ORGANIC LETTERS

2011
Vol. 13, No. 20
5636–5639

Catalytic Asymmetric Pictet–Spengler-Type Reaction for the Synthesis of Optically Active Indolo[3,4-*cd*][1]benzazepines

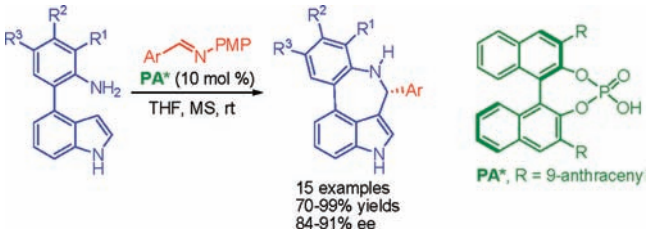
Dao-Juan Cheng, Hai-Bian Wu, and Shi-Kai Tian*

Joint Laboratory of Green Synthetic Chemistry, Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, China

tiansk@ustc.edu.cn

Received August 31, 2011

ABSTRACT



A new strategy has been introduced to develop a catalytic asymmetric Pictet–Spengler-type reaction by replacing the aldehyde with an imine. A range of 4-(2-aminoaryl)indoles smoothly undergo the chiral phosphoric acid catalyzed asymmetric Pictet–Spengler-type reaction with imines at room temperature to give structurally diverse indolo[3,4-*cd*][1]benzazepines in good to excellent yields and ee.

The Pictet–Spengler reaction, discovered 100 years ago,[1] is now widely employed in the construction of various nitrogen-containing heterocycles.[2] This transformation is generally accomplished by treatment of aldehydes with β-(hetero)arylethylamines in the presence of acidic catalysts, which promote imine formation and subsequent cyclization through an intramolecular Friedel–Crafts reaction (Scheme 1, path a). In recent years a number of catalytic asymmetric

(1) Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030–2036.

(2) For reviews, see: (a) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797–1842. (b) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341–3370. (c) Lorenz, M.; Van Linn, M. L.; Cook, J. M. *Curr. Org. Synth.* **2010**, *7*, 189–223. (d) Stöckigt, J.; Antonchick, A. P.; Wu, F.; Waldmann, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 8538–8564.

(3) (a) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558–10559. (b) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086–1087. (c) Wanner, M. J.; van der Haas, R. N. S.; de Cuba, K. R.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 7485–7487. (d) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404–13405. (e) Sewgobind, N. V.; Wanner, M. J.; Ingemann, S.; de Gelder, R.; van Maarseveen, J. H.; Hiemstra, H. *J. Org. Chem.* **2008**, *73*, 6405–6408. (f) Mergott, D. J.; Zuend, S. J.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 745–748. (g) Muratore, M. E.; Holloway, C. A.; Pilling, A. W.; Storer, R. I.; Trevitt, G.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 10796–10797. (h) Wanner, M. J.; Boots, R. N. A.; Eradus, B.; de Gelder, R.; van Maarseveen, J. H.; Hiemstra, H. *Org. Lett.* **2009**, *11*, 2579–2581. (i) Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2009**, *11*, 887–890. (j) Holloway, C. A.; Muratore, M. E.; Storer, R. I.; Dixon, D. J. *Org. Lett.* **2010**, *12*, 4720–4723. (k) Duce, S.; Pesciaioli, F.; Gramigna, L.; Bernardi, L.; Mazzanti, A.; Ricci, A.; Bartoli, G.; Bencivenni, G. *Adv. Synth. Catal.* **2011**, *353*, 860–864.

(4) (a) Raheem, I. T.; Thiara, P. S.; Jacobsen, E. N. *Org. Lett.* **2008**, *10*, 1577–1580. (b) He, Y.; Lin, M.; Li, Z.; Liang, X.; Li, G.; Antilla, J. C. *Org. Lett.* **2011**, *13*, 4490–4493.

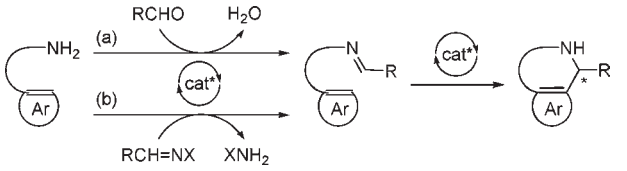
(5) (a) Liu, C.-R.; Li, M.-B.; Yang, C.-F.; Tian, S.-K. *Chem. Commun.* **2008**, 1249–1251. (b) Dong, D.-J.; Li, H.-H.; Tian, S.-K. *J. Am. Chem. Soc.* **2010**, *132*, 5018–5020. (c) Dong, D.-J.; Li, Y.; Wang, J.-Q.; Tian, S.-K. *Chem. Commun.* **2011**, *47*, 2158–2160. (d) Fang, F.; Li, Y.; Tian, S.-K. *Eur. J. Org. Chem.* **2011**, 1084–1091. (e) Jin, Y.-H.; Fang, F.; Zhang, X.; Liu, Q.-Z.; Wang, H.-B.; Tian, S.-K. *J. Org. Chem.* **2011**, *76*, 4163–4167.

(6) For other recent examples, see: (a) Mi, X.; Luo, S.; He, J.; Cheng, J.-P. *Tetrahedron Lett.* **2004**, *45*, 4567–4570. (b) Ke, B.; Qin, Y.; He, Q.; Huang, Z.; Wang, F. *Tetrahedron Lett.* **2005**, *46*, 1751–1753. (c) Temelli, B.; Unaleroglu, C. *Tetrahedron Lett.* **2005**, *46*, 7941–7943. (d) Temelli, B.; Unaleroglu, C. *Tetrahedron* **2006**, *62*, 10130–10135. (e) Soueidan, M.; Collin, J.; Gil, R. *Tetrahedron Lett.* **2006**, *47*, 5467–5470. (f) Esquivias, J.; Gómez-Arrayás, R.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 629–633. (g) Alonso, I.; Esquivias, J.; Gómez-Arrayás, R.; Carretero, J. C. *J. Org. Chem.* **2008**, *73*, 6401–6404. (h) Thirupathi, P.; Kim., S. S. *J. Org. Chem.* **2010**, *75*, 5240–5249. (i) Fan, R.; Wang, W.; Pu, D.; Wu, J. *J. Org. Chem.* **2007**, *72*, 5905–5907. (j) Qian, B.; Xie, P.; Xie, Y.; Huang, H. *Org. Lett.* **2011**, *13*, 2580–2583.

10.1021/ol202361t
Published on Web 09/26/2011

Pictet–Spengler reactions have been developed for the synthesis of optically active six-membered nitrogen-containing heterocycles with high enantioselectivity.[3,4] Nevertheless, to our knowledge, there is no catalytic asymmetric Pictet–Spengler-type reaction reported previously for the construction of chiral seven-membered ring systems.

Scheme 1. Proposed Pictet–Spengler-Type Reaction



Prompted by our recent exploration of new reactions through the complete cleavage of carbon–nitrogen double bonds,[5,6] we envisioned that a Pictet–Spengler-type reaction could occur by replacing the aldehyde with an imine because the same precursor for cyclization could be generated through transimination under acidic conditions (Scheme 1, path b).[7] Although the *N*-substituent of an imine would not go to the final product, it might affect reactivity and enantioselectivity through nonbonding interactions with a chiral acidic catalyst. We hoped that the formation of an amine or an ammonia equivalent, instead of water, as the byproduct would be beneficial to enhance enantioselectivity.

Much attention has been paid to the construction of indole-fused ring systems due to their broad range of interesting biological properties.[8] Catalytic asymmetric modification of the pyrrole ring of indole has recently emerged as a powerful approach to the construction of chiral indole-fused ring systems. However, they are limited to 1,2- and 2,3-fused indole derivatives (Figure 1).[9,3,10] Herein, we wish to report a catalytic asymmetric synthesis of optically active 3,4-fused indole derivatives, indolo[3,4-*cd*][1]benzazepines, through a chiral phosphoric acid catalyzed Pictet–Spengler-type reaction of 4-(2-aminoaryl)indoles with imines.

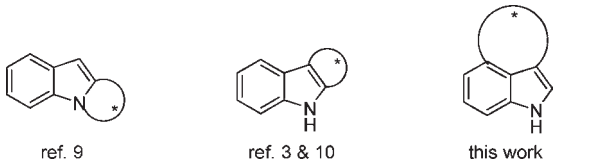


Figure 1. Chiral indole-fused ring systems based on the catalytic asymmetric modification of the pyrrole ring of indole.

Our investigation is based on Kundu's recent report on the synthesis of racemic indolo[3,4-*cd*][1]benzazepines through a trifluoroacetic acid catalyzed modified Pictet–Spengler reaction of 4-(2-aminoaryl)indoles with aldehydes.[11] Initially, we found that phosphoric acids were effective in catalyzing this transformation.[12] For example, treatment of 4-(2-aminophenyl)indole (**1a**) with aldehyde **2aa** (1.1 equiv) and 10 mol % of phosphoric acid **4a** in dichloromethane at room temperature resulted in the formation of indolo[3,4-*cd*][1]benzazepine **3a** in 99% yield and with 33% ee (Table 1, entry 1). To improve the enantioselectivity according to our aforementioned hypothesis, we replaced aldehyde **2aa** with imine **2ab** in the reaction and, gratifyingly, found that the enantioselectivity was enhanced to 39% for the same product albeit a decreased reaction rate was observed (Table 1, entry 2). Screening of solvents revealed that the reaction exhibited the best enantioselectivity in tetrahydrofuran (46% ee, Table 1, entry 8). It was fruitless to improve the enantioselectivity by replacing the *p*-methoxyphenyl group of imine **2ab** with another aryl group, a sulfonyl group, or a diphenylphosphinyl group (Table 1, entries 10–18). Nevertheless, the reactivity and enantioselectivity were dramatically affected by the structure of the chiral phosphoric acid (Table 1, entries 19–26), and the employment of commercially available catalyst **4d** enhanced the enantioselectivity to 82% ee (Table 1, entry 21). Finally, the addition of 3 Å molecular sieves and decreasing the concentration allowed the synthesis of indolo[3,4-*cd*]-[1]benzazepine **3a** with up to 90% ee (Table 1, entry 27). It is noteworthy that the enantioselectivity is much better than that obtained from the reaction with aldehyde **2aa** under the same conditions (83% ee, Table 1, entry 28).

Under the optimized reaction conditions, a range of 4-(2-aminoaryl)indoles smoothly underwent the asymmetric Pictet–Spengler-type reaction with various imines in the presence of 10 mol % of chiral phosphoric acid **4d** at room temperature to give structurally diverse indolo[3,4-*cd*][1]benzazepines in good to excellent yields and ee (Table 2). It is noteworthy that this reaction tolerated a variety of functional groups, such as alkoxy, halide, sulfonate, and

(7) For examples, see: (a) Zajac, W. W.; Walters, T. R.; Darcy, M. G. *J. Org. Chem.* **1988**, *53*, 5856–5860. (b) Giuseppone, N.; Schmitt, J.-L.; Schwartz, E.; Lehn, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 5528–5539.

(8) For reviews, see: (a) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2004**, *21*, 278–311. (b) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2005**, *22*, 73–103. (c) Kawasaki, T.; Higuchi, K. *Nat. Prod. Rep.* **2005**, *22*, 761–793. (d) Ishikura, M.; Yamada, K.; Abe, T. *Nat. Prod. Rep.* **2010**, *27*, 1630–1680.

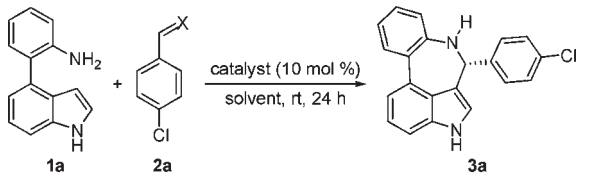
(9) (a) Bandini, M.; Eichholzer, A.; Tragni, M.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 3238–3241. (b) Enders, D.; Wang, C.; Raabe, G. *Synthesis* **2009**, 4119–4124. (c) Hong, L.; Sun, W.; Liu, C.; Wang, L.; Wang, R. *Chem.—Eur. J.* **2010**, *16*, 440–444. (d) Cai, Q.; Zheng, C.; You, S.-L. *Angew. Chem., Int. Ed.* **2010**, *49*, 8666–8669.

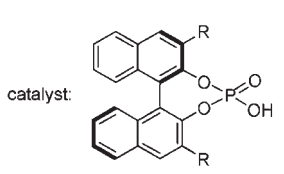
(10) (a) Bandini, M.; Melloni, A.; Piccinelli, F.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **2006**, *128*, 1424–1425. (b) Han, X.; Widenhoefer, R. A. *Org. Lett.* **2006**, *8*, 3801–3804. (c) Li, C.-F.; Liu, H.; Liao, J.; Cao, Y.-J.; Liu, X.-P.; Xiao, W.-J. *Org. Lett.* **2007**, *9*, 1847–1850. (d) Huang, H.; Peters, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 604–606. (e) Franzén, J.; Fisher, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 787–791. (f) Cai, Q.; Zhao, Z.-A.; You, S.-L. *Angew. Chem., Int. Ed.* **2009**, *48*, 7428–7431. (g) Zhang, J.-W.; Cai, Q.; Shi, X.-X.; Zhang, W.; You, S.-L. *Synlett* **2011**, 1239–1242.

(11) Saifuddin, M.; Agarwal, P. K.; Sharma, S. K.; Mandadapu, A. K.; Gupta, S.; Harit, V. K.; Kundu, B. *Eur. J. Org. Chem.* **2010**, 5108–5117.

(12) For reviews of asymmetric catalysis with chiral phosphoric acids, see: (a) Terada, M. *Synthesis* **2010**, 1929–1982. (b) Terada, M. *Chem. Commun.* **2008**, 4097–4112. (c) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744–5758.

Table 1. Optimization of Reaction Conditions[a]





4a, R = 1-naphthyl
4b, R = 2-naphthyl
4c, R = 9-phenanthrenyl
4d, R = 9-anthracenyl
4e, R = Ph
4f, R = 4-ClC$_6$H$_4$
4g, R = 4-O$_2$NC$_6$H$_4$
4h, R = ^{i}Pr$_3$C$_6$H$_2$
4i, R = SiPh$_3$

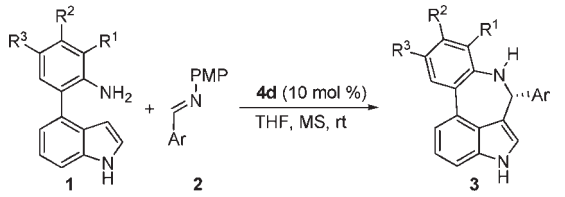
entry	**2a**	X	solvent	catalyst	yield/ %[b]	ee/ %[c]
1[d]	**2aa**	O	CH_2Cl_2	**4a**	99	33
2	**2ab**	NPMP	CH_2Cl_2	**4a**	98	39
3	**2ab**	NPMP	$CHCl_3$	**4a**	98	39
4	**2ab**	NPMP	PhMe	**4a**	83	28
5	**2ab**	NPMP	EtOAc	**4a**	95	39
6	**2ab**	NPMP	Et_2O	**4a**	91	42
7	**2ab**	NPMP	dioxane	**4a**	86	43
8	**2ab**	NPMP	THF	**4a**	96	46
9	**2ab**	NPMP	MeCN	**4a**	95	6
10	**2ac**	NPh	THF	**4a**	79	41
11	**2ad**	NC_6H_4Br-4	THF	**4a**	80	30
12	**2ae**	NC_6H_4Cl-4	THF	**4a**	83	33
13	**2af**	NC_6H_4Cl-2	THF	**4a**	76	34
14	**2ag**	NC_6H_4OH-2	THF	**4a**	95	45
15	**2ah**	NC_6H_4OMe-2	THF	**4a**	77	31
16	**2ai**	NNp-1	THF	**4a**	78	32
17	**2aj**	NSO_2Me	THF	**4a**	88	25
18	**2ak**	$NPOPh_2$	THF	**4a**	75	16
19	**2ab**	NPMP	THF	**4b**	83	49
20	**2ab**	NPMP	THF	**4c**	90	74
21	**2ab**	NPMP	THF	**4d**	90	82
22	**2ab**	NPMP	THF	**4e**	92	33
23	**2ab**	NPMP	THF	**4f**	60	29
24	**2ab**	NPMP	THF	**4g**	62	14
25	**2ab**	NPMP	THF	**4h**	84	34
26	**2ab**	NPMP	THF	**4i**	88	11
27[e,f]	**2ab**	NPMP	THF	**4d**	90	90
28[f]	**2aa**	O	THF	**4d**	99	83

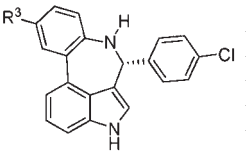
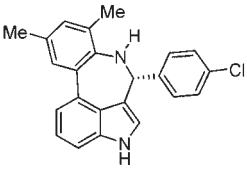
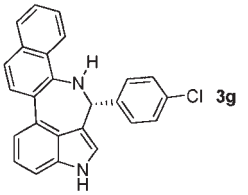
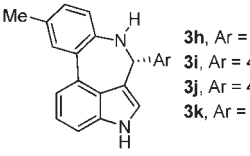
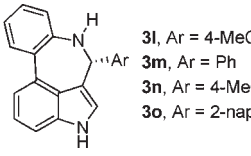
[a] Reaction conditions: **1a** (0.050 mmol), **2a** (1.1 equiv), catalyst **4** (10 mol %), solvent (1.0 mL), rt, 24 h. [b] Isolated yield. [c] Determined by chiral stationary phase HPLC analysis. [d] The reaction was run for 5 h. [e] The reaction was run for 70 h. [f] The reaction was run in 1.5 mL of THF in the presence of 3 Å molecular sieves (30 mg).

ester, and bulky groups next to the amino groups of 4-(2-aminoaryl)indoles.

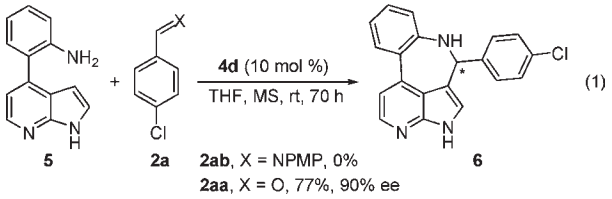
Significantly inferior reactivity was observed with a 4-(2-aminoaryl)-7-azaindole under the same reaction conditions. For example, the Pictet–Spengler-type reaction did not take place between 4-(2-aminophenyl)-7-azaindole (**5**) and imine **2ab** in the presence of 10 mol % of chiral phosphoric acid **4d** at room temperature (eq 1). Nevertheless, replacement of imine **2ab** with aldehyde **2aa** resulted in the formation of 7-azaindolo[3,4-*cd*][1]benzazepine **6** in 77% yield and with 90% ee.

Table 2. Catalytic Asymmetric Synthesis of Indolo[3,4-*cd*][1]-benzazepines[a]



entry	product		yield /%[b]	ee /%[c]
1		**3a**, R^3 = H	90	90
2		**3b**, R^3 = Me	98	91
3		**3c**, R^3 = OMe	99	90
4		**3d**, R^3 = OPh	94	90
5		**3e**, R^3 = OCF_3	95	90
6		**3f**	99	85
7		**3g**	80	91
8		**3h**, Ar = 4-FC_6H_4	95	90
9[d]		**3i**, Ar = 4-BrC_6H_4	97	90
10		**3j**, Ar = 4-$TsOC_6H_4$	71	85
11		**3k**, Ar = 3-ClC_6H_4	93	86
12		**3l**, Ar = 4-MeC_6H_4	74	89
13		**3m**, Ar = Ph	70	84
14		**3n**, Ar = 4-$MeOCOC_6H_4$	71	87
15		**3o**, Ar = 2-naphthyl	86	90

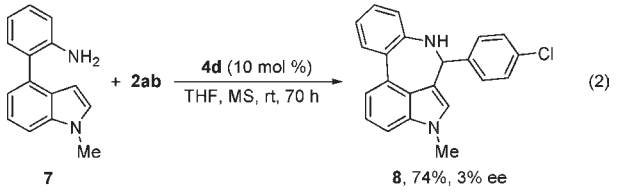
[a] Reaction conditions: **1** (0.050 mmol), **2** (1.1 equiv), catalyst **4d** (10 mol %), 3 Å molecular sieves (30 mg), THF (1.5 mL), rt, 70 h. [b] Isolated yield. [c] Determined by chiral stationary phase HPLC analysis. [d] The absolute configuration of product **3i** was determined by single crystal X-ray analysis, and that of the rest of the products was assigned by analogy.



(1)

To gain insight into the origin of enantioselectivity, the Pictet–Spengler-type reaction of 4-(2-aminophenyl)-1-methylindole (**7**) with imine **2ab** was carried out in the presence of

10 mol % of chiral phosphoric acid **4d** at room temperature (eq 2). In direct contrast to the results summarized in Table 2, this reaction only afforded 3% ee. This result clearly indicates that the indole NH moieties of 4-(2-aminoaryl)indoles are essential for the high enantioselectivity with regard to the formation of indolo[3,4-*cd*][1]benzazepines.[13]



7 **8**, 74%, 3% ee (2)

Our experimental results suggest that the arylamine byproduct and the indole NH moiety should play important roles to determine the enantioselectivity in the step of chiral phosphoric acid catalyzed asymmetric 7-endo-trig cyclization of the precursor generated through the transimination of imine **2** with 4-(2-aminoaryl)indole **1**. Although there is no direct evidence available at present, a possible complex is illustrated in Figure 2 for the formation of indolo[3,4-*cd*][1]benzazepine **3**. The cyclization precursor, the chiral phosphoric acid, and the arylamine byproduct are tentatively organized through hydrogen bonding interactions,[13] and such an organization should facilitate the cyclization step in a highly enantioselective manner.

In summary, we have presented a new strategy to extend the catalytic asymmetric Pictet–Spengler reaction to the construction of nitrogen-containing heterocycles by replacing the aldehyde with an imine. A range of 4-(2-aminoaryl)indoles smoothly undergo the asymmetric Pictet–Spengler-type reaction with imines in the presence of 10 mol % of a commercially available chiral phosphoric acid at room temperature to give structurally diverse indolo[3,4-*cd*][1]benzazepines in good to excellent yields and ee. This strategy extends the catalytic asymmetric Pictet–Spengler reaction, for the first time, to constructing seven-membered ring systems in a highly enantioselective manner.

(13) For related examples, see: (a) Jia, Y.-X.; Zhong, J.; Zhu, S.-F.; Zhang, C.-M.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5565–5567. (b) Lin, J.-H.; Xiao, J.-C. *Eur. J. Org. Chem.* **2011**, 4536–4539.

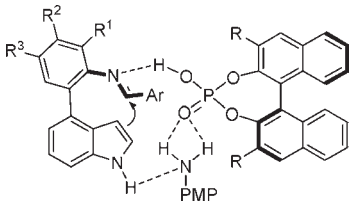


Figure 2. A possible complex for the formation of indolo[3,4-*cd*][1]benzazepine **3**.

Acknowledgment. We are grateful for the financial support from the National Natural Science Foundation of China (20972147 and 20732006) and the National Basic Research Program of China (973 Program 2010CB833300).

Supporting Information Available. Experimental procedures; characterization data; copies of ^{1}H NMR, ^{13}C NMR, and HPLC spectra for products; and crystal data for compound **3i**. This material is available free of charge via the Internet at http://pubs.acs.org.