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# A catalytic metal-free Ritter reaction to 3-substituted 3-aminooxindoles†

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**The first Ritter reaction of 3-substituted 3-hydroxyoxindoles with nitriles, catalyzed by $HClO_4$, is developed, which enables the synthesis of 3-substituted 3-aminooxindoles in good to excellent yield with rich diversity.**

The 3,3′-disubstituted oxindoles are widely distributed in bioactive natural products, drugs and pharmaceutically active compounds.[1] Among them, the 3-substituted-3-aminooxindoles are very useful and are present in several pharmaceutical candidates,[2] including the vasopressin VIb receptor antagonist SSR-149415[2b] and the potent gastrin/CCK-B receptor antagonist AG-041R.[2c] In addition, several natural bioactive products could be potentially accessed *via* 3-substituted 3-aminooxindoles, *e.g.* psychotrimine[2d] and chartelline A[2e] which contains a spiro ring system. Their biological activities are greatly affected by the configuration and the substituents at the C3 position of the oxindole, as revealed by structure–activity relationship studies.[1] Accordingly, the development of efficient methods for the synthesis of 3-substituted 3-aminooxindoles in sufficient quantities and diversity has received considerable attention, which would accelerate the structure–activity relationship studies (Fig. 1).

A variety of synthetic methods have been developed during the past decade, including the addition of nucleophiles to isatin derived ketoimines,[3] intramolecular cyclization reaction,[4] direct amination of 3-substituted oxindoles,[5] alkylation of 3-aminooxindole[6a] and other reactions[6b–e] (Scheme 1). Despite these achievements, the development of an efficient method for the synthesis of aminooxindoles from easily available starting materials with sufficient diversity is still highly desirable and of significant value.

With our efforts in the synthesis of 3,3-disubstituted oxindoles for biological evaluation,[7] we have developed the amination of unprotected 3-prochiral oxindoles using azodicarboxylates,[7a,b] $Hg(ClO_4)_2{\cdot}3H_2O$ catalyzed addition of allyltrimethylsilane to isatin ketoimines,[7c] and the first catalytic asymmetric addition of nucleophiles to isatin ketoimines using TMSCN.[7d] We are interested in preparing 3-substituted 3-aminooxindoles *via* the Ritter reaction[8] for three reasons: (1) the amide constitutes a very important functional group in phamaceuticals,[9] and much attention has been devoted to the synthesis of oxindoles with a C3 amido moiety to modulate the bioactivity;[10] (2) the Ritter reaction would be highly efficient to prepare quaternary aminooxindoles featuring a C3 amido group in rich structural diversity, as many nitriles are commercially available and both 3-aryl and 3-alkyl 3-hydroxyoxindoles **1** could be readily obtained in one step from isatins; (3) it is an atom-economical method.[11]

The acid catalyzed Ritter reaction is an important C–N bond forming reaction.[8] Carbenium ions were invoked as intermediates in this $SN_1$-type reaction, and substituents which can stabilize the intermediates would facilitate this reaction. A variety of catalytic Ritter reactions have been developed, but most of them are limited to alcohols with α-electron-releasing groups. As far as we knew, only one report was based on the employment of alcohols with an α-electron-withdrawing group. In 2006, Hu reported the use of a large excess of concentrated $H_2SO_4$ to promote the Ritter reaction of α-$CF_2H$ alcohols, and only $CH_3CN$ was used as the amidation reagent.[8f]

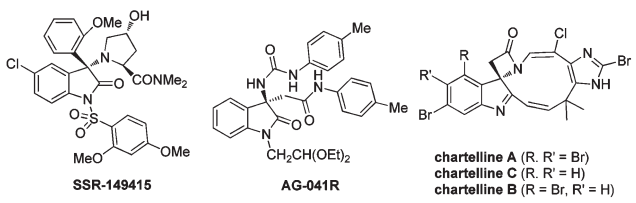
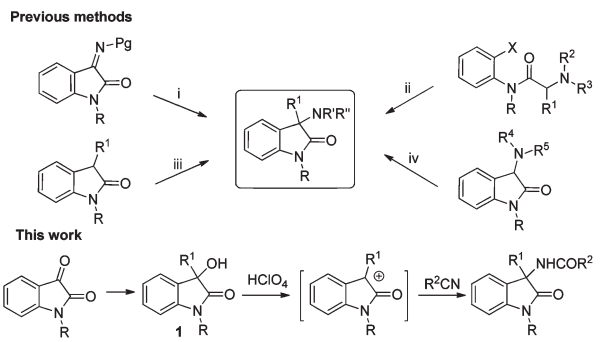



**Fig. 1** Representative bioactive compounds.




**Scheme 1** Methods for synthesis of 3-substituted-3-amino oxindoles.

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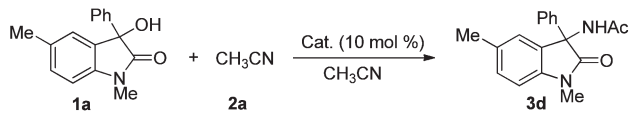
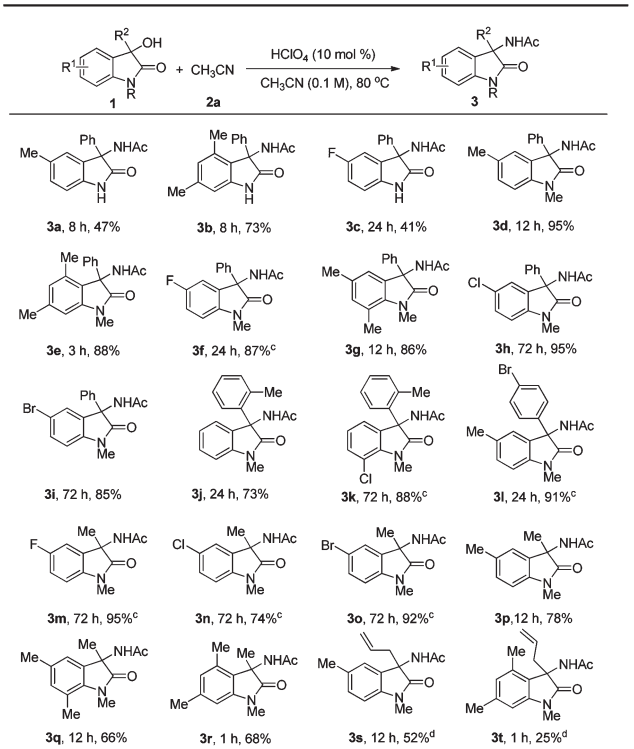
†Electronic supplementary information (ESI) available: Experimental procedures and characterizations, copies of $^1H$ NMR and $^{13}C$ NMR of new compounds. CCDC 859777. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25319d

**Table 1** Catalyst screening and conditions optimization




| Entry[a] | Cat. | Conc. (M) | Temp. (°C) | Time (h) | Conv.[b] (%) |
|---|---|---|---|---|---|
| 1 | $Hg(ClO_4)_2{\cdot}3H_2O$ | 0.2 | 50 | 48 | 61 |
| 2 | $In(ClO_4)_3{\cdot}8H_2O$ | 0.2 | 50 | 48 | 52 |
| 3 | $Al(ClO_4)_3{\cdot}9H_2O$ | 0.2 | 50 | 48 | 57 |
| 4 | $Fe(ClO_4)_3{\cdot}xH_2O$ | 0.2 | 50 | 48 | 64 |
| 5 | $Cu(ClO_4)_2{\cdot}6H_2O$ | 0.2 | 50 | 48 | 62 |
| 6 | TFA | 0.2 | 50 | 48 | — |
| 7 | HOTf | 0.2 | 50 | 48 | 86 |
| 8 | $HClO_4$ | 0.2 | 50 | 48 | 90 |
| 9 | $HClO_4$ | 0.2 | 80 | 24 | 96 |
| 10 | $HClO_4$ | 0.5 | 80 | 24 | 94 |
| 11 | $HClO_4$ | 0.1 | 80 | 12 | 97 (95)[c] |
| 12[d] | $HClO_4$ | 0.1 | 80 | 72 | 95 |

[a] On a 0.1 mmol scale. [b] Determined by $^1H$ NMR analysis of the crude mixture. [c] 0.3 mmol scale, isolated yield. [d] 5 mol% $HClO_4$.




[a] Reactions were run on a 0.3 mmol scale. [b] Isolated yield. [c] 20 mol% $HClO_4$. [d] 50 mol% $HClO_4$.

**Scheme 2** Scope of 3-hydroxyoxiondoles.

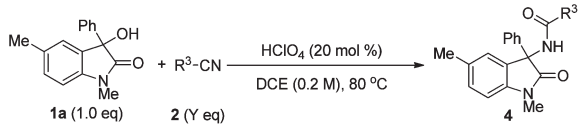
It was believed that the key point to develop a catalytic Ritter reaction of 3-hydroxyoxindoles **1** was to overcome the difficulty in the formation of the carbocationic intermediate, because of the electron-withdrawing effect of the amide group. Based on our recent finding that $Hg(ClO_4)_2{\cdot}3H_2O$ could catalyze the Friedel–Crafts arylation of 3-substituted-3-hydroxyoxindoles,[7e] we first tried using $Hg(ClO_4)_2{\cdot}3H_2O$ to catalyze the reaction of hydroxyindole **1a** and $CH_3CN$, and 61% conversion was observed after 48 hours at 50 °C by NMR analysis (entry 1, Table 1). Encouraged by this result, other metal perchlorate hydrates[12] were also examined, and In(III), Al(III), Fe(III) and Cu(II) derived perchlorate hydrates also worked, with similar reactivity (entries 2–5). Typical Brønsted acids were then tried. Trifluoroacetic acid was impotent for this reaction (entry 6). To our delight, HOTf and $HClO_4$ could catalyze this reaction much more efficiently than Lewis acids we screened. The cheap and easy to handle $HClO_4$ was chosen as the optimal catalyst, which also reduced the worry about heavy metal ion contamination of products. Raising the temperature from 50 to 80 °C, 96% conversion was obtained within 24 hours (entry 9). The influence of the concentration of **1a** was also checked, and lower concentration resulted in better reactivity (entries 9–11). When the reaction was carried out at 0.1 M of **1a**, the reaction worked efficiently to give product **3d** in 95% yield (entry 11). Lowering the catalyst loading to 5 mol% greatly slowed down the reaction rate (entry 12).

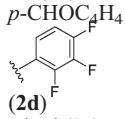
Based on the above results, the optimum reaction conditions to examine the scope of 3-substituted 3-hydroxyoxindoles **1** was determined as: run the reaction in air at 80 °C in $CH_3CN$, with the concentration of hydroxyoxindole **1** at 0.1 M. The amount of the catalyst $HClO_4$ was dependent on the reactivity of the substrates, as indicated in Scheme 2. We were pleased to find that a variety of 3-hydroxyoxindoles, with electron-donating or electron-withdrawing substituents at different positions on the aromatic ring, could afford the desired products **3** in good to excellent yield. Because of the poor solubility of unprotected hydroxyoxindoles **1** in $CH_3CN$, the yield of unprotected aminooxindoles **3a–c** was obviously lower than the corresponding *N*-methyl products **3d–f**. Both 3-aromatic and 3-aliphatic 3-hydroxyoxindoles were viable substrates under these reaction conditions, but 3-alkyl substituted ones were less reactive. The 3-allyl substituted 3-hydroxyoxindoles were the least reactive, and products **3s–t** were obtained in low yield, even using 50 mol % of $HClO_4$, but they were potentially useful synthon for the synthesis of fused indoline ring system and polycyclic framework present in many bioactive compounds.[13]

To demonstrate the generality of this method, we further examined if other nitriles could work with 3-substituted 3-hydroxyoxindoles **1**. After optimization, 1,2-dichloroethane (DCE) turned out to be the best solvent, and the reaction was carried out at 80 °C, using 20 mol% of $HClO_4$ as the catalyst. A wide array of nitriles, with aliphatic, vinyl or aromatic substituents, could work with hydroxyoxindoles **1a** to afford the desired products **4** in good to excellent yield (Table 2), except that 2,3,4-trifluorobenzonitrile **2d** and α-cyanoacetate **2j** gave the corresponding products **4c** and **4i** in moderate yields (entries 3 and 9). Accordingly, a variety of functional groups such as aldehyde, vinyl, cyclopropyl and ester group could be introduced to the amide moiety at the C3 position of oxindole.

We further examined if this protocol could be applied for the synthesis of 3-aminooxindoles with a spirolactam unit *via* an intramolecular Ritter reaction. The substrates **5a–b** were synthesized using procedures shown in the ESI.† Unfortunately, although we screened a lot of conditions, both **5a** and **5b** failed to give the desired spirocyclic lactams, but were converted to

**Table 2** Scope of nitriles




| Entry[a] | $R^3$ | Y | 4 | Time (h) | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | Ph (**2b**) | 5.0 | **4a** | 24 | 82 |
| 2 | *p*-CHOC$_4$H$_4$ (**2c**) | 1.5 | **4b** | 12 | 66 |
| 3 |  (**2d**) | 5.0 | **4c** | 36 | 35 |
| 4 | Vinyl (**2e**) | 10.0 | **4d** | 12 | 94 |
| 5 | Bn (**2f**) | 5.0 | **4e** | 24 | 70 |
| 6 | i-Pr (**2g**) | 5.0 | **4f** | 36 | 90 |
| 7 | Cyclopropyl (**2h**) | 5.0 | **4g** | 24 | 92 |
| 8 | n-Bu (**2i**) | 5.0 | **4h** | 20 | 81 |
| 9 | i-PrOOCCH$_2$ (**2j**) | 5.0 | **4i** | 20 | 41 |

[a] On a 0.3 mmol scale. [b] Isolated yield.

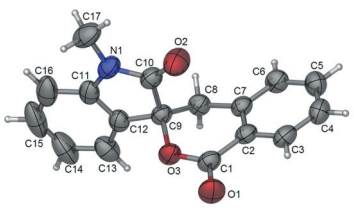
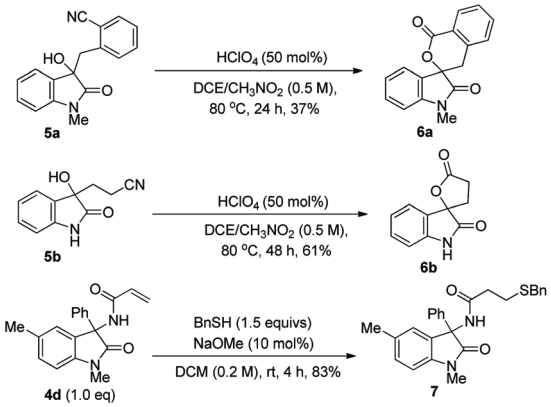



**Fig. 2** X-ray structure of compound **6a**.

spirocyclic lactones **6** in moderate yield, possibly because the cyano group of **5a** or **5b** was first hydrolyzed under the reaction conditions to a carboxylic acid moiety which further reacted with the hydroxyl group at C3 position to give the corresponding spirocyclic oxindole-lactone **6a** and **6b**.[14] Since the 3-hydroxyoxindoles **5a** and **5b** dissolved poorly in DCE, a mixed solvent of DCE and $CH_3NO_2$ (1/1, v/v) was used. When 50 mol% of $HClO_4$ was used, **5a** and **5b** were converted to **6a** and **6b** in 37% and 61% yield, respectively. The structure of product **6a** was further confirmed by X-ray analysis (Fig. 2).[15] This finding also provided a new protocol for the synthesis of spirocyclic oxindole-lactones, a structural motif of high synthetic interest.[16]

Since acrylonitrile worked well with hydroxyoxindoles, the resulting Ritter adducts such as **4d** could be easily modified to increase the diversity of the amide substituents at C3 position. For example, in the presence of 10 mol% NaOMe, product **4d** reacted with benzyl thiol at room temperature to give **7** in 83% yield.

In conclusion, we have developed the first catalytic Ritter reaction of 3-hydroxy oxindoles[17] to 3-substituted 3-aminooxindoles, which enables the synthesis of 3-substituted 3-aminooxindoles from easily available 3-alkyl and 3-aryl-3-hydroxyoxindoles and nitriles. The cheap and easy to handle $HClO_4$ was identified as a powerful catalyst for this reaction, which is carried out in air. The operationally simple and metal-free procedure and broad substrate scope make it potentially useful. Currently, our method is limited to the intermolecular Ritter reaction of differently substituted 3-hydroxyoxindoles and




nitriles. Our efforts in developing an intramolecular version reveal that spirocyclic oxindole-lactones are obtained under these conditions. The development of an intramolecular version and the application of this protocol to the synthesis of natural products and lead compounds for the medicinal chemistry is currently under way in our lab and will be the subject of future reports.

## Acknowledgements

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## Notes and references

1 For reviews, see: (*a*) C. V. Galliford and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2007, **46**, 8748; (*b*) C. Marti and E. M. Carreira, *Eur. J. Org. Chem.*, 2003, 2209; (*c*) B. M. Trost and M. K. Brennan, *Synthesis*, 2009, 3003; (*d*) F. Zhou, Y.-L. Liu and J. Zhou, *Adv. Synth. Catal.*, 2010, **352**, 1381; (*e*) K. Shen, X. Liu, L. Lin and X. Feng, *Chem. Sci.*, 2012, **3**, 327.

2 (*a*) M. Rottmann, C. McNamara, B. K. S. Yeung, M. C. S. Lee, B. Zou, B. Russell, P. Seitz, D. M. Plouffe, N. V. Dharia, J. Tan, S. B. Cohen, K. R. Spencer, G. E. González-Páez, S. B. Lakshminarayana, A. Goh, R. Suwanarusk, T. Jegla, E. K. Schmitt, H.-P. Beck, R. Brun, F. Nosten, L. Renia, V. Dartois, T. H. Keller, D. A. Fidock, E. A. Winzeler and T. T. Diagana, *Science*, 2010, **329**, 1175; (*b*) G. Griebel, J. Simiand, C. S-L. Gal, J. Wagnon, M. Pascal, B. Scatton, J.-P. Maffrand and P. Soubrie, *Proc. Natl. Acad. Sci. U. S. A.*, 2002, **99**, 6370; (*c*) M. Ochi, K. Kawasaki, H. Kataoka and Y. Uchio, *Biochem. Biophys. Res. Commun.*, 2001, **283**, 1118; (*d*) H. Takayama, I. Mori, M. Kitajima, N. Aimi and N. H. Lajis, *Org. Lett.*, 2004, **6**, 2945; (*e*) L. Chevolot, A.-M. Chevolot, M. Gajhede, C. Larsen, U. Anthoni and C. Christophersen, *J. Am. Chem. Soc.*, 1985, **107**, 4542.

3 (*a*) G. Lesma, N. Landoni, T. Pilati, A. Sacchetti and A. Silvani, *J. Org. Chem.*, 2009, **74**, 4537; (*b*) B. Alcaide, P. Almendros and C. Aragoncillo, *Eur. J. Org. Chem.*, 2010, 2845; (*c*) C. Sun, X. Lin and S. M. Weinreb, *J. Org. Chem.*, 2006, **71**, 3159; (*d*) T. Nishikawa, S. Kajii and M. Isobe, *Chem. Lett.*, 2004, **33**, 440; (*e*) H. Miyabe, Y. Yamaoka and Y. Takemoto, *J. Org. Chem.*, 2005, **70**, 3324; (*f*) A. Sacchetti, A. Silvani, F. G. Gatti, G. Lesma, T. Pilati and B. Trucchi, *Org. Biomol. Chem.*, 2011, **9**, 5515.

4 For recent examples: (*a*) I. Gorokhovik, L. Neuville and J. Zhu, *Org. Lett.*, 2011, **13**, 5536; (*b*) Y.-X. Jia, J. M. Hillgren, E. L. Watson, S. P. Marsden and E. P. Kündig, *Chem. Commun.*, 2008, 4040; (*c*) S. P. Marsden, E. L. Watson and S. A. Raw, *Org. Lett.*, 2008, **10**, 2905; (*d*) E. L. Watson, S. P. Marsden and S. A. Raw, *Tetrahedron Lett.*,

2009, **50**, 3318; (*e*) A. F. Bella, A. M. Z. Slawin and J. C. Walton, *J. Org. Chem.*, 2004, **69**, 5926.

5 (*a*) L. Cheng, L. Liu, D. Wang and Y.-J. Chen, *Org. Lett.*, 2009, **11**, 3874; (*b*) Z. Yang, Z. Wang, S. Bai, K. Shen, D. Chen, X. Liu, L. Lin and X. Feng, *Chem.–Eur. J.*, 2010, **16**, 6632; (*c*) S. Mouri, Z. Chen, H. Mitsunuma, M. Furutachi, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2010, **132**, 1255; (*d*) T. Bui, M. Borregan, C. Milite and C. F. Barbas III, *Org. Lett.*, 2010, **12**, 5696; (*e*) T. Zhang, L. Cheng, L. Liu, D. Wang and Y.-J. Chen, *Tetrahedron: Asymmetry*, 2010, **21**, 2800; (*f*) K. Shen, X. Liu, G. Wang, L. Lin and X. Feng, *Angew. Chem., Int. Ed.*, 2011, **50**, 4684; (*g*) L.-N. Jia, J. Huang, L. Peng, L.-L. Wang, J.-F. Bai, F. Tian, G.-Y. He, X.-Y. Xu and L.-X. Wang, *Org. Biomol. Chem.*, 2012, **10**, 236; (*h*) X. Companyó, G. Vakero, O. Pineda, T. Calvet, M. Bardia-Font, A. Moyano and R. Rios, *Org. Biomol. Chem.*, 2012, **10**, 431.

6 (*a*) T. Emura, T. Esaki, K. Tachibana and M. Shimizu, *J. Org. Chem.*, 2006, **71**, 8559; (*b*) A. K. Ghosh, G. Schiltz, R. S. Perali, S. Leshchenko, S. Kay, D. E. Walters, Y. Koh, K. Maedad and H. Mitsuya, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 1869; (*c*) P. Magnus and R. Turnbull, *Org. Lett.*, 2006, **8**, 3497; (*d*) S. J. O'Connor and Z. Liu, *Synlett*, 2003, 2135; (*e*) M. A. Loreto, A. Migliorini, P. A. Tardella and A. Gambacorta, *Eur. J. Org. Chem.*, 2007, 2365.

7 (*a*) Z.-Q. Qian, F. Zhou, T.-P. Du, B.-L. Wang, M. Ding, X.-L. Zhao and J. Zhou, *Chem. Commun.*, 2009, 6753; (*b*) F. Zhou, M. Ding, Y.-L. Liu and J. Zhou, *Adv. Synth. Catal.*, 2011, **353**, 2945; (*c*) Z.-Y. Cao, Y. Zhang, C.-B. Ji and J. Zhou, *Org. Lett.*, 2011, **13**, 6398; (*d*) Y.-L. Liu, F. Zhou, J.-J. Cao, C.-B. Ji, M. Ding and J. Zhou, *Org. Biomol. Chem.*, 2010, **8**, 3847; (*e*) F. Zhou, Z.-Y. Cao, J. Zhang, H.-B. Yang and J. Zhou, *Chem.–Asian J.*, 2011, **7**, 233; (*f*) M. Ding, F. Zhou, Y.-L. Liu, C.-H. Wang, X.-L. Zhao and J. Zhou, *Chem. Sci.*, 2011, **2**, 2035; (*g*) Y.-L. Liu, B.-L. Wang, J.-J. Cao, L. Chen, Y.-X. Zhang, C. Wang and J. Zhou, *J. Am. Chem. Soc.*, 2010, **132**, 15176; (*h*) Y.-L. Liu and J. Zhou, *Chem. Commun.*, 2012, **48**, 1919.

8 For a recent review, see: (*a*) A. Guérinot, S. Reymond and J. Cossy, *Eur. J. Org. Chem.*, 2012, 19. For using more than stoichiometric amount of acids: (*b*) J. J. Ritter and P. P. Minieri, *J. Am. Chem. Soc.*, 1948, **70**, 4045; (*c*) A. Mukherjee and R.-S. Liu, *Org. Lett.*, 2011, **13**, 660; (*d*) J. C. Baum, J. E. Milne, J. A. Murry and O. R. Thie, *J. Org. Chem.*, 2009, **74**, 2207; (*e*) P. Rubenbauer and T. Bach, *Chem. Commun.*, 2009, 2130; (*f*) J. Liu, C. Ni, Y. Li, L. Zhang, G. Wang and J. Hu, *Tetrahedron Lett.*, 2006, **47**, 6753. For catalytic version: (*g*) N. Ibrahim, A. S. K. Hashmi and F. Rominger, *Adv. Synth. Catal.*, 2011, **353**, 461; (*h*) R. Sanz, A. Martinez, V. Guilarte, J. M. Alvarez-Gutierrez and F. Rodriguez, *Eur. J. Org. Chem.*, 2007, 4642; (*i*) M. Barbero, S. Bazzi, S. Cadamuro and S. Dughera, *Eur. J. Org. Chem.*, 2009, 430; (*j*) M. Shi and G. Q. Tian, *Tetrahedron Lett.*, 2006, **47**, 8059.

9 (*a*) T. Cupido, J. Tulla-Puche, J. Spengler and F. Albericio, *Curr. Opin. Drug Discovery Dev.*, 2007, **10**, 768; (*b*) J. W. Bode, *Curr. Opin. Drug Discovery Dev.*, 2006, **9**, 765.

10 Based on a SciFinder survey, there are more than 300 patented structures containing a quaternary oxindole framework with an amido group at the C3 position of oxindole.

11 (*a*) B. M. Trost, *Science*, 1991, **254**, 1471; (*b*) P. A. Wender, *Chem. Rev.*, 1996, **96**, 1; (*c*) P. Anastas and N. Eghbali, *Chem. Soc. Rev.*, 2010, **39**, 301; (*d*) C.-J. Li and B. M. Trost, *Proc. Natl. Acad. Sci. U. S. A.*, 2008, **105**, 13197.

12 For a comprehensive review, see: (*a*) R. Dalpozzo, G. Bartoli, L. Sambri and P. Melchiorre, *Chem. Rev.*, 2010, **110**, 3501. For examples, see: (*b*) S. Kanemasa, Y. Oderaotoshi, S. Sakaguchi, H. Yamamoto, J. Tanaka, E. Wada and D. P. Curran, *J. Am. Chem. Soc.*, 1998, **120**, 3074; (*c*) J. Zhou and Y. Tang, *J. Am. Chem. Soc.*, 2002, **124**, 9030; (*d*) G. Bartoli, M. Bosco, M. Locatelli, E. Marcantoni, P. Melchiorre and L. Sambri, *Org. Lett.*, 2005, **7**, 427; (*e*) X.-X. Wu, L. Li and J.-L. Zhang, *Chem. Commun.*, 2011, **47**, 7824; (*f*) L. Wang, X. Liu, Z. Dong, X. Fu and X. Feng, *Angew. Chem., Int. Ed.*, 2008, **47**, 8670; (*g*) X. He, Q. Zhang, W. Wang, L. Lin, X. Liu and X. Feng, *Org. Lett.*, 2011, **13**, 804; (*h*) Y. Cai, S.-F. Zhu, G.-P. Wang and Q.-L. Zhou, *Adv. Synth. Catal.*, 2011, **353**, 2939.

13 (*a*) G. Lesma, N. Landoni, A. Sacchetti and A. Silvani, *Tetrahedron*, 2010, **66**, 4474; (*b*) A. Steven and L. E. Overman, *Angew. Chem., Int. Ed.*, 2007, **46**, 5488; (*c*) N. Duguet, A. M. Z. Slawin and A. D. Smith, *Org. Lett.*, 2009, **11**, 3858.

14 For a similar phenomenon: T. Kanda, S. Kato, T. Sugino, N. Kambe, A. Ogawa and N. Sonoda, *Synthesis*, 1995, 1102.

15 Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center. (CCDC 859777).

16 For the construction of spirocyclic oxindoles, see: (*a*) L.-H. Sun, L.-T. Shen and S. Ye, *Chem. Commun.*, 2011, **47**, 10136; (*b*) X.-N. Wang, Y.-Y. Zhang and S. Ye, *Adv. Synth. Catal.*, 2010, **352**, 1892; (*c*) G. Bergonzini and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2012, **51**, 971; (*d*) X. Jiang, Y. Cao, Y. Wang, L. Liu, F. Shen and R. Wang, *J. Am. Chem. Soc.*, 2010, **132**, 15328; (*e*) B. M. Trost, N. Cramer and S. M. Silverman, *J. Am. Chem. Soc.*, 2007, **129**, 12396; (*f*) G. Bencivenni, L.-Y. Wu, A. Mazzanti, B. Giannichi, F. Pesciaioli, M.-P. Song, G. Bartoli and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2009, **48**, 7200; (*g*) X.-H. Chen, Q. Wei, S.-W. Luo, H. Xiao and L.-Z. Gong, *J. Am. Chem. Soc.*, 2009, **131**, 13819; (*h*) A. P. Antonchick, C. Gerding-Reimers, M. Catarinella, M. Schurmann, H. Preut, S. Ziegler, D. Rauh and H. Waldmann, *Nat. Chem.*, 2010, **2**, 735; (*i*) K. Jiang, Z.-J. Jia, S. Chen, L. Wu and Y.-C. Chen, *Chem.–Eur. J.*, 2010, **16**, 2852; (*j*) B. Tan, N. Candeias and C. F. Barbas III, *Nat. Chem.*, 2011, **3**, 473; (*k*) Y.-B. Lan, H. Zhao, Z.-M. Liu, G.-G. Liu, J.-C. Tao and X. W. Wang, *Org. Lett.*, 2011, **13**, 4866; (*l*) Y.-X. Jia, D. Katayev, G. Bernardinelli, T. M. Seidel and E. P. Kündig, *Chem.–Eur. J.*, 2010, **16**, 6300; (*m*) V. Nair, S. Vellalth, M. Poonoth, R. Mohan and E. Suresh, *Org. Lett.*, 2006, **8**, 507; (*n*) P. R. Sebahar and R. M. Williams, *J. Am. Chem. Soc.*, 2000, **122**, 5666; (*o*) M. M.-C. Lo, C. S. Neumann, S. Nagayama, E. O. Perlstein and S. L. Schreiber, *J. Am. Chem. Soc.*, 2004, **126**, 6077; (*p*) H. Liu, G. Dou and D. Shi, *J. Comb. Chem.*, 2010, **12**, 633; (*q*) M. Presset, K. Mohanan, M. Hamann, Y. Coquerel and J. Rodriguez, *Org. Lett.*, 2011, **13**, 4124; (*r*) L. Liu, D. Wu, X. Li, S. Wang, H. Li, J. Li and W. Wang, *Chem. Commun.*, 2012, **48**, 1692; (*s*) X. Huang, J. Peng, L. Dong and Y.-C. Chen, *Chem. Commun.*, 2012, **48**, 2439; (*t*) L. Liu, D. Wu, S. Zheng, T. Li, X. Li, S. Wang, J. Li, H. Li and W. Wang, *Org. Lett.*, 2012, **14**, 134; (*u*) D. Du, Z. Hu, J. Jin, Y. Lu, W. Tang, B. Wang and T. Lu, *Org. Lett.*, 2012, **14**, 1274; (*v*) H. Zhao, Y.-B. Lan, Z.-M. Liu, Y. Wang, X.-W. Wang and J.-C. Tao, *Eur. J. Org. Chem.*, 2012, DOI: 10.1002/ejoc.201101810.

17 For 3-hydroxyoxindoles as synthon, see ref. 7*e* and (*a*) D. B. England, G. Merey and A. Padwa, *Org. Lett.*, 2007, **9**, 3805; (*b*) C. Guo, J. Song, J.-Z. Huang, P.-H. Chen, S.-W. Luo and L.-Z. Gong, *Angew. Chem., Int. Ed.*, 2012, **51**, 1046.