Reduction of Nitroarenes to Anilines with a Benzothiazoline: Application to Enantioselective Synthesis of 2-Arylquinoline Derivatives

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Abstract
The metal-free reduction of nitroarenes to aniline derivatives was accomplished in a short time by using a benzothiazoline as the hydrogen donor in combination with a Brønsted acid. An enantioselective synthesis of 2-arylquinolines was achieved by using 1-aryl-3-(2-nitrophenyl)propan-1-ones as starting materials and a combination of a benzothiazoline and a chiral phosphoric acid.

Key words benzothiazolines, phosphoric acids, isoquinolines, nitroarenes, anilines, reduction

Aniline is a fundamental motif, frequently found in pharmaceuticals, natural compounds, and building blocks. It is also an important building block for organic synthesis.1 A conventional method for the synthesis of aniline involves the reduction of aryl nitroarenes by using metals.2 The Béchamp reduction, which uses tin or zinc in the presence of a Brønsted acid at high temperature, is extensively employed.3 Alternatively, transition-metal-catalyzed reductions of nitroarenes with hydrogen gas are used under relatively mild reaction conditions. Palladium on carbon is a widely used catalyst in reductions performed in the laboratory and industry because it presents benefits with regards to cost and handling.4 However, the reduction using palladium is sometimes hampered by such issues as residuals, flammability, and chemoselectivity. The reduction of nitroarenes by using such organic reductants as trichlorosilane5 or phenyl(2-pyridyl)methanol6 has been developed. Recently, Uozumi and co-workers reported a reduction that used diboronic acid and water.7

We have reported an enantioselective transfer hydrogenation of ketimines, in which we used a benzothiazoline (2,3-dihydro-1,3-benzothiazole) as the hydrogen donor in combination with a chiral phosphoric acid.8,9 Benzothiazolines proved to be effective for the transfer hydrogenation of C=N bonds in a range of ketimines. To expand the utility of benzothiazolines, we set our sights on the reduction of nitroarenes. Here we describe a rapid metal-free reduction of nitroarenes that uses a combination of a benzothiazoline and a Brønsted acid. Furthermore, we applied this reaction to the enantioselective synthesis of 2-arylquinolines, starting from 1-aryl-3-(2-nitrophenyl)propan-1-ones (Scheme 1).

Scheme 1 Reduction of nitroarenes

At the outset, we examined the reduction of methyl 4-nitrobenzoate (1a) with 2-phenylbenzothiazoline (2a) in the presence of a catalytic amount of 10-camphorsulfonic acid.
acid (CSA) as a Brønsted acid (Scheme 2). Gratifyingly, aniline 3a was obtained in 44% yield, accompanied by the corresponding N-benzylamine 4aa in 19% yield. We already knew that the hydrolysis and condensation of benzothiazolines and benzaldehydes occur under these reaction conditions. We therefore believed that 4aa was formed by the reduction of imine 5aa, derived from 3a and 4-cyanobenzaldehyde.

In order to suppress the hydrolysis of the benzothiazoline 2a and to increase the yield of 3a, we added molecular sieves (MS), which had a pronounced effect; the addition of MS 4Å suppressed the formation of the benzylamine 4aa and gave aniline 3a in high yield (Table 1, entries 1–3). Next, we explored the effects of the Brønsted acid and of various 2-substituents on the benzothiazoline. A long reaction time was required in the absence of a Brønsted acid (entry 4). The 2-substituent on the benzothiazoline did not affect the yield (entries 5–7). During the investigations, we had difficulties purifying the aniline after the reaction, because an excess of benzothiazole 6 (Ar = Ph) was generated and the separation of the desired product 3a from 6 (Ar = Ph) was not a trivial issue. We surmised that the introduction of a carboxy group onto the benzothiazoline 2 might increase its polarity and facilitate separation. In addition, we expect-

Table 1 Effects of Molecular Sieves and Various Substituents on the Benzothiazoline

<table>
<thead>
<tr>
<th>Entry</th>
<th>H donor</th>
<th>MS</th>
<th>Time (h)</th>
<th>Yield (%) of 3a</th>
<th>Yield (%) of 4aa</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>MS 3Å</td>
<td>24</td>
<td>43</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>2a</td>
<td>MS 4Å</td>
<td>24</td>
<td>86</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>2a</td>
<td>MS 5Å</td>
<td>24</td>
<td>52</td>
<td>27</td>
</tr>
<tr>
<td>4b</td>
<td>2a</td>
<td>MS 4Å</td>
<td>48</td>
<td>88</td>
<td>&lt;8</td>
</tr>
<tr>
<td>5</td>
<td>2b</td>
<td>MS 4Å</td>
<td>19</td>
<td>84</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>2c</td>
<td>MS 4Å</td>
<td>24</td>
<td>87</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>2d</td>
<td>MS 4Å</td>
<td>10.5</td>
<td>75</td>
<td>&lt;38</td>
</tr>
<tr>
<td>8b</td>
<td>2e</td>
<td>MS 4Å</td>
<td>0.5</td>
<td>98</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>2e</td>
<td>MS 4Å</td>
<td>0.5</td>
<td>97</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>7</td>
<td>MS 4Å</td>
<td>20</td>
<td>23</td>
<td>-</td>
</tr>
</tbody>
</table>

* Reaction conditions: 1a (0.080 mmol), H donor (0.32 mmol), CSA (0.008 mmol), MS (100 mg), toluene (0.80 mL).
* Without CSA.
ed that the benzothiazoline bearing a carboxy group 2e might function as a Brønsted acid instead of CSA. We therefore attempted to perform the reaction with 2e in the absence of CSA (entries 8 and 9). As expected, benzothiazole 6e was readily removed from the crude mixture by filtration with dichloromethane. Gratifyingly, the use of 2e accelerated the reaction remarkably and improved the yield of 3a to 98% in 0.5 hours. We also examined the utility of the Hantzsch ester (7) as a hydrogen donor in place of a benzothiazoline, but this gave 3a in low yield (entry 10). Benzothiazoline 2e was therefore found to be the most suitable hydrogen donor for the present reduction.

Having clarified the optimal reaction conditions, we investigated the substrate scope. Nitroarenes bearing electron-withdrawing groups, such as an ester, nitrile, or ketone group, gave the desired anilines 3b–d in excellent yields (Scheme 3). Bromo- and iodo(nitro)benzenes provided the corresponding anilines 3e–i in good yields, except for 2-bromo-1-nitrobenzene. 4-Methoxy and 4-(benzyloxy)-1-nitrobenzenes gave the desired anilines 3m and 3n in moderate yields, because benzylamines 4ma and 4na were also formed. The reduction was completed in 0.5 hours for all substrates. Aliphatic nitro compounds, nitrobenzenes bearing vinyl groups, and trans-β-nitrostyrene were not suitable substrates for this reduction, and the corresponding anilines were not obtained.

The present reduction of nitroarenes was applied in a tandem reaction to synthesize 2-substituted chiral quinoline derivatives (Scheme 5).11 The tandem reaction consists of (I) reduction of a 1-aryl-3-(2-nitrophenyl)propan-1-one 9, (II) imine formation by intramolecular cyclization, and (III) asymmetric reduction by a chiral phosphoric acid and a benzothiazoline.12

We optimized the reaction conditions to furnish the desired 2-arylquinolines 10a–c in good yields and with excellent enantioselectivities by the combined use of benzothiazoline 2f and chiral phosphoric acid 8 (Scheme 6).13

In summary, we have developed a reduction of nitroarenes by using a benzothiazoline in the presence of a Brønsted acid. The reduction with a benzothiazoline bearing a carboxy group was completed in a short time. Selective reduction without use of metal reagents was achieved. A tandem reaction with a chiral phosphoric acid and a benzothiazoline gave 2-aryl tetrahydroquinoline derivatives with excellent enantioselectivities.

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**Scheme 3**  **Substrate scope of nitroarenes**

We hypothesized that the reduction proceeds by a radical pathway. 2,2,6,6-Tetramethylpiperidine 1-oxyl (TEMPO) and 2,6-di-tert-butyl-4-methylphenol (BHT) were added to the reaction mixture as radical scavengers. The addition of TEMPO suppressed the reduction completely, and 96% of 1a was recovered. On the other hand, amine 3a was obtained in 85% yield when BHT was added (Scheme 4). The latter result did not agree with our hypothesis, so we are exploring other reaction pathways.

**Scheme 4**  **Mechanistic study**

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**Scheme 5**  **Tandem reaction**

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**Scheme 6**  **Tandem reaction with phosphoric acid and benzothiazoline**
Scheme 6  Asymmetric synthesis of 2-substituted quinolines

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611639.

References and Notes


(12) Shibata, Y.; Yamanaka, M. J. Org. Chem. 2013, For a theoretical study on chiral phosphoric acid-catalyzed transfer hydrogenation using a benzothiazoline, see: 78, 3731.

(13) 2-Aryl-1,2,3,4-tetrahydroquinolines 10a–c; General Procedure

Under a N2 atmosphere, a mixture of the appropriate ketone 9 (0.10 mmol), benzothiazoline 2f (0.60 mmol), chiral phosphoric acid 8 (0.010 mmol), and MS 3 Å (600 wt%, activated) in toluene (1.0 mL) was refluxed for 2 days. When the reaction was complete (TLC), it was quenched by adding sat. aq NaHCO3. The crude mixture was filtered through a Celite pad and extracted with EtOAc (×3). The organic extracts were combined, washed with brine, dried (Na2SO4), and concentrated in vacuo. The residue was purified by preparative TLC.

2-Phenyl-1,2,3,4-tetrahydroquinoline (10a)

White solid; yield: 13 mg (60%, 92% ee); mp 52–54 °C; [α]D 24 –42 (c 0.75, CHCl3). 1H NMR (400 MHz, CDCl3): δ = 1.94–2.05 (m, 1 H), 2.09–2.15 (m, 1 H), 2.74 (dt, J = 4.8, 16.4 Hz, 1 H), 2.93 (ddd J = 5.6, 10.8, 16.4 Hz, 1 H), 4.04 (br s, 1 H), 4.43 (dd, J = 3.4, 9.2 Hz, 1 H), 6.53 (d, J = 8.4 Hz, 1 H), 6.65 (l, J = 7.6 Hz, 1 H), 6.99–7.02 (m, 2 H), 7.24–7.40 (m, 5 H). 13C NMR (100 MHz, CDCl3): δ = 26.4, 31.0, 56.3, 114.0, 117.2, 120.9, 126.6, 126.9, 127.5, 128.6, 129.3, 144.7, 144.8.