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Asymmetric Counterion Pair Catalysis: An Enantioselective Brønsted Acid-Catalyzed Protonation

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Dedicated to Prof. Dr. Andreas Pfaltz on the occasion of his 60th birthday.

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Abstract: A new asymmetric Brønsted acid-catalyzed cascade reaction involving a 1,4-addition, enantioselective protonation and 1,2-addition has been developed. This organocatalytic cascade not only provides for the first time 3- and 2,3-substituted tetrahydroquinolines and octahydroacridines in good yields with high dia- and enantioselectivities under mild reaction conditions but additionally represents the first example of a chiral Brønsted acid-catalyzed protonation reaction in an organocatalytic domino reaction. Furthermore, the new Brønsted acid-catalyzed hydride-proton-hydride transfer cascade can be applied to prepare new molecular scaffolds with up to three new stereocenters in an efficient one-pot reaction sequence.

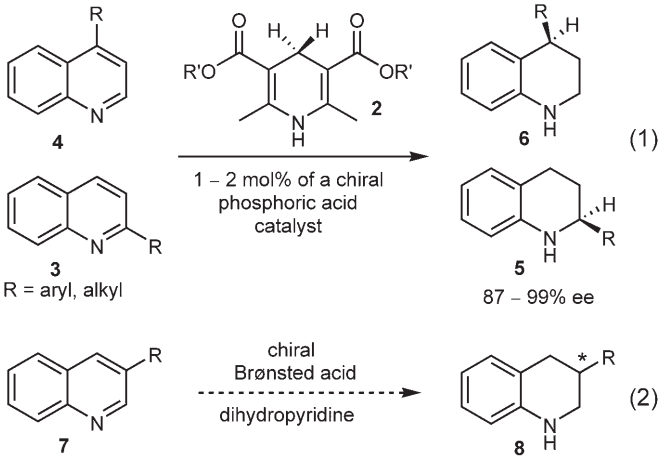
Keywords: BINOL phosphate; enantioselective isomerization; Hantzsch dihydropyridine; organocatalytic cascade reaction; transfer hydrogenation

The hydrogenation of unsaturated organic compounds, such as olefins, carbonyls, imines as well as aromatic and heteroaromatic compounds is one of the most important and utilized transformations in both academia and chemical industry.[1] Due to the constantly increasing number of optically and biologically active substances asymmetric reductions have become a central research area in enantioselective catalysis. So far, most of these enantioselective reductions rely on chiral transition metal catalysts and highly enantioselective hydrogenations of ketones, ketimines and alkenes are known.[2] However, most of these metal catalysts failed to give satisfactory results for the asymmetric hydrogenation of aromatic and heteroaromatic compounds and examples of efficient and highly selective transformations are rare.[3]

Within this context, and based on our previous work on organocatalytic transfer hydrogenations[4] we recently developed new highly enantioselective partial reductions of pyridines[5] and quinolines.[6] The corresponding products are not only of great synthetic importance in the preparation of pharmaceuticals, agrochemicals, and in materials science, but additionally many interesting alkaloid natural products contain these structural key elements.

With the newly developed enantioselective Brønsted acid-catalyzed transfer hydrogenation we were, for instance, able to reduce quinolines to the corresponding 2- or 4-substituted tetrahydroquinolines,[6] which we isolated in good yields and with excellent enantioselectivities [Scheme 1, Eq. (1)].

In this first organocatalytic transfer hydrogenation, the activation of the quinolines is achieved by a catalytic protonation through a chiral Brønsted acid which subsequently allows a cascade hydrogenation involving a 1,4-hydride addition, proton transfer and



Scheme 1. Brønsted acid-catalyzed enantioselective transfer hydrogenation of quinolines using Hantzsch dihydropyridine as the hydride source.

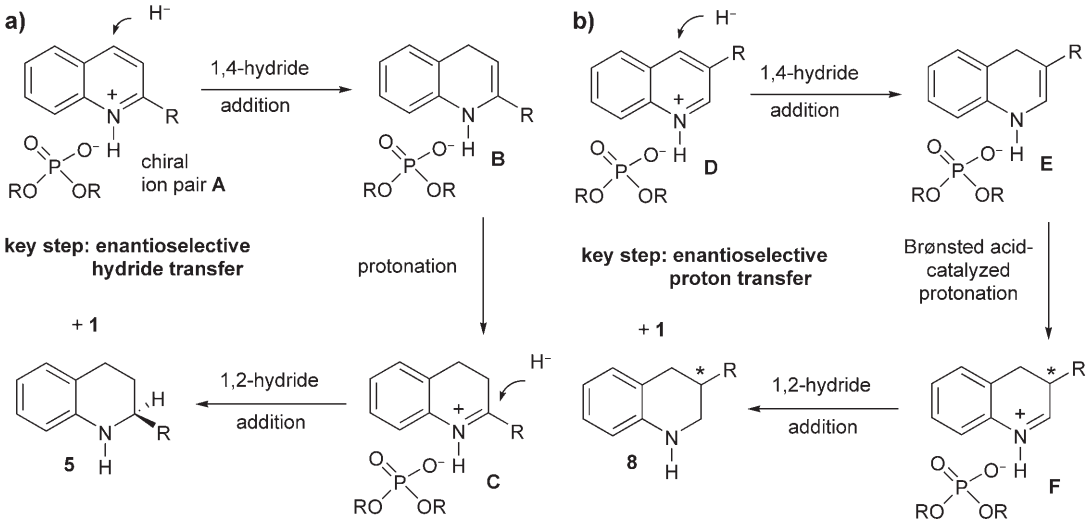


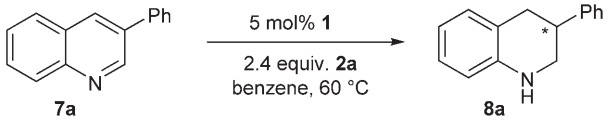
Figure 1. Key steps in the Brønsted acid catalyzed enantioselective transfer hydrogenation of 2- and 3-substituted quinolines: **a)** for 2- and 4-substituted quinolines enantioselectivity is induced by an asymmetric 1,4- or 1,2-hydride addition and **b)** in the case of 3-substituted quinolines through a new Brønsted acid catalyzed enantioselective protonation.

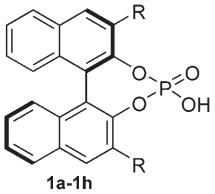
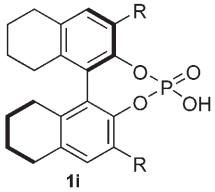
1,2 hydride addition to occur (Figure 1 a). In the first step of this enantioselective cascade a protonation of the quinoline **3** by a chiral phosphate catalyst **1** provides an intermediary chiral ion pair **A**.[4–9] This is now activated for the first hydride transfer from Hantzsch dihydropyridine **2** to the 4-position of the quinoline resulting in the formation of an enamine **B**. Subsequent Brønsted acid-catalyzed isomerization yields the iminium **C**, which is now susceptible for a second 1,2-hydride transfer to give the desired enantioenriched tetrahydroquinoline and the regenerated catalyst **1**. The mechanistic considerations of the asymmetric reduction cascade of 2- and 4-substituted quinolines illustrate that the key step in these reactions consists either of an enantioselective Brønsted acid-catalyzed 1,2- or 1,4-hydride addition (Figure 1 a). However, in case of 3-substituted quinolines the stereodetermining step in the cascade reaction must be different since both the 1,4- and 1,2-hydride addition of **D** and **F** do not provide a stereocenter (Figure 1 b). Hence, the key step of the asymmetric transfer hydrogenation of 3-substituted quinolines must be an enantioselective protonation[10] of the enamine which after 1,2-hydride addition results in the 3-substituted tetrahydroquinoline **8**.

Given the importance of tetrahydroquinolines[11] together with our recently developed transfer hydrogenations and cascade reactions we decided to examine the Brønsted acid-catalyzed enantioselective protonation within reduction of 3-substituted quinolines. This would not only be the first example of an asymmetric BINOL-phosphate-catalyzed protonation in general, but more importantly, it would for the first time provide direct access to optically active 3-substituted tetrahydroquinolines [Scheme 1, Eq. (2)].

Hence our initial investigations concentrated on the evaluation of various chiral Brønsted acid catalysts **1a–i** in the enantioselective hydride addition-protonation cascade of the 3-phenyl-substituted quinoline **7a** (Table 1). From this survey sterically more congested BINOL-phosphates, such as **1h** and **1i** emerged as the

Table 1. Chiral BINOL-phosphates in the enantioselective reduction of 3-substituted quinolines.



	Catalyst[a]	R	*ee* [%][b]
 1a-1h	**1a**	3,4,5-F-C_6H_2	7
	1b	3,5-(CF_3)-C_6H_3	10
	1c	3,5-(t-Bu),4-MeO-C_6H_2	11
	1d	4-C_6H_4-C_6H_4	10
 1i	**1e**	1-Naphthyl	14
	1f	2-Naphthyl	09
	1g	9-Phenanthryl	rac
	1h	$SiPh_3$	61
	1i	[H_8]-$SiPh_3$	**74**

[a] Reactions were performed with quinoline **7a**, **2a** (2.4 equiv.) in benzene at 60 °C with 5 mol% of catalyst **1**.

[b] Determined by HPLC analysis using a chiral stationary column.

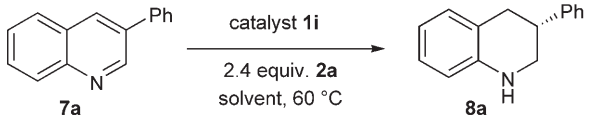
best catalysts for the enantioselective protonation process. The highest enantioselectivities were obtained with the 3,3-triphenylsilyl-substituted H_8-BINOL-phosphate **1i**, which provided the 3-phenyltetrahydroquinoline **8a** in 74% *ee*.

Further examinations focused on the solvent employed. While the reduction cascade could be performed in all solvents tested, the best selectivities were achieved in dibutyl ether (Table 2, entry 2). However, the yields were considerable lower as compared to other solvents. The best results with regard to both selectivity and reactivity were obtained in aromatic solvents (Table 2, entries 3–5). This tendency is in agreement with our earlier observations on Brønsted acid-catalyzed reactions where halogenated and aromatic solvents gave often superior selectivities.[5–8]

Next we examined the catalyst loading and solvent concentration (Table 3). While a decrease in catalyst loading resulted in lower enantioselectivities (entries 4 and 5) higher catalyst loadings (entries 1 and 2) or different solvent concentrations did not show improvements. Hence, the best enantioselection was observed if the reaction was carried out with 5 mol% of BINOL-phosphate **1i** in 0.05 M solutions of benzene.

In further experiments aiming to improve the enantioselectivities we decided to prepare different dihydropyridines **2a**–**e** and tested them in our Brønsted acid-catalyzed reduction reaction (Table 4, entries 1–5). Pleasingly, we found that the reaction proceeded with better enantiocontrol in all cases and the best selectivities of **8a** (81% *ee*) were obtained if the allyl ester **2e** was employed. Interestingly, further evaluation of the temperature revealed that better enantioselectivities were observed at higher (entries 5 and 6) as compared to lower temperatures (entries 7 and 8).

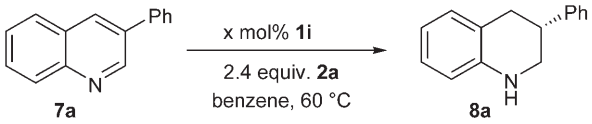
Table 2. Influence of solvent on the enantioselectivity of the protonation in the reduction cascade.



Entry[a]	Solvent	Yield [%][b]	*ee* [%][c]
1	$CHCl_3$	60	67
2	Bu_2O	34	78
3	Ph-H	89	**74**
4	Ph-CH_3	64	70
5	Ph-CF_3	85	71

[a] Reactions were performed with quinoline **7a**, Hantzsch ester **2a** (2.4 equiv) at 60 °C.
[b] Isolated yields after chromatography.
[c] Determined by HPLC analysis using a chiral stationary column.

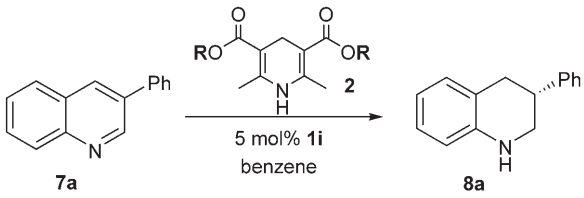
Table 3. Assessment of catalyst loading and solvent concentration.



Entry[a]	x [mol%] **1i**	M [mol/L]	*ee* [%][b]
1	20	0.05	70
2	10	0.05	71
3	05	0.05	**74**
4	02	0.05	62
5	01	0.05	41
8	05	0.033	73
9	05	0.20	70

[a] Reactions were performed with quinoline **7a**, Hantzsch ester **2a** (2.4 equiv.) at 60 °C.
[b] Determined by HPLC analysis using a chiral stationary column.

Table 4. Application of different dihydropyridines **2** and temperatures in the new Brønsted acid-catalyzed reduction cascade.

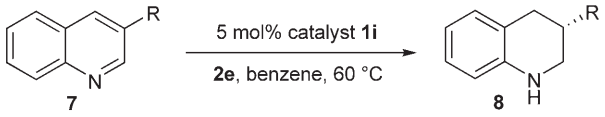


Entry[a]	R	2	*T* [°C]	*ee* [%][b]
1	ethyl	**2a**	60	74
2	isopropyl	**2b**	60	77
3	*tert*-butyl	**2c**	60	75
4	benzyl	**2d**	60	79
5	allyl	**2e**	70	79
6	allyl	**2e**	**60**	**81**
7	allyl	**2e**	50	71
8	allyl	**2e**	35	71

[a] Reactions were performed with quinoline **7a**, Hantzsch ester **2** (2.4 equiv.) and 5 mol% **1i**.
[b] Determined by HPLC analysis using a chiral stationary column.

With the optimized conditions in hand we explored the scope of the Brønsted acid-catalyzed enantioselective reduction cascade of various 3-substituted quino-

Table 5. Scope of the new Brønsted acid catalyzed enantioselective protonation in the reduction cascade.



Entry[a]	8	R	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**a**	Phenyl	48	76	84
2	**b**	4-C_6H_4-C_6H_4	22	58	82
3	**c**	3,5-(CF_3)-C_6H_3	22	30	80
4	**d**	2-Naphthyl	22	64	83
5	**e**	1-Naphthyl	22	84	77
6	**f**	3,5-(*t*-Bu)-4-OMeC_6H_2	22	35	77
7	**g**	2-F-C_6H_4	22	77	85
8	**h**	3-MeO-C_6H_4	22	67	85
9	**i**	3,5-Me-C_6H_3	48	59	80
10	**j**	2-Thiophenyl	44	50	86

[a] Reactions were performed with quinolines **7a–j**, Hantzsch ester **2e** (2.4 equiv.) and 5 mol% **1i**.
[b] Isolated yield after chromatography.
[c] Determined by HPLC analysis using a chiral stationary column.

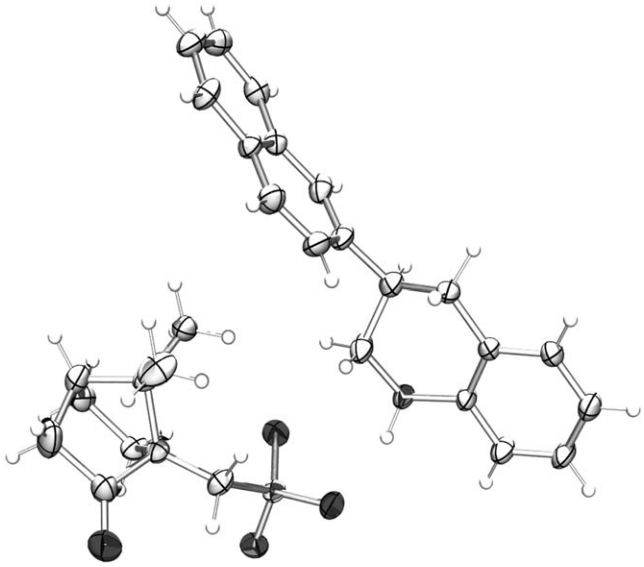
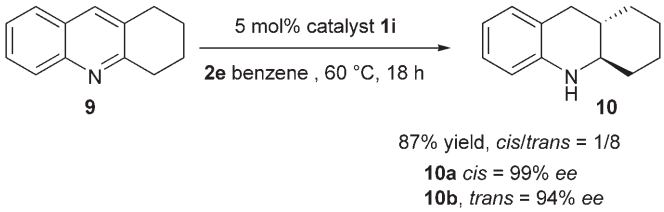


Figure 2. X-ray crystal structure of (−)-camphorsulfonic acid ammonium salt of **8d**.



Scheme 2. Brønsted acid-catalyzed enantioselective transfer hydrogenation of 2,3-substituted quinolines.

lines (Table 5). In general, high enantioselectivities and good isolated yields of several 3-aryl- and heteroaryl-substituted tetrahydroquinolines bearing either electron-donating or electron-withdrawing groups are observed.

The absolute configuration of the 3-substituted tetrahydroquinoline products was established by an X-ray crystal structure analysis of the camphorsulfonic acid ammonium salt of **8d** (Figure 2).

As a further demonstration of the utility and practicability of our newly developed Brønsted acid-catalyzed enantioselective reduction cascade we decided to additionally explore for the first time the reduction of 2,3-substituted quinolines (Scheme 2). Indeed, using the optimized reaction conditions elaborated before we were able to isolate the octahydroacridine **10** in good yield and with excellent diastereo- and enantioselectivities.[12]

In summary, we have developed an unprecedented enantioselective Brønsted acid-catalyzed transferhydrogenation of 3- and 2,3-substituted quinolines which provides the corresponding tetrahydroquinolines or octahydroacridines in good yields and with high enantioselectivities. In contrast to our earlier developed Brønsted acid-catalyzed asymmetric transfer hydrogenations of 2- and 4-substituted quinolines which proceed through an enantioselective hydride transfer as a key step, the here described reaction cascade involves a new enantioselective Brønsted acid-catalyzed proton transfer as the enantiodifferentiating step. This is not only the first example of an organocatalytic protonation in a cascade reaction but more importantly the new Brønsted acid-catalyzed hydride-proton-hydride transfer cascade can be applied to prepare new molecular scaffolds with up to three new stereocenters in a mild and efficient one-pot reaction sequence.

Experimental Section

General Procedure for Asymmetric Reduction of Quinolines

In a typical experiment the quinoline **7** (0.020 g), catalyst **1** (5 mol%) and Hantzsch dihydropyridine **2** (2.40 equiv.) were suspended at 0.05 M in benzene in a screw-capped vial. The resulting yellow solution was allowed to stir at 60 °C for 22–48 h. The solvent was evaporated under vacuum and the residue was purified by column chromatography on silica gel with toluene as eluent to afford the tetrahydroquinoline.

The yields and enantiomeric excesses are given in Table 5. Spectra and analytical data are provided in the supporting information.

Acknowledgements

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