OL Organic Letters

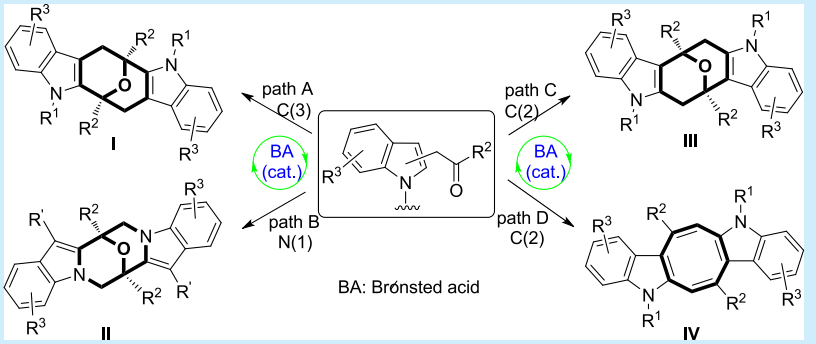
pubs.acs.org/OrgLett Letter

Brønsted Acid-Promoted Cyclodimerization of Indolyl Ketones: Construction of Indole Fused-Oxabicyclo[3.3.1]nonane and -Cyclooctatetraene Ring Systems

Lang Zhao, Zhi-Hua Yan, Shuai Tang, Zhong-Lin Wei, and Wei-Wei Liao*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c03895 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: A Brønsted acid-promoted cyclodimerization of C(3)-, C(2)-, or N(1)-substituted indole ketone derivatives is described. A wide range of structurally diverse bisindole fused-9-oxabicyclo[3.3.1]nonane and bisindole fused-cyclooctatetraene (COT) derivatives can be prepared in good to high yields with high efficiency.

As a privileged structural motif, the indole core is ubiquitously present in a range of biological compounds.[1] Among various indole ring-containing compounds, bisindole deriviatives have attracted considerable interest due to their broad range of biological properties and frequent occurrence in natural products,[1a,b,2] in which two indole units can be incorporated into fused or open systems. Therefore, various methods have been developed to construct these structurally diverse scaffolds,[3,4] in which the dimerization of two identical indole derivatives provides a direct and efficient strategy for accessing various bisindole derivatives.[3a,b,d−f] Among them, dehydrodimerization around the indole core is a common approach that affords various bisindole frameworks with an open system.[3a,b,d,e] In addition, a number of synthetic methods for the construction of bisindoles incorporating an extra cyclic ring between two indole rings via a cyclodimerization of two identical indole derivatives have also been demonstrated. For example, the cyclodimerizations of vinylindoles or indole-derived donor−acceptor cyclopropane molecules have proven to be quite efficient in assembling six- or five-membered ring systems fused with two indole moieties.[4]

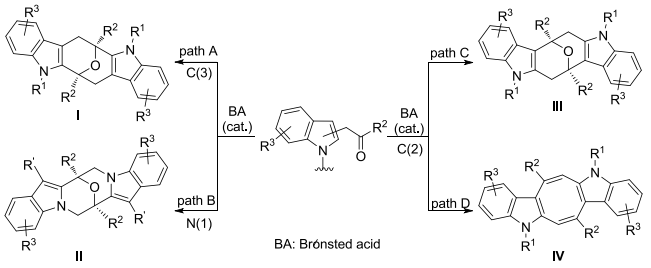
9-Oxabicyclo[3.3.1]nonane skeletons frequently occur in bioactive molecules and natural products, and compounds comprised of this oxatricyclic framework have shown potency toward HIV-1 inhibition and central nervous system diseases.[5,6] There are several established methods such as Brønsted acid-[7a−d] and transition metal (TM)-catalyzed reactions[7e,f] to construct such oxacyclic bridged-ring structures in recent decades.[7] For examples, Yao et al. reported a Brønsted acid-promoted dimerization of *o*-alkynylbenzaldehydes to provide a convenient one-step synthesis of symmetrical 2,3,6,7-dibenzo-9-oxabicyclo[3.3.1]nona-2,6-dienes in the presence of 45% aqueous HBF_4 in acetic acid.[7c] The Liu group has developed elegant TM-catalyzed cyclizations to prepare 9-oxabicyclo[3.3.1]nonadienes from 2-alkynyl-1-carbonylbenzenes via oxonium ion intermediates.[7e,f] However, the synthetic route for the construction of fused-9-oxabicyclo[3.3.1]nonane frameworks with the substituents at the bridgehead carbon is still limited. Furthermore, the development of bisindole fused-9-oxabicyclo[3.3.1]nonane derivatives is still unexploited considering the fact that structural elaboration of the indole core with additional ring fusion represents an efficient and useful approach for exploiting the indole scaffolds for new biological activities.[8]

With the goal of developing a practical and efficient synthetic approach for the construction of various polycyclic frameworks from readily accessible starting materials,[9] we

Received: November 25, 2020

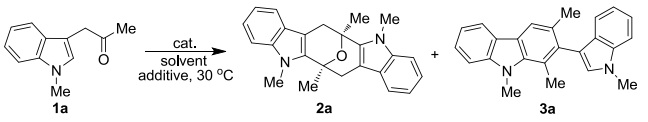
envisioned that the cyclodimerization of two identical indoles bearing a ketone moiety may provide an efficient approach for accessing indole fused-9-oxabicyclo[3.3.1]nonane derivatives via a facile electrophilic addition/cyclization sequence. Herein, we report a Brønsted acid-catalyzed cyclodimerization of C(3)-, C(2)-, or N(1)-substituted indole ketone substrates to prepare structurally diverse bisindole fused-9-oxabicyclo[3.3.1]nonane derivatives, coupled with the formation of bisindole fused-cyclooctatetraene (COT) from 2-substituted indole ketone substrates (Scheme 1).

Scheme 1. Working Plan



We initially examined the cyclodimerization of 3-substituted indole ketone **1a** in the presence of several Brønsted acids in toluene at 30 °C (Table 1, entries 1−5). The results indicated

Table 1. Optimal Reaction Conditions[a]



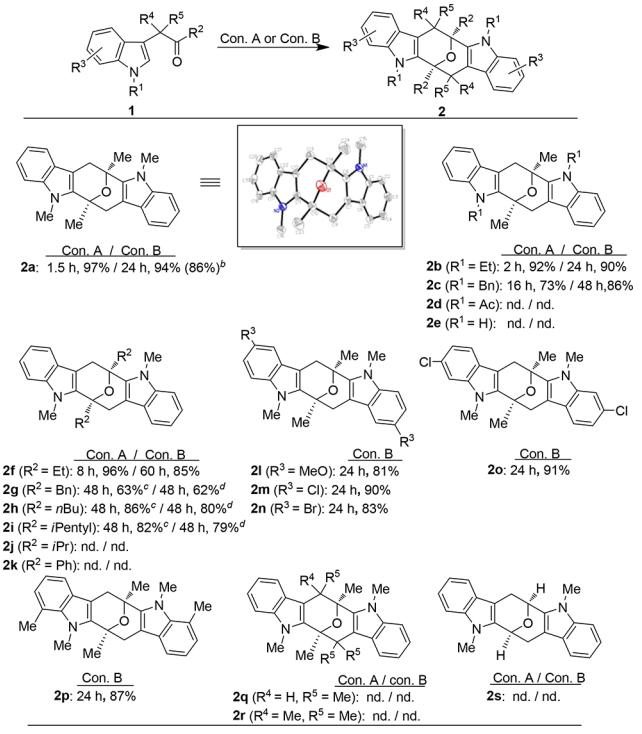
entry	catalyst (equiv)	solvent	t (h)	yield of **2a** (%)[b]
1	HOAc (3.0)	toluene	24	nd
2	TFA (3.0)	toluene	24	nd
3[c]	MsOH (3.0)	toluene	24	17
4	TfOH (3.0)	toluene	24	69
5	PPA (3.0)	toluene	24	14
6	$BF_3{\cdot}Et_2O$ (1.5)	toluene	24	38
7	TfOH (3.0)	hexane	24	65
8	TfOH (3.0)	DCM	24	19
9	TfOH (3.0)	n-Bu_2O	4	94
10	TfOH (3.0)	DMF	24	nd
11[d]	TfOH (0.75)	n-Bu_2O	1.5	97
12[d]	TfOH (0.3)	n-Bu_2O	11	34
13[e]	$HNTf_2$ (0.15)	toluene	24	94

[a]Reactions were performed with **1a** (0.4 mmol), catalyst, and solvent (0.2 M) at 30 °C under a nitrogen atmosphere. [b]Isolated yields. [c]A 49% yield of **3a** was obtained. [d]Na_2SO_4 (0.8 mmol, 2 equiv) was added. [e]At a concentration of 0.4 M.

that HOAc and TFA did not afford any desired product, while the desired bisindole fused-9-oxabicyclo[3.3.1]nonane **2a** could be obtained when organic sulfonic acids or PPA was employed. Lewis acids such $BF_3{\cdot}Et_2O$ and $TiCl_4$ gave inferior results (entry 6 and Table S1). Notably, carbazole **3a** could be observed when MsOH was employed. Though TfOH-catalyzed reaction gave a promising 69% yield, 300 mol % TfOH and the sluggish process made this transformation far from efficient. Next, in the presence of TfOH as a catalyst, different types of solvents were evaluated (entries 7−10). It turned out that the desired cyclodimerization of **1a** proceeded smoothly in n-Bu_2O and furnished the desired product **2a** in high yield with a short reaction time, while other solvents can afford **2a** with low to medium levels of production. However, a polar solvent failed to give any desired product (entry 10). Further investigation indicated that the addition of several additives such as Na_2SO_4 and 5 Å molecular sieves can facilitate this cyclodimerization with the smaller amount of TfOH, and a better result can be obtained in 97% yield in the presence of TfOH (0.75 equiv) and Na_2SO_4 within 1.5 h (entries 11 and 12). Although any attempts to further reduce the amount of TfOH failed to provide **2a** with reasonable yield by surveying other reaction parameters such as the reaction temperature and the reaction concentration, we were pleased to find that 15 mol % $HNTf_2$ enabled this cyclodimerization to procced well and afforded **2a** with comparable yield in toluene, albeit with a prolonged reaction time (for details, see the Supporting Information).

With the optimized reaction conditions in hand, the investigation of the substrate scope of the cyclodimerization of 3-substituted indole ketones was carried out first. As shown in Scheme 2, this cyclodimerization was amenable to a wide

Scheme 2. Substrate Scope for Cyclodimerization of 1[a]



[a]For condition A, reactions were performed with **1a** (0.4 mmol), TfOH (0.75 equiv), Na_2SO_4 (2 equiv), and n-Bu_2O (0.2 M) at 30 °C under a nitrogen atmosphere. For condition B, reactions were performed with **1a** (0.4 mmol), $HNTf_2$ (0.15 equiv), and toluene (0.4 M) at 30 °C under a nitrogen atmosphere. Yields of isolated products. The X-ray structure of **2a** is shown. [b]**1a** (2 mmol). [c]TfOH (3.0 equiv). [d]$HNTf_2$ (0.5 equiv).

range of C(3)-substituted indole ketones **1** bearing different R^1−R^3 groups, providing the bisindole fused-9-oxabicyclo[3.3.1]nonane products **2** in high yields in the presence of TfOH (Con. A) or $HNTf_2$ (Con. B). At first, different *N*-alkyl substituents (R^1) of 3-substituted indole substrates were evaluated and *N*-ethyl-substituted indole **1b**

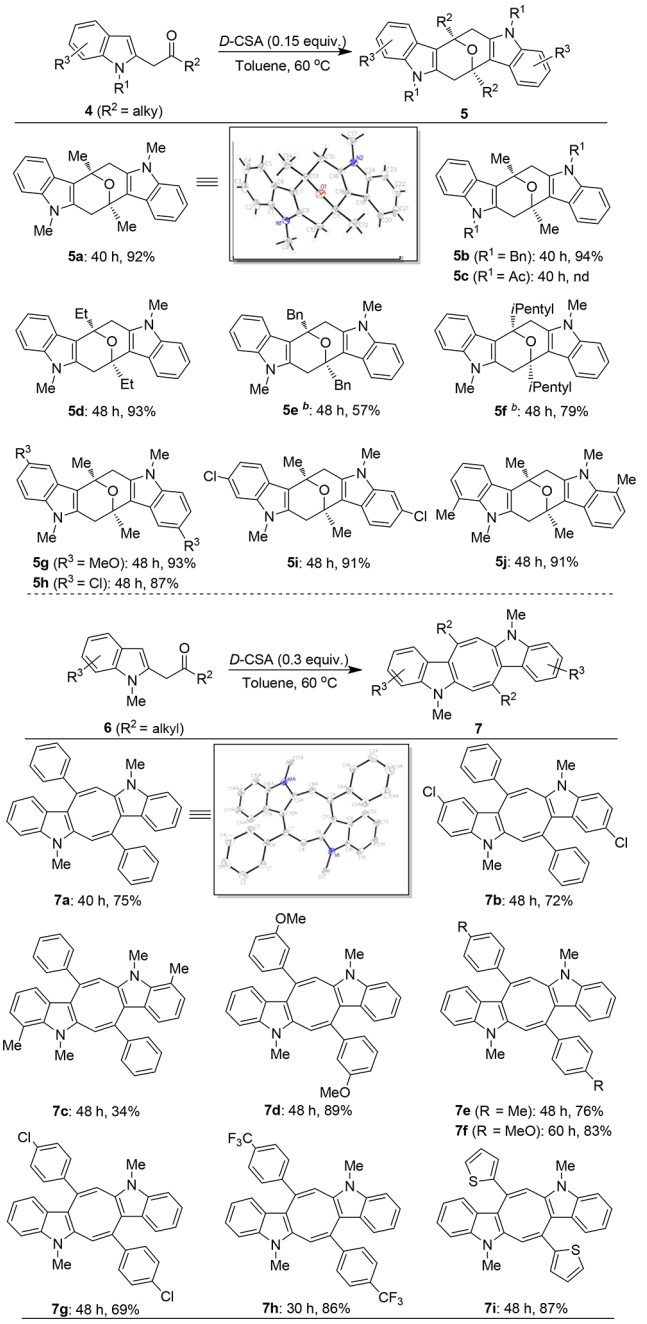
https://dx.doi.org/10.1021/acs.orglett.0c03895
Org. Lett. XXXX, XXX, XXX−XXX

provided a result similar to that of substrate **1a**, while a prolonged reaction time was required when *N*-benzyl indole **1c** was employed (**2c**). However, N-acylated indole and free (NH) indole analogues (**1d** and **1e**, respectively) failed to give any desired products. Substrates bearing alkyl groups such as ethyl, benzyl, *n*-butyl, and isopentyl groups can be employed in this cyclization to give the desired products (**2f**−**2i**, respectively) in good yields; the cyclodimerization reactions could not be applied to isopropyl and phenyl (R^2) ketone analogues (**1j** and **1k**, respectively), and no desired reactions occurred under the optimized reaction conditions, presumably due to the steric hindrance effects. In addition, various *N*-methylindoles with both electron-rich [OMe (**1l**) and Me (**1p**)] and electron-poor [Cl and Br (**1m**−**1o**)] groups (R^3) at the phenyl ring worked well and gave rise to the corresponding products (**2l**−**2p**) in good yields in the presence of 15 mol % $HNTf_2$, regardless of the substitution patterns. However, current BA-catalyzed cyclodimerization seemed to be sensitive to R^4 and R^5 groups, and no desired products were observed when either R^4 or R^5 was introduced (**2q** and **2r**). Additionally, treatment of a 3-substituted indole aldehyde with either TfOH or $HNTf_2$ led to a complex mixture (**2s**).

Next, we turned our attention to the feasibility of the cyclodimerization of C(2)-substituted indole ketones **4** by moving the ketone unit from C(3) to C(2) (Scheme 3). Although 2-substituted indole ketone **4a** contained a more nucleophilic C(3) site, initially performing the reactions of **4a** under the aforementioned reaction conditions did not give the desired product **5a** in reasonable yield. After modifying the reaction conditions (Table S2), we were pleased to find that isosteric bisindole fused-9-oxabicyclo[3.3.1]nonane isomer **5a** can be obtained in high yield in the presence of D-CSA (0.15 equiv) in toluene at 60 °C. It should be noted that the less acidic D-CSA was more efficient than strong BAs such as TfOH and $HNTf_2$, and no corresponding carbazole analogue was observed in the cyclodimerization of 2-substituted indole ketone **4a**. Subsequently, a range of C(2)-substituted indole ketones bearing different substituents (R^2 = alkyl, and R^3 = MeO, Me, or Cl) were examined, and the cyclodimerization reactions displayed good functional group compatibility and proceeded in high yields with a variety of different products formed (Scheme 3, **5b** and **5d**−**5j**).

When we directed our attention to the synthesis of bisindole fused-9-oxabicyclo[3.3.1]nonanes by using C(2)-substituted indolyl aryl ketones **6**, we found that this BA-catalyzed cyclodimerization gave bisindole fused cyclooctatetraenes **7**, instead of bisindole fused 9-oxabicyclo[3.3.1]nonanes **5**. Under the slightly modified reaction conditions (0.3 equiv of D-CSA), the cyclization of **6a** can procced smoothly to afford bisindole fused cyclooctatetraene **7a** in 75% yield. The 2-substituted indolyl aryl ketones bearing either electron-withdrawing or electron-donating groups (R^3 or R^2) with different substituent patterns are amenable to the reaction conditions and afforded the desired products (**7b**−**7i**) with good to high yields. Notably, the bisindole fused-cyclooctatetraene framework is the core structure of indole alkaloid caulerpin, which displayed antinociceptive and anti-inflammatory activities,[10] as well as indole-based optoelectronic materials that showed unique optoelectronic characteristics with wide optical band gaps and redox-active properties.[11] The structures of fused 9-oxabicyclo[3.3.1]nonanes and fused cyclooctatetraenes were unambiguously confirmed by the exemplification of X-ray

Scheme 3. Substrate Scope for Cyclodimerization of 4[a]



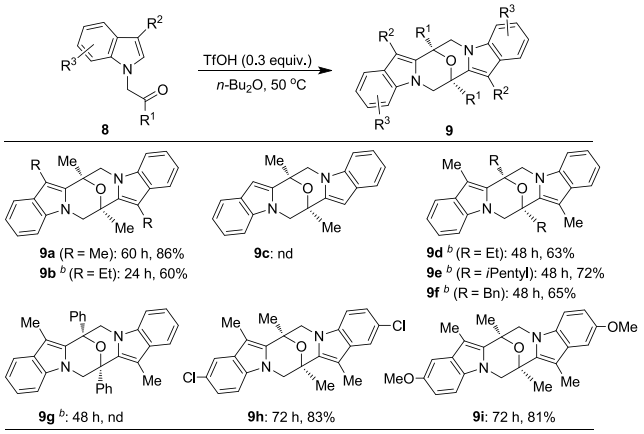
[a]Reactions were performed with **4** (0.2 mmol) and D-CSA (0.15 or 0.3 equiv) in toluene (0.2 M) under a nitrogen atmosphere. Yields of isolated products. [b]D-CSA (0.3 equiv). The X-ray structures of **5a** and **7a** are shown.

crystal structural analysis of products **2a**, **5a**, and **7a** (Schemes 2 and 3).

Encouraged by these results, we examined N(1)-substituted indolyl ketones **8** for the construction of bisindole aza-analogues **9** consequently (Scheme 4). To our delight, the desired cyclodimerization of N(1)-substituted indolyl ketone **8a** proceeded smoothly in the presence of 30 mol % TfOH and *n*-Bu_2O at 50 °C and delivered bisindole aza-analogue **9a** in 86% yield. C(3) ethyl-substituted indole **8b** was also examined, which gave the desired product **9b** in 60% yield under the slightly modified reaction conditions. However, substrate **8c**

https://dx.doi.org/10.1021/acs.orglett.0c03895
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 4. Substrate Scope for Cyclodimerization of 8[a]

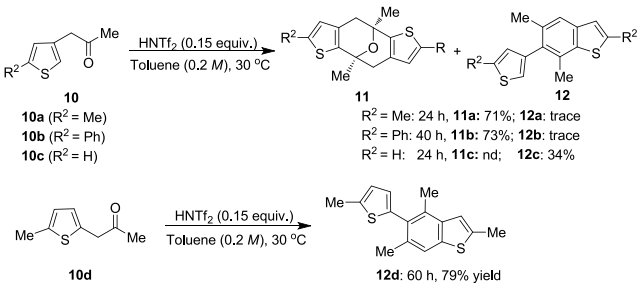


[a]Reactions were performed with **8** (0.2 mmol) and TfOH (0.3 equiv) in n-Bu_2O (0.2 M) under a nitrogen atmosphere. Yields of isolated products. [b]TfOH (0.75 equiv), 30 °C.

with the unshielded reactive C(3) site did not give the corresponding bisindole analogue **9c**. N(1)-substituted indolyl ketones bearing various R^1 substituents such as ethyl, isopentyl, and benzyl groups were well tolerated and gave the desired products in good yields (**9d**–**9f**), while aryl-substituted N(1)-substituted indole **8g** did not afford any desired product. In addition, N(1)-substituted indoles with both electron-rich [OMe (**8i**)] and electron-poor [Cl (**8h**)] groups (R^3) can furnish the desired products (**9h** and **9i**) in good yields (for details about the initial investigation of catalytic enantioselective cyclodimerization, see Schemes S3–S35).

Further extension of the application of this cyclodimerization to access other bisheteroarene fused 9-oxabicyclo[3.3.1]-nonanes was examined (Scheme 5). Other than indole

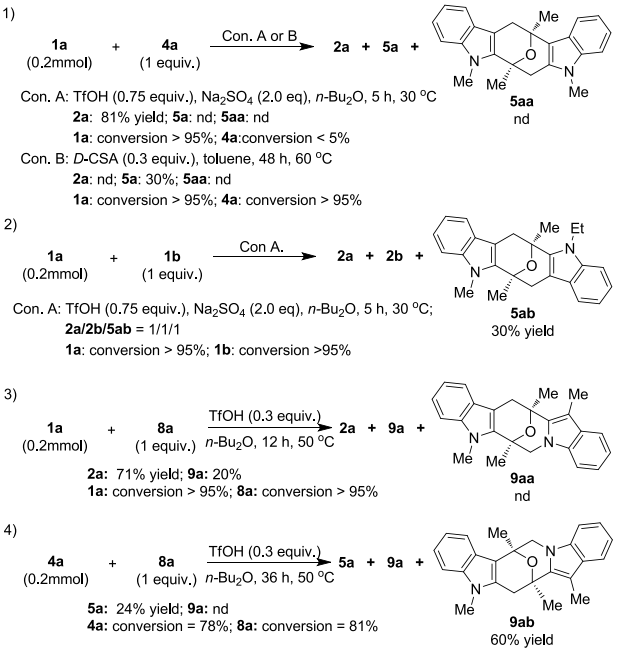
Scheme 5. Preparation of Bisheteroarene Fused 9-Oxabicyclo[3.3.1]nonanes



substrates, 5-substituted thiophenes **10** tethered ketone moieties at the C(3) position can readily deliver the desired fused polycyclic heterocyclic products (**11a** and **11b**) in good yields under the optimized reaction conditions. However, 5-unsubstituted analogue **10c** and thiophene **10d** tethered ketone moieties at the C(2) position gave the corresponding benzo-fused thiophenes (**12c** and **12d**). Additionally, BA-catalyzed cyclodimerizations of other electron-rich heteroarene analogues such as benzo-fused thiophene, pyrrole, and furan with the tethered ketone moieties did not give bisheteroarene fused-9-oxabicyclo[3.3.1]nonane derivatives (for details, see Scheme S1).

In addition, to explore the diversity of this transformation to access other asymmetric bisindole fused-9-oxabicyclo[3.3.1]-nonane derivatives, several cross cyclodimerization experiments were conducted (Scheme 6). Treatment of 3-substituted

Scheme 6. Cross Cyclodimerization Experiments



indole ketone **1a** and 2-substituted indole ketone **4a** with BA did not give cross cyclodimerized product **5aa** under either condition A or condition B and afforded the corresponding cyclodimerized product **2a** or **5a** instead. The cross cyclodimerization experiment between **1a** and **8a** also failed to give cross cyclization product **9aa**. Notably, the cyclodimerization between **1a** and **1b** or **4a** and **8a** delivered the corresponding cross cyclization product **5ab** (30% yield) or **9ab** (60% yield) along with a homogeneous cyclodimerization product (**2a**, **2b**, or **5a**), which indicated that the cyclodimerization may be prone to occur between indole substrates with similar reactivities.

On the basis of our results and the preceding reports,[7] a possible mechanism was proposed (for details, see Scheme S2).

In summary, we have developed a novel Brønsted acid-catalyzed cyclodimerization of C(3)-, C(2)-, or N(1)-substituted indole ketone derivatives, which provided a practical and efficient protocol for the preparation of structurally diverse bisindole fused 9-oxabicyclo[3.3.1]nonanes and bisindole fused cyclooctatetraenes (COT). Under the optimized reaction conditions, various bisindole fused 9-oxabicyclo[3.3.1]nonanes with the substituents at the bridgehead carbon can be prepared from readily available starting materials in good to high yields with efficiency.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03895.

Experimental procedures and analytical data for all new compounds (PDF)

https://dx.doi.org/10.1021/acs.orglett.0c03895
Org. Lett. XXXX, XXX, XXX−XXX

Accession Codes

CCDC 2036366−2036368 and 2036603 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

Wei-Wei Liao − *Department of Organic Chemistry, College of Chemistry, Jilin University, Changchun 130012, China;* orcid.org/0000-0001-6225-4258; Email: wliao@jlu.edu.cn

Authors

Lang Zhao − *Department of Organic Chemistry, College of Chemistry, Jilin University, Changchun 130012, China*

Zhi-Hua Yan − *Department of Organic Chemistry, College of Chemistry, Jilin University, Changchun 130012, China*

Shuai Tang − *Department of Organic Chemistry, College of Chemistry, Jilin University, Changchun 130012, China*

Zhong-Lin Wei − *Department of Organic Chemistry, College of Chemistry, Jilin University, Changchun 130012, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c03895

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors thank the NSFC (21772063) and the Open Project of the State Key Laboratory for Supramolecular Structure and Materials (sklssm202017) for financial support.

REFERENCES

(1) (a) Sundberg, R. J. *Indoles*; Academic Press: San Diego, 1996. (b) Ryan, K. S.; Drennan, C. L. Divergent Pathways in the Biosynthesis of Bisindole Natural Products. *Chem. Biol.* **2009**, *16*, 351−364. (c) Ma, Y. M.; Liang, X. A.; Kong, Y.; Jia, B. Structural Diversity and Biological Activities of Indole Diketopiperazine Alkaloids from Fungi. *J. Agric. Food Chem.* **2016**, *64*, 6659−6671.

(2) (a) Kam, T. S.; Choo, Y.-M. In *The Alkaloids*, Vol. *63*; Cordell, G. A., Ed.; Academic Press: Amsterdam, 2006; pp 181−337. (b) Shiri, M.; Zolfigol, M. A.; Kruger, H. G.; Tanbakouchian, Z. Bis- and Trisindolylmethanes (BIMs and TIMs). *Chem. Rev.* **2010**, *110*, 2250−2293. (c) Ueda, H. Synthetic Studies toward Dimeric Indole Alkaloids Based on Convergent Synthetic Strategy. *Chem. Pharm. Bull.* **2020**, *68*, 117−128.

(3) Natural product synthesis via oxidative coupling of the phenyl ring of indole: (a) Edwankar, C. R.; Edwankar, R. V.; Deschamps, J. R.; Cook, J. M. Nature-Inspired Stereospecific Total Synthesis of P-(+)-Dispegatrine and Four Other Monomeric Sarpagine Indole Alkaloids. *Angew. Chem., Int. Ed.* **2012**, *51*, 11762−11765. (b) Liang, K. J.; Yang, J.; Tong, X. G.; Shang, W. B.; Pan, Z. Q.; Xia, C. F. Biomimetic Synthesis of Moschamine-Related Indole Alkaloids via Iron-Catalyzed Selectively Oxidative Radical Coupling. *Org. Lett.* **2016**, *18*, 1474−1477. For the construction of the C(2)−C(2′) biindolyl, see: (c) Xu, X. H.; Liu, G. K.; Azuma, A.; Tokunaga, E.; Shibata, N. Synthesis of Indole and Biindolyl Triflones: Trifluoromethanesulfonylation of Indoles with Tf_2O/TTBP (2,4,6-tri-tert-butylpyridine) System. *Org. Lett.* **2011**, *13*, 4854−4857. For the construction of C(2)−C(3′) biindolyl, see: (d) Liang, Z. J.; Zhao, J. L.; Zhang, Y. H. Palladium-Catalyzed Regioselective Oxidative Coupling of Indoles and One-Pot Synthesis of Acetoxylated Biindolyls. *J. Org. Chem.* **2010**, *75*, 170−177. For the construction of C(3)−C(3′) biindolyl, see: (e) Li, Y.; Wang, W. H.; Yang, S. D.; Li, B. J.; Feng, C.; Shi, Z. J. Oxidative dimerization of N-protected and free indole derivatives toward 3,3′-biindoles via Pd-catalyzed direct C−H transformations. *Chem. Commun.* **2010**, *46*, 4553−4555. (f) Ren, H.; Song, J. R.; Li, Z. Y.; Pan, W. D. Oxazoline-/Copper-Catalyzed Alkoxyl Radical Generation: Solvent Switched to Access 3a,3a′-Bisfuroindoline and 3-Alkoxyl Furoindoline. *Org. Lett.* **2019**, *21*, 6774−6778.

(4) (a) Yin, L.; Wang, Y.; Sun, M.; Shi, F. Brønsted Acid-Catalyzed [3 + 2] Cyclodimerization of 3-Alkyl 2-vinylindoles Leading to the Diastereoselective Construction of a Pyrroloindole Framework. *Adv. Synth. Catal.* **2016**, *358*, 1093−1102. (b) Ivanova, O. A.; Budynina, E. M.; Chagarovskiy, A. O.; Rakhmankulov, E. R.; Trushkov, I. V.; Semeykin, A. V.; Shimanovskii, N. L.; Melnikov, M. Y. Domino Cyclodimerization of Indole-Derived Donor−Acceptor Cyclopropanes: One-Step Construction of the Pentaleno[1,6-a,b]indole Skeleton. *Chem. - Eur. J.* **2011**, *17*, 11738−11742. (c) Kawasaki, I.; Terano, M.; Yada, E.; Kawai, M.; Yamashita, M.; Ohta, S. Novel cyclodimerization of 1-tert-butoxycarbonyl-3-alkenylindole derivatives. *Tetrahedron Lett.* **2005**, *46*, 1199−1203.

(5) (a) Maurin, C.; Bailly, F.; Cotelle, P. Structure-Activity Relationships Of HIV-1 Integrase - Enzyme − Ligand Interactions. *Curr. Med. Chem.* **2003**, *10*, 1795−1810. (b) Dupont, R.; Jeanson, L.; Mouscadet, J. F.; Cotelle, P. Synthesis and HIV-1 Integrase Inhibitory Activities of Catechol and Bis-Catechol Derivatives. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3175−3178.

(6) (a) Wunsch, B.; Zott, M.; Hofner, G. Synthese enantiomerenreiner 6,10-Epoxybenzocycloocten-7-arnine mit ZNS-Aktivitat. *Arch. Pharm.* **1992**, *325*, 733−739. (b) Komala, I.; Ito, T.; Nagashima, F.; Yagi, Y.; Kawahata, M.; Yamaguchi, K.; Asakawa, Y. Gibberellin 3-oxidases in developing embryos of the southern wild cucumber, Marah macrocarpus. *Phytochemistry* **2010**, *71*, 1387−1394.

(7) (a) Kagan, J.; Agdeppa, D. A.; Chang, A. I.; Chen, S. A.; Harmata, M. A.; Melnick, B.; Patel, G.; Poorker, C.; Singh, S. P.; Watson, W. H.; Chen, J. S.; Zabel, V. Reactions of Phenylacetaldehydes in Fluorosulfuric Acid. *J. Org. Chem.* **1981**, *46*, 2916−2920. (b) Harmata, M.; Murray, T. Synthetic Methodology for the Preparation of Analogues of Kagan's Ether. *J. Org. Chem.* **1989**, *54*, 3761−3763. (c) Zhang, H.; Cui, W. C.; Hu, Z. L.; Yu, S. Y.; Wang, S. Z.; Yao, Z. J. Brønsted acid-promoted dimerization of o-alkynylbenzaldehydes: a onestep synthesis of functionalized Kagan's ether analogues. *RSC Adv.* **2012**, *2*, 5101−5104. (d) Terada, M.; Li, F.; Toda, Y. Chiral Silver Phosphate Catalyzed Transformation of orthoAlkynylaryl Ketones into 1H-Isochromene Derivatives through an Intramolecular-Cyclization/Enantioselective-Reduction Sequence. *Angew. Chem., Int. Ed.* **2014**, *53*, 235−239. (e) Bhunia, S.; Wang, K. C.; Liu, R. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 5063−5066. (f) Teng, T. M.; Das, A.; Huple, D. B.; Liu, R. S. Gold-Catalyzed Stereoselective Synthesis of 9-Oxabicyclo[3.3.1]nona-4,7-dienes from Diverse 1-Oxo-4-oxy-5-ynes: A Viable Formal [4 + 2] Cycloaddition on an s-trans-Heterodiene Framework. *J. Am. Chem. Soc.* **2010**, *132*, 12565−12567.

(8) (a) Hua, T. B.; Xiao, C.; Yang, Q. Q.; Chen, J. R. Recent advances in asymmetric synthesis of 2-substituted indoline derivatives. *Chin. Chem. Lett.* **2020**, *31*, 311−323. (b) Bandini, M.; Eichholzer, A. Catalytic Functionalization of Indoles in a New Dimension. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608−9644.

(9) (a) Wang, T. T.; Zhang, D.; Liao, W. W. Versatile synthesis of functionalized β- and γ-carbolines via Pd-catalyzed C−H addition to nitriles/cyclization sequences. *Chem. Commun.* **2018**, *54*, 2048−2051. (b) Wang, T. T.; Zhao, L.; Zhang, Y. J.; Liao, W. W. Pd-Catalyzed Intramolecular Cyclization via Direct C-H Addition to Nitriles: Skeletal Diverse Synthesis of Fused Polycyclic Indoles. *Org. Lett.* **2016**, *18*, 5002−5005. (c) Zhao, L.; Liao, W. W. Pd-Catalyzed intramolecular C-H addition to the cyano-group: construction of functionalized 2,3-fused thiophene scaffolds. *Org. Chem. Front.* **2018**, *5*, 801−805.

(10) (a) Su, J. Y.; Zhu, Y.; Zeng, L. M.; Xu, X. H. A New Bisindole from Alga Caulerpa serrulata. *J. Nat. Prod.* **1997**, *60*, 1043−1044. (b) Govenkar, M. B.; Wahidulla, S. Constituents of Chondria armata. *Phytochemistry* **2000**, *54*, 979−981.

(11) (a) Wang, F.; Li, X. C.; Lai, W. Y.; Chen, Y.; Huang, W.; Wudl, F. Synthesis and Characterization of Symmetric Cyclooctatetraindoles: Exploring the Potential as Electron-Rich Skeletons with Extended π-Systems. *Org. Lett.* **2014**, *16*, 2942−2945. (b) Wang, L.; Fang, Q.; Lu, Q.; Zhang, S. J.; Jin, Y. Y.; Liu, Z. Q. Octupolar (C3 and S4) Symmetric Cyclized Indole Derivatives: Syntheses, Structures, and NLO Properties. *Org. Lett.* **2015**, *17*, 4164−4167.

https://dx.doi.org/10.1021/acs.orglett.0c03895
Org. Lett. XXXX, XXX, XXX−XXX