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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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ABSTRACT

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.

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.[1,2] Moreover, chiral 1,3-diamines have found wide applications in asymmetric synthesis either as chiral auxiliaries or ligands.[3] Synthetic approaches readily available to access these molecules include asymmetric synthesis starting with optically pure 1,3-diols,[4] β-amino nitriles,[5] and β-amino cyanides[6], and other transformations such as stereoselective ring opening of special aziridines and epoxides,[7] kinetic resolution of racemic 1,3-diamines,[8] and diastereoselective Mannich reactions as well.[9] Asymmetric catalytic synthesis of chiral 1,3-diamines has been focused on 1,3-dipolar cycloaddition of hydrazones to olefins and enantioselective addition of enamides to imines.[10]

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.[11] 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-nitroiphenyl)-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.[12] List and co-workers recently described an asymmetric reductive amination of α-branched aldehydes, which proceeded with a dynamic kinetic resolution.[13] 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,[14] 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-

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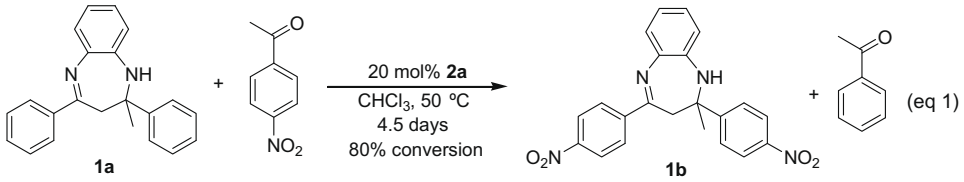
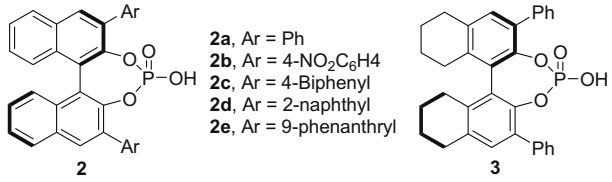


1a 1b



2 3

Figure 1. Chiral phosphoric acids evaluated in this study.

meric 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 **2e** with various Hantzsch esters (entries 5–8). In terms of enantioselectivity for **5a**, allyl Hantzsch ester **4b** turned out to be the optimal hydride source for the transfer hydrogenation (entry 6). Under the optimized conditions, the H8-binol derived phosphoric acid **3** provided the best results for the major diastereomer (entry 9).

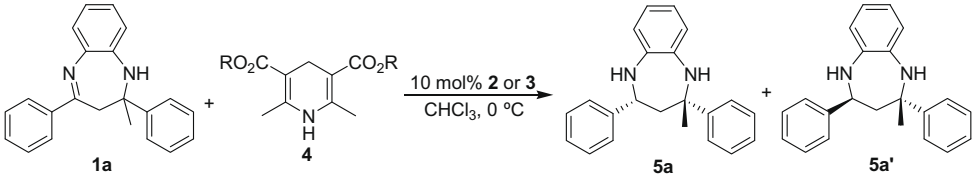
The generality of the optimal reaction conditions was examined for the dynamic kinetic transfer hydrogenation of various 2-methyl-2,4-diaryl-2,3-dihydrobenzo[*b*][1,4]diazepines (Table 2). In general, the electronically poor aryl substituent of **1** was beneficial to diastereoselectivity (entries 1–4 vs 5–6). Accordingly, the highest diastereomeric ratio of 8/1 was obtained for **1c** possessing a trifluoromethyl substituent (entry 1) while only 2/1 *dr* was observed for *para*-methyl substituted substrate **1g** (entry 5). On the contrary, the enantioselectivity did not rely on the electronic characteristic of the substituent (entries 1–4), but was influenced by the position of the same substituent in comparison of reactions involving **1d** and **1f** with those involving **1k** and **1l** (entries 2 and 4 vs entries 9–10). 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.[15] 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 (2*S*,4*R*)-**5a** and (2*S*,4*S*)-**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.[16] 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[a]

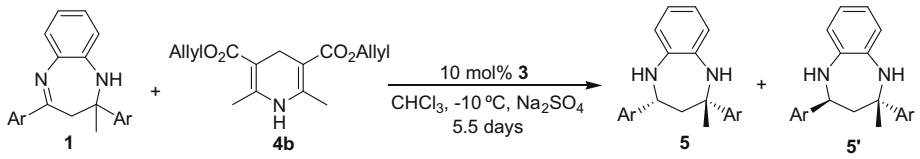


1a 4 5a 5a'

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

[a] Unless indicated otherwise, the reaction of **1a** (0.1 mmol) with a Hantzsch ester (0.23 mmol) was carried out at 0 °C.
[b] Determined by ^{1}H NMR and calculated on the basis of **1a**.
[c] *syn*/*anti* refers to **5a**/**5a**′ and was determined by ^{1}H NMR.
[d] The ee was determined by HPLC and that in parentheses is for **5a**′.
[e] The reaction was carried out at −10 °C 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**[a]



Entry	1	Ar	Yield[b] (%)	dr (*syn*/*anti*)[c]	ee[d] (%)
1	**1c**	4-$CF_3C_6H_4$	92	8/1	82 (85)
2	**1d**	4-BrC_6H_4	81	5/1	81 (87)
3	**1e**	4-ClC_6H_4	83	5/1	83 (86)
4	**1f**	4-FC_6H_4	89	5/1	82 (85)
5	**1g**	4-MeC_6H_4	63	2/1	84 (87)
6	**1h**	3-$MeOC_6H_4$	87	3/1	74 (75)
7	**1i**	4-PhC_6H_4	95	4/1	85 (94)
8	**1j**	2-Naphthyl	97	3/1	86 (92)
9	**1k**	3-FC_6H_4	84	4/1	73 (81)
10	**1l**	3-BrC_6H_4	87	6/1	63 (89)

[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 **5′**.
[c] *syn*/*anti* refers to **5**/**5′** and was determined by ^{1}H NMR.
[d] The ee was determined by HPLC and that in parentheses is for **5′**.

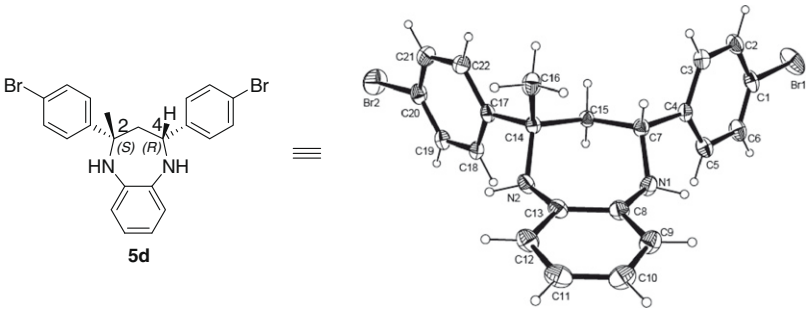
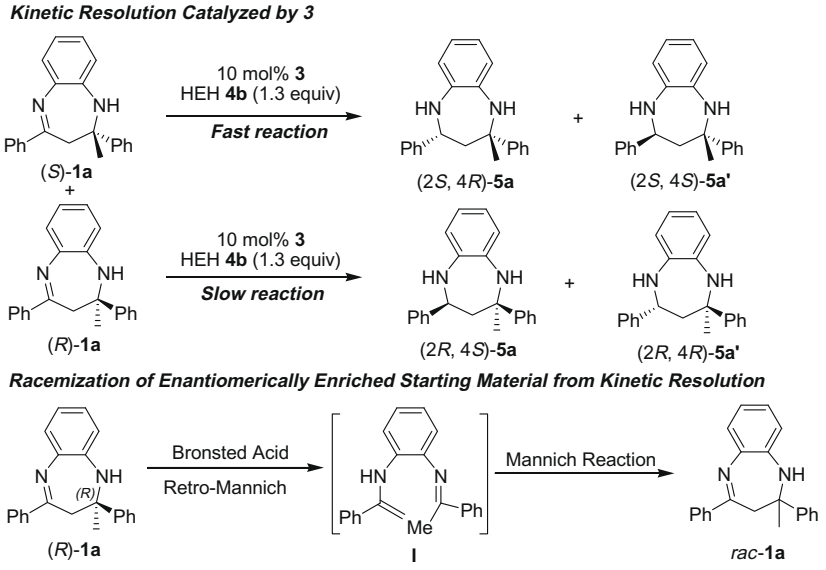


Figure 2. X-ray structure of **5d**.



Scheme 1. Explanation of the dynamic kinetic transfer hydrogenation.

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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.

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15. 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).
16. 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.