Organic LETTERS

Letter

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

pubs.acs.org/OrgLett

Highly Stereoselective Metal-Free Hydrogenations of Pyrrolo[1,2-*a*]quinoxalines

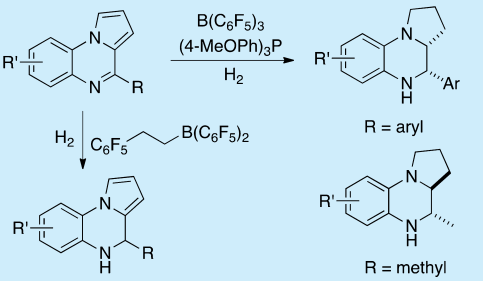
Xiaoqin Liu,[†,‡] Ting Liu,[†,‡] Wei Meng,*[,†,‡] and Haifeng Du*[,†,‡]

[†]Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, CAS Research/Education Center for Excellence in Molecular Sciences, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China

[‡]School of Chemical Science, University of Chinese Academy of Sciences, Beijing 100049, China

Supporting Information

ABSTRACT: A metal-free hydrogenation of pyrrolo[1,2-*a*]quinoxalines has been successfully realized by using the combination of $B(C_6F_5)_3$ and tris(4-methoxyphenyl)phosphine to furnish the corresponding 1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoxalines in 59−99% yields. For 4-aryl-substituted pyrrolo[1,2-*a*]quinoxalines, high *cis* selectivities were obtained, but *trans*-selectivities were achieved for the 4-methyl-substituted substrates.



Aliphatic polyfused heterocycles, which are the core frameworks of numerous natural or synthetic molecules with diverse biological or medicinal activities, have attracted intensive interest, and considerable efforts have been devoted to constructing these structures.[1] Catalytic hydrogenations of aromatic heterocycles have become an efficient and straightforward approach for their synthesis.[2] In comparison with the success of transition-metal catalysis, metal-free hydrogenations have not achieved substantial progress until the advent of frustrated Lewis pairs (FLPs).[3] A number of unsaturated compounds proved to be effective substrates for the FLP catalysis.[4] Notably, the metal-free hydrogenation of aromatic heterocycles as well as its asymmetric version has made an important advance in recent several years.[5] However, to the best of our knowledge, catalytic hydrogenations of aromatic polyfused heterocycles with FLPs have seldom been reported.

Hexahydropyrrolo[1,2-*a*]quinoxalines are important moieties present in a variety of biologically active molecules; for example, compounds **1**−**3** (Figure 1) exhibit some promising activities, such as antimicrobial, antitumor, anxiolytic, analgesic, and antiallergic, and act as candidates for diuretics, glucagon receptors antagonists, etc.[6] Several protocols have been developed for the synthesis of dihydropyrrolo[1,2-*a*]quinoxalines, including the Mannich reaction,[7] 1,3-dipolar cycloaddition reaction,[8] visible-light-induced photoredox catalysis,[9] modified Pictet−Spengler reaction,[10] reduction/cyclization,[11] and Pd-catalyzed intramolecular *N*-arylations.[12] However, there is still a lack of efficient methods for the construction of hexahydropyrrolo[1,2-*a*]quinoxalines. The direct catalytic hydrogenation of pyrrolo[1,2-*a*]quinoxalines seems to be an effective approach to access these compounds. Unfortunately, such a transformation has rarely been reported.

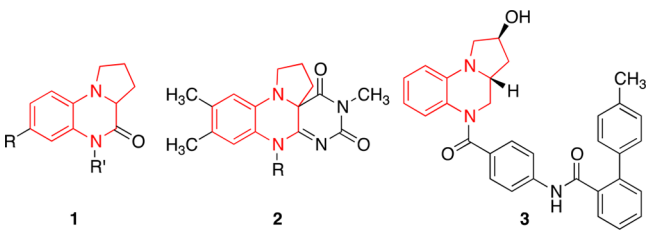


Figure 1. Representative biologically active molecules.

As part of our ongoing interest in the FLP catalysis, we have successfully realized the hydrogenation of several types of aromatic *N*-heterocycles, such as pyridines, quinolines, quinoxalines, 1,8-naphthyridines, and pyridazines.[13] Herein, we report our preliminary results for the FLP-catalyzed highly stereoselective hydrogenation of pyrrolo[1,2-*a*]quinoxalines.

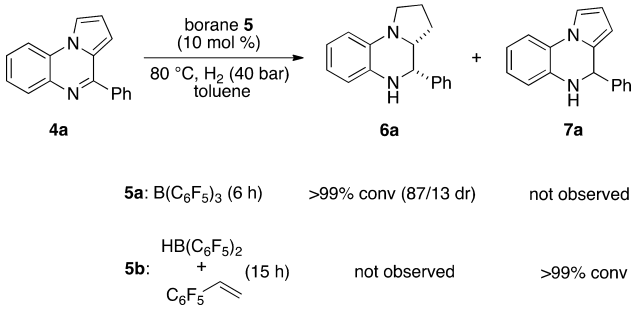
The metal-free hydrogenation of pyrrolo[1,2-*a*]quinoxaline **4a** was initially investigated by using 10 mol % of $B(C_6F_5)_3$ (**5a**)[14] as catalyst under H_2 (40 bar) at 80 °C in toluene (Scheme 1). We were pleased to find that this reaction went smoothly to give the hexahydropyrrolo[1,2-*a*]quinoxaline **6a** in a quantitative conversion with a good *cis* selectivity. In contrast, Lewis acid **5b** with relatively weaker acidity generated in situ by the hydroboration of pentafluorostyrene with $HB(C_6F_5)_2$, gave partially reduced product **7a** in a quantitative conversion instead of **6a**.

The $B(C_6F_5)_3$-catalyzed hydrogenation of pyrrolo[1,2-*a*]-quinoxaline **4a** was further optimized. When the reaction temperature was lowered to 70 °C, the stereoselectivity was significantly improved to >99/1 but with a dramatic loss of

Received: July 26, 2018

DOI: 10.1021/acs.orglett.8b02364
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Initial Studies on Hydrogenations of Pyrrolo[1,2-*a*]quinoxaline 4a



reactivity (Table 1, entries 1 vs 2). Solvents had a large influence on both reactivity and stereoselectivity (Table 1,

Table 1. Optimization of Reaction Conditions[a]

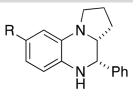
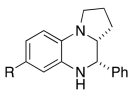
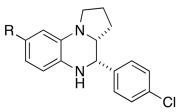
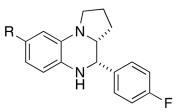
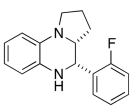
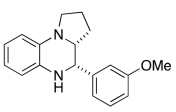
entry	solvent	phosphine **8**	time (h)	conv[b] (%)	dr[c]
1	toluene		6	>99	87/13
2[d]	toluene		12	50	>99/1
3	*n*-hexane		6	50	>99/1
4	*o*-xylene		6	43	87/13
5	DCM		6	22	nd
6	THF		6	trace	nd
7	toluene	Ph_3P (**8a**)	6	>99	91/9
8	toluene	$(4\text{-FPh})_3P$ (**8b**)	6	>99	85/15
9	toluene	$(4\text{-MeOPh})_3P$ (**8c**)	6	38	>99/1
10[e]	toluene	$(4\text{-MeOPh})_3P$ (**8c**)	10	>99	>99/1
11[f]	toluene	$(4\text{-MeOPh})_3P$ (**8c**)	12	>99	>99/1

[a]All of the reactions were carried out with pyrrolo[1,2-*a*]quinoxaline **4a** (0.10 mmol), $B(C_6F_5)_3$ (**5a**) (0.01 mmol), phosphine **8** (0.01 mmol), and H_2 (40 bar) in a solvent (0.5 mL) at 80 °C unless otherwise noted. [b]Determined by crude ^1H NMR. [c]Determined by crude ^1H NMR. [d]At 70 °C. [e]2 mol % of tris(4-methoxyphenyl)-phosphine **5c** was added. [f]1 mol % of **8c** and 5 mol % of **5a** was used.

entries 3–6). Additional Lewis bases were next subjected to the hydrogenation. The combination of 10 mol % of $B(C_6F_5)_3$ (**5a**) and triphenylphosphine (**8a**) or tris(4-fluorophenyl)-phosphine (**8b**) gave similar *cis* selectivities without loss of reactivities (Table 1, entries 1 vs 7 and 8). When tris(4-methoxyphenyl)phosphine (**8c**) was used, >99/1 dr was obtained, but the reaction was slowed sharply (Table 1, entry 9). Reducing the loading amount of **8c** from 10 to 2 mol % resulted in a quantitative conversion with >99/1 dr (Table 1, entry 10). Further treating the obtained product (>99/1 dr) with 10 mol % of $B(C_6F_5)_3$ (**5a**) at 80 °C without addition of **8c** led a partial isomerization (87/13 dr), which indicates the major role of phosphine Lewis base is likely to inhibit the isomerization instead of forming a frustrated Lewis pair with $B(C_6F_5)_3$. When a combination of 5 mol % of $B(C_6F_5)_3$ (**5a**) and 1 mol % of phosphine **8c** was used, the high reactivity and *cis* selectivity could be well maintained (Table 1, entry 11).

With the optimal reaction conditions in hand, a variety of 4-aryl-substituted pyrrolo[1,2-*a*]quinoxaline derivatives **4a–l** were subjected to this metal-free hydrogenation. As shown in Table 2, all the reactions proceeded smoothly with high stereoselectivities to give the desired *cis*-hexahydropyrrolo[1,2-*a*]quinoxalines **6a–l** in 59–99% yields. A gram-scale hydrogenation of pyrrolo[1,2-*a*]quinoxaline **4a** was successfully realized to afford *cis*-**6a** as a sole product in 87% yield

Table 2. Hydrogenations of Aryl-Substituted Pyrrolo[1,2-*a*]quinoxalines 4[a]

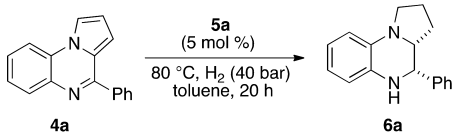
entry	product **6**	yield (%)[b]	dr[c]
			
1	**6a:** R = H	95	>99:1
2	**6b:** R = Cl	99	>99:1
3[d]	**6c:** R = CH_3	99	>99:1
			
4	**6d:** R = F	94	>99:1
5[e]	**6e:** R = OMe	89	91:9
			
6	**6f:** R = H	79	88:12
7	**6g:** R = CH_3	83	>99:1
			
8	**6h:** R = H	86	>99:1
9	**6i:** R = Cl	78	89:11
10[e]	**6j:** R = CH_3	92	>99:1
			
11	**6k**	99	>99:1
			
12[f]	**6l**	59	>99:1

[a]All of the reactions were carried out with pyrrolo[1,2-*a*]quinoxaline **4** (0.30 mmol), $B(C_6F_5)_3$ **5a** (0.015 mmol), and **8c** (0.003 mmol) under H_2 (40 bar) in toluene (1.5 mL) at 80 °C for 12 h unless otherwise noted. [b]Isolated yield for *cis*-isomer. [c]Determined by crude ^1H NMR. [d]100 °C for 18 h. [e]100 °C for 12 h. [f]140 °C for 20 h.

(Scheme 2). The relative configuration was determined according to the X-ray structure of compound **6a** (Figure 2).

Interestingly, when 4-methyl-substituted pyrrolo[1,2-*a*]-quinoxalines **4m–p** were employed as substrates for this hydrogenation, good to high *trans*-selectivities were afforded, and the *trans*-products **6m–p** were obtained in 70–96% yields (Scheme 3). The relative configuration was determined according to the X-ray structure of compound **6m** (Figure

Scheme 2. Gram-Scale Hydrogenation of 4a



DOI: 10.1021/acs.orglett.8b02364
Org. Lett. XXXX, XXX, XXX–XXX

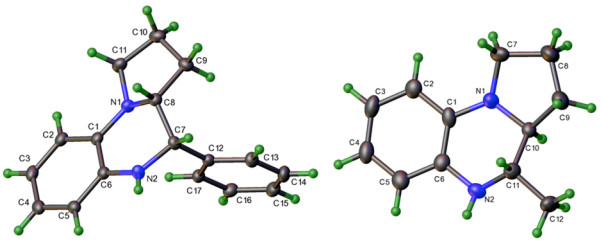
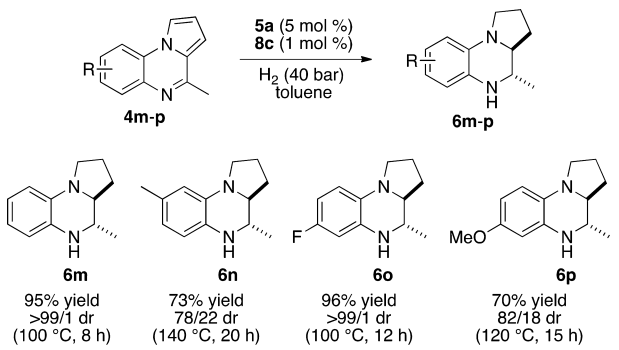


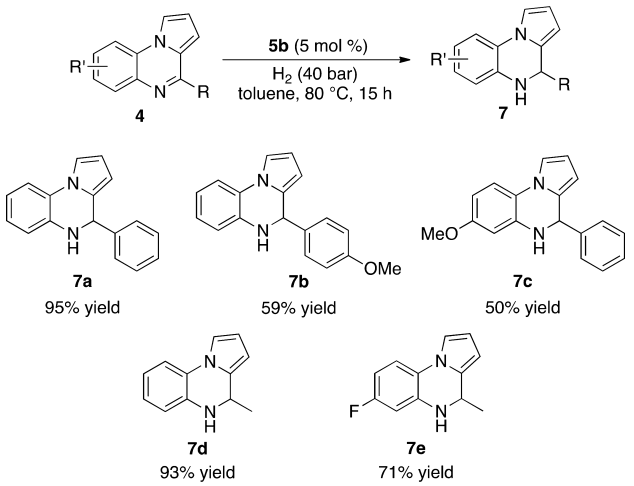
Figure 2. X-ray structures of compounds **6a** and **6m**

Scheme 3. Metal-Free Hydrogenation of 4-Methylpyrrolo[1,2-*a*]quinoxalines



2). Moreover, with the use of in situ generated borane Lewis acid **5b**, the partial hydrogenation of pyrrolo[1,2-*a*]-quinoxalines **4** was realized to furnish the corresponding dihydro products **7a**–**e** in 50–95% yields (Scheme 4).

Scheme 4. Partial Reductions of Pyrrolo[1,2-*a*]quinoxalines



In summary, a highly stereoselective metal-free hydrogenation of pyrrolo[1,2-*a*]quinoxalines was successfully realized by using 5 mol % of $B(C_6F_5)_3$ and 1 mol % of tris(4-methoxyphenyl)phosphine to furnish the corresponding 1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoxalines in 59–99% yields. For 4-aryl-substituted substrates, *cis*-isomers were predominantly obtained as the products. For 4-methyl-substituted substrates, *trans*-isomers were afforded as the major products. Moreover, a partial hydrogenation was also achieved using a weaker Lewis acid to give dihydro products in good to high yields. Further efforts on expanding the substrate scope and searching for effective chiral FLP catalysts for the asymmetric reaction 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.8b02364.

Experimental procedures for metal-free hydrogenation, characterization of substrates and products, and NMR spectra (PDF)

Accession Codes

CCDC 1850822 and 1853614 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 Authors

*E-mail: mengwei@iccas.ac.cn.
*E-mail: haifengdu@iccas.ac.cn.

ORCID

Wei Meng: 0000-0002-1555-3738
Haifeng Du: 0000-0003-0122-3735

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for generous financial support from the National Natural Science Foundation of China (21572231 and 21521002).

■ REFERENCES

(1) For selected examples, see: (a) Khuong-Huu, Q.; Chiaroni, A.; Riche, C.; Nguyen-Ngoc, H.; Nguyen-Viet, K.; Khuong-Huu, F. *J. Nat. Prod.* **2000**, *63*, 1015. (b) Nagata, T.; Nakagawa, M.; Nishida, A. *J. Am. Chem. Soc.* **2003**, *125*, 7484. (c) Mudur, S. V.; Swenson, D. C.; Gloer, J. B.; Campbell, J.; Shearer, C. A. *Org. Lett.* **2006**, *8*, 3191. (d) Nihei, K.-I.; Asaka, Y.; Mine, Y.; Yamada, Y.; Iigo, M.; Yanagisawa, T.; Kubo, I. *J. Nat. Prod.* **2006**, *69*, 975. (e) Young, I. S.; Kerr, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 1465. (f) Zhang, H.; Odeku, O. A.; Wang, X.-N.; Yue, J.-M. *Phytochemistry* **2008**, *69*, 271. (g) Mukhina, O. A.; Kuznetsov, D. M.; Cowger, T. M.; Kutateladze, A. G. *Angew. Chem., Int. Ed.* **2015**, *54*, 11516. (h) Li, E.; Jin, H.; Jia, P.; Dong, X.; Huang, Y. *Angew. Chem., Int. Ed.* **2016**, *55*, 11591.

(2) For leading reviews, see: (a) Zhou, Y.-G. *Acc. Chem. Res.* **2007**, *40*, 1357. (b) Kuwano, R. *Heterocycles* **2008**, *76*, 909. (c) Wang, D.-S.; Chen, Q.-A.; Lu, S.-M.; Zhou, Y.-G. *Chem. Rev.* **2012**, *112*, 2557. (d) Ye, Z.-S.; Shi, L.; Zhou, Y.-G. *Synlett* **2014**, *25*, 928. (e) Nagano, T.; Iimuro, A.; Yamaji, K.; Kita, Y.; Mashima, K. *Heterocycles* **2014**, *88*, 103. (f) Kuwano, R. *Phosphorus, Sulfur Silicon Relat. Elem.* **2015**, *190*, 715. (g) Bachrach, M.; Marks, T. J.; Notestein, J. M. *ACS Catal.* **2016**, *6*, 1455. (h) Zhao, D.; Candish, L.; Paul, D.; Glorius, F. *ACS Catal.* **2016**, *6*, 5978. (i) Giustra, Z. X.; Ishibashi, J. S. A.; Liu, S.-Y. *Coord. Chem. Rev.* **2016**, *314*, 134. (j) Chen, Z.-P.; Zhou, Y.-G. *Synthesis* **2016**, *48*, 1769. (k) Rayhan, U.; Kowser, Z.; Islam, M. N.; Redshaw, C.; Yamato, T. *Top. Catal.* **2018**, *61*, 560.

(3) For a seminal work, see: Welch, G. C.; San Juan, R. R.; Masuda, J. D.; Stephan, D. W. *Science* **2006**, *314*, 1124.

(4) For leading reviews, see: (a) Stephan, D. W.; Erker, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 46. (b) Soós, T. *Pure Appl. Chem.* **2011**, *83*, 667. (c) Erker, G. *Pure Appl. Chem.* **2012**, *84*, 2203. (d) Stephan, D. W. *Org. Biomol. Chem.* **2012**, *10*, 5740. (e) Paradies, J. *Angew. Chem.,*

DOI: 10.1021/acs.orglett.8b02364
Org. Lett. XXXX, XXX, XXX–XXX

Int. Ed. **2014**, *53*, 3552. (f) Stephan, D. W. *Acc. Chem. Res.* **2015**, *48*, 306. (g) Stephan, D. W.; Erker, G. *Angew. Chem., Int. Ed.* **2015**, *54*, 6400. (h) Stephan, D. W. *J. Am. Chem. Soc.* **2015**, *137*, 10018. (i) Stephan, D. W. *Science* **2016**, *354*, aaf7229. For leading reviews on asymmetric metal-free hydrogenations, see: (j) Liu, Y.; Du, H. *Huaxue Xuebao* **2014**, *72*, 771. (k) Feng, X.; Du, H. *Tetrahedron Lett.* **2014**, *55*, 6959. (l) Shi, L.; Zhou, Y.-G. *ChemCatChem* **2015**, *7*, 54. (m) Paradies. *Top. Organomet. Chem.* **2017**, *62*, 193. (n) Meng, W.; Feng, X.; Du, H. *Acc. Chem. Res.* **2018**, *51*, 191.

(5) For selected examples, see: (a) Geier, S. J.; Chase, P. A.; Stephan, D. W. *Chem. Commun.* **2010**, *46*, 4884. (b) Stephan, D. W.; Greenberg, S.; Graham, T. W.; Chase, P.; Hastie, J. J.; Geier, S. J.; Farrell, J. M.; Brown, C. C.; Heiden, Z. M.; Welch, G. C.; Ullrich, M. *Inorg. Chem.* **2011**, *50*, 12338. (c) Sumerin, V.; Chernichenko, K.; Nieger, M.; Leskelä, M.; Rieger, B.; Repo, T. *Adv. Synth. Catal.* **2011**, *353*, 2093. (d) Erős, G.; Nagy, K.; Mehdi, H.; Pápai, I.; Nagy, P.; Király, P.; Tárkányi, G.; Soós, T. *Chem. - Eur. J.* **2012**, *18*, 574. (e) Curless, L. D.; Clark, E. R.; Dunsford, J. J.; Ingleson, M. J. *Chem. Commun.* **2014**, *50*, 5270. (f) Mahdi, T.; del Castillo, J. N.; Stephan, D. W. *Organometallics* **2013**, *32*, 1971. (g) Scott, D. J.; Fuchter, M. J.; Ashley, A. E. *Angew. Chem., Int. Ed.* **2014**, *53*, 10218. (h) Hu, Q.; Tian, C.; Maxim, B.; Nie, W. *Huaxue Xuebao* **2015**, *73*, 1025. (i) Eisenberger, P.; Bestvater, B. P.; Keske, E. C.; Crudden, C. M. *Angew. Chem., Int. Ed.* **2015**, *54*, 2467.

(6) For selected examples, see: (a) Ghisla, S.; Ogata, H.; Massey, V.; Schonbrunn, A.; Abeles, R. H.; Walsh, C. T. *Biochemistry* **1976**, *15*, 1791. (b) Abou-Gharbia, M.; Freed, M. E.; McCaully, R. J.; Silver, P. J.; Wendt, R. L. *J. Med. Chem.* **1984**, *27*, 1743. (c) Kim, J.-M.; Bogdan, M. A.; Mariano, P. S. *J. Am. Chem. Soc.* **1991**, *113*, 9251. (d) Eckstein, J. W.; Hastings, J. W.; Ghisla, S. *Biochemistry* **1993**, *32*, 404. (e) Ohtake, Y.; Naito, A.; Hasegawa, H.; Kawano, K.; Marizono, D.; Taniguchi, M.; Tanaka, Y.; Matsukawa, H.; Naito, K.; Oguma, T.; EzureY; Tsuriya, Y. *Bioorg. Med. Chem.* **1999**, *7*, 1247. (f) Bolignano, D.; Coppolino, G.; Criseo, M.; Campo, S.; Romeo, A.; Buemi, M. *Curr. Pharm. Des.* **2007**, *13*, 865. (g) Tanimori, S.; Nishimura, T.; Kirihata, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4119. (h) Arán, V. J.; Kaiser, M.; Dardonville, C. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4506.

(7) (a) Cheeseman, G. W. H.; Rafiq, M. *J. Chem. Soc. C* **1971**, 2732. (b) Raines, S.; Chai, S. Y.; Palopoli, F. P. *J. Heterocycl. Chem.* **1976**, *13*, 711.

(8) Kim, H. S.; Kurasawa, Y.; Yoshii, C.; Masuyama, M.; Takada, A.; Okamoto, Y. *J. Heterocycl. Chem.* **1990**, *27*, 1115.

(9) He, Z.; Bae, M.; Wu, J.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2014**, *53*, 14451.

(10) (a) Kundu, B.; Sawant, D.; Chhabra, R. *J. Comb. Chem.* **2005**, *7*, 317. (b) Verma, A. K.; Jha, R. R.; Sankar, V. K.; Aggarwal, T.; Singh, R. P.; Chandra, R. *Eur. J. Org. Chem.* **2011**, *2011*, 6998. (c) Devi, R. V.; Garande, A. M.; Bhate, P. M. *Synlett* **2016**, *27*, 2807.

(11) Adegoke, E. A.; Alo, B. I.; Ogunsulire, F. O. *J. Heterocycl. Chem.* **1982**, *19*, 1169.

(12) Luo, X.; Chenard, E.; Martens, P.; Cheng, Y.-X.; Tomaszewski, M. *Org. Lett.* **2010**, *12*, 3574.

(13) (a) Liu, Y.; Du, H. *J. Am. Chem. Soc.* **2013**, *135*, 12968. (b) Wang, W.; Feng, X.; Du, H. *Org. Biomol. Chem.* **2016**, *14*, 6683. (c) Wang, W.; Meng, W.; Du, H. *Dalton Trans.* **2016**, *45*, 5945. (d) Zhang, Z.; Du, H. *Angew. Chem., Int. Ed.* **2015**, *54*, 623. (e) Zhang, Z.; Du, H. *Org. Lett.* **2015**, *17*, 2816. (f) Zhang, Z.; Du, H. *Org. Lett.* **2015**, *17*, 6266. (g) Zhou, Q.; Zhang, L.; Meng, W.; Feng, X.; Yang, J.; Du, H. *Org. Lett.* **2016**, *18*, 5189. (h) Li, S.; Meng, W.; Du, H. *Org. Lett.* **2017**, *19*, 2604. (i) Han, C.; Zhang, E.; Feng, X.; Wang, S.; Du, H. *Tetrahedron Lett.* **2018**, *59*, 1400.

(14) Massey, A. G.; Park, A. J. *J. Organomet. Chem.* **1964**, *2*, 245.

DOI: 10.1021/acs.orglett.8b02364
Org. Lett. XXXX, XXX, XXX−XXX