π^* orbital. To further quantify this interaction, a rotational potential energy surface scan was performed on the α-aldehyde group in intermediate **I** (Figure 2c). The strength of the $n\rightarrow\pi^*$ interaction was calculated (ΔG = 4.39 kcal/mol), indicating that this interaction may contribute significantly to conformational stabilization. In addition, the lone pair donation to the π^* orbital reduced the electrophilicity of the NHC-bound acylazolium moiety, protecting it from direct nucleophilic attack by the azide anion and thus preventing the formation of undesired acyl azide byproducts.[49,50]

The ongoing studies in our laboratories include the development of a new methodology and the construction of pesticide candidates. Therefore, we performed preliminary studies on the antibacterial activities of the obtained chiral azide-containing lactones to search for potent antimicrobial agrochemicals for plant protection. In vitro bioassay evaluations were performed to assess the inhibition activity against two plant pathogens, including *Xoc* (*Xanthomonas oryzae* pv *oryzicola*) and *Xac* (*Xanthomonas axonopodis* pv *citri*).[51−53] The above bacteria could lead to leaf blight and citrus canker, respectively, which could cause huge economic losses in the production of rice, orange, lemon, and so on. According to the analysis shown in Table 2, it was found that the different configurations of product **3v** performed excellent activities to inhibit both *Xoc* and *Xac*. But the antibacterial activities of derivative products (**4a**−**4b**) were obviously decreased. These results indicated that the azide group was a vital pharmacophore to show antibacterial activity. Additionally, the analogous compounds (**3a** and **3v**) also exhibited bioactivity variations, and **3v** performed with excellent antibacterial activity. The methyl group of compound **3v** may improve the lipophilicity and promote its penetration into the cytomembrane of bacteria.[54] Given the excellent antibacterial activity, the compounds (*R*-**3v**, *S*-**3v**, and ± -**3v**) were also examined with respect to the EC_{50} values (Table 3).

Table 2. In Vitro Antibacterial Activity of the Target Compounds against *Xoc* and *Xac* at 100 μg/mL[a]

compound	*Xoc* inhibition rate [%]	*Xac* inhibition rate [%]
(*R*)-**3a**	89.35 ± 0.89	53.62 ± 1.26
(*S*)-**3a**	72.91 ± 3.86	80.43 ± 0.52
(±)-**3a**	51.06 ± 2.76	38.14 ± 0.20
(*R*)-**3v**	65.47 ± 2.65	**97.30 ± 0.57**
(*S*)-**3v**	**97.89 ± 0.16**	**95.34 ± 0.36**
(±)-**3v**	97.70 ± 0.57	98.54 ± 0.12
(*S*)-**4a**	0.00	28.18 ± 0.81
(±)-**4a**	26.17 ± 1.93	17.25 ± 1.69
(*S*)-**4b**	47.57 ± 3.51	14.28 ± 0.99
(±)-**4b**	67.77 ± 2.52	0.00
BT[b]	35.90 ± 2.38	38.54 ± 2.22
TC[b]	69.24 ± 1.83	33.60 ± 2.42

[a]All data were average data of three replicates. The bold is used to highlight the notable highest inhibition rate of these compounds. [b]Commercial bactericide, BT = bismerthiazol was used as the positive control. TC = thiodiazole copper was used as the positive control.

Table 3. EC_{50} Values against *Xoc* and *Xac* of the Target Compounds

	Xoc		*Xac*	
compound	R^2	EC_{50}(μg/mL)	R^2	EC_{50}(μg/mL)
(*R*)-**3v**	0.97	661.6	0.91	7.9
(*S*)-**3v**	0.99	2.5	0.93	11.2
(±)-**3v**	0.98	3.0	0.98	3.7
BT	0.95	128.3	0.97	116.9
TC	0.92	50.5	0.94	168.6

https://doi.org/10.1021/acscatal.5c06307
ACS Catal. 2025, 15, 18750−18757

The EC_{50} values of the *S*-**3v** and ± -**3v** in the curative effect of *Xoc* were 2.5 and 3.0 μg/mL, respectively, which were superior to those of bismerthiazol (BT) and thiodiazole copper (TC) with EC_{50} values of 128.3 and 50.5 μg/mL. The EC_{50} value of compound *R*-**3v** was 661.6 μg/mL. The compounds *S*-**3v** and ± -**3v** showed excellent antibacterial activities compared with *R*-**3v**; the stereospecific binding of **3v** may exhibit differences for *Xoc*.[55] The EC_{50} values of the compound *R*-**3v**, *S*-**3v**, and ± -**3v** in the protective effect of *Xac* were 7.9, 11.2, and 3.7 μg/mL, respectively, superior to those of BT (116.9 μg/mL) and TC (168.6 μg/mL). The above results suggested that chiral azide molecules exhibited obviously superior antibacterial activities and provided a method to develop new chiral pesticide compounds.

CONCLUSIONS

In summary, we developed a new strategy for the NHC-catalyzed chemo- and enantioselective synthesis of chiral azide-containing lactones, which was assisted by the $n\rightarrow\pi^*$ interaction. The azide anion underwent asymmetric nucleophilic addition to enedial. The key to the success of our strategy was the interaction between the α-carbonyl group and the NHC-bound acylazolium moiety. The above process could guide the conformational locking of the α-carbonyl group and reduce the reactivity of the β-carbonyl in acylazolium, preventing direct nucleophilic addition by the azide anion and the formation of the byproduct acyl azide. Meanwhile, this weak interaction ensured excellent enantioselectivity in the construction of chiral azide-containing lactones. Furthermore, bioactivity studies of chiral azide-containing lactones and related derivatives for agricultural applications had been evaluated, which showed encouraging in vitro activities against *Xoc* and *Xac*. We hope our method will enrich the synthetic strategies of chiral azide-containing compounds.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.5c06307.

Experimental procedures, DFT calculations, characterization of all new compounds, and X-ray structure data of compound **4d** (PDF)

AUTHOR INFORMATION

Corresponding Authors

Pengcheng Zheng − *State Key Laboratory of Green Pesticide, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Guiyang 550025, China;* orcid.org/0000-0002-3575-4502; Email: zhengpc1986@163.com

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

Authors

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

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

Complete contact information is available at: https://pubs.acs.org/10.1021/acscatal.5c06307

Author Contributions

§X.L. and Q.W. contributed equally.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We acknowledge funding supports from the National Natural Science Foundation of China (22061007, 22071036, and U23A20201); the Frontiers Science Centre for Asymmetric Synthesis and Medicinal Molecules, Department of Education, Guizhou Province [Qianjiaohe KY (2020)004]; the Central Government Guides Local Science and Technology Development Fund Projects [Qiankehezhongyindi (2024) 007, (2023) 001]; the Program of Introducing Talents of Discipline to Universities of China (111 Program, D20023) at Guizhou University; the Singapore National Research Foundation under its NRF Investigator ship (NRF-NRFI2016-06) and Competitive Research Program (NRF-CRP22-2019-0002); the Ministry of Education, Singapore, under its MOE AcRF Tier 1 Award (RG7/20 and RG 84/22, RG70/21), MOE AcRF Tier 2 (MOE2019-T2-2-117 and MOE-T2EP10222-0006); a Chair Professorship Grant, and Nanyang Technological University.

REFERENCES

(1) Wang, J.; Horwitz, M. A.; Dürr, A. B.; Ibba, F.; Pupo, G.; Gao, Y.; Ricci, P.; Christensen, K. E.; Pathak, T. P.; Claridge, T. D. W.; Lloyd-Jones, G. C.; Paton, R. S.; Gouverneur, V. Asymmetric Azidation under Hydrogen Bonding Phase-Transfer Catalysis: A Combined Experimental and Computational Study. *J. Am. Chem. Soc.* **2022**, *144* (10), 4572−4584.

(2) Lindner, H.; Amberg, W. M.; Carreira, E. M. Iron-Mediated Photochemical Anti-Markovnikov Hydroazidation of Unactivated Olefins. *J. Am. Chem. Soc.* **2023**, *145* (41), 22347−22353.

(3) Huang, X.; Bergsten, T. M.; Groves, J. T. Manganese-Catalyzed Late-Stage Aliphatic C-H Azidation. *J. Am. Chem. Soc.* **2015**, *137* (16), 5300−5303.

(4) Joseph, D.; Lee, S. Reaction of Amide and Sodium Azide for the Synthesis of Acyl Azide, Urea, and Iminophosphorane. *Org. Lett.* **2022**, *24* (33), 6186−6191.

(5) Li, X.; Qi, X.; Hou, C.; Chen, P.; Liu, G. Palladium(II)-Catalyzed Enantioselective Azidation of Unactivated Alkenes. *Angew. Chem., Int. Ed.* **2020**, *59* (39), 17239−17244.

(6) Guo, W.; Jiang, F.; Li, S.; Sun, J. Organocatalytic Asymmetric Azidation of Sulfoxonium Ylides: Mild Synthesis of Enantioenriched α-azido Ketones Bearing a Labile Tertiary Stereocenter. *Chem. Sci.* **2022**, *13* (39), 11648−11655.

(7) Ding, P. G.; Hu, X. S.; Yu, J. S.; Zhou, J. Diastereodivergent Synthesis of α-Chiral Tertiary Azides through Catalytic Asymmetric Michael Addition. *Org. Lett.* **2020**, *22* (21), 8578−8583.

(8) Ding, P. G.; Hu, X. S.; Zhou, F.; Zhou, J. Catalytic Enantioselective Synthesis of α-chiral Azides. *Org. Chem. Front.* **2018**, *5* (9), 1542−1559.

(9) Sivaguru, P.; Ning, Y.; Bi, X. New Strategies for the Synthesis of Aliphatic Azides. *Chem. Rev.* **2021**, *121* (7), 4253−4307.

(10) Li, X.; Song, J. N.; Karmakar, S.; Lu, Y.; Lv, Y.; Liao, P.; Liu, Z. Transition-metal-free Azide Insertion of N-triftosylhydrazones Using a Non-metallic Azide Source. *Chem. Commun.* **2022**, *58* (99), 13783−13786.
(11) Meng, G.; Guo, T.; Ma, T.; Zhang, J.; Shen, Y.; Sharpless, K. B.; Dong, J. Modular Click Chemistry Libraries for Functional Screens Using a Diazotizing Reagent. *Nature* **2019**, *574* (7776), 86−89.
(12) Wang, R.; Wang, C. Y.; Liu, P.; Bian, K. J.; Yang, C.; Wu, B. B.; Wang, X. S. Enantioselective Catalytic Radical Decarbonylative Azidation and Cyanation of Aldehydes. *Sci. Adv.* **2023**, *9* (35), No. eadh5195.
(13) Banert, K.; Berndt, C.; Hagedorn, M.; Liu, H.; Anacker, T.; Friedrich, J.; Rauhut, G. Experimental and Theoretical Studies on the Synthesis, Spectroscopic Data, and Reactions of Formyl Azide. *Angew. Chem., Int. Ed.* **2012**, *51* (19), 4718−4721.
(14) Banert, K.; Berndt, C.; Firdous, S.; Hagedorn, M.; Joo, Y. H.; Rüffer, T.; Lang, H. Extremely Simple but Long Overlooked: Generation of α-Azido Alcohols by Hydroazidation of Aldehydes. *Angew. Chem., Int. Ed.* **2010**, *49* (52), 10206−10209.
(15) Banert, K.; Berndt, C.; Weigand, K. Synthesis of Geminal Azido-Halo Compounds and α-Azidoalkyl Esters from Aldehydes via α-Azido Alcohols. *Org. Lett.* **2017**, *19* (18), 4900−4903.
(16) Rokade, B. V.; Prabhu, K. R. Chemoselective Schmidt Reaction Mediated by Triflic Acid: Selective Synthesis of Nitriles from Aldehydes. *J. Org. Chem.* **2012**, *77* (12), 5364−5370.
(17) Wang, Q.; Liang, X.; Pan, M.; Chi, Y. R.; Zheng, P. NHC-Catalyzed and Brønsted Acid Copromoted E → Z Isomerization Mode of Breslow Intermediates Leading to Ralfuranones. *Org. Lett.* **2025**, *27* (20), 5074−5080.
(18) Liu, Y.; Chen, Q.; Mou, C.; Pan, L.; Duan, X.; Chen, X.; Chen, H.; Zhao, Y.; Lu, Y.; Jin, Z.; Chi, Y. R. Catalytic Asymmetric Acetalization of Carboxylic Acids for Access to Chiral Phthalidyl Ester Prodrugs. *Nat. Commun.* **2019**, *10*, 1675.
(19) Deng, R.; Pan, M.; Liu, J.; Zheng, P.; Chi, Y. R. Carbene-Catalyzed Enantioselective Addition of Sulfinate to Ketones. *Org. Lett.* **2024**, *26* (20), 4394−4399.
(20) Song, R.; Liu, Y.; Majhi, P. K.; Ng, P. R.; Hao, L.; Xu, J.; Tian, W.; Zhang, L.; Liu, H.; Zhang, X.; Chi, Y. R. Enantioselective Modification of Sulfonamides and Sulfonamide-Containing Drugsvia-carbene Organic Catalysis. *Org. Chem. Front.* **2021**, *8* (11), 2413−2419.
(21) Zhou, M.; Liu, J.; Deng, R.; Wang, Q.; Wu, S.; Zheng, P.; Chi, Y. R. Construction of Tetrasubstituted Silicon-Stereogenic Silanes via Conformational Isomerization and N-Heterocyclic Carbene-Catalyzed Desymmetrization. *ACS Catal.* **2022**, *12* (13), 7781−7788.
(22) Liu, J.; Zhou, M.; Deng, R.; Zheng, P.; Chi, Y. R. Chalcogen Bond-Guided Conformational Isomerization Enables Catalytic Dynamic Kinetic Resolution of Sulfoxides. *Nat. Commun.* **2022**, *13*, 4793.
(23) Liu, J.; Deng, R.; Liang, X.; Zhou, M.; Zheng, P.; Chi, Y. R. Carbene-Catalyzed and Pnictogen Bond-Assisted Access to P-Stereogenic Compounds. *Angew. Chem., Int. Ed.* **2024**, *63* (28), No. e202404477.
(24) Peng, P. K.; Isho, A.; May, J. A. Regio- and Enantioselective Synthesis of Acyclic Quaternary Carbons via Organocatalytic Addition of Organoborates to (Z)-Enediketones. *Nat. Commun.* **2024**, *15*, 504.
(25) Bartlett, G. J.; Choudhary, A.; Raines, R. T.; Woolfson, D. N. n→π* interactions in proteins. *Nat. Chem. Biol.* **2010**, *6* (8), 615−620.
(26) Newberry, R. W.; Raines, R. T. The n→π* Interaction. *Acc. Chem. Res.* **2017**, *50* (8), 1838−1846.
(27) Bürgi, H. B.; Dunitz, J. D.; Shefter, E. Chemical Reaction paths. IV. Aspects of O···C = O Interactions in Crystals. *Acta Crystallogr., Sect. B.* **1974**, *30* (6), 1517−1527.
(28) Allen, F. H.; Baalham, C. A.; Lommerse, J. P. M.; Raithby, P. R. Carbonyl-Carbonyl Interactions can be Competitive with Hydrogen Bonds. *Acta Crystallogr., Sect. B: Struct. Sci.* **1998**, *54* (3), 320−329.
(29) Bretscher, L. E.; Jenkins, C. L.; Taylor, K. M.; DeRider, M. L.; Raines, R. T. Conformational Stability of Collagen Relies on a Stereoelectronic Effect. *J. Am. Chem. Soc.* **2001**, *123* (4), 777−778.
(30) Bürgi, H. B.; Dunitz, J. D.; Shefter, E. Geometrical Reaction Coordinates. II. Nucleophilic Addition to a Carbonyl Group. *J. Am. Chem. Soc.* **1973**, *95* (15), 5065−5067.
(31) Choudhary, A.; Gandla, D.; Krow, G. R.; Raines, R. T. Nature of Amide Carbonyl-Carbonyl Interactions in Proteins. *J. Am. Chem. Soc.* **2009**, *131* (21), 7244−7246.
(32) Newberry, R. W.; VanVeller, B.; Guzei, I. A.; Raines, R. T. n→π* Interactions of Amides and Thioamides: Implications for Protein Stability. *J. Am. Chem. Soc.* **2013**, *135* (21), 7843−7846.
(33) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. Stereochemistry of Reaction Paths at Carbonyl Centres. *Tetrahedron* **1974**, *30* (12), 1563−1572.
(34) Filloux, C. M.; Lathrop, S. P.; Rovis, T. Multicatalytic, asymmetric Michael/Stetter Reaction of Salicylaldehydes and Activated Alkynes. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107* (48), 20666−20671.
(35) Reddi, Y.; Sunoj, R. B. Asymmetric Dual-Catalytic Cascade by Chiral N-Heterocyclic Carbene and Quinuclidine: Mechanism and Origin of Enantioselectivity in Benzofuranone Formation. *ACS Catal.* **2015**, *5* (3), 1596−1603.
(36) Jeong, H. M.; Lee, J. W.; Kim, D. K.; Ryu, D. H. Catalytic Asymmetric Formal C-C Bond Insertion Reaction of Aldehydes via 1,2-Acyl Shift: Construction of All-Carbon Quaternary Stereocenters with Three Carbonyl Groups. *ACS Catal.* **2024**, *14* (1), 131−137.
(37) Livingstone, K.; Siebold, K.; Meyer, S.; Martín-Heras, V.; Daniliuc, C. G.; Gilmour, R. Skeletal Ring Contractions via I(I)/I(III) Catalysis: Stereoselective Synthesis of cis-α,α-Difluorocyclopropanes. *ACS Catal.* **2022**, *12* (23), 14507−14516.
(38) Chen, Y.; Zhen, Q. Q.; Meng, F. J.; Yu, P. Y.; Xu, C. Lone Pair-π Interactions in Organic Reactions. *Chem. Rev.* **2024**, *124* (23), 13370−13396.
(39) Vik, E. C.; Li, P.; Pellechia, P. J.; Shimizu, K. D. Transition-State Stabilization by n→π* Interactions Measured Using Molecular Rotors. *J. Am. Chem. Soc.* **2019**, *141* (42), 16579−16583.
(40) Zheng, H.; Ye, H.; Yu, X.; You, L. Interplay between n→π* Interactions and Dynamic Covalent Bonds: Quantification and Modulation by Solvent Effects. *J. Am. Chem. Soc.* **2019**, *141* (22), 8825−8833.
(41) Chen, H.; Tang, X.; Ye, H.; Wang, X.; Zheng, H.; Hai, Y.; Cao, X.; You, L. Effects of n→π* Orbital Interactions on Molecular Rotors: The Control and Switching of Rotational Pathway and Speed. *Org. Lett.* **2021**, *23* (1), 231−235.
(42) Mo, J.; Chen, X.; Chi, Y. R. Oxidative γ-Addition of Enals to Trifluoromethyl Ketones: Enantioselectivity Control via Lewis Acid/N-Heterocyclic Carbene Cooperative Catalysis. *J. Am. Chem. Soc.* **2012**, *134* (21), 8810−8813.
(43) Nagao, K.; Ohmiya, H. N-Heterocyclic Carbene (NHC)/Metal Cooperative Catalysis. *Top. Curr. Chem.* **2019**, *377* (6), 35.
(44) Wang, K.; Li, Y.; Li, X.; Li, D.; Bao, H. Iron-Catalyzed Asymmetric Decarboxylative Azidation. *Org. Lett.* **2021**, *23* (22), 8847−8851.
(45) Shastin, A. V.; Tsyrenova, B. D.; Sergeev, P. G.; Roznyatovsky, V. A.; Smolyar, I. V.; Khrustalev, V. N.; Nenajdenko, V. G. Synthesis of a New Family of 1,1-Diazidoethenes: One-Pot Construction of 4-Azido-1,2,3-triazoles via Nitrene Cyclization. *Org. Lett.* **2018**, *20* (24), 7803−7806.
(46) Gong, Y.; Wang, C.; Zhou, F.; Liao, K.; Wang, X. Y.; Sun, Y.; Zhang, Y. X.; Tu, Z.; Wang, X.; Zhou, J. Sulfonyl-PYBOX Ligands Enable Kinetic Resolution of α-Tertiary Azides by CuAAC. *Angew. Chem., Int. Ed.* **2023**, *62* (18), No. e202301470.
(47) Chen, Y. X.; Huo, T.; Yin, Q.; Jiang, L. F.; Cheng, X.; Ma, H. X.; Jiang, Y. X.; Sun, M. Z.; Deng, Q. H. Azidobenziodazolones as Azido Sources for the Enantioselective Copper-Catalyzed Azidation of N-Unprotected 3-Trifluoromethylated Oxindoles. *Org. Lett.* **2023**, *25* (15), 2739−2744.

https://doi.org/10.1021/acscatal.5c06307
ACS Catal. 2025, 15, 18750−18757

(48) Fan, G.; Wang, Q.; Xu, J.; Zheng, P.; Chi, Y. R. Carbene-catalyzed Chemoselective Reaction of Unsymmetric Enedials for Access to Furo[2,3-b]pyrroles. *Nat. Commun.* **2023**, *14*, 4243.
(49) Yang, J.; Kojasoy, V.; Porter, G. J.; Raines, R. T. Pauli Exclusion by n→π* Interactions: Implications for Paleobiology. *ACS Cent. Sci.* **2024**, *10* (10), 1829−1834.
(50) De Sarkar, S.; Studer, A. Oxidative Amidation and Azidation of Aldehydes by NHC Catalysis. *Org. Lett.* **2010**, *12* (9), 1992−1995.
(51) Che, F. R.; Hu, J. Y.; Liao, M. H.; Luo, Z. F.; Long, H. Y.; Li, B. P.; Chi, Y. R.; Wu, X. X. Synthesis of P(V)-Stereogenic Phosphorus Compounds via Organocatalytic Asymmetric Condensation. *J. Am. Chem. Soc.* **2024**, *146* (49), 33763−33773.
(52) Li, B.; Hu, J.; Liao, M.; Xiong, Q.; Zhang, Y.; Chi, Y. R.; Zhang, X.; Wu, X. Catalyst Control over S(IV)-stereogenicity via Carbene-derived Sulfinyl Azolium Intermediates. *J. Am. Chem. Soc.* **2024**, *146* (36), 25350−25360.
(53) Lv, X.; Xu, J.; Sun, C.; Su, F.; Cai, Y.; Jin, Z.; Chi, Y. R. Access to Planar Chiral Ferrocenes via N-Heterocyclic Carbene-Catalyzed Enantioselective Desymmetrization Reactions. *ACS Catal.* **2022**, *12* (4), 2706−2713.
(54) Barreiro, E. J.; Kümmerle, A. E.; Fraga, C. A. M. The Methylation Effect in Medicinal Chemistry. *Chem. Rev.* **2011**, *111*, 5215−5246.
(55) Teng, K. P.; Liu, Q.; Zhang, M.; Naz, H.; Zheng, P. C.; Wu, X. X.; Chi, Y. R. Design and Enantioselective Synthesis of Chiral Pyranone Fused Indole Derivatives with Antibacterial Activities against Xanthomonas oryzae pv oryzae for Protection of Rice. *J. Agric. Food Chem.* **2024**, *72* (9), 4622−4629.

https://doi.org/10.1021/acscatal.5c06307
ACS Catal. 2025, 15, 18750−18757