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Cu-Catalyzed Concise Synthesis of Pyridines and 2-(1*H*)-Pyridones from Acetaldehydes and Simple Nitrogen Donors

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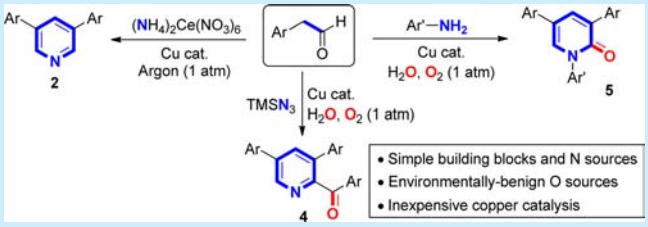
Supporting Information

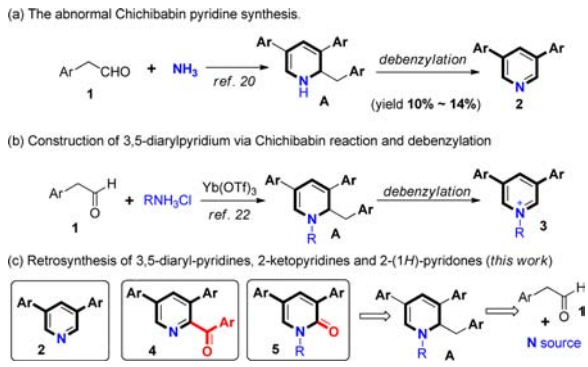
ABSTRACT: A highly selective copper-catalyzed concise synthesis of 3,5-diarylpyridine and 2-(1*H*)-pyridone has been achieved through cascade Chichibabin-type cyclization, C-(sp^3)−C(sp^3) cleavage, and aerobic oxidation. Azide, ceric ammonium nitrate (CAN), and 2-aminopyridine are disclosed as efficient nitrogen donors in this Cu-catalysis using O_2 as the oxidant. Water and molecular oxygen were employed as the oxygen source in the case of oxygenation.



Pyridine is one of the most prevalent and significant six-membered heterocyclic moieties which have broad applications in medicinal chemistry, natural products, organic synthesis, and functional materials.[1] Among them, 3,5-diaryl derivatives of pyridine and 2-(1*H*)-pyridone have been widely found in many biologically active molecules.[2] Although much effort has been spent on the development of the preparation of pyridine derivatives in recent years,[3] the synthesis of 3,5-diarylpyridine or 2-(1*H*)-pyridone is still generally dependent on the transition-metal catalyzed cross-coupling reactions of pyridine/pyridone substrates with other aryl partners.[2,4,5] Therefore, it is very attractive and highly desirable to develop more direct and concise approaches to construct 3,5-diarylpyridines and 2-(1*H*)-pyridones from simple and readily available starting materials.

Alternatively, 3,5-diarylpyridine or 2-(1*H*)-pyridone was constructed through double or multiple component cyclization of small building blocks.[6−17] Despite the significances of these methods for the pyridines and pyridones synthesis, these reactions usually suffer from multiple steps, unreadily available substrates, expensive noble metal catalysts, or limited substrate scopes. The low efficiencies in most cases also limit their applications. Through an abnormal Chichibabin pyridine synthesis process,[18,19] Eliel et al.[20] successfully achieved the synthesis of 3,5-diarylpyridines from phenyl acetaldehyde and aqueous ammonia (Scheme 1a). A debenzylation of the dihydropyridine intermediate **A** *via* C(sp^3)−C(sp^3) bond cleavage is involved in this transformation to afford the 3,5-diarylpyridine products. However, the reaction is limited to phenyl acetaldehyde and homoveratric aldehyde with low efficiencies (10−14% yields). Although a similar strategy has also been applied on the preparation of 2-substituted pyridinium,[21] the efficient 3,5-diarylpyridines synthesis is still desirable. Recently, Baran et al.[22] reported the first synthesis of 3,5-diphenylpyridinium **3** from phenyl acetaldehydes and amine hydrochlorides through an abnormal Chichibabin reaction and subsequent debenzylation process (Scheme 1b).

Scheme 1. Construction of 3,5-Diaryl Pyridine/Pyridium/Pyridone Using Simple and Readily Available Building Blocks



Inspired by the key dihydropyridine intermediate **A** in the above transformations, we envisioned that 3,5-diaryl 2-ketopyridines (**4**) could be afforded from intermediate **A** under oxidative conditions. Meanwhile, 3,5-diarylpyridines (**2**) and 2-(1*H*)-pyridones (**5**) also could be produced under oxidative conditions from species **A** after a debenzylation process (Scheme 1c). However, it is very challenging because the appropriate oxidative system and N-source should be carefully selected to control the oxidation of intermediate **A** before or after the debenzylation process. To the best of our knowledge, the efficient construction of 3,5-diarylpyridines (**2**), 3,5-diaryl-2-ketopyridines (**4**), or 2-(1*H*)-pyridones (**5**) through this cyclization strategy has not been achieved yet (Scheme 1c).

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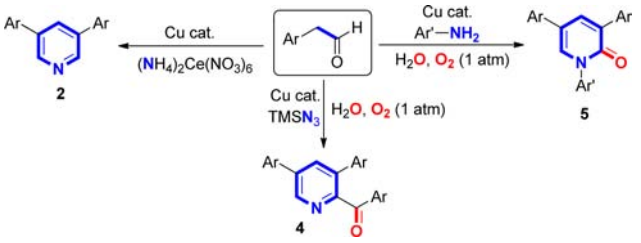
Herein, we describe a novel Cu-catalyzed highly chemoselective constructions of 3,5-diarylpyridines (**2**), 3,5-diaryl 2-ketopyridines (**4**), and 2-(1*H*)-pyridones (**5**) (Scheme 2), which

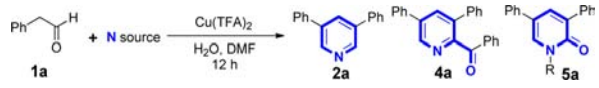
Scheme 2. Cu-Catalyzed Highly Chemoselective Constructions of 3,5-Diaryl Pyridines, 3,5-Diaryl-2-ketopyridines, and 2-(1*H*)-Pyridones



are important structural motifs in many biologically active molecules.[2] These approaches benefit from the simple aryl acetaldehydes and nitrogen donors, as well as the efficient pathways through cyclization, C−C bond cleavage, and aerobic oxidation. In addition, simple and environmentlly friendly water and molecular oxygen provide an O atom for the oxygenation process.

As a continuation of previous works on copper-catalyzed heteroarene constructions,[23] we commenced our investigation with screening of the nitrogen donors. It is interesting to find that when simple ammonium was used under Cu-catalysis, the desired 3,5-diarylpyridine product **2a** was obtained in 77% yield (entry 1, Table 1). Amazingly, the ceric ammonium nitrate (CAN) which was previously employed as an oxidant can donate a N atom to selectively afford **2a** in 93% yield (entry 2). In addition, the yield of **2a** slightly decreased in the absence of water (entry 4). We reasoned that water may facilitate the solubility of the copper catalyst and ammonium salt. Control experiments using

Table 1. Optimization of the Reaction Conditions[a]



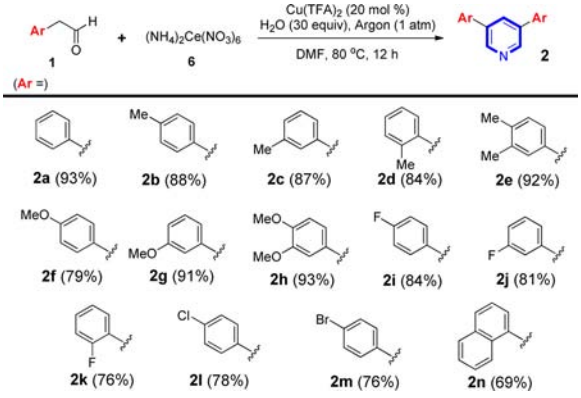
entry	N source	H_2O (equiv)	temp (°C)	gas (1 atm)	yield (%)[b] 2a/4a/5a
1	$(NH_4)_2CO_3$	30	80	argon	77/0/0
2	CAN	30	80	argon	93/0/0
3[c]	CAN	30	80	argon	62/0/0
4	CAN	0	80	argon	83/0/0
5	CAN	30	80	air	82/0/0
6	$TMSN_3$	0	80	O_2	0/trace/0
7[d]	$TMSN_3$	30	80	O_2	0/41/0
8[e]	$TMSN_3$	30	80	O_2	0/63/0
9[e,f]	$TMSN_3$	30	80	argon	0/0/0
10[c]	$TMSN_3$	30	80	O_2	0/0/0
11	Py-2-NH_2	20	120	O_2	0/0 /75
12[f]	Py-2-NH_2	20	120	argon	0/0/0
13[c]	Py-2-NH_2	20	120	O_2	0/0/0

[a]Reaction conditions: **1a** (1 mmol), nitrogen donor (0.25 mmol, 1 equiv), and Cu-catalyst (0.05 mmol) in DMF (3 mL), 12 h. [b]Isolated yields. [c]The reaction was carried out without the copper catalyst. [d]15 mol % of $Cu(TFA)_2$ was employed. [e]The reaction was carried out with $Cu(TFA)_2$ (15 mol %), NHPI (0.05 mmol), and AcOH (0.25 mmol). [f]The reactions did not work under Ar with catalytic amount or even 1.0 equiv of Cu-catalyst.

potassium nitrate instead of CAN did not work (see Supporting Information), which ruled out the possibility that the nitrate anion in CAN serves as the nitrogen donor. Interestingly, when trimethylsilyl azide ($TMSN_3$) was investigated as a N-donor, 3,5-diaryl 2-ketopyridine **4a** was selectively prepared in 41% yield under Cu-catalysis with molecular oxygen (entry 7, Table 1). The yield of **4a** was further promoted to 63% when NHPI (0.2 equiv) and acetic acid (1 equiv) were used as additives (entry 8). Control experiments in argon (entry 9) or in the absence of a copper catalyst (entry 10) did not work. When 2-aminopyridine was employed as the N-source, construction of the significant 2-(1*H*)-pyridone **5** was achieved (75%, entry 11). In contrast to Baran's work,[22] 3,5-diphenylpyridinium **3** was not detected. The copper catalyst and molecular oxygen are essential for this transformation (entries 12−13).

With the optimized conditions established, various aryl acetaldehydes were investigated for the construction of 3,5-diarylpyridine (Scheme 3). Electron-rich and -defficient aryl

Scheme 3. Substrate Scope for the Construction of 3,5-Diaryl Pyridine[a]

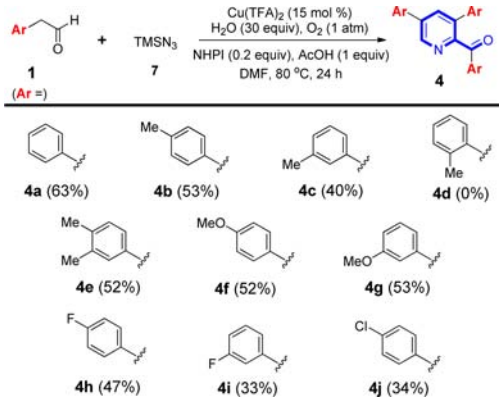


[a]Reaction conditions: see entry 2, Table 1. Isolated yields.

acetaldehydes performed well to generate the corresponding products with high efficiencies. Even the more sterically hindered naphth-1-yl acetaldehyde also worked well, affording **2n** in 69% yield.

2-Ketopyridine products were easily constructed from various aryl acetaldehydes by using $TMSN_3$ as the N-donor (Scheme 4).

Scheme 4. Substrate Scope for the Construction of 3,5-Diaryl 2-Ketopyridines[a]



[a]Reaction conditions: see entry 8, Table 1. Isolated yields.

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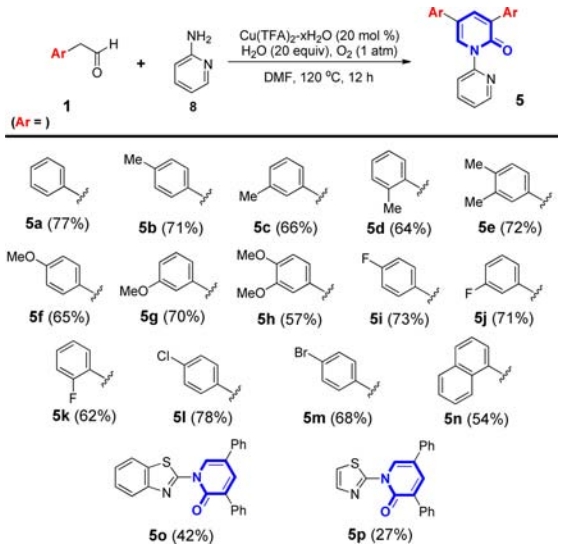
Electron-rich phenyl acetaldehydes afforded corresponding 2-ketopyridines in slightly dropped yields (**4b**−**4c**, **4e**−**4g**). The influence of steric hindrance has also been shown, since 2-ketopyridine **4d** could not be acquired from *ortho*-methyl phenyl acetaldehyde. The yields of halogen-substituted products were low (**4h**−**4j**).

The approach to 2-(1*H*)-pyridones **5** showed very good substrate tolerance (Scheme 5). Phenyl acetaldehydes with

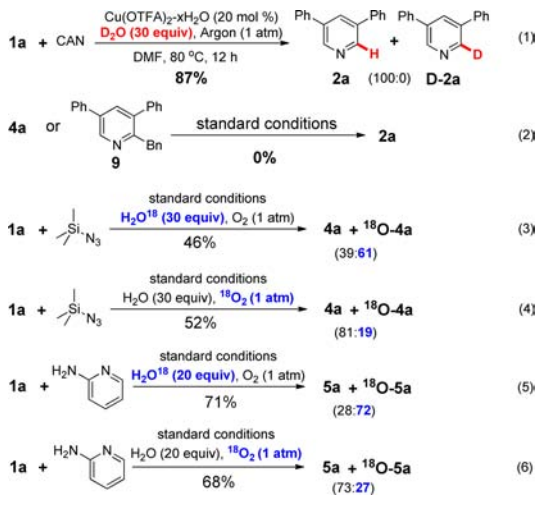
Scheme 5. Substrate Scope for the Construction of 2-(1*H*)-Pyridone[a]



[a]Reaction conditions: see entry 11, Table 1. Isolated yields.

different substituents on the phenyl ring provided corresponding 2-(1*H*)-pyridone products in good yields. Steric hindrance also showed an adverse influence on the yield. Furthermore, 2-amino benzothiazole and 2-amino thiazole were also tolerated in this transformation yielding the corresponding pyridone products **5o** and **5p**.

To gain more insight into the mechanisms, some control experiments were conducted. The result of the reaction with deuterium oxide (D_2O) suggested that no protonation occurred in the formation of 3,5-diarylpyridine product **2a** (eq 1).

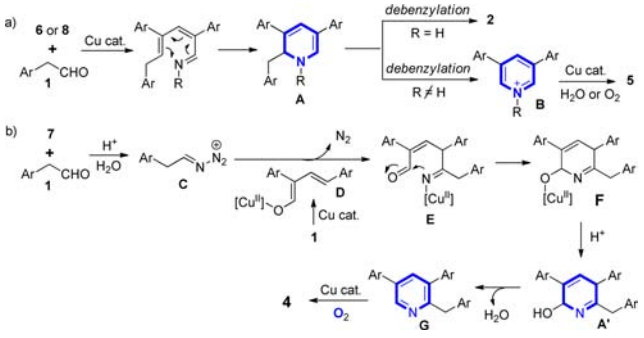


Moreover, 2-ketopyridine **4a** or 2-benzylpyridine **9** did not produce **2a** under standard conditions (eq 2), which indicates that debenzylation probably occurs before the aromatization step of intermediate **A** as previously reported.[20]

In order to investigate the oxygen source of the keto moiety in products **4** and **5**, the labeling experiments using $H_2{}^{18}O$ and $^{18}O_2$ have been conducted (eqs 3−6). The ^{18}O-**4a** and ^{18}O-**5a** products can be detected under both the $H_2{}^{18}O$ (eqs 3 and 5) and $^{18}O_2$ (eq 4 and 6) conditions. Considering the reaction with 1.0 equiv of the Cu-catalyst under Ar did not work (entries 9 and 12, Table 1), the above results demonstrate that both H_2O and O_2 could serve as the oxygen source in the construction of **4** and **5**.

Thus, the plausible mechanisms for these approaches are proposed as shown in Scheme 6. Initially, the Cu-catalyzed

Scheme 6. Plausible Mechanism for the Construction of 2, 4, and 5



condensation of aldehydes **1** with CAN **6** or amine **8** through an abnormal Chichibabin pyridine synthesis process[18−22] occurs to generate dihydropyridine intermediate **A** (Scheme 6a), which subsequently undergoes oxidative dealkylation[19g,20,22] to afford 3,5-diarylpyridine product **2** (R = H) or 3,5-diphenylpyridinium intermediate **B** (R ≠ H).[22] Under the Cu-catalyzed aerobic oxidative conditions, species **B** could be easily oxidized[24] to 2-(1*H*)-pyridone **5** (Scheme 6a).

Alternatively, under the acidic conditions, the aldehyde and $TMSN_3$ undergo a Schmidt reaction process to form intermediate **C**,[25] which could be detected on GC-MS. Subsequently, intermediate **C** is attached by species **D**, which is generated *via* Kneovenagel-type self-condensation of acetaldehyde, generating intermediate **E** with the release of N_2 gas. Then the intermediate **A**′ is produced through the relay of cyclization and protonation of intermediate **E**. Subsequently the dehydration process of intermediate **A**′ leads to the formation of 2-benzylpyridine **G**. Finally **G** is oxidized by O_2 at the active benzyl position to afford product **4**.[26]

In conclusion, we have developed a highly selective copper-catalyzed diverse construction of 3,5-diarylpyridines and 2-(1*H*)-pyridones through tandem Chichibabin-type cyclization, C-(sp^3)−C(sp^3) bond cleavage, and aerobic oxidation. Azide, CAN, and 2-aminopyridine are disclosed as efficient nitrogen donors in this Cu-catalysis using O_2 as the oxidant. Different pyridine-based heterocycles can be selectively constructed according to these nitrogenation processes from simple, inexpensive, and readily available N-donors. Further efforts on the applications of these protocols are ongoing in our group.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed results of the optimization of reaction conditions, isotope-labeling experiments, experimental procedures, charac-

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terization, and NMR spectra of products **2**, **4**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Roth, H. J.; Kleemann, A. *Drug Synthesis in Pharmaceutical Chemistry*; John Wiley and Sons: New York, 1988; Vol. *1*. (b) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell Science: Cambridge, 2000; pp 63−120.

(2) (a) Tagat, J. R.; McCombie, S. W.; Barton, B. E.; Jackson, J.; Shortall, J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2143. (b) Lucas, S.; Negri, M.; Heim, R.; Zimmer, C.; Hartmann, R. W. *J. Med. Chem.* **2011**, *54*, 2307. (c) Hibi, S.; Ueno, K.; Nagato, S.; Kawano, K.; Ito, K.; Norimine, Y.; Takenaka, O.; Hanada, T.; Yonaga, M. *J. Med. Chem.* **2012**, *55*, 10584.

(3) For reviews, see: (a) Varela, J. A.; Saa, C. *Chem. Rev.* **2003**, *103*, 3787. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644. (c) Heller, B.; Hapke, M. *Chem. Soc. Rev.* **2007**, *36*, 1085.

(4) For recent examples of synthesis of 3,5-diaryl pyridines from 3,5-dihalogenated substrates, see: (a) Adams, H.; Chekmeneva, E.; Hunter, C. A.; Misuraca, M. C.; Navarro, C.; Turega, S. M. *J. Am. Chem. Soc.* **2013**, *135*, 1853. (b) Lee, C. W.; Lee, J. Y. *Chem. Commun.* **2013**, *49*, 1446. (c) Liu, Y.; Li, J.-R.; Verdegaal, W. M.; Liu, T.-F.; Zhou, H.-C. *Chem.—Eur. J.* **2013**, *19*, 5637. (d) Mamane, V.; Aubert, E.; Peluso, P.; Cossu, S. *J. Org. Chem.* **2012**, *77*, 2579. (e) Hata, K.; Segawa, Y.; Itami, K. *Chem. Commun.* **2012**, *48*, 6642.

(5) For examples via C−H activation of pyridines, see: (a) Guo, P.-F.; Joo, J.-M.; Rakshit, S.; Sames, D. *J. Am. Chem. Soc.* **2011**, *133*, 16338. (b) Fortage, J.; Peltier, C.; Nastasi, F.; Puntoriero, F.; Tuyeras, F.; Griveau, S.; Bedioui, F.; Adamo, C.; Ciofini, I.; Campagna, S.; Laine, P. P. *J. Am. Chem. Soc.* **2010**, *132*, 16700. (c) Wasa, M.; Worrell, B. T.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 1275.

(6) For cyclization of dibenzyl ketones, see: (a) Lee, L. F.; Sing, Y. L. *J. Org. Chem.* **1990**, *55*, 380. (b) Thomas, A. D.; Asokan, J.; Asokan, C. V. *Tetrahedron* **2004**, *60*, 5069.

(7) For cyclization of an unsaturated imine, see: (a) Palacios, F.; Alonso, C.; Rubiales, G.; Ezpeleta, J. M. *Eur. J. Org. Chem.* **2001**, 2115−2122. (b) Winter, A.; Risch, N. *Synthesis* **2003**, 2667.

(8) For cyclization of an amino acid, see: (a) Panzella, L.; Di Donato, P.; Comes, S.; Napolitano, A.; Palumbo, A.; d'Ischia, M. *Tetrahedron Lett.* **2005**, *46*, 6457. (b) Wang, Q.; Wan, C.; Gu, Y.; Zhang, J.; Gao, L.; Wang, Z. *Green Chem.* **2011**, *13*, 578.

(9) For cyclization of acryloyl azide, see: Chuang, T.-H.; Chen, Y.-C.; Pola, S. *J. Org. Chem.* **2010**, *75*, 6625.

(10) For cyclization of an α,β-unsaturated ketone, see: Sim, Y.-K.; Lee, H.; Park, J.-W.; Kim, D.-S.; Jun, C.-H. *Chem. Commun.* **2012**, *48*, 11787.

(11) For cyclization of a ketoxime carboxylate, see: Zhao, M.-N.; Hui, R.-R.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Org. Lett.* **2014**, *16*, 3082.

(12) For cyclization of an amino acrylate, see: Knops, H.-J.; Born, L. *Tetrahedron Lett.* **1983**, *24*, 2973.

(13) For cyclization of a tetracyclone, see: Eagan, R. L.; Ogliaruso, M. A. *J. Org. Chem.* **1986**, *51*, 1544.

(14) For cyclization of an azomethine, see: Kappe, T.; Ajili, S.; Stadlbauer, W. *J. Heterocyclic Chem.* **1988**, *25*, 463.

(15) For cyclization of an acyl enamine, see: Collins, I.; Castro, J. L. *Tetrahedron Lett.* **1999**, *40*, 4069.

(16) For cyclization of an acrylamide, see: (a) Su, Y.; Zhao, M.; Han, K.; Song, G.; Li, X. *Org. Lett.* **2010**, *12*, 5462. (b) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Org. Lett.* **2011**, *13*, 3278.

(17) For examples of cycloadditions of two alkynes and one cyanide or isocyanate, see: (a) Suzuki, D.; Tanaka, R.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2002**, *124*, 3518. (b) Tanaka, R.; Yuza, A.; Watai, Y.; Suzuki, D.; Takayama, Y.; Sata, F.; Urabe, H. *J. Am. Chem. Soc.* **2005**, *127*, 7774. (c) Takahashi, T.; Tsai, F.-Y.; Li, Y.; Wang, H.; Kondo, Y.; Yamanaka, M.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **2002**, *124*, 5059. (d) Earl, R. A.; Vollhardt, K. P. C. *J. Org. Chem.* **1984**, *49*, 4786.

(18) For reviews, see: (a) Sagitullin, R. S.; Shkil, G. P.; Nosonova, I. I.; Ferber, A. A. *Khim. Geterotsikl. Soedi.* **1996**, 147. (b) Gelas, J. *Bull. Soc. Chim. Fr.* **1967**, 3093.

(19) (a) Chichibabin, A. E. *J. Russ Phys. Chem. Soc.* **1906**, *37*, 1229. (b) Frank, R. L.; Seven, R. P. *J. Am. Chem. Soc.* **1949**, *71*, 2629. (c) Patrick, T. M., Jr. *J. Am. Chem. Soc.* **1952**, *74*, 2984. (d) Farley, C. P.; Eliel, E. L. *J. Am. Chem. Soc.* **1956**, *78*, 3477. (e) Charman, H. B.; Rowe, J. M. *Chem. Commun.* **1971**, 476. (f) Suyama, K.; Adachi, S. *J. Org. Chem.* **1979**, *44*, 1417. (g) Burns, N. Z.; Jessing, M.; Baran, P. S. *Tetrahedron* **2009**, *65*, 6600. (h) Dagorn, F.; Yan, L.-H.; Gravel, E.; Leblanc, K.; Maciuk, A.; Poupon, E. *Tetrahedron Lett.* **2011**, *52*, 3523.

(20) Eliel, E. L.; McBride, R. T.; Kaufmann, St. *J. Am. Chem. Soc.* **1953**, *75*, 4291.

(21) (a) Yu, L.-B.; Chen, D.; Li, J.; Ramirez, J.; Wang, P. G. *J. Org. Chem.* **1997**, *62*, 208. (b) Snider, B. B.; Neubert, B. J. *Org. Lett.* **2005**, *7*, 2715.

(22) Burns, N. Z.; Baran, P. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 205.

(23) For recent Cu-catalyzed heterocyclic compound constructions, see: (a) Wang, Y.; Chen, C.; Peng, J.; Li, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 5323. (b) Li, B.-J.; Wang, H.-Y.; Zhu, Q.-L.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 3948. (c) Wang, Y.-F.; Zhu, X.; Chiba, S. *J. Am. Chem. Soc.* **2012**, *134*, 3679. (d) Chatterjee, I.; Froehlich, R.; Studer, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 11257. (e) Barluenga, J.; Lonzi, G.; Riesgo, L.; Lopez, L. A.; Tomas, M. *J. Am. Chem. Soc.* **2010**, *132*, 13200. (f) Xu, Z.; Zhang, C.; Jiao, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 11367. (g) Chen, F.; Qin, C.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 11487.

(24) (a) Schoeneboom, J. C.; Groetsch, S.; Christl, M.; Engels, B. *Chem.—Eur. J.* **2003**, *9*, 4641. (b) Demidov, O. P.; Borovlev, I. V.; Pisarenko, S. V.; Nemykina, O. A. *Chem. Heterocycl. Com.* **2009**, *45*, 619. (c) Zoltewicz, J. A.; Maier, N. M. *J. Org. Chem.* **1996**, *61*, 7018.

(25) Schmidt, K. F. Z. *Angew. Chem.* **1923**, *36*, 511.

(26) (a) Itoh, M.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2014**, *16*, 2050. (b) Pieber, B.; Kappe, C. O. *Green Chem.* **2013**, *15*, 320. (c) De Houwer, J.; Tehrani, K. A.; Maes, B. U. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 2745. (d) Julia, L.; Riera, J.; Teixido, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1101.

DOI: 10.1021/ol5035996
Org. Lett. 2015, 17, 584−587