Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

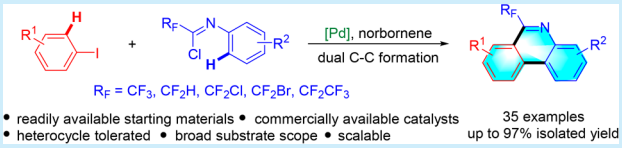
Expeditious Synthesis of 6-Fluoroalkyl-Phenanthridines via Palladium-Catalyzed Norbornene-Mediated Dehydrogenative Annulation

Zhuo Wang, Tongyu Li, Jinghui Zhao, Xiaonan Shi, Dequan Jiao, Han Zheng, Chen Chen,* and Bolin Zhu*

Tianjin Key Laboratory of Structure and Performance for Functional Molecules; Key Laboratory of Inorganic−Organic Hybrid Functional Materials Chemistry (Tianjin Normal University), Ministry of Education; College of Chemistry, Tianjin Normal University, Tianjin 300387, People's Republic of China

Supporting Information

ABSTRACT: A novel palladium-catalyzed, norbornene-mediated intermolecular dehydrogenative annulation approach for the synthesis of 6-fluoroalkyl-phenanthridines from aryl iodides and fluorinated imidoyl chlorides, which are important structural motifs for bioactive molecules, is reported. Fluorinated imidoyl chlorides served as a new type of electrophilic reagent in the Catellani-type reaction, which, in turn, could be readily prepared from various anilines and fluorinated carboxylic acids. Control experiments were carried out to study the mechanism of the reaction. This transformation is scalable and tolerates a broad range of functional groups.



Phenanthridines represent a class of fused heteroaromatic motifs found universally in many natural products,[1] biologically active molecules,[2] and in optoelectronic materials.[3] Well known members include trisphaeridine,[4] fagaronine,[5] and ethidium[6] (Figure 1). Moreover, the incorporation of a

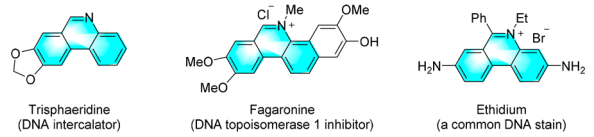
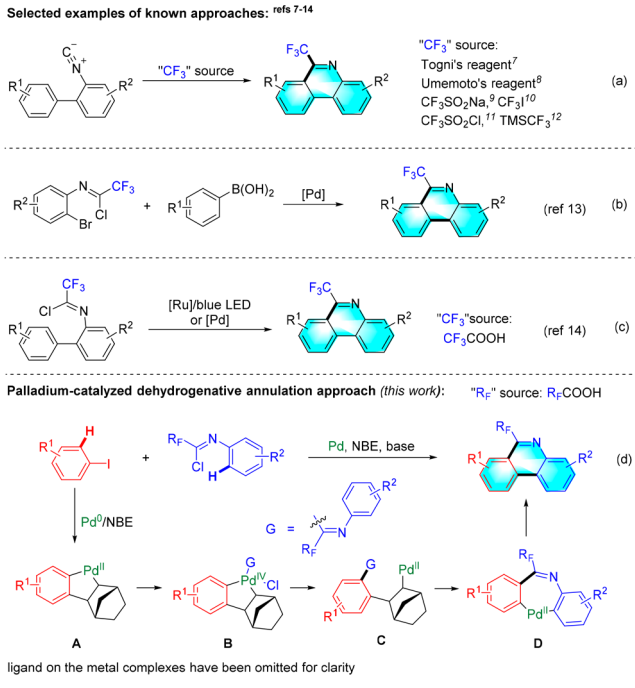


Figure 1. Biologically active phenanthridines.

fluoroalkyl group into phenanthridines often alters its physical and chemical properties, leading to improved biological functions, due to increased lipophilicity and metabolic stability. Therefore, the development of efficient methodologies to synthesize 6-fluoroalkyl-phenanthridines and their derivatives has become a subject of great interest during the past few years and many useful synthetic procedures have been explored. In one such transformation, trifluoromethylation of 2-arylisocynides was carried out using radical trifluoromethylating reagents, such as Togni's reagent,[7] Umemoto's reagent,[8] Langlois' reagent,[9] CF_3I,[10] CF_3SO_2Cl,[11] $TMSCF_3$,[12] and others (Scheme 1a). In recent years, fluorinated imidoyl chlorides have proven to be good building blocks for the synthesis of 6-fluoroalkyl-phenanthridines using transition metal catalysts. For example, Zhang and co-workers[13] prepared 6-trifluoromethyl-phenanthridines through palladium-catalyzed tandem Suzuki/C−H arylation reactions of *N*-aryltrifluoroacetimidoyl chlorides with arylboronic acids (Scheme 1b).

Scheme 1. Approaches To Access 6-Fluoroalkyl-phenanthridines



Later, Fu[14] achieved the intramolecular cyclization of *N*-biaryltrifluoroacetimidoyl chloride to obtain 6-trifluoromethyl-

Received: August 17, 2018

DOI: 10.1021/acs.orglett.8b02588
Org. Lett. XXXX, XXX, XXX−XXX

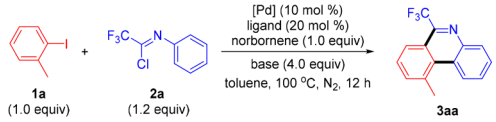
phenanthridines (Scheme 1c). Although many methods are available, the requirement of specific prefunctionalized starting materials and their low efficiencies limit the scope of these methods. Therefore, the development of expeditious approaches for the synthesis of 6-fluoroalkyl-phenanthridines from readily available starting materials is necessary.

Pd/norbornene (NBE) chemistry represents a powerful strategy that allows the efficient construction of polyfunctional aromatic and heteroaromatic compounds,[15] which was pioneered by Catellani and co-workers in 1997.[16] Further explorations by Catellani's group,[17] Lautens' group,[18] and others[19] have enriched and expanded the scope of this method. Taking advantage of the palladium/NBE catalysis, *ortho* and *ipso* bis-functionalization products can be obtained by coupling with an electrophile and a nucleophile simultaneously. In recent years, different types of electrophilic reagents have been found to react with a key aryl-NBE palladacycle intermediate in reactions, such as amination,[19e,g,20] arylation,[21] alkylation,[16,22] and acylation,[23] which result in *ortho*-functionalized products. In order to broaden the scope of this reaction, it becomes crucial to explore new electrophilic reagents for the synthesis of divergent polysubstituted arenes.

In 2016, Jiao and co-workers[24] developed an efficient approach to synthesize phenanthridinone derivatives by employing palladium/NBE cooperative catalysis. This protocol was easy to handle, and aryl carbamic chloride served as the electrophilic reagent to realize *ortho*-acylation. As part of our continued interest in the development of practical methodologies for highly efficient construction of heterocyclic molecules from readily available building blocks[25] and inspired by Jiao's work,[24] we surmised that biologically relevant 6-fluoroalkyl-phenanthridines could be obtained from aryl iodides and fluorinated imidoyl chlorides through a palladium-catalyzed Catellani-type *one-pot* dehydrogenative annulation reaction. Scheme 1d depicts a convergent synthetic route to the aforementioned scaffolds. We hypothesize that the reaction is initiated by Pd(0), which undergoes oxidative addition with aryl iodide, followed by insertion of the norbornene and ortho C−H activation to form the key Pd(II) intermediate **A**. Subsequent oxidative addition of the fluorinated imidoyl chlorides with **A** provides the Pd(IV) complex **B**, which undergoes reductive elimination to afford Pd(II) intermediate **C**. The target 6-fluoroalkyl-phenanthridines and Pd(0) are obtained by elimination of the β-C with the removal of norbornene along with activation of the C−H bond to afford Pd(II) intermediate **D**, which finally undergoes another reductive elimination, thereby completing the Pd cycle. To the best of our knowledge, synthesis of 6-fluoroalkyl-phenanthridines by using this strategy is still unknown and is challenging due to two adjacent C−C bond formations via C−H bond cleavage.[26] Recently, Pd/NBE chemistry has proven to be an important protocol that allows activation of both the *ipso*- and *ortho*-positions of arenes.[27−32] These results encouraged us to test our dehydrogenative protocol.

To test our hypothesis as shown in Scheme 1d, compounds **1a** and **2a** were initially chosen as the model substrates, which were reacted in the presence of $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), norbornene (1.0 equiv), and Cs_2CO_3 (4.0 equiv) in toluene (2.0 mL) at 100 °C under a nitrogen atmosphere. Gratifyingly, after 12 h, the expected product **3aa** was indeed obtained in 40% isolated yield (Table 1, entry 1). Inspired by this result, first, a range of solvents were tested, of which toluene was found to be the most efficient (Table 1, entries 2−4). A subsequent survey of a series of ligands indicated that $P(4\text{-F-}C_6H_4)_3$ was the most efficient ligand, giving a 52% yield of the product. In contrast to $P(4\text{-F-}C_6H_4)_3$, other ligands including diphosphines and monophosphines failed to show better catalytic reactivities (Table 1, entries 5−11). Among the catalysts investigated, $Pd(OAc)_2$ was found to be the most efficient one (Table 1, entries 12 and 13). To further improve the yield, various bases were examined, and to our delight, K_3PO_4 exhibited the best performance and afforded the product in 87% yield (Table 1, entries 14 and 15). Additionally, when the loading of norbornene was decreased to 50 mol %, the yield was only 50% (Table 1, entry 16). Moreover, use of 5 mol % $Pd(OAc)_2$ decreased the yield to 45%, due to the low conversion of starting materials (Table 1, entry 17). Finally, the reaction of **1a** (1.0 equiv) with **2a** (1.2 equiv) in the presence of $Pd(OAc)_2$ (10 mol %), $P(4\text{-F-}C_6H_4)_3$ (20 mol %), norbornene (1.0 equiv), and K_3PO_4 (4.0 equiv) in toluene (2.0 mL) under nitrogen atmosphere at 100 °C for 12 h was considered to be the most optimal.

Table 1. Optimization of Reaction Conditions[a]



1a (1.0 equiv) **2a** (1.2 equiv) **3aa**

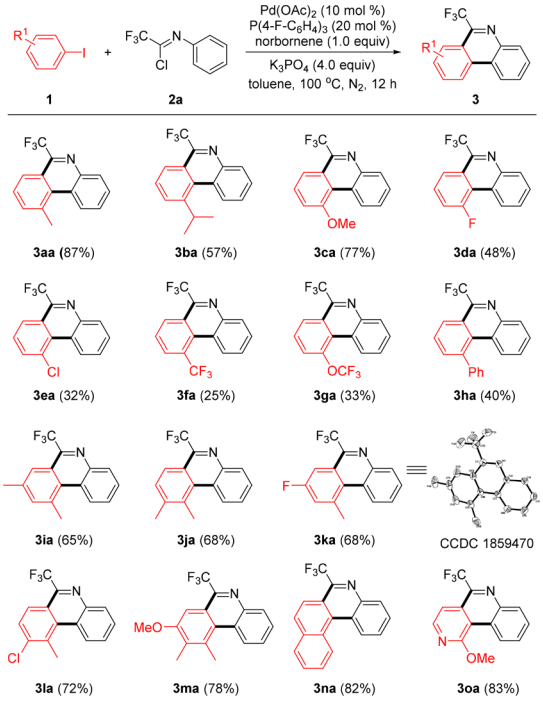
entry	[Pd]	ligand	base	yield[b] (%)
1	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	40%
2[c]	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	15%
3[d]	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	trace
4[e]	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	trace
5	$Pd(OAc)_2$	S-Phos	Cs_2CO_3	22%
6	$Pd(OAc)_2$	$P(2\text{-furyl})_3$	Cs_2CO_3	36%
7	$Pd(OAc)_2$	$P(4\text{-F-}C_6H_4)_3$	Cs_2CO_3	52%
8	$Pd(OAc)_2$	$P(4\text{-}CF_3\text{-}C_6H_4)_3$	Cs_2CO_3	50%
9[f]	$Pd(OAc)_2$	dppe	Cs_2CO_3	45%
10[f]	$Pd(OAc)_2$	dppf	Cs_2CO_3	43%
11[f]	$Pd(OAc)_2$	DPE-Phos	Cs_2CO_3	23%
12	$PdCl_2$	$P(4\text{-F-}C_6H_4)_3$	Cs_2CO_3	42%
13	$Pd(cod)Cl_2$	$P(4\text{-F-}C_6H_4)_3$	Cs_2CO_3	32%
14	$Pd(OAc)_2$	$P(4\text{-F-}C_6H_4)_3$	KOH	45%
15	**$Pd(OAc)_2$**	**$P(4\text{-F-}C_6H_4)_3$**	**K_3PO_4**	**87%**
16[g]	$Pd(OAc)_2$	$P(4\text{-F-}C_6H_4)_3$	K_3PO_4	50%
17[h]	$Pd(OAc)_2$	$P(4\text{-F-}C_6H_4)_3$	K_3PO_4	45%

[a]Reaction conditions: the reactions were carried out with **1a** (0.2 mmol), **2a** (0.24 mmol), [Pd] (0.02 mmol), ligand (0.04 mmol), norbornene (0.2 mmol), base (0.8 mmol), toluene (2.0 mL), nitrogen atmosphere, 12 h. [b]Isolated yield. [c]Xylene 2.0 mL. [d]$PhCF_3$ 2.0 mL. [e]MeCN 2.0 mL. [f]Ligand (0.02 mmol). [g]Norbornene (0.1 mmol). [h]5 mol % $Pd(OAc)_2$.

With optimal reaction conditions in hand, the scope of this methodology with respect to substituted aryl iodides was first examined. As shown in Scheme 2, a variety of iodoarenes were tested, all of which proved to be competent substrates for reaction with **2a**. In addition, regarding **1a**, a variety of *ortho*-substituents on the iodoarenes were tolerated in the reaction, which included isopropyl, methoxyl, fluoro, chloro, trifluoromethyl, trifluoromethoxyl, and phenyl groups, and the corresponding products **3aa**−**3ha** were isolated in moderate to excellent yields. Both electron-withdrawing and -donating groups on iodoarenes were tolerated, although substrates with electron-withdrawing groups gave products with relatively lower yields. Furthermore, multisubstituted aryl iodides with

DOI: 10.1021/acs.orglett.8b02588
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Variation of Aryl Iodides[a]

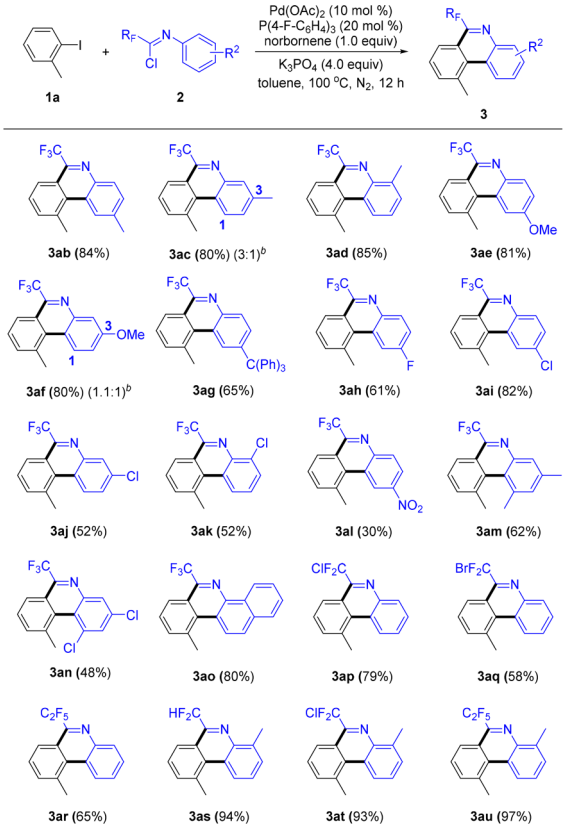


[a]Reaction conditions: the reactions were carried out with **1** (0.2 mmol), **2a** (0.24 mmol), $Pd(OAc)_2$ (0.02 mmol), $P(4\text{-F-}C_6H_4)_3$ (0.04 mmol), norbornene (0.2 mmol), K_3PO_4 (0.8 mmol) in toluene (2.0 mL) under a nitrogen atmosphere for 12 h.

versatile groups reacted smoothly to give the corresponding products in 65%−78% yields (**3ia**−**3ma**). Meanwhile the molecular structure of **3ka** was unambiguously confirmed by X-ray crystallographic analysis (CCDC 1859470; for other details, see the Supporting Information). Reaction with 1-iodonaphthalene provided **3na** in 82% yield. Notably, heteroaryl iodide **1o** was also found to be a suitable substrate, which reacted with **2a** to afford **3oa** in 83% yield.

The catalytic dehydrogenative annulation methodology was then extended to other fluorinated imidoyl chlorides, which could be easily prepared from the corresponding aniline and fluorinated carboxylic acids. As shown in Scheme 3, *p*-, *m*-, and *o*-methyl substituents on the aryl ring of **2** were well tolerated and the desired products **3ab**−**3ad** were obtained in 80−85% yields. Among them, *meta*-substituted substrate **2c** with **1a** resulted in a mixture of the products **3ac** with moderate regioselectivity (3:1). Different derivatives of **2** with electron-withdrawing and -donating groups on the phenyl ring were tested, which showed good performance, affording the corresponding products in moderate yields (**3ae**−**3al**). Moreover, multisubstituted fluorinated imidoyl chlorides were also compatible under these reaction conditions (**3am** and **3an**). Likewise, other fluorinated substrates **2p**−**2u** were also tested, wherein the corresponding 6-fluoroalkyl-phenanthridines **3ap**−**3au** were formed smoothly in moderate to excellent yields. Different CF_2X (X = Cl, Br, H, CF_3) groups could also be introduced into phenanthridines through these reactions. Notably, this transformation could very well introduce the CF_2Br group, which is potentially useful for the further elaboration of more valuable molecules through cross-coupling reactions.[33]

Scheme 3. Variation of Fluorinated Imidoyl Chlorides[a]

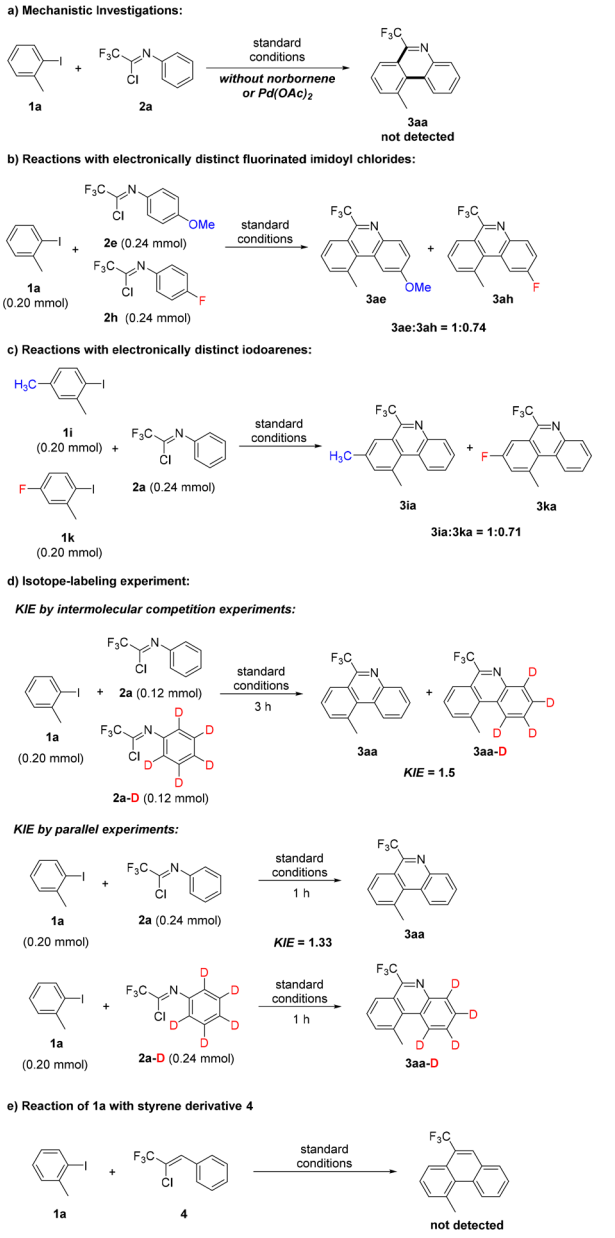


[a]Reaction conditions: the reactions were carried out with **1a** (0.2 mmol), **2** (0.24 mmol), $Pd(OAc)_2$ (0.02 mmol), $P(4\text{-F-}C_6H_4)_3$ (0.04 mmol), norbornene (0.2 mmol), K_3PO_4 (0.8 mmol) in toluene (2.0 mL) under a nitrogen atmosphere for 12 h. [b]Regioselectivity ratio (the major isomer is substituted at the 3-position as indicated).

To gain insight into the mechanism, several control experiments were carried out. In order to understand the role of each component, when the reactions were carried out by excluding either norbornene or the Pd catalyst, desired dehydrogenative annulation product **3aa** was not obtained (Scheme 4a). Competing reactions with fluorinated imidoyl chloride substrates bearing different electronic properties were investigated. ^1H NMR analysis indicated that the more electron-rich substrate **2e** had a higher reaction rate (**3ae**:**3ah** = 1:0.74) probably due to the fact that the C−H activation process occurs easily (Scheme 4b). Next, an equimolar mixture of **1i** and **1k** that differed in electronic effects was also examined. The ^1H NMR analysis of this product mixture revealed a slight preference for more electron-rich iodoarenes (**3ia**:**3ka** = 1:0.71) (Scheme 4c). Then, to study the kinetic isotope effects (KIE) in the reactions, intermolecular competition experiments were performed under standard conditions for 3 h. The reaction of **1a** with **2a** and **2a-D** provided a mixture of the products **3aa** and **3aa-D** in 20% combined yield, and the ratio of **3aa**: **3aa-D** was 1.5. Furthermore, a parallel experiment was also performed under standard conditions for 1 h. The KIE was 1.33 (for details, see the Supporting Information). The KIE values suggested that the C−H bond activation step is not the rate-determining step of this reaction (Scheme 4d). It is noteworthy that the cyclization product was not detected with styrene derivative **4** as the substrate under the standard conditions, which

DOI: 10.1021/acs.orglett.8b02588
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 4. Control Experiments



demonstrated that the imine group probably played a key role in this transformation (Scheme 4e). Moreover, scale-up of **1a** to 4 mmol (872 mg) with 4.8 mmol (996 mg) of **2a** provided the corresponding 6-trifluoromethyl-phenanthridines **3aa** in 84% yield (878 mg).[34]

In conclusion, we developed a useful strategy to synthesize 6-fluoroalkyl-phenanthridines from simple aryl iodides and fluorinated imidoyl chlorides, through dual C−H bond activations. Fluorinated imidoyl chlorides served as a new type of electrophilic reagent in Pd/NBE catalysis, which, in turn, could be readily prepared from various anilines and fluorinated carboxylic acids. The good tolerance for functional groups on fluorinated imidoyl chlorides and aryl iodides indicated its high potential for constructing biologically active fluorinated phenanthridine heterocycles. Further applications of this method to synthesize various other heterocycles are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02588.

Experimental procedures and full spectroscopic data for all new compounds (PDF)

Accession Codes

CCDC 1859470 contains 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 Authors

*E-mail: tjnuchenchen@163.com (C.C.).
*E-mail: hxxyzbl@gmail.com (B.Z.).

ORCID

Chen Chen: 0000-0002-5388-9611
Bolin Zhu: 0000-0002-6846-566X

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported jointly by the Doctoral Program Foundation of Tianjin Normal University (043135202-XB1703), NSFC (21572160), and the Foundation of the Development Program of Future Expert in Tianjin Normal University (WLQR201706; WLQR201811). We are also grateful to the Tianjin Key Laboratory of Structure and Performance for Functional Molecules, Key Laboratory of Inorganic−Organic Hybrid Functional Materials Chemistry (Tianjin Normal University), Ministry of Education, and the Program for Innovative Research Team in University of Tianjin (TD13-5074) for financial support.

■ REFERENCES

(1) (a) Viladomat, F.; Selles, M.; Cordina, C.; Bastida, J. *Planta Med.* **1997**, *63*, 583. (b) Ali, A. A.; El Saved, H. M.; Abdalliah, O. M.; Steglich, W. *Phytochemistry* **1986**, *25*, 2399. (c) Krane, B. D.; Fagbule, M. O.; Shamma, M.; Gozler, B. *J. Nat. Prod.* **1984**, *47*, 1.

(2) (a) Bernardo, P. H.; Wan, K.-F.; Sivaraman, T.; Xu, J.; Moore, F. K.; Hung, A. W.; Mok, H. Y. K.; Yu, V. C.; Chai, C. L. L. *J. Med. Chem.* **2008**, *51*, 6699. (b) Merz, K.-H.; Muller, T.; Vanderheiden, S.; Eisenbrand, G.; Marko, D.; Bräse, S. *Synlett* **2006**, *2006*, 3461. (c) Zhu, S.; Ruchelman, A. L.; Zhou, N.; Liu, A. A.; Liu, L. F.; LaVoie, E. J. *Bioorg. Med. Chem.* **2005**, *13*, 6782. (d) Lewis, W. G.; Green, L. G.; Grynszpan, F.; Radic, Z.; Carlier, P. R.; Taylor, P.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 1053. (e) Lynch, M. A.; Duval, O.; Sukhanova, A.; Devy, J.; MacKay, S. P.; Waigh, R. D.; Nabiev, I. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2643.

(3) (a) Stevens, N.; O'Connor, N.; Vishwasrao, H.; Samaroo, D.; Kandel, E. R.; Akins, D. L.; Drain, C. M.; Turro, N. J. *J. Am. Chem. Soc.* **2008**, *130*, 7182. (b) Bondarev, S. L.; Knyukshto, V. N.; Tikhomirov, S. A.; Pyrko, A. N. *Opt. Spectrosc.* **2006**, *100*, 386. (c) Zhang, J.; Lakowicz, J. R. *J. Phys. Chem. B* **2005**, *109*, 8701.

(4) Abdel-Halim, O. B.; Morikawa, T.; Ando, S.; Matsuda, H.; Yoshikawa, M. *J. Nat. Prod.* **2004**, *67*, 1119.

(5) Phillips, S. D.; Castle, R. N. *J. Heterocycl. Chem.* **1981**, *18*, 223.

DOI: 10.1021/acs.orglett.8b02588
Org. Lett. XXXX, XXX, XXX−XXX

(6) Sripada, L.; Teske, J. A.; Deiters, A. *Org. Biomol. Chem.* **2008**, *6*, 263.
(7) (a) Lübbesmeyer, M.; Leifert, D.; Schäfer, H.; Studer, A. *Chem. Commun.* **2018**, *54*, 2240. (b) Gorbanev, Y.; Leifert, D.; Studer, A.; O'Connell, D.; Chechik, V. *Chem. Commun.* **2017**, *53*, 3685. (c) Zhang, B.; Mück-Lichtenfeld, C.; Daniliuc, C. G.; Studer, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 10792.
(8) (a) Wang, R.; Jiang, H.; Cheng, Y.; Kadi, A. A.; Fun, H.-K.; Zhang, Y.; Yu, S. *Synthesis* **2014**, *46*, 2711. (b) Cheng, Y.; Jiang, H.; Zhang, Y.; Yu, S. *Org. Lett.* **2013**, *15*, 5520.
(9) (a) Li, J.; Caiuby, C. A. D.; Paixao, M. W.; Li, C.-J. *Eur. J. Org. Chem.* **2018**, *2018*, 2498. (b) Fang, J.; Shen, W.-G.; Ao, G.-Z.; Liu, F. *Org. Chem. Front.* **2017**, *4*, 2049. (c) Sakamoto, R.; Kashiwagi, H.; Selvakumar, S.; Moteki, S. A.; Maruoka, K. *Org. Biomol. Chem.* **2016**, *14*, 6417. (d) Liu, Y.-R.; Tu, H.-Y.; Zhang, X.-G. *Synthesis* **2015**, *47*, 3460.
(10) (a) Wang, Y.; Wang, J.; Li, G.-X.; He, G.; Chen, G. *Org. Lett.* **2017**, *19*, 1442. (b) Zhang, B.; Studer, A. *Org. Lett.* **2014**, *16*, 3990.
(11) Tang, X.; Song, S.; Liu, C.; Zhu, R.; Zhang, B. *RSC Adv.* **2015**, *5*, 76363.
(12) (a) Stephens, D. E.; Chavez, G.; Valdes, M.; Dovalina, M.; Arman, H.; Larionov, O. V. *Org. Biomol. Chem.* **2014**, *12*, 6190. (b) Wang, Q.; Dong, X.; Xiao, T.; Zhou, L. *Org. Lett.* **2013**, *15*, 4846.
(13) Wang, W.-Y.; Feng, X.; Hu, B.-L.; Deng, C.-L.; Zhang, X.-G. *J. Org. Chem.* **2013**, *78*, 6025.
(14) (a) Fu, W.; Zhu, M.; Xu, F.; Fu, Y.; Xu, C.; Zou, D. *RSC Adv.* **2014**, *4*, 17226. (b) Zhu, M.; Fu, W.; Zou, G.; Xu, C.; Wang, Z. *J. Fluorine Chem.* **2014**, *163*, 23.
(15) (a) Zhou, Q.; Liu, Z.-S.; Gao, Q.; Cheng, H.-G. *Chem. - Eur. J.* **2018**, DOI: 10.1002/chem.201802818. (b) Kim, D.-S.; Park, W.-J.; Jun, C.-H. *Chem. Rev.* **2017**, *117*, 8977. (c) Della Ca', N.; Fontana, M.; Motti, E.; Catellani, M. *Acc. Chem. Res.* **2016**, *49*, 1389. (d) Ye, J.; Lautens, M. *Nat. Chem.* **2015**, *7*, 863. (e) Zhu, H.; Ye, C.; Chen, Z. *Youji Huaxue* **2015**, *35*, 2291. (f) Ferraccioli, R. *Synthesis* **2013**, *45*, 581. (g) Martins, A.; Mariampillai, B.; Lautens, M. *Top. Curr. Chem.* **2009**, *292*, 1. (h) Catellani, M.; Motti, E.; Della Ca', N. *Acc. Chem. Res.* **2008**, *41*, 1512.
(16) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 119.
(17) (a) Xu, D.; Dai, L.; Catellani, M.; Motti, E.; Della Ca', N.; Zhou, Z. *Org. Biomol. Chem.* **2015**, *13*, 2260. (b) Motti, E.; Della Ca', N.; Xu, D.; Piersimoni, A.; Bedogni, E.; Zhou, Z.-M.; Catellani, M. *Org. Lett.* **2012**, *14*, 5792. (c) Maestri, G.; Motti, E.; Della Ca', N.; Malacria, M.; Derat, E.; Catellani, M. *J. Am. Chem. Soc.* **2011**, *133*, 8574. (d) Della Ca', N.; Maestri, G.; Malacria, M.; Derat, E.; Catellani, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 12257. (e) Larraufie, M.-H.; Maestri, G.; Beaume, A.; Derat, É.; Ollivier, C.; Fensterbank, L.; Courillon, C.; Lacôte, E.; Catellani, M.; Malacria, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 12253. (f) Motti, E.; Della Ca', N.; Deledda, S.; Fava, E.; Panciroli, F.; Catellani, M. *Chem. Commun.* **2010**, *46*, 4291. (g) Maestri, G.; Della Ca', N.; Catellani, M. *Chem. Commun.* **2009**, *32*, 4892. (h) Della Ca', N.; Sassi, G.; Catellani, M. *Adv. Synth. Catal.* **2008**, *350*, 2179. (i) Motti, E.; Faccini, F.; Ferrari, I.; Catellani, M.; Ferraccioli, R. *Org. Lett.* **2006**, *8*, 3967. (j) Faccini, F.; Motti, E.; Catellani, M. *J. Am. Chem. Soc.* **2004**, *126*, 78. (k) Ferraccioli, R.; Carenzi, D.; Rombola, O.; Catellani, M. *Org. Lett.* **2004**, *6*, 4759.
(18) (a) Luo, B.; Gao, J.-M.; Lautens, M. *Org. Lett.* **2016**, *18*, 4166. (b) Qureshi, Z.; Schlundt, W.; Lautens, M. *Synthesis* **2015**, *47*, 2446. (c) Qureshi, Z.; Weinstabl, H.; Suhartono, M.; Liu, H.; Thesmar, P.; Lautens, M. *Eur. J. Org. Chem.* **2014**, *2014*, 4053. (d) Sickert, M.; Weinstabl, H.; Peters, B.; Hou, X.; Lautens, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 5147. (e) Weinstabl, H.; Suhartono, M.; Qureshi, Z.; Lautens, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 5305. (f) Liu, H.; El-Salfiti, M.; Lautens, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 9846. (g) Chai, D. I.; Thansandote, P.; Lautens, M. *Chem. - Eur. J.* **2011**, *17*, 8175. (h) Candito, D. A.; Lautens, M. *Org. Lett.* **2010**, *12*, 3312. (i) Martins, A.; Candito, D. A.; Lautens, M. *Org. Lett.* **2010**, *12*, 5186. (j) Candito, D. A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6713. (k) Zhao, Y.-B.; Mariampillai, B.; Candito, D. A.; Laleu, B.; Li, M.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1849. (l) Gericke, K. M.; Chai, D. I.; Bieler, N.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1447. (m) Martins, A.; Lautens, M. *Org. Lett.* **2008**, *10*, 5095. (n) Mariampillai, B.; Alliot, J.; Li, M.; Lautens, M. *J. Am. Chem. Soc.* **2007**, *129*, 15372. (o) Rudolph, A.; Rackelmann, N.; Lautens, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1485. (p) Hulcoop, D. G.; Lautens, M. *Org. Lett.* **2007**, *9*, 1761. (q) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148. (r) Lautens, M.; Piguel, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 1045.
(19) For some typical reports, see: (a) Zuo, Z.; Wang, H.; Fan, L.; Liu, J.; Wang, Y.; Luan, X. *Angew. Chem., Int. Ed.* **2017**, *56*, 2767. (b) Zhang, B.-S.; Hua, H.-L.; Gao, L.-Y.; Liu, C.; Qiu, Y.-F.; Zhou, P.-X.; Zhou, Z.-Z.; Zhao, J.-H.; Liang, Y.-M. *Org. Chem. Front.* **2017**, *4*, 1376. (c) Fan, L.; Liu, J.; Bai, L.; Wang, Y.; Luan, X. *Angew. Chem., Int. Ed.* **2017**, *56*, 14257. (d) Sui, X.; Ding, L.; Gu, Z. *Chem. Commun.* **2016**, *52*, 13999. (e) Pan, S.-F.; Ma, X.-J.; Zhong, D.-N.; Chen, W.-Z.; Liu, M.-C.; Wu, H.-Y. *Adv. Synth. Catal.* **2015**, *357*, 3052. (f) Lei, C.; Jin, X.; Zhou, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 13397. (g) Shi, H.; Babinski, D. J.; Ritter, T. *J. Am. Chem. Soc.* **2015**, *137*, 3775. (h) Dong, Z.; Wang, J.; Ren, Z.; Dong, G. *Angew. Chem., Int. Ed.* **2015**, *54*, 12664. (i) Huang, Y.; Zhu, R.; Zhao, K.; Gu, Z. *Angew. Chem., Int. Ed.* **2015**, *54*, 12669. (j) Zhou, P.-X.; Ye, Y.-Y.; Liu, C.; Zhao, L.-B.; Hou, J.-Y.; Chen, D.-Q.; Tang, Q.; Wang, A.-Q.; Zhang, J.-Y.; Huang, Q.-X.; Xu, P.-F.; Liang, Y.-M. *ACS Catal.* **2015**, *5*, 4927. (k) Wu, X.-X.; Shen, Y.; Chen, W.-L.; Chen, S.; Xu, P.-F.; Liang, Y.-M. *Chem. Commun.* **2015**, *51*, 16798. (l) Zhang, H.; Chen, P.; Liu, G. *Angew. Chem., Int. Ed.* **2014**, *53*, 10174. (m) Narbonne, V.; Retailleau, P.; Maestri, G.; Malacria, M. *Org. Lett.* **2014**, *16*, 628. (n) Jiao, L.; Bach, T. *J. Am. Chem. Soc.* **2011**, *133*, 12990.
(20) For some typical reports of amination, see: (a) Dong, Z.; Dong, G. *J. Am. Chem. Soc.* **2013**, *135*, 18350. (b) Sun, F.; Gu, Z. *Org. Lett.* **2015**, *17*, 2222. (c) Chen, Z.-Y.; Ye, C.-Q.; Zhu, H.; Zeng, X.-P.; Yuan, J.-J. *Chem. - Eur. J.* **2014**, *20*, 4237. (d) Zhou, P.-X.; Ye, Y.-Y.; Ma, J.-W.; Zheng, L.; Tang, Q.; Qiu, Y.-F.; Song, B.; Qiu, Z.-H.; Xu, P.-F.; Liang, Y.-M. *J. Org. Chem.* **2014**, *79*, 6627.
(21) For some typical reports of arylation, see: (a) Catellani, M.; Motti, E.; Baratta, S. *Org. Lett.* **2001**, *3*, 3611. (b) Dong, Z.; Wang, J.; Dong, G. *J. Am. Chem. Soc.* **2015**, *137*, 5887. (c) Wang, X.-C.; Gong, W.; Fang, L.-Z.; Zhu, R.-Y.; Li, S.; Engle, K. M.; Yu, J.-Q. *Nature* **2015**, *519*, 334.
(22) For some typical reports of alkylation, see: (a) Lei, C.; Jin, X.; Zhou, J. *ACS Catal.* **2016**, *6*, 1635. (b) Sui, X.; Zhu, R.; Li, G.; Ma, X.; Gu, Z. *J. Am. Chem. Soc.* **2013**, *135*, 9318.
(23) For some typical reports of acylation, see: (a) Fan, X.; Gu, Z. *Org. Lett.* **2018**, *20*, 1187. (b) Wang, J.; Zhang, L.; Dong, Z.; Dong, G. *Chem.* **2016**, *1*, 581. (c) Sun, F.; Li, M.; He, C.; Wang, B.; Li, B.; Sui, X.; Gu, Z. *J. Am. Chem. Soc.* **2016**, *138*, 7456.
(24) Li, X.; Pan, J.; Song, S.; Jiao, N. *Chem. Sci.* **2016**, *7*, 5384.
(25) (a) Han, F.; Yang, W.; Zhao, A.; Zheng, R.; Ji, C.; Liu, X.; Liu, G.; Chen, C. *Asian J. Org. Chem.* **2018**, *7*, 1124. (b) Chen, C.; Hou, L.; Cheng, M.; Su, J.; Tong, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 3092. (c) Chen, C.; Hu, J.; Su, J.; Tong, X. *Tetrahedron Lett.* **2014**, *55*, 3229. (d) Chen, C.; Su, J.; Tong, X. *Chem. - Eur. J.* **2013**, *19*, 5014.
(26) (a) Zhang, J.; Ugrinov, A.; Zhao, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 6681. (b) Li, B.-J.; Wang, H.-Y.; Zhu, Q.-L.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 3948. (c) Patureau, F. W.; Besset, T.; Kuhl, N.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2154. (d) Umeda, N.; Tsurugi, H.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4019.
(27) Whyte, A.; Olson, M. E.; Lautens, M. *Org. Lett.* **2018**, *20*, 345.
(28) (a) Ding, L.; Sui, X.; Gu, Z. *ACS Catal.* **2018**, *8*, 5630. (b) Xu, S.; Jiang, J.; Ding, L.; Fu, Y.; Gu, Z. *Org. Lett.* **2018**, *20*, 325.
(29) (a) Liu, C.; Liang, Yu.; Zheng, N.; Zhang, B.-S.; Feng, Y.; Bi, S.; Liang, Y.-M. *Chem. Commun.* **2018**, *54*, 3407. (b) Shen, Y.; Wu, X.-X.; Chen, S.; Xia, Y.; Liang, Y.-M. *Chem. Commun.* **2018**, *54*, 2256.
(30) (a) Qian, G.; Bai, M.; Gao, S.; Chen, H.; Zhou, S.; Cheng, H.-G.; Yan, W.; Zhou, Q. *Angew. Chem., Int. Ed.* **2018**, *57*, 10980. (b) Wu, C.; Cheng, H.-G.; Chen, R.; Chen, H.; Liu, Z.-S.; Zhang, J.; Zhang, Y.; Zhu, Y.; Geng, Z.; Zhou, Q. *Org. Chem. Front.* **2018**, *5*,

DOI: 10.1021/acs.orglett.8b02588
Org. Lett. XXXX, XXX, XXX−XXX

2533. (c) Cheng, H.-G.; Wu, C.; Chen, H.; Chen, R.; Qian, G.; Geng, Z.; Wei, Q.; Xia, Y.; Zhang, J.; Zhang, Y.; Zhou, Q. *Angew. Chem., Int. Ed.* **2018**, *57*, 3444. (d) Chen, S.; Liu, Z.-S.; Yang, T.; Hua, Y.; Zhou, Z.; Cheng, H.-G.; Zhou, Q. *Angew. Chem., Int. Ed.* **2018**, *57*, 7161. (e) Liu, Z.-S.; Qian, G.; Gao, Q.; Wang, P.; Cheng, H.-G.; Wei, Q.; Liu, Q.; Zhou, Q. *ACS Catal.* **2018**, *8*, 4783.

(31) (a) Dong, Z.; Lu, G.; Wang, J.; Liu, P.; Dong, G. *J. Am. Chem. Soc.* **2018**, *140*, 8551. (b) Wang, J.; Li, R.; Dong, Z.; Liu, P.; Dong, G. *Nat. Chem.* **2018**, *10*, 866. (c) Yoon, K.-Y.; Dong, G. *Angew. Chem., Int. Ed.* **2018**, *57*, 8592. (d) Li, R.; Dong, G. *Angew. Chem., Int. Ed.* **2018**, *57*, 1697.

(32) (a) Elsayed, M. S. A.; Griggs, B.; Cushman, M. *Org. Lett.* **2018**, *20*, 5228. (b) Bai, L.; Liu, J.; Hu, W.; Li, K.; Wang, Y.; Luan, X. *Angew. Chem., Int. Ed.* **2018**, *57*, 5151.

(33) (a) Gu, J.-W.; Zhang, X. *Org. Lett.* **2015**, *17*, 5384. (b) Jiang, H.; Lu, W.; Yang, K.; Ma, G.; Xu, M.; Li, J.; Yao, J.; Wan, W.; Deng, H.; Wu, S.; Zhu, S.; Hao, J. *Chem. - Eur. J.* **2014**, *20*, 10084. (c) Wu, Y.-M.; Li, Y.; Deng, J. *J. Fluorine Chem.* **2006**, *127*, 223.

(34) Scalability of 6-trifluoromethyl-phenanthridines **3aa** was described in the Supporting Information.

DOI: 10.1021/acs.orglett.8b02588
Org. Lett. XXXX, XXX, XXX−XXX