ORGANIC LETTERS

2013
Vol. 15, No. 4
740–743

Pd-Catalyzed Asymmetric Allylic Alkylations of 3-Substituted Indoles Using Chiral P/Olefin Ligands

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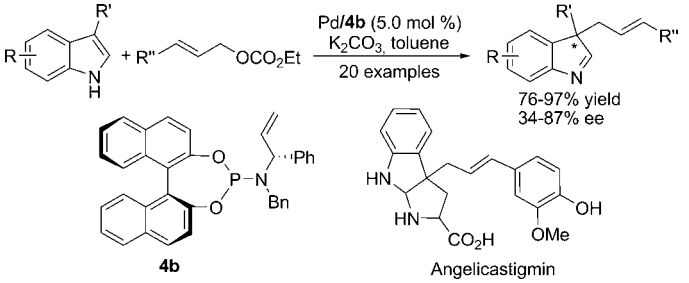
Received November 29, 2012

ABSTRACT



A palladium-catalyzed asymmetric allylic alkylation of 3-substituted indoles using P/olefin ligands was successfully achieved to afford a variety of indolenines containing a quaternary carbon stereocenter in high yields with up to 87% ee. Significantly, this reaction provides a concise access to a stereoisomer of the natural product Angelicastigmin.

Regio- and enantioselective functionalization of indoles has become an extremely attractive subject in synthetic chemistry because indole moieties are widely present in biologically or medically important compounds.[1] In contrast to the intensive studies on asymmetric C-3 alkylations of 3-unsubstituted indoles through either Friedel–Crafts reactions[2] or allylic alkylations,[3] transition-metal-catalyzed allylic alkylation of 3-substitituted indoles for the generation of highly desirable indolenines containing a quaternary carbon stereocenter have rarely been reported.[4–7] In 2005, Tamaru and co-workers described a C-3 selective Pd-catalyzed alkylation of indoles promoted by triethylborane using allyl alcohols (Scheme 1).[7a] Subsequently, the

(1) (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. *Chem. Rev.* **2011**, *111*, PR215. (b) Joucla, L.; Djakovitch, L. *Adv. Synth. Catal.* **2009**, *351*, 673. (c) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608. (d) Bartoli, G.; Bencivenni, G.; Dalpozzo, R. *Chem. Soc. Rev.* **2010**, *39*, 4449.

(2) For leading reviews, see: (a) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550. (b) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Synlett* **2005**, 1199. (c) You, S.-L.; Cai, Q.; Zeng, M. *Chem. Soc. Rev.* **2009**, *38*, 2190.

(3) For leading references, see: (a) Malkov, A. V.; Davis, S. L.; Baxendale, I. R.; Mitchell, W. L.; Kočovský, P. *J. Org. Chem.* **1999**, *64*, 2751. (b) Trost, B. M.; Krische, M. J.; Berl, V.; Grenzer, E. M. *Org. Lett.* **2002**, *4*, 2005. (c) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Org. Lett.* **2004**, *6*, 3199. (d) Bandini, M.; Melloni, A.; Piccinelli, F.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **2006**, *128*, 1424. (e) Ma, S.; Yu, S.; Peng, Z.; Guo, H. *J. Org. Chem.* **2006**, *71*, 9865. (f) Cheung, H. Y.; Yu, W.-Y.; Lam, F. L.; Au-Yeung, T. T.-L.; Zhou, Z.; Chan, T. H.; Chan, A. S. C. *Org. Lett.* **2007**, *9*, 4295. (g) Mo, H.; Bao, W. *Adv. Synth. Catal.* **2009**, *351*, 2845. (h) Hoshi, T.; Sasaki, K.; Sato, S.; Ishii, Y.; Suzuki, T.; Hagiwara, H. *Org. Lett.* **2011**, *13*, 932. (i) Liu, W.-B.; He, H.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2008**, *10*, 1815. (j) Stanley, L. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 7841. (k) Wu, Q.-F.; He, H.; Liu, W.-B.; You, S.-L. *J. Am. Chem. Soc.* **2010**, *132*, 11418. (l) Liu, Z.; Liu, L.; Shafiq, Z.; Wu, Y.-C.; Wang, D.; Chen, Y.-J. *Tetrahedron Lett.* **2007**, *48*, 3963.

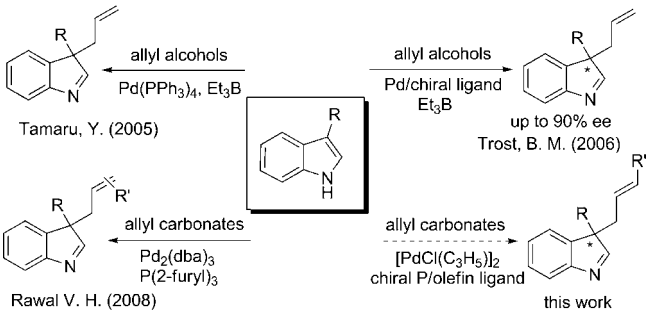
(4) For leading reviews on Pd-catalyzed asymmetric allyl alkylations, see: (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (c) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258.

(5) For selected examples on using indolenines in synthesis, see: (a) Robinson, R.; Suginome, H. *J. Chem. Soc.* **1932**, 298. (b) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *J. Am. Chem. Soc.* **1954**, *76*, 4749. (c) Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872. (d) He, F.; Bo, Y.; Altom, J. D.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771. (e) Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628.

(6) For examples on organocatalyzed reactions, see: (a) Cai, Q.; You, S.-L. *Org. Lett.* **2012**, *14*, 3040. (b) Austin, J. F.; Kim, S.-G.; Sinz, C. J.; Xiao, W.-J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5482. (c) Xiao, Y.-C.; Wang, C.; Yao, Y.; Sun, J.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2011**, *50*, 10661. (d) Bajtos, B.; Yu, M.; Zhao, H.; Pagenkopf, B. L. *J. Am. Chem. Soc.* **2007**, *129*, 9631.

10.1021/ol3032736
Published on Web 02/07/2013

Scheme 1. Pd-Catalyzed Allylic Alkylations of 3-Substituted Indoles



Trost group reported an asymmetric version of this transformation.[7b] Recently, Rawal and co-workers developed a general and high-yielding method for Pd-catalyzed alkylation of indoles using allyl carbonates (Scheme 1).[7c] Significantly, the same group successfully expanded nucleophiles to benzyl carbonates very recently.[7d] However, to the best of our knowledge, the asymmetric version of this reaction with allyl carbonates has not been reported except that You and co-workers described an asymmetric intramolecular reaction lately.[7e] Searching for a suitable chiral ligand to realize this asymmetric reaction is still of great interest.

As part of our general interest in the development of novel chiral olefin ligands[8–10] for asymmetric catalysis, we found that P/olefin ligands were highly effective for Pd-catalyzed asymmetric alkylations of indoles, pyrroles, and oximes.[10d–g] Herein, we report our primary efforts on the Pd-catalyzed asymmetric alkylation of 3-substituted indoles with allyl carbonates using P/olefin ligands.

The asymmetric palladium-catalyzed allylic alkylation of 3-substituted indoles was examined with 3-methylindole (**1a**) and allyl carbonate **2a** using chiral P/terminal-olefin ligands **4a** and **4b** (Scheme 2). It was found that 93% yield and 76% ee were obtained with phosphite/olefin ligand **4b**. A controlled experiment using ligand **4c** gave product **3a** with a contrary absolute configuration in lower yield and ee, which indicates that the olefin moieties are essential for the obtained high reactivity and enantioselectivity (Scheme 2).

Scheme 2. Initial Studies on Pd-Catalyzed Asymmetric Allylic Alkylations of 3-Substituted Indoles with P/Olefin Ligands

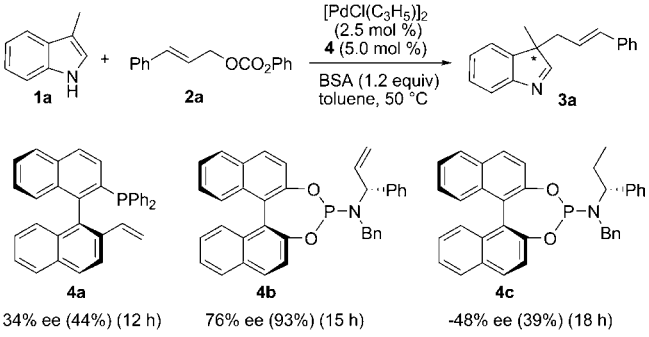
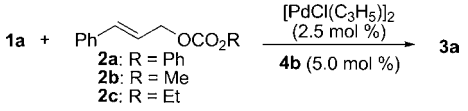


Table 1. Optimization of Reaction Conditions[a]



entry	allyl carbonates	base	solvent	time (h)	yield[b] (%)	ee[c] (%)
1	**2a**	BSA	toluene	15	93	76
2	**2b**	BSA	toluene	13	94	78
3	**2c**	BSA	toluene	13	91	80
4	**2b**	BSA	CH_2Cl_2	23	67	66
5	**2b**	BSA	dioxane	22	76	68
6	**2b**	BSA	CH_3CN	18	53	48
7	**2b**	BSA	benzene	16	89	70
8	**2b**	Et_3N	toluene	26	94	80
9	**2b**	Na_2CO_3	toluene	21	36	77
10	**2b**	K_2CO_3	toluene	2	96	80
11	**2b**	Cs_2CO_3	toluene	2	98	74
12	**2b**	---	toluene	17	32	80

[a] All reactions were carried out with **1a** (0.20 mmol), **2** (0.24 mmol), Pd/**4b** = 1/1 (5 mol % Pd), base (0.24 mmol), solvent (1.5 mL) unless otherwise stated. [b] Isolated yield based on **1a**. [c] The ee was determined by chiral HPLC.

(7) For examples on metal-catalyzed reactions, see: (a) Kimura, M.; Futamata, M.; Mukai, R.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, *127*, 4592. (b) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314. (c) Kagawa, N.; Malerich, J. P.; Rawal, V. H. *Org. Lett.* **2008**, *10*, 2381. (d) Zhu, Y.; Rawal, V. H. *J. Am. Soc. Chem.* **2012**, *134*, 111. (e) Xu, Q.-L.; Dai, L.-X.; You, S.-L. *Chem. Sci.* **2013**, *4*, 97.

(8) For leading reviews on chiral olefin ligands, see: (a) Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 3364. (b) Johnson, J. B.; Rovis, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 840. (c) Defieber, C.; Grützmacher, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4482. (d) Shintani, R.; Hayashi, T. *Aldrichim. Acta* **2009**, *42*, 31. (e) Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *Synlett* **2011**, 1345. (f) Tian, P.; Dong, H.-Q.; Lin, G.-Q. *ACS Catal.* **2012**, *2*, 95. (g) Feng, X.; Du, H. *Asian J. Org. Chem.* **2012**, *1*, 204.

(9) For examples on chiral olefin ligands, see: (a) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508. (b) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628. (c) Wang, Z.-Q.; Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 5336. (d) Li, Q.; Dong, Z.; Yu, Z.-X. *Org. Lett.* **2011**, *13*, 1122. (e) Trost, B. M.; Burns, A. C.; Tautz, T. *Org. Lett.* **2011**, *13*, 4566. (f) Maire, P.; Deblon, S.; Breher, F.; Geier, J.; Böhler, C.; Rüegger, H.; Schönberg, H.; Grützmacher, H. *Chem.—Eur. J.* **2004**, *10*, 4198. (g) Shintani, R.; Duan, W.-L.; Nagano, T.; Okada, A.; Hayashi, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 4611. (h) Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 3139. (i) Maire, P.; Breher, F.; Schönberg, H.; Grützmacher, H. *Organometallics* **2005**, *24*, 3207. (j) Hahn, B. T.; Tewes, F.; Fröhlich, R.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 1143. (k) Thaler, T.; Guo, L.-N.; Steib, A. K.; Raducan, M.; Karaghiosoff, K.; Mayer, P.; Knochel, P. *Org. Lett.* **2011**, *13*, 3182. (l) Jin, S.-S.; Wang, H.; Xu, M.-H. *Chem. Commun.* **2011**, *47*, 7230. (m) Chen, G.; Gui, J.; Li, L.; Liao, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 7681. (n) Xue, F.; Li, X.; Wan, B. *J. Org. Chem.* **2011**, *76*, 7256.

(10) For olefin ligands developed by our group, diene ligand: (a) Hu, X.; Zhuang, M.; Cao, Z.; Du, H. *Org. Lett.* **2009**, *11*, 4744. (b) Wang, Y.; Hu, X.; Du, H. *Org. Lett.* **2010**, *12*, 5482. P/olefin ligand: (c) Liu, Z.; Du, H. *Org. Lett.* **2010**, *12*, 3054. (d) Cao, Z.; Liu, Y.; Liu, Z.; Feng, X.; Zhuang, M.; Du, H. *Org. Lett.* **2011**, *13*, 2164. (e) Cao, Z.; Liu, Z.; Liu, Y.; Du, H. *J. Org. Chem.* **2011**, *76*, 6401. (f) Liu, Z.; Cao, Z.; Du, H. *Org. Biomol. Chem.* **2011**, *9*, 5369. (g) Liu, Y.; Cao, Z.; Du, H. *J. Org. Chem.* **2012**, *77*, 4479. S/olefin ligand: (h) Feng, X.; Wang, Y.; Wei, B.; Yang, J.; Du, H. *Org. Lett.* **2011**, *13*, 3300. (i) Feng, X.; Nie, Y.; Yang, J.; Du, H. *Org. Lett.* **2012**, *14*, 624.

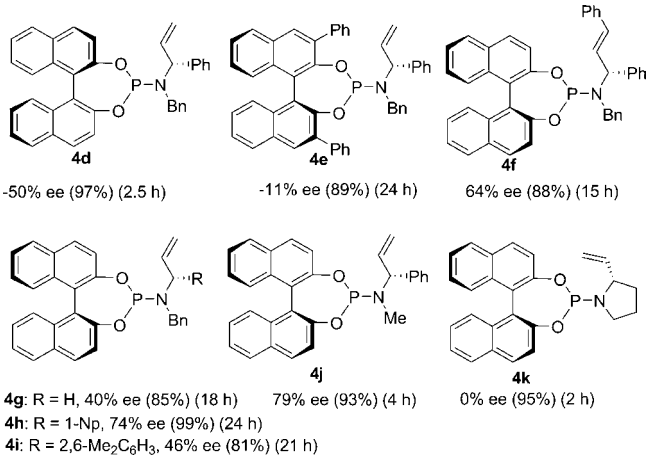
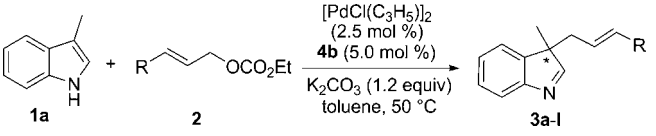


Figure 1. Selective chiral P/olefin ligands for Pd-catalyzed asymmetric allylic alkylation of 3-substituted indole **1a**.

Table 2. Pd(0)-Catalyzed Asymmetric Allylic Alkylation of 3-Methylindole (**1a**)[a]



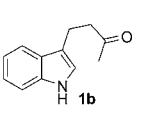
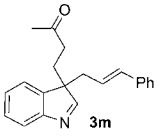
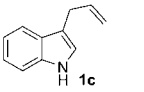
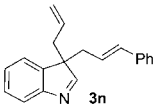
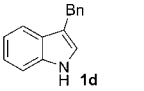
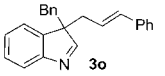
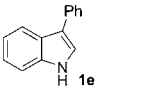
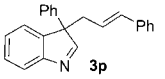
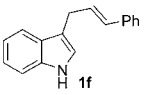
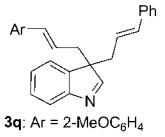
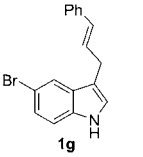
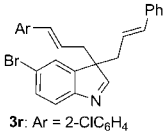
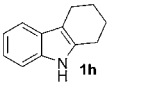
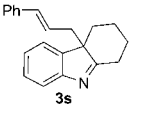
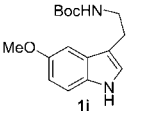
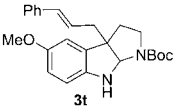
entry	product (**3**)	time (h)	yield[b] (%)	ee[c] (%)
1	**3a**: R = Ph	2	96	80
2	**3b**: R = 4-$CF_3C_6H_4$	2	91	74
3	**3c**: R = 4-ClC_6H_4	2	90	78
4	**3d**: R = 3-ClC_6H_4	2	95	72
5	**3e**: R = 3-$MeOC_6H_4$	2	94	82
6	**3f**: R = 2-ClC_6H_4	2	96	87
7	**3g**: R = 2-$MeOC_6H_4$	2	97	86
8	**3h**: R = 2-$BnOC_6H_4$	2.5	92	83
9	**3i**: R = 2-^{i}PrOC_6H_4	5.5	95	82
10	**3j**: R = 2-MeC_6H_4	2	95	83
11	**3k**: R = 1-naphthyl	2	94	77
12	**3l**: R = H	4	90	47

[a] All reactions were carried out with indole **1a** (0.40 mmol), **2** (0.48 mmol), $[PdCl(C_3H_5)]_2$ (2.5 mol %), **4b** (5 mol %), K_2CO_3 (0.48 mmol), toluene (1.5 mL) unless otherwise stated. [b] Isolated yield based on **1a**. [c] The ee was determined by chiral HPLC.

With this promising result in hand, a variety of reaction conditions including allyl carbonates, bases, and solvents were next examined. As shown in Table 1, the asymmetric reactions of allyl carbonates **2a**–**c** and indole **1a** gave similar yields and ee's (entries 1–3). Solvents and bases were found to have obvious impacts on both reactivity and selectivity, and the combination of toluene and K_2CO_3 gave the optimal results (Table 1, entries 2, 4–11). The alkylation reaction can still proceed without addition of any bases, but led a lower yield (Table 1, entry 12).

Under the optimal reaction condition (Table 1, entry 10), phosphite/olefin ligands **4d**–**k** were then tested

Table 3. Pd(0)-Catalyzed Asymmetric Allylic Alkylation of 3-Substituted Indoles[a]

entry	indoles (**1**)	product (**3**)	time (h)	yield (%)[b]	ee (%)[c]
1	 **1b**	 **3m**	7	95	78
2	 **1c**	 **3n**	2.5	92	73
3	 **1d**	 **3o**	3	91	71
4	 **1e**	 **3p**	2	93	73
5	 **1f**	 **3q**: Ar = 2-$MeOC_6H_4$	2	93	86
6	 **1g**	 **3r**: Ar = 2-ClC_6H_4	2.5	96	80
7	 **1h**	 **3s**	40	89	34
8	 **1i**	 **3t**	3	76	76

[a] All reactions were carried out with indole **1** (0.40 mmol), **2** (0.48 mmol), $[PdCl(C_3H_5)]_2$ (2.5 mol %), **4b** (5 mol %), K_2CO_3 (0.48 mmol), toluene (1.5 mL) unless otherwise stated. [b] Isolated yield based on **1**. [c] The ee was determined by chiral HPLC.

(Figure 1). Ligand **4d** bearing a (*R*)-binaphthyl skeleton gave the desired product **3a** in 97% yield with 50% ee for the contrary absolute configuration. Ligand **4e** derived from 3,3′-Ph_2BINOL led a very low ee. Ligand **4f** incorporated with internal olefin was also effective for this transformation. Moreover, the amine moieties (ligands **4g**–**k**) were found to have a large effect on the enantioselectivity. Overall, in term of both reactivity and selectivity, ligand **4b** proved to be a better ligand for this reaction.

Subsequently, using 5 mol % of palladium and ligand **4b**, the allyl carbonate scope was investigated for the alkylation of indole **1a** in toluene in the presence of K_2CO_3 as base. As shown in Table 2, a wide range of arylallyl carbonates **2a**–**k** were well tolerated for this reaction to give the corresponding indolenines **3a**–**k** in 90–97% yields with 72–87% ee's (entries 1–11). It is noteworthy that *ortho*-substituted cinnamyl carbonates

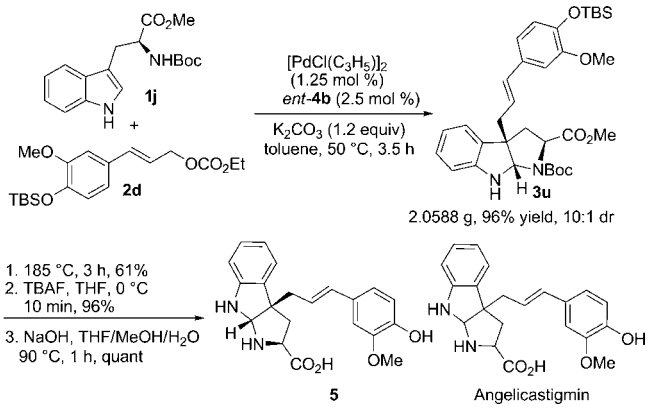
2f−**j** gave higher ee's (Table 2, entries 1−5 vs 6−10). Simple allyl carbonate **2l** was also an effective substrate for this reaction to furnish the desired product **3l** in high yield but with moderate ee (Table 2, entry 12).

The asymmetric allyl alkylation can be further extended to a variety of 3-substituted indoles, and all these reactions can proceed smoothly to give the desired indolenines **3m**−**r** in high yields with 71−86% ee's (Table 3, entries 1−6). When tetrahydrocarbazole **1h** was employed as a substrate, the reaction went relatively slower to afford product **3s** in 89% yield with 34% ee (Table 3, entry 7). Interestingly, asymmetric allyl alkylation of 3-substituted indole **1i** bearing a pendant nucleophile with carbonate **2c** can occur an intramolecular addition to afford product **3t** in 76% yield with 76% ee accompanied with a small amount of further *N*-alkylation byproducts (19% yield, 75% ee) (Table 3, entry 8).

The application of this established method for the natural product synthesis was next examined. Angelicastigmin, a new alkaloid, was isolated from the root of *Angelica polymorpha* maxim by Pachaly and co-workers in 2000.[11] To our pleasure, using 2.5 mol % of Pd/*ent*-**4b** catalysts, the asymmetric allyl alkylation of 3-substituted indole **1j** with carbonate **2d** can quickly construct compound **3u** in 96% yield with 10:1 dr (Scheme 3). Followed by deprotection of the Boc and TBS groups, and hydrolysis of the ester group, compound **5**, a stereoisomer of Angelicastigmin, can be conveniently synthesized in good yield (Scheme 3).[12,13]

In summary, a palladium-catalyzed asymmetric allylic alkylation of 3-substituted indoles with allyl carbonates

Scheme 3. Tentative Synthesis of Angelicastigmin



was realized using chiral phosphite/olefin ligands, and a wide range of highly desirable indolenines bearing a quaternary carbon stereocenter were obtained in high yields with up to 87% ee. Particularly, this method provides a quick access to one stereoisomer of the natural product Angelicastigmin. Further studies on expanding the substrate scope and exploring their applications in the synthesis of important compounds are underway in our laboratory.

Acknowledgment. The authors are thankful for the financial support from the National Natural Science Foundation of China (21072194, 21172222, 21222207) and 973 program (2010CB833300).

Supporting Information Available. The procedure for palladium-catalyzed asymmetric alkylation and synthesis of Angelicastingmin, characterization of products, and data for the determination of enantiomeric excesses. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(13) The absolute configuration of compound **5** is determined by NOE study. One diastereoisomer of compound **5** was also prepared using ligand **4b** (see Supporting Information). However, due to their NMR spectra are not exactly identical with the spectra reported in ref 11, we tentatively judge that compound **5** and its diastereoisomer are stereoisomers of the natural product Angelicastigmin.