OL | Organic Letters

Letter

Cite This: Org. Lett. 2019, 21, 6624−6627

pubs.acs.org/OrgLett

NaOH-Promoted Chemoselective Cascade Cyclization of Cyclopropyl Esters with Unsaturated Imines: Access to Bioactive Cyclopenta[c]pyridine Derivatives

Dingwu Pan,[†,⊥] Chengli Mou,[‡,⊥] Ningning Zan,[†] Ya Lv,[†] Bao-An Song,[†] Yonggui Robin Chi,[†,§] and Zhichao Jin*[,†]

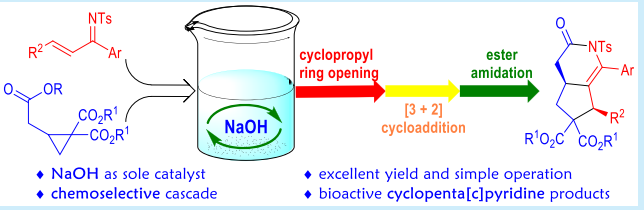
[†]Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University, Huaxi District, Guiyang 550025, China

[‡]Guizhou University of Traditional Chinese Medicine, Huaxi District, Guiyang 550025, China

[§]Division of Chemistry & Biological Chemistry, School of Physical & Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

Supporting Information

ABSTRACT: A chemoselective cascade cycloaddition reaction is developed for green and efficient access to cyclopenta[c]pyridine derivatives. Simple and inexpensive NaOH is used as the sole catalyst for this process. The δ-carbon of cyclopropyl ester is activated as a nucleophilic carbon to initiate highly chemoselective cascade reactions. Cyclopenta[c]pyridines bearing various substituents are afforded in excellent yields. Preliminary studies on the bioactivities of the afforded products show promising antibacterial activities for potential applications in plant protections.



Cyclopenta[c]pyridines are frequently found as core structures in natural products and bioactive synthetic molecules (Figure 1a).[1] For instance, pyracyclumines B and C are key alkali fragments isolated from the roots of Anacyclus pyrethrum, a traditional medicine for treatment of epilepsy.[1c] Tishaviolamine A is one of the important components in the extract of Viola tianshanica, a plant that has long been used as a traditional Uygur medicine to treat pharyngalgia, headache, fever, and acute pyogenic infection.[1b] These functional molecules contain substituted cyclopenta[c]pyridine cores in

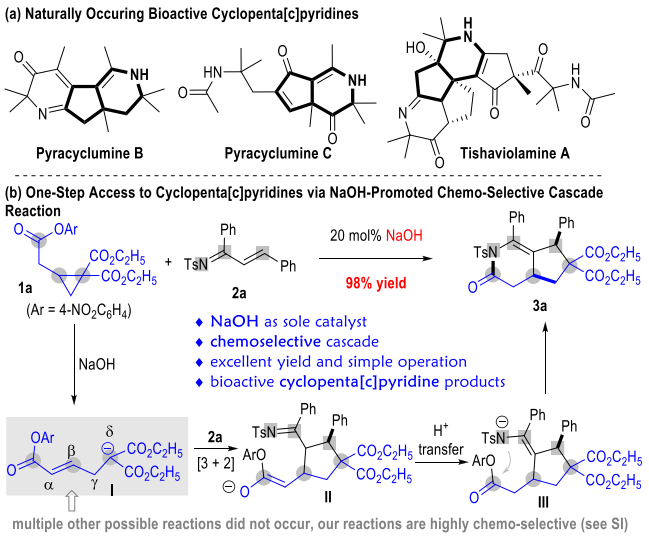
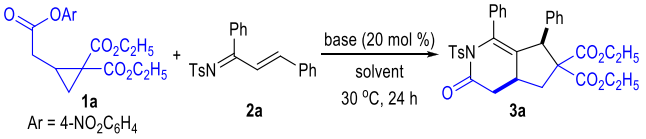


Figure 1. Cyclopenta[c]pyridines and our method for their quick and green access.

Table 1. Condition Optimization[a]



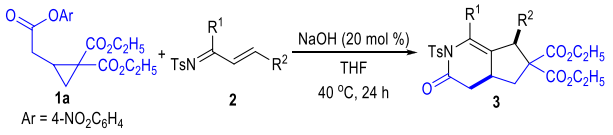
entry	base	solvent	yield (%)[b]	dr[c]
1	NaOH	THF	84	4:1
2	$NaOCH_3$	THF	83	3:1
3	KO*t*Bu	THF	52	4:1
4	Cs_2CO_3	THF	37	4:1
5	DBU	THF	<5	-
6	NaOH	EtOAc	54	3:1
7	NaOH	H_2O	<5	-
8	NaOH	toluene	<5	-
9[d]	**NaOH**	**THF**	**98**	**4:1**

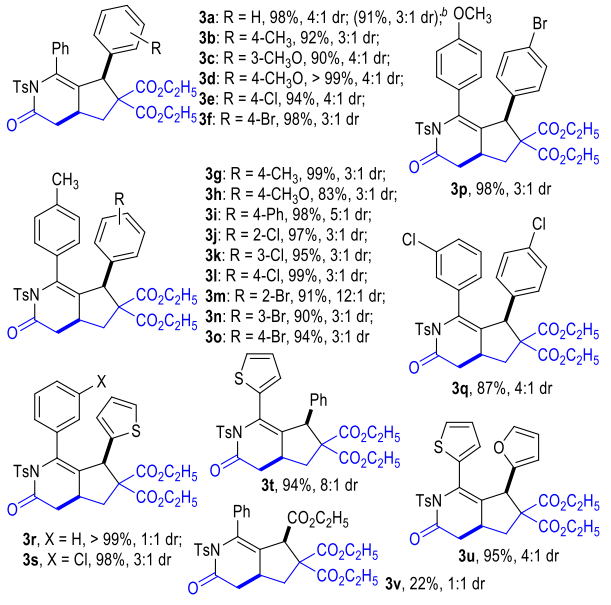
[a]Reaction conditions: **1a** (0.10 mmol), **2a** (0.05 mmol), base (0.01 mmol), solvent (1.0 mL), 30 °C, 24 h. [b]Isolated yields of **3a**. [c]dr values were determined by ^{1}H NMR on the crude product mixture. [d]**1a** (0.075 mmol), **2a** (0.05 mmol), NaOH (0.01 mmol), THF (1.0 mL), 40 °C, 24 h.

Received: June 17, 2019
Published: August 14, 2019

DOI: 10.1021/acs.orglett.9b02088
Org. Lett. 2019, 21, 6624−6627

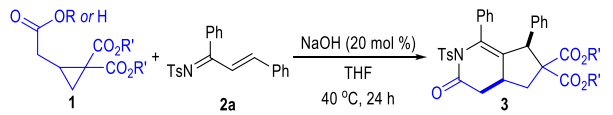
Scheme 1. Scope of α,β-Unsaturated Imines 2[a,b]

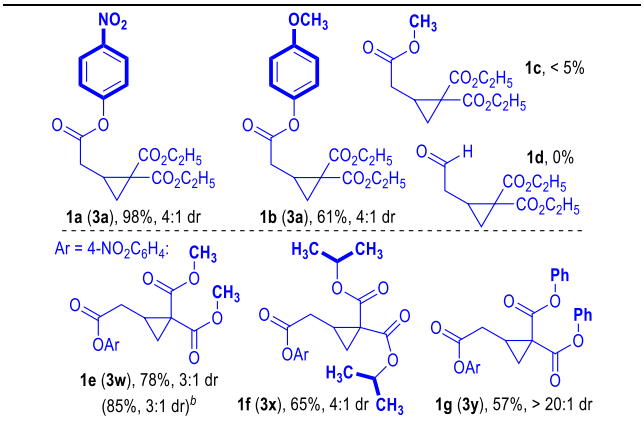




[a]Reactions were carried out under condition as in Table 1, entry 9. Yield was isolated yield. dr value was determined by ^{1}H NMR on the crude product mixture. [b]Data in parentheses indicate the results from the reaction carried out at 1.0 mmol scale based on **2a**.

Scheme 2. Scope of Ester Substrates 1[a]

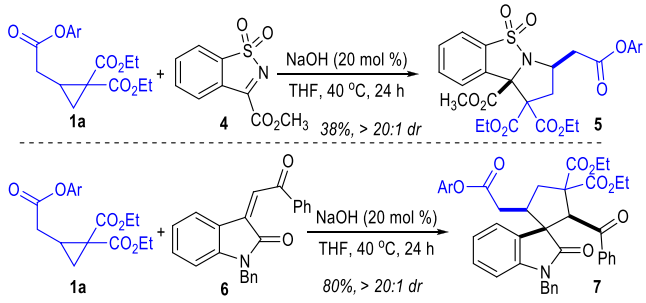




[a]Reactions were carried out under conditions as in Table 1, entry 9. Yields were isolated yields. dr values were determined by ^{1}H NMR on the crude product mixture. [b]Data in parentheses indicate the results from the reaction carried out at 1.0 mmol scale based on **2a**.

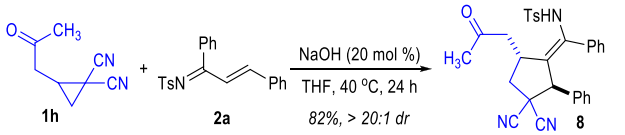
either racemic or enantiomerically pure forms. Therefore, the rapid construction and bioactivity evaluation of substituted cyclopenta[c]pyridine derivatives are of considerable interests. However, despite of their importance, the preparation of this class of cyclopenta[c]pyridine derivatives remains challenging,

Scheme 3. Reactions of 1a with Imine 4 and Enone 6[a]



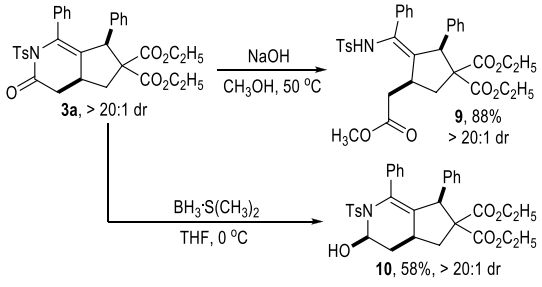
[a]Reactions were carried out under conditions as in Table 1, entry 9. Yields were isolated yields. dr values were determined by ^{1}H NMR on the crude product mixture.

Scheme 4. Reaction of 2-Cyclopropyl Ketone 1h with 2a[a]



[a]Reactions were carried out under conditions as in Table 1, entry 9. Yields were isolated yields. dr values were determined by ^{1}H NMR on the crude product mixture.

Scheme 5. Synthetic Transformation of 3a



and long synthetic steps have been required.[2] Cascade cyclization reactions promoted by simple and inexpensive small molecules are promising strategies for the synthesis of these complex structures.[3]

Here, we report a one-step method for highly efficient access to bicyclic cyclopenta[c]pyridine derivatives bearing multiple substituents (Figure 1b). Our reactions use NaOH as the only catalyst, and most of the reactions give desired products with over 90% yields. The key reaction processes include a NaOH-promoted activation of a 2-cyclopropyl ester (e.g., **1a**) to form intermediate **I** bearing multiple reactive carbons. Although multiple different reactions from intermediate **I** are possible (see SI), we are delighted to see that with α,β-unsaturated imines as the other substrate the reaction cascades are highly chemoselective. Briefly, formal [3 + 2] reaction initiated from addition of the δ-carbon of intermediate **I** to unsaturated imine **2a** forms intermediate **II**.[4] Related [3 + 2] process was observed before by Jørgensen and co-workers in which 2-cyclopropyl ketones were activated by amine/thiourea catalysts to react with nitroalkenes.[5] Proton transfer of **II** gives intermediate **III**, which subsequently undergoes lactam formation to afford cyclopenta[c]pyridine product **3a** with excellent yield. Several of the cyclopenta[c]pyridine products from our approach exhibit

DOI: 10.1021/acs.orglett.9b02088
Org. Lett. 2019, 21, 6624−6627

Table 2. Inhibition Rate of Compounds 3 against Bacteria[a]

Compound	*X. oryzae* pv. *oryzae* (%)[a]		*X. axonopodis* pv. *citri* (%)[a]		*P. syringae* pv. *actinidiae*(%)[a]	
	100 μg/mL	50 μg/mL	100 μg/mL	50 μg/mL	100 μg/mL	50 μg/mL
3a	29.6 ± 4.7	18.9 ± 1.2	37.8 ± 2.1	16.1 ± 1.8	22.6 ± 3.3	0
3c	13.2 ± 3.5	0	38.8 ± 2.7	11.4 ± 1.9	54.1 ± 2.0	22.6 ± 0.7
3e	63.1 ± 2.4	23.9 ± 6.2	23.1 ± 1.1	0	24.3 ± 3.5	0
3f	22.6 ± 2.2	5.2 ± 3.0	14.9 ± 4.0	0	48.9 ± 4.9	12.5 ± 2.0
3g	25.7 ± 3.9	16.6 ± 1.9	6.9 ± 2.7	0	45.4 ± 3.7	12.4 ± 2.5
3m	9.7 ± 1.9	0	33.5 ± 2.5	8.8 ± 2.9	33.4 ± 4.3	9.4 ± 1.3
3q	4.0 ± 2.4	0	19.6 ±4.1	8.8 ± 0.5	50.2 ± 3.6	17.2 ± 2.2
3r	42.2 ± 1.3	15.2 ± 2.3	30.6 ± 3.8	13.9 ± 1.5	28.7 ± 3.2	5.1 ± 3.0
3s	21.3 ± 1.9	7.7 ± 1.4	17.8 ± 2.8	0	31.2 ± 5.9	9.9 ± 3.0
Bismerthiazol[b]	48.1 ± 0.5	11.2 ± 1.7	-[c]	-[c]	-[c]	-[c]
Thiodiazole-Cu[b]	-[c]	-[c]	23.7 ± 4.5	13.5 ± 2.8	27.2 ± 3.5	8.7 ± 1.0
DMSO[d]	0	0	0	0	0	0

[a]All data were average data of three replicates. [b]Commercial bactericide, used as the positive control. [c]Not tested. [d]DMSO was used as the negative control.

encouraging antibacterial activities against *X. oryzae* pv *oryzae*,[6] *X. axonopodis* pv *citri*,[7] and *P. syringae* pv *actinidiae*.[8]

We chose 2-cyclopropyl ester **1a** and α,β-unsaturated imine **2a** as the model substrates to search for suitable reaction conditions (Table 1). We initially intended to use *N*-heterocyclic carbene (NHC) organic catalysts to activate the ester substrates[9] for cascade reactions. We found that NHC did not participate in the reaction, and the reaction proceeded smoothly with the presence of a simple base alone. For example, a variety of common inorganic bases could efficiently promote the cascade process and give the desired cyclopenta[c]pyridine products in moderate to good yields with moderate diastereoselectivities (Table 1, entries 1−4). Organic bases tested for this transformation were generally ineffective (e.g., entry 5). Organic solvents with high polarities could serve as suitable medium for this NaOH-catalyzed process (e.g., entry 6), while the reactions could not proceed well in either aqueous system or nonpolar organic solvents (entries 7−8). The product yield could be dramatically improved by slightly increasing the reaction temperature to 40 °C. Under this temperature, the loading of **1a** could be decreased and the desired product **3a** could be obtained in almost quantitative yield without erosion of the diastereoselectivity (entry 9). Further decreasing the amount of either NaOH or ester **1a** led to some drops on the product yields (see SI for details).

Having established optimized reaction conditions (Table 1, entry 9), we next examined the scope of α,β-unsaturated imines (**2**) bearing various substituents (Scheme 1). Both substituents R^1 and R^2 of the imine substrate **2** could be phenyl rings with different substitution patterns. The fused cyclopenta[c]pyridine products **3** were afforded in generally excellent yields with moderate to excellent diastereoselectivities (**3a** to **3q**). Heteroaromatic groups were also well tolerated on both sides of the imine substrates **2**, with the corresponding products afforded in excellent yields (**3r** to **3u**). It is worth noting that the aromatic R^2 group could be replaced with an ester substituent, although the corresponding product **3v** was only afforded in a low yield with a poor diastereoselectivity under current reaction conditions.

We then examined the scope of the 2-cyclopropyl ester substrates (**1**) (Scheme 2). The electron deficient 4-nitrophenol group on **1a** could be switched to an electron-rich aromatic group (**1b**), although the product yield decreased to 61%. Replacing the R group on ester substrate **1** with a simple methyl group (**1c**) resulted in only trace formation of the final product. It is worth noting that the cyclopropyl aldehyde **1d** cannot be used as a reaction partner for this NaOH-promoted cycloaddition reaction with the imine **2a**. Both substrates decomposed without any cycloaddition products formed. Both aliphatic and aromatic substituents were well tolerated as the R′ groups on the ester substrates **1**, with the corresponding products afforded in moderate yields (**1e** to **1g**). Notably, excellent diastereoselectivity (>20:1) could be observed when using ester substrate **1g** bearing phenyls as the R′ groups.

Electron deficient cyclic imine **4** and enone **6** can also be used as suitable electrophiles in the NaOH-promoted reactions with the 2-cyclopropyl ester **1a** (Scheme 3). However, in these cases, pyrrole **5** and cyclopentane **7** from formal [3 + 2] cycloaddition reactions were afforded as the final products in moderate to good yields.

2-Cyclopropyl ketone substrate **1h** could also serve as an effective substrate in the cycloaddition reaction with α,β-unsaturated imine **2a** (Scheme 4). The [3 + 2] cyclization product **8** could be isolated in 82% yield as a single diastereomer under the current optimized reaction conditions.

The multifunctionalized cyclopenta[c]pyridine product (**3a**) is amenable for further transformations (Scheme 5). For example, addition of methanol to the lactam moiety of **3a** under a basic condition could produce ester **9** in 88% yield. The lactam group in **3a** could be selectively reduced by BH_3 (without affecting the ester groups) to afford *N*,*O*-hemiaminal adduct **10** with 58% yield.

The cyclopenta[c]pyridine products (**3**) obtained from our reactions were evaluated for their bioactivities with potential uses in plant protections (Table 2). *X. oryzae* pv *oryzae* is a harmful bacterium that causes leaf blast in rice and seriously damages rice production.[6] Bismerthiazol is widely used an agrochemical in controlling the rice leaf blast via inhibition of *X. oryzae* pv *oryzae*.[10] To our delight, several of our cyclopenta[c]pyridine products showed excellent inhibition rate against *X. oryzae* pv *oryzae*. For example, products **3a** and **3r** showed similar antibacterial activities as the bismerthiazol, and product **3e** provided a better effect in the inhibition of *X. oryzae* pv *oryzae*.

X. axonopodis pv *citri*[7] and *P. syringae* pv *actinidiae*[8] are widespread bacteria that cause decay in various kinds of fruits. Our cyclopenta[c]pyridine products showed encouraging antibacterial activities against both *X. axonopodis* pv *citri* and

DOI: 10.1021/acs.orglett.9b02088
Org. Lett. 2019, 21, 6624−6627

P. syringae pv *actinidiae* (Table 2). For example, compounds **3a**, **3c**, **3m**, and **3r** exhibited superior antibacterial activities against *X. axonopodis* pv *citri*, compared to the commercially used thiodiazole-copper.[11] Our products **3c**, **3f**, **3g**, **3m**, **3q**, and **3s** all showed better results than thiodiazole-copper in the inhibition of *P. syringae* pv *actinidiae*.

In summary, we have developed a chemoselective cascade cycloaddition reaction promoted by simple and inexpensive NaOH. Cyclopenta[c]pyridine derivatives are afforded as the final products in up to quantitative yields. The δ-carbon of the in situ generated α,β-unsaturated carboxylic ester is activated as the nucleophile to react with α,β-unsaturated imines in highly chemoselective manners. The multifunctional cyclopenta[c]-pyridine products obtained from our method exhibit encouraging antibacterial activities with potential applications in the development of new green pesticides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02088.

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

Accession Codes

CCDC 1911186−1911188 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 Author

*E-mail: zcjin@gzu.edu.cn.

ORCID

Yonggui Robin Chi: 0000-0003-0573-257X

Zhichao Jin: 0000-0003-3003-6437

Author Contributions

⊥These authors contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge financial support from the National Natural Science Foundation of China (No. 21772029, 21801051), National Key Technologies R Program (No. 2014BAD23B01), The 10 Talent Plan (Shicengci) of Guizhou Province [2016] 5649, Guizhou Province Returned Oversea Student Science and Technology Activity Program (2014)-2, Science and Technology Department of Guizhou Province [2018]2802, [2019]1020, Guizhou University, the Guizhou Province First-Class Disciplines Project (Yiliu Xueke Jianshe Xiangmu)-GNYL(2017) 008, Guizhou University of Traditional Chinese Medicine QMYY [2017]101 (China). Singapore National Research Foundation (NRF-NRFI2016-06), the Ministry of Education of Singapore (MOE2013-T2-2-003; MOE2016-T2-1-032; RG108/16), A*STAR Individual Research Grant (A1783c0008), Nanyang Research Award Grant, and Nanyang Technological University.

■ REFERENCES

(1) For selected examples, see: (a) Murphy, S. K.; Zeng, M. S.; Herzon, S. B. *Science* **2017**, *356*, 956. (b) Chen, Q. B.; Aisa, H. K. *Phytochemistry* **2017**, *144*, 233. (c) Chen, Q. B.; Gao, J.; Zou, G. A.; Xin, X. L.; Aisa, H. K. *J. Nat. Prod.* **2018**, *81*, 1474.

(2) For selected reviews, see: (a) Williams, R. M.; Cox, R. J. *Acc. Chem. Res.* **2003**, *36*, 127. (b) Van Ornum, S. G.; Champeau, R. M.; Pariza, R. *Chem. Rev.* **2006**, *106*, 2990. (c) Miller, K. A.; Williams, R. M. *Chem. Soc. Rev.* **2009**, *38*, 3160. (d) Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439. (e) Bach, T.; Hehn, J. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 1000. (f) Mercado-Marin, E. V.; Garcia-Reynaga, P.; Romminger, S.; Pimenta, E. F.; Romney, D. K.; Lodewyk, M. W.; Williams, D. E.; Andersen, R. J.; Miller, S. J.; Tantillo, D. J.; Berlinck, R. G. S.; Sarpong, R. *Nature* **2014**, *509*, 318. (g) Hong, J. *Chem. - Eur. J.* **2014**, *20*, 10204.

(3) (a) Xu, M.-M.; Wang, H.-Q.; Wan, Y.; Wang, S.-L.; Shi, F. *J. Org. Chem.* **2017**, *82*, 10226. (b) Li, J.; Zhang, W.-W.; Wei, X.-J.; Hao, W.-J.; Li, G.; Tu, S.-J.; Jiang, B. *Org. Lett.* **2017**, *19*, 4512. (c) Shen, Z.-J.; Shi, H.-N.; Hao, W.-J.; Tu, S.-J.; Jiang, B. *Chem. Commun.* **2018**, *54*, 11542. (d) Sun, M.; Zhu, Z.-Q.; Gu, L.; Wan, X.; Mei, G.-J.; Shi, F. *J. Org. Chem.* **2018**, *83*, 2341. (e) Li, H.; Hao, W.-J.; Wang, M.; Qin, X.; Tu, S.-J.; Zhou, P.; Li, G.; Wang, J.; Jiang, B. *Org. Lett.* **2018**, *20*, 4362. (f) Li, C.; Xu, D.-N.; Ma, C.; Mei, G.-J.; Shi, F. *J. Org. Chem.* **2018**, *83*, 9190. (g) Li, S.-S.; Zhu, S.; Chen, C.; Duan, K.; Liu, Q.; Xiao, J. *Org. Lett.* **2019**, *21*, 1058.

(4) (a) Zu, L. S.; Li, H.; Xie, H. X.; Wang, J.; Jiang, W.; Tang, Y.; Wang, W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3732. (b) Tan, B.; Shi, Z.; Chua, P. J.; Zhong, G. F. *Org. Lett.* **2008**, *10*, 3425.

(5) Blom, J.; Vidal-Albalat, A.; Jørgensen, J.; Barløse, C. L.; Jessen, K. S.; Iversen, M. V.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2017**, *56*, 1.

(6) (a) Mew, T. W. *Annu. Rev. Phytopathol.* **1987**, *25*, 359. (b) Li, P.; Shi, L.; Yang, X.; Yang, L.; Chen, X.-W.; Wu, F.; Shi, Q.-C.; Xu, W.-M.; He, M.; Hu, D.-Y.; Song, B.-A. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 1677. (c) Song, X.; Li, P.; Li, M.; Yang, A.; Yu, L.; Luo, L.; Hu, D.; Song, B. *Pestic. Biochem. Physiol.* **2018**, *147*, 11.

(7) (a) Gottwald, T. R.; Mcguire, R. G.; Garran, S. *Phytopathology* **1988**, *78*, 739. (b) Gao, M.; Yu, L.; Li, P.; Song, X.; Chen, Z.; He, M.; Song, B. *Pestic. Biochem. Physiol.* **2017**, *138*, 37.

(8) (a) Takikawa, Y.; Serizawa, S.; Ichikawa, T.; Tsuyumu, S.; Goto, M. *Nippon Shokubutsu Byori Gakkaiho* **1989**, *55*, 437. (b) Miyoshi, T.; Shimizu, S.; Sawada, H. *Nippon Shokubutsu Byori Gakkaiho* **2012**, *78*, 92. (c) Reglinski, T.; Vanneste, J. L.; Wurms, K.; Gould, E.; Spinelli, F.; Rikkerink, E. *Front. Plant Sci.* **2013**, *4*, 1.

(9) For comments and reviews on NHC-catalyzed ester activation, see: Chauhan, P.; Enders, D. *Angew. Chem., Int. Ed.* **2014**, *53*, 1485. For selected examples, see: (b) Hao, L.; Du, Y.; Lv, H.; Chen, X.; Jiang, H.; Shao, Y.; Chi, Y. R. *Org. Lett.* **2012**, *14*, 2154. (c) Hao, L.; Chen, S.; Xu, J.; Tiwari, B.; Fu, Z.; Li, T.; Lim, J.; Chi, Y. R. *Org. Lett.* **2013**, *15*, 4956. (d) Chen, S.; Hao, L.; Zhang, Y.; Tiwari, B.; Chi, Y. R. *Org. Lett.* **2013**, *15*, 5822. (e) Fu, Z.; Xu, J.; Zhu, T.; Leong, W. W. Y.; Chi, Y. R. *Nat. Chem.* **2013**, *5*, 835. (f) Xu, J.; Jin, Z.; Chi, Y. R. *Org. Lett.* **2013**, *15*, 5028. (g) Fu, Z.; Jiang, K.; Zhu, T.; Torres, J.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2014**, *53*, 6506. (h) Mou, C.; Wu, J.; Huang, Z.; Sun, J.; Jin, Z.; Chi, Y. R. *Chem. Commun.* **2017**, *53*, 13359.

(10) (a) Wang, X.; Li, P.; Li, Z.; Yin, J.; He, M.; Xue, W.; Chen, Z.; Song, B. *J. Agric. Food Chem.* **2013**, *61*, 9575. (b) Wang, P.-Y.; Zhou, L.; Zhou, J.; Wu, Z.-B.; Xue, W.; Song, B.-A.; Yang, S. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 1214. (c) Liang, X. Y.; Yu, X. Y.; Pan, X. Y.; Wu, J.; Duan, Y. B.; Wang, J. X.; Zhou, M. G. *Mol. Plant Pathol.* **2018**, *19*, 116.

(11) (a) Zhang, L.; Wang, J.; Zhu, G.-N.; Su, L. *Exp. Toxicol. Pathol.* **2010**, *62*, 163. (b) Li, P.; Hu, D.; Xie, D.; Chen, J.; Jin, L.; Song, B. *J. Agric. Food Chem.* **2018**, *66*, 3093. (c) Wang, P.-Y.; Wang, M.-W.; Zeng, D.; Xiang, M.; Rao, J.-R.; Liu, Q.-Q.; Liu, L.-W.; Wu, Z.-B.; Li, Z.; Song, B.-A.; Yang, S. *J. Agric. Food Chem.* **2019**, *67*, 3535.

DOI: 10.1021/acs.orglett.9b02088
Org. Lett. 2019, 21, 6624−6627