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Multicomponent Ugi Reaction of Indole-*N*-carboxylic Acids: Expeditious Access to Indole Carboxamide Amino Amides

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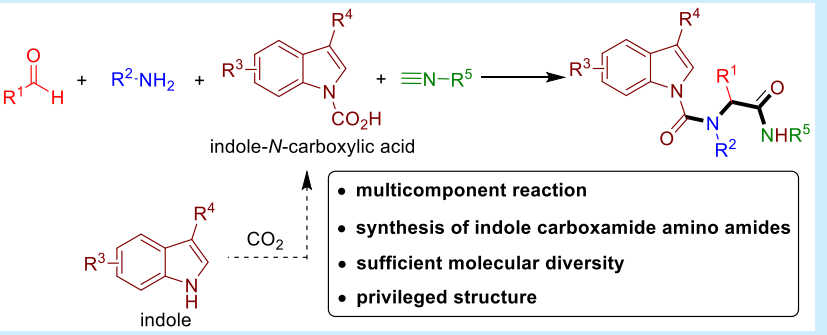
Supporting Information

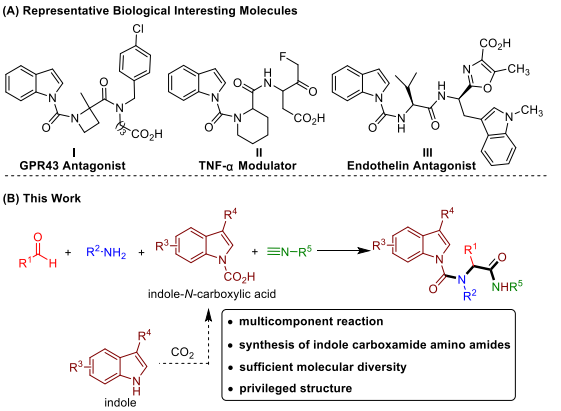


ABSTRACT: A novel multicomponent Ugi-type reaction for the synthesis of indole carboxamide amino amides from aldehydes, amines, isocyanides, and indole-*N*-carboxylic acids, which were simply prepared from indoles and CO_2, is described. This method provides an expeditious and practical access to indole tethered peptide units, along with the achievement of remarkable structural diversity and brevity. Gram-scale reaction was conducted to demonstrate the scalability, and the products could be transformed to new indole derivatives.

Multicomponent reactions (MCRs) are defined as a reaction process involving three or more reactants, and almost all the atoms of the reactants are incorporated in the final products.[1] Due to the advantages of rendering sufficient structural diversity, molecule complexity,[2] atom economy,[3] and simple operation, the MCRs have been widely used in drug discovery, natural products synthesis,[4] biology, and material science.[5] The world-renowned multicomponent Ugi reaction has been used as a useful tool in organic chemistry, especially in peptides and complex macrocyclic compounds synthesis.[6] Notably, the asymmetric Ugi reaction protocol has been well established by Wulff, Wang, Zhu, and Tan, respectively.[7] Interestingly, a Ugi-type five-component reaction was developed since 1961.[8] This process involves the condensation of an alcohol, an amine, a carbonyl compound, an isocyanide, and CO_2 to deliver an α-(alkoxylcarbonylamino)amide. Despite these advances, the investigation of the Ugi reaction for synthesis of biological interesting molecules remains interesting and importance.

As a type of significant privileged structure, indoles are widely distributed in nature and exhibit various important biological activities.[9] Typically, indole carboxamide amino amide derivatives have been constantly researched in medicinal chemistry (Scheme 1A). For example, indole carboxamide amino amide derivatives **I** and **II** were selected as a GPR43 antagonist and TNF-α modulator, respectively.[10] von Geldern and co-workers reported that indole carboxamide amino amide

Scheme 1. Ugi Reaction of Indole-*N*-carboxylic Acid



derivative **III** is an endothelin antagonist with an IC_{50} of 5.9 nM against the endothelin-A receptor.[11] Consequently, the synthesis and functionalization of indoles have received extensive attention.[12] Typically, MCR processes have been frequently applied in indole synthesis and functionalization.[13]

With respect to indoles in the Ugi reaction, the literature mainly relies on a post-Ugi reaction cascade of the indole ring,[14] while the distinct and general reaction mode involving

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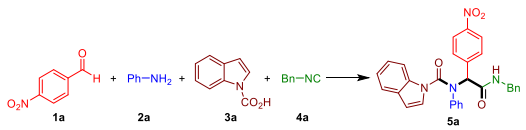
indole as fundamental building blocks are rarely reported. During the course of our study toward indoles and MCRs,[15] we assumed that a rational MCR using a single reactant replacement strategy for indoles could be realized, in which indoles could be transformed to indole-*N*-carboxylic acids and act as versatile building blocks in the Ugi reaction.[16] This process would probably constitute a biologically valuable indole carboxamide amino amide scaffold. Herein, we would like to report a multicomponent Ugi-type reaction-enabled synthesis of indole carboxamide amino amides (Scheme 1B).

We commenced our study by investigating 4-nitrobenzaldehyde **1a**, aniline **2a**, indole-*N*-carboxylic acid **3a**, and benzyl isocyanide **4a**. Initially, these four reagents were mixed together in methanol at room temperature, and a desired product **5a** was indeed formed in 53% yield (Table 1, entry 1).

Table 1. Reaction Optimization[a]



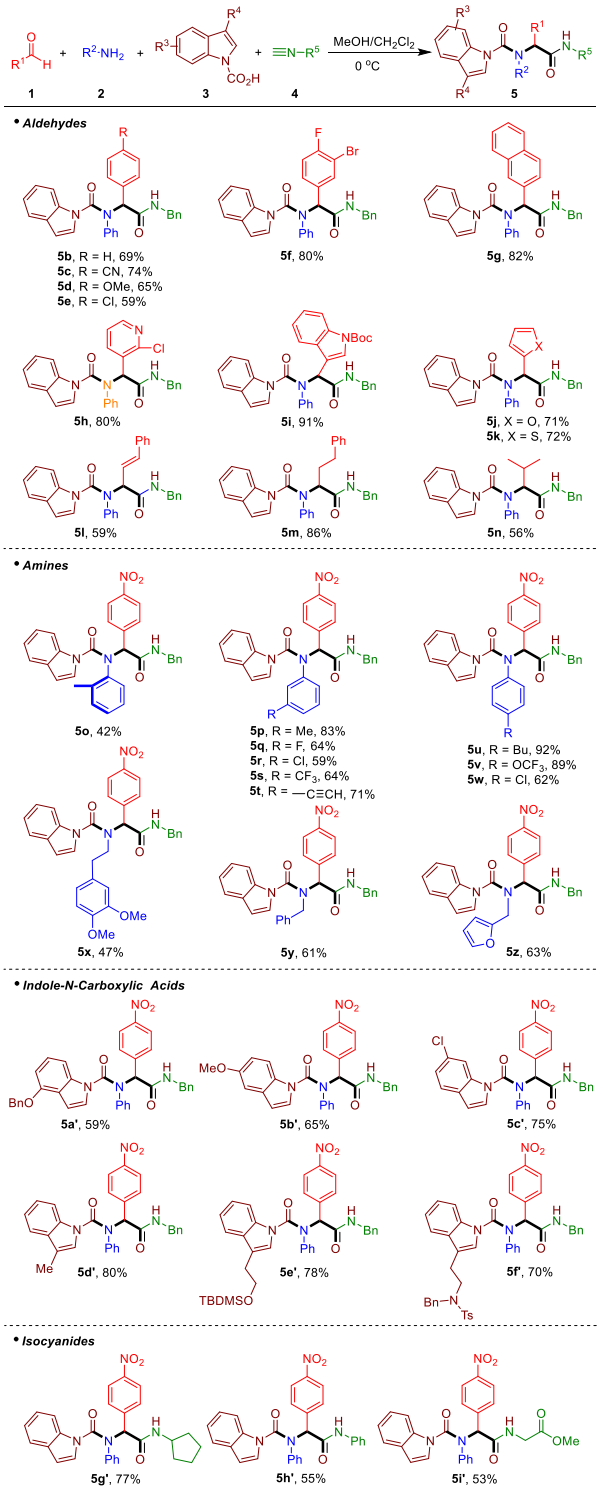
entry	solvent	additive	t (°C)	time (h)	yield (%)
1	MeOH	–	25	12	53
2	EtOH	–	25	12	49
3	THF	–	25	12	29
4	MeCN	–	25	12	33
5	toluene	–	25	12	30
6	CH_2Cl_2	–	25	12	39
7[b]	MeOH	4 Å MS	25	12	41
8	MeOH	–	0	12	55
9	MeOH	–	0	24	67
10	MeOH	–	−10	24	51
11[c]	MeOH/CH_2Cl_2	–	0	24	73
12[c,d]	MeOH/CH_2Cl_2	TsOH	0	24	72
13[c,d]	MeOH/CH_2Cl_2	BF_3–Et_2O	0	24	39

[a]Reaction conditions: **1a** (0.24 mmol), **2a** (0.24 mmol), **3a** (0.2 mmol), and **4a** (0.24 mmol) were added to solvent (2 mL) and stirred at corresponding temperature. [b]30 mg of 4 Å molecule sieve were added. [c]MeOH/CH_2Cl_2 = 2:1. [d]20 mol % additive was added.

The structure of **5a** was identified by standard characterization including ^{1}H NMR, ^{13}CNMR, and mass spectrometry analysis. The next survey of solvents showed that ethanol, THF, CH_3CN, toluene, and CH_2Cl_2 were inferior for leading to lower yields (entries 2−6). Besides, the addition of 4 Å MS in methanol solution would also decrease the yield (entry 7). Interestingly, when the reaction temperature was lowered to 0 °C, the reaction would give a slightly higher yield (entry 8, 55%). When the reaction time was extended to 24 h, the yield would be improved to 67% (entry 9). When the reaction was conducted at −10 °C for 24 h, the yield would decrease (entry 10). The next optimization showed that a mixed solvent of methanol and CH_2Cl_2 would be superior (entry 11). Furthermore, the attempt to add TsOH and BF_3−Et_2O as the catalyst failed and no improvements were observed (entries 12−13).

With the optimized reaction conditions in hand, we next investigated the substrate scope. As shown in Scheme 2, various aldehydes proceeded well in this MCR, and valuable functional groups such as cyano, methoxy, fluoro, chloro, and bromo were tolerated (**5b**−**5f**). 2-Naphthyl aldehyde and heterocyclic aldehydes with the scaffolds of pyridine, indole, furan, and thiophene were compatible in this process to deliver the products in good yields (**5h**−**5k**). In addition, the unsaturated cinnamaldehyde was also applicable (**5l**). The aliphatic aldehydes including 3-phenylpropanal and isobutyraldehyde could engage in this MCR well (**5m** and **5n**).

Scheme 2. Substrate Scope[a]



[a]Reaction conditions: **1** (0.24 mmol), **2** (0.24 mmol), **3** (0.2 mmol), and **4** (0.24 mmol) were added to solvent (MeOH/CH_2Cl_2 = 2:1, 2 mL) under argon and stirred at 0 °C for 24 h. Yields refer to isolated products.

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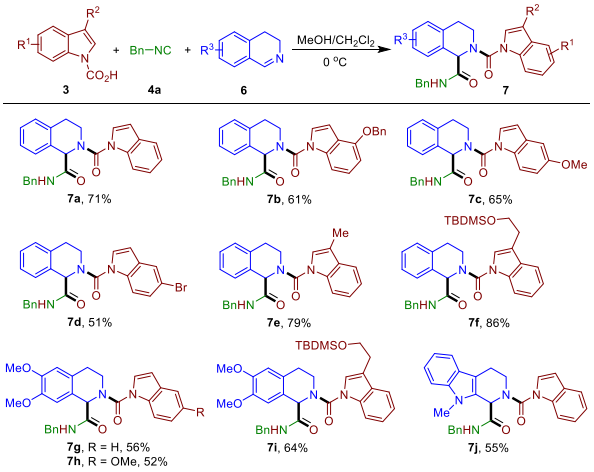
Meanwhile, a variety of amines were also subjected to this process. For anilines, the *ortho*-, *meta*-, and *para*- substitutions were tolerable and various functional groups such as alkane, fluoro, chloro, trifluoromethyl, trifluoromethoxy, and alkyne exhibited tolerance (**5o**−**5w**). Among them, the electron-donating groups could give higher yields than the electron-withdrawing groups. Moreover, the alkyl amines such as 3,4-dimethoxyphenylethyl amine, benzyl amine, and furan-2-ylmethanamine could participate in this MCR smoothly to produce the products in moderate to good yields (**5x**−**5z**). On the other hand, various functionalized indoles could be easily transformed to indole-*N*-carboxylic acids upon carboxylation with CO_2. These structural differential and functionalized indole-*N*-carboxylic acids could well engage in this MCR to assemble with aldehydes, amines, and isocyanides for rapid entry to functionalized indole-*N*-carboxamides in moderate to good yields (**5a′**−**5f′**). The methoxy, chloro, bromo, protected alcohol and amine were also compatible, and these functional groups could offer ample opportunity for late-stage derivatization. Finally, the scope of isocyanides was also tested. Besides the benzyl isocyanide, the cyclopentanyl isocyanide, phenyl isocyanide, and methyl glycine ester derived isocyanide were well applicable in this four-component MCR to furnish the corresponding products in good yields (**5g′**−**5i′**). Given the importance of indole derivatives in natural products and drug discovery, this method provides a simple and distinct access to these molecules from rapidly accessible starting materials.

Meanwhile, we also investigate this MCR scope by employing dihydroisoquinolines to replace imines.[17] As shown in Scheme 3, the dihydroisoquinoline **6a** could participate in this MCR smoothly to assemble with indole-*N*-carboxylic acid **3a** and benzyl isocyanide **4a** under modified reaction conditions, and this could deliver the desired indole carboxamide amino amide products in moderate to good yields (**7a**−**7f**). Various substitutions in the indole ring, including benzyloxy, methoxy, bromo, methyl, and protected alcohol, were tolerable. In addition, a variety of dihydroisoquinolines were also tested. The dimethoxy-substituted dihydroisoquinoline **6b** and tetrahydrocarboline **6c** were found to be well applicable in this process, and the corresponding products could be furnished in moderate yields (**7g**−**7j**). Considering the importance of indoles and dihydroisoquinolines in organic synthesis and medicinal chemistry, this method offered an expeditious entry to these molecules.

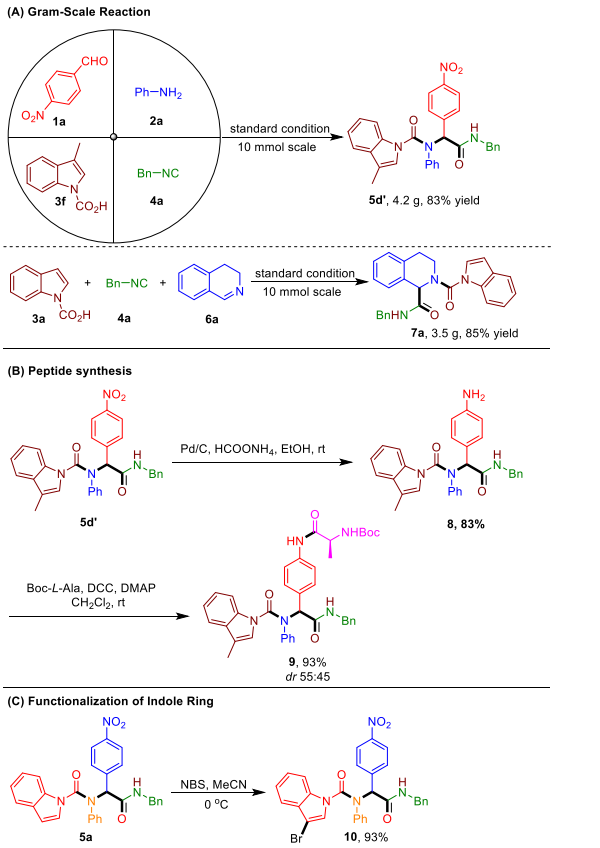
Scheme 3. Substrate Scope with Dihydroisoquinolines[a]



[a]Reaction conditions: **3** (0.3 mmol), **4** (0.24 mmol), and **6** (0.2 mmol) were added to solvent ($MeOH/CH_2Cl_2$ = 2:1, 2 mL) under argon and stirred at 0 °C for 24 h. Yields refer to isolated products.

Furthermore, the scalability of this method was investigated (Scheme 4A). For example, a four-component reaction of aldehyde **1a**, amine **2a**, indole-*N*-carboxylic acid **3f**, and isocyanide **4a** was conducted in 10 mmol scale, while the product **5d′** could be obtained in 83% yield (4.2 g). Meanwhile, the three-component reaction of indole-*N*-carboxylic acid **3a**, isocyanide **4a**, and dihydroisoquinoline **6a** was also carried out in 10 mmol scale to deliver the product **7a** in 85% yield with a simple recrystallization treatment (3.5 g). Therefore, this Ugi reaction of indole-*N*-carboxylic acids could be easily scaled up demonstrating it is a practical method. On the other hand, synthetic application was also established. Product **5d′** could be applied to peptide synthesis by reduction and further coupling with Boc-L-alanine to deliver compound **9** (Scheme 4B). Additionally, the indole ring of **5a** was brominated with NBS to give the derivate **10** (Scheme 4C).

Scheme 4. Gram-Scale Reaction and Synthetic Application



Based on these results, a plausible reaction mechanism was proposed (Figure 1). Initially, the aldehyde **1** would condense with amine **2** to deliver imine **A**, which would be protonated by indole-*N*-carboxylic acid **3** to give iminium species **B** and anion **C**. Then the isocyanide **4** would undergo addition to **B** and give intermediate **D**, which would engage in further addition by **C** to provide **E**. Finally, a Mumm rearrangement of **E** would furnish the product **5** to constitute the Ugi reaction process. Therefore, the utilization of indole-*N*-carboxylic acid **3** could introduce the privileged indole scaffolds to this MCR

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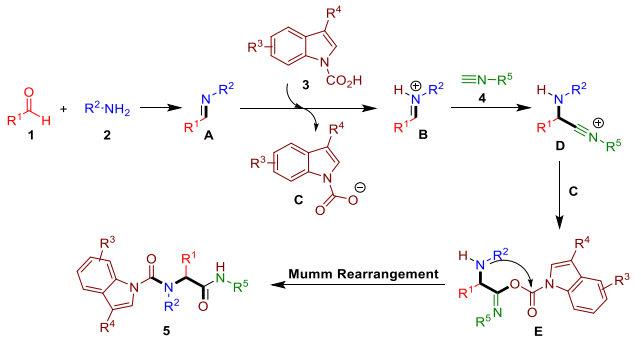

Figure 1. Proposed reaction mechanism.

process for the rapid synthesis of indole carboxamide amino amides.

In summary, a multicomponent reaction for the synthesis of indole carboxamide amino amides has been successfully developed. This protocol offers a rapid approach to indole tethered peptide units, along with the achievement of remarkable structural diversity and brevity. The process is also featured with readily available starting materials, simple operation and good scalability, and would be synthetic useful in organic synthesis and medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01871.

Full experimental procedures, characterization data, and NMR spectra data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews, see: (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (b) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. - Eur. J.* **2000**, *6*, 3321. (c) Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. (d) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (e) de Graaff, C.; Ruijter, E.; Orru, R. V. A. *Chem. Soc. Rev.* **2012**, *41*, 3969. (f) Garbarino, S.; Ravelli, D.; Protti, S.; Basso, A. *Angew. Chem., Int. Ed.* **2016**, *55*, 15476. (g) Zhu, J. P., Bienaymé, H., Eds. *Multicomponent Reactions*; Wiley-VCH: Weinheim, Germany, 2005. (h) Müller, T. J. J., Ed. *Multicomponent Reactions, Vol. 1 and 2*; Georg Thieme: Stuttgart, Germany, 2014.

(2) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 6234.

(3) Marson, C. M. *Chem. Soc. Rev.* **2012**, *41*, 7712.

(4) Touré, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439.

(5) Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083.

(6) For selected examples, see: (a) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrückner, C. *Angew. Chem.* **1959**, *71*, 386. (b) Ugi, I.; Steinbrückner, C. *Angew. Chem.* **1960**, *72*, 267. (c) Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 8. (d) Waki, M.; Meienhofer, J. *J. Am. Chem. Soc.* **1977**, *99*, 6075. (e) Kunz, H.; Pfrengle, W. *J. Am. Chem. Soc.* **1988**, *110*, 651. (f) Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1995**, *117*, 7842. (g) Chapman, T. M.; Davies, I. G.; Gu, B.; Block, T. M.; Scopes, D. I. C.; Hay, P. A.; Courtney, S. M.; McNeill, L. A.; Schofield, C. J.; Davis, B. G. *J. Am. Chem. Soc.* **2005**, *127*, 506. (h) Wessjohann, L. A.; Kreye, O.; Rivera, D. G. *Angew. Chem., Int. Ed.* **2017**, *56*, 3501. (i) Rivera, D. G.; Wessjohann, L. A. *J. Am. Chem. Soc.* **2006**, *128*, 7122. (j) Madhavachary, R.; Abdelraheem, E. M. M.; Rossetti, A.; Twarda-Clapa, A.; Musielak, B.; Kurpiewska, K.; Kalinowska-Tluscik, J.; Holak, T. A.; Dömling, A. *Angew. Chem., Int. Ed.* **2017**, *56*, 10725.

(7) (a) Zhao, W. J.; Huang, L.; Guan, Y.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2014**, *53*, 3436. (b) Zhang, Y.; Ao, Y. F.; Huang, Z. T.; Wang, D. X.; Wang, M. X.; Zhu, J. P. *Angew. Chem., Int. Ed.* **2016**, *55*, 5282. (c) Zhang, J.; Yu, P. Y.; Li, S. Y.; Sun, H.; Xiang, S. H.; Wang, J.; Houk, K. N.; Tan, B. *Science* **2018**, *361*, eaas8707.

(8) (a) Ugi, I.; Steinbrückner, C. *Chem. Ber.* **1961**, *94*, 2802. (b) Keating, T. A.; Armstrong, R. W. *J. Org. Chem.* **1998**, *63*, 867. (c) Hulme, C.; Ma, L.; Romano, J. J.; Morton, G.; Tang, S. Y.; Cherrier, M. P.; Choi, S.; Salvino, J.; Labaudiniere, R. *Tetrahedron Lett.* **2000**, *41*, 1889.

(9) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489.

(10) (a) Saniere, L. R. M.; Pizzonero, M. R.; Triballeau, N.; Vandeghinste, N. E. R.; de Vos, S. I. J.; Brys, R. C. X.; Pourbaix-l'ebraly, C. D. *PCT Int. Appl.* WO 2012098033, 2012. (b) Miller, K.; Diu-Hercend, A.; Hercend, T.; Lang, P.; Weber, P.; Golec, J.; Mortimore, M. *PCT Int. Appl.*WO 2003088917, 2003.

(11) vonGeldern, T. W.; Kester, J. A.; Bal, R.; WuWong, J. R.; Chiou, W.; Dixon, D. B.; Opgenorth, T. J. *J. Med. Chem.* **1996**, *39*, 968.

(12) (a) Xu, Z. R.; Wang, Q.; Zhu, J. P. *Chem. Soc. Rev.* **2018**, *47*, 7882. (b) Taber, D. F.; Tirunahari, P. K. *Tetrahedron* **2011**, *67*, 7195. (c) Nagaraju, K.; Ma, D. W. *Chem. Soc. Rev.* **2018**, *47*, 8018. (d) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873.

(13) Shiri, M. *Chem. Rev.* **2012**, *112*, 3508.

(14) For selected examples, see: (a) Zhang, L.; Zhao, F.; Zheng, M. Y.; Zhai, Y.; Liu, H. *Chem. Commun.* **2013**, *49*, 2894. (b) La Spisa, F.; Meneghetti, F.; Pozzi, B.; Tron, G. C. *Synthesis* **2015**, *47*, 489.

(15) (a) Huang, B.; Zeng, L. W.; Shen, Y. Y.; Cui, S. L. *Angew. Chem., Int. Ed.* **2017**, *56*, 4565. (b) Shen, Y. Y.; Huang, B.; Zeng, L. W.; Cui, S. L. *Org. Lett.* **2017**, *19*, 4616. (c) Zeng, L. W.; Huang, B.; Shen, Y. Y.; Cui, S. L. *Org. Lett.* **2018**, *20*, 3460. (d) Chen, R. J.; Zeng, L. W.; Huang, B.; Shen, Y. Y.; Cui, S. L. *Org. Lett.* **2018**, *20*, 3377. (e) Chen, R. J.; Liu, Y.; Cui, S. L. *Chem. Commun.* **2018**, *54*, 11753. (f) Shen, Y. Y.; Wang, C. R.; Chen, W.; Cui, S. L. *Org. Chem. Front.* **2018**, *5*, 3574. (g) Zhang, Y.; Zheng, J.; Cui, S. L. *J. Org. Chem.* **2014**, *79*, 6490. (h) Zheng, J.; Zhang, Y.; Cui, S. L. *Org. Lett.* **2014**, *16*, 3560.

(16) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463.

(17) Rossetti, A.; Sacchetti, A.; Gatti, M.; Pugliese, A.; Roda, G. *Chem. Heterocycl. Compd.* **2017**, *53*, 1214.

DOI: 10.1021/acs.orglett.9b01871
Org. Lett. XXXX, XXX, XXX−XXX