Organic LETTERS

Letter

pubs.acs.org/OrgLett

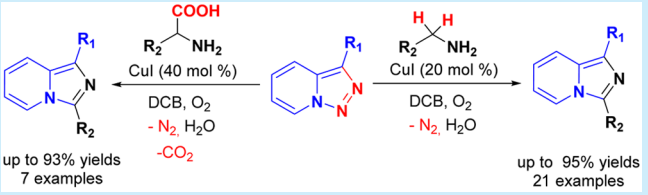
Copper-Catalyzed Denitrogenative Transannulation Reaction of Pyridotriazoles: Synthesis of Imidazo[1,5-*a*]pyridines with Amines and Amino Acids

Abhisek Joshi, Darapaneni Chandra Mohan, and Subbarayappa Adimurthy*

Academy of Scientific & Innovative Research, CSIR−Central Salt & Marine Chemicals Research Institute, G. B. Marg, Bhavnagar-364 002, Gujarat, India

Supporting Information

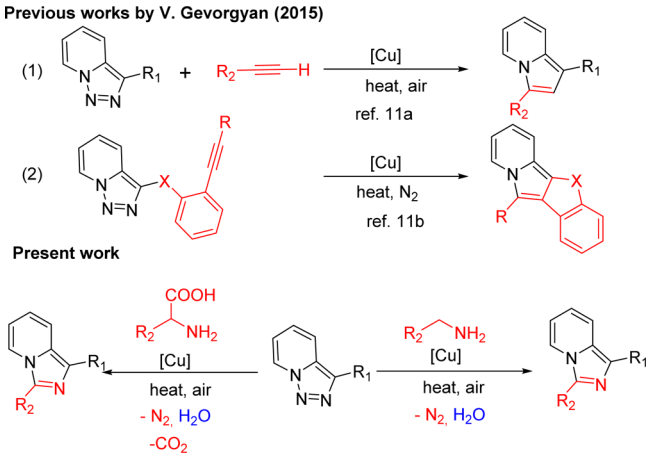
ABSTRACT: The copper-catalyzed aerobic oxidative synthesis of imidazo[1,5-*a*]pyridines via cascade denitrogenative transannulation reaction of pyridotriazoles with benzylamines with good functional group tolerance is developed. The present methodology is also applicable to amino acids to obtain imidazo[1,5-*a*]pyridines via decarboxylative oxidative cyclization.



Transition-metal-catalyzed C−H bond amination represents a powerful strategy for the synthesis of azaheterocycles.[1] Particularly, imidazo[1,5-*a*]pyridines are highly valuable organic scaffolds and are useful in many areas of research including pharmaceuticals and material science.[2−4] Therefore, it is not surprising that, in spite of the existing methods,[5−8] the development of new versatile and efficient protocols for their synthesis is of continuing interest. There are limited methods to obtain imidazo[1,5-*a*]pyridines, despite their wide range of biological activities.[2−4] The newly recognized transition-metal-catalyzed formation of diazo compounds from 1,2,3-triazoles via a ring opening pathway, which could be used for the generation of metallocarbene intermediates, has led to the further subjection of a wide range of synthetically useful transformations such as direct heterocycles synthesis, cycloadditions, ring expansions, and ylide formation,[9,10] and recently copper-catalyzed denitrogenative transannulations of pyridotriazoles for the synthesis of substituted indolizines have been reported by Gevorgyan et al.[11] (Scheme 1, eqs 1 and 2). Encouraged by these previous successes and our recent work on copper-catalyzed aerobic oxidative amination of C(sp3)−H bonds for the syntheses of fused nitrogen-containing heterocycles[12] and imidazo[1,5-*a*]pyridines[13] under mild conditions, we hypothesized that subjecting the pyridotriazole and benzylamine would obtain the imidazo[1,5-*a*]pyridines under copper catalysis. To the best of our knowledge, these later transformations have been scarcely investigated to date. Herein, we report the denitrogenative transannulation of pyridotriazoles with benzylamines and amino acids (decarboxylation) for the synthesis of imidazo[1,5-*a*]pyridines using copper catalysis (Scheme 1). The synthetic scope encompasses pyridotriazole with a variety of benzylamines and amino acids.

To test our initial hypothesis, we first examined the denitrogenative transannulation of pyridotriazole **1a** with benzyl amine **2a** in the presence of 10 mol % of CuI in dichlorobenzene at room temperature in a closed tube, and no

Scheme 1

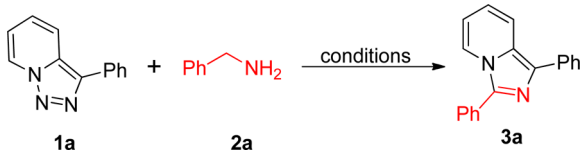


reaction was observed up to 24 h (Table 1, entry 1). When the same reaction was performed at 80 °C, a trace of **3a** was isolated (Table 1, entry 2). Upon further raising of the reaction temperature to 120 and 150 °C, the desired product **3a** was isolated in 24% and 68% yield respectively (Table 1, entries 3 and 4). In the latter entry, the reaction time was 6 h; at high temperature with a long reaction time the product decomposition was observed.[14] With other copper sources (i.e., CuBr, CuCl, $Cu(OAc)_2$, and $Cu(OTf)_2$), no improvement in yield was observed (Table 1, entries 5−8). However, with $CuBr_2$, a comparable but relatively low yield for **3a** was observed (Table 1, entry 9). By increasing the catalyst (CuI) loading to 20 mol %, **3a** was obtained in 82% yield (Table 1, entry 10). Upon further screening of different solvents (DMSO, DMF, DMA, NMP, and toluene), no reaction was observed (Table 1, entries

Received: December 10, 2015

DOI: 10.1021/acs.orglett.5b03509
Org. Lett. XXXX, XXX, XXX−XXX

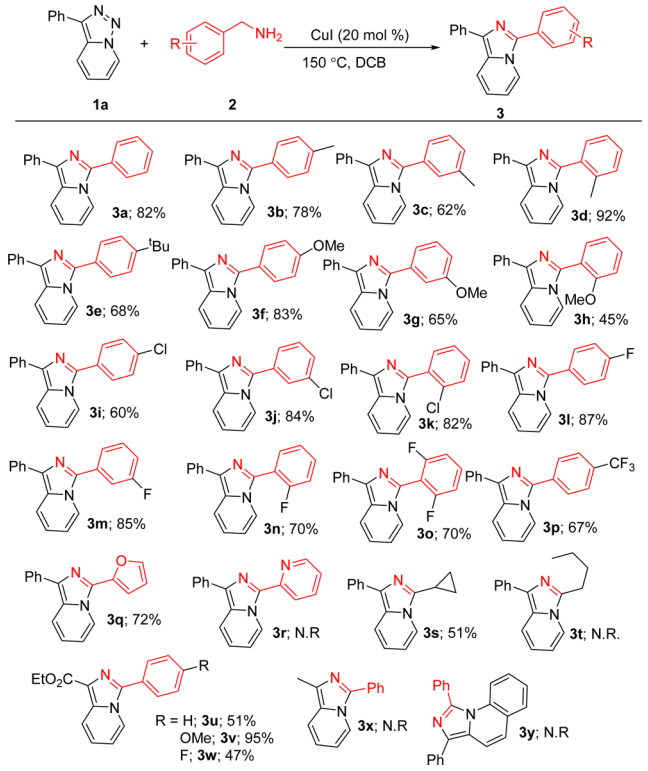
Table 1. Optimization Conditions for 3a[a]



entry	catalyst (mol %)	solvent	temp	time (h)	yield (%)
1	CuI (10)	DCB	rt	24	nr
2	CuI (10)	DCB	80	24	trace
3	CuI (10)	DCB	120	24	24
4	CuI (10)	DCB	150	6	68
5	CuBr (10)	DCB	150	8	32
6	CuCl (10)	DCB	150	8	37
7	$Cu(OTf)_2$ (10)	DCB	150	8	23
8	$Cu(OAc)_2$ (10)	DCB	150	8	47
9	$CuBr_2$ (10)	DCB	150	8	65
10	**CuI (20)**	**DCB**	**150**	**6**	**82**
11	CuI (20)	DMSO	150	6	0
12	CuI (20)	DMF	150	6	0
13	CuI (20)	DMA	150	6	0
14	CuI (20)	DMF	150	6	0
15	CuI (20)	NMP	150	6	nr
16	CuI (20)	toluene	150	6	nr
17	–	DCB	150	6	nr
18	CuI (20)	–	150	6	74
19[b]	CuI (20)	DCB	150	6	37
20[c]	CuI (20)	DCB	150	6	10

[a]Conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), catalyst, solvent (1.0 mL), in an oil bath, closed tube, isolated yield. [b]Oxygen atmosphere. [c]Argon atmosphere. nr: no reaction.

Scheme 2. Substrate scope of transannulation of triazolo[1,5-*a*]pyridines with amines[a]



[a]Conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), catalyst, solvent (1 mL), in an oil bath in a closed tube, 6 h, isolated yield.

11–16). Without a copper iodide catalyst no reaction was observed (Table 1, entry 17), and the yield decreased under neat conditions (Table 1, entry 18). To further study the effect of atmosphere, reactions have been performed under nitrogen and oxygen atmospheres instead of within a closed tube (Table 1, entries 19 and 20); the yield decreased drastically. The best **3a** yield was obtained under the conditions of entry 10; these parameters were set as optimal for further transannulation of pyridotriazole with different benzylamines (Scheme 2).

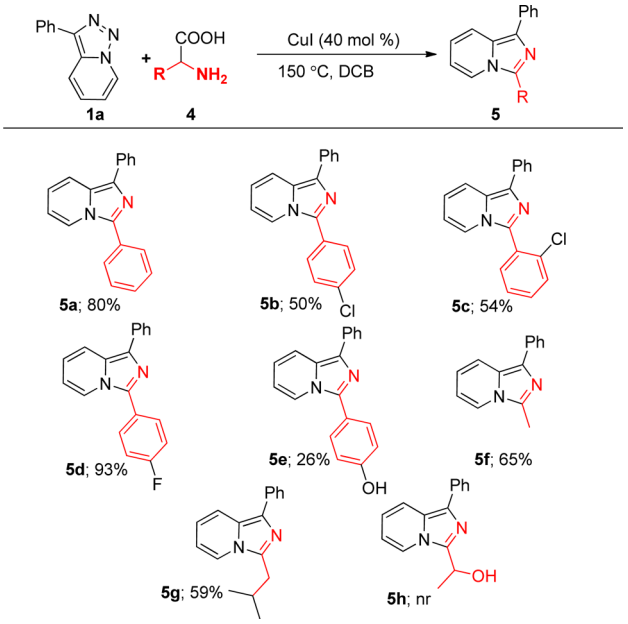
The reaction of 3-phenyl[1,2,3]triazolo[1,5-*a*]pyridine (**1a**), with a neutral, electron-rich substituent at the *para-*/*meta-*/*ortho-* position of benzyl amines such as –Me, –^{t}Bu, –OMe, reacted very smoothly and gave good to excellent yields (63–92%) of the desired products **3a**–**3g**. However, 2-MeO benzyl amine gave a comparatively low yield (45%) of desired product **3h**; this may be due to the steric effect of the *ortho*-methoxy position. Next we have checked the substrate scope of partially electron-withdrawing substituents such as –Cl (*para*, *meta*, and *ortho*), –F (*para*, *meta* and *ortho*), and disubstituted –F (2, 6-position), they also reacted efficiently and gave moderate to excellent yields of products **3j**–**3o**. It may be noted that, halide substituted imidazopyridine derivatives were well tolerated and which could be further applied in traditional cross-coupling reactions. Pleasingly we found that the present system was also applicable to a strong electron-withdrawing substituent under typical conditions, to afford the desired product **3p** in moderate yield (67%). Additionally the present system is applicable to heteroamines, and aliphatic cyclic amines such as furfurylamine and cyclopropyl methyl amine reacted smoothly and produced the corresponding imidazo[1,5-*a*]pyridines (**3q** and **3s**) in moderate yield. However, the present system is not applicable for azaheterocyclic amines (2-picolyl amine) and simple aliphatic amines; in both cases, starting substrate decomposition was observed (**3r** and **3t**). Moreover, we performed the reaction of triazolo[1,5-*a*]pyridinecarboxylate with different benzyl amines, and the corresponding products (**3u**, **3v**, and **3w**) were obtained in good to moderate yields (47–95%). With a methyl substituted substrate, decomposition of starting substrates was observed. Finally, we also tried using a heteroaryl such as quinoline triazole under the optimized conditions; the ring opening is not observed (starting substrate recovered).

Although this route to the formation of a double C–N bond was only realized for a particular class of substrates, triazolo[1,5-*a*]pyridine, it represents a major developmental strategy to obtain imidazo[1,5-*a*]pyridine derivatives via a denitrogenative transannulation reaction of pyridotriazoles with copper catalysis by a ring opening mechanism.

α-Amino acids are more readily available and more stable than other starting materials in nature. Therefore, the decarboxylative reaction of *α*-amino acids provides a very efficient synthetic method for synthesis of azaheterocycles. Recently utilization of *α*-amino acids for synthesis of heterocyclic compounds are increasing drastically.[15] Further, we have been evaluating the present strategy of denitrogenative transannulation reaction of pyridotriazoles with some amino acids and their derivatives under the optimized conditions of Scheme 2, and the results are included in Scheme 3. Triazolo[1,5-*a*]pyridine **1a** reacts with substituted phenyl glycine derivatives (4-Cl, 2-Cl, 4-F, and 4-OH), alanine, and leucin, producing the corresponding imidazo[1,5-*a*]pyridines in moderate to excellent yields via decarboxylation followed by transannulation.

DOI: 10.1021/acs.orglett.5b03509
Org. Lett. XXXX, XXX, XXX–XXX

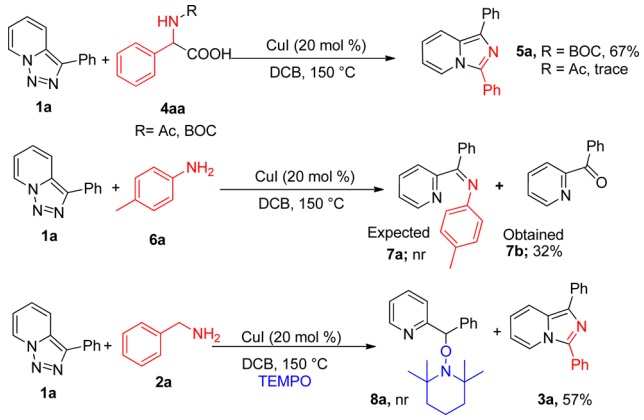
Scheme 3. Transannulation of Triazolo[1,5-*a*]pyridine with Amino Acids[a]



[a]Conditions: **1a** (0.2 mmol), **4** (0.6 mmol), catalyst, solvent (1 mL), in an oil bath, closed tube, 24 h, isolated yield.

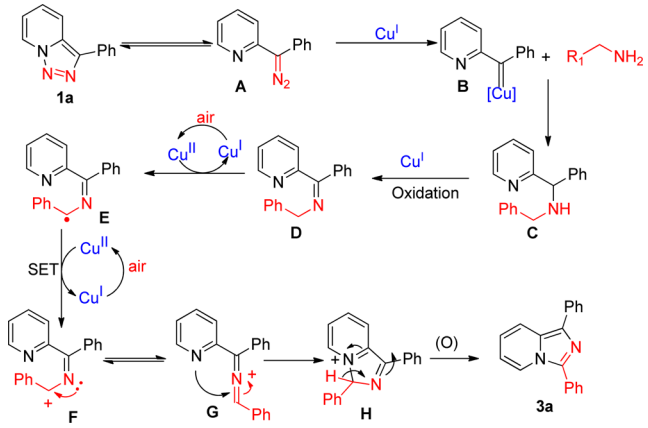
To establish the reaction mechanism, control experiments were performed (Scheme 4). When the reaction of triazolo[1,5-*a*]pyridine **1a** reacted with N-protected phenyl glycine (R = Ac, BOC) under the optimized conditions, BOC containing phenyl glycine gave a moderate yield of **5a** and in the case of Ac containing phenyl glycine a trace of **5a** was obtained. With *p*-toluidine **6a** under the optimized conditions, no imine product **7a** formation was observed. But we have isolated 32% of phenyl(pyridin-2-yl)methanone **7b**; it might be formed by the hydrolysis of **7a** at high temperature. Further study of the reaction was conducted by the addition of radical scavenger TEMPO under optimized conditions to determine whether the reaction proceeds via a radical pathway or an ionic path; under these conditions no adduct formation was observed. However, the yield of the product decreased drastically. This experiment clearly indicates that the reaction may proceed via copper−carbene formation followed by oxidation to give imidazo[1,5-*a*]pyridines.

Scheme 4. Controlled Experiments



Based on these results, existing literature,[11,16] and our previous findings on imidazo[1,5-*a*]pyridines,[13] we have postulated a working mechanism for this transformation (Scheme 5). First, the *α*-imino diazo compound **A** generates the Cu−carbene complex **B**, which is generated from triazolo[1,5-*a*]pyridine **1a**. Migratory insertion of benzylamine at the carbene C atom of **B** forms the intermediate **C**,[11,16] which further undergoes oxidative dehydrogenation to provide imine intermediate **D**. Such intermediate formation was further confirmed by the control experiments (Scheme 4). Subsequently **D** further undergoes single electron transfer in the process (intermediates **E**−**G**).[17] Attacking the ring nitrogen lone pair of electrons from **G** leads to a cyclic intermediate **H**. Finally, aromatization of **H** will give the desired product **3a**.

Scheme 5. Plausible Mechanism



We have developed an efficient copper-catalyzed aerobic oxidation followed by denitrogenative transannulation of pyridotriazoles with benzyl amines and amino acids to obtain imidazo[1,5-*a*]pyridine derivatives. In this system, we utilized molecular oxygen (O_2) from air as the sole oxidant, commercially available benzylamines, and amino acids, which make the present transformation more sustainable.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03509.

^{1}H and ^{13}C NMR spectra for all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: adimurthy@csmcri.org.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

CSIR-CSMCRI Communication No. 204/2015. A.J. and D.C.M. are thankful to AcSIR for their Ph.D. enrollment and the "Analytical Discipline and Centralized Instrumental Facilities" for providing instrumentation facilities. A.J. and D.C.M. are also thankful to CSIR and UGC, New Delhi for their fellowships. We thank DST, Government of India (SR/

DOI: 10.1021/acs.orglett.5b03509
Org. Lett. XXXX, XXX, XXX−XXX

S1/OC-13/2011), for financial support. We also thank CSIR-CSMCRI (OLP-0076) for partial assistance.

REFERENCES

(1) (a) Ramirez, T. A.; Zhao, B.; Shi, Y. *Chem. Soc. Rev.* **2012**, *41*, 931. (b) Ke, J.; He, C.; Liu, H.; Li, M.; Lei, A. *Chem. Commun.* **2013**, *49*, 7549. (c) Dong, W.; Wang, L.; Parthasarathy, K.; Pan, F.; Bolm, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 11573. (d) Li, J.; Neuville, L. *Org. Lett.* **2013**, *15*, 1752. (e) Chen, H.; Sanjaya, S.; Wang, Y.-F.; Chiba, S. *Org. Lett.* **2013**, *15*, 212. (f) Yang, Y.; Xie, C.; Xie, Y.; Zhang, Y. *Org. Lett.* **2012**, *14*, 957. (g) Armstrong, A.; Collins, J. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 2282. (h) Rakshit, S.; Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9585. (i) Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Commun.* **2009**, 5061. (j) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (k) Davies, H. M. L.; Long, M. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3518.

(2) (a) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell Science: Oxford, U.K., 2000; Chapter 25. (b) Katritzky, A. R.; *Comprehensive Heterocyclic Chemistry III*; Elsevier: Oxford, U.K., 2008; Vol. *11*. (c) El Khadem, H. S.; Kawai, J.; Swartz, D. L. *Carbohydr. Res.* **1989**, *189*, 149.

(3) (a) Degoey D. A.; Flentge, C. A.; Flosi, W. J.; Grampovnik, D. J.; Kempf, D. J.; Klein, L. L.; Yeung, M. C.; Randolph, J. T.; Wang, X. C.; Yu, S. U.S. Pat. Appl. Publ. U.S. 2005148623; *Chem. Abstr.* **2005**, *143*, 133693. (b) Kim, D.; Wang, L.; Hale, J. J.; Lynch, C. L.; Budhu, R. J.; MacCoss, M.; Mills, S. G.; Malkowitz, L.; Gould, S. L.; DeMartino, J. A.; Springer, M. S.; Hazuda, D.; Miller, M.; Kessler, J.; Hrin, R. C.; Carver, G.; Carella, A.; Henry, K.; Lineberger, J.; Schleifc, W. A.; Eminic, E. A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2129. (c) Nakatsuka, M.; Shimamura, T. Jpn. Kokai Tokkyo Koho JP2001035664;. *Chem. Abstr.* **2001**, *134*, 170632. (d) Tominaga, G.; Kohama, R.; Takano, A. Jpn. Kokai Tokkyo Koho JP2001006877; *Chem. Abstr.* **2001**, *134*, 93136.

(4) (a) Kitazawa, D.; Tominaga, G.; Takano, A. Jpn. Kokai Tokkyo Koho JP 2001057292;. *Chem. Abstr.* **2001**, *134*, 200276. (b) Salassa, L.; Garino, C.; Albertino, A.; Volpi, G.; Nervi, C.; Gobetto, R.; Hardcastle, K. I. *Organometallics* **2008**, *27*, 1427. (c) Nakamura, H.; Yamamoto, H. PCT Int. Appl. WO 2005043630. *Chem. Abstr.* **2005**, *142*, 440277. (d) Kim, D.; Wang, L.; Hale, J. J.; Lynch, C. L.; Budhu, R. J.; MacCoss, M.; Mills, S. G.; Malkowitz, L.; Gould, S. L.; DeMartino, J. A.; Springer, M. S.; Hazuda, D.; Miller, M.; Kessler, J.; Hrin, R. C.; Carver, G.; Carella, A.; Henry, K.; Lineberger, J.; Schleif, W. A.; Emini, E. A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2129.

(5) (a) Zimmer, H.; Glasgow, D. G.; McClanahan, M.; Novinson, T. *Tetrahedron Lett.* **1968**, *9*, 2805. (b) Li, Q.; Woods, K. W.; Claiborne, A.; Gwaltney, S. L.; Barr, K. J.; Liu, G.; Gehrke, L.; Credo, R. B.; Hui, Y. H.; Lee, J.; Warner, R. B.; Kovar, P.; Nukkala, M. A.; Zielinski, N. A.; Tahir, S. K.; Fitzgerald, M.; Kim, K. H.; Marsh, K.; Frost, D.; Ng, S.-C.; Rosenberg, S.; Sham, H. L. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 465.

(6) (a) Shibahara, F.; Kitagawa, A.; Yamaguchi, E.; Murai, T. *Org. Lett.* **2006**, *8*, 5621. (b) Shibahara, F.; Sugiura, R.; Yamaguchi, E.; Kitagawa, A.; Murai, T. J. *J. Org. Chem.* **2009**, *74*, 3566. (c) Wang, J.; Mason, R.; VanDerveer, D.; Feng, K.; Bu, X. R. *J. Org. Chem.* **2003**, *68*, 5415. (f) Katritzky, A. R.; Qiu, G. *J. Org. Chem.* **2001**, *66*, 2862.

(7) (a) Pelletier, G.; Charette, A. B. *Org. Lett.* **2013**, *15*, 2290. (b) Wang, Q.; Zhang, S.; Guo, F.; Zhang, B.; Hu, P.; Wang, Z. *J. Org. Chem.* **2012**, *77*, 11161. (c) Yan, Y.; Zhang, Y.; Zha, Z.; Wang, Z. *Org. Lett.* **2013**, *15*, 2274.

(8) (a) Li, M.; Xie, Y.; Ye, Y.; Zou, Y.; Jiang, H.; Zeng, W. *Org. Lett.* **2014**, *16*, 6232. (b) Wang, H.; Xu, W.; Wang, Z.; Yu, L.; Xu, K. *J. Org. Chem.* **2015**, *80*, 2431.

(9) (a) Davies, H. M. L.; Alford, J. S. *Chem. Soc. Rev.* **2014**, *43*, 5151. (b) Gulevich, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2013**, *52*, 1371. (c) Chattopadhyay, B.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 862. (d) Yang, Y.; Zhou, M.-B.; Ouyang, X.-H.; Pi, R.; Song, R.-J.; Li, J.-H. *Angew. Chem., Int. Ed.* **2015**, *54*, 6595.

(10) (a) Zhang, W. B.; Xiu, S.-D.; Li, C.-Y. *Org. Chem. Front.* **2015**, *2*, 47. (b) Wang, Y.; Lei, X.; Tang, Y. *Chem. Commun.* **2015**, *51*, 4507. (c) Lei, X.; Li, L.; He, Y.-P.; Tang, Y. *Org. Lett.* **2015**, *17*, 5224. (d) Miura, T.; Tanaka, T.; Matsumoto, K.; Murakami, M. *Chem. - Eur. J.* **2014**, *20*, 16078.

(11) (a) Helan, V.; Gulevich, A. V.; Gevorgyan, V. *Chem. Sci.* **2015**, *6*, 1928. (b) Shi, Y.; Gevorgyan, V. *Chem. Commun.* **2015**, *51*, 17166.

(12) (a) Mohan, D. C.; Rao, S. N.; Adimurthy, S. *J. Org. Chem.* **2013**, *78*, 1266. (b) Mohan, D. C.; Rao, S. N.; Ravi, C.; Adimurthy, S. *Asian J. Org. Chem.* **2014**, *3*, 609. (c) Mohan, D. C.; Donthiri, R. R.; Rao, S. N.; Adimurthy, S. *Adv. Synth. Catal.* **2013**, *355*, 2217. (d) Donthiri, R. R.; Pappula, V.; Reddy, N. N. K.; Bairagi, D.; Adimurthy, S. *J. Org. Chem.* **2014**, *79*, 11277. (e) Mohan, D. C.; Ravi, C.; Rao, S. N.; Adimurthy, S. *Org. Biomol. Chem.* **2015**, *13*, 3556. (f) Mohan, D. C.; Ravi, C.; Pappula, V.; Adimurthy, S. *J. Org. Chem.* **2015**, *80*, 6846.

(13) Mohan, D. C.; Rao, S. N.; Ravi, C.; Adimurthy, S. *Org. Biomol. Chem.* **2015**, *13*, 5602.

(14) The progress of the reaction was monitored by the TLC; initially, the reaction showed good conversion at 150 °C, and by increasing the reaction time, the desired product formation was decreased. By monitoring the reaction by TLC, the time was optimized to 6 h to avoid decomposition of the product.

(15) (a) Wang, Q.; Zhang, S.; Guo, F.; Zhang, B.; Hu, P.; Wang, Z. J. *J. Org. Chem.* **2012**, *77*, 11161. (b) Xu, K.; Wang, Z.; Zhang, J.; Yu, L.; Tan, J. *Org. Lett.* **2015**, *17*, 4476.

(16) (a) Zhao, X.; Zhang, Y.; Wang, J. *Chem. Commun.* **2012**, *48*, 10162. (b) Du, Z.; Xing, Y.; Lu, P.; Wang, Y. *Org. Lett.* **2015**, *17*, 1192.

(17) (a) Zhou, N.; Xie, T.; Liu, L.; Xie, Z. *J. Org. Chem.* **2014**, *79*, 6061. (b) Su, Y.; Sun, X.; Wu, G.; Jiao, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 9808. (c) Yan, R.; Liu, X.; Pan, C.; Zhou, X.; Li, X.; Kang, X.; Huang, G. *Org. Lett.* **2013**, *15*, 4876. (d) Bluhm, M. E.; Ciesielski, M.; Görls, H.; Döring, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 2962. (e) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. *Chem. Rev.* **2013**, *113*, 6234.

DOI: 10.1021/acs.orglett.5b03509
Org. Lett. XXXX, XXX, XXX−XXX