

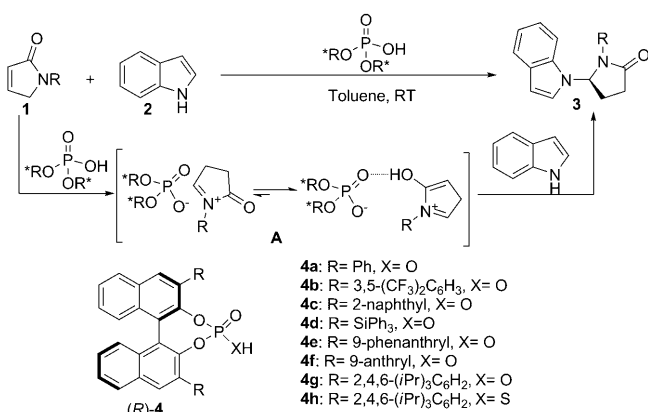
Enantioselective N–H Functionalization of Indoles with α,β -Unsaturated γ -Lactams Catalyzed by Chiral Brønsted Acids**

Yinjun Xie, Yingwei Zhao, Bo Qian, Lei Yang, Chungu Xia, and Hanmin Huang*

Chiral indole motifs are privileged heterocyclic structures in drug discovery and widely exist in synthetic bioactive compounds and natural products.^[1] Therefore, intense effort has been devoted to the direct enantioselective functionalization of indole cores for the synthesis of optically active indole derivatives.^[2] While many asymmetric alkylation methods exist for the functionalization of indoles at the C3 or C2 atom,^[3] the asymmetric functionalization of indoles at the N atom is limited.^[4] This limitation probably results from the intrinsic lower reactivity of the N atom compared to the C3 and C2 atoms of the indole core. One way to circumvent this problem is to use a base as a catalyst to facilitate the cleavage of the acidic proton on the N atom and make the N atom prone to alkylation.^[4b–c] The conjugate base of a chiral phosphoric acid could be produced by the abstraction of the acidic proton by another substrate.^[5] As such, a chiral phosphoric acid would function as a catalyst to promote the N alkylation of an indole under the appropriate reaction conditions. Herein we report a Brønsted acid catalyzed enantioselective N-alkylation reaction of indoles that selectively affords chiral N-alkylated indole derivatives with excellent enantioselectivity (up to 95 % *ee*).

The cyclic *N*-acyliminium ions are highly reactive electrophiles and are extensively utilized for the construction of nitrogen-containing ring systems by C–C bond-formation reactions.^[6] By using this strategy, the research groups of Jacobsen and Dixon have successfully installed pyrrolidinone moieties at the C2- and C3-positions of an indole using cyclic *N*-acyliminium ions as electrophiles.^[7] However, to the best of our knowledge, the enantioselective N alkylation of an indole with this type of reactive species has never been explored, despite the fact that the structural motifs of the corresponding products could act as useful precursors to more complex

alkaloid natural product targets.^[8] The α,β -unsaturated γ -lactam **1** could also act as a surrogate for the cyclic *N*-acyliminium ion since it could be easily converted into the *N*-acyliminium ion upon accepting an acidic proton from an appropriate Brønsted acid.^[9] This interesting and unique feature prompted us to surmise that the use of a chiral phosphoric acid, instead of an achiral Brønsted acid, would give rise to a chiral conjugate base/*N*-acyliminium ion pair **A** by protonation of the α,β -unsaturated γ -lactam. In this case, the acidic N–H atom of the indole would interact with the conjugate base of the chiral Brønsted acid through hydrogen bonding, thus activating the N atom to react with the cyclic *N*-acyliminium ion. The N-selective asymmetric functionalization of indoles would be expected to provide facile access to chiral indole derivatives that contain pyrrolidinone moieties, which are prominent features of many natural products and pharmaceuticals (Scheme 1).^[8a,b,10]



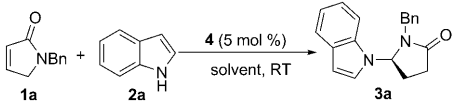
Scheme 1. Enantioselective N functionalization of indoles.

[*] Y. Xie, Y. Zhao, B. Qian, Dr. L. Yang, Prof. Dr. C. Xia, Prof. Dr. H. Huang
 State Key Laboratory for Oxo Synthesis and Selective Oxidation
 Lanzhou Institute of Chemical Physics
 Chinese Academy of Sciences, Lanzhou, 730000 (China)
 Fax: (+86) 931-496-8129
 E-mail: hmhuang@licp.cas.cn
 Prof. Dr. H. Huang
 State Key Laboratory of Applied Organic Chemistry
 Lanzhou University, Lanzhou, 730000 (China)
 Y. Xie, Y. Zhao
 Graduate School of the Chinese Academy of Sciences (China)

[**] This work was supported by the Chinese Academy of Sciences and the National Natural Science Foundation of China (20802085). We are grateful to Prof. A. Lei for providing the in situ IR instrument.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201102046>.

To explore our hypothesis, the reaction of α,β -unsaturated γ -lactam **1a** with indole **2a** catalyzed by phosphoric acids **4** was examined (Table 1) for the optimization of the reaction conditions. In the presence of 5 mol % of **4a** in toluene at room temperature, the reaction of **1a** with 1.2 equivalents of indole gave the desired product **3a** in 29 % yield and 22 % *ee*, together with a trace amount of the C3-alkylation by-product (less than 5 % yield). Under these reaction conditions several phosphoric acids (**4**; Scheme 1), which have a variety of substituents at the 3- and 3'-positions of the binaphthyl scaffold, were tested, and the results are listed in Table 1. The sterically congested phosphoric acid catalysts were found to be crucial for the activity and enantioselectivity, with the catalyst **4g**, which bears bulky 2,4,6-triisopropylphenyl groups

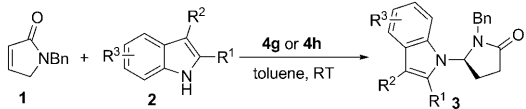
Table 1: Optimization of the reaction conditions.^[a]


Entry	Cat.	Solvent	Yield [%] ^[b]	ee [%] ^[c]
1	4a	toluene	29	22
2	4b	toluene	21	0
3	4c	toluene	15	19
4	4d	toluene	53	9
5	4e	toluene	50	11
6	4f	toluene	80	56
7	4g	toluene	75	87
8	4g	CH ₂ ClCH ₂ Cl	65	66
9	4g	Et ₂ O	80	81
10	4g	benzene	60	60
11	4g	o-xylene	66	82
12 ^[d]	4g	toluene	85	87
13 ^[e]	4h	toluene	65	90

[a] Reaction conditions: **4** (5 mol %), **1a** (0.2 mmol), indole **2a** (0.24 mmol), toluene (1.5 mL), at room temperature (15–20 °C) for 24 h. [b] Yield of the isolated product. [c] Determined by HPLC analysis using a chiral stationary phase. [d] Reaction time was 36 h. [e] 10 mol % of **4h** was used and the reaction time was 36 h. Bn = benzyl.

at the 3- and 3'-positions, being the most active and enantioselective (Table 1, entry 7). A screen of the solvents revealed that the reaction proceeded with significantly higher yields and stereoselectivities in aprotic solvents (toluene, Et₂O, and THF) than protic solvents, which could form hydrogen bonds with either the catalyst or the substrates. Toluene was the best choice of solvent amongst the solvents examined (Table 1, entries 7–11; see the Supporting Information for details), and up to 85 % yield and 87 % ee of product **3a** could be obtained when the reaction time was prolonged to 36 hours (Table 1, entry 12). We realized that a more rigid or tighter ion pair might increase the enantioselectivity. Thus, the Brønsted acid **4g**, which contains the larger sulfur atom in the corresponding conjugate base and therefore would lead to a more rigid ion pair, was employed in this reaction. For this reaction an excellent enantioselectivity of up to 90 % ee was obtained,^[11] albeit with a relatively lower yield (Table 1, entry 13).

With the optimized reaction conditions in hand, the reactions of a variety of indoles were carried out using either catalyst **4g** or **4h** (Table 2). For indoles **2a–2h**, both **4g** and **4h** were used (Table 2, entries 1–8), whereas only **4h** was used for the C2-substituted, C3-substituted, and C2,C3-disubstituted indoles **2i–2t** (Table 2, entries 9–20). The reactions of **2a–2g** revealed that a change in the substitution pattern on the benzene ring of the indole core had no pronounced effect on the yield and enantioselectivity. The yields for the reactions of **2a–2g** were generally higher when **4g** was used as a catalyst, but the enantioselectivities were relatively lower than those obtained with **4h** (Table 2, entries 1–7). The substituents at the C2- and C3-positions of the indole had a great influence on the reactivity when **4h** was used. For example, the introduction of a substituent at the C2-position of the indole core gave the corresponding N-alkylation products with

Table 2: Substrate scope of indoles.^[a]


Entry	R ¹ , R ²	R ³	Yield [%] ^[b]	ee [%] ^[c]
1	H, H	H	3a , 65 (85)	90 (87)
2	H, H	5-Me	3b , 44 (82)	90 (83)
3	H, H	5-OMe	3c , 71 (72)	90 (86)
4	H, H	5-F	3d , 38 (71)	86 (80)
5	H, H	5-Br	3e , 25 (72)	88 (80)
6	H, H	4-Br	3f , 24 (87)	90 (83)
7	H, H	6-Cl	3g , 25 (65)	90 (86)
8	Me, H	H	3h , 38 (81)	93 (93)
9	2-MePh, H	H	3i , 42	91
10	H, Me	H	3j , 95	82
11	Me, Me	H	3k , 98	94
12	–(CH ₂) ₃ –	H	3l , 96	91
13	–(CH ₂) ₄ –	H	3m , 96	95
14	–(CH ₂) ₅ –	H	3n , 91	92
15	–(CH ₂) ₆ –	H	3o , 91	87
16	Et, Me	H	3p , 94	93
17	Me, (CH ₂) ₄ CH ₃	H	3q , 90	92
18	–(CH ₂) ₄ –	5-Me	3r , 94	86
19	–(CH ₂) ₄ –	5-Cl	3s , 92	86
20	Me, Me	5-Cl	3t , 94	90

[a] Reaction conditions: **1** (0.2 mmol), indole **2** (0.24 mmol), **4h** (10 mol %), toluene (1.5 mL), at room temperature for 36 h. [b] Yield of the isolated product. The data in parentheses was obtained using **4g** (5 mol %) instead of **4h** as the catalyst. [c] Determined by HPLC analysis using a chiral stationary phase.

higher enantioselectivities but lower yields (Table 2, entries 8 and 9 versus entry 1). In contrast, for indole substrate **2j**, which has a substituent at the C3-position, the use of **4h** as a catalyst led to the formation of product **3j** in 95 % yield with moderate enantioselectivity (Table 2, entry 10 versus 8). Gratifyingly, the 2,3-disubstituted indoles **2k–2t** proved to be suitable substrates for the present reaction and the desired products **3k–3t** were afforded in 90–98 % yields and 86–95 % ee (Table 2, entries 11–20). Remarkably, a range of 2,3-fused indoles, with a variety of ring sizes, could be tolerated to give the corresponding adducts without affecting the yields and ee values (Table 2, entries 12–15, 18, and 19). In further experiments, the amide protection group of **1** was varied and the results revealed that only the C3-alkylation product was obtained with low ee values when the phenyl or Boc was used as a protection group instead of benzyl.^[12] The reason for this result is not clear at the present stage. The absolute configuration of the N-alkylation product **3f** was determined to be *S* by single-crystal X-ray analysis (Figure 1).^[13] The absolute configurations of other products obtained by this method were tentatively assigned by analogy.

The N-alkylation product **3m** could be converted into pyrrolidinone **5** by the cleavage of the benzyl group upon exposure to Na/NH₃ in THF (85 % yield; Scheme 2). Protection and then reduction of the amide moiety in **5** afforded pyrrolidine **6** in 45 % yield over two steps. In addition, the functionalized indole structure **3** could be used as the starting material for the efficient construction of some N-fused ring

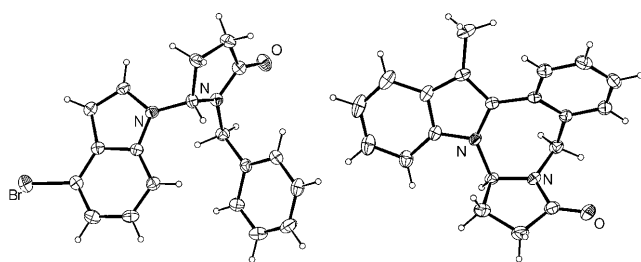
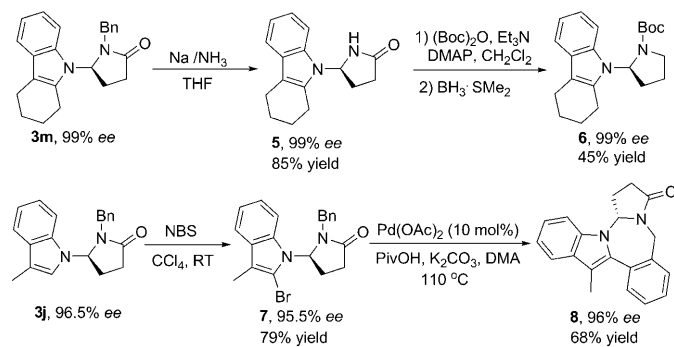


Figure 1. X-ray structure of the enantiomerically pure **3f** (left) and **8** (right). Thermal ellipsoids are set at 30% probability.

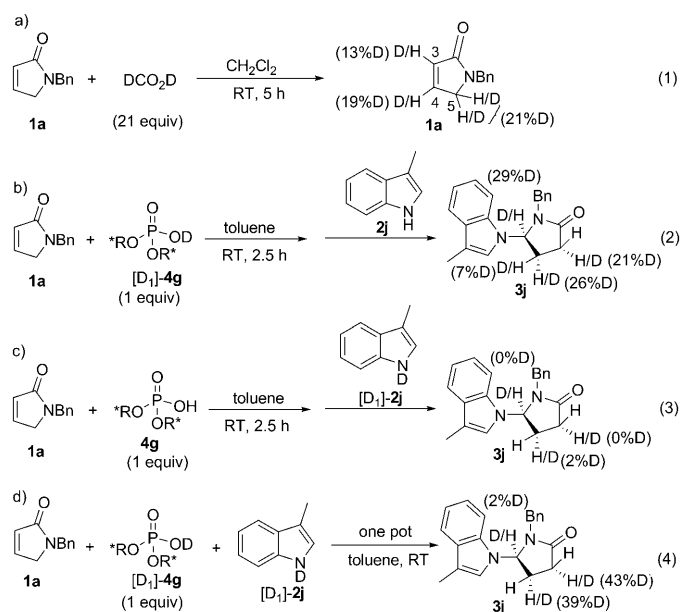
systems. The brominated compound **7** was readily prepared by the treatment of **3j** with NBS. The subsequent palladium-catalyzed intramolecular C-H functionalization of **7** afforded the desired structurally N-fused polycyclic compound **8**, which could potentially find valuable applications in medicinal chemistry.^[14] The structure of **8** was also confirmed unambiguously by single-crystal X-ray analysis.^[13]

The nonlinear effect studies of the current reaction rule out the possibility that two or more molecules of the catalyst



Scheme 2. Transformations of the N functionalized products. Boc = *tert*-butoxycarbonyl, DMA = dimethylacetamide, DMAP = 4-dimethylaminopyridine, NBS = *N*-bromosuccinimide, Piv = trimethylacetyl, THF = tetrahydrofuran.

are involved in the transition state of the present catalytic system (see the Supporting Information). Bocchi et al. have proposed a mechanism for the formation of an *N*-acyliminium ion from an α,β -unsaturated γ -lactam under acidic reaction conditions.^[9c] To rationalize the reaction pathway and elucidate the effect of the Brønsted acid we carried out labeling experiments. As depicted in Scheme 3a, after treatment of **1** with DCO₂D at room temperature the ¹H NMR analysis of the recovered starting material revealed extensive deuterium incorporation at the 3-, 4-, and 5-positions of lactam **1a**. This H/D scrambling suggests that the protonation of the lactam in the formation of the *N*-acyliminium ion is reversible. Further experiments were carried out with deuterium-labeled phosphoric acid [D₁]-**4g** and indole [D₁]-**2j**, respectively. After treatment of **1a** with 1.0 equivalent of deuterated Brønsted acid [D₁]-**4g** at room temperature for 2.5 hours, the resulting intermediate reacted with the 3-methylindole **2j**, to afford the corresponding product **3j** with H/D scrambling^[15] in 90%



Scheme 3. Deuterium-labeling experiments.

yield upon isolation (Scheme 3b). In contrast, when the undeuterated **4g** and deuterated indole [D₁]-**2j** were used under identical reaction conditions, the corresponding adduct was obtained in 87% yield almost without any deuterium incorporation (Scheme 3c). This result clearly shows that the Brønsted acid acts as a proton source to react with the α,β -unsaturated γ -lactam **1a** for the generation of the *N*-acyliminium ion, and the ion-formation step is prior to the indole alkylation step. Furthermore, when this reaction was conducted in one pot with [D₁]-**2j**, **1a**, and a stoichiometric amount of [D₁]-**4g** as the reactants, we observed that only the 3- and 4-positions of the pyrrolidone ring were extensively deuterated in the desired product **3j**, as shown in Scheme 3d. This lack of deuterium scrambling in the 5 position suggests that the indole alkylation step may not be the turnover-limiting step in our catalytic system.

Further insights into the mechanism were obtained from in situ FTIR experiments. The stoichiometric reaction of phosphoric acid **4g** with **1a** was monitored by using in situ FTIR to detect the formation of the ion pair **A**. We were delighted to observe that the kinetic profiles clearly revealed the consumption of **1a** and the formation of a new species. The specific IR spectra of the newly formed species revealed that the enol-type *N*-acyliminium ion **B** (Figure 2) was most likely involved in the contact ion pair (see the Supporting Information for details). Moreover, the results of HRMS (ESI) analysis also supported the formation of the contact ion pair **A**.^[16]

On the basis of the above results, a plausible working model for the present reaction is proposed in Figure 2. The free hydroxy group in the enol-type cyclic *N*-acyliminium ion **B** captures the conjugate Brønsted base of the phosphoric acid **4g** in the contact ion pair, presumably by intermolecular hydrogen bonding. Assisted by the conjugate base, the acidic

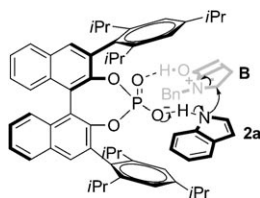


Figure 2. Proposed working model for asymmetric induction in the N functionalization of indole catalyzed by a chiral phosphoric acid.

N–H group of the indole **2a** is prone to nucleophilic addition to the cyclic *N*-acyliminium ion. As shown in Figure 2, the chiral environment created by the 1,1'-binaphthyl backbone, and the congested 3- and 3'-substituents of the catalyst **4g**^[13] cause the indole to approach from the *Re* face of the *N*-acyliminium ion **B** to stereoselectively furnish the corresponding *S*-configured product.

In summary, we have developed a novel and efficient Brønsted acid catalyzed intermolecular enantioselective N alkylation of indoles with α,β -unsaturated γ -lactams as electrophiles, thus providing a highly enantioselective method for the synthesis of chiral pyrrolidinones containing indole moieties from simple starting materials. The approach opens a new application of chiral Brønsted acids toward enantioselective N functionalization of indoles. Further studies to extend the reaction scope are in progress.

Received: March 23, 2011

Published online: May 17, 2011

Keywords: asymmetric catalysis · Brønsted acids · indoles · *N*-acyliminium ions · N functionalization

- [1] For reviews, see: a) G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875; b) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *106*, 2875; c) U. Scholz, E. Winterfeldt, *Nat. Prod. Rep.* **2000**, *17*, 349.
- [2] For reviews: a) M. Zeng, S.-L. You, *Synlett* **2010**, 1289; b) M. Bandini, A. Eichholzer, *Angew. Chem.* **2009**, *121*, 9786; *Angew. Chem. Int. Ed.* **2009**, *48*, 9608; c) S.-L. You, Q. Cai, M. Zeng, *Chem. Soc. Rev.* **2009**, *38*, 2190; d) T. B. Poulsen, K. A. Jørgensen, *Chem. Rev.* **2008**, *108*, 2903; e) M. Bandini, A. Melloni, A. Umani-Ronchi, *Angew. Chem.* **2004**, *116*, 560; *Angew. Chem. Int. Ed.* **2004**, *43*, 550.
- [3] For selected examples of the asymmetric C alkylation of indoles, see: a) M. Johannsen, *Chem. Commun.* **1999**, 2233; b) K. B. Jensen, J. Thorhauge, R. G. Hazell, K. A. Jørgensen, *Angew. Chem.* **2001**, *113*, 164; *Angew. Chem. Int. Ed.* **2001**, *40*, 160; c) J. F. Austin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 1172; d) J. Zhou, Y. Tang, *J. Am. Chem. Soc.* **2002**, *124*, 9030; e) M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 10558; f) R. P. Herrera, V. Sgarzani, L. Bernardi, A. Ricci, *Angew. Chem.* **2005**, *117*, 6734; *Angew. Chem. Int. Ed.* **2005**, *44*, 6576; g) D. A. Evans, K. R. Fandrick, H.-J. Song, *J. Am. Chem. Soc.* **2005**, *127*, 8942; h) Y.-Q. Wang, J. Song, H. Li, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 8156; i) J. Seayad, A. M. Seayad, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 1086; j) M. Terada, K. Sorimachi, *J. Am. Chem. Soc.* **2007**, *129*, 292; k) M. J. Wanner, R. N. S. van der Haas, K. R. de Cuba, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem.* **2007**, *119*, 7629; *Angew. Chem. Int. Ed.* **2007**, *46*, 7485; l) Y.-X. Jia, J. Zhong, S.-F. Zhu, C.-M. Zhang, Q.-L. Zhou, *Angew. Chem.* **2007**, *119*, 5661; *Angew. Chem. Int. Ed.* **2007**, *46*, 5565; m) Q. Kang, Z.-A. Zhao, S.-L. You, *J. Am. Chem. Soc.* **2007**, *129*, 1484; n) I. T. Raheem, P. S. Thiara, E. A. Peterson, E. N. Jacobsen, *J. Am. Chem. Soc.* **2007**, *129*, 13404; o) J. Itoh, K. Fuchibe, T. Akiyama, *Angew. Chem.* **2008**, *120*, 4080; *Angew. Chem. Int. Ed.* **2008**, *47*, 4016; p) D. J. Mergott, S. J. Zuend, E. N. Jacobsen, *Org. Lett.* **2008**, *10*, 745; q) L. Yang, Q. Zhu, S. Guo, B. Qian, C. Xia, H. Huang, *Chem. Eur. J.* **2010**, *16*, 1638.
- [4] a) B. M. Trost, M. J. Krische, V. Berl, E. M. Grenzer, *Org. Lett.* **2002**, *4*, 2005; b) M. Bandini, A. Eichholzer, M. Tragni, A. Umani-Ronchi, *Angew. Chem.* **2008**, *120*, 3282; *Angew. Chem. Int. Ed.* **2008**, *47*, 3238; c) H.-L. Cui, X. Feng, J. Peng, J. Lei, K. Jiang, Y.-C. Chen, *Angew. Chem.* **2009**, *121*, 5847; *Angew. Chem. Int. Ed.* **2009**, *48*, 5737; d) L. M. Stanley, J. F. Hartwig, *Angew. Chem.* **2009**, *121*, 7981; *Angew. Chem. Int. Ed.* **2009**, *48*, 7841; e) D. Enders, C. Wang, G. Raabe, *Synthesis* **2009**, 4119; f) L. Hong, W.-S. Sun, C.-X. Liu, L. Wang, R. Wang, *Chem. Eur. J.* **2010**, *16*, 440. During the preparation of this manuscript, two reports on the N alkylation of an indole using different strategies were published, see: g) Q. Cai, C. Zheng, S.-L. You, *Angew. Chem.* **2010**, *122*, 8848; *Angew. Chem. Int. Ed.* **2010**, *49*, 8666; h) B. M. Trost, M. Osipov, G. Dong, *J. Am. Chem. Soc.* **2010**, *132*, 15800.
- [5] For recent reviews on Brønsted acid and Brønsted acid/base catalysis, see: a) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999; b) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; c) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713; d) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744; e) M. Terada, *Chem. Commun.* **2008**, 4097; f) X. Yu, W. Wang, *Chem. Asian J.* **2008**, *3*, 516; g) G. Adair, S. Mukherjee, B. List, *Aldrichimica Acta* **2008**, *41*, 31; h) M. Terada, *Synthesis* **2010**, 1929.
- [6] For reviews, see: a) B. E. Maryanoff, H.-C. Zhang, J. H. Cohen, I. J. Turchi, C. A. Maryanoff, *Chem. Rev.* **2004**, *104*, 1431; b) J. Royer, M. Bonin, L. Micouin, *Chem. Rev.* **2004**, *104*, 2311.
- [7] a) Ref [3n]; b) E. A. Peterson, E. N. Jacobsen, *Angew. Chem.* **2009**, *121*, 6446; *Angew. Chem. Int. Ed.* **2009**, *48*, 6328; c) M. E. Muratore, C. A. Holloway, A. W. Pilling, R. I. Storer, G. Trevitt, D. J. Dixon, *J. Am. Chem. Soc.* **2009**, *131*, 10796.
- [8] a) G. Massiot, C. Delaude, *The Alkaloids*, Vol. 27 (Ed.: A. Brossi, Academic Press, New York, **1986**, chap. 3; b) A. Elbein, R. I. Molyneux, *Alkaloids, Chemical and Biological Perspectives*, Vol. 5 (Ed.: S. W. Pelletier), Wiley, New York, **1990**, pp. 1–54; c) B. Atta-ur-Rahman, *Indole Alkaloids*, Harwood Academic, Chichester, **1998**; d) U. Galm, M. H. Hager, S. G. V. Lanen, J. Ju, J. S. Thorson, B. Shen, *Chem. Rev.* **2005**, *105*, 739.
- [9] a) L. Planas, J. Perard-Viret, J. Royer, M. Selkti, A. Thomas, *Synlett* **2002**, 1629; b) I. Bausanne, A. Chiaroni, H.-P. Husson, C. Riche, J. Royer, *Tetrahedron Lett.* **1994**, *35*, 3931; c) V. Bocchi, L. Chierici, G. P. Gardini, *Tetrahedron* **1970**, *26*, 4073.
- [10] a) X. J. Duan, X. M. Li, B. G. Wang, *J. Nat. Prod.* **2007**, *70*, 1210; b) S. R. Donohue, J. H. Krushinski, V. W. Pike, E. Chernet, L. Phebus, A. K. Chesterfield, C. C. Felder, C. Halldin, J. M. Schaus, *J. Med. Chem.* **2008**, *51*, 5833.
- [11] C. H. Cheon, H. Yamamoto, *J. Am. Chem. Soc.* **2008**, *130*, 9246.
- [12] Pyrrole was also used as a substrate for the present reaction, but only the C2 addition product was obtained with 58% ee. For details, see the Supporting Information.
- [13] CCDC 803584 (**3f**), 818066 (**4g**), and 815285 (**8**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See the Supporting Information for details.
- [14] N-fused pyrrolidine and indole structures could be found in many biologically active compounds: a) P. Desos, B. Serkiz, P. Morain, J. Lepagnol, A. Cordi, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 3003; b) C. J. Cobley, E. Foucher, J.-P. Lecouve, I. C. Lennon,

- J. A. Ramsden, G. Thominot, *Tetrahedron: Asymmetry* **2003**, *14*, 3431; c) T. Hata, Y. Sano, R. Sugawara, A. Matsumae, K. Kanamori, T. Shima, T. Hoshi, *J. Antibiot. Ser. A* **1956**, *9*, 141; d) J. Ewing, G. K. Hughes, E. Ritchie, W. C. Taylor, *Nature* **1952**, *169*, 618; e) N. Yoda, N. Hirayama, *J. Med. Chem.* **1993**, *36*, 1461.
- [15] The full assignment of the proton signals of **3j** was obtained by 2D NMR techniques, see the Supporting Information for details.
- [16] For the use of ESI-MS to characterize contact ion pairs, see: a) W. Schrader, P. P. Handayani, J. Zhou, B. List, *Angew. Chem.* **2009**, *121*, 1491; *Angew. Chem. Int. Ed.* **2009**, *48*, 1463; b) M. Sickert, C. Schneider, *Angew. Chem.* **2008**, *120*, 3687; *Angew. Chem. Int. Ed.* **2008**, *47*, 3631. See the Supporting Information for details.
-