Catalytic Asymmetric Cyclopropanation with Diazooxindole

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Received: 12.10.2012; Accepted after revision: 12.11.2012

Abstract: The first catalytic asymmetric cyclopropanation using styrene and diazooxindole was achieved with Rh$_2$(S-PTTL)$_4$. The reaction proceeded smoothly with 1 mol% catalyst loading to provide a good yield of the biologically important spiro-cyclopropyl-oxindole product with moderate to good enantioselectivity and excellent diastereoselectivity.

Key words: asymmetric catalysis, spiro compounds, carbenoids, cyclopropanation, oxindole

Spirooxindole is a privileged heterocyclic motif that exists in a large number of bioactive natural alkaloids and pharmaceutical candidates. For example, MI-219 is an inhibitor of the p53-MDM2 protein–protein interaction (Figure 1). A highly functionalized spiro cyclobutyloxindole, welwitindolinone A isonitrile isolated from blue-green algae by Moore et al. possesses antifungal activity. Recently, spiroxindoles having spiro[2,4]system have been studied for application to medicinal chemistry. Spiro cyclopropyloxindole 1, especially, is a potent HIV-1 non-nucleoside reverse transcriptase inhibitor. Spiro epoxyoxyoxindole 2 also shows biological activity as a potent inhibitor of differentiation in promyelocytic leukemia cells. The biological activity of many organic compounds is closely linked to stereochemistry, a phenomenon referred to as the ‘lock-and-key’ model. Because of the potential biological importance of these compounds, catalytic enantio- and diastereoselective methods are needed for the synthesis of the spirooxindole framework.

The enantioselective synthesis of these scaffolds is difficult because they have a highly hindered spirocyclic quaternary carbon center. Specifically, the catalytic chiral asymmetric synthesis of spirooxindole containing a cyclopropane ring remains a challenging task in the current organic synthesis. In a program for the development of biologically significant compounds, the stereoselective construction of spirooxindoles has also been of our interest. Recently, Baltoli and Bencivenni et al. reported the first enantioselective access to spiro cyclopropyloxindoles via an organocatalytic Michael–alkylation cascade reaction using methyleneindolinone and bromonitromethane to give the nitrofunctionalized spiro cyclopropyloxindoles. For accessing the spiro cyclopropyloxindoles, metal-catalyzed cyclopropanation using diazo compounds of alkenes has provided an alternative approach.

Figure 1 Biologically active spirooxindole compounds

Scheme 1 Catalytic asymmetric synthesis of spiro cyclopropyloxindole via a metal carbenoid intermediate

The catalytic asymmetric cyclopropanation using various olefins with diazooxindoles would provide a reliable method for preparing chiral spiro cyclopropyloxindoles containing various functional groups (Scheme 1). Carreira et al. (2003) reported a racemic synthesis of spiro cyclopropyloxindoles through cyclopropanation with diazooxindole for the total synthesis of spirotryprostatin B. This report describes a catalytic asymmetric synthesis of spiro cyclopropyloxindoles through transition-metal-catalyzed asymmetric cyclopropanation with diazooxindole.
was added slowly to a mixture of styrene, metal salt, and solvent at room temperature. Initially, Cu(I) triflate, an efficient catalyst for cyclopropanation, was used. However, the reaction became sluggish, despite consumption of the diazooxindole (Table 1 entry 1). The use of the more electron-enriched ethyl vinyl ether also failed to give the desired product. The reaction using [Ru(p-cymene)Cl₂]₂ resulted in only a trace amount of product (Table 1 entry 2). In addition, Cu(I) and Co(II) acetate did not promote the reaction, and starting material was recovered (Table 1, entries 3 and 4). In contrast, Rh₂(OAc)₄ smoothly catalyzed the reaction to give the cyclopropanation adduct in 97% yield with 95:5 diastereoselectivity (Table 1, entry 5). The NOE analysis of the major product revealed that the amide moiety of oxindole and the phenyl group was in trans configuration (see Supporting Information).

### Table 1: Racemic Cyclopropanation of Diazooxindole

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal salt</th>
<th>Yield (%)</th>
<th>trans/cis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuOTf</td>
<td>n.o. b</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>[Ru(p-cymene)Cl₂]₂</td>
<td>trace</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>CuOAc</td>
<td>n.r. b</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>Co(OAc)₂</td>
<td>n.r. b</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>Rh₂(OAc)₄</td>
<td>&gt;99</td>
<td>95:5</td>
</tr>
</tbody>
</table>

*Conditions: 5 mol% catalyst were used. b n.o. = not obtained; n.r. = no reaction.

Initial screening of metal salts resulted in the use of chiral rhodium(II) catalyst, and results summarizing commercially available chiral rhodium catalysts are shown in Table 2. Davies et al. showed that the proline-derived chiral rhodium(II) catalyst, and results summarizing commercially available chiral rhodium catalysts are shown in Table 2. Davies et al. showed that the proline-derived chiral rhodium(II) catalyst, and results summarizing commercially available chiral rhodium catalysts are shown in Table 2. Davies et al. showed that the proline-derived chiral rhodium(II) catalyst, and results summarizing commercially available chiral rhodium catalysts are shown in Table 2.

**Table 2: Catalytic Asymmetric Cyclopropanation with Diazooxindole**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst X</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
<th>trans/cis (%)</th>
<th>ee of trans (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh₂(S-TBSP)₄</td>
<td>5 r.t.</td>
<td>94:6</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Rh₂(S-PTTL)₄</td>
<td>5 r.t.</td>
<td>97:3</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Rh₂(S-PTTL)₄</td>
<td>2.5 0</td>
<td>&gt;99</td>
<td>98:2</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>Rh₂(S-PTTL)₄</td>
<td>2.5 –40</td>
<td>31</td>
<td>97:3</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>Rh₂(S-PTTL)₄</td>
<td>1 0</td>
<td>&gt;99</td>
<td>98:2</td>
<td>66</td>
</tr>
<tr>
<td>6</td>
<td>Rh₂(S-PTTL)₄</td>
<td>1 0</td>
<td>&gt;99</td>
<td>97:3</td>
<td>66</td>
</tr>
</tbody>
</table>

*Combined yield of diastereomer. b Determined by crude NMR. c Diazooxindole was added in one portion and stirred for 1 h.

at the 4-position on the phenyl ring gave the product in moderate enantioselectivity with excellent diastereoselectivity (Table 3, entries 1 and 4). 4-Methylstyrene afforded the product with similar selectivity (Table 3, entry 5). The reaction using 4-methoxystyrene was also possible and produced a high chemical yield of product with 48% ee (Table 3, entry 6). The reaction using 1-pentene gave the product in 65% yield with acceptable diastereoselectivity (trans/cis = 88:12, Table 3, entry 7). The trans product exhibited greater enantioselectivity in up to 74% ee.

The high trans selectivity observed in Tables 1–3 is explained in Scheme 2. For the Rh-catalyzed cyclopropanation using ary1 diazoacetate, the styrene attacks with its phenyl group pointing away from the bulky rhodium surface to avoid unfavorable interaction (TS₁ in Scheme 2). The C=C bond of styrene is expected to approach from the amide side because a partial positive charge in the amide oxygen (TS₂). Then, the alkene rotates to form spiro cyclopropyloxindole (TS₃). As a result, the trans relation of the amide carbonyl and phenyl group is expected to be the most favorable. The reaction mechanism via the perpendicular approach of the alkene to the rhodium(II)–carbon axis is also possible.

In conclusion, the chiral rhodium-catalyzed catalytic asymmetric cyclopropanation of diazooxindole for con-
Entry R Yield (%) a ee of trans (%)
1 4-ClC₆H₄ >99 97.3 65
2 3-ClC₆H₄ 98 98.2 60
3 2-ClC₆H₄ 92 96.4 66
4 4-FC₆H₄ >99 96.4 64
5 4-MeC₆H₄ >99 96.4 62
6 4-MeOC₆H₄ >99 93.7 48
7 n-C₆H₄ 65 88.12 74

a Diazooxindole was added in one portion and stirred for 1 h.

b Combined yield of diastereomers.

c Determined by crude NMR.

Scheme 2 Proposed mechanism for the trans-selective formation of spiro cyclopropyloxindole

Construction of spiro-cyclopropyloxindoles was achieved successfully. This is the first report of an enantioselective reaction using diazooxindole. This novel method provides access to a variety of substituted cyclopropyloxindoles and will be useful in medicinal chemistry applications.

General Procedure for the Catalytic Asymmetric Cyclopropanation with Styrene and Diazooxindole (Table 2, Entry 6)

Rh₂(S-PTTL)₄ (0.0015 mmol, 2.1 mg) was added to a two-necked round-bottom flask containing a magnetic stir bar under an Ar atmosphere, followed by addition of CH₂Cl₂ (0.5 mL) to the flask. Styrene (0.75 mmol) and diazooxindole (0.15 mmol) in CH₂Cl₂ (2.0 mL) were added at 0 °C. After stirring for 1 h, the solvent was removed under reduced pressure, and the diastereomeric ratio was determined by crude ¹H NMR analysis. The resulting crude mixture was purified by silica gel column chromatography (hexane–EtOAc = 2:1 to 0:1) to afford the cyclopropyloxindole. ¹H NMR (500 MHz, CDCl₃); δ = 9.39 (br, 1H), 7.30–7.19 (m, 5H), 7.08 (t, J = 7.7 Hz, 1H), 6.96 (d, J = 7.5 Hz, 1H), 6.66 (m, 1H), 5.95 (d, J = 7.5 Hz, 1H), 3.56 (t, J = 8.6 Hz, 1H), 2.24–2.21 (m, 1H), 2.04–2.02 (m, 1H); ¹³C NMR (125 MHz, CDCl₃); δ = 179.1, 141.1, 134.9, 130.0, 128.3, 127.9, 127.4, 126.5, 121.4, 109.7, 36.1, 33.7, 22.6; HRMS: m/z calcd for C₁₆H₁₂NO [M – H]: 234.0924; found: 234.0928; IR (neat): 2922, 1704, 1619, 1467, 1218 cm⁻¹; [α]D = +104.3 (c = 1.0, CHCl₃, 98.2% dr, 66% ee); Enantiomeric excess was determined by HPLC with a Chiralpack AD-H column [hexane–2-ProOH (70:30), 1.0 mL/min, 254 nm]; tₗₗ (minor enantiomer) = 5.1 min; t₉₉ (major enantiomer) = 6.3 min.

Acknowledgment

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and the Takeda Science Foundation.

Supporting Information

for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References


