Dynamic kinetic asymmetric transfer hydrogenation of racemic 2,4-diaryl-2,3-dihydrobenzo[b][1,4]diazepines catalyzed by chiral phosphoric acids

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Dynamic kinetic Transfer hydrogenation reaction of 2-methyl-2,4-diaryl-2,3-dihydrobenzo[b][1,4]diazepines, using phosphoric acids as catalysts and Hantzsch ester as hydride source, has been studied. A 3,3'-H8-binol derived phosphoric acid has been identified the optimal chiral catalyst for this transformation, affording 1,3-diamine derivatives with up to 8/1 dr, 86% ee and 94% ee for the major and minor diastereomers, respectively.

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Chiral 1,3-diamines constitute core structural motifs present in natural products and bioactive substrates and serve as chiral building blocks commonly used in organic synthesis. Moreover, chiral 1,3-diamines have found widespread applications in asymmetric synthesis either as chiral auxiliaries or ligands. Synthetic approaches readily available to access these molecules include asymmetric synthesis starting with optically pure 1,3-diols, β-amino nitriles, and β-amino cyanides, and other transformations such as stereoselective ring opening of special aziridines and epoxides, kinetic resolution of racemic 1,3-diamines, and diastereoselective Mannich reactions as well. Asymmetric catalytic synthesis of chiral 1,3-diamines has been focused on 1,3-dipolar cycloaddition of hydrazines to olefins and enantioselective addition of enamides to imines.

Despite the presence of these synthetic methods, new catalytic asymmetric transformations to access optically pure 1,3-diamines are still in great demand. 2-Methyl-2,4-diaryl-2,3-dihydrobenzo[b][1,4]diazepines can be conveniently obtained from a Mannich-type reaction of o-phenylenediamines and ketones using Yb(OTf)3 as a catalyst. Enantioselective reduction of these compounds would be an attractive approach to access 1,3-diamine derivatives. We found that 2-methyl-2,4-diphenyl-2,3-dihydrobenzo[b][1,4]diazepine (1a) and its starting materials, acetophenone and o-phenylenediamine, could rapidly and reversely transform into each other as 1a reacted with p-nitroacetophenone to furnish 2-methyl-2,4-bis(4-nitrophenoxy)-2,3-dihydrobenzo [b] [1,4]diazepine (1b) and acetophenone in 80% conversion in the presence of 20 mol % of phosphoric acid 2a (Eq. 1). This finding prompted us to envision if it would be possible to initiate a dynamic kinetic asymmetric hydrogenation of 2-methyl-2,4-diaryl-2,3-dihydrobenzo[b][1,4]diazepines (1), allowing a facile synthesis of chiral 1,3-diamines bearing a quaternary stereogenic center.

Asymmetric transfer hydrogenation of prochiral imines has emerged as a valuable biomimetic method for the generation of optically active amines, which was pioneered by List, Rueping, and MacMillan, independently. List and co-workers recently described an asymmetric reductive amination of α-branched aldehydes, which proceeded with a dynamic kinetic resolution. However, the application of the biomimetic procedure to the reduction of 2,4-diaryl-2,3-dihydrobenzo[b][1,4]diazepines has not been reported. Herein, we will present our effort on the dynamic kinetic transfer hydrogenation of 2-methyl-2,4-diaryl-2,3-dihydrobenzo[b][1,4]diazepines 1 using phosphoric acids 2 and 3 as chiral catalysts, leading to the formation of 1,3-diamines 5 in high yields with good to high stereoselectivity (Fig. 1).

At the outset of this study, we evaluated structurally different chiral phosphoric acids for the transfer hydrogenation of 2-methyl-2,4-diphenyl-2,3-dihydrobenzo[b][1,4]diazepine 1a conducted in chloroform at 0 °C using ethyl Hantzsch ester 4a as a hydride source (Table 1). The phosphoric acids examined all showed high catalytic activity, each of which afforded the model reaction in high conversion, but provided different enantioselectivity for both 5a and the diastereomer 5a (entries 1–5). However, the diastereo-
mestic ratio of 5a/5a’ was seemingly independent of the catalyst structure. Interestingly, the minor diastereomer 5a’ was obtained in higher ee than the major diastereomer 5a. The substituent on the Hantzsch ester also had impact on the stereoselectivity as indicated by the transfer hydrogenation of 1a catalyzed by 2 with various Hantzsch esters (entries 5–8). In terms of enantioselectivity, the minor diastereomers were always isolated with higher enantioselectivity (79–94% ee) than the major ones (63–86% ee).

The absolute configuration of the products was assigned by X-ray analysis. The X-ray structure of 5d indicated the S configuration at C2 and the R configuration at C4 (Fig. 2).

The dynamic kinetic transfer hydrogenation could be best explained by the reaction pathway shown in Scheme 1. We proposed that the (S)-enantiomer among racemic 1a underwent a fast transfer hydrogenation under catalysis of the Brønsted acid such as 3, diastereo- and enantioselectively furnishing (2S,4R)-5a and (2S,4S)-5a, respectively, while meanwhile the (R)-1a participated in a slow transfer hydrogenation and the unhydrogenated (R)-1a rapidly racemized via the sequential retro-Mannich and Mannich reactions. The racemization was confirmed by a finding that the starting material was recovered as racemates. The racemic 1a from the racemization of (R)-1a again underwent the dynamic kinetic transfer hydrogenation following the reaction procedure as shown in Scheme 1.

In conclusion, we have disclosed a dynamic kinetic transfer hydrogenation of 2-methyl-2,4-diaryl-2,3-dihydrobenzo[b][1,4]diazepines using phosphoric acids as catalysts. This reaction provided a synthetic approach to access 1,3-diamines in high yields with good to high ee for the major diastereomers and high to excellent ee for minor diastereomers. Our next study will be focused on the improvement of the stereoselectivity.

Table 1
Evaluation of phosphoric acids and Hantzsch esters

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>R (4)</th>
<th>Time (day)</th>
<th>Conv (%)</th>
<th>dr (syn/anti)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>Et (4a)</td>
<td>3</td>
<td>93</td>
<td>2/1</td>
<td>50 (65)</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>Et (4a)</td>
<td>2</td>
<td>93</td>
<td>3/1</td>
<td>50 (59)</td>
</tr>
<tr>
<td>3</td>
<td>2c</td>
<td>Et (4a)</td>
<td>3</td>
<td>96</td>
<td>3/1</td>
<td>60 (72)</td>
</tr>
<tr>
<td>4</td>
<td>2d</td>
<td>Et (4a)</td>
<td>3</td>
<td>91</td>
<td>2/1</td>
<td>60 (77)</td>
</tr>
<tr>
<td>5</td>
<td>2c</td>
<td>Et (4a)</td>
<td>3</td>
<td>97</td>
<td>2/1</td>
<td>63 (77)</td>
</tr>
<tr>
<td>6</td>
<td>2e</td>
<td>Allyl (4b)</td>
<td>3</td>
<td>85</td>
<td>2/1</td>
<td>64 (69)</td>
</tr>
<tr>
<td>7</td>
<td>2e</td>
<td>i-Pr (4c)</td>
<td>3</td>
<td>87</td>
<td>2/1</td>
<td>57 (85)</td>
</tr>
<tr>
<td>8</td>
<td>2a</td>
<td>Allyl (4b)</td>
<td>2</td>
<td>93</td>
<td>3/1</td>
<td>66 (73)</td>
</tr>
<tr>
<td>9</td>
<td>3</td>
<td>Allyl (4b)</td>
<td>5.5</td>
<td>90</td>
<td>2/1</td>
<td>80 (78)</td>
</tr>
</tbody>
</table>

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a Unless indicated otherwise, the reaction of 1a (0.1 mmol) with a Hantzsch ester (0.23 mmol) was carried out at 0 ºC.

b Determined by 1H NMR and calculated on the basis of 1a.

c syn/anti refers to 5a/5a’ and was determined by 1H NMR.

d The ee was determined by HPLC and that in parentheses is for 5a’.

e The reaction was carried out at -10 ºC with 1.3 equiv 4b.
Table 2
Asymmetric reduction of 2-methyl-2,4-diaryl-2,3-dihydrobenzo[b][1,4]diazepines 1 catalyzed by phosphoric acid 3

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>Ar</th>
<th>Yield (%)</th>
<th>dr (syn/anti)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1c</td>
<td>4-CF₃C₆H₄</td>
<td>92</td>
<td>8/1</td>
<td>82 (85)</td>
</tr>
<tr>
<td>2</td>
<td>1d</td>
<td>4-BrC₆H₄</td>
<td>81</td>
<td>5/1</td>
<td>81 (87)</td>
</tr>
<tr>
<td>3</td>
<td>1e</td>
<td>4-ClC₆H₄</td>
<td>83</td>
<td>5/1</td>
<td>83 (86)</td>
</tr>
<tr>
<td>4</td>
<td>1f</td>
<td>4-FC₆H₄</td>
<td>89</td>
<td>5/1</td>
<td>82 (85)</td>
</tr>
<tr>
<td>5</td>
<td>1g</td>
<td>4-MeC₆H₄</td>
<td>83</td>
<td>2/1</td>
<td>84 (87)</td>
</tr>
<tr>
<td>6</td>
<td>1h</td>
<td>3-MeOC₆H₄</td>
<td>87</td>
<td>3/1</td>
<td>74 (75)</td>
</tr>
<tr>
<td>7</td>
<td>1i</td>
<td>4-PhC₆H₄</td>
<td>93</td>
<td>4/1</td>
<td>85 (94)</td>
</tr>
<tr>
<td>8</td>
<td>1j</td>
<td>2-Naphthyl</td>
<td>97</td>
<td>3/1</td>
<td>86 (92)</td>
</tr>
<tr>
<td>9</td>
<td>1k</td>
<td>3-FC₆H₄</td>
<td>84</td>
<td>4/1</td>
<td>73 (81)</td>
</tr>
<tr>
<td>10</td>
<td>1l</td>
<td>3-BrC₆H₄</td>
<td>87</td>
<td>6/1</td>
<td>63 (89)</td>
</tr>
</tbody>
</table>

a Unless indicated otherwise, the reaction of 1 (0.1 mmol) with a Hantzsch ester (0.13 mmol) was carried out at 0°C.
b Isolated overall yield of 5 and 50.
c syn/anti refers to 5/50 and was determined by 1H NMR.
d The ee was determined by HPLC and that in parentheses is for 50.

Figure 2. X-ray structure of 5d.

Scheme 1. Explanation of the dynamic kinetic transfer hydrogenation.
Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.bmcl.2009.05.039.

References and notes


10. Crystallographic data for the structure of 5d have been deposited in the Cambridge Crystallographic Data Centre (deposition number: CCDC 731486). Copies of these data can be obtained free of charge via the Internet at www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

11. The recovered 1a from the hydrogenation reaction of 1a with ethyl Hantzsch ester (4a) in 93% conversion using catalyst 2a was determined to be racemic while 5a was isolated with 43% ee.