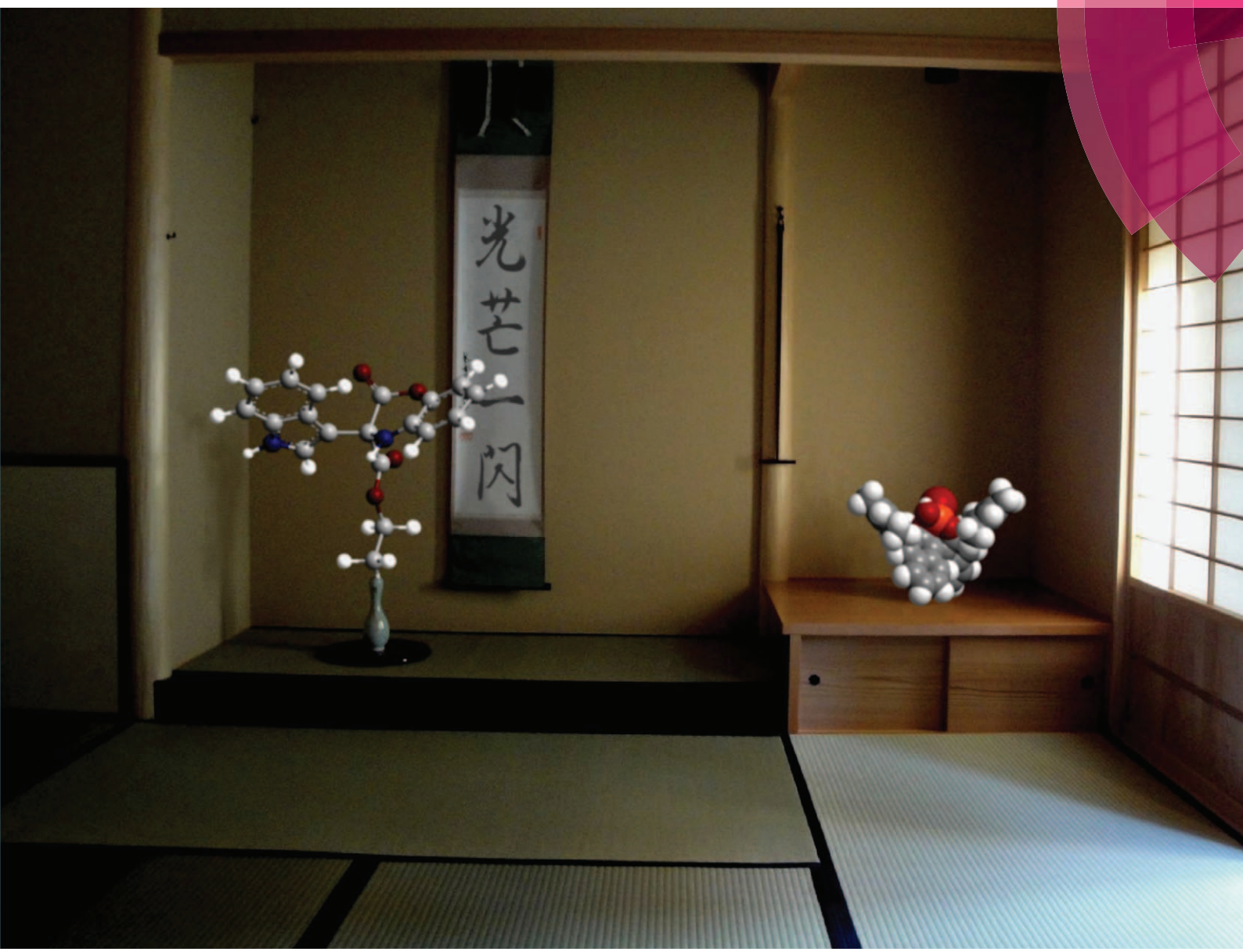
Volume 12 | Number 5 | 7 February 2014 | Pages 711–856

Organic & Biomolecular Chemistry

www.rsc.org/obc



ISSN 1477-0520

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

Keiji Maruoka *et al.*

Chiral Brønsted acid-catalyzed enantioselective addition of indoles to ketimines

Organic & Biomolecular Chemistry

COMMUNICATION

Chiral Brønsted acid-catalyzed enantioselective addition of indoles to ketimines†

Taichi Kano, Ryosuke Takechi, Ryohei Kobayashi and Keiji Maruoka*

Cite this: *Org. Biomol. Chem.*, 2014, **12**, 724

Received 5th November 2013,
Accepted 26th November 2013

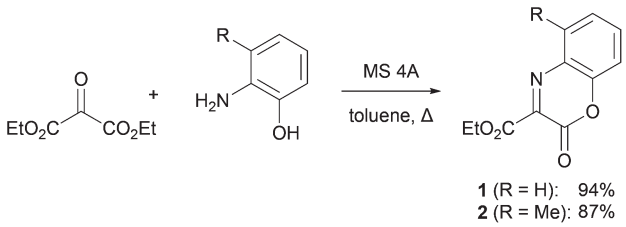
DOI: 10.1039/c3ob42190b

www.rsc.org/obc

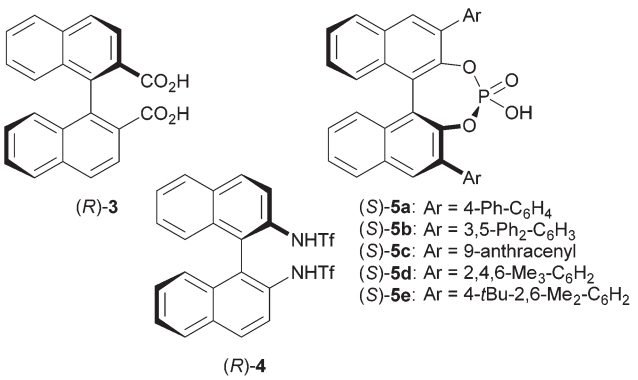
A highly enantioselective addition of indoles to a readily available ketimine was found to be catalyzed by a chiral phosphoric acid. This organocatalytic process represents a rare example of an addition reaction to a non-aromatic ketimine.

Imines are suitable substrates for chiral Brønsted acid-catalyzed asymmetric transformations.[1,2] Among them, ketimines are far less frequently employed in such organocatalytic reactions compared to reactive and readily available aldimines,[3,4] although synthetically important α-tertiary amines having a chiral tetrasubstituted carbon center are formed by the addition of carbon nucleophiles to unsymmetrical ketimines.[5] Moreover, most of the examples reported to date are limited to the reaction of ketimines substituted with an aryl or trifluoromethyl group on their imine carbons. For instance, in the Brønsted acid-catalyzed enantioselective addition of indoles to ketimines, either *C*-aryl or *C*-trifluoromethyl ketimines were employed except for a few examples.[4,6] In this context, we have been interested in the development of a Brønsted acid-catalyzed enantioselective addition of indoles to ketimines substituted with flexible functional groups. Herein, we wish to report a highly enantioselective addition of indoles to ketimines having modifiable substituents catalyzed by a chiral phosphoric acid.

To overcome the low reactivity of ketimines, we chose ketimines **1** and **2**,[3j,7] which are sterically less congested and strongly activated by two different ester groups, as the ideal electrophiles. Ketimines **1** and **2** substituted by versatile ester functional groups and a removable *N*-protecting group are readily prepared from commercially available 2-aminophenol or 2-amino-3-methylphenol and diethyl ketomalonate (Scheme 1).



Scheme 1 Preparation of ketimines **1** and **2**.

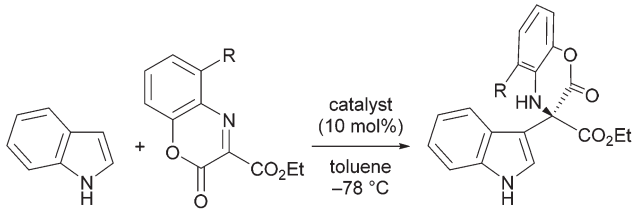


Our initial investigation began by evaluating the effect of acid catalysts and solvents in the reaction of indole (**6a**) with ketimine **1** or **2** (Table 1). In the presence of 10 mol% of dicarboxylic acid (*R*)-**3** or bistriflamide (*R*)-**4** as a chiral Brønsted acid catalyst, the reaction between **6a** and ketimine **1** in toluene gave only a trace amount of the desired product **7a** or no product, probably due to the relatively low acidity of the catalyst (entries 1 and 2). On the other hand, chiral phosphoric acid catalysts were found to be effective for this reaction, and we then investigated various chiral phosphoric acid catalysts (*S*)-**5a–e** (entries 3–7). Aromatic substituents on 3,3′-positions of the catalyst significantly affected enantioselectivity, and the catalyst (*S*)-**5d** having sterically demanding 2,4,6-trimethylphenyl groups was found to be the optimal catalyst (entry 6). When the reaction using ketimine **2** instead of **1** was carried

Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan. E-mail: maruoka@kuchem.kyoto-u.ac.jp; Fax: +81-75-753-4041; Tel: +81-75-753-4041

†Electronic supplementary information (ESI) available: Experimental details. CCDC 933242. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ob42190b

Table 1 Asymmetric addition of indole **6a** to ketimines[a]

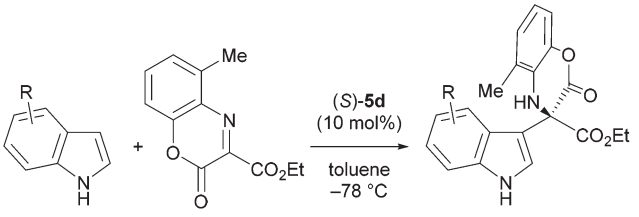


6a **1**: (R = H) **2**: (R = Me) **7a**: (R = H) **8a**: (R = Me)

Entry	Ketimine	Catalyst	Time (h)	Yield[b] (%)	ee[c] (%)
1	**1**	(*R*)-**3**	2	Trace	—
2	**1**	(*R*)-**4**	2	nd	—
3	**1**	(*S*)-**5a**	2	99	46
4	**1**	(*S*)-**5b**	3	99	60
5	**1**	(*S*)-**5c**	3	99	75
6	**1**	(*S*)-**5d**	2	99	93
7	**1**	(*S*)-**5e**	3	99	90
8	**2**	(*S*)-**5d**	5	98	>99
9[d]	**2**	(*S*)-**5d**	18	30	96
10[e,f]	**2**	(*S*)-**5d**	23	29	94

[a] Unless otherwise specified, the reaction of indole **6a** (0.06 mmol) with a ketimine (0.05 mmol) was carried out in the presence of a catalyst (0.005 mmol) in toluene (1.0 mL) at −78 °C. [b] Isolated yield. [c] Determined by HPLC using a chiral column. [d] Use of CH_2Cl_2 as a solvent. [e] Use of THF as a solvent. [f] The reaction was performed at 0 °C.

Table 2 Asymmetric addition of various indoles **6** to ketimine **2**[a]



6 **2** **8**

Entry	Indole	R	Time (h)	Yield[b] (%)	ee[c] (%)
1	**6a**	H	5	98	>99
2[d]	**6a**	H	28	99	99
3	**6b**	5-Me	3	99	>99
4	**6c**	5-MeO	12	99	>99
5	**6d**	5-Br	5	99	99
6	**6e**	6-Me	3	82	>99
7	**6f**	6-MeO	6	98	99
8[e]	**6g**	6-Br	4	99	94
9	**6h**	7-Me	5	99	94

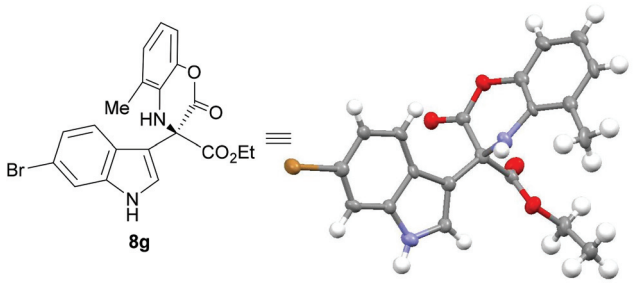
[a] Unless otherwise specified, the reaction of indole **6** (0.06 mmol) with ketimine **2** (0.05 mmol) was carried out in the presence of catalyst **5d** (0.005 mmol) in toluene (1.0 mL) at −78 °C. [b] Isolated yield. [c] Determined by HPLC using a chiral column. [d] Use of 1 mol% of **5d**. [e] Performed at −40 °C.

out, the corresponding product **8a** was obtained in excellent yield with virtually complete enantioselectivity (entry 8). Among the solvents tested, toluene gave the best result with respect to yield and selectivity (entry 8 *vs.* entries 9 and 10).

With the optimal reaction conditions, we then tested the scope of the reaction by varying the substituent on the indole ring, and the results are summarized in Table 2. The substituent on the 5-, 6- or 7-position did not significantly affect the enantioselectivity (entries 3–9). The reaction with 6-bromoindole was performed at an increased temperature (−40 °C) because of poor solubility in toluene (entry 8). It should be noted that the catalyst loading could be reduced to 1 mol% without loss of enantioselectivity, while a longer reaction time was required (entry 2). The absolute configuration of the addition product **8g** was determined to be *R* by single-crystal X-ray analysis (Fig. 1): accordingly, indole should approach from the *Si* face of the N-protonated ketimine **2** under the influence of chiral phosphoric acid catalyst (*S*)-**5d**.

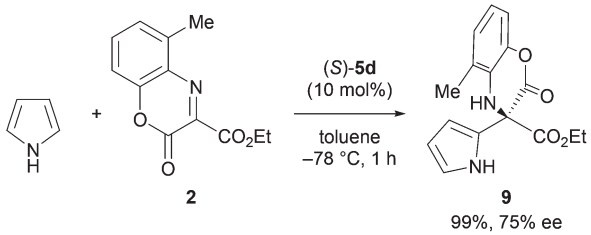
The reaction with other heteroaromatic compounds as nucleophiles was also investigated (Scheme 2). The reaction of pyrrole with ketimine **2** gave the desired product **9** in excellent yield with good enantioselectivity, although the reaction conditions were not optimized for this reaction.[4b,k]

The obtained additional product **8a** was a versatile intermediate in organic synthesis and converted to important chiral building blocks without loss of optical purity. For instance, after protection of **8a** by tosylation, treatment of lactone **10** with DIBAL-H in THF in the presence of MS4A provided lactol **11** (Scheme 3).[8] This transformation represents



8g

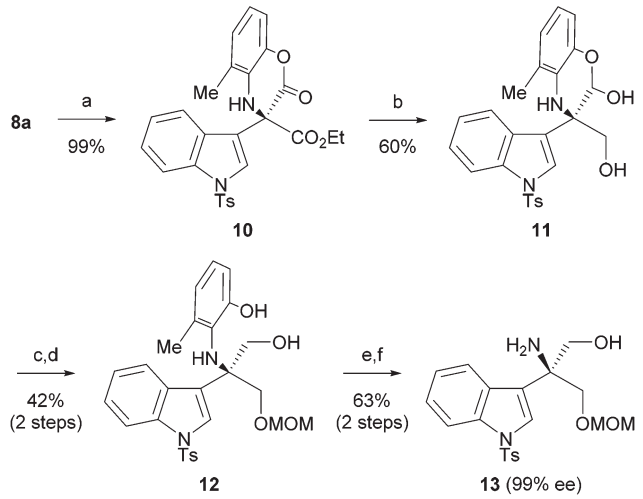
Fig. 1 X-ray crystal structure of **8g** with ellipsoids set at 50% probability.



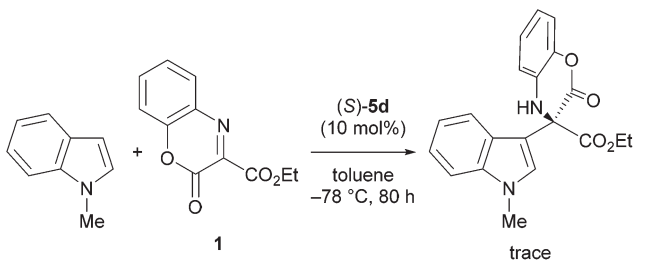
2 **9** 99%, 75% ee

Scheme 2 Asymmetric addition of pyrrole to ketimine **2**.

the functional differentiation of two ester groups in **10**. After selective protection of the primary alcohol group of **11** with MOMCl,[9] reduction of the lactol moiety with $NaBH_4$ under reflux conditions gave diol **12**. The aromatic *N*-substituent of **12** was removed by the oxidative carbon–nitrogen bond cleavage. Thus, diacetylation of the hydroxyl groups of **12**,[10]



Scheme 3 Transformation and deprotection of **8a**. Reagents and conditions: (a) TsCl, Et_3N, DMAP, dioxane, 95 °C, 12 h; (b) DIBAL-H, MS4A, THF, r.t., 1 h; (c) $NaBH_4$, MeOH-THF, r.t., 1 h; MOMCl, DBU, THF, r.t., 1 h; (d) $NaBH_4$, EtOH, reflux, 1.5 h; (e) Ac_2O, pyridine, r.t., 1 h; (f) CAN, CH_3CN, H_2O, –15 °C, 15 min; aq. KOH, 80 °C, 2 h.



Scheme 4 Asymmetric addition of *N*-methylindole to ketimine **1**.

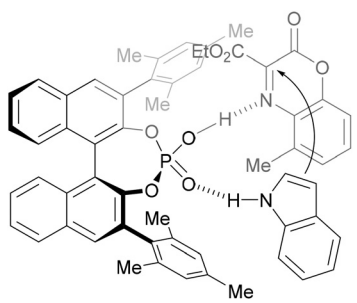


Fig. 2 Proposed reaction model.

treatment with ceric ammonium nitrate (CAN) and deacetylation by a basic workup gave amino alcohol **13**.[11]

When the use of *N*-methylindole as a nucleophile was attempted, only a trace amount of the corresponding adduct was detected, even with an extended reaction time (80 h) (Scheme 4). Hence, this result suggested that indole is activated through the hydrogen bonding between the hydrogen atom on the nitrogen of indoles and phosphoric acid catalysts **5** in the present reaction as shown in Fig. 2. Based on the observed stereochemistry, indole seems to approach the *Si*-face of ketimine **2**, both substrates being oriented and activated by the catalyst through two hydrogen bonds.[4a,j] When the reaction product **7a** was treated with catalyst (*S*)-**5d** and 1 equiv. of 5-methylindole in toluene for 2.5 hours, neither a change in the optical purity of **7a** nor retro-addition was observed even at room temperature. Hence, the stereoselectivity observed in the present reaction must have originated from the C–C bond-forming step.

In summary, we have developed a highly enantioselective addition of indoles to ketimine **2** catalyzed by a chiral phosphoric acid. This organocatalytic process represents a rare example of an addition reactions to a non-aromatic ketimine. Further application of the reactive and useful ketimine for analogous reactions is under investigation.

Notes and references

1 For reviews on organocatalytic reactions, see: (*a*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2001, **40**, 3726; (*b*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2004, **43**, 5138; (*c*) A. Berkessel and H. Gröger, *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*, Wiley-VCH, Weinheim, 2005; (*d*) *Enantioselective Organocatalysis*, ed. P. I. Dalko, Wiley-VCH, Weinheim, 2007.

2 For a review on a Brønsted acid-catalyzed asymmetric transformations, see: M. Terada, *Synthesis*, 2010, 1929.

3 For selected organocatalytic asymmetric construction of tetrasubstituted carbon using ketimines, see: (*a*) W. Zhuang, S. Saaby and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2004, **43**, 4476; (*b*) V. A. Sukach, N. M. Golovach, V. V. Pirozhenko, E. B. Rusanov and M. V. Vovk, *Tetrahedron: Asymmetry*, 2008, **19**, 761; (*c*) Z. Hou, J. Wang, X. Liu and X. Feng, *Chem.–Eur. J.*, 2008, **14**, 4484; (*d*) B. Jiang, J. J. Dong, Y. G. Si, X. L. Zhao, Z. G. Huang and M. Xua, *Adv. Synth. Catal.*, 2008, **350**, 1360; (*e*) C. Baudequin, A. Zamfir and S. B. Tsogoeva, *Chem. Commun.*, 2008, 4637; (*f*) D. Enders, K. Gottfried and G. Raabe, *Adv. Synth. Catal.*, 2010, **352**, 3147; (*g*) N. Hara, R. Tamura, Y. Funahashi and S. Nakamura, *Org. Lett.*, 2011, **13**, 16621; (*h*) L. Li, M. Han, M. Xiao and Z. Xie, *Synlett*, 2011, 1727; (*i*) Y.-L. Liu, T.-D. Shi, F. Zhou, X.-L. Zhao, X. Wang and J. Zhou, *Org. Lett.*, 2011, **13**, 3826; (*j*) T. Kano, S. Song, Y. Kubota and K. Maruoka, *Angew. Chem., Int. Ed.*, 2012, **51**, 1191; (*k*) N. Hara, S. Nakamura, M. Sano, R. Tamura, Y. Funahashi and N. Shibata, *Chem.–Eur. J.*, 2012, **18**, 9276; (*l*) W. Yan, D. Wang, J. Feng, P. Li, D. Zhao and R. Wang, *Org. Lett.*, 2012, **14**, 2512; (*m*) A. Parra, R. Alfaro, L. Marzo, A. Moreno-Carrasco, J. L. G. Ruano and J. Alemán, *Chem. Commun.*, 2012, **48**, 9759; (*n*) F.-G. Zhang, X.-Y. Zhu, S. Li, J. Niea and J.-A. Ma, *Chem. Commun.*, 2012, **48**, 11552; (*o*) D. Wang, J. Liang, J. Feng, K. Wang, Q. Sun, L. Zhao, D. Li, W. Yan and R. Wang, *Adv. Synth. Catal.*, 2013, **355**, 548. See also ref. 4.

4 For Brønsted acid-catalyzed asymmetric addition of indoles to ketimines, see: (*a*) Y.-X. Jia, J. Zhong, S.-F. Zhu, C.-M. Zhang and Q.-L. Zhou, *Angew. Chem., Int. Ed.*, 2007, **46**, 5565; (*b*) M. Abid, L. Teixeira and B. Török, *Org. Lett.*, 2008, **10**, 933; (*c*) M. Rueping and B. J. Nachtsheim, *Synlett*, 2010, 119; (*d*) M. Rueping, S. Raja and A. Núñez, *Adv. Synth. Catal.*, 2011, **353**, 563; (*e*) R. Husmann, E. Sugiono, S. Mersmann, G. Raabe, M. Rueping and C. Bolm, *Org. Lett.*, 2011, **13**, 1044; (*f*) X. Yu, Y. Wang, G. Wu, H. Song, Z. Zhou and C. Tang, *Eur. J. Org. Chem.*, 2011, 3060; (*g*) J. Hermeke and P. H. Toy, *Tetrahedron*, 2011, **67**, 4103; (*h*) Q. Yin and S.-L. You, *Chem. Sci.*, 2011, **2**, 1344; (*i*) M. Righi, F. Bartoccini, S. Lucarini and G. Piersanti, *Tetrahedron*, 2011, **67**, 7923; (*j*) E. Aranzamendi, N. Sotomayor and E. Lete, *J. Org. Chem.*, 2012, **77**, 2986; (*k*) J. Feng, W. Yan, D. Wang, P. Li, Q. Sun and R. Wang, *Chem. Commun.*, 2012, **48**, 8003; (*l*) Y. Qian, C. Jing, C. Zhai and W.-h. Hu, *Adv. Synth. Catal.*, 2012, **354**, 301.

5 For reviews, see: (*a*) R. Bloch, *Chem. Rev.*, 1998, **98**, 1407; (*b*) D. A. Cogan and J. A. Ellman, *J. Am. Chem. Soc.*, 1999, **121**, 268; (*c*) O. Riant and J. Hannedouche, *Org. Biomol. Chem.*, 2007, **5**, 873; (*d*) M. Shibasaki and M. Kanai, *Chem. Rev.*, 2008, **108**, 2853; (*e*) J. Clayden, M. Donnard, J. Lefranc and D. Tetlow, *Chem. Commun.*, 2011, **47**, 4624.

6 For pioneering studies on the Brønsted acid-catalyzed asymmetric Friedel–Crafts reaction of indoles, see: (*a*) M. Terada and K. Sorimachi, *J. Am. Chem. Soc.*, 2007, **129**, 292; (*b*) Q. Kang, Z.-A. Zhao and S.-L. You, *J. Am. Chem. Soc.*, 2007, **129**, 1484.

7 H. Miyabe, Y. Yamaoka and Y. Takemoto, *J. Org. Chem.*, 2006, **71**, 2099.

8 Use of other reducing agents such as $LiAlH_4$ and $NaBH_4$ resulted in partial racemization.

9 When **11** was treated with MOMCl in the presence of strong bases such as NaH, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) and 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), the lactol moiety was selectively protected. Without pretreatment of **11** with $NaBH_4$ before MOM protection, the use of DBU as a base resulted in no reaction.

10 Without acetylation, the C–N bond cleavage was inhibited by a side reaction involving the primary alcohol group of **12**.

11 (*a*) S. Kobayashi, J. Kobayashi, H. Ishiani and M. Ueno, *Chem.–Eur. J.*, 2002, **8**, 4185; (*b*) J. Wolfer, T. Bekele, C. J. Abraham, C. Dogo-Isonagie and T. Lectka, *Angew. Chem., Int. Ed.*, 2006, **45**, 7398.