Organic LETTERS

Letter

pubs.acs.org/OrgLett

N-Heterocyclic Carbene Catalyzed [4 + 2] Annulation Reactions with in Situ Generated Heterocyclic *ortho*-Quinodimethanes

Jianfeng Xu,* Shiru Yuan, and Maozhong Miao

Department of Chemistry, Zhejiang Sci-Tech University, Hangzhou 310018, PR China

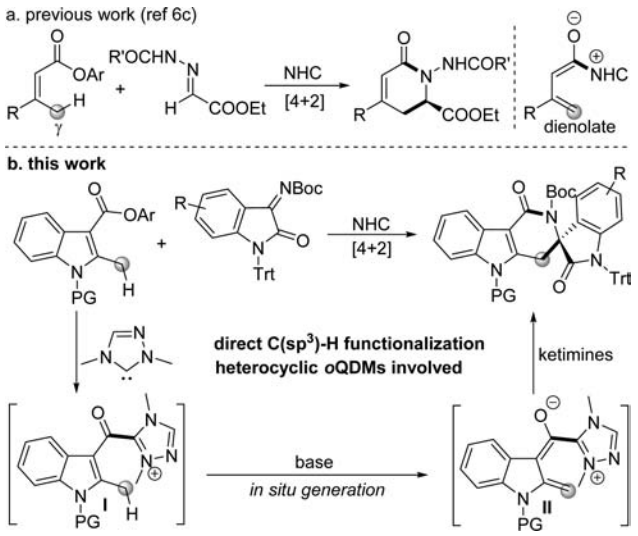
Supporting Information

ABSTRACT: An efficient strategy for the in situ generation of heterocyclic *ortho*-quinodimethanes (*o*QDMs) from 2-methyl-heteroarene-3-carboxylic esters by *N*-heterocyclic carbene (NHC) catalysis is disclosed. These heterocyclic *o*QDMs undergo highly enantioselective [4 + 2] annulation reactions with isatin-derived ketimines to afford optically pure heteroarene-fused *δ*-lactams bearing a quaternary stereogenic center. The main features of this reaction include challenging direct C(sp^3)−H bond functionalizations, excellent enantioselectivities, readily available starting materials, mild reaction conditions, high efficiency, and operational simplicity.

Heterocyclic *ortho*-quinodimethanes (*o*QDMs) represent a class of highly reactive intermediates that have been widely exploited for the construction of complex polycyclic heteroaromatic compounds with multiple stereogenic centers through direct C(sp^3)−H bond functionalization.[1] Traditionally, heterocyclic *o*QDMs can be obtained by a variety of methods[2] including flash vacuum pyrolysis of cyclohexene-fused heterocycles,[2a,b] tautomerization of 2-methyl-heteroarene-3-imino derivatives,[2c,d] 1,4-elimination of vicinal halomethyl substituted heterocycles,[2e,f] cheletropic extrusion of sulfur dioxide from heteroaromatic-fused-3-sulfolenes,[2g,h] and thermal ring-opening of heteroaryl-cyclobutene derivatives.[2i] Nevertheless, none of those dearomative approaches have been applied in the catalytic asymmetric preparation of enantiomerically enriched molecules due to their typical requirement of high temperatures and harsh reaction conditions.[3] Recently, accompanied by the rapid development of organocataylsis, several elegant catalytic asymmetric protocols have been successfully established to synthesize chiral compounds with in situ generated catalyst-bound heterocyclic *o*QDMs.[4] In 2011, Melchiorre's group reported the pioneering secondary-amine-catalyzed enantioselective Diels−Alder reaction of heterocyclic *o*QDMs with alkenes to afford optically pure tetrahydrocarbazoles.[4a,b] Later, Chi's group realized a [4 + 2] annulation reaction of heterocyclic *o*QDMs with ketones to furnish indole-fused *δ*-lactones via oxidative *N*-heterocyclic carbene (NHC) catalysis.[4c] However, despite the fact that the catalytic asymmetric annulation reactions of heterocyclic *o*QDMs with unsaturated C−C bonds and C−O bonds have been well studied, to the best of our knowledge, the corresponding reactions with unsaturated C−N bonds remain an issue to be addressed. Herein we wish to disclose our recent progress on developing a highly enantioselective [4 + 2] annulation reaction of 2-methyl-heteroarene-3-carboxylic esters with isatin-derived ketimines using in situ generated heterocyclic *o*QDMs as the key intermediates.

In the past decade, *N*-heterocyclic carbene (NHC) catalysis has emerged as a powerful tool for the construction of structurally complex and biologically active compounds.[5] Carboxylic esters are inexpensive, readily available, and bench stable substrates; we are interested in the activation of carboxylic esters via NHC catalysis for asymmetric synthesis.[6] During our recent endeavors toward the direct *γ*-functionalization of *α*,*β*-unsaturated carboxylic esters via in situ generated NHC-bound dienolate intermediates (Scheme 1a),[6c] we envisioned that when 2-methyl-indole-3-carboxylic esters were employed as the starting materials, addition of NHC catalyst to

Scheme 1. Previous Work and This Work with a Projected Working Hypothesis



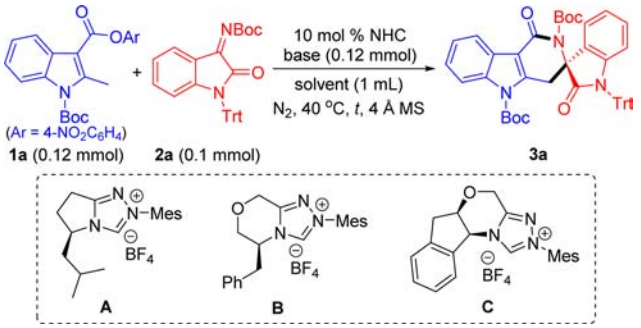
Received: June 22, 2016
Published: July 8, 2016

DOI: 10.1021/acs.orglett.6b01831
Org. Lett. 2016, 18, 3822−3825

esters would form the corresponding NHC-bound acyl azolium intermediates **I** with subsequent deprotonation of intermediates **I** affording NHC-bound indole-2,3-quinodimethane intermediates **II**, which could undergo formal [4 + 2] annulation reactions with isatin-derived ketimines to furnish enantiomerically enriched indole-fused δ-lactams bearing a quaternary stereogenic center (Scheme 1b). Notably, indole-fused δ-lactams are common scaffolds that widely exist in many pharmaceuticals and biologically active compounds such as 5-HT_3 antagonist[7a,b] and MK2 inhibitors.[7c] Meanwhile, indole-fused δ-lactams also behave as vital precursors in the preparation of γ-carbolines[8a] and tetrahydro-γ-carboline.[8b]

Experimentally, we started to test the feasibility of our hypothesis by using *N*-Boc-2-methyl-indole-3-carboxylic ester **1a** and isatin-derived ketimine **2a** as the model substrates, and the key results are summarized in Table 1. To our delight, when

Table 1. Optimization of Reaction Conditions[a]



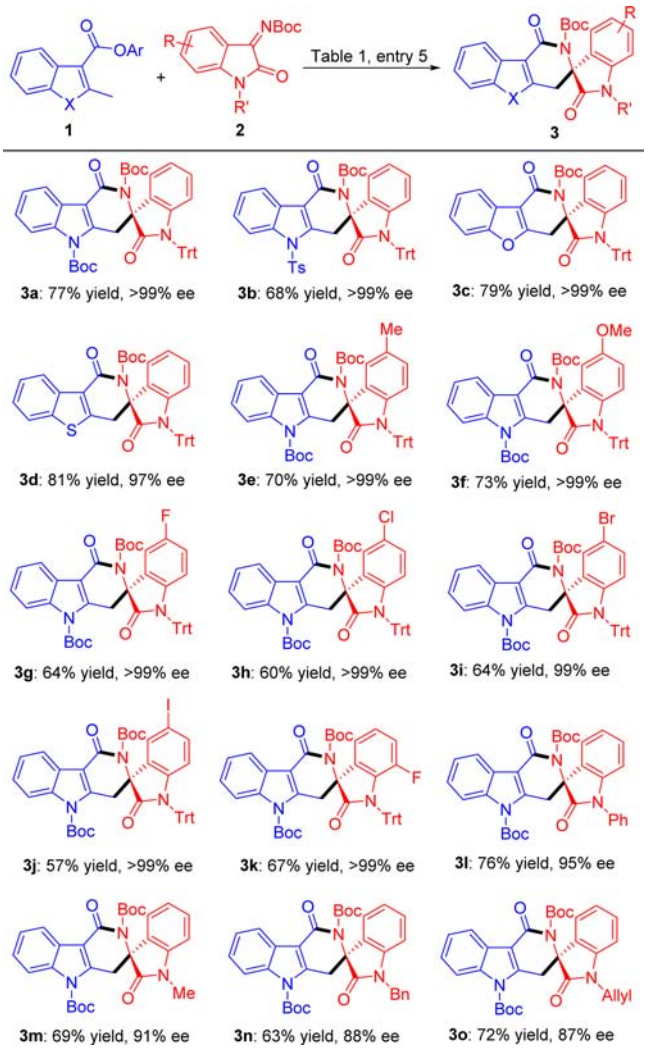
entry	cat.	base	solvent	*t* (h)	yield (%)[b]	ee (%)[c]
1	**A**	K_2CO_3	THF	24	43	98
2	**A**	Cs_2CO_3	THF	24	56	98
3	**A**	DBU	THF	12	65	98
4	**B**	DBU	THF	12	61	98
5	**C**	**DBU**	**THF**	**12**	**77**	**>99**
6	**C**	DBU	toluene	12	58	>99
7	**C**	DBU	$CHCl_3$	12	41	>99
8	**C**	DBU	EtOAc	12	71	>99
9	**C**	DBU	CH_3CN	12	53	98
10[d]	**C**	DBU	THF	24	51	>99
11		DBU	THF	24	trace	

[a]Reaction conditions unless otherwise specified: **1a** (0.12 mmol), **2a** (0.1 mmol), NHC (10 mol %), base (0.12 mmol), solvent (1 mL), 4 Å MS (100 mg, powder), 40 °C for 24 or 12 h. [b]Isolated yield based on **2a**. [c]Enantiomeric excess of **3a**, determined via chiral-phase HPLC analysis; absolute configuration of the major enantiomer was assigned based on X-ray structure of **3i** (see Figure 1 and the Supporting Information). [d]5 mol % of NHC **C** was used. Trt = trityl, Mes =2,4,6-trimethylphenyl, DBU = 1,8-diazabicycloundec-7-ene.

the L-leucine-derived NHC precatalyst **A**[9] was used as an NHC catalyst and K_2CO_3 was used as a base, after 24 h the desired [4 + 2] annulation product, **3a**, was successfully isolated in 43% yield and 98% ee (Table 1, entry 1). Replacing K_2CO_3 with Cs_2CO_3 led to **3a** with an improved 56% yield (entry 2). Strong organic base such as 1,8-diazabicycloundec-7-ene (DBU) could mediate this reaction more efficiently by affording **3a** in 65% yield after 12 h (entry 3). With DBU as the optimal base, we next set out to investigate the NHC precatalyst. The use of L-phenylalanine-derived NHC precatalyst **B**[10] as an NHC catalyst resulted in a slight decrease in yield (entry 4), whereas aminoindanol-derived NHC precatalyst **C**,[11] first reported by Bode and co-workers, furnished **3a** in 77% isolated yield and >99% ee (entry 5). Further studies on the solvent effect suggested that a variety of polar and nonpolar solvents are all compatible with this reaction, and tetrahydrofuran (THF) gave **3a** in the highest yield and ee (entries 5–9). Finally, an attempt to slow down the catalyst loading was not satisfactory because 5 mol % of precatalyst **C** not only prolonged the reaction time but also led to a drop in yield (entry 10). Without NHC, only a trace of desired product **3a** was observed from thin-layer chromatography (entry 11).

With the optimized reaction conditions in hand (Table 1, entry 5), we then evaluated the scope of this formal [4 + 2] annulation reaction (Scheme 2). The use of *N*-tosyl (Ts)-

Scheme 2. Scope of Reactions[a]



[a]Reaction conditions: **1** (0.12 mmol), **2** (0.1 mmol), NHC **C** (10 mol %), DBU (0.12 mmol), THF (1 mL), 4 Å MS (100 mg, powder), 40 °C for 12 h. Isolated yields based on **2**; ee's were determined via chiral phase HPLC analysis.

protected 2-methyl-indole-3-carboxylic esters afforded desired product **3b** in 68% yield and >99% ee. Remarkably, replacing the indole moiety of the ester substrate with other heterocycles such as benzofuran and benzothiophene could also successfully formed the corresponding heterocyclic *o*QDM intermediates, leading to products **3c** and **3d** in good yields and excellent

DOI: 10.1021/acs.orglett.6b01831
Org. Lett. 2016, 18, 3822–3825

enantioselectivities. A broad range of ketimines with diverse electronic and steric properties on the isatin phenyl ring were next explored. The use of 5-Me- and 5-OMe-substituted isatin-derived ketimines furnished the desired products **3e** and **3f** in 70% yield/>99% ee and 73% yield/>99% ee, respectively. Ketimines with electron-withdrawing substituents such as 5-F, 5-Cl, 5-Br, 5-I, and 7-F on their isatin phenyl ring were all suitable substrates for this reaction, resulting in the corresponding products **3g−k** in around 60% yield and >99% ee. The substitution patterns on the isatin lactam ring were also investigated. *N*-Phenyl-substituted isatin-derived ketimine formed product **3l** in 76% yield and 95% ee. The employment of a less bulky alkyl protecting group such as Me, Bn, and Allyl was found to be compatible under the optimal conditions, giving desired products **3m−o** in good yields and around 90% ee.

To determine the absolute configuration of the chiral heteroarene-fused *δ*-lactam products, a single crystal of compound **3i** was isolated for X-ray crystallographic analysis (Figure 1), and the newly formed stereogenic center of **3i** was

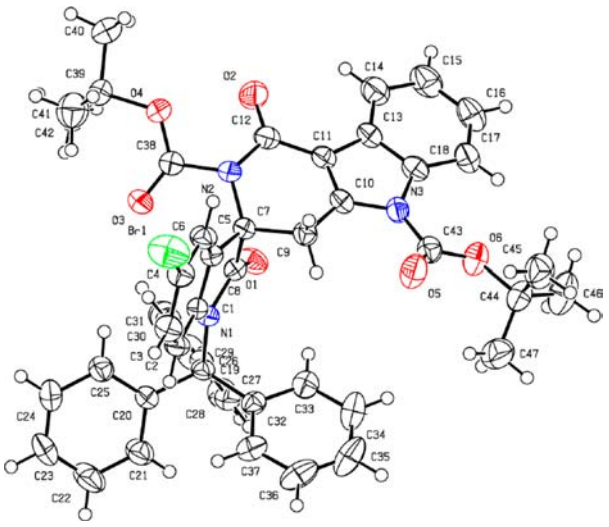


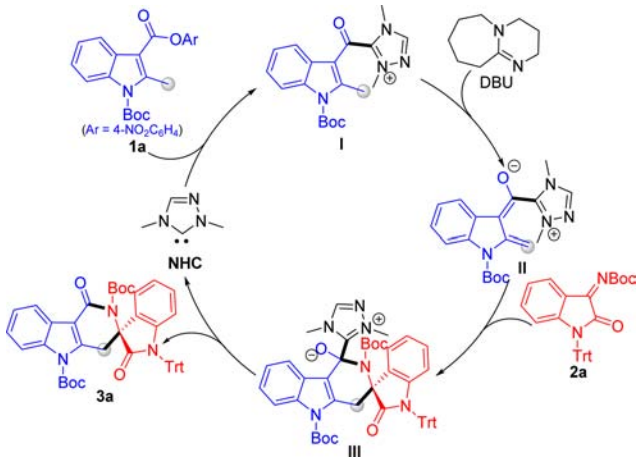
Figure 1. ORTEP diagram of **3i**.

confirmed to be (*S*).[12] The configurations of other chiral products were assigned on the assumption of a uniform mechanistic pathway.

A postulated catalytic cycle is depicted in Scheme 3. Reaction of *N*-Boc-2-methyl-indole-3-carboxylic ester **1a** with NHC catalyst forms NHC-bound acyl azolium intermediate **I**. DBU-mediated deprotonation on the indole benzylic sp^3 carbon of NHC-bound acyl azolium intermediate **I** successfully affords indole-2,3-quinodimethane intermediate **II**. This key indole-2,3-quinodimethane intermediate, **II**, behaves as a 1,4-dipolarophile, which undergoes a Mannich-type addition with isatin-derived ketimine **2a** followed by lactamization to furnish intermediate **III**. Elimination of the NHC catalyst from intermediate **III** eventually releases indole-fused *δ*-lactam **3a** as the annulation product.

The trityl (Trt) protecting group that was employed in this reaction not only helped to improve the enantioselectivites of the desired products (compared **3a** with **3l**, **3m**, **3n**, and **3o**) but also can be readily removed under mild reaction conditions. For instance, both of the Trt and Boc protecting groups were successfully removed by treatment of **3a** with trifluoroacetic

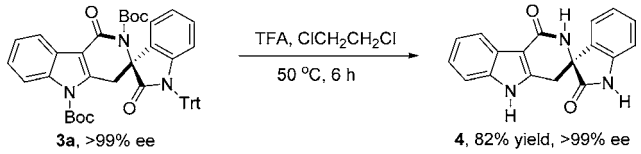
Scheme 3. Postulated Catalytic Cycle[a]



[a]For easy understanding, a simplified NHC structure is used instead of NHC **C**.

acid (TFA) in 1,2-dichloroethane at 50 °C for 6 h, affording **4** in 82% yield without erosion of enantioselectivity (Scheme 4).[13]

Scheme 4. Deprotection of 3a



We have developed an efficient strategy to produce heterocyclic *ortho*-quinodimethanes from 2-methyl-heteroarene-3-carboxylic esters by NHC catalysis. These in situ generated heterocyclic *o*QDMs behave as 1,4-dipolarophiles to undergo a formal [4 + 2] annulation reaction with isatin-derived ketimines to afford chiral heteroarene-fused *δ*-lactams bearing a quaternary stereogenic center in moderate to good yields and high to excellent enantioselectivities. The main features of this reaction include challenging direct C(sp^3)−H bond functionalizations, excellent enantioselectivities, readily available starting materials, mild reaction conditions, high efficiency, and operational simplicity. Further studies to develop a novel method for the direct enantioselective functionalization of more challenging 2-methyl-arene-1-carboxylic esters are being pursued 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.6b01831.

Experimental procedures, full spectroscopic data for all new compounds, and copies of ^{1}H, ^{13}C NMR, and HPLC spectra (PDF)

X-ray crystallographic data for **3i** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jfxu@zstu.edu.cn.

DOI: 10.1021/acs.orglett.6b01831
Org. Lett. 2016, 18, 3822−3825

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the National Natural Science Foundation of China (Grant No. 21302169), the Natural Science Foundation of Zhejiang Province (Grant No. LQ16B020001), the Natural Science Foundation of Zhejiang Sci-Tech University (Grant No. 15062018-Y), as well as the Zhejiang Provincial Top Key Academic Discipline of Chemical Engineering and Technology of Zhejiang Sci-Tech University for financial support.

■ REFERENCES

(1) For general reviews on heteroaromatic oQDMs, see (a) Chou, T. S. *Rev. Heteroatom. Chem.* **1993**, *8*, 65. (b) Collier, S. J.; Storr, R. C. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Gilchrist, T. L., Eds.; Pergamon: New York, 1998; Vol. *10*, pp 25−48. For two reviews of indole-based *o*QDMs, see (c) Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35. (d) Pindur, U.; Erfanian-Abdoust, H. *Chem. Rev.* **1989**, *89*, 1681. For selected examples of furan-based *o*QDMs, see (e) Chou, C. H.; Trahanovsky, W. S. *J. Am. Chem. Soc.* **1986**, *108*, 4138. (f) Leung, M. K.; Trahanovsky, W. S. *J. Am. Chem. Soc.* **1995**, *117*, 841.

(2) For selected traditional examples, see (a) Jullien, J.; Pechine, J. M.; Perez, F.; Piade, J. J. *Tetrahedron Lett.* **1979**, *20*, 3079. (b) Trahanovsky, W. S.; Cassady, T. J.; Woods, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 6691. (c) Gallagher, T.; Magnus, P.; Huffman, J. *J. Am. Chem. Soc.* **1982**, *104*, 1140. (d) Gallagher, T.; Magnus, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 4750. (e) Saroja, B.; Srinivasan, P. C. *Tetrahedron Lett.* **1984**, *25*, 5429. (f) Chadwick, D. J.; Plant, A. *Tetrahedron Lett.* **1987**, *28*, 6085. (g) Chou, T. S.; Tso, H. H. *Org. Prep. Proced. Int.* **1989**, *21*, 257. (h) Chou, T. S.; Chou, S. S. P. *J. Chin. Chem. Soc.* **1992**, *39*, 625. (i) Garcia Martinez, A.; Herrera Fernandez, A.; Moreno Jimenez, F.; Garcia Fraile, A.; Subramanian, L. R.; Hanack, M. *J. Org. Chem.* **1992**, *57*, 1627. For selected recent examples using new methods to form heterocyclic *o*QDMs, see (j) Kuroda, N.; Takahashi, Y.; Yoshinaga, K.; Mukai, C. *Org. Lett.* **2006**, *8*, 1843. (k) Zhou, L.; Zhang, M.; Li, W.; Zhang, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 6542. (l) Zhou, L.; Xu, B.; Zhang, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 9092.

(3) For enantioselective reactions of heterocyclic oQDMs using chiral auxiliaries, see (a) Magnus, P.; Gallagher, T.; Brown, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 2105. (b) Magnus, P.; Cairns, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 217. (c) Zhao, S.; Andrade, R. B. *J. Am. Chem. Soc.* **2013**, *135*, 13334.

(4) (a) Liu, Y.; Nappi, M.; Arceo, E.; Vera, S.; Melchiorre, P. *J. Am. Chem. Soc.* **2011**, *133*, 15212. (b) Liu, Y.; Nappi, M.; Escudero-Adan, E. C.; Melchiorre, P. *Org. Lett.* **2012**, *14*, 1310. (c) Chen, X.; Yang, S.; Song, B.-A.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2013**, *52*, 11134. For another catalytic asymmetric reaction using heterocyclic *o*QDMs as a reactive diene, see (d) Xiao, Y.-C.; Zhou, Q.-Q.; Dong, L.; Liu, T.-Y.; Chen, Y.-C. *Org. Lett.* **2012**, *14*, 5940.

(5) For selected recent reviews on NHC catalysis, see (a) Zeitler, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7506. (b) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (c) Marion, N.; Diez-Gonzalez, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988. (d) Nair, V.; Menon, R. S.; Biju, A. T.; Sinu, C. R.; Paul, R. R.; Jose, A.; Sreekumar, V. *Chem. Soc. Rev.* **2011**, *40*, 5336. (e) Rong, Z. Q.; Zhang, W.; Yang, G. Q.; You, S.-L. *Curr. Org. Chem.* **2011**, *15*, 3077. (f) Cohen, D. T.; Scheidt, K. A. *Chem. Sci.* **2012**, *3*, 53. (g) Douglas, J.; Churchill, G.; Smith, A. D. *Synthesis* **2012**, *44*, 2295. (h) Chen, X.-Y.; Ye, S. *Synlett* **2013**, *24*, 1614. (i) De Sarkar, S.; Biswas, A.; Samanta, R. C.; Studer, A. *Chem. - Eur. J.* **2013**, *19*, 4664. (j) Ryan, S. J.; Candish, L.; Lupton, D. W. *Chem. Soc. Rev.* **2013**, *42*, 4906. (k) Connon, S. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 1203. (l) Mahatthananchai, J.; Bode, J. W. *Acc. Chem. Res.* **2014**, *47*, 696. (m) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. *Nature* **2014**, *510*, 485. (n) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev.* **2015**, *115*, 9307.

(6) (a) Fu, Z.; Xu, J.; Zhu, T.; Leong, W. W. Y.; Chi, Y. R. *Nat. Chem.* **2013**, *5*, 835. (b) Hao, L.; Chen, S.; Xu, J.; Tiwari, B.; Fu, Z.; Li, T.; Lim, J.; Chi, Y. R. *Org. Lett.* **2013**, *15*, 4956. (c) Xu, J.; Jin, Z.; Chi, Y. R. *Org. Lett.* **2013**, *15*, 5028. (d) Xu, J.; Mou, C.; Zhu, T.; Song, B. − A.; Chi, Y. R. *Org. Lett.* **2014**, *16*, 3272. (e) Xu, J.; Chen, X.; Wang, M.; Zheng, P.; Song, B. − A.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2015**, *54*, 5161. (f) Chen, X.; Fong, J. Z. M.; Xu, J.; Mou, C.; Lu, Y.; Yang, S.; Song, B.-A.; Chi, Y. R. *J. Am. Chem. Soc.* **2016**, *138*, 7212. For other selected NHC catalyzed activation of esters, see (g) Ryan, S. J.; Candish, L.; Lupton, D. W. *J. Am. Chem. Soc.* **2009**, *131*, 14176. (h) Chauhan, J.; Enders, D. *Angew. Chem., Int. Ed.* **2014**, *53*, 1485. (i) Fu, Z.; Jiang, K.; Zhu, T.; Torres, J.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2014**, *53*, 6506. (j) West, T. H.; Daniels, D. S. B.; Slawin, A. M. Z.; Smith, A. D. *J. Am. Chem. Soc.* **2014**, *136*, 4476. (k) Zhang, Z.; Zeng, X.; Xie, D.; Chen, D.; Ding, L.; Wang, A.; Yang, L.; Zhong, G. *Org. Lett.* **2015**, *17*, 5052. (l) Que, Y.; Li, T.; Yu, C.; Wang, X.; Yao, C. *J. Org. Chem.* **2015**, *80*, 3289.

(7) (a) Kilpatrick, G. J.; Hagan, R. M.; Oxford, A. W.; North, P. C.; Tyers, M. B. *Drugs Future* **1992**, *17*, 660. (b) Coates, l. H.; Oxford, A. W.; North, P. C.; Price, B. J. European Patent EP 353983, 1994. (c) Revesz, L.; Schlapbach, A.; Aichholz, R.; Dawson, J.; Feifel, R.; Hawtin, S.; Littlewood-Evans, A.; Koch, G.; Kroemer, M.; Möbitz, H.; Scheufler, C.; Velcicky, J.; Huppertz, C. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4719.

(8) (a) Beccalli, E. M.; Broggini, G.; Marchesini, A.; Rossi, E. *Tetrahedron* **2002**, *58*, 6673. (b) Lv, J.; Li, J.; Zhang-Negrerie, D.; Shang, S.; Gao, Q.; Du, Y.; Zhao, K. *Org. Biomol. Chem.* **2013**, *11*, 1929.

(9) Chiang, P. C.; Rommel, M.; Bode, J. W. *J. Am. Chem. Soc.* **2009**, *131*, 8714.

(10) Piel, I.; Steinmetz, M.; Hirano, K.; Fröhlich, R.; Grimme, S.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 4983.

(11) He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418.

(12) CCDC 1484696 contains the supplementary crystallographic data for **3i**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(13) Nakamura, S.; Hyodo, K.; Nakamura, M.; Nakane, D.; Masuda, H. *Chem. - Eur. J.* **2013**, *19*, 7304.

DOI: 10.1021/acs.orglett.6b01831
Org. Lett. 2016, 18, 3822−3825