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One-Pot Synthesis of Pyrrolo[1,2-*a*]quinoxaline Derivatives via a Copper-Catalyzed Aerobic Oxidative Domino Reaction

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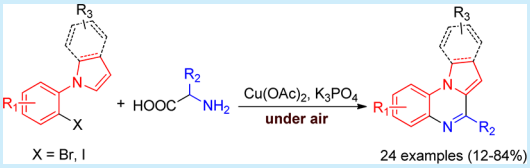
Supporting Information

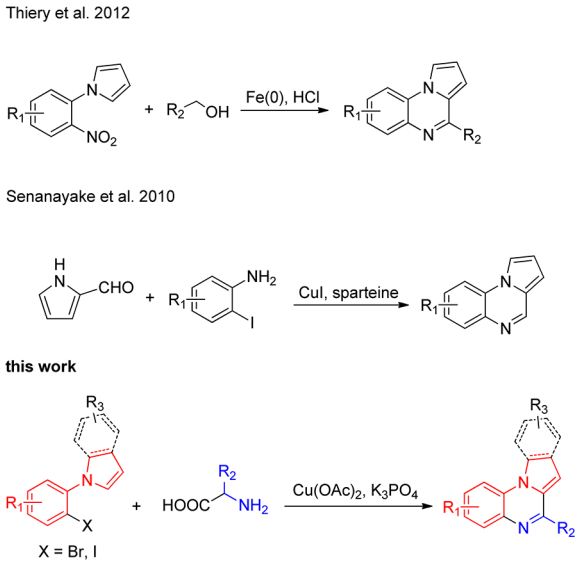
ABSTRACT: A copper-catalyzed process for the synthesis of pyrrolo[1,2-*a*]quinoxalines from readily available α-amino acids and 1-(2-halophenyl)-1*H*-pyrroles is described. Different functional groups were well tolerated to give the corresponding products.



The pyrrolo[1,2-*a*]quinoxaline skeleton is present in various biologically active agents and plays an important role in medicinal chemistry. For example, some substituted (phenylamino) pyrrolo[1,2-*a*]quinoxaline-carboxylic acid derivatives promised utilization for a novel class of potent inhibitors of the human protein kinase CK2.[1] Some 5,6-dihydro-indolo[1,2-*a*]quinoxalines exhibit antifungal activities in vitro against the phytopathogenic fungi and revealed their potential role as novel promising lead candidates for further design and synthesis of agricultural fungicides.[2] 2-(Aminomethyl)-4-phenylpyrrolo[1,2-*a*]-quinoxalines have been found to possess a central dopamine antagonist activity.[3] Furthermore, many derivatives have been proven to possess other biological activities, including in vitro antiparasitic activities,[4] potential nonpeptide glucagon receptor antagonist activities,[5] 5-HT_3 receptors,[6] antiproliferative activity,[7] and antimycobacterial agents.[8] In addition, some of them are also used as fluorescent probes for amyloid fibril.[9]

Due to their great value, the preparation of pyrrolo[1,2-*a*]quinoxalines has gained much attention.[10] Unsubstituted pyrrolo[1,2-*a*]quinoxalines were first synthesized from 2-(1*H*-pyrrol-1-yl)anilines and HCO_2H by Cheeseman and Tuck in 1965.[11] Two other traditional strategies have been followed. One synthetic method utilized acyl chlorides with 2-(1*H*-pyrrol-1-yl)anilines to access the acetamides, followed by reaction with $POCl_3$ to obtain the pyrrolo[1,2-*a*]quinoxalines according to the Bischler−Napieralski reaction.[12] The other method involves the reaction between 2-(1*H*-pyrrol-1-yl)-anilines and aldehydes to obtain the intermediates, followed by an oxidation process to give the target compounds.[13] In those cases, volatile and toxic reagents such as aldehydes were used, and multistep syntheses led to low atom economy. Recently, the Thiery group reported an Fe(0)-catalyzed strategy from nitroarenes and alcohols to assemble these compounds,[14] but this strategy needs excessive Fe catalyst and volatile HCl (Scheme 1). The Senanayake group developed a Cu-catalyzed strategy from 2-formylpyrroles and *o*-amino-iodoarenes to construct pyrrolo[1,2-*a*]quinoxalines,[15] but this method involved an expensive ligand. Therefore, it is highly desirable to develop an efficient, minimally toxic, and convenient approach for the synthesis of those heterocycles.

Scheme 1. Different protocols for the syntheses of pyrrolo[1,2-*a*] quinoxalines



Recently, copper-catalyzed Ullmann coupling reactions have made significant progress, and many *N*-heterocycles have been synthesized by us[16] and other groups.[17] However, most of the reactions were performed under a nitrogen or argon atmosphere. In addition, most of the cyclization reactions which occurred at the C-2 position of pyrroles or indoles require acid to activate the pyrrole ring system. Furthermore, reports regarding Cu-catalyzed construction of pyrrolo[1,2-*a*]quinoxalines are still rare. Herein, we report an efficient,

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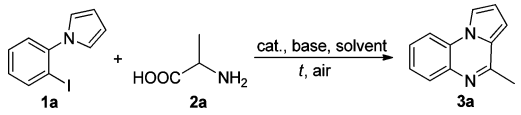
minimally toxic, and convenient Cu-catalyzed one-pot domino reaction of α-amino acids and 1-(2-halophenyl)-1*H*-pyrroles for the synthesis of pyrrolo[1,2-*a*]quinoxalines in air.

To identify the best reaction conditions, 1-(2-iodophenyl)-1*H*-pyrrole (**1a**) and alanine (**2a**) were initially used as the model substrates under different conditions (Table 1). The

Table 1. Optimization of Reaction Conditions[a]



1a 2a 3a

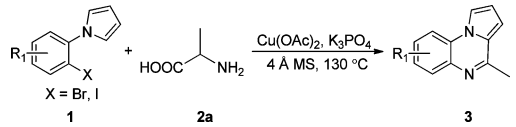
entry	cat.	base	solvent	*t*, °C	yield, %[b]
1	CuBr	K_2CO_3	DMSO	130	32
2	CuI	K_2CO_3	DMSO	130	13
3	CuCl	K_2CO_3	DMSO	130	15
4	$Cu(OAc)_2$	K_2CO_3	DMSO	130	52
5	$CuCl_2{\cdot}2H_2O$	K_2CO_3	DMSO	130	trace
6	$CuBr_2$	K_2CO_3	DMSO	130	trace
7	$CuSO_4{\cdot}5H_2O$	K_2CO_3	DMSO	130	trace
8	$Cu(CF_3SO_3)_2$	K_2CO_3	DMSO	130	46
9	–	K_2CO_3	DMSO	130	0
10	$Cu(OAc)_2$	KTB	DMSO	130	trace
11	$Cu(OAc)_2$	K_3PO_4	DMSO	130	56
12	$Cu(OAc)_2$	NaOH	DMSO	130	16
13	$Cu(OAc)_2$	Cs_2CO_3	DMSO	130	48
14	$Cu(OAc)_2$	K_3PO_4	NMP	130	12
15	$Cu(OAc)_2$	K_3PO_4	DMF	130	49
16	$Cu(OAc)_2$	K_3PO_4	dioxane	130	trace
17	$Cu(OAc)_2$	K_3PO_4	PhCl	130	0
18	$Cu(OAc)_2$	K_3PO_4	DMSO	150	37
19	$Cu(OAc)_2$	K_3PO_4	DMSO	110	16
20	$Cu(OAc)_2$	K_3PO_4	DMSO	130	67[c]
21	$Cu(OAc)_2$	K_3PO_4	DMSO	130	trace[d]

[a]Reaction conditions: 1-(2-iodophenyl)-1*H*-pyrrole (**1a**) (0.3 mmol), 2-aminoacetic acid (**2a**) (1.2 mmol), catalyst (0.06 mmol), base (1.5 mmol), solvent (3 mL), under air, 3 h. [b]Isolated yield. [c]Reaction with 4 Å molecular sieves (4 Å MS). [d]Reaction was performed under nitrogen.

efficiency of different Cu catalysts was tested using K_2CO_3 as the base in DMSO under air at 130 °C (entries 1–8). We found that the copper salts have a remarkable impact on the reaction yield, and $Cu(OAc)_2$ gave the best yield. Reaction without a catalyst was also explored with no corresponding product observed (entry 9). Different bases were screened (entries 4 and 10–13), and K_3PO_4 showed the best activity. Subsequently, the evaluation of solvents reveals that DMSO was superior to NMP, DMF, dioxane, and PhCl (entries 11 and 14–17). Only 37% and 16% isolated yields were obtained when the reaction temperature was varied (entries 18 and 19). The yield was further improved by using 4 Å molecular sieves (entry 20). Finally, we attempted the reaction under a N_2 atmosphere (entry 21), and only a trace amount of product was observed.

Under the optimal conditions, the scope of 1-(2-halophenyl)-1*H*-pyrroles was investigated. As shown in Table 2, most of the tested substrates provided moderate to good yields. Reactions with 1-(2-halophenyl)-1*H*-pyrroles containing electron-withdrawing groups proceeded smoothly to give the target products (entries 3–9). Other representatives with electron-neutral (H) and electron-donating (4-Me) groups were also found to be suitable for this transformation, although

Table 2. Preparation of Compounds 3a–i[a]



1 2a 3

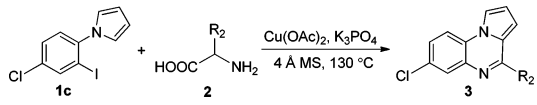
entry	1	3	yield, %[b]
1	R_1 = H, X = I, **1a**	**3a**	67
2	R_1 = H, X = Br, **1b**	**3a**	54
3	R_1 = 4-Cl, X = I, **1c**	**3b**	78
4	R_1 = 4-CF_3, X = I, **1d**	**3c**	81
5	R_1 = 4-F, X = I, **1e**	**3d**	71
6	R_1 = 4-CN, X = I, **1f**	**3e**	78
7	R_1 = 4-OCF_3, X = Br, **1g**	**3f**	83
8	R_1 = 5-F, X = Br, **1h**	**3g**	59
9	R_1 = 5-Cl, X = Br, **1i**	**3h**	62
10	R_1 = 4-Me, X = I, **1j**	**3i**	47
11	R_1 = 4-Me, X = Br, **1k**	**3i**	38

[a]Reaction conditions: **1** (0.3 mmol), **2a** (1.2 mmol), $Cu(OAc)_2$ (0.06 mmol), K_3PO_4 (1.5 mmol), DMSO (3 mL), 4 Å MS, under air, 3 h. [b]Isolated yield.

the yields were lower (entries 1, 2, 10, and 11). It is worth mentioning that the substrates bearing an iodine group had higher reactivity than those bearing a bromide group (entries 1, 2, 10, and 11).

Encouraged by these promising results, we further investigated substituted α-amino acids as shown in Table 3.

Table 3. Preparation of Compounds 3j–p[a]



1c 2 3

entry	2	3	yield, %[b]
1	R_2 = Me, **2a**	**3b**	78
2	R_2 = H, **2b**	**3j**	72
3	R_2 = Et, **2c**	**3k**	75
4	R_2 = Pr, **2d**	**3l**	69
5	R_2 = *i*-Pr, **2e**	**3m**	46
6	R_2 = *i*-Bu, **2f**	**3n**	67
7	R_2 = Cy, **2g**	**3o**	35
8	R_2 = Ph, **2h**	**3p**	12

[a]Reaction conditions: **1c** (0.3 mmol), **2** (1.2 mmol), $Cu(OAc)_2$ (0.06 mmol), K_3PO_4 (1.5 mmol), DMSO (3 mL), 4 Å MS, under air, 3 h. [b]Isolated yield.

Diverse α-amino acids that underwent the reaction with 1-(4-chloro-2-iodophenyl)-1*H*-pyrrole **1c** worked well to give the corresponding products. Notably, the α-amino acids with a Cy group and a Ph group showed lower reactivity, with only 35% and 12% yields, respectively. Conversion rates of the raw materials are low. One possible reason is that the steric hindrance caused by the R_2 group made the pyrrole ring system less reactive.

To expand the applicability of this method, we next examined the substituted 1-(2-halophenyl)-1*H*-indoles as shown in Table 4. Different functional groups at different positions of **1l–1q** were tolerated in the reaction to afford the target products in 48% to 84% yields. Moreover, the attachments of a 3-Me group to the indole ring afford a higher yield than those without it (entries 1–4). It is obvious that the

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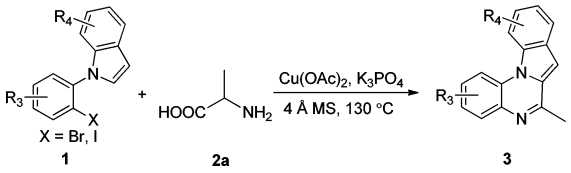
Table 4. Preparation of Compounds 3q−t[a]



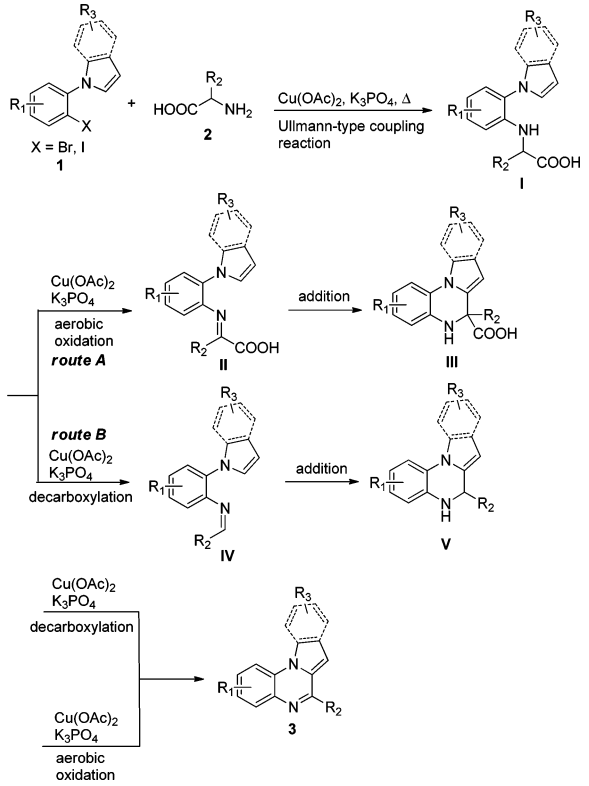
entry	1	3	yield, %[b]
1	R_3 = H, R_4 = H, X = I, **1l**	**3q**	74
2	R_3 = H, R_4 = H, X = Br, **1m**	**3q**	63
3	R_3 = H, R_4 = 3-Me, X = I, **1n**	**3r**	84
4	R_3 = H, R_4 = 3-Me, X = Br, **1o**	**3r**	65
5	R_3 = H, R_4 = 6-Cl, X = I, **1p**	**3s**	56
6	R_3 = 4-Me, R_4 = H, X = Br, **1q**	**3t**	48

[a]Reaction conditions: **1** (0.3 mmol), **2a** (1.2 mmol), $Cu(OAc)_2$ (0.06 mmol), K_3PO_4 (1.5 mmol), DMSO (3 mL), 4 Å MS, under air, 3 h. [b]Isolated yield.

3-Me group increased the nucleophilicity of the ring system, which facilitates intramolecular attack of the C-2 position of the indole to afford the cyclized products.

An assumed pathway for the formation of pyrrolo[1,2-*a*]quinoxaline derivatives is illustrated in Scheme 2 according to

Scheme 2. Proposed Reaction Mechanism



the results above and previous research.[18] First, the Cu-catalyzed Ullmann-type coupling reaction occurs between substrates **1** and **2** to afford intermediate **I**. Next, **I** can undergo two pathways (route A and route B). Through route A, aerobic oxidation of **I** leads to **II**, then intramolecular addition of **II** affords **III**, and decarboxylation of **III** gives final product **3**. Through route B, decarboxylation of **I** gives **IV**. Subsequently intramolecular addition of **IV** yields **V**. Finally, aerobic oxidation of **V** provides **3**.

The UV−vis absorption and emission spectra of **3q**, **3r**, **3s**, and **3t** in highly dilute solution were collected (in ESI).

In conclusion, we have developed an efficient and convenient Cu-catalyzed one-pot domino reaction from 1-(2-halophenyl)-1*H*-pyrroles and readily available *α*-amino acids for the synthesis of pyrrolo[1,2-*a*]quinoxalines in air. The domino process includes Ullmann-type *N*-arylation, aerobic oxidation, intramolecular addition, and decarboxylation. It is interesting that the intramolecular addition step was achieved under conditions with a base rather than an acid. By further elaboration and diversification of the various functional groups, a wide range of *N*-heterocycles can be produced. This Cu-catalyzed one-pot process has potential applications in the synthesis of biologically and medicinally relevant compounds.

■ ASSOCIATED CONTENT

Supporting Information

Experiment details, spectra data, UV−vis absorption and emission spectra, and ^1H and ^{13}C NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01167.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Guillon, J.; Le Borgne, M.; Rimbault, C.; Moreau, S.; Savrimoutou, S.; Pinaud, N.; Baratin, S.; Marchivie, M.; Roche, S.; Bollacke, A.; Pecci, A.; Alvarez, L.; Desplat, V.; Jose, J. *Eur. J. Med. Chem.* **2013**, *65*, 205−222.

(2) Xu, H.; Fan, L.-l. *Eur. J. Med. Chem.* **2011**, *46*, 1919−1925.

(3) Guillon, J.; Boulouard, M.; Lisowski, V.; Stiebing, S.; Lelong, V.; Dallemagne, P.; Rault, S. *J. Pharm. Pharmacol.* **2000**, *52*, 1369−1375.

(4) (a) Guillon, J.; Grellier, P.; Labaied, M.; Sonnet, P.; Leger, J.-M.; Deprez-Poulain, R.; Forfar-Bares, I.; Dallemagne, P.; Lemaitre, N.; Pehourcq, F.; Rochette, J.; Sergheraert, C.; Jarry, C. *J. Med. Chem.* **2004**, *47*, 1997−2009. (b) Guillon, J.; Mouray, E.; Moreau, S.; Mullie, C.; Forfar, I.; Desplat, V.; Belisle-Fabre, S.; Pinaud, N.; Ravanello, F.; Le-Naour, A.; Leger, J.-M.; Gosmann, G.; Jarry, C.; Deleris, G.; Sonnet, P.; Grellier, P. *Eur. J. Med. Chem.* **2011**, *46*, 2310−2326. (c) Guillon, J.; Moreau, S.; Mouray, E.; Sinou, V.; Forfar, I.; Fabre, S. B.; Desplat, V.; Millet, P.; Parzy, D.; Jarry, C.; Grellier, P. *Bioorg. Med. Chem.* **2008**, *16*, 9133−9144. (d) Guillon, J.; Forfar, I.; Mamani-Matsuda, M.; Desplat, V.; Saliege, M.; Thiolat, D.; Massip, S.; Tabourier, A.; Leger, J.-M.; Dufaure, B.; Haumont, G.; Jarry, C.; Mossalayi, D. *Bioorg. Med. Chem.* **2007**, *15*, 194−210.

(5) Guillon, J.; Dallemagne, P.; Pfeiffer, B.; Renard, P.; Manechez, D.; Kervran, A.; Rault, S. *Eur. J. Med. Chem.* **1998**, *33*, 293−308.

(6) (a) Prunier, H.; Rault, S.; Lancelot, J.-C.; Robba, M.; Renard, P.; Delagrange, P.; Pfeiffer, B.; Caignard, D.-H.; Misslin, R.; Guardiola-Lemaitre, B.; Hamon, M. *J. Med. Chem.* **1997**, *40*, 1808−1819. (b) Butini, S.; Budriesi, R.; Hamon, M.; Morelli, E.; Gemma, S.; Brindisi, M.; Borrelli, G.; Novellino, E.; Fiorini, I.; Ioan, P.; Chiarini,

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Org. Lett. XXXX, XXX, XXX−XXX

A.; Cagnotto, A.; Mennini, T.; Fracasso, C.; Caccia, S.; Campiani, G. *J. Med. Chem.* **2009**, *52*, 6946−6950.
(7) (a) Desplat, V.; Geneste, A.; Begorre, M.-A.; Fabre, S. B.; Brajot, S.; Massip, S.; Thiolat, D.; Mossalayi, D.; Jarry, C.; Guillon, J. *J. Enzyme Inhib. Med. Chem.* **2008**, *23*, 648−658. (b) Desplat, V.; Moreau, S.; Gay, A.; Fabre, S. B.; Thiolat, D.; Massip, S.; Macky, G.; Godde, F.; Mossalayi, D.; Jarry, C.; Guillon, J. *J. Enzyme Inhib. Med. Chem.* **2010**, *25*, 204−215.
(8) Guillon, J.; Reynolds, R. C.; Leger, J.-M.; Guie, M.-A.; Massip, S.; Dallemagne, P.; Jarry, C. *J. Enzyme Inhib. Med. Chem.* **2004**, *19*, 489−495.
(9) Gemma, S.; Colombo, L.; Forloni, G.; Savini, L.; Fracasso, C.; Caccia, S.; Salmona, M.; Brindisi, M.; Joshi, B. P.; Tripaldi, P.; Giorgi, G.; Taglialatela-Scafati, O.; Novellino, E.; Fiorini, I.; Campiani, G.; Butini, S. *Org. Biomol. Chem.* **2011**, *9*, 5137−5148.
(10) (a) He, Z.; Bae, M.; Wu, J.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2014**, *53*, 14451−14455. (b) Verma, A. K.; Jha, R. R.; Sankar, V. K.; Aggarwal, T.; Singh, R. P.; Chandra, R. *Eur. J. Org. Chem.* **2011**, 6998−7010. (c) Agarwal, P. K.; Sawant, D.; Sharma, S.; Kundu, B. *Eur. J. Org. Chem.* **2009**, 292−303. (d) Biswas, S.; Batra, S. *Eur. J. Org. Chem.* **2013**, 4895−4902. (e) Mishra, A.; Batra, S. *Eur. J. Org. Chem.* **2010**, 4832−4840.
(11) Cheeseman, G. W. H.; Tuck, B. *Chem. Ind. (London, U. K.)* **1965**, 1382.
(12) Cheeseman, G. W. H.; Tuck, B. J. *Chem. Soc. C* **1966**, 852−5.
(13) Kaminskii, V. A.; Moskovkina, T. V.; Borodina, S. V. *Chem. Heterocycl. Compd.* **1992**, *28*, 97−100.
(14) Pereira, M. d. F.; Thiery, V. *Org. Lett.* **2012**, *14*, 4754−4757.
(15) Reeves, J. T.; Fandrick, D. R.; Tan, Z.; Song, J. J.; Lee, H.; Yee, N. K.; Senanayake, C. H. *J. Org. Chem.* **2010**, *75*, 992−994.
(16) (a) Huang, A.; Chen, Y.; Zhou, Y.; Guo, W.; Wu, X.; Ma, C. *Org. Lett.* **2013**, *15*, 5480−5483. (b) Huang, A.; Liu, H.; Ma, C. *RSC Adv.* **2013**, *3*, 13976−13982. (c) Huang, A.; Feng, L.; Qiao, Z.; Yu, W.; Zheng, Q.; Ma, C. *Tetrahedron.* **2013**, *69*, 642−646.
(17) (a) Nandwana, N. K.; Pericherla, K.; Kaswan, P.; Kumar, A. *Org. Biomol. Chem.* **2015**, *13*, 2947−2950. (b) Yang, B.; Mao, Z.; Zhu, X.; Wan, Y. *Catal. Commun.* **2015**, *60*, 92−95. (c) Kong, L.; Zhou, Y.; Huang, H.; Yang, Y.; Liu, Y.; Li, Y. *J. Org. Chem.* **2015**, *80*, 1275−1278. (d) Jia, F.-C.; Xu, C.; Cai, Q.; Wu, A.-X. *Chem. Commun.* **2014**, *50*, 9914−9916. (e) Yang, D.; Wang, Y.; Yang, H.; Liu, T.; Fu, H. *Adv. Synth. Catal.* **2012**, *354*, 477−482. (f) Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453−2455.
(18) (a) Xu, W.; Jin, Y.; Liu, H.; Jiang, Y.; Fu, H. *Org. Lett.* **2011**, *13*, 1274−1277. (b) Sang, P.; Xie, Y.; Zou, J.; Zhang, Y. *Org. Lett.* **2012**, *14*, 3894−3897. (c) Wang, L.-X.; Xiang, J.-F.; Tang, Y.-L. *Eur. J. Org. Chem.* **2014**, *2014*, 2682−2685.

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Org. Lett. XXXX, XXX, XXX−XXX