Organic LETTERS

Letter

pubs.acs.org/OrgLett

Synthesis of Indolizines via Reaction of 2-Substitued Azaarenes with Enals by an Amine-NHC Relay Catalysis

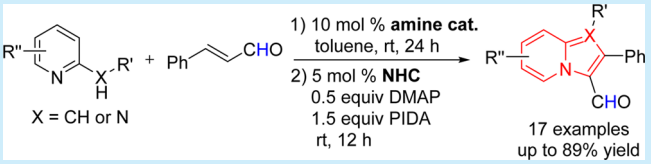
Hongxian Li,[†] Xiangmin Li,[†] Yang Yu,[†] Jianjun Li,[†] Yuan Liu,[†] Hao Li,*[,†] and Wei Wang*[,†,‡]

[†]State Key Laboratory of Bioengineering Reactor, Shanghai Key Laboratory of New Drug Design, and School of Pharmacy, East China University of Science and Technology, 130 Mei-long Road, Shanghai 200237, China

[‡]Department of Chemistry and Chemical Biology, University of New Mexico, Albuquerque, New Mexico 87131-0001, United States

Supporting Information

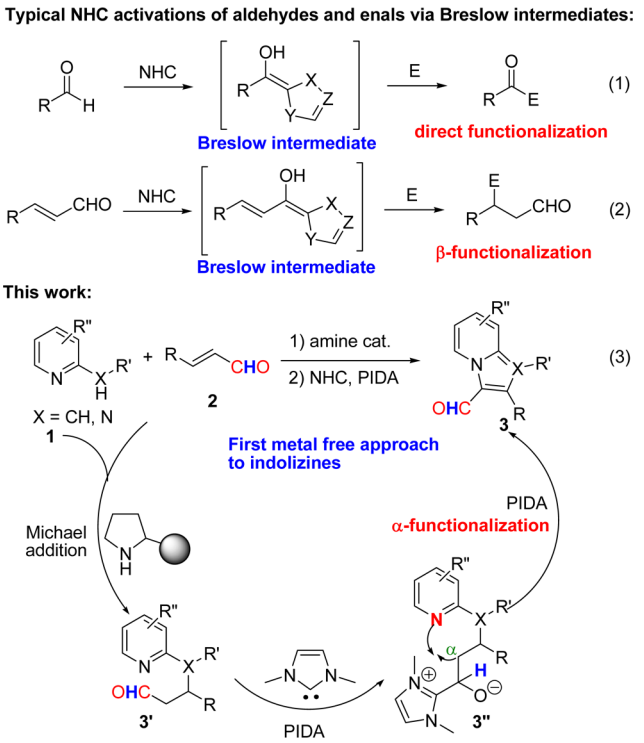
ABSTRACT: A metal-free catalytic strategy for the facile synthesis of biologically relevant molecular architectures indolizines and imidazopyridines has been developed. The process is promoted by amine and *N*-heterocyclic carbene (NHC) relay catalysis via Michael addition-[3 + 2] fusion of simple azaarenes and α,β-unsaturated aldehydes. The preparative power is demonstrated in the synthesis of anxiolytic drug saripidem via two simple one-pot operations with overall 45% yield.



The synthesis of "privileged" structures indolizines and imidazopyridines has received significant attention recently,[1] mainly fueled by their attractive and broad biological properties,[2] such as anti-HIV,[3] anti-inflammatory,[4] and CNS depression agents[5] activities. In addition to the traditional methods such as the Scholtz and the Tschitschibabin reactions,[6] the more efficient catalytic processes have been developed for their preparation, but dominated by transition metal catalysis. The attractive features of these approaches employ readily accessible reactants of alkynes[7−11] or activated alkenes such as α,β-unsaturated carboxylic acids and nitroolefins,[12,13] and pyridines. However, to the best of our knowledge, an organocatalytic formation of indolizines and imidazopyridines has not been reported.

Great success has been achieved in NHC catalysis in the recent past, contributed from many laboratories including Enders, Bode, Rovis, Scheidt, Glorius, Chi, Ye, and others.[14] In typical NHC catalysis with aldehydes, the "Breslow intermediate" is generally formed.[15] The interaction of NHC with aldehydes and enals generates essential enolates (*Umpolung*) and homoenolates for direct[16] (Scheme 1, eq 1) and β-functionalizations (eq 2), respectively.[17] Herein, we wish to report a new NHC promoted (diacetoxyiodo)benzene (PIDA) medicated oxidative C−N bond formation between α-carbon of aldehydes and "N" of pyridine in **3**″ (Scheme 1, eq 3). Importantly, the new bond connection provides the first metal-free approach to heterocyclic structures **3** with a broad reaction scope, capable of producing indolizines and imidazopyridines. Furthermore, by careful manipulation of reaction conditions, we are able to engineer amine and NHC catalysis into a synthetically efficient operation. We found that, unlike the reported cases of metal catalysis with α,β-unsaturated carboxylic acids,[13] in which the essential carboxylic acid serves as activation and leaving group, the versatile aldehyde group is retained in the frameworks, thus giving trisubstituted structures.

Scheme 1. Synthesis of Indolizines via Amine and NHC Carbene Relay Catalysis of Azaarenes and Enals



Such substitution pattern is not easily accessed,[18] but is present in molecules with a wide range of biologically activities.[19]

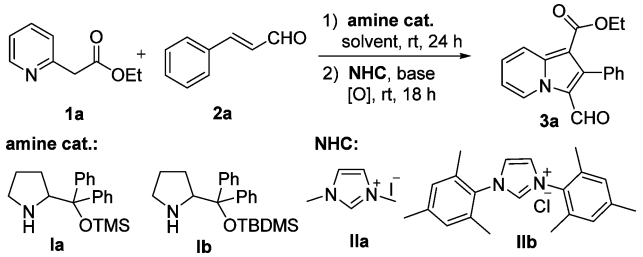
Received: February 23, 2017

DOI: 10.1021/acs.orglett.7b00566
Org. Lett. XXXX, XXX, XXX−XXX

The chemistry was inspired by our recent studies via harnessing new reactivities of vinylpyridines as nonclassic electrophiles for organocatalyzed Michael and aza-Morita–Baylis–Hillman reactions.[20] We designed 2-substituted pyridine derivatives **1** as a new class of nucleophiles for an iminium mediated Michael addition reaction with enals **2**. The adducts then serve as precursors for the subsequent NHC catalyzed [3 + 2] annulation reaction.

The complicated nature of the amine catalyzed Michael addition and subsequent NHC promoted [3 + 2] annulation reaction required probing a number of factors. The simple combination of amine **Ia** (20 mol %) and NHC **IIa** (20 mol %) with 2-pyridylacetate **1a** (0.2 mmol) and *trans*-cinnamic aldehyde **2a** (0.4 mmol) in the presence of 4-dimethylaminopyridine (DMAP) (3.0 equiv) as base and PIDA as oxidant (4.0 equiv) in toluene did not produce the desired product **3a** rather than a complicated mixture (Table 1). However, we found that

Table 1. Optimization of Reaction Conditions[a]



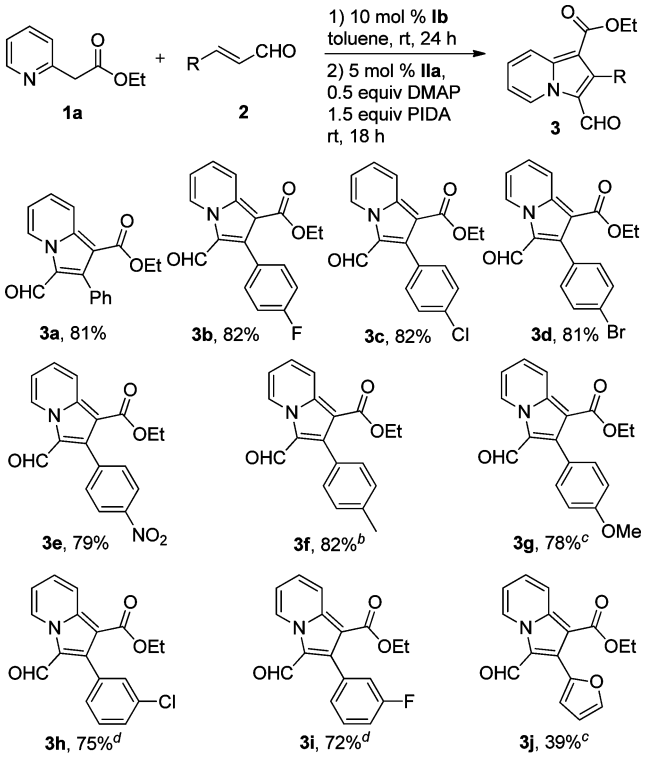
entry	cat (mol %)	[O] (equiv)	base (equiv)	yield (%)[b]
1	**Ia** (20)/**IIa** (20)	PIDA (4)	DMAP (3)	61
2	**Ia** (20)/**IIa** (20)		DMAP (3)	
3	**Ia** (20)/-	PIDA (4)	DMAP (3)	trace
4	**Ia** (20)/**IIb** (20)	PIDA (4)	DMAP (3)	trace
5	**Ib** (20)/**IIa** (20)	PIDA (4)	DMAP (3)	75
6	**Ib** (20)/**IIa** (20)	PIDA (4)	TEA (3)	71
7	**Ib** (20)/**IIa** (20)	PIDA (4)	DBU (3)	trace
8	**Ib** (20)/**IIa** (20)	CAN (4)	DMAP (3)	trace
9	**Ib** (20)/**IIa** (20)	H_2O_2 (4)	DMAP (3)	22
10	**Ib** (20)/**IIa** (20)	PIDA (1.5)	DMAP (3)	79
11	**Ib** (10)/**IIa** (5)	PIDA (1.5)	DMAP (3)	72
12	**Ib** (10)/**IIa** (5)	PIDA (1.5)	DMAP (1.5)	76
13	**Ib** (10)/**IIa** (5)	PIDA (1.5)	DMAP (0.5)	81

[a]Unless specified, 2-pyridylacetate **1a** (0.2 mmol), *trans*-cinnamic aldehyde **2a** (0.4 mmol), and amine catalysts (20 mol %) in 2 mL of toluene were stirred for 24 h. Then NHC catalyst (20 mol %), oxidant (4 equiv) and DMAP (3 equiv) were added into the reaction mixture for another 18 h at rt. [b]Isolated yield.

the preformation of the Michael adduct **3a**′ from the reaction of **1a** with **2a** in the presence of amine catalysts **Ia** (20 mol %) in toluene for 24 h was necessary. Without requiring purification of the Michael adduct, direct addition of **IIa**, PIDA, and DMAP (3.0 equiv) into the reaction mixture for another 18 h at rt enabled to deliver the desired trisubstituted indolizine product **3a** in 61% yield (entry 1). The oxidant was essential for the cyclolization reaction. The process could not occur without it (entry 2). Furthermore, the carbene catalyst was also very important for this reaction. Only a trace amount of product was detected when NHC **IIa** was removed from the reaction system (entry 3). The solvent screening revealed that toluene was the choice for this reaction.[21] The bulky carbene catalyst **IIb** gave poorer results (entry 4). However, the hindered amine catalyst **Ib** delivered the better outcome (75% yield, entry 5). Different bases were tested for this process too (entries 6 and 7). TEA afforded a similar yield to that of DMAP (entry 6). However, no reaction took place when 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used (entry 7). Further optimization of reaction conditions revealed that the oxidant was critical for this reaction as well. Other oxidants produced inferior yields (entries 8 and 9). Decreasing the amount of PIDA to 1.5 equiv could still retain the similar reaction efficiency (entry 10). A similar trend was observed with decreasing the catalyst loadings to 10 mol % of **Ib** and 5 mol % of **IIa** (entry 11) and base DMAP (0.5 equiv, entries 12 and 13).

With the optimal conditions in hand, we turned our attention to probe the scope of α,β-unsaturated aldehydes for this new process (Scheme 2). The results of the studies showed that the

Scheme 2. Scope of α,β-Unsaturated Aldehydes[a]



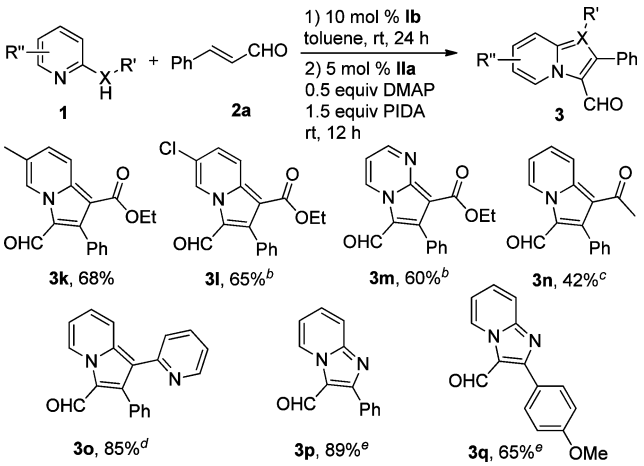
[a]Reaction conditions: unless specified, see experimental section, Supporting Information. [b]The first reaction was run for 3 d at rt. [c]The first reaction was run for 7 d at rt. [d]Twenty mol % **A** was used in the second step.

reactions serve as a general approach to structurally diverse indolizines **3**. Both electron-withdrawing and -donating substituents on enals were tolerated, providing the products in good yields. Highly active enals bearing electron-withdrawing groups proceeded more smoothly (**3b–e** and **3h–i**). Longer reaction time were required for the Michael addition reaction for electron donating enals but without affecting the total yields (**3f–g**). Moreover, generally difficult enal (much less reactive) (*E*)-3-(furan-2-yl)acrylaldehyde **2j** still delivered product **3j** in 39% yield.

Next, we examined the structural effect of pyridine components using *trans*-cinnamic aldehyde **2a** as a reaction partner (Scheme 3). Electron-donating and-withdrawing

DOI: 10.1021/acs.orglett.7b00566
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 3. Scopes of Azaarenes[a]



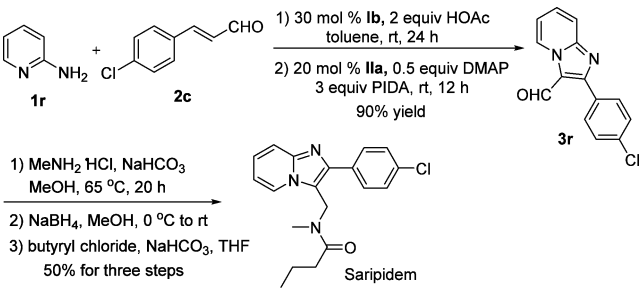
[a]Isolated yields. [b]The first reaction was run for 4 d at 50 °C. [c]Twenty mol % **A** was used in the second step. [d]The first reaction was run for 6 d at 50 °C. [e]Thirty mol % **II** and 2 equiv of HOAc were used in the first step; 20 mol % **A** and 3 equiv of PIDA were used in the second step.

groups have limited impact on the process (**3k–l**). It is noted that the Michael addition step was sluggish for **1l**. Notably, medicinally interesting substrate ethyl 2-(pyrimidin-2-yl)acetate **1m** displayed a comparable reactivity to form the corresponding product **3m** in 60% yield. In addition to esters, ketone was found as an alternative to afford indolizine **3n** bearing a versatile carbonyl functionality. Furthermore, we also identified pyridyl as an activating moiety, thus delivering new bispyridine structure **3o** in high yield (85%). Finally, in addition to carbon-centered nucleophiles, we found 2-aminopyridines "N" could serve as effective Michael donors for the conjugate addition reaction assisted by HOAc (2.0 equiv). Importantly, under the standard conditions, the adducts were smoothly transformed into medicinally relevant imidazopyridines **3p–q**, the scaffold of anxiolytic drugs saripidem, zolpidem, and alpidem.[22]

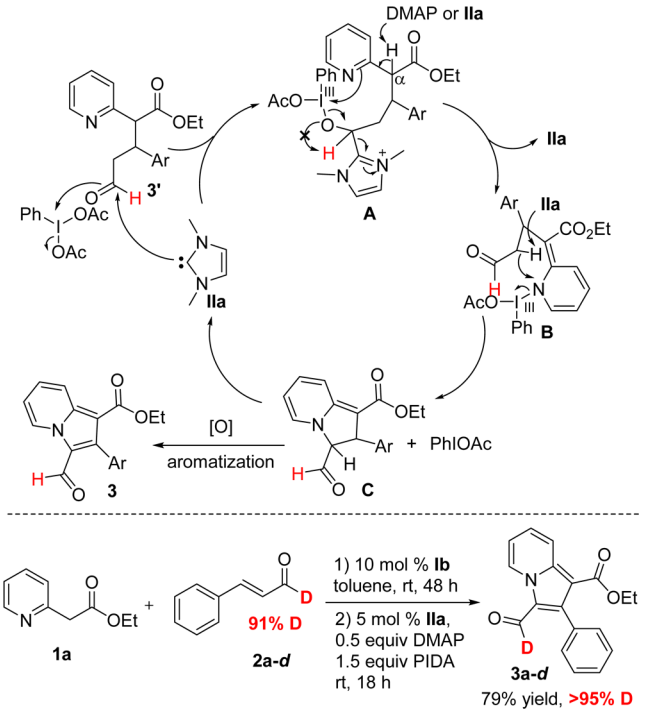
The synthetic utility of the process is demonstrated in the synthesis of biologically valuable targets. The versatile aldehyde handle in imidazo[1,2-α]pyridine **3r** produced from the reaction of 2-aminopyridine **1r** with enal **2c** under the slightly modified conditions enabled to prepare saripidem, an anxiolytic drug,[22a,23] efficiently executed by a 3-step "one-pot" operation with overall 45% yield (Scheme 4). Reductive amination with aldehyde **3r** was followed by acylation delivered the target.

A tentative catalytic cycle of the **IIa** promoted cyclization reaction is proposed (Scheme 5). The **IIa** catalyzes the

Scheme 4. Efficient Synthesis of Imidazopyridine Drug Saripidem



Scheme 5. Proposed Catalytic Cycle and Deuterated Labeling Study



complexation of the oxygen anion, produced from **IIa** and aldehyde adduct, with PIDA to give **A**. Such a complexation blocks 1,2-H migration to oxygen anion to form the critical Breslow intermediate in a typical NHC carbene catalysis. This hypothesis is supported by our deuterium labeling experiment using deuterated aldehyde **2a–d** as reactant (Scheme 5). We observed that the deuterium was retained in the aldehyde product **3a–d** under the above optimized reaction conditions. An intramolecular attack takes place subsequently between the electrophilic I(III) and the enhanced nucleophilic pyridine "N" by a base (DMAP or **IIa**) assisted deprotonation of acidic α-H[24] and concurrent release of NHC **IIa** to give intermediate aldehyde **B**. An intramolecular cyclization between the nucleophilic α-carbon promoted by **IIa** deprotonation of α-H and pyridine "N" produces intermediate **C** and PhIOAc. Finally, oxidative aromatization of the resulting intermediate **C** by PIDA delivers the indolizine product **3**.

In summary, we have developed the first metal-free strategy for the synthesis of indolizines and imidazopyridines by using an efficient Michael-[3 + 2] annulation reaction from azaarenes and α,β-unsaturated aldehydes. The reactions are catalyzed by the amine and NHC relay catalysis in the presence of PIDA as oxidant with broad scope. Notably, a new reactivity without forming a Breslow intermediate is harnessed for a new bond construction between α-carbon of aldehydes and "N" of pyridines. The synthetic efficiency is demonstrated for practical synthesis of anxiolytic drug saripidem through two operationally simple "one-pot" reactions in overall 45% yield. The detailed mechanistic insights of NHC-PIDA mediated process and further exploration of the new reactivity for novel transformations are under investigation in our laboratories.

DOI: 10.1021/acs.orglett.7b00566
Org. Lett. XXXX, XXX, XXX–XXX

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00566.

Experiment details and spectroscopic data (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: hli77@ecust.edu.cn.
*E-mail: wwang@unm.edu.

ORCID

Wei Wang: 0000-0001-6043-0860

Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support of this research from the program for the National Science Foundation of China (21372073, 21572054, and 21572055), the Fundamental Research Funds for the Central Universities, and the China 111 Project is gratefully acknowledged.

■ REFERENCES

(1) For reviews, see: (a) Shipman, M. In *Science of Synthesis*; Thomas, E. J., Ed;, Georg Thieme: Stuttgart, 2001; Vol. *10*, p 745. (b) El-Ashry, E.-S. H.; Ibrahim, I. E.-S. l. *Adv. Heterocycl. Chem.* **2003**, *84*, 71. (c) Majumdar, K. C.; Debnath, P.; Roy, N.; De, B. *Curr. Org. Chem.* **2011**, *15*, 1760.

(2) For reviews, see: (a) Flitsch, W. In *Comprehensive Heterocyclic Chemistry II*, Katritzky, A. R., Rees, C.W., Scriven, E. F. V., Ed., Pergamon Press: Oxford, 1996; p 237. (b) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*; Wiley-VCH: Weinheim, 2003. (c) Singh, G. S.; Mmatli, E. E. *Eur. J. Med. Chem.* **2011**, *46*, 5237.

(3) Facompre, M.; Tardy, C.; Bal-Mahieu, C.; Colson, P.; Perez, C.; Manzanares, I.; Cuevas, C.; Bailly, C. *Cancer Res.* **2003**, *63*, 7392.

(4) (a) Molyneux, R. J.; James, L. F. *Science* **1982**, *216*, 190. (b) Oslund, R. C.; Cermak, N.; Gelb, M. H. *J. Med. Chem.* **2008**, *51*, 4708.

(5) Harrell, W. B. *J. Pharm. Sci.* **1970**, *59*, 275.

(6) Scholtz reaction: (a) Scholtz, M. *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 734. (b) Boekelheide, V.; Windgassen, R. J., Jr. *J. Am. Chem. Soc.* **1959**, *81*, 1456. Tschitschibabin reaction: (a1) Tschitschibabin, A. E. *Ber. Dtsch. Chem. Ges. B* **1927**, *60*, 1607. (b1) Hurst, J.; Melton, T.; Wibberley, D. G. *J. Chem. Soc.* **1965**, *46*, 2948. Dipolar cycloadditions: (a2) Pohjala, E. *Tetrahedron Lett.* **1972**, *13*, 2585. (b2) Fang, X.; Wu, Y. M.; Deng, J.; Wang, S. W. *Tetrahedron* **2004**, *60*, 5487.

(7) Cu and Au catalyzed intramolecular cyclizations: (a) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074. (b) Schwier, T.; Sromek, A. W.; Yap, D. M. L.; Chernyak, D.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 9868. (c) Hardin, A. R.; Sarpong, R. *Org. Lett.* **2007**, *9*, 4547. (d) Zhang, L.; Li, X.; Liu, Y.; Zhang, D. *Chem. Commun.* **2015**, *51*, 6633.

(8) Cu and Au catalyzed intermolecular cyclizations: (a) Chuprakov, S.; Hwang, F. W.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 4757. (b) Helan, V.; Gulevich, A. V.; Gevorgyan, V. *Chem. Sci.* **2015**, *6*, 1928.

(9) Sm catalyzed intermolecular cyclizations: Wang, X.; Li, S.-Y.; Pan, Y.-M.; Wang, H.-S.; Liang, H.; Chen, Z.-F.; Qin, X.-H. *Org. Lett.* **2014**, *16*, 580.

(10) Cu and Au catalyzed three-component reactions: (a) Yan, B.; Liu, Y. *Org. Lett.* **2007**, *9*, 4323. (b) Albaladejo, M. J.; Alonso, F.; Yus, M. *Chem. - Eur. J.* **2013**, *19*, 5242.

(11) Palladium catalyzed cyclizations: (a) Chai, D. I.; Lautens, M. *J. Org. Chem.* **2009**, *74*, 3054. (b) Ye, S.; Liu, J.; Wu, J. *Chem. Commun.* **2012**, *48*, 5028. (c) Aggarwal, T.; Jha, R. R.; Tiwari, R. K.; Kumar, S.; Kotla, S. K. R.; Kumar, S.; Verma, A. K. *Org. Lett.* **2012**, *14*, 5184.

(12) Barluenga, J.; Lonzi, G.; Riesgo, L.; López, L. A.; Tomás, M. *J. Am. Chem. Soc.* **2010**, *132*, 13200.

(13) Yang, Y.-Z.; Xie, C.-S.; Xie, Y.-H.; Zhang, Y.-H. *Org. Lett.* **2012**, *14*, 957.

(14) For selected reviews, see: (a) Biju, A. T.; Kuhl, N.; Glorius, F. *Acc. Chem. Res.* **2011**, *44*, 1182. (b) Nair, V.; Menon, R. S.; Biju, A. T.; Sinu, C. R.; Paul, R. R.; Jose, A.; Sreekumar, V. *Chem. Soc. Rev.* **2011**, *40*, 5336. (c) Grossmann, A.; Enders, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 314. (d) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511. (e) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev.* **2015**, *115*, 9307.

(15) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719.

(16) For selected examples of NHC catalyzed direct functionalizations: (a) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4558. (b) Liu, Q.; Perreault, S.; Rovis, T. *J. Am. Chem. Soc.* **2008**, *130*, 14066. (c) Fang, X.; Chen, X.; Lv, H.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 11782. (d) Biju, A. T.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 9761.

(17) For selected examples of NHC catalyzed β-functionalizations: (a) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370. (b) Nair, V.; Vellalath, S.; Poonoth, M.; Suresh, E. *J. Am. Chem. Soc.* **2006**, *128*, 8736. (c) Lathrop, S. P.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 13628. (d) Cardinal-David, B.; Raup, D. E. A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 5345.

(18) (a) Mohan, D. C.; Ravi, C.; Pappula, V.; Adimurthy, S. *J. Org. Chem.* **2015**, *80*, 6846. (b) Liu, R.-R.; Hong, J.-J.; Lu, C.-J.; Xu, M.; Gao, J.-R.; Jia, Y.-X. *Org. Lett.* **2015**, *17*, 3050.

(19) (a) Bailly, C. *Curr. Med. Chem.: Anti-Cancer Agents* **2004**, *4*, 363. (b) Sharma, V.; Kumar, V. *Med. Chem. Res.* **2014**, *23*, 3593.

(20) (a) Wang, S.-N.; Li, X.-M.; Liu, H.-W.; Xu, L.; Zhuang, J.-C.; Li, J.; Li, H.; Wang, W. *J. Am. Chem. Soc.* **2015**, *137*, 2303. (b) Chen, J.; Li, J.-J.; Wang, J.-Z.; Li, H.; Wang, W.; Guo, Y.-W. *Org. Lett.* **2015**, *17*, 2214.

(21) 32% in CH_3CN, 54% in THF, 47% in $CHCl_3$, 35% in $ClCH_2CH_2Cl$, 21% in DMF.

(22) (a) Okubo, T.; Yoshikawa, R.; Chaki, S.; Okuyama, S.; Nakazato, A. *Bioorg. Med. Chem.* **2004**, *12*, 423. (b) Du, B.; Shan, A.; Zhang, Y.; Zhong, X.; Chen, D.; Cai, K. *Am. J. Med. Sci.* **2014**, *347*, 178.

(23) Wang, H.-G.; Wang, Y.; Liang, D.-D.; Liu, L.-Y.; Zhang, J.-C.; Zhu, Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 5678.

(24) For the related studies, see: (a) Liang, D.-D.; He, Y.-M.; Liu, L.-Y.; Zhu, Q. *Org. Lett.* **2013**, *15*, 3476. (b) Rao, D. N.; Rasheed, S.; Vishwakarma, R. A.; Das, P. *RSC Adv.* **2014**, *4*, 25600.

DOI: 10.1021/acs.orglett.7b00566
Org. Lett. XXXX, XXX, XXX−XXX