Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Journal Name

RSCPublishing

COMMUNICATION

Highly Enantioselective Synthesis of Bisoxindoles with Two Vicinal Quarternary Stereocenters via Lewis Base Mediated Addition of Oxindoles to Isatin-Derived Ketimines

Cite this: DOI: 10.1039/xoxxoooooox

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

www.rsc.org/

Zhongkai Tang,[†,a] Yan Shi,[†,a] Haibin Mao,[a] Xuebin Zhu,[a] Weipeng Li,[a]Yixiang Cheng,[a] Wen-Hua Zheng,*[,a] and Chengjian Zhu*[, a, b]

A highly efficient asymmetric organocatalytic addition of 3-substituted oxindole to isatin-derived ketimine is reported with excellent stereocontrol (>99:1 dr, >99% ee) under mild conditions. This method provides access to bisoxindoles structure moiety with two vicinal quaternary stereogenic centers.

Enantioselective synthesis of chiral compounds bearing a quaternary stereogenic center is one of the most challenging research areas in asymmetric catalysis[1]. In contrast, asymmetric catalytic highly diastereoselective and enantioselective construction of two vicinal quaternary centers is a much more formidable problem in organic synthesis[2]. Hence it is urgent to develop a highly efficient asymmetric catalytic methodology to meet this challenging task.

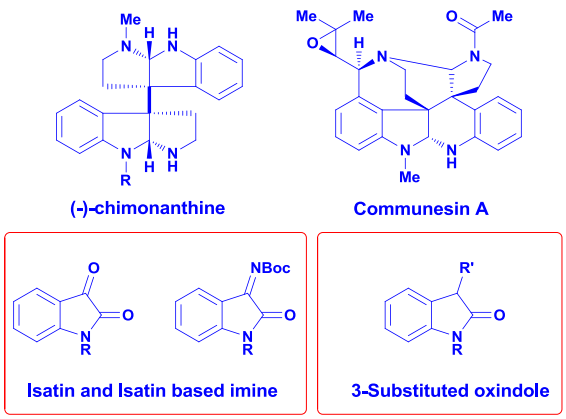


Figure 1. Isatin/oxindole basic structural motif and natural products bearing bis-indole moiety

Oxindoles bearing a tetrasubstituted carbon stereocenter at the 3-position are popular found in many biologically important natural products[3]. In recent years, some elegant examples of highly enantioselective construction of 3,3-disubstituted oxindole structure motif with different transition-metal catalysts or organocatalysts are reported[4]. There are two major strategies to get chiral oxindole products. One is nucleophilic addition to isatin or isatin derived imines, which provides access to a series of chiral 3-hydroxyloxindoles and 3-aminooxindoles. Another one is reaction with 3-substituted oxindole as nucleophile with a wide variety of electrophiles, including, alkylation, oxygenation, amination and halogenation[5]. Recently, natural alkaloids containing bis-indole structural moiety and two vicinal chiral quaternary carbon centers at the same time (**Figure 1**) has been shown to have highly biological activity and hence has enormously abstracted organic synthetic chemists' attention[6]. Although there were many excellent examples of synthesis of single chiral oxindoles, bisoxindole containing two continuous chiral quaternary carbon centers are still limited. To the best of our knowledge, there are no examples of highly enantioselective addition of 3-substituted oxindole to isatin derived imine[7]. Herein, we report a highly efficient protocol for synthesis of bis-oxindoles bearing two vicinal quaternary stereogenic centers.

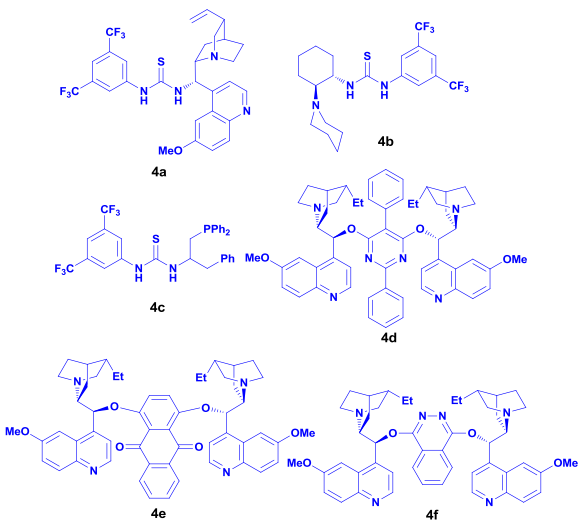
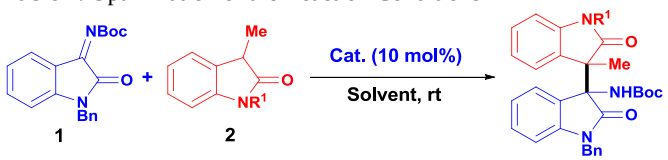


Figure 2. Structure of the catalysts.

We started investigation the reaction of N-Boc ketimine **1a** with 3-subsititued-2-oxindole **2a** in toluene in the presence of 10 mol% lewis base catalysts. We are delighted to find the reaction works well under those known catalysts **4a-4c** as H –bond donors and **4d-4f** as the Lewis base catalysts (**Figure 2**)(**Table 1**, entry 1-6). Based on yield, diastereoselectivity and enantioselectivity, catalyst **4f** is the best catalyst in this reaction, affording the desired product in 81% yield, >99:1 d.r. and 77% *ee*. Furthermore, solvent screening shows polar solvents (such as DMF, methanol) and DCM are less suitable than ether's type solvents (entry 7-13), and the methyl tertbutyl ether (MTBE) is the best solvent (87% *ee*). And different substituents on the nitrogen of 3-methyl oxindole are further examined (entry 14-16), and the alkyl substituted substates show similiar reactivity and enantioselectivity, but the Boc protected 3-methyl oxindole is not a good substrate in this reaction (25% *ee*), other substituents work worse. Lowering the reaction temperature did increase the enantioselectivity, with erosion of yield (entry 17-19). Considering the balance between yield and *ee*, we selected 10°C as the optimal reaction temperature.

Table 1. Optimization of the Reaction Conditions [a]

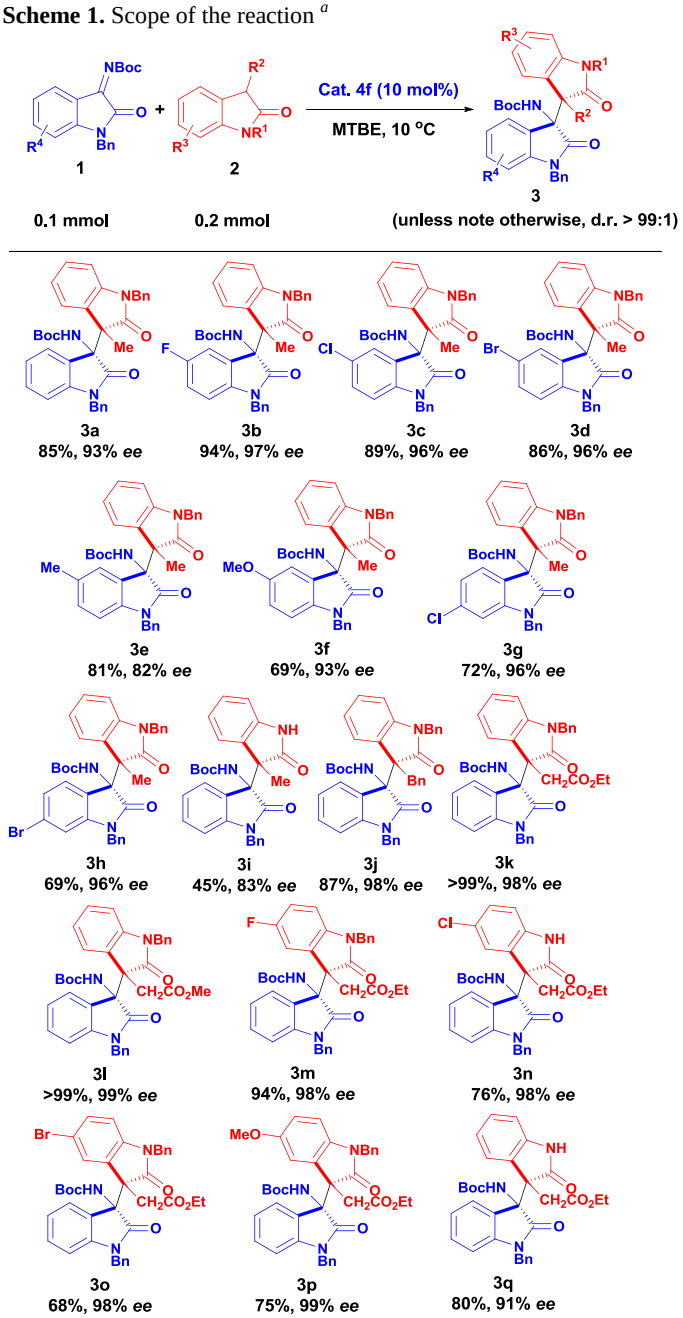


entry	R^1	Cat.	Solvent	Yield (%)[b]	d. r.[c]	e.e. (%)[d]
1	Bn	**4a**	Toluene	54	99:1	4
2	Bn	**4b**	Toluene	45	98:2	9
3	Bn	**4c**	Toluene	61	98:2	13
4	Bn	**4d**	Toluene	73	96:4	14
5	Bn	**4e**	Toluene	65	> 99:1	-35
6	Bn	**4f**	Toluene	81	> 99:1	77
7	Bn	**4f**	DMF	63	98:2	8
8	Bn	**4f**	MeOH	59	98:2	10
9	Bn	**4f**	DCM	35	> 99:1	15
10	Bn	**4f**	Et_2O	81	> 99:1	85
11	Bn	**4f**	MTBE	90	> 99:1	87
12	Bn	**4f**	THF	70	> 99:1	7
13	Bn	**4f**	Hexane	73	96:4	21
14	Me	**4f**	MTBE	80	> 99:1	81
15	Et	**4f**	MTBE	83	> 99:1	85
16	Boc	**4f**	MTBE	55	> 99:1	25
17[e]	Bn	**4f**	MTBE	85	> 99:1	93
18[f]	Bn	**4f**	MTBE	70	> 99:1	95
19[g]	Bn	**4f**	MTBE	40	> 99:1	96

[a]Unless otherwise noted, the reaction was carried out with 0.10 mmol of **1**, 0.12 mmol of **2**, 10 mol% of catalyst **4** in the solvent (1 mL) for **24** h. [b]Yield of isolated product. [c]Determined by ^{1}H NMR analysis of the crude products. [d]*ee* of the major diastereoisomer were determined by chiral HPLC analysis. [e]The reaction was carried out at 10 °C, [f]The reaction was carried out at 0 °C, [g]The reaction was carried out at -10 °C.

With the optimal condition in hand, the substrates' scope was then explored. As summarized, a wide variety of N-Boc ketimines and 3-subsititued oxindoles were tolerated, the corresponding products (**3a-3q**) were obtained in excellent yield, excellent diastereoselectivity and excellent *ee* (**Scheme 1**). In all cases the diastereoselectivity was > 99:1. Substrates of the imine bearing either electronic-withdrawing or electronic-donating groups in ether 5-or 6 position of oxindoles all afforded the corresponding products in good to excellent yield and enantioselectivity (**3a-3h**, 69-94% yield, 82-97% *ee*). In particular, N-unprotected oxindole works well under the optimal condition (83% *ee*) with a little lower yield. Meanwhile, oxindoles with different substituent in the 3-position are tolerated, gave the desired products in excellent enanitoseletivity (**3j**, **3k** and **3l**, 98% *ee*, 98% *ee* and 99% *ee* respectively). Furthermore, 3-substituted oxindole with different electronic charactered group in the 5 position were also viable substrates, thus affording the products **3m-3p** in good yield and excellent selectivities.

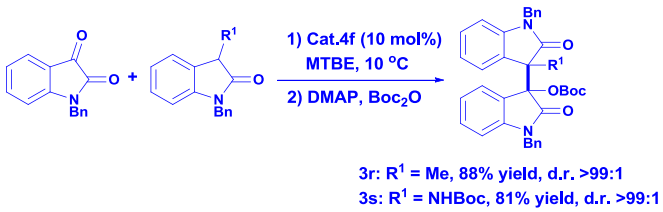
Scheme 1. Scope of the reaction [a]



[a]For detail, see the supporting information. Yield of isolated product.

As a further demonstration of the broad substrates scope, benzyl-protected isatin selected as substrate to react with 3-substituted oxindoles (**Scheme 2**). The reaction works well in excellent yield and diastereselectivity. However the ee of **3r** and **3s** were disappointed (less than 5% ee). The absolute configuration of 3l was determined by X-ray analysis (**Figure 3**).

Scheme 2. Addition of isatin with 2-oxindole



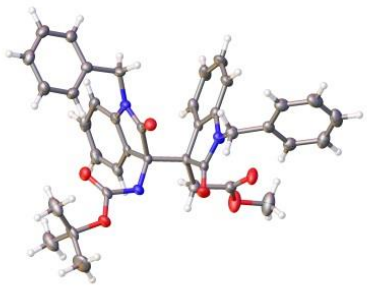


Figure 3. X-ray crystal structure of product **3l**.

According to the result of this reaction, we have proposed the possible mechanism (**Figure 4**).[8] The enolated 2-oxindole was deprotonated and stabilized by the selected catalyst at the same time. Then, the C=N bond, which was activated by the H-bond via protonated quinuclidine nitrogen, was attacked preferably from the *Re*-face of the kemine by oxindole to get the highly enantioselective products. Nevertheless, further studies should be required to elucidate the mechanism.

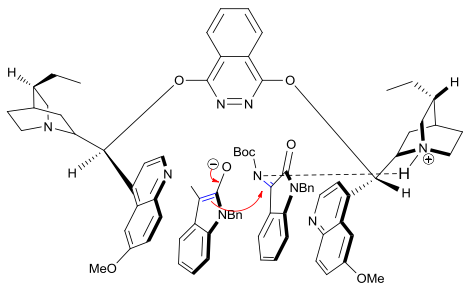


Figure 4. Proposed possible mechanism.

Conclusions

In summary, we have developed a highly efficient method for diastereoselective and enantioselective addition of 3-substituted-2-oxindoles to N-Boc ketimines catalyzed by chiral lewis base catalyst. The new method provides a highly enantioselective synthesis of bis-oxindole with two chiral vicinal quaternary carbon centers. Further application of the methodology for the synthesis of natural and bioactive compounds is currently underway and will be reported in due course.

We gratefully acknowledge the National Natural Science Foundation of China (21372114, 21172106, 21074054), the National Basic Research Program of China (2010CB923303) and the Research Fund for the Doctoral Program of Higher Education of China (20120091110010) for their financial support.

Notes and references

[a]*State Key Laboratory of Coordination Chemistry, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing, 210093 P.R. China.* [b]*State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, CAS, Shanghai, 200032, P.R. China.*

E-mail: cjzhu@nju.edu.cn. wzheng@nju.edu.cn

† Z. Tang and Y. Shi contributed equally to this work.
Electronic Supplementary Information (ESI) available; crystallographic data (CCDC 988539); imited experimental and spectral data; See DOI: 10.1039/c000000x/

1 For selected reviews: (a) K. Fuji, *Chem. Rev*., 1993, **93**, 2037; (b) E. J. Corey, *Angew. Chem. Int. Ed.*, 1998, **37**, 388; (c) K. C. Nicolaou, D. J. Edmonds and P. G. Bulger, *Angew. Chem. Int. Ed.*, 2006, **45**, 7134; (d) J. Zhou, *Chem. Asian. J*., 2010, **5**, 422; (e) R. Rios, *Chem. Soc. Rev*., 2012, **41**, 1060; (f) A. Grossmann and D. Enders, *Angew. Chem. Int. Ed.*, 2012, **51**, 314; (g) G.S. Singh and Z.Y. Desta, *Chem. Rev*., 2012, **112**, 6104.

2 (a) H. Li and S. J. Danishefsky, *Angew. Chem. Int. Ed.*, 2003, **42**, 36; (b) G. Zeni and R. C. Larock, *Chem. Rev.*, 2004, **104**, 2285; (c) X-H. Chen, X-Y. Xu and L-Z. Gong, *J. Am. Chem. Soc*., 2006, **128**, 14802; (d) C. V. Galliford and K. A. Scheidt, *Angew. Chem. Int. Ed.*, 2007, **46**, 8748; (e) F. Zhou, Y.-L. Liu and J. Zhou, *Adv. Synth. Catal*., 2010, **352**, 1381; (f) X. F. Wang, Q. L. Hua, Y. Cheng, X. L. An and W. J. Xiao, *Angew. Chem. Int. Ed.*, 2010, **49**, 8349; (g) X. F. Wang, J. An and W. J. Xiao, *Org. Lett*., 2011, **13**, 808; (h) B. Tan, N. R. Candeisa and C. F. III. Barbas, *Nat. Chem*., 2011, **3**, 473; (i) W. Hou, B. Zheng, J. Chen and Y.Peng, *Org. Lett*., 2012, **14**, 2378; (j) N. R. Ball-Jones, J. J. Badillo and A. K. Franz, *Org. Biomol. Chem.*, 2012, **10**, 5165; (k) G. S. Singh and Z. Y. Desta, *Chem. Rev*., 2012, **112**, 6104; (l) W. Yang, Y. Yang, D. M. Du, *Org. Lett*., 2013, **15**, 1190; (m) Y. L. Liu, X. Wang, Y. L. Zhao and J. Zhou, *Angew. Chem.. Int. Ed.*, 2013, **52**, 13735; (n) L. Hong and R. Wang, *Adv. Synth.Catal.*, 2013, **355**, 1023; (o) Y.L. Zhao, Y. Wang, J. Cao, Y.M. Liang and P.F. Xu, *Org. Lett.* 2014, **16**, 2438-2441.

3 (a) M. Ochi, Y. Kawasaki, H. Kataoka and Y. Uchio, *Biochem. Biopnys. Res. Commun*., 2001, **283**, 1118; (b) P. Wu, Y. Hsu and C. W. Jao, *J. Nat. Prod*., 2006, **69**, 1467; (c) A. Steven and L. E. Overman, *Angew. Chem. Int. Ed.*, 2007, **46**, 5488; (d) R. Pettipher and T. T. Hansel, *Drug News Persect* ., 2008, **21** , 317; (e) L. Mei, X. Tang and M. Shi, *Org. Biomol. Chem*., 2014, **12**, 1149.

4 (a) A. F. Bella, A. M.Z. Slawin and J. C. Walton, *J. Org. Chem*., 2004, **69**, 5926; (b) B. M. Trost and M. U. Frederisen, *Angew. Chem. Int. Ed*., 2005, **44,** 308; (c) B. M. Trost and Y. Zhang, *J. Am. Chem. Soc*. 2006, **128**, 4590; (d) T. Emura, T. Esaki, K. Tachinana and M. Shimizu, *J. Org. Chem.*, 2006, **71**, 8559; (e) C. Sun, X. Lin and S. M. Weinreb, *J. Org. Chem*., 2006, **71**, 3159; (f) P. Magnus and R. Turnbull, *Org. Lett*. 2006, **8**, 3497; (g) S. Ogawa, N. Shibata, J. Inagaki, S. Nakamura, T. Toru and M. Shiri, *Angew. Chem. Int. Ed*.,

2007, **46**, 8666; (h) S.P. Marsden, E.L. Watson and S.A. Sraw, *Org. Lett*., 2008, **10**, 2905; (i) T. Ishimaru, N. Shibata, T. Horikawa, T. Toru and M. Shiro, *Angew. Chem. Int. Ed*., 2008, **47**, 4157; (j) D. Sano, K. Nagata and T. Itoh, *Org. Lett*., 2008, **10**, 1593; (k) X. Tian, K. Jiang, J. Peng, W. Du and Chen. Y-C. *Org. Lett.*, 2008, **10**, 3583; (l) T. Bui, S. Syed and C. F., III. Barbas, *J. Am. Chem. Soc*., 2009, **131**, 8758; (m) Y. H. Shi, Z.Wang, Y. Shi and W. P. Deng, *Tetrahedron*., 2012, **68**, 3649; (n) M. Hayashi, M. Sano, Y. Funahashi and S. Nakamura, *Angew. Chem. Int. Ed.,* 2013, **52**, 5557.

5 (a) M. Beyer and O. Schiemann, *J. Org. Chem*., 2003, **68**, 2209; (b) M. Tsuda, Y. Kasai, K. Komastu, T. Sone, M. Tanaka, Y. Mikami and J. Kobayashi, *Org. Lett*., 2004, **6**, 3087; (c) T. J. Greshock, A. W. Grubbs, P. Jiao, D.T. Wicklow, R. M. Williams, *Angew. Chem. Int. Ed.,* 2008, **47**, 3537; (d) S. Tsukamoto, T. Kawabata, H. Kato, T. J. Greshock, H. Hirota and R. M. Williams, *Org. Lett.*, 2009, **11**, 1297; (e) L. Zu, S. Zhang, H. Xie and W. Wang, *Org. Lett*., 2009, **11**, 1627; (f) X. F. Wang, Q. L. Hua, Y. Cheng, X. L. An, Q. Q and W. J. Xiao, *Angew. Chem. Int. Ed.,* 2010, **49**, 8349; (g) X. F. Wang, J. An and W. J. Xiao, *Org. Lett*., 2011, **13**, 808; (h) B. Tan, N. R. Candeisa and C. F. III. Barbas, *Nat. Chem*., 2011, **3**, 473; (i) W. Hou, B. Zheng, J. Chen and Y. Peng, *Org. Lett*., 2012, **14**, 2378; (j) A. Noole, I. Jarving, F. Werner, M. Lopp, A. Malkov and T. Kanger, *Org. Lett*., 2012, **14**, 4922; (k) W. Yang, Y. Yang, D. M. Du, *Org. Lett*., 2013, **15**, 1190; (l) Y. L. Liu, X. Wang, Y. L. Zhao and J. Zhou, *Angew. Chem. Int. Ed.*, 2013, **52**, 13735; (m) P. Chauhan and S. S. Chimni, *Tetrahedron: Asymmetry.,* **2**013, **24**, 343.

6 (a) A. Numata, C. Takahashi, M. Imachi, T. Ito and T. Hasegawa, *Tetrahedro Lett*., 1993, **34**, 2355; (b) B. M. Trost and O. Maksim, *Angew. Chem. Int. Ed.,* 2013, **52**, 9176.(c) A. Noole, M. Oseka, T. Pehk, M. Oeven, I. Jarving, M. R. J. Elsegood, A. V. Malkov, M. Lopp and T. Kanger, *Adv. Synth.Catal.*, 2013, **355**, 829.

7 (a) C. Y. Jin, Y. Wang, Y. Z. Liu, C. Shen and P. F. Xu, *J. Org. Chem*. 2012, **77**, 11307; (b) H. Mao, A. Lin and C. Zhu, *Org. Lett*., 2013, **15**, 4062; (c) A. Noole, V. Andrei and T. Kanger, *Sythesis*. 2013, **45**, 2520; (d) F. Manoni, S. J. Connon, *Angew. Chem. Int. Ed.* 2014, **53**, 1.

8 (a) L. Cheng, L. Liu, D. Wang and Y. Chen, J. *Org. Lett*., 2009, **11**, 3874; (b) N. Hara, S. Nakamura, M. Sano and N. Shibata, *Chem. Eur. J*., 2012, **18**, 9276; (c) Y. L. Liu and J. Zhou, *Chem. Commum.* 2013, **49**, 4421; (d) F. L. Hu, Y. Wei, M. Shi, S. Pindi and G. Li, *Org. Biomol. Chem*., 2013, **11**, 1921.

