Ruthenium-Catalyzed Enantioselective Propargylation of Indoles with Propargylic Alcohols

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

Institute of Engineering Innovation, School of Engineering, The University of Tokyo, Yayoi, Bunkyo-ku, Tokyo 113-8656, Japan
Fax +81(3)58411175; E-mail: ynishiba@sogo.t.u-tokyo.ac.jp
Received 28 July 2008; revised 7 August 2008

Abstract: Ruthenium-catalyzed enantioselective propargylation of 1-(triisopropylsilyl)-1H-indoles with propargylic alcohols gives the corresponding β-propargylated indoles in good yields with high enantioselectivity. Reactions with 1-(1-naphthyl)prop-2-yn-1-ol achieve the highest enantioselectivity (up to 95% ee).

Key words: asymmetric synthesis, Friedel–Crafts alkylation, ruthenium, indoles, propargylic alcohols

Indoles represent a structural motif in a number of natural bioactive products. A variety of methods to obtain optically active indoles have been reported by Lewis acid and Brønsted acid catalyzed enantioselective Friedel–Crafts alklylation of indoles.1,2 We have recently disclosed the enantioselective propargylation of aromatic compounds such as 2-alkylfurans and N,N-dimethylaniline with propargylic alcohols catalyzed by a chiral thiolate-bridged di-ruthenium complex3 to afford the corresponding propargylated products in good yields with high enantioselectivity (up to 94% ee).4 This is the first example of the enantioselective propargylation of aromatic compounds. As an extension of our study, we have more recently found the ruthenium-catalyzed enantioselective propargylation of indoles with propargylic alcohols to give the corresponding β-propargylated indoles in good to high yields (Scheme 1).5

Scheme 1

Indoles represent a structural motif in a number of natural bioactive products. A variety of methods to obtain optically active indoles have been reported by Lewis acid and Brønsted acid catalyzed enantioselective Friedel–Crafts alklylation of indoles.1,2 We have recently disclosed the enantioselective propargylation of aromatic compounds such as 2-alkylfurans and N,N-dimethylaniline with propargylic alcohols catalyzed by a chiral thiolate-bridged di-ruthenium complex3 to afford the corresponding propargylated products in good yields with high enantioselectivity (up to 94% ee).4 This is the first example of the enantioselective propargylation of aromatic compounds. As an extension of our study, we have more recently found the ruthenium-catalyzed enantioselective propargylation of indoles with propargylic alcohols to give the corresponding β-propargylated indoles in good to high yields (Scheme 1).5 In this reaction system, the introduction of a bulky group, such as the triisopropylsilyl (TIPS) moiety,
at the nitrogen of indole dramatically increased the enantioselectivity of the propargylated indoles (Scheme 2).\textsuperscript{5} 
Herein, we describe a practical method for the preparation of \(\beta\)-propargylated indoles from reactions of 1-(triisopropylsilyl)-1\(H\)-indole with propargylic alcohols catalyzed by a chiral thiolate-bridged diruthenium complex.

As described in our previous paper, we have already found that the highest enantioselectivity was observed when 1-(1-naphthyl)prop-2-yn-1-ol (1g) was used as a substrate.\textsuperscript{3} Typical results are shown in Table 1. In fact, the reaction of 1-(1-naphthyl)prop-2-yn-1-ol (1g) with 1-(triisopropylsilyl)-1\(H\)-indole (3 equiv) in 1,2-dichloroethane in the presence of a catalytic amount of a chiral thiolate-bridged diruthenium complex.

\begin{table}[h]
\centering
\caption{Ruthenium-Catalyzed Enantioselective Propargylation of 1-(Triisopropylsilyl)-1\(H\)-indole with Propargylic Alcohols 1\textsuperscript{a}}
\begin{tabular}{|c|c|c|c|c|}
\hline
Entry & \textbf{Ar of 1} & \textbf{Time (h)} & \textbf{Yield} & \textbf{ee} \\
\hline
1 & Ph (1a) & 7 & 3a, 77 & 78 \\
2 & 4-MeC_6H_4 (1b) & 10 & 3b, 70 & 71 \\
3 & 4-ClC_6H_4 (1c) & 7 & 3c, 72 & 79 \\
4 & 4-PhC_6H_4 (1d) & 10 & 3d, 76 & 90 \\
5 & 2-PhC_6H_4 (1e) & 30 & 3e, 63 & 83 \\
6 & 3,5-Ph_2C_6H_3 (1f) & 7 & 3f, 98 & 80 \\
7 & 1-naphthyl (1g) & 23 & 3g, 81 & 92 \\
8 & 2-naphthyl (1h) & 7 & 3h, 82 & 84 \\
\hline
\end{tabular}
\textsuperscript{a} Reaction conditions: 1a–h (0.20 mmol), 1-(triisopropylsilyl)-1\(H\)-indole (0.60 mmol), ruthenium complex (0.010 mmol, generated in situ from [Cp*RuCl\(_2\)]\(_2\) and 2), NH_4BF_4 (0.020 mmol), DCE (5 mL).
\textsuperscript{b} Isolated yield of 3.
\textsuperscript{c} Determined by HPLC.
\end{table}

\textbf{Scheme 3} A large-scale reaction of 1-(1-naphthyl)prop-2-yn-1-ol (1g) with 1-(triisopropylsilyl)-1\(H\)-indole
olate-bridged diruthenium complex, which was prepared in situ from the tetrancular ruthenium(II) complex \([\text{Cp}^*\text{RuCl}]_4\) and chiral disulfide \(2\) in tetrahydrofuran at room temperature for 12 hours, and ammonium tetrafluoroborate at 40 °C for 23 hours afforded 3-[1-(1-naphthalenyl)prop-2-ynyl]-1-(trisopropylsilyl)-1\(H\)-indole (3g) in 72% isolated yield with 93% ee \((R)\) (Scheme 3). After recrystallization of the deprotected indole, enantiomerically pure \(\beta\)-propargylated indole 4 was obtained in 55% isolated yield.

Next, the propargylation of other 1-(trisopropylsilyl)-1\(H\)-indoles bearing a substituent in the 5- or 6-position of the indole ring with \(1g\) was carried out under the same reaction conditions. Typical results are shown in Table 2. The introduction of a methyl group at the 5- or 6-position of the indole ring gave a similar enantioselectivity (Table 2, entries 2 and 3). The same enantioselectivity was observed when a chloro moiety is presented at 5-position of the indole ring (Table 2, entry 4). On the other hand, the introduction of methoxy or fluoro moiety at the 5- or 6-position of the indole ring gave a slightly lower enantioselectivity (Table 2, entries 5–7).

In summary, we have developed an efficient and practical method for the preparation of \(\beta\)-propargylated indoles from reactions of 1-(trisopropylsilyl)-1\(H\)-indole with propargylic alcohols catalyzed by a chiral thiolate-bridged diruthenium complex. This method provides a novel protocol for the asymmetric Friedel–Crafts alkylation.

### Table 2  Ruthenium-Catalyzed Enantioselective Propargylation of 1-(Triisopropylsilyl)-1\(H\)-indoles with 1g

<table>
<thead>
<tr>
<th>Entry</th>
<th>Indole</th>
<th>Time (h)</th>
<th>Yield(^a) (%)</th>
<th>ee(^c) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Indole1" /></td>
<td>23</td>
<td>3g, 81</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Indole2" /></td>
<td>20</td>
<td>3i, 82</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Indole3" /></td>
<td>24</td>
<td>3j, 83</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Indole4" /></td>
<td>20</td>
<td>3k, 78</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Indole5" /></td>
<td>20</td>
<td>3l, 71</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="Indole6" /></td>
<td>48</td>
<td>3m, 51</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7" alt="Indole7" /></td>
<td>24</td>
<td>3n, 78</td>
<td>81</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: \(1g\) (0.20 mmol), 1-(trisopropylsilyl)-1\(H\)-indoles (0.60 mmol), ruthenium complex (0.010 mmol, generated in situ from \([\text{Cp}^*\text{RuCl}]_4\) and \(2\)), \(\text{NH}_4\text{BF}_4\) (0.020 mmol), \(\text{DCE}\) (5 mL).

\(^b\) Isolated yield of 3.

\(^c\) Determined by HPLC.
tion of indoles by using propargylic alcohols as a new type of electrophile.

1H NMR (270 MHz) and 13C NMR (67.8 MHz) spectra were measured on a Jeol Excalibur 270 spectrometer using CDCl3 as solvent. HPLC analyses were performed on a Hitachi L-7100 apparatus equipped with a UV detector using 25 cm × 4.6 mm Daicel Chiral OD and Chiralpak IA columns. Mass spectra were measured on a Jeol JMS-700 mass spectrometer.

All reactions were carried out under a dry N2 atmosphere. Chiral disulfide 2 was prepared according to our previous procedure.1 1-Phenyl-prop-2-yn-1-ol (1a) is commercially available. Preparation of other propargylic alcohols was carried out according to literature methods.6 1-[(Triisopropylsilyl)-1H-indole was prepared according to the literature method.7 DCE and THF were distilled under N2. All products were fully characterized.5

3-[1-(1-Naphthyl)prop-2-ynyl]-1-(triisopropylsilyl)-1H-indole (3g); Typical Procedure

In a 200-mL round-bottomed flask were placed [Cp*RuCl]4 (55.3 mg, 0.05 mmol) and bis[(E)-1-6-phenyl-1,1′,4′,1″-terphenyl-2″-yl] disulfide (21.8 mg, 0.05 mmol) under N2. Anhyd THF (10 mL) was added and the mixture was magnetically stirred at r.t. for 12 h. The solvent was evaporated in vacuo. Then, NH4BF4 (21.8 mg, 0.18 mmol) and anhyd DCE (50 mL) were added under N2, and the mixture was magnetically stirred at r.t. After the addition of 1g (365 mg, 2.0 mmol) and 1-[(1-naphthyl)prop-2-yn-1-ol (1.64 g, 6.0 mmol), the reaction flask was kept at 40 °C for 23 h. The solvent was concentrated under reduced pressure by an aspirator, and then the residue was purified by flash column chromatography (silica gel, hexane–EtOAc; hexane only to 100:1) to give 3g (634 mg, 72%) as a pale yellow oil; 93% ee [HPLC (Daicel Chiralpak OD and Chiralpak IA columns. Mass spectra were measured on a Jeol Excalibur 270 spectrometer using CDCl3 as solvent.

References


Acknowledgment

This work was supported by Grants-in-Aid for Scientific Research for Young Scientist (S) (No. 19675002) and for Scientific Research on Priority Areas (No. 18066003) from the Ministry of Education, Culture, Sports, Science and Technology, Japan. K.K. acknowledges the Global COE Program for Chemistry Innovation.
Enantioselective Propargylation of Indoles


