One-Pot Syntheses

DOI: 10.1002/anie.201107308

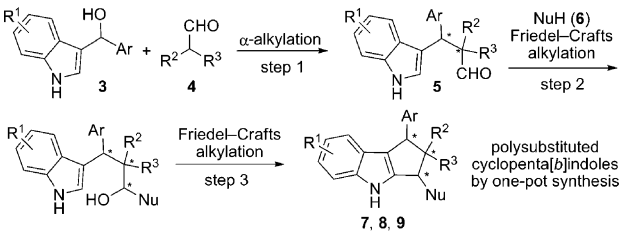
Multistep One-Pot Synthesis of Enantioenriched Polysubstituted Cyclopenta[*b*]indoles**

*Biao Xu, Zhi-Lei Guo, Wan-Yan Jin, Zhi-Ping Wang, Yun-Gui Peng, and Qi-Xiang Guo**

The development of asymmetric methodologies for the synthesis of chiral indoles has been a long-standing project in organic synthesis. Indole skeletons are heterocyclic systems and are present in numerous alkaloid products, pharmaceuticals, and agrochemicals.[1] Cyclopenta[*b*]indole skeletons can be found in a number of indole alkaloids,[2] but have not been extensively reported. Compounds that contain such a unit exhibit a wide range of biological activities.[3] For example, 2-aminocyclopenta[*b*]indoles,[4a] cyclopenta[*b*]indole-substituted acetic acids,[4b] and a series of yuehchukene analogues[5] have been successfully synthesized and used in medicinal chemistry. Although a number of methods have been developed for the synthesis of cyclopenta[*b*]indoles,[6] only few of them are asymmetric and especially catalytic asymmetric methods.[7] To the best of our knowledge, there is only one example of the synthesis of chiral cyclopenta[*b*]indoles by asymmetric catalysis with acceptable enantioselectivities.[8] The development of efficient methods for the construction of cyclopenta[*b*]indole units is therefore highly desirable. As a continuation of the work of our research group toward the catalytic asymmetric α-alkylation of carbonyl compounds,[9] we rationally designed a one-pot[10] three-step reaction, which consisted of the α-alkylation of an aldehyde, catalyzed by a primary-amine-substituted thiourea,[11] and two consecutive Brønsted acid catalyzed Friedel–Crafts reactions of an indole,[12] to construct chiral polysubstituted cyclopenta[*b*]indoles (Scheme 1). Herein, we report these consecutive organocatalyzed reactions, which gave structurally diverse cyclopenta[*b*]indoles in high yields (up to 85%), and with excellent diastereoselectivities (up to > 99:1) and enantioselectivities (up to 99% *ee*).

The reactions shown in Scheme 1 were realized in three stages. In the first stage, we examined the α-alkylation of isobutylaldehyde **4a** with 3-indolylmethanol **3a** (step 1) under catalysis by chiral amines **1** and acids **2**. Although several methods for the asymmetric amine-based catalysis have been used in similar α-alkylation reactions of aldehydes with diarylmethanol compounds,[11] to date α,α-disubstituted aldehydes have not been used as donors. For the method reported herein, α,α-disubstituted aldehydes were very important precursors because they could produce aldehydes **5** (Scheme 1), which could not be enolated during the following Friedel–Crafts alkylations; thus, there were fewer side reactions in this method. Several amine-based catalysts were investigated in the α-alkylation reaction of aldehyde **4a**. As shown in Table 1, primary-amine-substituted thioureas were good catalysts for promoting this α-alkylation reaction (Table 1, entries 1–7). Catalyst **1h**, which was used by Chen and co-workers,[7c] was not a suitable choice for the reaction (Table 1, entry 8). Thiourea **1a** was chosen as the catalyst for the α-alkylation because good yields and high enantioselectivities could be obtained (Table 1, entry 1). After examining various solvents, we found that $CHCl_3$ was the best solvent with regard to yield and enantioselectivity (Table 1, entry 1). The number of equivalents of isobutylaldehyde **4a** also greatly influenced the yield. For example, the yield increased significantly when the number of equivalents of **4a** was reduced to 1.2 (Table 1, entry 12 versus entry 1). The impact of different acids was also examined. The compatibility between the primary amine and the chiral acid was investigated first. Both (*S*,*S*)-**1b** and (*R*,*R*)-**1i** could cooperate with (*R*)-**2d** to promote the alkylation efficiently, but the enantioselectivities were worse than that obtained with *p*-nitrobenzoic acid **2a** (Table 1, entries 13, 14, and 15). After screening the compatibilities of acid additives with both **1a** and **1b** (see the Supporting Information), the combination of thiourea **1a** and N-Boc-protected amino acid **2e** turned out to be the best choice of catalyst for this α-alkylation with regard to yield (71%) and enantioselectivity (90% *ee*; Table 1, entry 16).

After establishing the optimal reaction conditions for the α-alkylation of the aldehyde (Scheme 1, step 1), we examined the feasibility of Brønsted acid catalyzed consecutive Friedel–Crafts alkylations in steps 2 and 3. For these transformations, we first chose N-Bn-protected indole **6a** as the nucleophile, 4-methylbenzenesulfonic acid (*p*-TsOH) as the catalyst, and



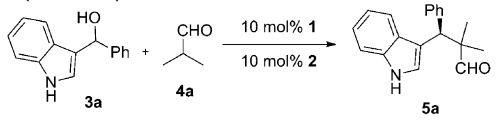
Scheme 1. General strategy for the multistep one-pot synthesis of chiral cyclopenta[*b*]indoles.

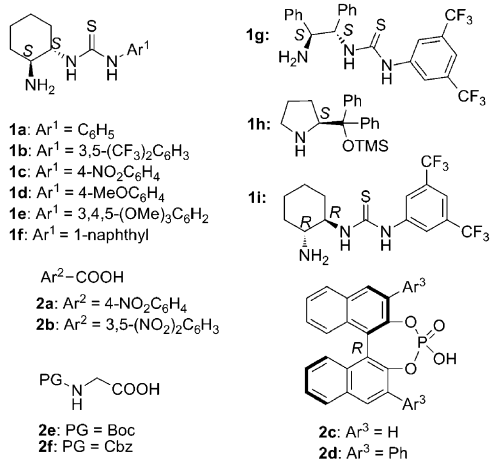
[*] B. Xu, Z.-L. Guo, W.-Y. Jin, Z.-P. Wang, Prof. Y.-G. Peng, Prof. Q.-X. Guo
Education Ministry Key Laboratory on Luminescence and Real-Time Analysis, School of Chemistry and Chemical Engineering
Southwest University
Chongqing 400715 (China)
E-mail: qxguo@swu.edu.cn

[**] We are grateful for financial support from the NSFC (20902074) and the Fundamental Research Funds for the Central Universities (XDJK2011C054).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201107308.

Table 1: Screening of catalysts and optimization of reaction conditions for step 1 (Scheme 1).[a]

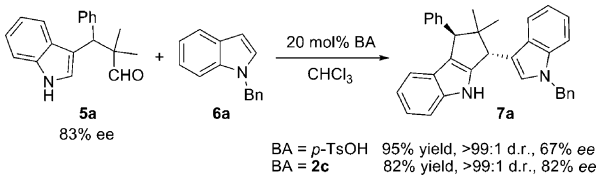




Entry	1	2	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**1a**	**2a**	$CHCl_3$	48	65	89
2	**1b**	**2a**	$CHCl_3$	24	75	83
3	**1c**	**2a**	$CHCl_3$	48	83	75
4	**1d**	**2a**	$CHCl_3$	48	60	85
5	**1e**	**2a**	$CHCl_3$	48	51	84
6	**1f**	**2a**	$CHCl_3$	48	67	85
7	**1g**	**2a**	$CHCl_3$	46	86	78
8	**1h**	HOAc	$CHCl_3$	64	50	−64[d,e]
9	**1a**	**2a**	toluene	48	29	90
10	**1a**	**2a**	*m*-xylene	96	63	89
11	**1a**	**2a**	benzene	96	44	87
12	**1a**	**2a**	$CHCl_3$	48	81	89[f]
13	**1b**	**2d**	CH_2Cl_2	24	63	50[f]
14	**1i**	**2d**	CH_2Cl_2	24	86	−51[e,f,g]
15	**1i**	**2a**	CH_2Cl_2	24	73	−80[e,g]
16	**1a**	**2e**	$CHCl_3$	40	71	90[f]

[a] Reaction conditions: **3a** (0.1 mmol), **4a** (1 mmol), **1** (0.01 mmol), **2** (0.01 mmol) in solvent (1 mL). [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Reaction conditions: **3a** (0.2 mmol), **4a** (0.24 mmol), **1h** (0.01 mmol), and HOAc (0.02 mmol) in $CHCl_3$ (0.4 mL). [e] Negative *ee* value indicates the formation of the enantiomer of **5a**. [f] 1.2 equiv of **4a** were used. [g] 2 mL of solvent were used. Boc = *tert*-butyloxycarbonyl, Cbz = benzyloxycarbonyl, PG = protecting group, TMS = trimethylsilyl.

$CHCl_3$ as the solvent. Our choice was based on the following: 1) a 3-indolylmethanol species would be formed and then produce an active vinylogous imino intermediate through dehydration when the indole reacted with the aldehyde under acidic conditions;[11a–d] and 2) the Brønsted acid catalyst was compatible with that used in step 1 and the solvent was the same as that used in step 1; thus, the multistep reactions could proceed in a one-pot manner. In addition, product **7a** represented a potentially useful bisindole subunit, which exists in many natural and pharmaceutical compounds, such as the natural product yuehchukene.[5] The reaction between **5a** (see Table 1, entry 2) and **6a** was promoted by *p*-TsOH in

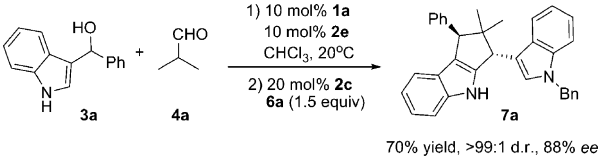


Scheme 2. Synthesis of cyclopenta[*b*]indole **7a**. BA = Brønsted acid. Bn = benzyl.

$CHCl_3$ and proceeded smoothly to give the desired product **7a** in high yield (95%) and excellent diastereoselectivity (>99:1), however, the enantioselectivity of **7a** decreased greatly (83% *ee* versus 67% *ee*). We then optimized the reaction conditions by screening different Brønsted acid catalysts (see the Supporting Information). Finally, compound **7a** was obtained in good yield (82%), with excellent diastereoselectivity (>99:1) and almost unchanged enantioselectivity (82% *ee*), by using **2c** as the catalyst (Scheme 2).

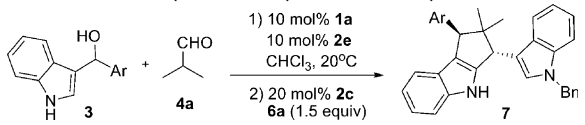
The optimal reaction conditions for step 1 and the consecutive steps 2 and 3 were thus established. The compatibilities of the catalysts and use of the same solvents enabled these two procedures to be performed in a one-pot manner. We thus tried to merge the procedures with the third stage shown in Scheme 1, without isolating intermediate **5a**. The reaction of **3a** and **4a** was performed in $CHCl_3$ with **1a** and **2e** as catalysts. After the starting material **3a** had been consumed completely, the N-Bn-protected indole **6a** was added to the reaction system. We found that the Friedel–Crafts reaction in step 2 could not proceed if no additional acid was added after completion of step 1; the addition of Brønsted acid to steps 2 and 3 of this one-pot procedure was thus investigated again (see the Supporting Information). The multistep one-pot procedure proceeded smoothly and gave the desired product **7a** in good yield, with excellent diastereoselectivity and good enantioselectivity, by using a combination of **1a**, **2e**, and **2c** as the catalyst (Scheme 3). Notably, the total yield of **7a** was enhanced greatly when these three reactions were carried out in a one-pot manner (70%) instead of in two separate procedures (58%).

With the optimized general procedure in hand, we investigated the substrate scope of these consecutive transformations. We first examined the substrate scope of 3-indolylmethanol compounds (Tables 2 and 3). Both electron-rich and electron-deficient aryl groups were tolerated and gave the desired products **7b**–**7r** in good yields and with good enantioselectivities (Table 2). Notably, only one diastereoisomer was obtained in these examples. An *ortho*-substituted phenyl group greatly improved the enantioselectivity. Excellent enantioselectivities were obtained when 2-F-, 2-Cl-, and 2-Br-phenyl-, and 1-naphthyl-substituted (1*H*-indol-3-yl)aryl-



Scheme 3. Synthesis of cyclopenta[*b*]indole **7a** in one pot.

Table 2: Substrate scope of 3-indolylmethanol compounds.[a]

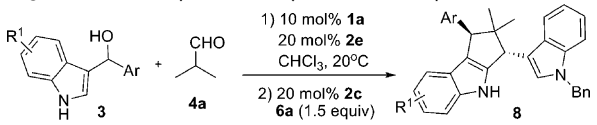


3 4a 7

Entry	7	Ar	t_1/t_2 [h][b]	Yield [%][c]	d.r.[d]	*ee* [%][e]
1	**7b**	2-FC_6H_4	87/56	66	>99:1	91[f]
2	**7c**	3-FC_6H_4	87/102	68	>99:1	85[f]
3	**7d**	4-FC_6H_4	88/99	61	>99:1	88
4	**7e**	2-ClC_6H_4	135/78	70	>99:1	95[f]
5	**7f**	4-ClC_6H_4	135/70	68	>99:1	88
6	**7g**	2-BrC_6H_4	135/54	80	>99:1	95[f]
7	**7h**	4-BrC_6H_4	81/108	63	>99:1	89[f]
8	**7i**	4-CNC_6H_4	207/126	53	>99:1	94[f]
9	**7j**	4-$CF_3C_6H_4$	159/96	65	>99:1	88[f]
10	**7k**	4-*t*BuC_6H_4	48/48	67	>99:1	84
11	**7l**	2-$MeOC_6H_4$	68/72	45	>99:1	87
12	**7m**	3-$MeOC_6H_4$	120/62	85	>99:1	86
13	**7n**	4-$MeOC_6H_4$	24/72	81	>99:1	88
14	**7o**	3-MeC_6H_4	88/70	82	>99:1	90
15	**7p**	4-MeC_6H_4	39/72	81	>99:1	88
16	**7q**	1-naphthyl	144/72	73	>99:1	94
17	**7r**	2-naphthyl	120/62	70	>99:1	88

[a] Reaction conditions: **3** (0.2 mmol), **4a** (0.24 mmol), **1a** (0.02 mmol), **2e** (0.02 mmol), **2c** (0.04 mmol), **6a** (0.3 mmol) in $CHCl_3$ (2 mL). [b] Reaction time: t_1 for step 1, t_2 for step 2. [c] Yield of isolated product. [d] Determined by ^{1}H NMR spectroscopy. [e] Determined by HPLC analysis on a chiral stationary phase. [f] 20 mol% of **2e** were used.

Table 3: Substrate scope of 3-indolylmethanol compounds.[a]

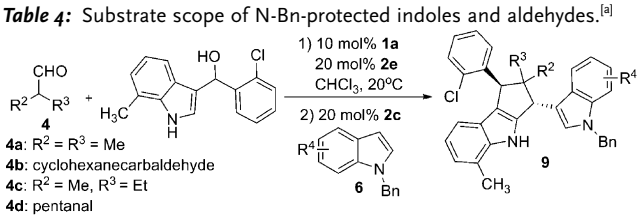


3 4a 8

Entry	8	Ar	R^1	t_1/t_2 [h][b]	Yield [%][c]	d.r.[d]	*ee* [%][e]
1	**8a**	1-naphthyl	6-F	112/48	67	>99:1	93
2	**8b**	1-naphthyl	5-Cl	96/131	47	>99:1	94
3	**8c**	1-naphthyl	5-Br	96/131	43	>99:1	94
4	**8d**	1-naphthyl	5-MeO	87/50	60	>99:1	94[f]
5	**8e**	1-naphthyl	5-CH_3	105/60	46	>99:1	92[f]
6	**8f**	1-naphthyl	6-CH_3	39/48	62	>99:1	93
7	**8g**	2-BrC_6H_4	5-MeO	96/65	62	>99:1	92
8	**8h**	2-BrC_6H_4	5-CH_3	96/65	68	>99:1	94
9	**8i**	2-BrC_6H_4	6-CH_3	84/48	66	>99:1	93
10	**8j**	2-BrC_6H_4	7-CH_3	94/48	62	>99:1	98
11	**8k**	2-ClC_6H_4	5-MeO	84/60	58	>99:1	94
12	**8l**	2-ClC_6H_4	5-CH_3	112/48	73	>99:1	92
13	**8m**	2-ClC_6H_4	6-CH_3	112/48	71	>99:1	92
14	**8n**	2-ClC_6H_4	7-CH_3	96/46	82	>99:1	99

[a] Reaction conditions: **3** (0.2 mmol), **4a** (0.24 mmol), **1a** (0.02 mmol), **2e** (0.04 mmol), **2c** (0.04 mmol), **6a** (0.3 mmol) in $CHCl_3$ (2 mL). [b] Reaction time: t_1 for step 1, t_2 for step 2. [c] Yields of isolated products. [d] Determined by ^{1}H NMR spectroscopy. [e] Determined by HPLC analysis on a chiral stationary phase. [f] 20 mol% of **2e** were used.

Table 4: Substrate scope of N-Bn-protected indoles and aldehydes.[a]

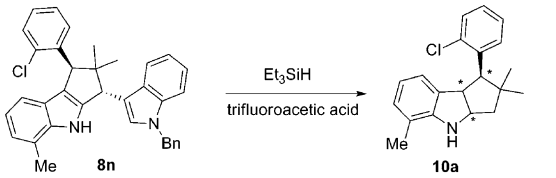


Entry	9	4	R^4	t_1/t_2 [h][b]	Yield [%][c]	d.r.[d]	ee [%][e]
1	**9a**	**4a**	6-F	141/60	73	>99:1	99
2	**9b**	**4a**	5-Cl	141/60	82	>99:1	94
3	**9c**	**4a**	5-CH_3	141/60	69	>99:1	97
4	**9d**	**4a**	6-CH_3	141/60	82	>99:1	98
5	**9e**	**4a**	7-CH_3	141/60	77	>99:1	94
6	**9f**	**4b**	H	168/60	68	>99:1	93
7	**9g**	**4c**	H	136/70	78	≈67:33	99
8	**9h**	**4d**	H	136/70	35	≈85:15	90
9	**9i**	**4e**	H	211/72	38	≈87:13	92

[a] Reaction conditions: diarylalcohol (0.2 mmol), **4a** (0.24 mmol), **1a** (0.02 mmol), **2e** (0.04 mmol), **2c** (0.04 mmol), **6** (0.3 mmol) in $CHCl_3$ (2 mL). [b] Reaction time: t_1 for step 1, t_2 for step 2. [c] Yields of isolated products. [d] Determined by ^{1}H NMR spectroscopy. [e] Determined by HPLC analysis on a chiral stationary phase.

methanol compounds were used as electrophiles (Table 2, entries 1, 4, 6, and 16). The reaction with a (1*H*-indol-3-yl)arylmethanol compounds that bears a 4-CN-substituted phenyl group produced product **7i** with an excellent enantioselectivity of 94% *ee* (Table 2, entry 8). The substrate scope with respect to the substituent on the indole ring was also explored (Table 3). (1*H*-Indol-3-yl)arylmethanol compounds that bear both electron-withdrawing and electron-donating substituents on the indole ring were good reaction partners and able to participate in these reactions with excellent stereochemical outcomes. In particular, greatly improved enantioselectivities could be obtained with a 7-Me-substituted indole moiety. For example, reactions of 3-indolylmethanol compounds derived from 7-Me-substituted indole, and *ortho*-substituted phenyl aldehydes produced compounds **8j** and **8n** in 98% *ee* and 99% *ee*, respectively (Table 3, entries 10 and 14).

The substrate scope of N-Bn-protected indoles and aldehydes were investigated next (Table 4). N-Bn-protected indoles bearing electron-withdrawing or electron-donating groups were all suitable reaction partners and gave the corresponding cyclopenta[*b*]indoles **9** in good yields, and with excellent enantioselectivities and diastereoselectivities (Table 4, entries 1–5). Cyclopenta[*b*]indoles with much greater structural complexities could be obtained by changing the aldehyde component. For example, spiro[cyclohexane-cyclopenta[*b*]indole] **9f** could be synthesized with excellent enantioselectivity by using a cyclohexanecarbaldehyde in the asymmetric multistep one-pot procedure (Table 4, entry 6). The use of an unsymmetric α,α-disubstituted aldehyde, such as 2-methylbutanal **4c**, in this procedure resulted in the formation of a cyclopenta[*b*]indole that contains three adjacent chiral carbon centers, one of which was a chiral quaternary carbon center (Table 4, entry 7). α-Unsubstituted aliphatic aldehydes, such as pentanal and hexanal, were also able to participate in this reaction and gave the desired products with excellent enantioselectivities, good diastereoselectivities, and in acceptable yields (Table 4, entries 8 and 9).



Scheme 4. Synthesis of cyclopenta[*b*]indolines.

The absolute configuration of **8j** (1*S*,3*R*) was established by X-ray single-crystal analysis.[13] The configuration at C1 and C3 of compounds **7**, **8**, and **9** were assigned by analogy with those of **8j** (see the Supporting Information).

The cyclopenta[*b*]indole **8n** was readily and stereoselectively converted to fused indoline **10a** by reduction (Scheme 4). Thus, both indoles and indolines could be accessed efficiently. The mechanism for the disconnection of the N-Bn-protected indole unit is unclear.

In conclusion, we have described a highly efficient diastereoselective and enantioselective one-pot multistep reaction for the construction of cyclopenta[*b*]indoles. This process was achieved through consecutive α-alkylation, which was catalyzed by a primary-amine-substituted thiourea, and two Brønsted acid catalyzed Friedel–Crafts alkylation reactions. Structurally diverse cyclopenta[*b*]indoles were obtained in high yields, with excellent diastereoselectivities and enantioselectivities, under mild reaction conditions. The cyclopenta[*b*]indoles could be converted into cyclopenta[*b*]indolines without loss of stereoselectivity.

Received: October 17, 2011
Published online: December 13, 2011

Keywords: alkylations · indoles · multistep reactions · one-pot syntheses · organocatalysis

[1] For reviews, see: a) G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875; b) M. Bandini, A. Eichholzer, *Angew. Chem.* **2009**, *121*, 9786; *Angew. Chem. Int. Ed.* **2009**, *48*, 9608; c) A. J. Kochanowska-Karamyan, M. T. Hamann, *Chem. Rev.* **2010**, *110*, 4489.

[2] For a review, see: P. S. steyn, R. Vleggar, *Fortschr. Chem. Org. Naturst.* **1985**, *48*, 1.

[3] a) A. A. Asselin, L. G. Humber, J. Komlossy, *J. Med. Chem.* **1976**, *19*, 792; b) A. A. Asselin, L. G. Humber, T. A. Dobson, U.S. Patent 4057599, **1977**; c) A. A. Failli, R. J. Steffan, A. F. Kreft, T. J. Caggiano, C. E. Caufield, U.S. Patent 5830911, **1998**; d) Y. C. Kong, K. H. Ng, K. H. Wat, A. Wong, I. F. Saxena, K. F. Cheng, P. P. H. But, H. T. Chang, *Planta Med.* **1985**, *51*, 304; e) K. F. Cheng, M. K. Cheung, Y. C. Kong, *Aust. J. Chem.* **1997**, *50*, 349; f) G. Dionne, A. A. Asselin, L. G. Humber, U.S. Patent 4235903, **1980**.

[4] a) J. P. Kondaji, K. Venkatesh, K. E. Jemes, WO 2009140448A1, **2009**; b) M. C. Hillier, J. F. Marcoux, D. Zhao, E. J. J. Grabowski, A. E. McKeiwn, R. D. Tillyer, *J. Org. Chem.* **2005**, *70*, 8385; c) K. R. Campos, M. Journet, S. Lee, E. J. J. Grabowski, R. D. Tillyer, *J. Org. Chem.* **2005**, *70*, 268.

[5] For selected examples for the synthesis of yuehchukene, see: a) K. F. Cheng, Y. C. Kong, T. Y. Chan, *J. Chem. Soc. Chem. Commun.* **1985**, 48; b) J. H. Sheu, Y. K. Chen, H. F. Chung, S. F. Lin, P. J. Sung, *J. Chem. Soc. Perkin Trans. 1* **1998**, 1959; for yuehchukene anologies, see: c) K. F. Cheng, T. T. Chan, T. F. Lai, Y. C. Kong, *J. Chem. Soc. Perkin Trans. 1* **1988**, 3317; d) K. F. Cheng, G. A. Cao, Y. W. Yu, Y. C. Kong, *Synth. Commun.* **1994**, *24*, 65.

[6] For examples for the synthesis of racemic cyclopenta[*b*]indoles, see: a) H. Ratni, D. Blum-kaelin, H. Dehmlow, P. Hartman, P. Jablonski, R. Masciadri, C. Maugeais, A. Patiny-Adam, N. Panday, M. Wright, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1654; b) E. M. Ferreira, B. M. Stoltz, *J. Am. Chem. Soc.* **2003**, *125*, 9578; c) K. Saito, H. Sogou, T. Suga, H. Kusama, N. Iwasawa, *J. Am. Chem. Soc.* **2011**, *133*, 689; d) Q. Xiao, P. E. Floreancig, *Org. Lett.* **2008**, *10*, 1139; e) N.-W. Tsent, M. Lautens, *J. Org. Chem.* **2009**, *74*, 1809; f) E. P. Balskus, C. T. Walsh, *J. Am. Chem. Soc.* **2009**, *131*, 14648; g) C. Ferrer, C. H. M. Amijs, A. M. Echavarren, *Chem. Eur. J.* **2007**, *13*, 1358.

[7] For examples for the synthesis of chiral cyclopenta[*b*]indoles, see: a) F. Churruca, M. Fousteris, Y. Ishikawa, M. V. W. Rekowski, C. Hounsou, T. Surrey, A. Giannis, *Org. Lett.* **2010**, *12*, 2096; b) A. Shafiee, V. Upadhyay, E. G. Corley, M. Biba, D. Zhao, J.-F. Marcoux, K. R. Campos, M. Journet, A. O. King, R. D. Larsen, E. J. J. Grabowski, R. P. Volante, R. D. Tillyer, *Tetrahedron: Asymmetry* **2005**, *16*, 3094; c) B. Han, Y.-C. Xiao, Y. Yao, Y.-C. Chen, *Angew. Chem.* **2010**, *122*, 10387; *Angew. Chem. Int. Ed.* **2010**, *49*, 10189.

[8] J. A. Schiffner, T. H. Wöste, M. Oestreich, *Eur. J. Org. Chem.* **2010**, 174.

[9] Q.-X. Guo, Y.-G. Peng, J.-W. Zhang, L. Song, Z. Feng, L.-Z. Gong, *Org. Lett.* **2009**, *11*, 4620.

[10] For selected reviews, see: a) Ł. Albrecht, H. Jiang, K. A. Jørgensen, *Angew. Chem.* **2011**, *123*, 8642; *Angew. Chem. Int. Ed.* **2011**, *50*, 8492; b) D. Enders, C. Grondal, H. R. M. Matthias, *Angew. Chem.* **2007**, *119*, 1590; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570; For selected examples of one-pot multistep reactions, see: c) P. Cao, X.-L. Sun, B.-H. Zhu, Q. Shen, Z. Xie, Y. Tang, *Org. Lett.* **2009**, *11*, 3048; d) X. Wang, K. Ding, *Chem. Eur. J.* **2006**, *12*, 4568; e) A. Sniady, M. W. Bedore, T. F. Jamison, *Angew. Chem.* **2011**, *123*, 2203; *Angew. Chem. Int. Ed.* **2011**, *50*, 2155; f) P. Li, S. L. Buchwald, *Angew. Chem.* **2011**, *123*, 6520; *Angew. Chem. Int. Ed.* **2011**, *50*, 6396.

[11] For selected examples of α-alkylation of aldehydes and ketones by enamine catalysis, see: a) R. R. Shaikh, A. Mazzanti, M. Petrini, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2008**, *120*, 8835; *Angew. Chem. Int. Ed.* **2008**, *47*, 8707; b) P. G. Cozzi, F. Benfatti, L. Zoli, *Angew. Chem.* **2009**, *121*, 1339; *Angew. Chem. Int. Ed.* **2009**, *48*, 1313; c) A. Gualandi, E. Emer, M. G. Capdevila, P. G. Cozzi, *Angew. Chem.* **2011**, *123*, 7988; *Angew. Chem. Int. Ed.* **2011**, *50*, 7842; d) G. Bergonzini, S. Vera, P. Melchiorre, *Angew. Chem.* **2010**, *122*, 9879; *Angew. Chem. Int. Ed.* **2010**, *49*, 9685; e) F. Benfatti, E. Benedetto, P. G. Cozzi, *Chem. Asian J.* **2010**, *5*, 2047; f) L. Zhang, L. Cui, X. Li, J. Li, S. Luo, J.-P. Cheng, *Chem. Eur. J.* **2010**, *16*, 2045; g) A. R. Brown, W.-H. Kuo, E. N. Jacobsen, *J. Am. Chem. Soc.* **2010**, *132*, 9286.

[12] For selected examples of Friedel–Crafts alkylation reactions of indoles by Brønsted acid catalysis, see: a) F.-L. Sun, M. Zeng, Q. Gu, S.-L. You, *Chem. Eur. J.* **2009**, *15*, 8709; b) C. Ramesh, J. Banerjee, R. Pal, B. Das, *Adv. Synth. Catal.* **2003**, *345*, 557; c) Q. Kang, Z.-A. Zhao, S.-L. You, *J. Am. Chem. Soc.* **2007**, *129*, 1484; d) F.-L. Sun, X.-J. Zheng, Q. Gu, Q.-L. He, S.-L. You, *Eur. J. Org. Chem.* **2010**, 47.

[13] CCDC 848551 (**8j**) contains 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.

