OL | Organic Letters

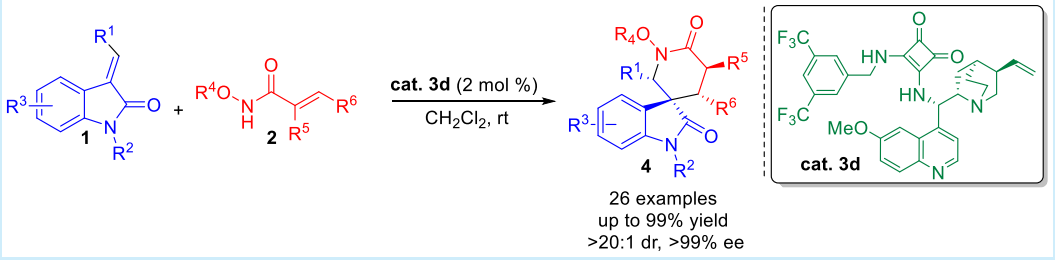
pubs.acs.org/OrgLett Letter

Organocatalytic Aza-Michael/Michael Cyclization Cascade Reaction: Enantioselective Synthesis of Spiro-oxindole Piperidin-2-one Derivatives

Qing-Gang Tang, Sen-Lin Cai, Chuan-Chuan Wang, Guo-Qiang Lin, and Xing-Wen Sun*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c00779 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: A simple, direct, and highly enantioselective synthesis of spiro-oxindole piperidin-2-one derivatives was achieved through an aza-Michael/Michael cyclization cascade sequence using a squaramide catalyst. The desired products were obtained in excellent yields (up to 99%) and good to high stereoselectivities (up to >20:1 dr and up to 99% ee) under mild conditions.

The aza-Michael reaction, a well-known straightforward reaction to construct a carbon−nitrogen bond, is frequently applied as the shortest method to synthesize β-aminocarbonyl compounds, such as β-amino aldehydes[1] and ketones,[2] β-amino acids,[3] β-lactams,[4] and their derivatives.[5] During the past decades, numerous asymmetric aza-Michael reactions have been reported[6] in which primary amines, *N*-protected secondary amines (Boc, Cbz, or Ts group), succinimides, and hydrazines were used as nitrogen nucleophiles. To the best of our knowledge, *N*-alkoxyl acylamides are rarely utilized as nitrogen nucleophiles to react with unsaturated ketones or esters. Therefore, great efforts are still being contributed to the exploration of new nitrogen nucleophiles for catalytic asymmetric aza-Michael reactions.

A spiro-oxindole scaffold bearing a quaternary carbon stereocenter at the 3-position, especially with an *N*-heterocycle, is a ubiquitous structural moiety in many bioactive natural products and synthetic compounds. For example, horsfiline (Figure 1),[7] isolated from the traditional herbal medicine plant *Horsfieldia superba*, displays analgesic effects. Cipargamin (NITD609),[8] a novel antimalarial lead compound in clinic trials, has demonstrated very effective capability in reducing transmission to the *Anopheles stephensi* mosquito vector. (+)-Alantrypinone,[9] an insecticidal alkaloid isolated from the micro fungi of the genera *Aspergillus* and *Penicillium*, is currently a lead compound for the development of a safer insecticide based on its selective antagonist effect for housefly γ-aminobutyric acid (GABA) receptors. Compound **V**,[10] reported by Roche Holding, shows potent inhibitory activity against p53 protein. Although a number of catalytic syntheses

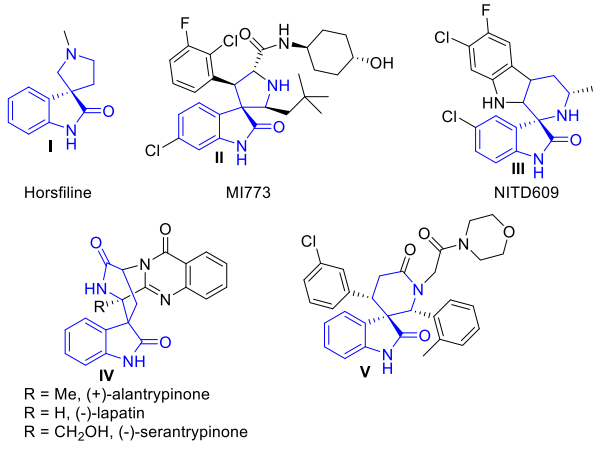


Figure 1. Bioactive natural and synthetic compounds containing a spiro-oxindole scaffold.

were reported for these *N*-heterocycle spirooxindoles,[11] concise and elegant strategies are still in great demand, particularly for the enantioselective synthesis of spiro-oxindole piperidin-2-one scaffolds.[12]

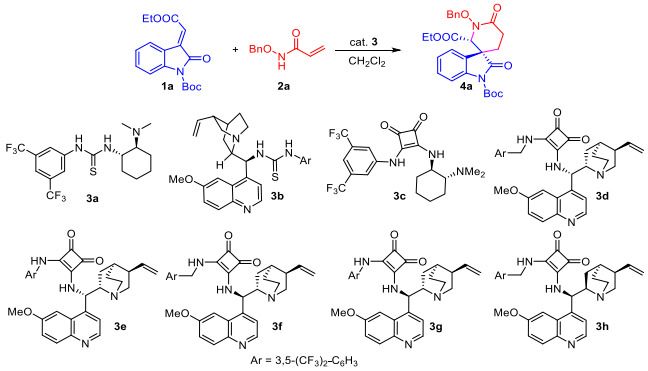
Received: February 29, 2020

Currently, organocatalytic asymmetric domino or cascade reactions provide an alternative powerful strategy, in addition to transition-metal catalysis, for the synthesis of complex compounds with contiguous multiple stereocenters.[13] In the past several years, our group has focused on the development of asymmetric organocatalytic cascade reactions, resulting in series of novel methods for highly stereoselective synthesis of all-carbon membered spiro-oxindoles.[14]

We conceived that the reactions of 3-methyleneindolinones and α,β-disubstituted acylamides could be activated through anchoring to a bifunctional organocatalyst by hydrogen bonds to undergo an aza-Michael/Michael cyclization cascade sequence, leading to the formation of spiro-oxindole piperidin-2-ones. To examine the possibility of this hypothesis, *N*-Boc-protected 3-methyleneindolinone **1a** and *N*-benzyloxy acrylamide **2a** were used in a model reaction to optimize the suitable catalytic system and reaction conditions. The representative results are summarized in Table 1.

Our study began with screening a set of organocatalysts **3a**–**3h**. To our delight, the cascade reaction proceeded readily when thiourea catalyst **3a** was used, providing the desired product **4a** in moderate yield (59%), along with good diastereoselectivity (8:1 dr) and enantioselectivity (89% ee) (Table 1, entry 1). Thiourea catalyst **3b** could improve enantioselectivity (93% ee), albeit with slightly lower diastereoselectivity (6:1 dr) (Table 1, entry 2). Squaramides **3c**–**3h** offered interesting results, with **3d** being identified as the best catalyst for reaction yield (88%) and stereoselectivity (>20:1 dr and 97% ee) (Table 1, entry 4). Squaramides **3c** and **3f** afforded the desired product with opposite configuration, but in low yields (Table 1, entries 3 and 6). Squaramides **3e** and **3g** proved to be much less effective, and only a trace amount of product was detected (Table 1, entries 5 and 7).

Table 1. Screening of Organocatalysts and Solvents[a]



entry	catalyst	solvent	yield[b] (%)	dr[c]	ee[d] (%)
1	**3a**	CH_2Cl_2	59	8:1	89
2	**3b**	CH_2Cl_2	36	6:1	93
3	**3c**	CH_2Cl_2	33	3:1	−63
4	**3d**	CH_2Cl_2	88	>20:1	97
5	**3e**	CH_2Cl_2	trace	nd	n.d.
6	**3f**	CH_2Cl_2	37	>20:1	−56
7	**3g**	CH_2Cl_2	trace	nd	n.d.
8	**3h**	CH_2Cl_2	89	>20:1	−84
9	**3d**	$CHCl_3$	86	>20:1	95
10	**3d**	CCl_4	57	>20:1	90
11	**3d**	THF	27	>20:1	92
12	**3d**	toluene	66	>20:1	93
13	**3d**	DCE[e]	83	>20:1	95
14	**3d**	MTBE	42	>20:1	89
15	**3d**	brine	66	76:24	73
16	**3d**[f]	CH_2Cl_2	84	>20:1	97
17	**3d**[g]	CH_2Cl_2	64	>20:1	97

[a]Typical reaction conditions: **1a** (0.10 mmol), **2a** (0.12 mmol), cat. **3** (5 mol %) in solvent (0.5 mL), at 25 °C for 48 h. [b]Yield of isolated product. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture before purification. [d]The ee values were determined by HPLC analysis on Chiral AD-H column with 70:30 *n*-hexane/*i*-PrOH as eluant. [e]DCE = 1,2-dichloroethane. [f]**3d**: 2 mol %. [g]**3d**: 1 mol %.

Next, a variety of solvents were investigated. CH_2Cl_2 (Table 1, entry 4) was regarded as the best solvent for this cascade reaction although other halogenated solvents, including $CHCl_3$ (Table 1, entry 9) and DCE (Table 1, entry 13), could generate the desired product in excellent yields and stereoselectivities. When the reaction was conducted in a polar solvent like THF (Table 1, entry 11) or MTBE (Table 1, entry 14), **4a** was obtained in low yield. Nonpolar solvent CCl_4 (Table 1, entry 10) or toluene (Table 1, entry 12) could produce **4a** in medium yields. It is worth mentioning that the reaction proceeded smoothly in brine, affording **4a** as the major diastereomer (76:24 dr) in moderate yield (66%) with good enantioselectivity (73% ee, Table 1, entry 15).

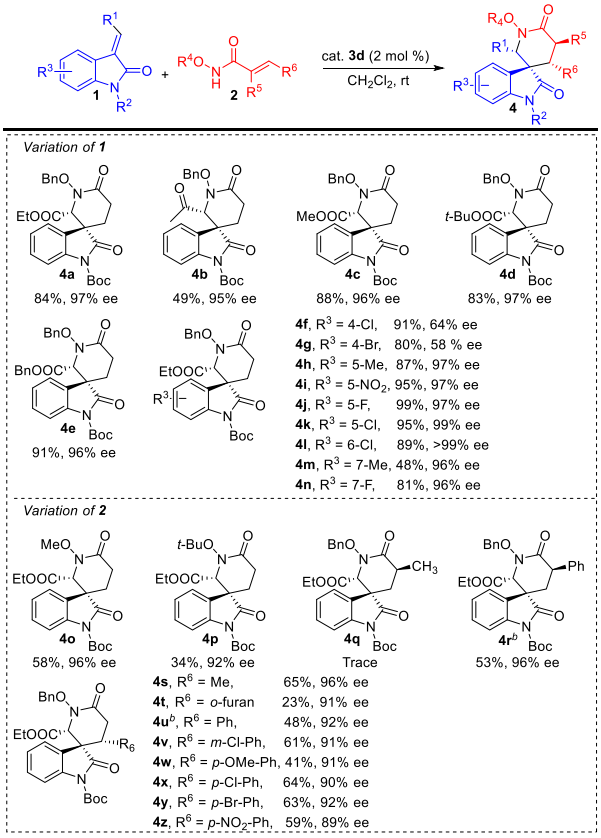
To further optimize this cascade transformation, catalyst loading amount, reaction temperature, and concentration were also examined. As a result of lower catalyst loading amount (2 mol % or 1 mol %), only a slightly decreased yield was observed when 2 mol % catalyst loading was used (Table 1, entries 16 and 17). The reactions were insensitive to the reaction temperature in the range between 10 and 40 °C. Higher reaction concentration could keep the enantioselectivity, albeit with lower yields. Thus, the optimal conditions were to conduct the reaction in CH_2Cl_2 with 2 mol % of squaramide **3d** at room temperature (see SI Table 1 for details).

With the optimized conditions in hand, the reaction scope of various 3-methyleneindolinones (Scheme 1) was studied. As for the R^1 substitutions, 3-acetyl methyleneindolinone could afford **4b** in moderate yield (49%) and good enantioselectivity (95% ee). The benzyl ester substrate **4e** gave slightly higher yield (91%) than Me-, Et- and *t*-Bu-substituted esters (**4a**, **4c**, and **4d**). As for the R^3 substitutions, both 4-Cl and 4-Br led to poor enantioselectivities, probably due to the steric effect (**4f** and **4g**). Substituents at the C-5, C-6, and C-7 positions of the oxindole ring were well tolerated, with the electron-withdrawing groups offering slightly higher yields than the electron-donating groups (**4h**, **4m** vs **4i**–**l** and **4n**).

The scope and limitations of various *N*-protected acrylamides were also examined. Both *N*-methoxy and *N*-*tert*-butoxy acylamides could provide the desired products, with the former giving **4o** in moderate yield (58%) and good enantioselectivity (96% ee) and the latter causing a slight decrease in both yield (34%) and enantioselectivity (92% ee) for **4p**. The substitutions at α-position of acylamide showed significant impact on its reactivity. The phenyl substituent gave higher yield and enantioselectivity (**4r**, 53% yield, 96% ee), while the methyl substituted acylamide was almost ineffective (**4q**, trace). The substituents at β-position, regardless of their electronic properties, were well tolerated (**4s**-**4z**). Obviously, the steric hindrance at both α and β positions of acylamides led to decrease in yields (23–65%), albeit with excellent stereoselectivities (89–96% ee). It was noteworthy that the diastereomeric ratios were excellent in all cases (>20:1 dr), and the absolute configurations of **4r** and **4u** were unambiguously

https://dx.doi.org/10.1021/acs.orglett.0c00779
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Synthesis of Spirooxindoles 4[a]

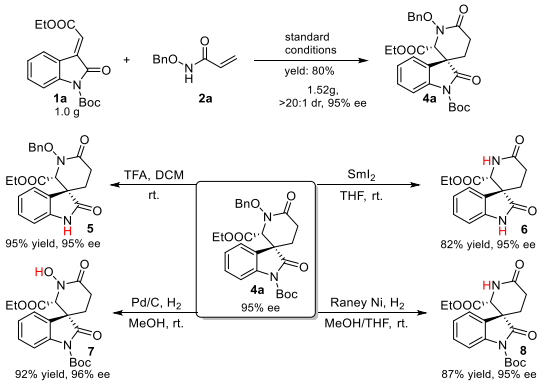


[a]Typical reaction conditions: **1** (0.20 mmol), **2** (0.24 mmol), and cat. **3d** (2 mol %) in CH_2Cl_2 (1.0 mL) at 25 °C for 48 h. Yields for the isolated products were shown. Diastereomeric excesses were determined by ^1H NMR analysis of the crude products before purification, and the ratio was >20:1 if not noted otherwise. Enantiomeric ratios were determined by chiral HPLC analysis. [b]X-ray diffraction analysis.

determined according to the single-crystal X-ray diffraction analysis.

To demonstrate the practical utility and efficiency of this method, a gram-scale reaction was carried out under the standard conditions, providing the desired product **4a** in good yield (80%) and stereoselectivity (>20:1 dr, 95% ee). Further transformations of **4a** were shown in Scheme 2. Selective

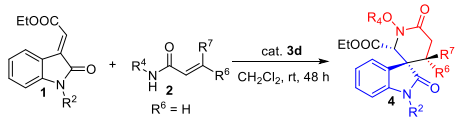
Scheme 2. Gram-Scale Synthesis of 4a Followed by Transformations



removal of *N*-Boc or *N*-OBn group from lactam moieties was achieved through treatment with trifluoroacetic acid or hydrogenation over Raney Ni to give indolone **5** (95% yield, 95% ee) or lactam **8** (87% yield, 95% ee), respectively. On the other hand, SmI_2 could effectively cleave both *N*-Boc or *N*-OBn groups, leading to bis- free lactam **6** (82% yield, 95% ee). Notably, hydrogenation over palladium−carbon could afford the *N*-hydroxy lactam **7** (92% yield, 96% ee).

Control experiments were performed in order to investigate the stereochemical outcome of this cascade reaction (Table 2).

Table 2. Control Experiments



entry	R^2	R^4	R^7	yield (%)
1	Boc	OBn	H	0[a]
2	Cbz	OBn	H	91, >20:1 dr, 96% ee
3	Ac	OBn	H	90, 1:1 dr, 0% ee
4	Bn	OBn	H	0
5	Boc	Ts	H	0
6	Boc	Boc	H	0
7	Boc	PMP	H	0
8	Boc	OBn	Ph	0

[a]Without cat. **3d**.

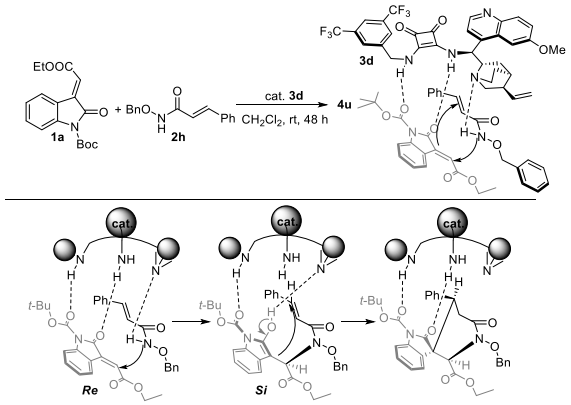
The *N*-Cbz-protected 3-methyleneindolinone provided **4a′** with an excellent yield and enantioselectivity (90% yield, > 20:1 dr, 96% ee), but the *N*-acetyl-protected 3-methyleneindolinone could not afford any stereocontrol (**4b′**, 90% yield, 1:1 dr, 0% ee). Furthermore, the *N*-Bn-protected 3-methyleneindolinone only gave a trace amount of **4c′**. These results indicated that the carbonyl group (Boc, Cbz, and Ac) was essential for reaction yields through a hydrogen-bond interaction with the catalyst and the good stereocontrol came from the steric hindrance of Boc and Cbz groups. When the *N*-OBn in acrylamide was replaced with *N*-Ts, *N*-Boc, or *N*-PMP, the cascade reaction did not take place at all. Additionally, (*Z*)-*N*-OBn-3-phenylacrylamide (**2q**) could not deliver any desired product.

On the basis of the absolute configuration of the adducts and the results of control experiments, the transition state and mechanism were proposed to rationalize the outcome of stereoselectivities (Scheme 3). The squaramide part in the catalyst orients and activates methyleneindolinones via hydrogen bonding. Simultaneously, the *α,β*-substituted acylamides were activated by the tertiary amine of the quinine part in the catalyst, leading to *N*-Michael *Re* face addition of *α,β*-substituted acylamides to activated 3-methyleneindolinone succeeded by the intermolecular *Si* face Michael addition resulted in an irreversible cyclization, furnishing the desired enantioenriched and less steric hindrance product.

In summary, we have developed an asymmetric aza-Michael/Michael cyclization cascade reaction of 3-methyleneindolinones with *α,β*-substituted acylamides, providing an efficient access to spiro-oxindole piperidin-2-one derivatives using squaramide as the catalyst. The reaction generates three stereogenic centers and a quaternary carbon center in such spiro-oxindole piperidin-2-one derivatives in high yield (up to 99%) and excellent stereoselectivities (>20:1 dr, 99% ee). To

https://dx.doi.org/10.1021/acs.orglett.0c00779
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Proposed mechanism for the cascade reaction



the best of our knowledge, our cascade reaction is one of the first few cases to use bifunctional squaramide for catalytic asymmetric aza-Michael/Michael cyclization involving α,β-substituted acylamide. Further studies on this tandem reaction and their application in synthesizing biologically active compounds are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00779.

Experimental details, characterization data, and spectral data (PDF)

Accession Codes

CCDC 1841563 and 1879638 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

Xing-Wen Sun − *Department of Chemistry, Fudan University, Shanghai 200433, China;* orcid.org/0000-0003-0432-7935; Email: sunxingwen@fudan.edu.cn

Authors

Qing-Gang Tang − *Department of Chemistry, Fudan University, Shanghai 200433, China*

Sen-Lin Cai − *Department of Chemistry, Fudan University, Shanghai 200433, China*

Chuan-Chuan Wang − *Department of Chemistry, Fudan University, Shanghai 200433, China*

Guo-Qiang Lin − *Department of Chemistry, Fudan University, Shanghai 200433, China; CAS Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00779

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge financial support from the National Natural Science Foundation of China (21472019).

■ REFERENCES

(1) Lin, Q.; Meloni, D.; Pan, Y.; Xia, M.; Rodgers, J.; Shepard, S.; Li, M.; Galya, L.; Metcalf, B.; Yue, T.-N.; Liu, P.; Zhou, J. *Org. Lett.* **2009**, *11*, 1999.

(2) (a) Cai, Q.; Zheng, C.; You, S.-L. *Angew. Chem., Int. Ed.* **2010**, *49*, 8666. (b) Liu, J.-D.; Chen, Y.-C.; Zhang, G.-B.; Li, Z.-Q.; Chen, P.; Du, J.-Y.; Tu, Y.-Q.; Fan, C.-A. *Adv. Synth. Catal.* **2011**, *353*, 2721. (c) Yang, H.-M.; Li, L.; Li, F.; Jiang, K.-Z.; Shang, J.-Y.; Lai, G.-Q.; Xu, L.-W. *Org. Lett.* **2011**, *13*, 6508. (d) Robinson, J. R.; Fan, X.; Yadav, J.; Carroll, P. J.; Wooten, A. J.; Pericas, M. A.; Schelter, E. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2014**, *136*, 8034. (e) Zhang, J.; Zhang, Y.; Liu, X.; Guo, J.; Cao, W.; Lin, L.; Feng, X. *Adv. Synth. Catal.* **2014**, *356*, 3545. (f) Avidan-Shlomovich, S.; Ghosh, H.; Szpilman, A. M. *ACS Catal.* **2015**, *5*, 336. (g) Wu, L.; Jin, R.; Li, L.; Hu, X.; Cheng, T.; Liu, G. *Org. Lett.* **2017**, *19*, 3047.

(3) (a) Vesely, J.; Ibrahem, I.; Rios, R.; Zhao, G.-L.; Xu, Y.; Cordova, A. *Tetrahedron Lett.* **2007**, *48*, 2193. (b) Enders, D.; Goeddertz, D. P.; Beceno, C.; Raabe, G. *Adv. Synth. Catal.* **2010**, *352*, 2863.

(4) (a) Fernandez, M.; Reyes, E.; Vicario, J. L.; Badia, D.; Carrillo, L. *Adv. Synth. Catal.* **2012**, *354*, 371. (b) Du, J.-Y.; Zeng, C.; Han, X.-J.; Qu, H.; Zhao, X.-H.; An, X.-T.; Fan, C.-A. *J. Am. Chem. Soc.* **2015**, *137*, 4267.

(5) (a) Pandey, G.; Balakrishnan, M.; Swaroop, P. S. *Eur. J. Org. Chem.* **2008**, *2008*, 5839. (b) Enders, D.; Wang, C.; Liebich, J. X. *Chem. - Eur. J.* **2009**, *15*, 11058. (c) Farwick, A.; Helmchen, G. *Adv. Synth. Catal.* **2010**, *352*, 1023. (d) Bao, X.; Cao, Y.-X.; Chu, W.-D.; Qu, H.; Du, J.-Y.; Zhao, X.-H.; Ma, X.-Y.; Wang, C.-T.; Fan, C.-A. *Angew. Chem., Int. Ed.* **2013**, *52*, 14167. (e) Azuma, T.; Murata, A.; Kobayashi, Y.; Inokuma, T.; Takemoto, Y. *Org. Lett.* **2014**, *16*, 4256. (f) Sanchez-Rosello, M.; Acena, J. L.; Simon-Fuentes, A.; del Pozo, C. *Chem. Soc. Rev.* **2014**, *43*, 7430. (g) Barron, B. J.; Wong, W.-T.; Chiu, P.; Hii, K. K. *ACS Catal.* **2016**, *6*, 4189. (h) Klier, L.; Tur, F.; Poulsen, P. H.; Jørgensen, K. A. *Chem. Soc. Rev.* **2017**, *46*, 1080.

(6) (a) Hamashima, Y.; Suzuki, S.; Tamura, T.; Somei, H.; Sodeoka, M. *Chem. - Asian J.* **2011**, *6*, 658. (b) Jiang, J.; Cai, Y.; Chen, W.; Lin, L.; Liu, X.; Feng, X. *Chem. Commun.* **2011**, *47*, 4016. (c) Wang, J.; Li, P.; Choy, P. Y.; Chan, A. S. C.; Kwong, F. Y. *ChemCatChem* **2012**, *4*, 917. (d) Weiss, M.; Borchert, S.; Remond, E.; Juge, S.; Groeger, H. *Heteroat. Chem.* **2012**, *23*, 202. (e) Xiao, X.; Liu, X.; Dong, S.; Cai, Y.; Lin, L.; Feng, X. *Chem. - Eur. J.* **2012**, *18*, 15922. (f) Bradshaw, B.; Luque-Corredera, C.; Bonjoch, J. *Org. Lett.* **2013**, *15*, 326. (g) Miyaji, R.; Asano, K.; Matsubara, S. *Org. Lett.* **2013**, *15*, 3658. (h) Lauber, A.; Zelenay, B.; Cvengros, J. *Chem. Commun.* **2014**, *50*, 1195. (i) Yang, X.; Chen, Z.; Cai, Y.; Huang, Y.-Y.; Shibata, N. *Green Chem.* **2014**, *16*, 4530. (j) Saito, K.; Moriya, Y.; Akiyama, T. *Org. Lett.* **2015**, *17*, 3202. (k) Hayama, N.; Azuma, T.; Kobayashi, Y.; Takemoto, Y. *Chem. Pharm. Bull.* **2016**, *64*, 704. (l) Humphrey, G. R.; Dalby, S. M.; Andreani, T.; Xiang, B.; Luzung, M. R.; Song, Z. J.; Shevlin, M.; Christensen, M.; Belyk, K. M.; Tschaen, D. M. *Org. Process Res. Dev.* **2016**, *20*, 1097. (m) Riano, I.; Diaz, E.; Uria, U.; Reyes, E. m.; Carrillo, L.; Vicario, J. L. *Chem. Commun.* **2016**, *52*, 2330. (n) Zhang, S.; Cha, L.; Li, L.; Hu, Y.; Li, Y.; Zha, Z.; Wang, Z. *J. Org. Chem.* **2016**, *81*, 3177. (o) Zhao, K.; Zhi, Y.; Li, X.; Puttreddy, R.; Rissanen, K.; Enders, D. *Chem. Commun.* **2016**, *52*, 2249. (p) Du, K.; Yang, H.; Guo, P.; Feng, L.; Xu, G.; Zhou, Q.; Chung, L. W.; Tang, W. *Chem. Sci.* **2017**, *8*, 6247. (q) Kim, H.; Kim, Y.; Kim, S.-G. *J. Org. Chem.* **2017**, *82*, 8179.

(7) (a) Jossang, A.; Jossang, P.; Hadi, H. A.; Sevenet, T.; Bodo, B. *J. Org. Chem.* **1991**, *56*, 6527. (b) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748.

(8) (a) Rottmann, M.; McNamara, C.; Yeung, B. K. S.; Lee, M. C. S.; Zou, B.; Russell, B.; Seitz, P.; Plouffe, D. M.; Dharia, N. V.; Tan, J.; Cohen, S. B.; Spencer, K. R.; González-Páez, G. E.; Lakshminarayana, S. B.; Goh, A.; Suwanarusk, R.; Jegla, T.; Schmitt, E.; Beck, H.-P.;

https://dx.doi.org/10.1021/acs.orglett.0c00779
Org. Lett. XXXX, XXX, XXX−XXX

Brun, R.; Nosten, F.; Renia, L.; Dartois, V.; Keller, T. H.; Fidock, D. A.; Winzeler, E. A.; Diagana, T. T. *Science* **2010**, *329*, 1175. (b) Zhou, F.; Liu, Y. L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381.

(9) (a) Larsen, T. O.; Frydenvang, K.; Frisvad, J. C.; Christophersen, C. *J. Nat. Prod.* **1998**, *61*, 1154. (b) Ariza, M. R.; Larsen, T. O.; Petersen, B. O.; Duus, J.; Christophersen, C.; Barrero, A. F. *J. Nat. Prod.* **2001**, *64*, 1590. (c) Hibino, S.; Choshi, T. *Nat. Prod. Rep.* **2001**, *18*, 66. (d) Wu, M.; Ma, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 9759.

(10) (a) Chen, L.; Ding, Q. J.; Liu, J. J.; Yang, S.; Zhang, Z. M. US2007213341A1, 2007. (b) Ding, Q. J.; Liu, J. J.; Zhang, Z. M. WO2007104714A1, 2007.

(11) (a) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (b) Chen, X. H.; Wei, Q.; Luo, S. W.; Xiao, H.; Gong, L. Z. *J. Am. Chem. Soc.* **2009**, *131*, 13819. (c) Miller, K. A.; Tsukamoto, S.; Williams, R. M. *Nat. Chem.* **2009**, *1*, 63. (d) Li, S. M. *Nat. Prod. Rep.* **2010**, *27*, 57. (e) White, J. D.; Li, Y.; Ihle, D. C. *J. Org. Chem.* **2010**, *75*, 3569. (f) Cao, Y.; Jiang, X.; Liu, L.; Shen, F.; Zhang, F.; Wang, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 9124. (g) Tan, B.; Zeng, X.; Leong, W. W.; Shi, Z.; Barbas, C. F., III; Zhong, G. *Chem. - Eur. J.* **2012**, *18*, 63. (h) Khalafi-Nezhad, A.; Mohammadi, S. *ACS Comb. Sci.* **2013**, *15*, 512. (i) Cheng, D. J.; Ishihara, Y.; Tan, B.; Barbas, C. F., III *ACS Catal.* **2014**, *4*, 743. (j) Zhang, H. M.; Gao, Z. H.; Ye, S. *Org. Lett.* **2014**, *16*, 3079. (k) Liu, Y.; Xue, J.; Sun, Z.; Liu, D.; Xing, Y.; Li, Y. *Asian J. Org. Chem.* **2016**, *5*, 43. (l) Jayakumar, S.; Louven, K.; Strohmann, C.; Kumar, K. *Angew. Chem., Int. Ed.* **2017**, *56*, 15945.

(12) (a) Jiang, K.; Jia, Z. J.; Chen, S.; Wu, L.; Chen, Y. C. *Chem. - Eur. J.* **2010**, *16*, 2852. (b) Yang, W.; Du, D.-M. *Chem. Commun.* **2013**, *49*, 8842. (c) Yu, F.; Huang, R.; Ni, H.; Fan, J.; Yan, S.; Lin, J. *Green Chem.* **2013**, *15*, 453. (d) Huang, X.; Pham, K.; Yi, W. B.; Zhang, X. F.; Clamens, C.; Hyatt, J. H.; Jasinsk, P.; Tayvah, U.; Zhang, W. *Adv. Synth. Catal.* **2015**, *357*, 3820.

(13) (a) Grossmann, A.; Enders, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 314. (b) Zhuo, C.-X.; Zhang, W.; You, S.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 12662. (c) Aleman, J.; Cabrera, S. *Chem. Soc. Rev.* **2013**, *42*, 774. (d) Noble, A.; Anderson, J. C. *Chem. Rev.* **2013**, *113*, 2887. (e) Volla, C. M. R.; Atodiresei, I.; Rueping, M. *Chem. Rev.* **2014**, *114*, 2390. (f) Chauhan, P.; Mahajan, S.; Kaya, U.; Hack, D.; Enders, D. *Adv. Synth. Catal.* **2015**, *357*, 253. (g) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev.* **2015**, *115*, 9307. (h) Vetica, F.; De Figueiredo, R. M.; Orsini, M.; Tofani, D.; Gasperi, T. *Synthesis* **2015**, *47*, 2139. (i) Afewerki, S.; Cordova, A. *Chem. Rev.* **2016**, *116*, 13512. (j) Ardkhean, R.; Caputo, D. F. J.; Morrow, S. M.; Shi, H.; Xiong, y.; Anderson, E. A. *Chem. Soc. Rev.* **2016**, *45*, 1557. (k) Xie, X.; Huang, W.; Peng, C.; Han, B. *Adv. Synth. Catal.* **2018**, *360*, 194.

(14) (a) Sun, Q.-S.; Chen, X.-Y.; Zhu, H.; Lin, H.; Sun, X.-W.; Lin, G.-Q. *Org. Chem. Front.* **2015**, *2*, 110. (b) Sun, Q. S.; Zhu, H.; Chen, Y. J.; Yang, X. D.; Sun, X. W.; Lin, G. Q. *Angew. Chem., Int. Ed.* **2015**, *54*, 13253. (c) Tan, Y.; Feng, E.-L.; Sun, Q.-S.; Lin, H.; Sun, X.; Lin, G.-Q.; Sun, X.-W. *Org. Biomol. Chem.* **2017**, *15*, 778. (d) Wang, C.-C.; Huang, J.; Li, X.-H.; Kramer, S.; Lin, G.-Q.; Sun, X.-W. *Org. Lett.* **2018**, *20*, 2888.

https://dx.doi.org/10.1021/acs.orglett.0c00779
Org. Lett. XXXX, XXX, XXX−XXX