Halogen Bond-Catalyzed Friedel-Crafts Reactions of Aldehydes and Ketones Using a Bidentate Halogen Bond Donor Catalyst: Synthesis of Symmetrical Bis(indolyl)methanes

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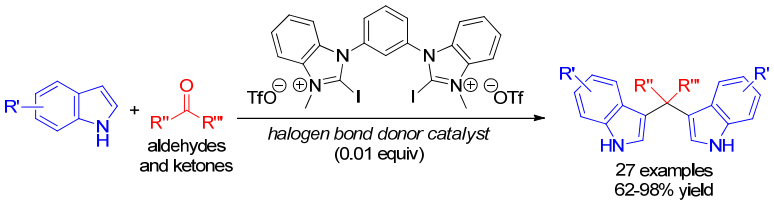
Supporting Information Placeholder



ABSTRACT: The use of a halogen bond donor to catalyze Friedel-Crafts reactions of indoles with a range of aldehydes and ketones to directly produce bis(indolyl)methanes, including the natural products arsindoline A, arundine, trisindoline, and vibrindole A, is reported. The bidentate catalyst used in these reactions proved to be more effective than a monondentate analogue, a thiourea commonly used as an organocatalyst, and even a trityl cation that has been used previously in the synthesis of bis(indolyl)methanes.

While halogen bonds,[1] which in some ways can be considered to be functionally akin to hydrogen bonds, have been known and studied in a variety of contexts for quite some time,[2] the use of organic halides as halogen bond donors to catalyze organic transformations is a relatively unexplored aspect of organocatalysis.[3] Early studies of such applications of halogen bonds focused on the activation of carbon-nitrogen double bonds for reduction,[4,5] Mannich reactions,[6,7] and Diels-Alder reactions,[6-8] and carbon/silicon-halogen bonds in Ritter-type[9-11] and conceptually related reactions involving cationic intermediates.[12-17] Only more recently has halogen bond-catalyzed reactions of carbonyl groups been examined. For example, halogen bond catalysis of the Diels-Alder reaction between cyclopentadiene and methyl vinyl ketone has been studied,[18,19] as have tandem Michael/Henry reactions of α,β-unsaturated aldehydes,[20] nucleophilic addition reactions to aldehydes for chalcone synthesis,[21] and Michael addition reactions to α,β-unsaturated ketones,[22-25] and Mukiyama aldol reactions.[26] Other recent examples of halogen bond catalysis include thioamide activation,[27] iodonium ylide activation for cross-enolate couplings,[28] *N*-glycofunctionalization of amides,[29] α-C-H amination of ethers,[30] bromocarbocyclization reactions,[31] cyclopropyl ketone ring-openings,[32] a Nazarov cyclization reaction,[33] carbon nucleophile additions to *N*-acylimminium ions,[34] and [4+2] cylcloaddition reactions of 2-vinylindoles.[35] Importantly, a water soluble amino acid-based halogen bond donor catalyst has been described for use in aqueous reactions,[36] and the first highly enantioselective example of halogen bond catalysis in any context has been reported.[37] It is against this backdrop that we report what is to our knowledge the first application of an organic halide halogen bond donor as a catalyst in Friedel-Crafts reactions[17] of aldehyde and ketone electrophiles and indole nucleophiles.

We have previously studied the use of a chiral phosphoric acid as a catalyst in Friedel-Crafts reactions of indoles,[38] and were interested in studying the potential of halogen bond catalysis of similar reactions. Given the enduring interest in the synthesis of symmetrical bis(indolyl)methanes **1** (Figure 1),[39,40] many of which are naturally occurring and have interesting biological activities, and their conversion to more complicated natural[41] and unnatural structures,[42] we focused our efforts on the catalytic synthesis of such compounds.

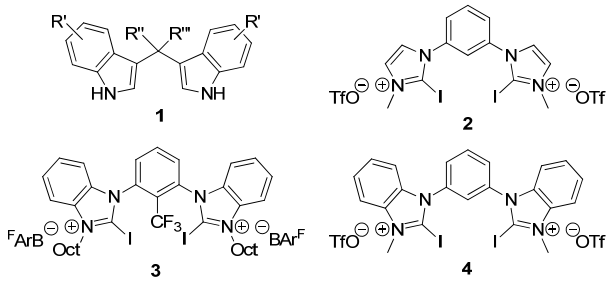
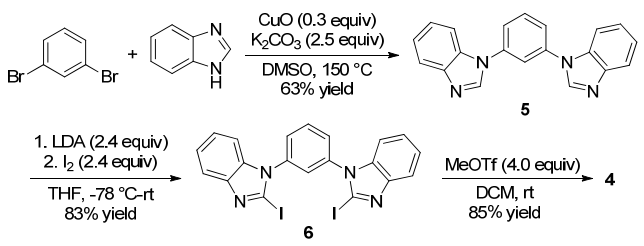


Figure 1. Structures of bis(indolyl)methanes (**1**) and bidentate halogen bond donors (**2-4**).

A survey of the literature makes it clear that bidentate halogen bond donors such as **2**[13] and **3**[22] are generally more efficient catalysts than monodentate compounds, and therefore, based on available materials, we targeted **4** (Figure 1) as the catalyst for our studies. Catalyst **4** was synthesized as outlined in Scheme 1. Specifically, intermediate **5** was prepared according to the litera-

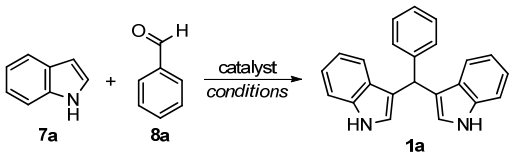
ture method from 1,3-dibromobenzene and benzimidazole,[43] and this was subsequently deprotonated and iodinated to generate **6**, which was then methylated to afford **4** using procedures similar to those used for the synthesis of **2** (Scheme 1).[13,16]

Scheme 1. Synthesis of 4

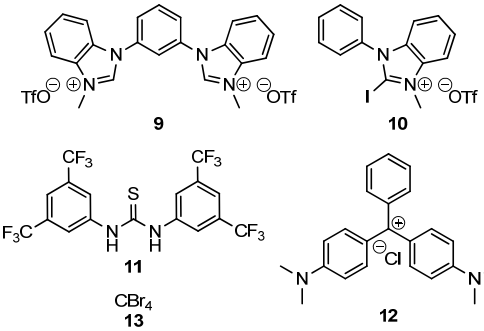


With catalyst **4** prepared, we turned our attention to study its use as a halogen bond donor in the catalytic synthesis of **1a**, the reduced form of triaryl cation antibiotic turbomycin B,[44] from indole (**7a**) and benzaldehyde (**8a**) (Table 1). Gratifyingly, **1a** was synthesized in very high yield from a 4:1 ratio of **7a**:**8a** using 0.1 equiv of **4** as catalyst in MeCN at room temperature in our very first unoptimized reaction (entry 1). Changing the solvent to THF did not improve the situation (entry 2), and lowering the catalyst loading increased the time required for complete reaction (entries 3 and 4). However, heating the reaction to 70 °C in MeCN using 0.01 equiv of **4** afforded excellent yield of **1a** in a short period of time (entry 5), even on a 10 mmol scale (entry 6). Therefore, these conditions were used for further studies. When no catalyst was used, **1a** was not formed (entry 7), as was the case when unalkylated **6** was used (entry 8), indicating the importance of the charged nature of **4**. Furthermore, in order to confirm the requirement of the iodine atoms in **4** for catalysis, **9** (prepared by alkylation of **5**)[45] was used in place of **4**, and no **1a** was formed even using a higher loading and a longer reaction time (entry 9). Evidence for halogen bonding being responsible for catalysis rather than the presence of a hidden acid was provided by the observation that the addition of increasing amounts of Bu_4NI to the standard reaction conditions resulting in increasing inhibition of the formation of **1a** (entries 10 and 11), while the addition of pyridine or $i Pr_2EtN$ did not produce such a dramatic effect (entries 12 and 13). Furthermore, the addition of BHT did not affect the reaction (entry 14), nor did changing the counter ions from triflate groups to tetrafluoroborate groups (entry 15). Monoiodide **10**[45] was also examined as a catalyst, but when 0.01 equiv of it was used, a much longer reaction time was required for a high yield of **1a** compared to when **4** was used (entry 16). Even doubling the loading of **10** to 0.02 equiv did not produce **1a** with the efficiency of 0.01 equiv of **4** (entry 17). Finally, we examined commonly used hydrogen bond donor thiourea **11**, malachite green (**12**), which was previously used to catalyze such reactions,[40i] and carbon tetrabromide (**13**), which was previously used to activate aldehydes in aldol reacitons.[21] Thiourea **11** was unable to catalyze the formation of **1a** (entry 18), and **12** and **13** proved to be much less efficient catalysts compared to **4** (entries 19 and 20).

Table 1. Friedel-Crafts reactions between indole (7a) and benzaldehyde (**8a**) to synthesize **1a**[a]



Entry[a]	Catalyst (equiv)	Solvent	Temp	Time (h)	Yield[b] (%)
1	**4** (0.1)	MeCN	rt	1.5	90
2	**4** (0.1)	THF	rt	2.5	83
3	**4** (0.01)	MeCN	rt	28	94
4	**4** (0.05)	MeCN	rt	6	93
5	**4** (0.01)	MeCN	70 °C	3	94
6	**4** (0.01)	MeCN	70 °C	3	95[c]
7	none	MeCN	70 °C	24	0
8	**6** (0.01)	MeCN	70 °C	24	0
9	**9** (0.05)	MeCN	70 °C	24	0
10	**4** (0.01), Bu_4NI (0.02)	MeCN	70 °C	3	50
11	**4** (0.01), Bu_4NI (0.1)	MeCN	70 °C	3	0
12	**4** (0.01), pyridine (0.02)	MeCN	70 °C	3	70
13	**4** (0.01), iPr_2EtN (0.02)	MeCN	70 °C	3	52
14	**4** (0.01), BHT (0.02)	MeCN	70 °C	3	87
15	4-BF_4 (0.01)	MeCN	70 °C	3	92
16	**10** (0.01)	MeCN	70 °C	23	78
17	**10** (0.02)	MeCN	70 °C	20	85
18	**11** (0.01)	MeCN	70 °C	24	0
19	**12** (0.01)	MeCN	70 °C	72	55
20	**13** (0.01)	MeCN	70 °C	72	68



[a]Conditions: **7a** (4.0 mmol), **8a** (1.0 mmol), catalyst, solvent (2.0 mL). [b]Isolated yield. [c]Reaction performed using 40 mmol **7a**, 10.0 mmol **8a** in MeCN (20 mL).

Having identified reaction conditions (**4** (0.01 mmol), **7** (4 mmol), **8** (1 mmol), MeCN (2 mL), 70 °C) that afforded **1a** efficiently from **7a** and **8a** in excellent yield using catalyst **4** at a low loading level, we next studied their general applicability by reacting various indoles with a range of aldehydes and ketones (see Figure SI-1 for structures) to produce a wide range of bis(indolyl)methanes **1** (Figure 2).[45] For example, methyl-substituted benzaldehydes **8b-d** afforded excellent yields of the corresponding products **1b-d** regardless of the position of the substituent, but ortho-substituted **1d** did require a significantly longer time for the reaction to complete. Furthermore, 2,6-dimethylbenzldehyde (**8e**) only reacted to a very limited extent to form **1e**, even after heating for 72 h. Significantly, no such steric effects were observed when either TFA or I_2 was used to catalyze the synthesis of **1b-d**. Also, both of these catalysts led to high yield of **1e** after 72 h at rt. Other substituted benzaldehydes such as **8f-m**, including ones with potentially reducible or acid labile groups, afforded **1f-m** cleanly and efficiently. Basic heteroaromatic aldehyde **8n** also reacted to afford arsindoline A (**1n**)[46] in good yield. Even alkyl aldehydes **8o-p** reacted using our conditions to afford **1o-p**, while electron-withdrawing group activated aldehyde **8q** reacted to afford **1q** even more efficiently. Ethyl pyruvate (**8r**) reacted to produce **1r** in good yield. Istatins **1s-t** reacted efficiently to afford trisindoline (**1s**)[47] and **1t**, respectively, as did cyclohexanone (**8u**) to afford **1p**. Even substituted indoles **7b-f** reacted with **8a** using our conditions to produce **1v-z** in excellent yields. Finally, we reacted volatile aldehydes formaldehyde (**8u**) and acetaldehyde (**8v**) with **7a**, but used them in a 4-fold excess rather than as the limiting reagent, to produce arundine (**1aa**)[48] and vibrindole A (**1ab**),[49] respectively, in good yields after extended reaction times at rt. Thus, all things considered, it seems that **4** is indeed a good catalyst for the synthesis of a wide range of bis(indoyl)methanes **1** from simple indole and carbonyl compound starting materials.

With regard to the mechanism of these reactions, based on the results summarized in Table 1, and the steric effects observed in the synthesis of **1b-e,** it seems plausible that **4** can enhance the electrophilicity of the aldehyde or ketone starting material **8** through a pair of halogen bonds as in complex **A** (Scheme 2), thereby facilitating nucleophilic addition of **7** to afford complex **B**. This in turn can lose an equivalent of water to generate azafulvene intermediate **C**,[40g,i] which can react with another equivalent of **7** to afford final product **1**. The notion of electrophile activation by halogen bonding was supported by ^{13}C NMR analysis of a 1:1 mixture of **8a**:**4** showed a 0.2 ppm downfield shift of the aldehyde carbon signal of **8a** (Figure SI-2a), and a similar upfield shift for the signal corresponding to the iodine-bearing carbon atoms of **4** (Figure SI-2b), results similar to what has been reported by others.[25,32] Additionally, ^1H NMR analysis of **4** indicated that heating it at 70 °C in MeCN for 72 h did not lead to any noticeable decomposition, providing further evidence against hidden acid or I_2 catalysis being operative in these reactions. Finally, it should be noted that attempts to isolate **C** (from **7a** and **8a**) failed, and only **1a** was obtained in every instance. Thus, it seems that the conversion of **C** to **1** is facile and does not require catalysis using our reaction conditions.

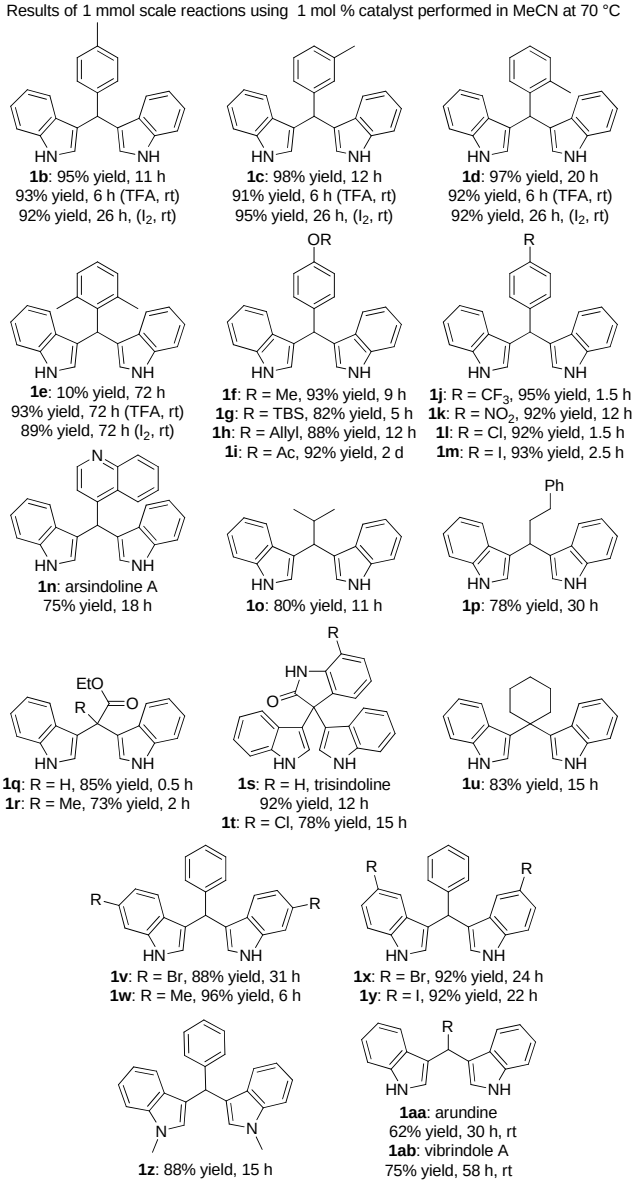
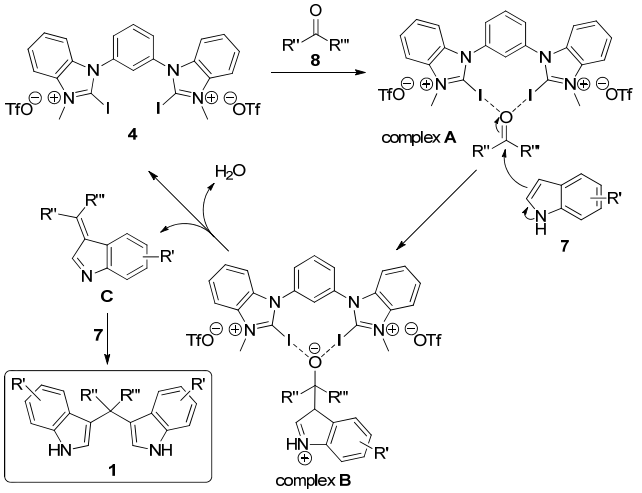


Figure 2. Bis(indolyl)methanes **1a-ab** synthesized.

In summary, we have demonstrated that the concept of halogen bond catalysis can be extended to the use of a bidentate halogen bond donor to the catalysis of Friedel-Crafts reactions of aldehyde and ketone electrophilic starting materials with indole nucleophiles to afford a broad range of symmetrical bis(indolyl)methanes, including some natural products with interesting biological activities. We are now examining the synthesis and use of chiral analogues of **4** with the hope that they will be able to serve as efficient and highly enantioselective catalysts in the types of asymmetric Friedel-Crafts reactions that we previously reported with only moderate stereoselectivity using a chiral phosphoric acid catalyst.[38] Not only do we hope to increase the enantioselectivity of such reactions, but we also expect that the neutral nature of catalysts such as **4** will allow for a broader substrate scope than is possible when using a strongly acidic catalyst.

Scheme 2. Proposed reaction mechanism



ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Detailed experimental procedures, compound characterization data, NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Desiraju, G. R.; Ho, P. S.; Kloo, L.; Legon, A. C.; Marquardt, R.; Metrangolo, P.; Politzer, P.; Resnati, G.; Rissanen, K. *Pure Appl. Chem.* **2013**, *85*, 1711.

(2) Cavallo, G.; Metrangolo, P.; Milani, R.; Pilati, T.; Priimagi, A.; Resnati, G.; Terraneo, G. *Chem. Rev.* **2016**, *116*, 2478.

(3) (a) Jungbauer, S. H.; Schindler, S.; Kniep, F.; Walter, S. M.; Rout, L.; Huber, S. M. *Synlett* **2013**, *24*, 2624. (b) Bulfield, D.; Huber, S. M. *Chem.-Eur. J.*, **2016**, *22*, 14434. (c) Nagorny, P.; Sun, Z. *Beilstein J. Org. Chem.* **2016**, *12*, 2834. (d) Breugst, M.; von der Heiden, D.; Schmauck, J. *Synthesis* **2017**, *49*, 3224. (e) Sutar, R. L.; Huber, S. M. *ACS Catal.* **2019**, *9*, 9622.

(4) Bruckmann, A.; Pena, M. A.; Bolm, C. *Synlett* **2008**, *19*, 900.

(5) He, W.; Ge, Y.-C.; Tan, C.-H. *Org. Lett.* **2014**, *16*, 3244.

(6) Takeda, Y.; Hisakuni, D.; Lin C.-H.; Minakata, S. *Org. Lett.* **2015**, *17*, 318.

(7) Haraguchi, R.; Hoshino, S.; Sakai, M.; Tanazawa, S.; Morita, Y.; Komatsu, T.; Fukuzawa, S. *Chem. Commun.* **2018**, *54*, 10320.

(8) Kaasik, M.; Metsala, A.; Kaabel, S.; Kriis, K.; Järving, I.; Kanger, T. *J. Org. Chem.* **2019**, *84*, 4294.

(9) Walter, S. M.; Kniep, F.; Herdtweck, E.; Huber, S. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 7187.

(10) Kniep, F.; Walter, S. M.; Herdtweck, E.; Huber, S. M. *Chem.-Eur. J.* **2012**, *18*, 1306.

(11) Kniep, F.; Rout, L.; Walter, S. M.; Bensch, H. K. V.; Jungbauer, S. H.; Herdtweck, E.; Huber, S. M. *Chem. Commun.* **2012**, *48*, 9299.

(12) Kniep, F.; Jungbauer, S. H.; Zhang, Q.; Walter, S. M.; Schindler, S.; Schnapperelle, I.; Herdtweck, E.; Huber, S. M. *Angew. Chem. Int. Ed.* **2013**, *52*, 7028.

(13) Castelli, R.; Schindler, S.; Walter, S. M.; Kniep, F.; Overkleeft, H. S.; Van der Marel, G. A.; Huber, S. M.; Codée, J. D. C. *Chem.-Asian J.* **2014**, *9*, 2095.

(14) Tsuji, N.; Kobayashi, Y.; Takemoto, Y. *Chem. Commun.* **2014**, *50*, 13691.

(15) Saito, M.; Tsuji, N.; Kobayashi, Y.; Takemoto, Y. *Org. Lett.* **2015**, *17*, 3000.

(16) Jungbauer, S. H.; Huber, S. M. *J. Am. Chem. Soc.* **2015**, *137*, 12110.

(17) Dreger, A.; Engelage, E.; Mallick, B.; Beer, P. D.; Huber, S. M. *Chem. Commun.* **2018**, *54*, 4013.

(18) Jungbauer, S. H.; Walter, S. M.; Schindler, S.; Rout, L.; Kniep, F.; Huber, S. M. *Chem. Commun.* **2014**, *50*, 6281.

(19) Heinen, F.; Engelage, E.; Dreger, A.; Weiss, R.; Huber, S. M. *Angew. Chem. Int. Ed.* **2018**, *57*, 3830.

(20) Arai, T.; Suzuki, T.; Inoue, T.; Kuwano, S. *Synlett* **2017**, *28*, 122.

(21) Kazi, I.; Guha, S.; Sekar, G. *Org. Lett.* **2017**, *19*, 1244.

(22) Gliese, J.-P.; Jungbauer, S. H.; Huber, S. M. *Chem. Commun.* **2017**, *53*, 12052.

(23) von der Heiden, D.; Detmar, E.; Kuchta, R.; Breugst, M. *Synlett* **2018**, *29*, 1307.

(24) Squitieri, R. A.; Fitzpatrick, K. P.; Jaworski, A. A.; Scheidt, K. A. *Chem. Eur. J.* **2019**, *25*, 10069.

(25) Ge, Y.-C.; Yang, H.; Heusler, A.; Chua, Z.; Wong, M. W.; Tan, C.-H. *Chem. Asian J.* **2019**, *14*, 2656.

(26) Matsuzaki, K.; Uno, H.; Tokunaga, E.; Shibata, N. *ACS Catal.* **2018**, *8*, 6601.

(27) Matsuzawa, A.; Takeuchi, S.; Sugita, K. *Chem.-Asian J.* **2016**, *11*, 2863.

(28) Saito, M.; Kobayashi, Y.; Tsuzuki, S.; Takemoto, Y. *Angew. Chem. Int. Ed.* **2017**, *56*, 7653.

(29) Kobayashi, Y.; Nakatsuji, Y.; Li, S.; Tsuzuki, S.; Takemoto, Y. *Angew. Chem. Int. Ed.* **2018**, *57*, 3646.

(30) Pan, Z.; Fan, Z.; Lu, B.; Cheng, J. *Adv. Synth. Catal.* **2018**, *360*, 1761.

(31) Chan, Y.-C.; Yeung, Y.-Y. *Angew. Chem. Int. Ed.* **2018**, *57*, 3483.

(32) Xu, C.; Loh, C. C. J. *J. Am. Chem. Soc.* **2019**, *141*, 5381.

(33) Dreger, A.; Wonner, P.; Engelage, E.; Walter, S. M.; Stoll, R.; Huber, S. M. *Chem. Commun.* **2019**, *55*, 8262.

(34) Chan, Y.-C.; Yeung, Y.-Y. *Org. Lett.* **2019**, *21*, 5665.

(35) Kuwano, S.; Suzuki, T.; Yamanaka, M.; Tsutsumi, R.; Arai, T. *Angew. Chem. Int. Ed.* **2019**, *58*, 10220.

(36) Bergamaschi, G.; Lascialfari, L.; Pizzi, A.; Espinoza, M. I. M.; Demitri, N.; Milani, A.; Gori, A.; Metrangolo, P. *Chem. Commun.* **2018**, *54*, 10718.

(37) Kuwano, S.; Suzuki, T.; Hosaka, Y.; Arai, T. *Chem. Commun.* **2018**, *54*, 3847.

(38) Hermeke, J.; Toy, P. H. *Tetrahedron* **2011**, *67*, 4103.

(39) For a brief review on the isolation, bioactivity and synthesis of bis(indolyl)methanes, see: Praveen, P. J.; Parameswaran, P. S.; Majik, M. S. *Synthesis* **2015**, *47*, 1827.

(40) For representative methods for the synthesis of bis(indolyl)methanes, see: (a) Chen, D.; Yu, L.; Wang, P. G. *Tetrahedron Lett.* **1996**, *37*, 4467. (b) Denis, J.-N.; Mauger, H.; Vallée, Y. *Tetrahedron Lett.* **1997**, *38*, 8515. (c) Bandgar, B. P.; Shaikh, K. A. *Tetrahedron Lett.* **2003**, *44*, 1959. (d) Sato, S.; Sato, T. *Carbohydrate Res.* **2005**, *340*, 2251. (e) Abe, T.; Nakamura, S.; Yanada, R.; Choshi, T.; Hibino, S.; Ishikura, M. *Org. Lett.* **2013**, *15*, 3622. (f) Bahuguna, A.; Sharma, R.; Sagara, P. S.; Ravikumar, P. C. *Synlett* **2017**, *28*, 117. (g) Deb, M. L.; Deka, B.; Saikia, P. J.; Baruah, P. K. *Tetrahedron Lett.* **2017**, *58*, 1999. (h) Noland, W. E.; Kumar, H. V.; Flick, G. C.; Aspros, C. L.; Yoon, J. H.; Wilt, A. C.; Dehkordi, N.; Thao, S.; Schneerer, A. K.; Gao, S.; Tritch, K. J. *Tetrahedron* **2017**, *73*, 3913. (i) Boekell, N. G.; Cerone, D. J.; Boucher, M. M.; Quach, P. K.; Tentchou, W. B. N.; Reavis, C. G.; Okoh, I. I.; Reid, J. O. A.; Berg, H. E.; Chang, B. A.; Brindle, C. S. *SynOpen* **2017**, *1*, 97. (j) Ling, F.; Xiao, L.; Fang, L.; Feng, C.; Xie, Z.; Lv, Y.; Zhong, W. *Org. Biomol. Chem.* **2018**, *16*, 9274. (k) Tornquist, B. L.; de Paula Bueno, G.; Willig, J. C. M.; de Oliveira, I. M.; Stefani, H. A.; Rafique, J.; Saba, S.; Iglesias, B. A.; Botteselle, G. V.; Manarin, F. *ChemistrySelect* **2018**, *3*, 6358.

(41) Sathieshkumar, P. P.; Latha, P.; Nagarajan, R. *Eur. J. Org. Chem.* **2017**, 3161.

(42) Challa, C.; Ravindran, J.; Konai, M. M.; Varughese, S.; Jacob, J.; Kumar, B. S. D.; Haldar, J.; Lankalapalli, R. S. *ACS Omega* **2017**, *2*, 5187.

(43) (a) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164. (b) Ganta, S.; Chand, D. K. *Dalton Trans.* **2015**, *44*, 15181.

(44) Gillespie, D. E.; Brady, S. F.; Bettermann, A. D.; Cianciotto, N. P.; Liles, M. R.; Rondon, M. R.; Clardy, J.; Goodman, R. M.; Handelsman, J. *Appl. Environ. Microbiol.* **2002**, *68*, 4301.

(45) See Supporting Information for details.

(46) Cai, S.-X.; Li, D.-H.; Zhu, T.-J.; Wang, F.-P.; Xiao, X.; Gu, Q.-Q. *Helv. Chim. Acta* **2010**, *93*, 791.

(47) Yoo, M.; Choi, S.-U.; Choi, K. Y.; Yon, G. H.; Chae, J.-C.; Kim, D.; Zylstra, G. J.; Kim, E. *Biochem. Biophys. Res. Commun.* **2008**, *376*, 96.

(48) Khuzhaev, B. U.; Aripova, S. F.; Shakirov, R. S. *Chem. Nat. Compd.* **1994**, *30*, 635.

(49) Bell, R.; Carmeli, S.; Sar, N. *J. Nat. Prod.* **1994**, *57*, 1587.