ORGANIC LETTERS

2007
Vol. 9, No. 26
5561−5564

Remarkable Effect of *N*-Substituent on Enantioselective Ruthenium-Catalyzed Propargylation of Indoles with Propargylic Alcohols

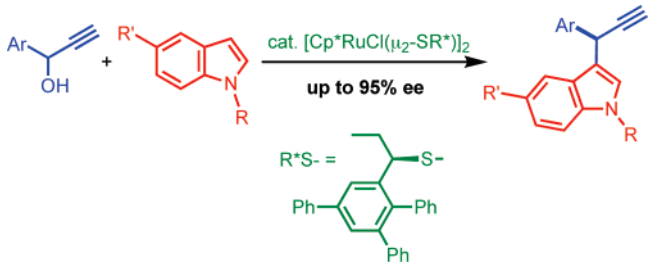
Hiroshi Matsuzawa, Keiichiro Kanao, Yoshihiro Miyake, and Yoshiaki Nishibayashi*

Institute of Engineering Innovation, School of Engineering, The University of Tokyo, Yayoi, Bunkyo-ku, Tokyo 113-8656, Japan

ynishiba@sogo.t.u-tokyo.ac.jp

Received October 16, 2007

ABSTRACT



Ruthenium-catalyzed enantioselective propargylation of indoles with propargylic alcohols affords the corresponding *β*-propargylated indoles in good yields with a high enantioselectivity (up to 95% ee). A remarkable effect of the nature of the *N*-substituent of indoles is observed for the enantioselectivity of the propargylated indoles. The preparative method described in this paper may provide a novel protocol for asymmetric Friedel–Crafts alkylation of indoles using propargylic alcohols as a new type of electrophiles.

The indole unit is the most universal heterocycle in nature. Owing to the great structural diversity of biologically active indoles, the indole unit has become an important structural component in many pharmaceuticals. For 100 years, the synthesis and functionalization of indoles have been the most active areas in organic synthesis because substituted indoles are well-known to be capable of binding to many receptors with high affinity.[1,2] So far, a great number of Lewis acid and Br*ϕ*nsted acid catalyzed asymmetric Friedel−Crafts alkylations of indole derivatives have appeared for obtaining optically active indoles.[3,4] In these asymmetric reactions, however, available electrophiles are only limited to epoxides, carbonyl compounds, activated alkenes, and their analogues.

Quite recently, we have developed the enantioselective propargylation of aromatic compounds such as 2-alkylfurans and *N*,*N*-dimethylaniline with propargylic alcohols catalyzed

(1) For recent reviews, see: (a) Tokuyama, H.; Fukuyama, T. *Chem. Rec.* **2002**, *2*, 37. (b) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (c) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (d) Lewis, S. E. *Tetrahedron* **2006**, *62*, 8655.

(2) For a recent example, see: Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172.

(3) For recent reviews, see: (a) Jørgensen, K. A. *Synthesis* **2003**, 1117. (b) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550. (c) Bandini, M.; Emer, E.; Tommasi, S.; Umani-Ronchi, A. *Eur. J. Org. Chem.* **2006**, 3527.

(4) For recent examples of asymmetric Friedel−Crafts alkylation of indole derivatives, see: (a) Esquivias, J.; Arrayas, R. G.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 629. (b) Wang, Y.-Q.; Song, J.; Hong, R.; Li, H. *J. Am. Chem. Soc.* **2006**, *128*, 8156. (c) Li, H.; Wang, Y.-Q.; Deng, L. *Org. Lett.* **2006**, *8*, 4063. (d) Lu, S.-F.; Du, D.-M.; Xu, J. *Org. Lett.* **2006**, *8*, 2115. (e) Jia, Y.-X.; Zhu, S.-F.; Zhou, Q.-L. *J. Org. Chem.* **2006**, *71*, 75. (f) Li, C.-F.; Liu, H.; Liao, J.; Cao, Y.-J.; Liu, X.-P.; Xiao, W.-J. *Org. Lett.* **2007**, *9*, 1847. (g) Yang, H.; Hong, Y.-T.; Kim, S. *Org. Lett.* **2007**, *9*, 2281. (h) Terada, M.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 292. (i) Kang, Q.; Zhao, Z.-A.; You, S.-L. *J. Am. Chem. Soc.* **2007**, *129*, 1484. (j) Dong, H.-M.; Lu, H.-H.; Lu, L.-Q.; Chen, C.-B.; Xiao, W.-J. *Adv. Synth. Catal.* **2007**, *349*, 1597. (k) Terada, M.; Yokoyama, S.; Sorimachi, K.; Uraguchi, D. *Adv. Synth. Catal.* **2007**, *349*, 1863. (l) Jia, Y.-X.; Zhong, J.; Zhu, S.-F.; Zhang, C.-M.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5565. (m) Evans, D. A.; Fandrick, K. R.; Song, H.-J.; Scheidt, K. A, Xu, R. *J. Am. Chem. Soc.* **2007**, *129*, 10029.

10.1021/ol7025203 CCC: $37.00
Published on Web 11/29/2007

by chiral thiolate-bridged diruthenium complexes to give the corresponding propargylated products in good yields with a high enantioselectivity (up to 94% ee).[5] This was the first example of asymmetric Friedel−Crafts propargylation of aromatic compounds. As an extension of our study, we have now found the ruthenium-catalyzed enantioselective propargylation of indole derivatives with propargylic alcohols.[6] A remarkable effect of the nature of *N*-substituent of indoles was observed on the enantioselectivity of the produced propargylated indoles, although the *N*-substituent is relatively apart from the reactive β-position of indoles. Thus, the introduction of a bulky group such as *tert*-butyldimethylsilyl or triisopropylsilyl group at the nitrogen atom of indole dramatically increased the enantioselectivity of the propargylated indoles. A preliminary result of enantioselective propargylation of indoles is described here.

Treatment of 1-phenyl-2-propyn-1-ol (**1a**) with indole (10 equiv to **1a**) in $ClCH_2CH_2Cl$ in the presence of a catalytic amount of a chiral thiolate-bridged diruthenium complex, which was prepared in situ from the tetranuclear ruthenium(II) complex $[Cp^*RuCl]_4$ and a chiral disulfide (**2a**)[7] in THF (tetrahydrofuran) at room temperature for 12 h, and NH_4BF_4 at 60 °C for 3 h afforded 3-(1-phenyl-2-propynyl)indole (**3a**) in 71% isolated yield with 35% ee (Scheme 1; Table 1, run 1). The introduction of a methyl group as *N*-substituent of indole much improved the enantioselectivity (Table 1, run 2), in contrast to the presence of a bulky group such as a benzyl or phenyl moiety as the *N*-substituent of indole (Table 1, runs 3 and 4). No reaction occurred at all when a *tert*-butoxycarbonyl (Boc) group was used as *N*-substituent of indole. The use of *N*-(trimethylsilyl)indole resulted in the formation of only **3a** with 37% ee (Table 1, run 5), indicating that the deprotection of the trimethylsilyl group easily proceeded before the propargylation of *N*-(trimethylsilyl)-indole. The introduction of a bulky silyl group such as a *tert*-butyldimethylsilyl or triisopropylsilyl moiety gave the corresponding propargylated indoles with much higher enantioselectivity (Table 1, runs 6 and 7). The reaction of *N*-(triisopropylsilyl)indole proceeded similarly even at 40 °C (Table 1, run 8). Even the use of 3 equiv of *N*-(triisopropylsilyl)indole to **1a** worked well (Table 1, run 9). As reported in our previous paper,[5] a similar enantioselectivity of propargylation of aromatic compounds such as 2-methylfuran and *N*,*N*-dimethylaniline with **1a** has been observed using **2a** as a chiral ligand.

Scheme 1

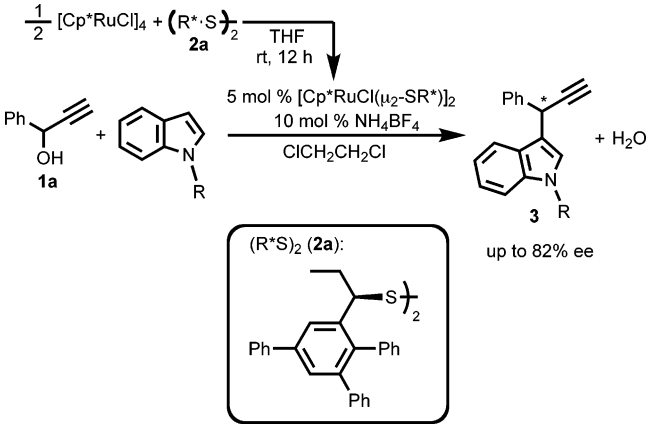


Table 1. Ruthenium-Catalyzed Enantioselective Propargylation of Indoles with Propargylic Alcohol (**1a**)[a]

run	R of indole (equiv to **1a**)	T (°C)	time (h)	yield[b] (%)	ee[c] (%)
1	H (10)	60	3	**3a**, 71	35
2	Me (10)	60	3	**3b**, 77	61
3	$PhCH_2$ (10)	60	3	**3c**, 68	41
4	Ph (10)	60	3	**3d**, 74	40
5	$SiMe_3$ (10)	60	3	**3a**, −	37[d]
6	$SiMe_2{}^t$Bu (10)	60	3	**3e**, 63	73
7	Si^iPr_3 (10)	60	3	**3f**, 74	75
8	Si^iPr_3 (10)	40	7	**3f**, 70	82
9	Si^iPr_3 (3)	40	7	**3f**, 77	78

[a] All reactions of **1a** (0.20 mmol) with indole were carried out in the presence of a ruthenium complex (0.010 mmol, generated in situ from $[Cp^*RuCl]_4$ and **2a**) and NH_4BF_4 (0.020 mmol) in $ClCH_2CH_2Cl$ (5 mL). [b] Isolated yield of **3**. [c] Determined by HPLC (see the Supporting Information for experimental details). [d] The ee value of **3a**.

The catalytic propargylation of *N*-(triisopropylsilyl)indole (3 equiv to **1**) with other propargylic alcohols (**1**) was investigated at 40 °C by using **2a** as a chiral ligand. Typical results are shown in Table 2. The presence of a substituent in the benzene ring of the propargylic alcohols had some effect on the enantioselectivity. The introduction of a methyl group at the para position of the benzene ring of **1a** slightly decreased the enantioselectivity (Table 2, run 2), while the introduction of a phenyl group at the para or ortho position of the benzene ring of **1a** increased the enantioselectivity (Table 2, runs 4 and 5). When 1-(1-naphthyl)-2-propyn-1-ol (**1g**) was used as a substrate, the highest enantioselectivity was achieved (Table 2, run 7).

The propargylation of other *N*-(triisopropylsilyl)indoles bearing a substituent at 5-position of the indole ring with **1g** under similar reaction conditions afforded a good yield of products with a high enantioselectivity, irrespective of the nature of the substituent (Table 3). On the other hand, the introduction of a substituent at 2-position of the indole ring dramatically decreased the enantioselectivity of the product.

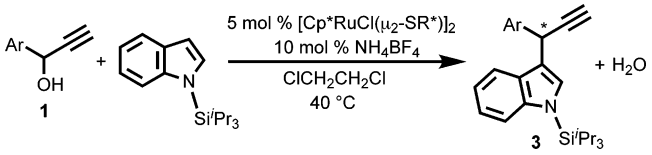
To obtain more information about the enantioselective propargylation of aromatic compounds, the stereochemistry of the propargylated product **3l** was determined. The reaction

(5) Matsuzawa, H.; Miyake, Y.; Nishibayashi, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 6488.

(6) Recently, propargylation of indoles catalyzed by iodine,[6a] $Sc(OTf)_3$,[6b] $InCl_3$,[6c] Amberlyst-15,[6d] and $FeCl_3$[6e] has been reported, but enantioselective propargylation has not yet been reported until now. (a) Liu, Z.; Liu, Z.; Shafiq, Z.; Wu, Y.-C.; Wang, D.; Chen, Y.-J. *Tetrahedron Lett.* **2007**, *48*, 3963. (b) Yadav, J. S.; Reddy, B. V. S.; Rao, K. V. R.; Kumar, G. G. K. S. N. *Tetrahedron Lett.* **2007**, *48*, 5573. (c) Liu, Z.; Liu, L.; Shafiq, Z.; Wu, Y.-C.; Wang, D.; Chen, Y.-J. *Synthesis* **2007**, 1961. (d) Yadav, J. S.; Reddy, B. V. S.; Kumar, G. G. K. S. N.; Rao, K. V. R. *Chem. Lett.* **2007**, *36*, 942. (e) Jana, U.; Maiti, S.; Biswas, S. *Tetrahedron Lett.* **2007**, *48*, 7160.

(7) Inada, Y.; Nishibayashi, Y.; Uemura, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 7715.

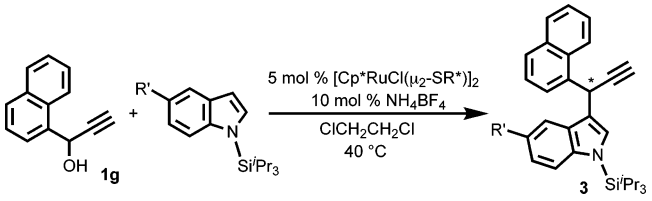
Table 2. Ruthenium-Catalyzed Enantioselective Propargylation of *N*-(Triisopropyl)indole with Propargylic Alcohols (**1**)[a]



run	Ar of **1**	time (h)	yield[b] (%)	ee[c] (%)
1	Ph (**1a**)	7	**3f**, 77	78
2	*p*-MeC$_6$H$_4$ (**1b**)	10	**3g**, 70	71
3	*p*-ClC$_6$H$_4$ (**1c**)	7	**3h**, 72	79
4	*p*-PhC$_6$H$_4$ (**1d**)	10	**3i**, 76	90
5	*o*-PhC$_6$H$_4$ (**1e**)	30	**3j**, 63	83
6	3,5-Ph$_2$C$_6$H$_3$ (**1f**)	7	**3k**, 98	80
7	1-naphthyl (**1g**)	23	**3l**, 81	92
8	2-naphthyl (**1h**)	7	**3m**, 82	84

[a] All reactions of **1** (0.20 mmol) with *N*-(triisopropyl)indole (0.60 mmol) were carried out in the presence of a ruthenium complex (0.010 mmol, generated in situ from [Cp*RuCl]$_4$ and **2a**) and NH$_4$BF$_4$ (0.020 mmol) in ClCH$_2$CH$_2$Cl (5 mL). [b] Isolated yield of **3**. [c] Determined by HPLC (see the Supporting Information for experimental details).

Table 3. Ruthenium-Catalyzed Enantioselective Propargylation of *N*-(Triisopropyl)indoles with **1g**[a]



run	R′ of indole	time (h)	yield[b] (%)	ee[c] (%)
1	H	23	**3l**, 81	92
2	Me	20	**3n**, 82	95
3	Cl	20	**3o**, 78	91
4	OMe	20	**3p**, 71	87

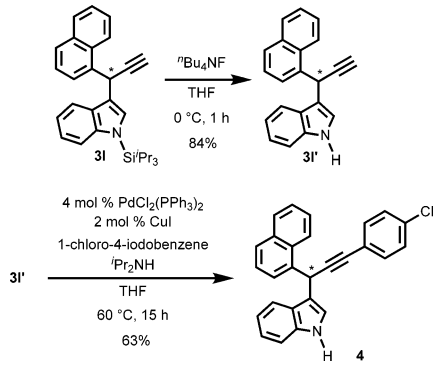
[a] All reactions of 1-(1-naphthyl)-2-propyn-1-ol (**1g**) (0.20 mmol) with *N*-(triisopropyl)indoles (0.60 mmol) were carried out in the presence of a ruthenium complex (0.010 mmol, generated in situ from [Cp*RuCl]$_4$ and **2a**) and NH$_4$BF$_4$ (0.020 mmol) in ClCH$_2$CH$_2$Cl (5 mL). [b] Isolated yield of **3**. [c] Determined by HPLC (see the Supporting Information for experimental details).

of **3l′**, which was obtained by deprotection of **3l**, with 1-chloro-4-iodobenzene in the presence of a catalytic amount of palladium complex at 60 °C for 15 h gave **4** in 63% isolated yield (Scheme 2).[8] The X-ray analysis of a major enantioisomer of **4** indicates that the absolute configuration of **3l** should be *R*.[9] This result supports our previously proposed reaction pathway[5,7] in the propargylation of aromatic compounds, where the $\pi-\pi$ interaction of phenyl rings between the chiral ligand and allenylidene moieties was considered to play an important role to achieve the high

(8) (a) Blum, J.; Baidossi, W.; Badreih, Y.; Hoffman, R. E.; Schumann, H. *J. Org. Chem.* **1995**, *60*, 4738. (b) Ohta, K.; Goto, T.; Endo, Y. *Inorg. Chem.* **2005**, *44*, 8569.

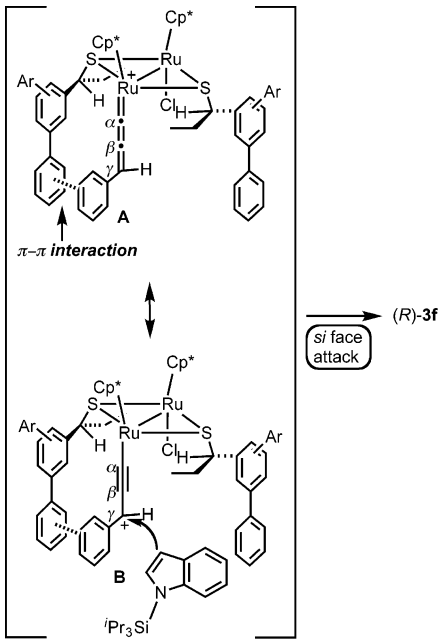
(9) An ORTEP drawing of major enantioisomer of **4** is included in the Supporting Information as Figure S1.

Scheme 2



enantioselectivity as shown in Scheme 3. Here, indole should attack the alkynyl complex (**B**) having a cationic γ-carbon from *si* face, where **B** is a resonance structure of the allenylidene complex (**A**) prepared from a propargylic alcohol and the diruthenium complex.

Scheme 3



In summary, we have found the ruthenium-catalyzed enantioselective propargylation of indoles with propargylic alcohols to give the corresponding β-propargylated indoles in good yields with a high enantioselectivity (up to 95% ee). A remarkable effect of the nature of *N*-substituent of indoles was observed on the enantioselectivity of the produced propargylated indoles. The preparative method described in this paper may provide a novel protocol for asymmetric Friedel−Crafts alkylation of indoles by using propargylic alcohols as a new type of electrophiles. Further work is currently in progress to broaden its synthetic applicability to natural products and pharmaceuticals.

Acknowledgment. This work was supported by Grants-in-Aid for Scientific Research for Young Scientists (S) (No. 19675002) and for Scientific Research on Priority Areas (No. 18066003) from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and Industrial Technology Research Grant Program in 2005 from New Energy and Industrial Technology Development Organization (NEDO) of Japan. Y.N. thanks the Shorai Foundation for Science and Technology.

Supporting Information Available: Experimental procedures and spectral data for all new compounds. Crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL7025203