ChemComm
Chemical Communications

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: Z. Ge, L. Yang, Y. you, Z. Wang, K. Xie, M. Zhou, J. Zhao and W. Yuan, *Chem. Commun.*, 2020, DOI: 10.1039/C9CC09939E.

ROYAL SOCIETY OF CHEMISTRY View Article Online
DOI: 10.1039/C9CC09939E

Journal Name

COMMUNICATION

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Asymmetric dearomatization of 2-nitrobenzofurans by organocatalyzed one-step Michael addition to access 3,3'-disubstituted oxindoles

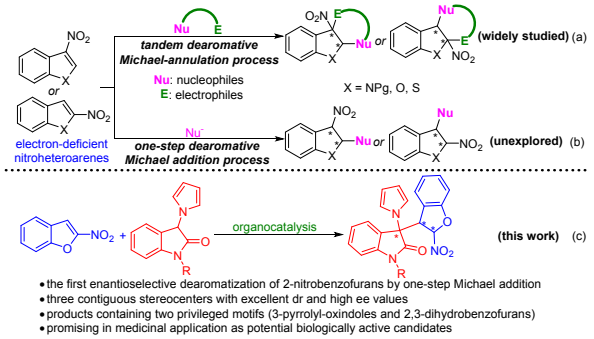
Zhen-Zhen Ge,[a,d,§] Lei Yang,[a,d,§] Yong You,[b] Zhen-Hua Wang,[b] Ke-Xin Xie,[c] Ming-Qiang Zhou,[a] Jian-Qiang Zhao,[b]* and Wei-Cheng Yuan[a,b]*

An efficient enantioselective dearomatization of 2-nitrobenzofurans was realized via an organocatalyzed one-step Michael addition process. This method provides a facile strategy to access a range of structurally diverse 3,3'-disubstituted oxindoles, which are featured with an intriguing combination of two privileged motifs including 3-pyrrolyl-substituted-oxindoles and 2,3-dihydrobenzofurans substructures, in excellent results.

Catalytic asymmetric dearomatization of simple planar aromatic compounds has emerged as one of powerful and reliable strategies for the construction of enantioenriched there-dimensional molecules.[1] Notably, the vast majority of the reported asymmetric dearomative reactions are typically focused on the application of the intrinsic nucleophilicity of electron-rich arenes and heteroarenes.[1,2] Actually, installing a suitable electron-withdrawing substituent on the arenes and heteroarenes can reverse them into electron-deficient compounds thus serving as electrophiles for umpolung-like reactions.[3] In this context, creative reactions for the construction of interesting cyclic compounds with innovative structures would be expected by using electron-deficient arenes and heteroarenes. Therefore, exploring new methods to realize the asymmetric dearomatization of electron-deficient aromatic compounds in organic synthesis remains in high demand and has bright prospect.

Electron-deficient nitroheteroarenes, such as 2- and 3-nitroindoles,[4,5] 2-nitrobenzofurans,[6] 2- and 3-nitrobenzothiophenes,[5f,5o,6a,6e,7] have been used as C2 synthons for various enantioselective dearomative annulation reactions in recent years. It is noteworthy that almost all of these asymmetric reactions undergo a tandem dearomatization/annulation process for the formation of polycyclic structures, mainly relying on the first electrophilicity and the sequential nucleophilicity of electron-deficient nitroheteroarenes (Scheme 1, a).[4-7] Despite the success of these reactions, however, to the best of our knowledge, the involvement of electron-deficient nitroheteroarenes as Michael acceptors just undergoing one-step dearomative Michael addition has remained unexplored (Scheme 1, b). As part of our continuing efforts on the research of the asymmetric dearomatization of electron-deficient nitroheteroarenes,[4,5b,5c,5e,5i,6b,6d,6e,7] we were intrigued by the possibility of only one-step dearomative Michael addition to electron-deficient nitroheteroarenes with suitable nucleophiles under a catalytic asymmetric control. If successful, undoubtedly, the dearomative Michael addition reaction will lead to the formation of chiral 2,3-disubstituted-2,3-dihydrobenzo-heterocycle skeletons (Scheme 1, b), which are ubiquitous structural units in a number of biologically active compounds.[8]

Scheme 1 Outline of this work.



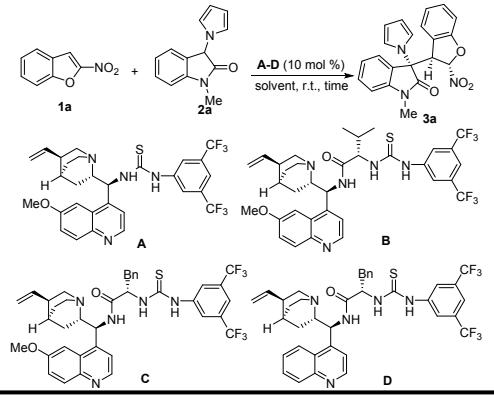
3-Monosubstituted oxindoles have emerged as a type of robust nucleophiles, and they can react with various electrophiles via asymmetric catalysis to generate structurally diverse 3,3'-disubstituted oxindoles,[9] which are commonly occurring structural motifs found in many natural products and pharmaceuticals.[10] Inspired by the elegant works in this field, we chose to focus on the catalytic asymmetric dearomative Michael addition of 3-pyrrolyl-oxindoles[11] to 2-

[a] National Engineering Research Center of Chiral Drugs, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu, 610041, China.
[b] Institute for Advanced Study, Chengdu University, Chengdu 610106, China. E-mail: yuanwc@cioc.ac.cn; zhaojianqiang@cdu.edu.cn
[c] Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu 610041, China
[d] University of Chinese Academy of Sciences, Beijing, 100049, China
§These authors contributed equally.

† Electronic Supplementary Information (ESI) available: Experimental procedures, spectral data of new compounds, and crystallographic data. CCDC 1943699. For ESI and crystallographic data in CIF or other electronic format. See DOI: 10.1039/x0xx00000x

nitrobenzofurans for constructing chiral 3,3'-disubstituted oxindoles, which are featured with an intriguing combination of two privileged motifs including 3-pyrrolyl-substituted-oxindoles and 2,3-dihydrobenzofurans substructures (Scheme 1, c). Notably, this work represents the first example of catalytic asymmetric dearomatizaiton of electron-deficient nitroheteroarenes only via one-step Michael addition process. Herein, we report our successful study on the reaction with a multiple hydrogen-bonding bifunctional-thiourea catalyst, affording optically enriched 3,3'-disubstituted oxindoles bearing three contiguous stereocenters including one quaternary and two tertiary stereogenic centers (Scheme 1, c), and on the further exploration for the potentially promising application of the products in medicinal chemistry.

Table 1. Optimization of reaction conditions[a]

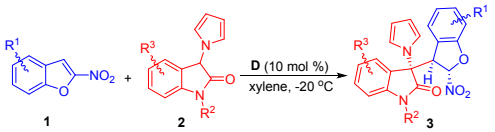


entry	A-D	solvent	time (h)	yield (%)[b]	dr[c]	ee (%)[c]
1	**A**	toluene	24	89	89:11	52
2	**B**	toluene	16	97	82:18	76
3	**C**	toluene	15	98	88:12	79
4	**D**	toluene	15	99	91:9	87
5	**D**	CH_2Cl_2	20	82	89:11	86
6	**D**	$CHCl_3$	18	87	88:12	83
7	**D**	xylene	18	98	92:8	89
8	**D**	mesitylene	20	99	90:10	86
9	**D**	MTBE	48	84	92:8	90
10[d]	**D**	xylene	28	99	96:4	94
11[e]	**D**	xylene	40	99	97:3	96

[a]Unless otherwise noted, the reactions were carried out with **1a** (0.12 mmol), **2a** (0.1 mmol), and 10 mol % catalyst in 1.0 mL of solvent at room temperature. [b]Isolated yields. [c]Determined by chiral HPLC analysis. [d]Run at 0 °C. [e]Run at -20 °C. MTBE = methyl *tert*-butyl ether.

Initially, the reaction of 2-nitrobenzofuran **1a** and 3-pyrrolyl-oxindole **2a** in toluene at room temperature was selected as the model reaction for optimizing conditions (Table 1). To our delight, with 10 mol % quinine-derived thiourea **A** as the catalyst, the expected dearomative Michael addition product **3a** could be obtained in 89% yield with 89:11 dr, albeit with 52% ee (Table 1, entry 1). The optimization was then continued with some other multiple hydrogen-bonding thiourea catalysts **B**-**D**. It was found that catalysts **B** and **C** derived respectively from quinine with *L*-valine and *L*-phenylalanine, could efficiently promote the dearomative Michael addition reaction and furnish **3a** in quantitative yield with moderate dr and good ee (Table 1, entry 2-3). More delightfully, catalyst **D** derived from cinchonidine and *L*-phenylalanine could give **3a** in 99% yield with 91:9 dr and high to 87% ee (Table 1, entry 4). And then, screening of solvents revealed that xylene was the best in the light of the chemical yield, dr and ee values (Table 1, entry 7 vs entries 4-6 and 8-9). Afterwards, lowering the reaction temperature from room temperature to 0 °C resulted in slightly improved dr and ee values (Table 1, entry 10). Ultimately, a set of excellent results (99% yield, 97:3 dr and 96% ee) could be obtained by further reducing the reaction temperature to -20 °C (Table 1, entry 11).

Table 2. Substrate scope of 2-nitrobenzofurans and 3-pyrrolyl-oxindoles[a]



2a, R^2 = Me, R^3 = H; **2b**, R^2 = Et, R^3 = H; **2c**, R^2 = Bn, R^3 = H
2d, R^2 = allyl, R^3 = H; **2e**, R^2 = Me, R^3 = 5-F; **2f**, R^2 = Me, R^3 =5-Cl
2g, R^2 = Me, R^3 = 6-Cl; **2h**, R^2 = Me, R^3 =7-Cl; **2i**, R^2 = Me, R^3 = 5-Br
2j, R^2 = Me, R^3 =5-Me

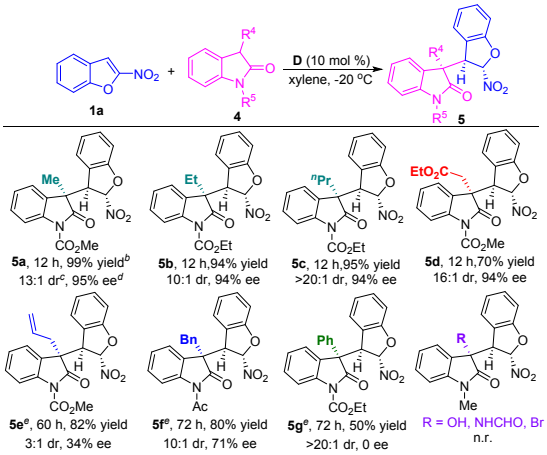
entry	R^1 (**1**)	**2**	time (h)	**3**/yield (%)[b]	dr[c]	ee (%)[d]
1	5-F (**1b**)	**2a**	40	**3b**/92	>20:1	95
2	7-F (**1c**)	**2a**	40	**3c**/91	>20:1	88
3	5-Cl (**1d**)	**2a**	38	**3d**/99	>20:1	95
4	5-Br (**1e**)	**2a**	38	**3e**/95	>20:1	96
5	6-Br (**1f**)	**2a**	45	**3f**/99	>20:1	95
6	7-Br (**1g**)	**2a**	39	**3g**/91	>20:1	87
7	5-NO_2 (**1h**)	**2a**	24	**3h**/99	>20:1	90
8	5-Me (**1i**)	**2a**	48	**3i**/99	>20:1	96
9	6-Me (**1j**)	**2a**	48	**3j**/99	>20:1	96
10	5-OMe (**1k**)	**2a**	90	**3k**/97	>20:1	93
11	5-Bu^t (**1l**)	**2a**	45	**3l**/99	>20:1	95
12	5,7-Br_2 (**1m**)	**2a**	35	**3m**/92	>20:1	91
13	**1a**	**2b**	66	**3n**/92	17:1	89
14	**1a**	**2c**	66	**3o**/89	13:1	91
15	**1a**	**2d**	90	**3p**/97	10:1	86
16	**1a**	**2e**	40	**3q**/98	>20:1	93
17	**1a**	**2f**	40	**3r**/99	>20:1	92
18	**1a**	**2g**	45	**3s**/98	>20:1	95
19	**1a**	**2h**	40	**3t**/97	>20:1	90
20	**1a**	**2i**	40	**3u**/95	>20:1	92
21	**1a**	**2j**	66	**3v**/98	>20:1	95

[a]The reactions were carried out with **1** (0.12 mmol), **2** (0.1 mmol), and 10 mol % catalyst **D** in 1.0 mL of xylene at -20 °C for the specified time. [b]Isolated yields. [c]Determined by ^{1}H NMR. [d]Determined by chiral HPLC analysis.

Having identified the optimal reaction conditions, the scope and limitation of the asymmetric dearomative Michael addition was explored (Table 2). As for 2-nitrobenzofurans, the first obvious scenario is that only one stereoisomer (>20:1 dr) was formed among all the cases examined (Table 2, entries 1-12). Diverse electron-withdrawing substituents, such as F-, Cl-, Br-, and NO_2-, regardless of their positions in the phenyl ring of 2-nitrobenzofurans, were well tolerated in the dearomative Michael addition reaction with **2a**, providing products **3b-h** in high to excellent yields with 87-96% ee values (entries 1-7). Meanwhile, electron-donating groups, such as Me-, MeO- and ^{t}Bu-, were also compatible with the developed reaction conditions, leading to the formation of **3i-l** in 96-99% yields with 93-96% ee (entries 8-11). Additionally, the reactivity and stereoselectivity were hardly affected by the incorporation of doubly substituents on the aromatic ring, just as **3m** was

obtained in 92% yield with 91% ee (entry 12). On the other hand, the nucleophiles 3-pyrrolyl-oxindole substrates were further investigated (Table 2, entries 13-21). The ethyl, benzyl, and allyl group in the *N*1-position are well tolerated, affording **3n-p** in 89-97 yields with high to excellent dr and 86-91% ee (entries 13-15). Substrates bearing electron-withdrawing substituents such as F- and Br- at the C5-position of the 3-pyrrolyl-oxindole were able to furnish their corresponding products **3q** and **3u** in acceptable results (entries 16-17). Nevertheless, chloric substituent at the C5, C6, and C7-positions is well tolerated, generating products **3r-t** in almost quantitative yield with excellent dr and ee values (entries 18-20). Additionally, electron-donating group such as methyl group on the C5-position of oxindole skeleton had no effect on the reactivity and stereoselectivity (entry 21). The absolute and relative configuration of product **3d** was determined to be (*C2S*, *C10S*, *C11R*) by single crystal X-ray analysis.[12,13]

Scheme 2 Substrate scope of other 3-substituted oxindoles with 2-nibenzofuran.[a]

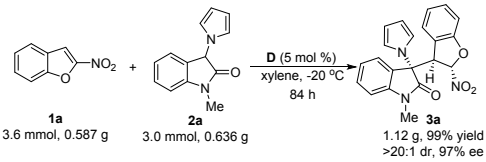


[a]Unless otherwise noted, the reactions were carried out with **1a** (0.12 mmol), **4** (0.1 mmol), and 10 mol % catalyst **D** in 1.0 mL of xylene at -20 °C for the specified time. [b]Isolated yields. [c]Determined by ^{1}H NMR. [d]Determined by chiral HPLC analysis. [e]Run for at rt.

Encouraged by the remarkable results of the above reactions, we continued our attempt to investigate the dearomative Michael addition reaction of 2-nitrobenzofuran **1a** with other 3-monosubstituted oxindoles (Scheme 2). Under the standard reaction conditions, different substituents at C-3 position of 3-monosubstituted oxindoles such as methyl, ethyl and propyl, were found to be suitable for the transformation, generating products **5a-c** in quantitative yields with excellent enantioselectivities. In addition, ethyl ester substituted oxindole also could react with **1a**, providing dearomative Michael adduct **5d** in 70% yield, with 16:1 dr and 94% ee. As for 3-allyl oxindole and 3-benzyl oxindole, due to their low reactivity, the reactions run at room temperature, delivering the corresponding products **5e** and **5f** in good yields with 34% and 71% ee, respectively. In addition, 3-aryl oxindoles reacted with **1a** and provided the desired **5g** in moderate yield with excellent dr but in the racemate. Disappointedly 3-hetero-substitution, such as 3-hydroxyoxindole, 3-formylaminooxindole and 3-bromooxindole, was able to entirely inhibit the reaction with **1a**.

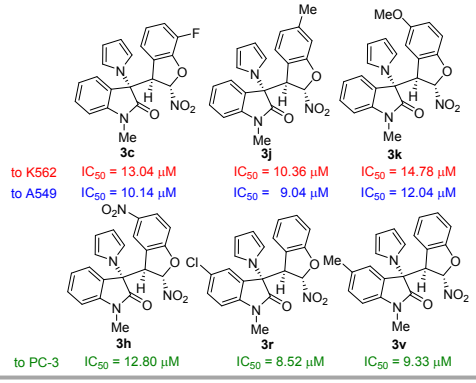
In order to demonstrate the potential applicability of the catalytic asymmetric dearomative Michael addition, the reaction of **1a** and **2a** was carried out on a gram scale, which is 23 times larger than the scale of the model reaction. As showed in Scheme 3, under the standard conditions, **3a** could be smoothly obtained in almost quantitative yield and no any loss in the dr and ee values, even with only 5 mol % catalyst loading. This gram-scale experiment suggests that the developed catalyst system has good scalability and the potential value in organic synthesis.

Scheme 3 Gram-scale experiment.



With the successful generation of divers optically pure 3,3'-disubstituted oxindoles bearing chiral 2-nitro-2,3-dihydrobenzofuran substructures (Table 2), we finally attempted to identify the potential bioactivity of these compounds. Some randomly selected compounds were subjected to in vitro cytotoxicity test against different human cancer cells, including K562 leukemia cells, A549 lung cancer cells, and PC-3 prostate cancer cells.[14] The preliminary results revealed that all of the tested 12 compounds exhibited cytotoxicity against the cell lines of K562, A549, and PC-3 with IC_{50} values in the micromolar range (see Supporting Information).[15] Particularly, compound **3c**, **3j**, and **3k** showed impressive cytotoxicity to the K562 leukemia cells and A549 lung cancer cells with promising IC_{50} values (Scheme 4). Meanwhile, to the PC-3 prostate cancer cells, compounds **3h**, **3r**, and **3v** showed significant cytotoxicity with IC_{50} values in the low micromolar range, even lower than that of commercially available broad-spectrum anticancer drug cisplatin as a positive control. These results suggest that this type of 3,3'-disubstituted oxindole derivatives might be promising in medicinal applications after further structural modulation and biological investigations.

Scheme 4 Biological activities evaluation



In summary, an efficient asymmetric dearomatization of 2-nitrobenzofurans was accomplished by using a chiral multiple hydrogen-bonding thiourea as the catalyst only via one-step Michael addition process. With the developed protocol, a range of structurally diverse 3,3'-disubstituted oxindoles, bearing three contiguous stereocenters including

one quaternary and two tertiary stereogenic centers, could be smoothly obtained in excellent results (up to 99% yield, >20:1 dr and 96% ee) under mild conditions. These products are featured with an intriguing combination of two privileged motifs including 3-pyrrolyl-substituted-oxindoles and 2,3-dihydrobenzofurans substructures. This work represents the first example of catalytic asymmetric dearomatizaiton of electron-deficient nitroheteroarenes via a single reaction process. Importantly, a preliminary biological evaluation indicated the products have moderate to good cytotoxicity in vitro against different human cancer cells. Further exploration on the catalytic asymmetric dearomatization of electron-deficient heteroarenes for the construction of more interesting molecules is currently underway.

We are grateful for financial support from the National NSFC (21572223, 21871252, and 21901024), the National Key R&D Program of China (2018YFC0807301-3), the Project of Youth Science and Technology Innovation Team of Sichuan Province (2016TD0027).

Notes and references

1. For selected reviews on the catalytic asymmetric dearomatization reactions, see: (a) C.-X. Zhuo, W. Zhang and S.-L. You, *Angew. Chem., Int. Ed.*, 2012, **51**, 12662; (b) C.-X. Zhuo, C. Zheng, S.-L. You, *Acc. Chem. Res.*, 2014, **47**, 2558; (c) W.-T. Wu, L. Zhang and S.-L. You, *Chem. Soc. Rev.* 2016, **45**, 1570; (e) W.-T. Wu, L. Zhang and S.-L. You, *Acta Chim. Sinica.*, 2017, **75**, 419; (d) G. Huang and B. Yin, *Adv. Synth. Catal.*, 2019, **361**, 405.
2. For selected recent examples, see: (a) Z.-P. Yang, C. Zheng, L. Huang, C. Qian and S.-L. You, *Angew. Chem. Int. Ed.*, 2017, **56**, 1530; (b) L.-W. Feng, H. Ren, H. Xiong, P. Wang, L. Wang and Y. Tang, *Angew. Chem. Int. Ed.*, 2017, **56**, 3055; (c) F. Jiang, D. Zhao, X. Yang, F.-R. Yuan, G.-J. Mei and F. Shi, *ACS Catal.*, 2017, **7**, 6984; (d) H.-F. Tu, C. Zheng, R.-Q. Xu, X.-J. Liu and S.-L. You, *Angew. Chem. Int. Ed.,* 2017, **56**, 3237; (e) M.-C. Zhang, D.-C. Wang, M.-S. Xie, G.-R. Qu, H.-M. Guo and S.-L. You, *Chem.*, 2019, **15**, 156.
3. For selected examples, see: (a) I. Chataigner, S. R. Piettre, *Org. Lett.*, 2007, **9**, 4159; (b) S. Lee, I. Chataigner, S. R. Piettre, *Angew. Chem. Int. Ed.*, 2011, **50**, 472. (c) B. M. Trost, V. Ehmke, B. M. O'Keefe and D. A. Bringley, *J. Am. Chem. Soc.*, 2014, **136**, 8213.
4. J.-Q. Zhao, X.-J. Zhou, Y.-Z. Chen, X.-Y. Xu, X.-M. Zhang and W.-C. Yuan, *Adv. Synth. Catal.*, 2018, **360**, 2482.
5. For selected examples see: (a) Awata, A.; Arai, T. *Angew. Chem. Int. Ed.*, 2014, **53**, 10462; (b) J.-Q. Zhao, M.-Q. Zhou, Z.-J. Wu, Z.-H. Wang, D.-F. Yue, X.-Y. Xu, X.-M. Zhang and W.-C. Yuan, *Org. Lett*., 2015, **17**, 2238; (c) J.-Q. Zhao, Z.-J. Wu, M.-Q. Zhou, X.-Y. Xu, X.-M. Zhang and W.-C. Yuan, *Org. Lett.*, 2015, **17**, 5020; (d) Y. Li, F. Tur, R. P. Nielsen, H. Jiang, F. Jensen and K. A. Jørgensen, *Angew. Chem. Int. Ed*., 2016, **55**, 1020; (e) D.-F. Yue, J.-Q. Zhao, X.-Z. Chen, Y. Zhou, X.-M. Zhang, X. Y. Xu and W.-C. Yuan, *Org. Lett*., 2017, **19**, 4508; (f) Q. Cheng, F. Zhang, Y. Cai, Y.-L. Guo and S. L. You, *Angew. Chem. Int. Ed*., 2018, **57**, 2134; (g) H.-M. Wang, J.-Y. Zhang, Y.-S. Tu and J.-L. Zhang, *Angew. Chem. Int. Ed.*, 2019, **58**, 5422; (h) K.-Z. Li, T. P. Gonçalves, K.-W. Huang and Y. Lu, *Angew. Chem. Int. Ed.* 2019, **58**, 5427; (i) X.-M. Chen, C.-W. Lei, D.-F. Yue, J.-Q. Zhao, Z.-H. Wang, X.-M. Zhang, X.-Y. Xu and W.-C. Yuan, *Org. Lett.*, 2019, **21**, 5452.
6. (a) Q. Cheng, H.-J. Zhang, W.-J. Yue and S.-L. You, *Chem.*, 2017, **3**, 428; (b) J.-Q. Zhao, X.-J. Zhou, Y. Zhou, X.-Y. Xu, X.-M. Zhang and W.-C. Yuan, *Org. Lett*. 2018, **20**, 909; (c) L. Liang H.-Y. Niu, D.-C. Wang, X.-H. Yang, G.-R. Qu and H.-M. Guo, *Chem. Commun.*, 2019, **55**, 553; (d) J.-Q. Zhao, Y. Yang, X.-J. Zhou, Y. You, Z.-H. Wang, M.-Q. Zhou, X.-M. Zhang, X.-Y. Xu and W.-C. Yuan, *Org. Lett.*, 2019, **21**, 660; (e) X.-J. Zhou, J.-Q. Zhao, X.-M. Chen, J.-R. Zhuo, Y.-P. Zhang, Y.-Z. Chen, X.-M. Zhang, X.-Y. Xu and W.-C. Yuan, *J. Org. Chem.*, 2019, **84**, 4381; (f) X.-H. Yang, J.-P. Li, D.-C.Wang, M.-S. Xie, G.-R. Qu and H.-M. Guo, *Chem. Commun*., 2019, **55**, 9144.
7. D.-F. Yue, J.-Q. Zhao, Y.-Z. Chen, X.-M. Zhang, X.-Y. Xu and W.-C. Yuan, *Adv. Synth. Catal.*, 2018, **360**, 1420.
8. For recent review, see: Z. Chen, M. Pitchakuntal and Y. Jia, *Nat. Prod. Rep.*, 2019, **36**, 666.
9. For selected reviews, see: (a) Y.-L. Liu and J. Zhou, *Adv. Synth. Catal.*, 2010, **352**, 1381; (b) K. Shen, X. Liu, L. Lin and X. Feng, *Chem. Sci.*, 2012, **3**, 327; (c) R. Rios, *Chem. Soc. Rev.*, 2012, **41**, 1060; (d) R. Dalpozzo, G. Bartoli and G. Bencivenni, *Chem. Soc. Rev.*, 2012, **41**, 7247; (e) L. Hong and R. Wang, *Adv. Synth. Catal.*, 2013, **355**, 1023; (f) D. Cheng, Y. Ishihara, B. Tan and C. F. Barbas III, *ACS Catal.*, 2014, **4**, 743; (g) J.-S. Yu, F. Zhou, Y.-L. Liu and J. Zhou, *Synlett,* 2015, **26**, 2491; (h) J. Kaur, S. S. Chimni, S. Mahajan and A. Kumar, *RSC Adv.*, 2015,**5**, 52481; (i) G.-J. Mei and F. Shi, *Chem. Commun.* 2018, **54**, 6607; (j) Y. C. Zhang, F. Jiang and F. Shi, *Acc. Chem. Res.*, 2019, 10.1021/acs.accounts.9b00549. For selected relevant examples about the synthesis of chiral nitrogenous heterocycles including oxindoles, see: (k) L.-J. Zhou, Y.-C. Zhang, F. Jiang, G. He, J. Yan, H. Lu, S. Zhang and F. Shi, *Adv. Synth. Catal.*, 2016, **358**, 3069; (l) W. Guo, Y. Liu and C. Li, *Org. Lett.*, 2017, **19**, 1044; (m) C. Ma, J.-Y. Zhou, Y.-Z. Zhang, G.-J. Mei and F. Shi, *Angew. Chem. Int. Ed.*, 2018, **57**, 5398.
10. (a) B. S. Jensen, *CNS Drug Rev.*, 2002, **8**, 353; (b) C. V. Galliford and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2007, **46**, 8748; (c) J. J. Badillo, N. V. Hanhan and A. K. Franz, *Curr. Opin. Drug Discovery Dev.*, 2010, **13**, 758; (d) G. S. Singh and Z. Y. Desta, *Chem. Rev.*, 2012, **112**, 6104; (e) T. L. Pavlovska, R. Redkin, V. V. Lipson and D. V. Atamanuk, *Mol. Diversity*, 2016, **20**, 299.
11. (a) B.-D. Cui, Y. You, J. -Q. Zhao, J. Zuo, Z. -J. Wu, X. -Y. Xu, X. -M. Zhang and W. -C. Yuan, *Chem. Commun*., 2015, **51**, 757; (b) Y. You, Z.-J. Wu, J.-F. Chen, Z.-H. Wang, X.-Y. Xu, X.-M. Zhang and W.-C. Yuan, *J. Org. Chem*., 2016, **81**, 5759; (c) K. Wang, L. Wang, X. Liu, D. Li, H. Zhu, P. Wang, Y. Liu, D. Yang and R. Wang, *Org. Lett.*, 2017, **19**, 4351; (d) W.-T. Fan, N.-K. Li, L. Xu, C. Qiao and X.-W. Wang, *Org. Lett*., 2017, **19**, 6626; (e) N.-K. Li, W.-T. Fan, J.-Q. Zhang, B.-B. Sun, J.-B. Chen and X.-W. Wang, *Chem. Commun.,* 2018, **54**, 2260.
12. CCDC-1943699 (**3d**) contains the supplementary crystallographic data for this paper.
13. A possible activation mode to account for the stereochemistry of the Michael addition process was proposed, for the details see ESI.
14. (a) T. J. J. Mosmann, *Immunol. Methods* 1983, **65**, 55; (b) M. C. D. A. Alley, Scudiero, A. Monks, M. L. Hursey, M. J. Czerwinski, D. L. Fine, B. J. Abbott, R. H. Shoemaker and M. R. Boyd, *Cancer Res.* 1988, **48**, 589.
15. For details on the biological activities evaluation, see ESI.