Brønsted Acid Catalyzed Asymmetric Silylation of Alcohols

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Abstract We report a catalytic enantioselective desymmetrization of meso-1,2-diols by monosilylation using a chiral enantiopure Brønsted acid as catalyst and hexamethyldisilazane (HMDS) as silyl source.

Key words enantioselective Brønsted acid catalysis, silyl transfer, meso-diols, desymmetrization, asymmetric counteranion-directed catalysis (ACDC)

The silylation of alcohols is a widespread transformation in organic synthesis, typically used to introduce protecting groups. Frequently employed protocols involve basic conditions and a silyl chloride or triflate reagent. Recently, the first examples of catalytic asymmetric alcohol silylations have been described. Interestingly, these methods are based on electrophilic silicon reagents employed under basic conditions.1 Recently, the first examples of catalytic asymmetric alcohol silylations have been described.2a Interestingly, these methods are based on electrophilic silicon reagents employed under basic conditions. We were intrigued to design catalytic cycles that are based on an acidic activation of basic silicon sources, which are susceptible to proton desilylation. Here we report our studies on the Brønsted acid catalyzed desymmetrization of meso-diols using hexamethyldisilazane (HMDS) as silyl source.

The enantioselective desymmetrization of meso-diols is one of the most prominent strategies to access the corresponding monoprotected derivatives in their enantiopure form. This reaction is commonly realized by stereoselective acyl transfer reactions. However, the introduced acyl group may not always be suited as a protecting group in a given synthetic context, thus rendering further functional group transformations necessary. As an alternative, highly efficient catalytic enantioselective monosilylations of meso-diols have been developed by Hoveyda, Snapper and co-workers.2a-c In analogy to the most common protocols for the silyl protection of alcohols, which are typically carried out under basic conditions, these reactions involve the use of an enantiopure basic catalyst in combination with an achiral stoichiometric base such as Hüning's base. Despite the predominance of basic conditions for the silyl protection of alcohols, non-enantioselective protocols using acid catalysts in combination with basic silyl transfer reagents have also been developed.1,4

Based on the mechanism of this type of transformation, we hypothesized that it should be possible to render the overall process enantioselective by utilizing a chiral enantiopure Brønsted acid catalyist (Scheme 1).5 Accordingly, protonation of the basic silicon source should generate an ion pair consisting of a cationic silylium source accompanied by the enantiopure counteranion.

The reaction of this ion pair intermediate with the diol substrate could then potentially proceed enantioselectively via a desymmetrization reaction.
We began by studying several prospective silyl transfer reagents utilizing TRIP (4a) as reference catalyst (Table 1). Comparaibly non-basic silylating agents trimethylsilyl chloride (2a) and allyltrimethylsilane (2b) proved to be inefficient for product formation under the reaction conditions tested (entries 1 and 2 in Table 1). However, switching to more basic silyl transfer reagents enabled reactivity with moderate to good conversion, albeit with limited stereoinduction (entries 3–6 in Table 1). Further screening revealed HMDS (2g) and its derivatives as the most promising reagents (entries 7–10 in Table 1). We thus continued our studies with the commercially available and inexpensive HMDS as silyl source and further optimized the reaction conditions. Through these studies we identified catalyst 5 (STRIP) as best catalyst for this transformation, giving good conversion and stereoinduction in our model reaction (83% conversion and 94:6 er, entry 11 in Table 1).

**Table 1. Identification of a Suitable Silylating Agent and Catalyst**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nu-SiR&lt;sub&gt;3&lt;/sub&gt;</th>
<th>Equiv</th>
<th>Conv. (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>er&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMSCl</td>
<td>1.2</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>2a</td>
<td>1.2</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>2c</td>
<td>1.2</td>
<td>20</td>
<td>63:37</td>
</tr>
<tr>
<td>4</td>
<td>TMSCN</td>
<td>1.2</td>
<td>11</td>
<td>63:37</td>
</tr>
<tr>
<td>5</td>
<td>2e</td>
<td>0.6</td>
<td>42</td>
<td>38.5:61.5</td>
</tr>
<tr>
<td>6</td>
<td>2f</td>
<td>1.2</td>
<td>8</td>
<td>50:50</td>
</tr>
<tr>
<td>7</td>
<td>2g</td>
<td>0.6</td>
<td>78</td>
<td>81.5:18.5</td>
</tr>
<tr>
<td>8</td>
<td>2h</td>
<td>0.6</td>
<td>60</td>
<td>78:22</td>
</tr>
<tr>
<td>9</td>
<td>2i</td>
<td>0.6</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>2j</td>
<td>0.6</td>
<td>21</td>
<td>81:19</td>
</tr>
<tr>
<td>11</td>
<td>2g</td>
<td>0.6</td>
<td>83</td>
<td>94:6</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by <sup>1</sup>H NMR using 1,1,2,2-tetrachloroethane as an internal standard.

<sup>b</sup> Determined by HPLC on a chiral stationary phase.

<sup>c</sup> (S)-STRIP (5; see Table 2) was used as catalyst.

**Table 2. Substrate Scope of the STRIP-Catalyzed Desymmetrization of meso-Diols**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Time (d)</th>
<th>Yield (%)</th>
<th>er&lt;sup&gt;*&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>3a</td>
<td>3</td>
<td>84</td>
<td>95:5</td>
</tr>
<tr>
<td>2</td>
<td>4-MeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>3b</td>
<td>2</td>
<td>96</td>
<td>95:5</td>
</tr>
<tr>
<td>3</td>
<td>3-MeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>3c</td>
<td>7</td>
<td>92</td>
<td>93.5:6.5</td>
</tr>
<tr>
<td>4</td>
<td>2-MeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>3d</td>
<td>7</td>
<td>91</td>
<td>90:10</td>
</tr>
<tr>
<td>5</td>
<td>4-&lt;i&gt;i&lt;/i&gt;-PrC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>3e</td>
<td>1</td>
<td>99</td>
<td>92.5:7.5</td>
</tr>
<tr>
<td>6&lt;sup&gt;+&lt;/sup&gt;</td>
<td>4-FC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>3f</td>
<td>10</td>
<td>77</td>
<td>95:5</td>
</tr>
<tr>
<td>7</td>
<td>4-CIC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>3g</td>
<td>1</td>
<td>87</td>
<td>95.5:4.5</td>
</tr>
<tr>
<td>8</td>
<td>2-CIC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>3h</td>
<td>5</td>
<td>94</td>
<td>89:11</td>
</tr>
<tr>
<td>9</td>
<td>4-BrC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>3i</td>
<td>6</td>
<td>76</td>
<td>90.5:9.5</td>
</tr>
<tr>
<td>10</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;-</td>
<td>3j</td>
<td>7</td>
<td>99&lt;sup&gt;†&lt;/sup&gt;</td>
<td>75.5:24.5&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by HPLC on a chiral stationary phase.

<sup>b</sup> Reaction was conducted at 40 °C

<sup>c</sup> Carbon tetrachloride was used as solvent instead of cyclohexane.

<sup>d</sup> Amount of catalyst 5 used was 10 mol%.

<sup>e</sup> Compound 2h was used as a silylating reagent instead of 2g.

<sup>f</sup> Conversion determined by <sup>1</sup>H NMR using 1,1,2,2-tetrachloroethane as an internal standard.

<sup>g</sup> Determined by GC on a chiral stationary phase.
With optimal reaction conditions in hand, we continued to
study the scope of the Brønsted acid catalyzed desymmetriza-
tion of meso-diols (Table 2). The reaction turned out to
be tolerant of both electron-rich (entries 1–5 in Table 2) as
well as electron-poor (entries 6–9 in Table 2) aromatic sub-
stituents, giving moderate to good yields (76–99%) and en-
antioselectivities (89:11 to 95.5:4.5 er) in all cases. When
studying the effects of regioisomerism, we found that para-
substitution led to superior results as compared to both meta- and ortho-substitution (entries 2–4 in Table 2). Aliphatic substrates, as exemplified by cis-1,2-cyclohexane-
diol, showed good reactivity, albeit with reduced stereo-
duction (entry 10 in Table 2).

In summary, we have developed a catalytic asymmetric
desymmetrization of meso-1,2-diols by monosilylation. Our
method employs STRIP (5) as enantioselective catalyst, to-
gether with HMDS (2g) as silyl source. Moderate to good re-
results were obtained with a number of aryl-substituted
meso-diols. Further studies on the use of this type of
Brønsted acid catalyzed enantioselective silylation are cur-
rently ongoing in our laboratories.

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Supporting Information

Supporting information for this article is available online at

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(7) For further screening of reaction conditions and catalysts, see
the Supporting Information.

(8) The following procedure is representative: To a solution of cata-
lyst 5 (3.6 mg, 5.00 μmol) in cyclohexane (1.0 mL) HMDS (2g,
12.5 μL, 0.0600 mmol) was added at r.t. and the resulting
mixture was stirred for 2 h, after which, meso-diol 1a (21.4 mg,
0.100 mmol) was added. The reaction was judged to be com-
plete when the reaction mixture turned into a clear, homoge-
neous solution. The solvent was removed by evaporation and
the crude mixture was purified by silica gel column chromato-
graphy (hexane–EtOAc, 95:5), giving 3a (24.0 mg, 84%) as a color-
less solid. 1H NMR (500 MHz, CD2Cl2): δ = 7.22–7.30 (m, 10 H),
4.74 (d, J = 5.0 Hz, 1 H), 4.71 (d, J = 5.0 Hz, 1 H), 2.39 (br, 1 H),
−0.09 (s, 9 H). 13C NMR (125 MHz, CD2Cl2): δ = 141.6, 141.5,
128.3, 128.2, 128.1, 128.0, 127.9, 79.6, 78.9, 0.00. HRMS (ESI, +ve): m/z [M + Na]+, found: 309.1287; calcd for C17H22NaO2Si: 309.1281.