Organic LETTERS

Letter

pubs.acs.org/OrgLett

Synthesis of Quinoline-Fused 1-Benzazepines through a Mannich-Type Reaction of a C,N-Bisnucleophile Generated from 2-Aminobenzaldehyde and 2-Methylindole

Lijun Min,[†] Bin Pan,[†] and Yanlong Gu*[,†,‡]

[†]Key Laboratory of Material Chemistry for Energy Conversion and Storage, Ministry of Education, School of Chemistry and Chemical Engineering, Huazhong University of Science and Technology, Wuhan 430074, China

[‡]State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Lanzhou 730000, China

Supporting Information

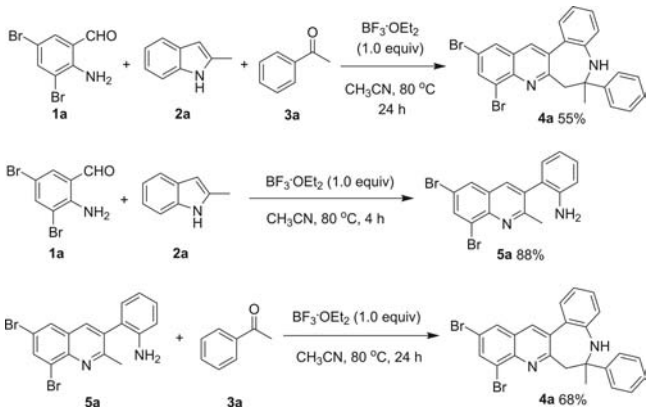
ABSTRACT: Various quinoline-fused 1-benzazepine derivatives were synthesized using the C,N-1,6-bisnucleophile generated in situ from *o*-aminobenzaldehyde and 2-methylindole through a Mannich-type reaction.

The Mannich-type reaction is widely used in organic synthesis.[1] Bisnucleophiles are often used in the Mannich type reaction, with which some important heterocycles can be synthesized.[2] A special Mannich type reaction of a C,N-bisnucleophile is the Pictet−Spengler reaction.[3] However, this reaction is strictly reserved for aromatic nucleophiles. While great attention has been paid to the design of C,N-bisnucleophiles with an aromatic C-based nucleophilic center for the Pictet−Spengler reaction,[4] far less effort has been spent on the development of nonaromatic C,N-bisnucleophile for Mannich-type reactions.[5,6]

Alkyl-substituted azaarenes have been demonstrated to constitute a unique class of C-based nucleophiles,[7] which can be activated by either transitional metals[8] or acid catalysts.[9] To the best of our knowledge, although the reactivities of alkyl-substituted azaarenes have been extensively investigated, the use of this type of molecule in the construction of a bisnucleophile has yet to be reported. In this paper, we will describe the use of a novel C,N-bisnucleophile in a Mannich-type reaction for the first time. The bisnucleophile involves not only a moiety of methyl quinoline but also an NH_2 group. This C−H bond functionalization reaction enabled the formation of a class of quinoline-fused 1-benzazepine derivatives, which cannot be attained with other methods.

Although the structure of the C,N-bisnucleophile looks complex, the compound can be synthesized from two commercially available chemicals, 2-aminobenzaldehyde and 2-methylindole. The discovery was accidental, originating from our attempts to synthesize dihydroquinoline from 2-aminobenzaldehyde derivative **1a**, 2-methylindole **2a**, and acetophenone **3a**.[10] As shown in Scheme 1, an unexpected product, a quinoline-fused 1-benzazepine derivative **4a**, was obtained. The structure of **4a** has been unambiguously confirmed by X-ray structural analysis.[11] Conditions including the catalyst, solvent, temperature, and reaction time were then filtered to determine the best parameters (see the Supporting Information, Table S1). A yield of 55% for **4a** is obtained in acetonitrile at 80 °C after 24 h of reaction in the presence of 1.0 equiv of $BF_3{\cdot}Et_2O$.

Scheme 1. Synthesis of 4a and Two Controlled Experiments



A survey of the literature revealed that Seidel et al.[12] observed an indole-to-quinoline transformation by using 2-aminobenzaldehyde as the counter-reagent of indole, producing a 3-(2-aminophenyl)quinoline derivative in the presence of an acid. To understand the mechanism of the present reaction, we treated a mixture of **1a** and **2a** with $BF_3{\cdot}Et_2O$ in acetonitrile. In agreement with our predictions, compound **5a** was formed, and the yield reached 88% after 4 h of reaction (Scheme 1). Interestingly, **5a** can react readily with **3a** to form **4a** in 68% yield.

On the basis of these observations, we propose a plausible mechanism in Figure 1. The initial event involves the formation of an intermediate (**I**) from **1a** and **2a**. Then, the NH_2 group acts as a nucleophile to attack the C2 position of the indole ring

Received: November 14, 2015
Published: January 12, 2016

DOI: 10.1021/acs.orglett.5b03287
Org. Lett. 2016, 18, 364−367

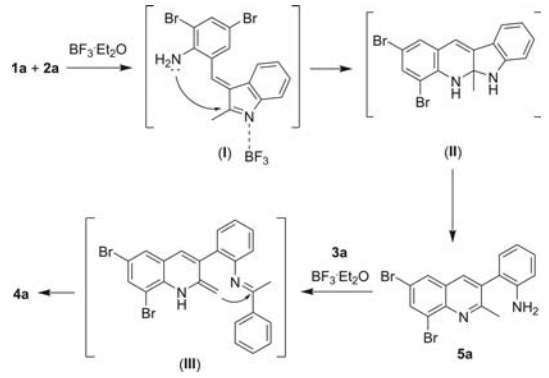


Figure 1. Plausible mechanism of the model reaction.

to form an intermediate (**II**). Cleavage of an endocyclic C−N bond results in the formation of **5a**. The activation effect of the quinoline ring confers good nucleophilicity to the methyl group of **5a**.[13] Therefore, **5a** can act as a novel 1, 6-C,N-bisnucleophile to react with acetophenone to form **4a**. The last step in the mechanism appears to be a variation of the Mannich-type reaction, in which the conventional enol-activated C-based nucleophile was changed into an enamine-activated one.

The substrate scope of the model reaction was then investigated, and the results are shown in Figure 2. First, various ketones were subjected to reactions with **1a** and **2a**. Acetophenones with both electron-donating and electron-withdrawing groups participated in the condensation reaction smoothly, providing the desired products in yields ranging from 26% to 70% (**4b** to **4h**). 1-Acetonaphthalene also works well, and the expected product **4i** was obtained in 53% yield. Ketones with heterocyclic groups, such as furanyl and thienyl, can also be used in this condensation (**4j** and **4k**). It should be noted that low yields were obtained in some cases (**4b**, **4c**, **4f**, and **4j**). It was found that although **1a** and **2a** can be converted **5a** in these cases, it is hard to convert **5a** further into the desired products. Reactions with aliphatic ketones, such as acetone and methyl isobutyl ketone, are also successful (**4l** and **4m**). Certain acid-liable groups, such as hydroxyl and double bonds, can be delivered without incident into the skeleton of products (**4n** and **4o**). When cyclic ketones were used, the expected products could be obtained in generally good to excellent yields (**4p** to **4w**). The highest yield, 90%, was obtained with cyclohexanone. A reaction scaled up to 10 mmol provided a uniform result. Cyclic ketones with endocyclic heteroatoms, such as oxygen and nitrogen, are also substrates that can viably react with **1a** and **2a** (**4x** and **4y**). This reaction was also able to synthesize a ferrocenyl-containing product, **4z**. Although the product was obtained in 24% yield, considering the fact that acetylferrocene is rather sensitive to acid, we think that this result is remarkable. However, our attempt to use amino group containing ketones, such as 4-(dimethylamino)-acetophenone and 1-methyl-4-piperidone, failed. This result indicates a limitation of the present reaction. The reactivities of certain 2-aminobenzaldehyde derivatives were also examined by using cyclohexanone and **2a** as standard substrates. The reactions proceeded smoothly with chloro- or bromo-substituted *o*-aminobenzaldehydes, and the corresponding products were obtained in moderate-to-good yields (**4aa**−**4ac**). 2-Amino-4,5-dimethoxybenzaldehyde can also react with **2a** and cyclohexanone, but due to the insufficient condensation

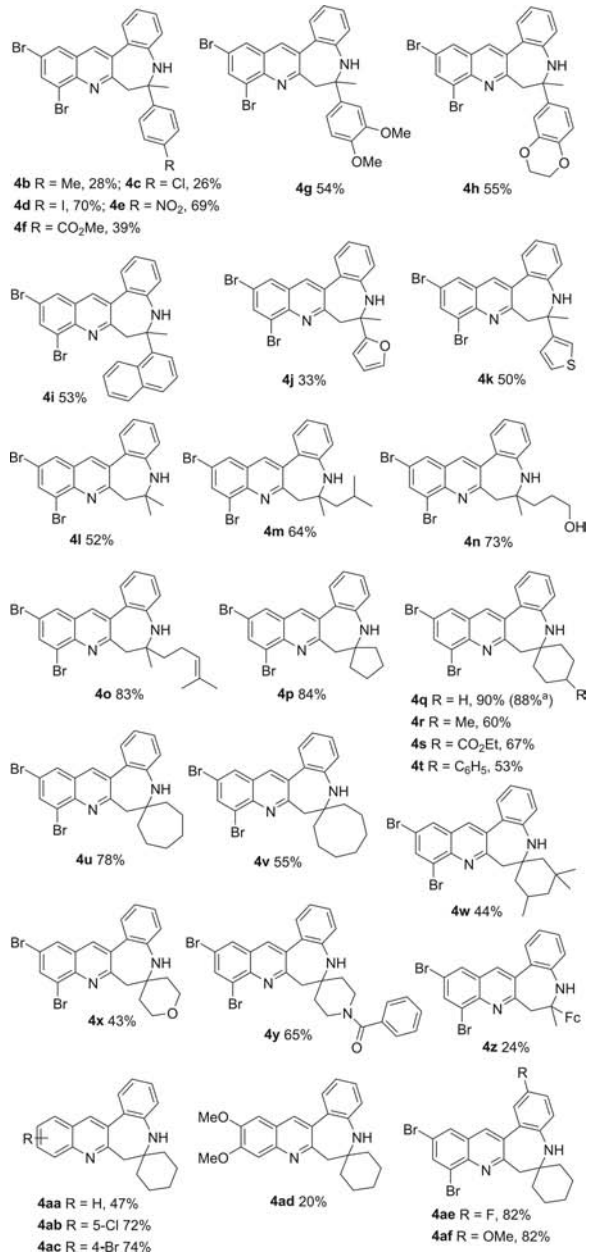


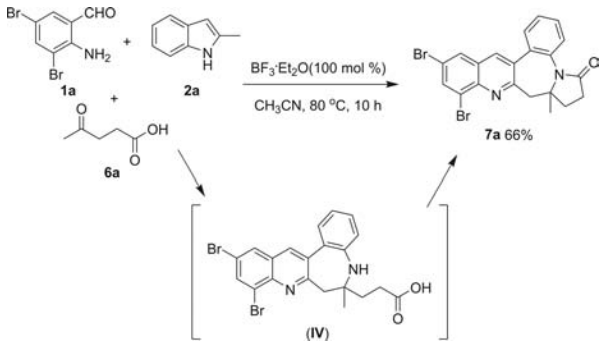
Figure 2. Substrate scope of the model reaction. (a) The reaction was performed on a 10 mmol scale.

of the aldehyde and **2a**, the desired product was obtained only in 20% yield. Two indole derivatives, namely, 2-methyl-5-fluoroindole and 2-methyl-5-methoxyindole, also readily participated in this type of condensation, which produced the desired products **4ae** and **4af** in yields exceeding 80%. Notably, the obtained products possess a skeleton of benzazepine, which is a crucial pharmacophore in drug discovery, and the derivatives of which exhibit a broad spectrum of biological activity.[14] Although these heterocycles are important, their syntheses are generally laborious, and their chemistry has not been well studied.[15] The present reaction offered a straightforward approach to access a new class of benzazepines, which cannot be attained with conventional routes.

Levulinic acid **6a** was also subjected to the conditions of this reaction. As shown in Scheme 2, a novel heterocyclic compound, **7a**, was obtained in 66% yield. In this reaction, the formation of **7a** should be a result of an intramolecular

DOI: 10.1021/acs.orglett.5b03287
Org. Lett. 2016, 18, 364−367

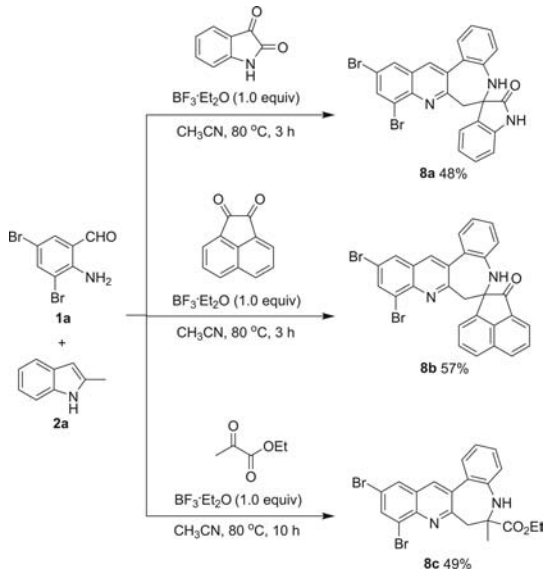
Scheme 2. Three-Component Reaction of 1a, 2a, and 6a



amidation of an intermediate (**IV**), which was generated from a condensation of **1a**, **2a**, and the ketocarbonyl group of **6a**.

Likewise, isatin, acenaphthenequinone, and ethyl pyruvate were also applicable as electrophilic counterparts in the title condensations, resulting in Mannich-type cyclization products **8a–c** in moderate yields (Scheme 3).

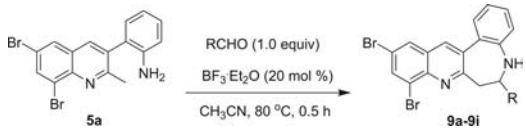
Scheme 3. Condensation of 1a and 2a with Other Ketocarbonyl-Containing Electrophiles



We also tried to use aldehyde to replace the ketone component, but that failed. A messy mixture could always be obtained in this case. Failure may have resulted from the inherent scrambling of the two aldehydes toward the electrophilic reaction with **2a**. To solve this problem, we used the presynthesized compound **5a** instead of a two-component mixture of **1a** and **2a**. As shown in Table 1, various benzaldehydes reacted readily with **5a**, with the aid of $BF_3·Et_2O$ catalyst, providing **9a–e** in generally good yields (entries 1–5). Aldehydes with heterocyclic groups, such as 2-furanyl, 2-thienyl, and 2-pyridinyl, participated in this reaction as well. These reactions produced the desired products **9f–h** in moderate-to-good yields (entries 6–8). The use of cinnamaldehyde proved to be successful as well (entry 9).

However, when an aliphatic aldehyde, phenylpropionaldehyde, was used, the predicted product was not obtained. Instead, **10a** was obtained in 61% yield (Scheme 4). It is not unreasonable because the reactions of anilines and enolizable

Table 1. Reactions of 5a with Different Aldehydes[a]

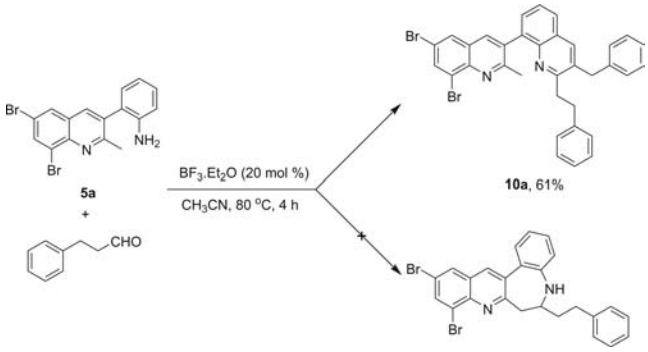


entry	R	product	yield[b] (%)
1	C_6H_5	**9a**	72
2	4-$MeOC_6H_4$	**9b**	85
3	4-$CF_3SC_6H_4$	**9c**	87
4	4-$NO_2C_6H_4$	**9d**	80
5	2-$NO_2C_6H_4$	**9e**	83
6	2-furanyl	**9f**	50
7	2-thienyl	**9g**	65
8	2-pyridinyl	**9h**	42
9	$C_6H_5CH{=}CH$	**9i**	38

[a]Key: **5a**, 0.2 mmol; aldehyde, 0.2 mmol; $BF_3·Et_2O$, 0.04 mmol; acetonitrile, 1 mL, 80 °C, 0.5 h. [b]Isolated yield.

aldehyde are well-known and have been widely used in the synthesis of substituted quinolines.[16]

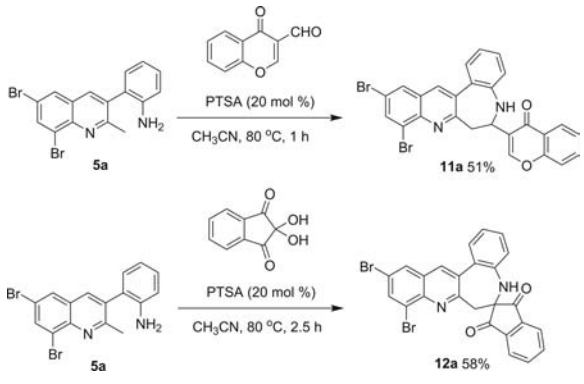
Scheme 4. Reactions of 5a with Phenylpropionaldehyde



Interestingly, when chromone-3-carbaldehyde was used, only the formyl group condensed with **5a**, and the ketocarbonyl remained unchanged (Scheme 5). Likewise, ninhydrin hydrate reacted with **5a**, providing **12a** in 58% yield (Scheme 5).

In conclusion, a three-component Mannich-type reaction of *o*-aminobenzaldehyde, 2-methylindole, and ketone has been developed. The reaction produced various quinoline-fused 1-benzazepine derivatives in a straightforward manner. The key intermediate of this reaction is a hitherto-unreported C,N-1,6-

Scheme 5. Reactions of 5a with Chromone-3-carbaldehyde and Ninhydrin Hydrate



DOI: 10.1021/acs.orglett.5b03287
Org. Lett. 2016, 18, 364–367

bisnucleophile that was generated from *o*-aminobenzaldehyde and 2-methylindole through an indole-to-quinoline transformation. Numerous keto- or aldocarbonyl containing compounds can be used as electrophiles to react with this bisnucleophile, thus significantly enriching the product diversity. The yields in this reaction are only moderate in most cases at the present stage. However, the transformation itself is interesting, and the results can aid further investigations, which are currently ongoing in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03287.

Experimental procedure, crystal structure of the compound **4a**, spectroscopic data of the obtained products, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

X-ray data for compound **4a** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: klgyl@hust.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China for financial support (21173089 and 21373093). We are grateful to the Analytical and Testing Centre of HUST. The Cooperative Innovation Center of Hubei Province is acknowledged. This work is also supported by the fundamental research funds for the central universities in China (2014ZZGH019).

■ REFERENCES

(1) (a) Van Leeuwen, P. W. N. M. Mannich-Type Reactions. In *Science of Synthesis, C-1 Building Blocks in Organic Synthesis*; Merino, P., Ed.; Georg Thieme Verlag: Stuttgart, 2014; Vol. 2, pp 311−331. (b) Carreira, E. M.; Yamamoto, H. C−C Bond Formation. Mannich Reaction. In *Comprehensive Chirality*; Akiyama, T., Ed.; Gakushuin University: Tokyo, 2012; Vol. 6, pp 69−96.

(2) Knochel, P.; Molander, G. A. The bimolecular and intramolecular Mannich and related reactions. In *Comprehensive Organic Synthesis*, 2nd ed.; Akiyama, T., Ed.; Gakushuin University: Tokyo2014; Vol. 2, pp 629−681.

(3) (a) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797−1842. (b) Stockigt, J.; Antonchick, A. P.; Wu, F. − R.; Waldmann, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 8538−8564.

(4) (a) Xu, H.; Fan, L. − L. *Eur. J. Med. Chem.* **2011**, *46*, 1919−1925. (b) Barve, I. J.; Chen, C. − Y.; Salunke, D. B.; Chung, W. − S.; Sun, C. − M. *Chem. - Asian J.* **2012**, *7*, 1684−1690. (c) Augustine, J. K.; Bombrun, A.; Alagarsamy, P.; Jothi, A. *Tetrahedron Lett.* **2012**, *53*, 6280−6287. (d) Patil, N. T.; Mutyala, A. K.; Lakshmi, P. G. V. V; Raju, P. V. K.; Sridhar, B. *Eur. J. Org. Chem.* **2010**, *2010*, 1999−2010. (e) David, E.; Pellet-Rostaing, S.; Lemaire, M. *Tetrahedron* **2007**, *63*, 8999−9006. (f) Pandey, A. K.; Sharma, R.; Singh, A.; Shukla, S.; Srivastava, K.; Puri, S. K.; Kumar, B.; Chauhan, P. M. S. *RSC Adv.* **2014**, *4*, 26757−26770.

(5) (a) Kanagaraj, K.; Pitchumani, K. *J. Org. Chem.* **2013**, *78*, 744−751. (b) Gao, W. − C.; Jiang, S.; Wang, R. − L.; Zhang, C. *Chem. Commun.* **2013**, *49*, 4890−4892. (c) Mondal, B.; Pan, S. C. *Org. Biomol. Chem.* **2014**, *12*, 9789−9792. (d) Muthukrishnan, M.; Mujahid, M.; Punitharasu, V.; Dnyaneshwar, D. A. *Synth. Commun.* **2010**, *40*, 1391−1398.

(6) (a) Mezheritskii, V. V.; Antonov, A. N.; Milov, A. A.; Lysenko, K. A. *Russ. J. Org. Chem.* **2010**, *46*, 844−854. (b) Majumdar, K. C.; Taher, A.; Ponra, S. *Synlett* **2010**, *2010*, 735−740. (c) Mohite, A. R.; Sultane, P. R.; Bhat, R. G. *Tetrahedron Lett.* **2012**, *53*, 30−35.

(7) (a) Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 14092−14093. (b) Blank, B.; Kempe, R. *J. Am. Chem. Soc.* **2010**, *132*, 924−925. (c) Qian, B.; Guo, S.; Shao, J.; Zhu, Q.; Yang, L.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2010**, *132*, 3650−3651.

(8) (a) Rueping, M.; Tolstoluzhsky, N. *Org. Lett.* **2011**, *13*, 1095−1097. (b) Obora, Y.; Ogawa, S.; Yamamoto, N. *J. Org. Chem.* **2012**, *77*, 9429−9433. (c) Wang, F. − F.; Luo, C. − P.; Deng, G.; Yang, L. *Green Chem.* **2014**, *16*, 2428−2431.

(9) (a) Komai, H.; Yoshino, T.; Matsunaga, S.; Kanai, M. *Org. Lett.* **2011**, *13*, 1706−1709. (b) Zhu, Z. − Q.; Bai, P.; Huang, Z. − Z. *Org. Lett.* **2014**, *16*, 4881−4883. (c) Qian, B.; Shi, D.; Yang, L.; Huang, H. *Adv. Synth. Catal.* **2012**, *354*, 2146−2150.

(10) We have recently begun focusing on developing three-component reactions of aldehydes with two different nucleophiles: (a) Li, M.; Taheri, A.; Liu, M.; Sun, S.; Gu, Y. *Adv. Synth. Catal.* **2014**, *356*, 537−556. (b) Pan, X.; Li, M.; Gu, Y. *Chem. - Asian J.* **2014**, *9*, 268−274. (c) Gu, Y.; Liu, C.; Zhou, L.; Jiang, D. *Asian J. Org. Chem.* **2015**, DOI: 10.1002/ajoc.201500497. (d) Taheri, A.; Lai, B.; Cheng, C.; Gu, Y. *Green Chem.* **2015**, *17*, 812−816. (e) Sun, S.; Cheng, C.; Yang, J.; Taheri, A.; Jiang, D.; Zhang, B.; Gu, Y. *Org. Lett.* **2014**, *16*, 4520−4523. (f) Yang, J.; Li, H.; Li, M.; Peng, J.; Gu, Y. *Adv. Synth. Catal.* **2012**, *354*, 688−700. (g) Yang, J.; Tan, J. − N.; Gu, Y. *Green Chem.* **2012**, *14*, 3304−3317. (h) Gu, Y.; Barrault, J.; Jerome, F. *Adv. Synth. Catal.* **2009**, *351*, 3269−3278.

(11) CCDC no. 1436294; see also the Supporting Information.

(12) Vecchione, M. K.; Sun, A. X.; Seidel, D. *Chem. Sci.* **2011**, *2*, 2178−2181.

(13) (a) Huang, J.; Li, L. − T.; Li, H. − Y.; Husan, E.; Wang, P.; Wang, B. *Chem. Commun.* **2012**, *48*, 10204−10206. (b) Xu, L.; Shao, Z.; Wang, L.; Xiao, J. *Org. Lett.* **2014**, *16*, 796−799. (c) Xiao, F.; Chen, S.; Chen, Y.; Huang, H.; Deng, G. − J. *Chem. Commun.* **2015**, *51*, 652−654.

(14) (a) Shamma, M. *The Alkaloids*; Academic Press: New York, 1972. (b) Renfroe, B.; Harrington, C.; Proctor, G. R. *Heterocyclic Compounds: Azepines*; Wiley Interscience: New York, 1984. (c) Matsubara, J.; Kitano, K.; Otsubo, K.; Kawano, Y.; Ohtani, T.; Bando, M.; Kido, M.; Uchida, M.; Tabusa, F. *Tetrahedron* **2000**, *56*, 4667−4682. (d) Aranapakam, V.; Albright, J. D.; Grosu, G. T.; Chan, P. T.; Coupet, J.; Saunders, T.; Ru, X.; Mazandarani, H. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1733−1736. (e) Corbel, J. C.; Uriac, P.; Huet, J.; Martin, C. A. E.; Advenier, C. *Eur. J. Med. Chem.* **1995**, *30*, 3−13.

(15) (a) Ramig, K.; Greer, E. M.; Szalda, D. J.; Razi, R.; Mahir, F.; Pokeza, N.; Wong, W.; Kaplan, B.; Lam, J.; Mannan, A.; Missak, C.; Mai, D.; Subramaniam, G.; Berkowitz, W. F.; Prasad, P.; Karimi, S.; Lo, N. H.; Kudzma, L. V. *Eur. J. Org. Chem.* **2010**, *2010*, 2363−2371. (b) Acosta, L. M.; Palma, A.; Bahsas, A. *Tetrahedron* **2010**, *66*, 8392−8401. (c) Wang, L.; Huang, J.; Peng, S.; Liu, H.; Jiang, X.; Wang, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 1768−1772. (d) Acosta-Quintero, L. M.; Jurado, J.; Nogueras, M.; Palma, A.; Cobo, J. *Eur. J. Org. Chem.* **2015**, *2015*, 5360−5369.

(16) (a) Bharate, J. B.; Bharate, S. B.; Vishwakarma, R. A. *ACS Comb. Sci.* **2014**, *16*, 624−630. (b) Anvar, S.; Mohammadpoor-Baltork, I.; Tangestaninejad, S.; Moghadam, M.; Mirkhani, V.; Khosropour, A. R.; Landarani Isfahani, A.; Kia, R. *ACS Comb. Sci.* **2014**, *16*, 93−100. (c) Tanaka, S.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2006**, *71*, 800−803.

DOI: 10.1021/acs.orglett.5b03287
Org. Lett. 2016, 18, 364−367