Synthetic Methods

International Edition: DOI: 10.1002/anie.201508570
German Edition: DOI: 10.1002/ange.201508570

Enantioselective Synthesis of 3a-Amino-Pyrroloindolines by Copper-Catalyzed Direct Asymmetric Dearomative Amination of Tryptamines

Chuan Liu, Ji-Cheng Yi, Zhong-Bo Zheng, Yong Tang, Li-Xin Dai, and Shu-Li You**

Abstract: *A direct asymmetric dearomative amination of tryptamines with O-(2,4-dinitrophenyl)hydroxylamine (DPH) was achieved using CuBr-bisoxazoline complex as a catalyst, affording 3a-amino-pyrroloindolines in good to excellent enantioselectivity under mild reaction conditions. Furthermore, the synthetic value of this method was demonstrated in the total synthesis of (−)-psychotriasine in a highly concise manner.*

Pyrroloindolines exist as key frameworks in a large number of indole alkaloids and pharmacological compounds[1] that exhibit interesting biological properties.[2] Among those, 3a-amino-pyrroloindoline and derivatives[3] are privileged structures (Figure 1) that have attracted considerable attention[4] owing to their distinctive structures and remarkable antibacterial and antitumor properties.[3e,f,5] For example, (+)-psychotrimine was first synthesized by Takayama and co-workers by employing an asymmetric Ireland–Claisen rearrangement as a key step.[4e] Meanwhile, Baran and co-workers have made great progress in the total synthesis of psychotrimine,[4b] kapakahine F[4c] and kapakahine B[4c] through direct indole–aniline coupling reactions. Recently, Liao, Deng, and their co-workers reported a unified strategy for the syntheses of (−)-psychotriasine and (+)-pestalazine B, based on the advanced intermediates of 3a-amino-pyrroloindolines.[4i]

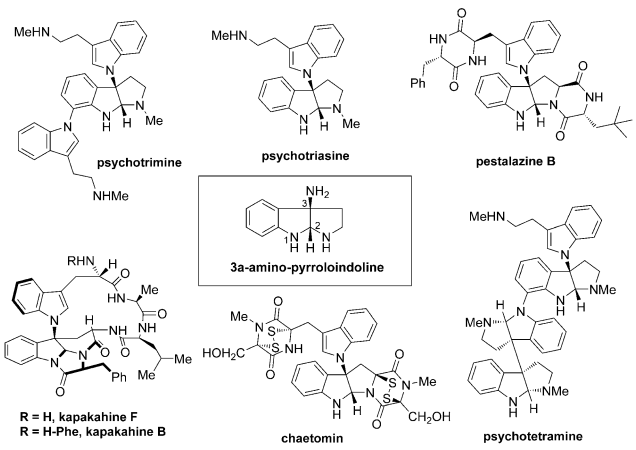


Figure 1. Representative 3a-amino-pyrroloindoline-containing natural products.

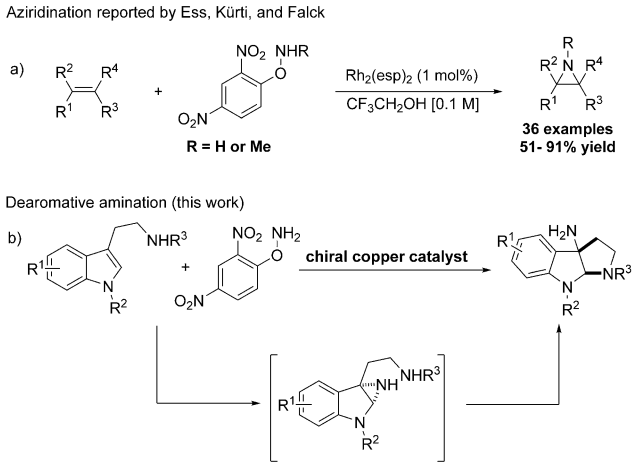
From a synthetic perspective, 3a-amino-pyrroloindoline is a key intermediate for the synthesis of these natural products.[6] However, to date, only limited enantioselective methodologies have been developed for the synthesis of 3a-amino-pyrroloindoline derivatives.[7] In 2012, the enantioselective synthesis of 3a-amino-pyrroloindoline derivatives was first reported by Antilla and co-workers[7a] using a chiral phosphoric-acid-catalyzed dearomatization reaction of tryptamine derivatives with DEAD (diethyl azodicarboxylate). Later Toste's group[7b] disclosed a highly enantioselective synthesis of C3-diazenated pyrroloindolines by a chiral anion phase-transfer (CAPT) catalysis technique. Then, 3a-amino-pyrroloindolines could be obtained through a reduction reaction.[4i]

Despite these achievements, the development of direct approaches to construct protecting-group-free 3a-amino-pyrroloindolines remains highly desirable, and the catalytic asymmetric version has not been reported.[8] In line with our interest in developing catalytic asymmetric dearomatization (CADA) reactions,[9,10] we envisioned that the unprotected 3a-amino-pyrroloindolines could be afforded by direct asymmetric dearomative amination of tryptamines with O-(2,4-dinitrophenyl)hydroxylamine (DPH) **2**, which has been elegantly introduced as an amination reagent by Ess, Kürti, Falck, and their co-workers (Scheme 1).[11] Herein, we report our preliminary results on the enantioselective synthesis of 3a-amino-pyrroloindolines by copper-catalyzed intermolecular asymmetric dearomative amination of tryptamines.

Our initial studies focused on testing the reaction between tryptamine **1a** and DPH with various chiral copper complexes.[12] These efforts led to the identification of bisoxazoline **L1** as a promising ligand. Further evaluation of copper source (Table 1, entries 1–9) revealed that CuBr is optimal, affording product **3a** in 53% yield and 63% *ee* (Table 1, entry 4). Encouraged by these results, different solvents were further examined, and the polar protic solvent 2,2,2-trifluoroethanol was found to be the best one in terms of enantioselectivity (73% *ee*; Table 1, entry 14). Furthermore, different chiral bisoxazoline ligands were evaluated, and chiral ligands were found to play a critical role in the enantioselective control. Compound **3a** was obtained in 75% *ee* with cyclopropane-linked ligand **L2** (Table 1, entry 19), and in 78% *ee*

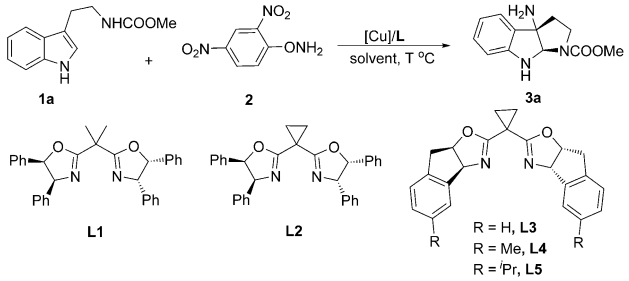
[*] Dr. C. Liu, J.-C. Yi, Dr. Z.-B. Zheng, Prof. Dr. Y. Tang, Prof. L.-X. Dai, Prof. Dr. S.-L. You
State Key Laboratory of Organometallic Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
345 Lingling Lu, Shanghai 200032 (China)
E-mail: tangy@sioc.ac.cn
slyou@sioc.ac.cn
Prof. Dr. Y. Tang, Prof. Dr. S.-L. You
Collaborative Innovation Center of
Chemical Science and Engineering
Tianjin (China)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201508570.



Scheme 1. Proposed copper-catalyzed asymmetric dearomative amination of tryptamines.

Table 1: Optimization of the reaction conditions.[a]



Entry	[Cu]	Solvent	L	Yield [%][b]	*ee* [%][c]
1	$Cu(OTf)\cdot 0.5\,PhMe$	HFIP/EtOH	**L1**	21	57
2	$[Cu(CH_3CN)_4PF_6]$	HFIP/EtOH	**L1**	14	50
3	CuCl	HFIP/EtOH	**L1**	66	61
4	CuBr	HFIP/EtOH	**L1**	53	63
5	CuI	HFIP/EtOH	**L1**	trace	–
6	CuTc	HFIP/EtOH	**L1**	17	51
7	$Cu(OAc)_2$	HFIP/EtOH	**L1**	21	53
8	$Cu(acac)_2$	HFIP/EtOH	**L1**	15	55
9	$Cu(Cl_4O)_2\cdot 6H_2O$	HFIP/EtOH	**L1**	20	47
10	CuBr	HFIP	**L1**	54	70
11	CuBr	MeOH	**L1**	44	71
12	CuBr	EtOH	**L1**	23	55
13	CuBr	*i*-PrOH	**L1**	21	51
14	CuBr	CF_3CH_2OH	**L1**	43	73
15	CuBr	EtOAc	**L1**	trace	–
16	CuBr	toluene	**L1**	5	–
17	CuBr	CH_3CN	**L1**	14	51
18	CuBr	DCM	**L1**	trace	–
19	CuBr	CF_3CH_2OH	**L2**	50	75
20	CuBr	CF_3CH_2OH	**L3**	60	78
21	CuBr	CF_3CH_2OH	**L4**	51	84
22	CuBr	CF_3CH_2OH	**L5**	43	88
23[d]	CuBr	CF_3CH_2OH	**L5**	44	92
24[d,e]	**CuBr**	**CF_3CH_2OH/MeOH**	**L5**	**65**	**90**
25[d]	CuBr	MeOH	**L5**	68	84

[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.2 mmol), metal (10 mol%), **L** (11 mol%) in solvent (3.0 mL) at rt, unless otherwise noted. After 8 h, another batch of **2** (0.1 mmol) was added in one portion. [b] Isolated yields. [c] Determined by HPLC analysis. [d] Reaction at −20°C. [e] CF_3CH_2OH (1.5 mL) and MeOH (1.5 mL) were used as co-solvents.

with indano scaffold ligand **L3** (Table 1, entry 20). To our delight, when methyl groups were introduced (ligand **L4**), the *ee* was improved to 84% (Table 1, entry 21). Finally, ligand **L5** with isopropyl groups was found to be the best one, providing product **3a** in 43% yield and 88% *ee* (Table 1, entry 22). Conducting the reaction at −20°C further enhanced the enantioselectivity to 92% *ee* (Table 1, entry 23). When methanol and 2,2,2-trifluoroethanol were used as co-solvents,[12] product **3a** was obtained in 65% yield and 90% *ee* (Table 1, entry 24). Notably, reaction in methanol alone gave an increased yield but decreased enantioselectivity (68% yield, 84% *ee*; Table 1, entry 25).

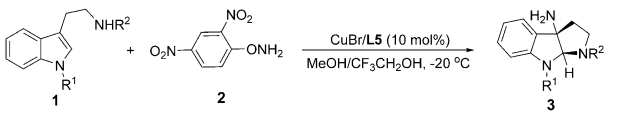
With the optimized reaction conditions in hand (Table 1, entry 24), we turned to explore the substrate scope (Table 2). Typical electron-withdrawing N-protecting groups ($R^2 = CO_2Me$, Boc, Ts, CO_2Ph) on the side chain of tryptamine were all well tolerated, providing the desired 3a-amino-pyrroloindoline products in good to excellent *ee* and moderate yields (86–90% *ee*, 40–65% yield; Table 2, **3a**–**d**). Furthermore, the reactions of substrates bearing either an electron-rich ($R^1 = Me$, Bn, allyl) or electron-poor ($R^1 = CO_2Me$) substituent on the indole nitrogen atom proceeded smoothly (81–92% *ee*, 42–50% yield; Table 2, **3e**–**h**).

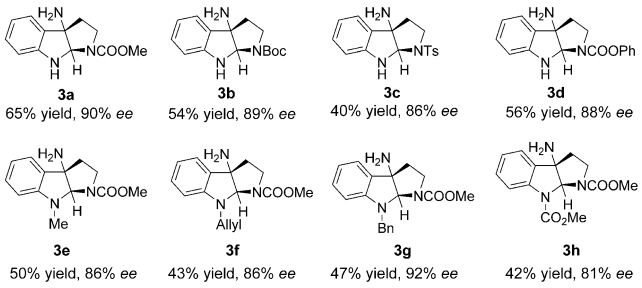
Next, the substrate scope of substituted tryptamines was explored. Tryptamine derivatives bearing either an electron-donating group (5-MeO, 5-Me, 6-Me, 7-Me) or an electron-withdrawing group (4-Cl, 4-Br, 5-F, 5-Cl, 5-Br, 6-F, 6-Cl, 7-Br) on the indole core were found to be well tolerated, affording the corresponding 3a-amino-pyrroloindolines in moderate yields with excellent enantioselectivity (33–69% yield, 82–95% *ee*; Table 3). Notably, the compatibility of the Br substituent provides the potential for further transformation by cross-coupling reactions. Although the yields are moderate, the reactions in general are clean by TLC (thin layer chromatography) detection, and the products are easy to be purified. The moderate yields are likely due to the formation of unidentified oligomers and the side reactions of primary amines **3** with DPH.

The synthetic value of this methodology has been demonstrated by the total synthesis of (−)-psychotriasine. In the presence of $(CuOTf)_2\cdot PhMe$, 3a-amino-pyrroloindoline **3a** was reacted with diaryliodonium salt **4**, affording compound **5** in 64% yield,[4i] which was then converted to compound **6** by a Larock annulation reaction (Scheme 2).[4d] Further reduction of **6** with $LiAlH_4$ gave (−)-psychotriasine in 85% yield. Such an asymmetric total synthesis of (−)-psychotriasine features 31.8% overall yield in four steps from methyl (2-(1*H*-indol-3-yl)ethyl)carbamate (**1a**). Furthermore, the total synthesis of (−)-psychotriasine suggested the absolute configuration of product **3a** as (3*S*,8*R*).[3h,12]

In conclusion, we have developed a copper-catalyzed direct asymmetric dearomative amination of substituted tryptamines with DPH for the synthesis of 3a-amino-pyrroloindolines, a privileged

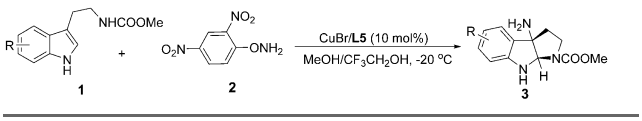
Table 2: Substrate scope: N-protecting groups.[a]

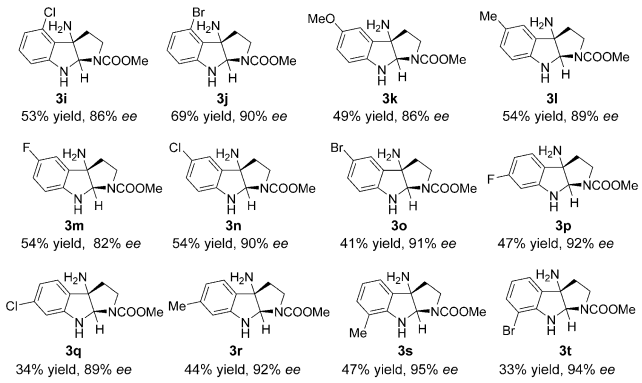




[a] Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), CuBr (0.02 mmol), **L5** (0.022 mmol) in CF_3CH_2OH (1.5 mL) and MeOH (1.5 mL) at −20 °C. After 8 h, another batch of **2** (0.1 mmol) was added in one portion. Yield refers to isolated products. The *ee* values were determined by HPLC analysis.

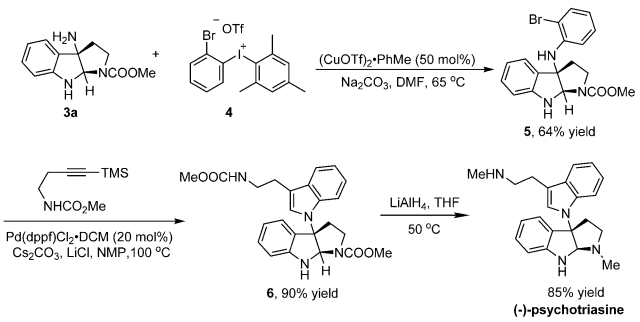
Table 3: Substrate scope: substituent on indole core.[a]





[a] Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), CuBr (0.02 mmol), **L5** (0.022 mmol) in CF_3CH_2OH (1.5 mL) and MeOH (1.5 mL) at −20 °C. After 8 h, another batch of **2** (0.1 mmol) was added in one portion. Yield refers to isolated products. The *ee* values were determined by HPLC analysis.

structure present in various indole alkaloids. This method provides facile access to structurally diverse 3a-amino-pyrroloindolines in good to excellent enantioselectivity and moderate yields under mild reaction conditions. Furthermore, the synthetic value of this new method was demonstrated in the total synthesis of (−)-psychotriasine in a highly concise manner.



Scheme 2. Total synthesis of (−)-psychotriasine.

Acknowledgements

We thank the National Basic Research Program of China (973 Program 2015CB856600) and the National Natural Science Foundation of China (21332009, 21421091) for generous financial support.

Keywords: asymmetric catalysis · copper · dearomatization · pyrroloindolines · tryptamines

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 751–754
Angew. Chem. **2016**, *128*, 761–764

[1] a) S. Takano, K. Ogasawara in *The Alkaloids*, *Vol. 36* (Ed.: A. Brossi), Academic, New York, **1989**, p. 225; b) U. Anthoni, C. Christophersen, P. H. Nielsen in *Alkaloids*: *Chemical & Biological Perspectives*, *Vol. 13* (Ed.: S. W. Pelletier), Pergamon, Oxford, **1999**, p. 163; c) T. Suzuki, J.-H. Choi, T. Kawaguchi, K. Yamashita, A. Morita, H. Hirai, K. Nagai, T. Hirose, S. Ōmura, T. Sunazuka, H. Kawagishi, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4246.

[2] a) K. P. Shaw, Y. Aracava, A. Akaike, J. W. Daly, D. L. Rickett, E. X. Albuquerque, *Mol. Pharmacol.* **1985**, *28*, 527; b) M. Varoglu, T. H. Corbett, F. A. Valeriote, P. Crews, *J. Org. Chem.* **1997**, *62*, 7078; c) Y. Usami, J. Yamaguchi, A. Numata, *Heterocycles* **2004**, *63*, 1123; d) C.-J. Zheng, C.-J. Kim, K. S. Bae, Y.-H. Kim, W.-G. Kim, *J. Nat. Prod.* **2006**, *69*, 1816; e) C. Bunders, J. Cavanagh, C. Melander, *Org. Biomol. Chem.* **2011**, *9*, 5476.

[3] a) Y. Nakao, B. K. S. Yeung, W. Y. Yoshida, P. J. Scheuer, M. Kelly-Borges, *J. Am. Chem. Soc.* **1995**, *117*, 8271; b) B. K. S. Yeung, Y. Nakao, R. B. Kinnel, J. R. Carney, W. Y. Yoshida, P. J. Scheuer, M. Kelly-Borges, *J. Org. Chem.* **1996**, *61*, 7168; c) Y. Nakao, J. Kuo, W. Y. Yoshida, M. Kelly, P. J. Scheuer, *Org. Lett.* **2003**, *5*, 1387; d) H. Takayama, I. Mori, M. Kitajima, N. Aimi, N. H. Lajis, *Org. Lett.* **2004**, *6*, 2945; e) G.-Y. Li, B.-G. Li, T. Yang, J.-F. Yan, G.-Y. Liu, G.-L. Zhang, *J. Nat. Prod.* **2006**, *69*, 1374; f) G. Ding, L. Jiang, L. Guo, X. Chen, H. Zhang, Y. Che, *J. Nat. Prod.* **2008**, *71*, 1861; g) C. Pérez-Balado, Á. R. de Lera, *Org. Biomol. Chem.* **2010**, *8*, 5179; h) H. Zhou, H.-P. He, Y.-H. Wang, X.-J. Hao, *Helv. Chim. Acta* **2010**, *93*, 1650.

[4] a) Y. Matsuda, M. Kitajima, H. Takayama, *Org. Lett.* **2008**, *10*, 125; b) T. Newhouse, P. S. Baran, *J. Am. Chem. Soc.* **2008**, *130*, 10886; c) T. Newhouse, C. A. Lewis, P. S. Baran, *J. Am. Chem. Soc.* **2009**, *131*, 6360; d) T. Newhouse, C. A. Lewis, K. J. Eastman, P. S. Baran, *J. Am. Chem. Soc.* **2010**, *132*, 7119; e) N. Takahashi, T. Ito, Y. Matsuda, N. Kogure, M. Kitajima, H. Takayama, *Chem. Commun.* **2010**, *46*, 2501; f) K. Foo, T. Newhouse, I. Mori, H. Takayama, P. S. Baran, *Angew. Chem. Int. Ed.* **2011**, *50*, 2716; *Angew. Chem.* **2011**, *123*, 2768; g) T. Araki, T. Ozawa, H. Yokoe, M. Kanematsu, M. Yoshida, K. Shishido, *Org. Lett.* **2013**, *15*, 200; h) H. Zhang, H. Kang, L. Hong, W. Dong, G. Li, X. Zheng, R. Wang, *Org. Lett.* **2014**, *16*, 2394; i) Q. Li, T. Xia, L. Yao, H. Deng, X. Liao, *Chem. Sci.* **2015**, *6*, 3599.

[5] a) A. L. Kung, S. D. Zabludoff, D. S. France, S. J. Freedman, E. A. Tanner, A. Vieira, S. Cornell-Kennon, J. Lee, B. Wang, J. Wang, K. Memmert, H.-U. Naegeli, F. Petersen, M. J. Eck, K. W. Bair, A. W. Wood, D. M. Livingston, *Cancer Cell* **2004**, *6*, 33; b) M. A. Schallenberger, T. Newhouse, P. S. Baran, F. E. Romesberg, *J. Antibiot.* **2010**, *63*, 685; c) K. M. Cook, S. T. Hilton, J. Mecinovic, W. B. Motherwell, W. D. Figg, C. J. Schofield, *J. Biol. Chem.* **2009**, *284*, 26831.

[6] a) M. Movassaghi, O. K. Ahmad, S. P. Lathrop, *J. Am. Chem. Soc.* **2011**, *133*, 13002; b) S. P. Lathrop, M. Movassaghi, *Chem. Sci.* **2014**, *5*, 333.

[7] a) Z. Zhang, J. C. Antilla, *Angew. Chem. Int. Ed.* **2012**, *51*, 11778; *Angew. Chem.* **2012**, *124*, 11948; b) H. M. Nelson, S. H. Reisberg, H. P. Shunatona, J. S. Patel, F. D. Toste, *Angew. Chem. Int. Ed.* **2014**, *53*, 5600; *Angew. Chem.* **2014**, *126*, 5706; c) T. Benkovics, I. A. Guzei, T. P. Yoon, *Angew. Chem. Int. Ed.* **2010**, *49*, 9153; *Angew. Chem.* **2010**, *122*, 9339; For racemic synthesis of aminopyrroloindolines and 3-azido furoindolines, see: d) S. Beaumont, V. Pons, P. Retailleau, R. H. Dodd, P. Dauban, *Angew. Chem. Int. Ed.* **2010**, *49*, 1634; *Angew. Chem.* **2010**, *122*, 1678; e) H. Yin, T. Wang, N. Jiao, *Org. Lett.* **2014**, *16*, 2302.

[8] During the preparation of this manuscript, Xie, Zhu, and Lai reported a racemic rhodium-catalyzed dearomative amination of tryptamines: Z. Shen, Z. Xia, H. Zhao, J. Hu, X. Wan, Y. Lai, C. Zhu, W. Xie, *Org. Biomol. Chem.* **2015**, *13*, 5381.

[9] For recent reviews on catalytic asymmetric dearomatization reaction of indoles, see: a) C.-X. Zhuo, W. Zhang, S.-L. You, *Angew. Chem. Int. Ed.* **2012**, *51*, 12662; *Angew. Chem.* **2012**, *124*, 12834; b) L. M. Repka, S. E. Reisman, *J. Org. Chem.* **2013**, *78*, 12314; c) Q. Ding, X. Zhou, R. Fan, *Org. Biomol. Chem.* **2014**, *12*, 4807; d) C.-X. Zhuo, C. Zheng, S.-L. You, *Acc. Chem. Res.* **2014**, *47*, 2558; Selected recent examples from our group: e) Q.-F. Wu, H. He, W.-B. Liu, S.-L. You, *J. Am. Chem. Soc.* **2010**, *132*, 11418; f) Q.-F. Wu, W.-B. Liu, C.-X. Zhuo, Z.-Q. Rong, K.-Y. Ye, S.-L. You, *Angew. Chem. Int. Ed.* **2011**, *50*, 4455; *Angew. Chem.* **2011**, *123*, 4547; g) X. Zhang, L. Han, S.-L. You, *Chem. Sci.* **2014**, *5*, 1059; h) X. Zhang, W.-B. Liu, H.-F. Tu, S.-L. You, *Chem. Sci.* **2015**, *6*, 4525.

[10] Selected recent examples on asymmetric dearomatization reactions of indoles: a) J. F. Austin, S.-G. Kim, C. J. Sinz, W.-J. Xiao, D. W. C. MacMillan, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5482; b) B. M. Trost, J. Quancard, *J. Am. Chem. Soc.* **2006**, *128*, 6314; c) S. B. Jones, B. Simmons, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 13606; d) L. M. Repka, J. Ni, S. E. Reisman, *J. Am. Chem. Soc.* **2010**, *132*, 14418; e) O. Lozano, G. Blessley, T. Martinez del Campo, A. L. Thompson, G. T. Giuffredi, M. Bettati, M. Walker, R. Borman, V. Gouverneur, *Angew. Chem. Int. Ed.* **2011**, *50*, 8105; *Angew. Chem.* **2011**, *123*, 8255; f) S. Zhu, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2012**, *134*, 10815; g) J. E. Spangler, H. M. L. Davies, *J. Am. Chem. Soc.* **2013**, *135*, 6802; h) H. Xiong, H. Xu, S. Liao, Z. Xie, Y. Tang, *J. Am. Chem. Soc.* **2013**, *135*, 7851; i) M.-C. Tong, X. Chen, J. Li, R. Huang, H. Tao, C.-J. Wang, *Angew. Chem. Int. Ed.* **2014**, *53*, 4680; *Angew. Chem.* **2014**, *126*, 4768; j) L. Liao, C. Shu, M. Zhang, Y. Liao, X. Hu, Y. Zhang, Z. Wu, W. Yuan, X. Zhang, *Angew. Chem. Int. Ed.* **2014**, *53*, 10471; *Angew. Chem.* **2014**, *126*, 10639; k) C. Romano, M. Jia, M. Monari, E. Manoni, M. Bandini, *Angew. Chem. Int. Ed.* **2014**, *53*, 13854; *Angew. Chem.* **2014**, *126*, 14074; l) Y.-C. Zhang, J.-J. Zhao, F. Jiang, S.-B. Sun, F. Shi, *Angew. Chem. Int. Ed.* **2014**, *53*, 13912; *Angew. Chem.* **2014**, *126*, 14132; m) X. Zhao, X. Liu, H. Mei, J. Guo, L. Lin, X. Feng, *Angew. Chem. Int. Ed.* **2015**, *54*, 4032; *Angew. Chem.* **2015**, *127*, 4104; n) C. Shen, R.-R. Liu, R.-J. Fan, Y.-L. Li, T.-F. Xu, J.-R. Gao, Y.-X. Jia, *J. Am. Chem. Soc.* **2015**, *137*, 4936.

[11] a) J. L. Jat, M. P. Paudyal, H. Gao, Q.-L. Xu, M. Yousufuddin, D. Devarajan, D. H. Ess, L. Kürti, J. R. Falck, *Science* **2014**, *343*, 61; For DPH as a primary amine resource in amination of aromatic boronic acids, see: b) C. Zhu, G. Li, D. H. Ess, J. R. Falck, L. Kürti, *J. Am. Chem. Soc.* **2012**, *134*, 18253.

[12] For details, see the Supporting Information.

Received: September 13, 2015
Revised: November 4, 2015
Published online: November 25, 2015

