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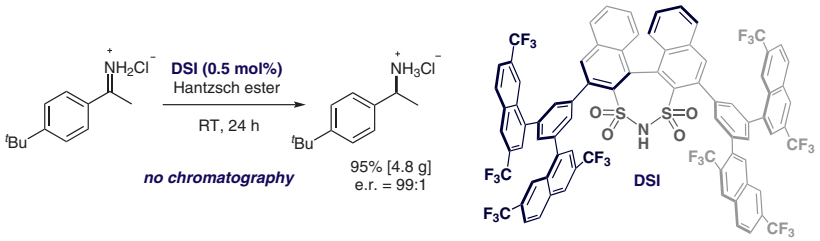
Chiral Brønsted Acids Catalyze Asymmetric Additions to Substrates that Are Already Protonated: Highly Enantioselective Disulfonimide-Catalyzed Hantzsch Ester Reductions of NH–Imine Hydrochloride Salts

Vijay N. Wakchaure
Carla Obradors
Benjamin List*

Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, 45470, Mülheim an der Ruhr, Germany
list@kofo.mpg.de



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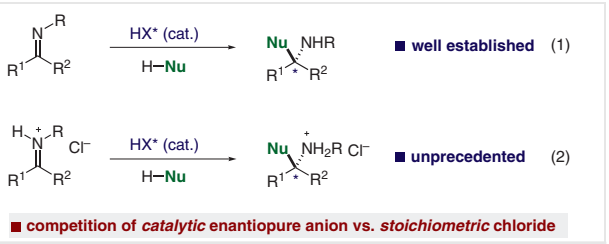
Abstract While imines are frequently used substrates in asymmetric Brønsted acid catalysis, their corresponding salts are generally considered unsuitable reaction partners. Such processes are challenging because they require the successful competition of a catalytic amount of a chiral anion with a stoichiometric amount of an achiral one. We now show that enantiopure disulfonimides enable the asymmetric reduction of N–H imine hydrochloride salts using Hantzsch esters as hydrogen source. Our scalable reaction delivers crystalline primary amine salts in great efficiency and enantioselectivity and the discovery suggests potential of this approach in other Brønsted acid catalyzed transformations of achiral iminium salts. Kinetic studies and acidity data suggest a bifunctional catalytic activation mode.

Key words Brønsted acids, N–H imine hydrochloride salt, primary amine, disulfonimide (DSI), organocatalytic reduction



Scheme 1 The challenge of using iminium salts in asymmetric Brønsted acid catalysis.

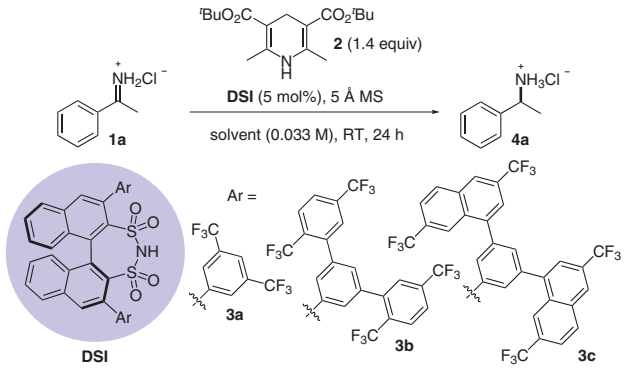
Chiral Brønsted acids are powerful organocatalysts for a great variety of asymmetric nucleophilic additions to imines (Scheme 1, eq. 1).[1] In such reactions, the imine is protonated by the chiral Brønsted acid, with the resulting chiral anion directing the enantiofacial differentiation upon attack of the nucleophile onto the iminium cation. In contrast, the use of iminium salts in asymmetric Brønsted acid catalysis has been entirely unprecedented (Scheme 1, eq. 2).

This limitation of asymmetric Brønsted acid catalysis is perhaps unsurprising because additions to such salts would require overcoming the background reactivity mediated by a stoichiometric amount of a strong achiral acid with a catalytic amount of a chiral one. Here we show that unique enantiopure disulfonimides (DSI) can be designed that catalyze highly enantioselective Hantzsch ester reductions of N–H imine hydrochloride salts.

Enantiopure, α-chiral amines represent an important pharmacophore that can be found in a vast number of biologically active substances.[2] Catalytic asymmetric imine reductions and reductive aminations of carbonyl compounds are efficient approaches toward these motifs.[3] Enantioselective Brønsted acid organocatalysis has contributed with a diverse palette of methodologies using silanes, boranes, and Hantzsch esters as the hydrogen source.[4–7] Despite these advances, such reductions have generally been limited to *N*-aryl or *N*-alkyl imines (Scheme 1, eq. 1). The asymmetric catalytic reduction of unsubstituted N–H imines would be an attractive strategy to directly furnish valuable primary amines. However, such reductions have been less studied and only very few examples appear in the literature.[8,9] A notable exception by Zhang et al. is the rhodium/bis(phosphine)thiourea-catalyzed asymmetric high-pressure hydrogenation (10 atm) of N–H imine hydrochloride salts, leading to excellent yields and enantioselectivities via anion-binding catalysis.[8a]

Our previous studies using N–H imines in Brønsted acid catalysis revealed a competitive transimination reaction of the intrinsically nucleophilic primary amine product with the starting imine. Consequently, we observed the enantioselective formation of C_2-symmetric secondary amine products, instead of the desired primary amines.[10] We speculated that if N–H imine hydrochloride salts would be used instead of the free imines, the corresponding ammonium salt products should not engage in the transimination, thereby potentially preventing the reductive dimerization. However, while anion-binding catalysis has shown utility in addition reactions to iminium salt equivalents,[11] the introduction of a stoichiometric, achiral anion (i.e., Cl^-) renders such a reaction design highly challenging, as the underlying principle of asymmetric-counteranion-directed catalysis (ACDC)[12] is undermined. Nonetheless, we speculated that a Brønsted acid catalyst stronger than HCl (pK_a = 10.3 in CH_3CN) could rapidly exchange the counterion of the N–H imine salt and overcome the background reactivity. Alternatively, a catalyst enabling a bifunctional mechanism, in which the nucleophile also interacts with the catalyst, could possibly be used to overcome the background reactivity.[13]

Table 1 Optimization of the Reaction Conditions[a]



Entry	Catalyst	Solvent	Conv. (%)[b]	e.r.[c]
1	–	MTBE	20	–
2	**3a**	MTBE	full	83.5:16.5
3	**3b**	MTBE	full	91:9
4	**3c**	MTBE	full	97.5:2.5
5	**3c**	MeCy	75	99:1
6[d]	**3c**	$CHCl_3$	full	93:7
7	**3c**	MTBE–MeCy (1:2)[f]	full	99:1
8[e]	**3c**	MTBE–MeCy (1:2)[f]	full	98.5:1.5

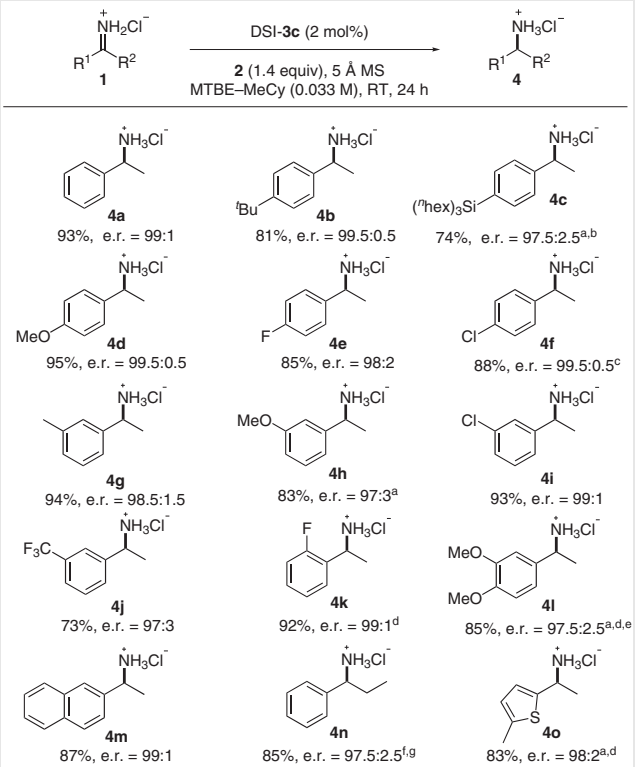
[a] Reactions were performed on a 0.03 mmol scale.
[b] Determined by GC.
[c] Determined by HPLC, see the Supporting Information.
[d] 5 h.
[e] 2 mol% of catalyst.
[f] MTBE = methyl *tert*-butyl ether; MeCy = methylcyclohexane.

We commenced our studies with the reduction of N–H imine HCl salt **1a** in the presence of Hantzsch ester **2** as the hydrogen source using catalyst DSI-**3a**[4c,10,14] (pK_a = 8.5 in CH_3CN). Remarkably, the catalyst indeed outperformed the background reactivity (20%, Table 1, entry 1), and the corresponding primary amine HCl salt **4a** was obtained with promising enantioselectivity (entry 2). A systematic catalyst development (entries 3 and 4) led to a sequential increase of the steric bulk at 3,3′-positions of the (*S*)-BINOL-derived backbone. Gratifyingly, catalyst **3c**, with the novel 3,5-bis[3,7-bis(trifluoromethyl)naphthalen-1-yl]phenyl substituent, afforded an excellent e.r. of 97.5:2.5 (entry 4). A solvent screening revealed a 1:2 mixture of MTBE–MeCy to be optimal, affording the amine HCl salt product with a high e.r. of 99:1 (entry 7). Moreover, the catalyst loading can be reduced to 2 mol% with negligible deterioration of enantioselectivity (entry 8).

The insolubility of the amine hydrochloride product in the solvent mixture allowed us to isolate it without column chromatography, but rather via a simple filtration. After completion of the reaction, the mixture was filtered through Celite and washed with a mixture of MTBE/isohexane, which removes the catalyst, excess of Hantzsch ester, and the Hantzsch ester oxidation product. In contrast, the desired amine HCl salt remains on the Celite and was collected by washing with a mixture of MeOH–CH_2Cl_2 in >99% purity (based on ^{1}H NMR). It is noteworthy that this procedure led to a slight enhancement of enantiopurity (crude e.r. = 98.5:1.5, after workup e.r. = 99:1).

With the optimized reaction conditions in hand, we next explored the scope of the enantioselective reduction of N–H imine HCl salts (Scheme 2).[15]

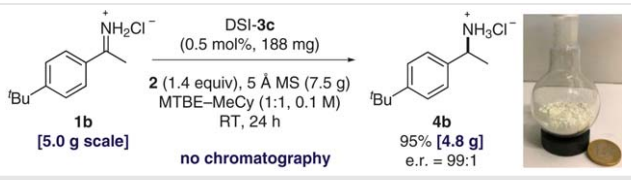
A variety of N–H imine HCl salt substrates were efficiently reduced in the presence of DSI-**3c** (2 mol%) to afford the corresponding primary amine HCl salts in good yields and with excellent enantioselectivities. N–H imine HCl salts bearing electron-donating *para* substituents are well tolerated. For example, *p*-*tert*-butyl-substituted imine HCl salt **1b** provided amine HCl salt **4b** in 81% yield and with an e.r. of 99.5:0.5. Similarly, *p*-trihexylsilyl- and *p*-methoxy-substituted iminium salts cleanly provide the products **4c** and **4d** with excellent enantioselectivity. Substrates with electron-withdrawing *para* substituents, such as fluorine or chlorine atoms, could also be used, furnishing products **4e** and **4f** with excellent enantioselectivity. Substitutions at the *meta* position are equally well tolerated and both electron-donating and electron-withdrawing groups provided the corresponding amine HCl salts in good yields and excellent enantioselectivities (products **4g–j**). *m*-Methoxy substrate (**1h**) was found to be less reactive and required 5 mol% catalyst loading. *o*-Fluoro-substituted imine HCl salt **1k** also reacted more slowly and provided amine HCl salt **4k** in 92% yield and with an e.r. of 99:1. *m*,*p*-Disubstitution led to similar results (product **4l**). 2-Naphthyl N–H imine HCl



Scheme 2 Exploration of the substrate scope. Reactions were performed on a 0.25 mmol scale. The e.r. was determined by HPLC analysis of the isolated HCl salt of amine products. [a] 5 mol% of catalyst. [b] Slower addition of imine HCl salt **1c** in MeCy, at 15 °C, 8 h. [c] 48 h. [d] 96 h. [e] Reaction was performed in MTBE–$CHCl_3$. [f] 72 h. [g] At 10 °C.

salt afforded amine HCl salt product **4m** in good yield and with an e.r. of 99:1. Interestingly, phenylethyl-substituted N–H imine HCl salt **1n** was reduced at 10 °C in 85% yield with an e.r. of 97.5:2.5. A heterocyclic substrate, thiophene derivative **1o**, efficiently underwent the reduction to afford the corresponding amine HCl salt **4o** in 83% yield and with an e.r. of 98:2.

To illustrate the practicality of our methodology, imine HCl salt **1b** was reduced on a 5 gram scale by employing only 0.5 mol% (188 mg) of DSI-**3c** to afford the desired amine HCl salt **4b** in 95% yield and with an e.r. of 99:1 without requiring column chromatography (Scheme 3). Catalyst DSI-**3c** can be recovered in 76% yield via flash column chromatography followed by acidification.



Scheme 3 Scale-up reaction with a chromatography-free protocol

Concerning the reaction mechanism, the following observations have been made: both salts **1a** and **4a** are essentially insoluble in MTBE or MeCy and our reaction generally occurs under heterogeneous conditions. However, even under completely homogeneous conditions (in $CHCl_3$), the reaction proceeds efficiently and with high enantioselectivity (e.r. = 93:7, Table 1, entry 6).[16] Furthermore, we found that the *p*-trihexylsilyl-substituted imine salt **1c** was completely soluble in MeCy and efficiently underwent the reduction with 5 mol% of DSI-**3c** with moderate enantioselectivity (e.r. = 74.5:25.5). Remarkably though, slow addition of imine salt **1c** to the reaction mixture resulted in 74% yield and an e.r. of 97.5:2.5 (Scheme 2). Apparently, slowly adding the substrate suppresses the non-enantioselective background reaction, suggesting the chiral DSI counterion to be catalytically more efficient than the chloride counterion. These results exclude the involvement of 'anionic phase-transfer catalysis', an elegant approach developed by Toste et al.[17]

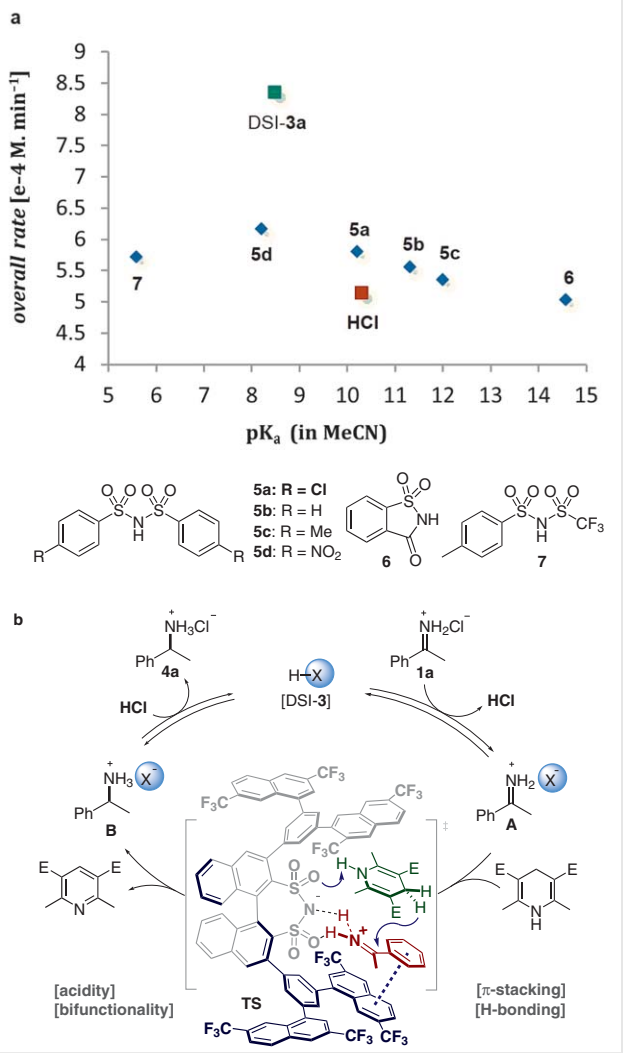
Finally, we studied the effect of the catalyst structure on the reaction rate toward rationalizing the high enantioselectivity of our methodology and proposing a reasonable overall mechanism. Monitoring the reduction of iminium salt **1a** by ^{1}H NMR in $CDCl_3$ indeed revealed a great acceleration when comparing DSI-**3a** (pK_a = 8.5) and HCl (pK_a = 10.3; Scheme 4, a). This observation is consistent with our initial hypothesis that the higher acidity of the DSI catalyst could aid in surpassing the background reactivity, providing a more efficient pathway to the enantiopure product. However, a significant increase of the reaction rate was also observed when using the less acidic and acyclic bisaryldisulfonimide **5a** as the catalyst (pK_a = 10.2). Accordingly, it is not only the acid strength but possibly also the bifunctional nature of the DSI motif that facilitates the catalytic and enantioselective pathway.[13] Indeed, a progressive increase in the pK_a slowly decreased the reaction rate from catalyst **5d** (pK_a = 8.2) to **5a** (10.2), **5b** (11.3), **5c** (12.0), and saccharin **6** (14.6).

In contrast, the more acidic aryl trifluoromethyldisulfonimide **7** (pK_a = 5.6) moderately decelerates the reaction, presumably due to an insufficient basicity of its counterion. Furthermore, cyclic catalyst DSI-**3a**, bearing aromatic 3,3′-substituents, outperforms chemically similar though acyclic catalysts such as bisaryldisulfonimide **5d** reasonably due to π-stacking interactions with the substrate, which may accelerate ion pairing and the transfer hydrogenation.

Based on these studies, we propose a catalytic cycle that is initiated by a fast counteranion exchange between imine salt **1a** and DSI-**3c**.[18] The resulting iminium ion pair **A** rapidly reacts with Hantzsch ester **2** in a bifunctional fashion (Scheme 4, b), which leads to an enantiomerically enriched primary amine salt **B** along with the corresponding Hantzsch pyridine. Subsequently, the amine salt undergoes a counterion exchange with HCl to provide product salt **4a**. A plausible transition state similar to **TS** rationalizes the

transfer of the axial chirality of catalyst DSI-**3c** to the final product. Thus, π-stacking interactions favor the aromatic substituent of the iminium ion substrate closer to the catalyst leading to the stereoselective addition of hydride to the *re*-face of the iminium ion.

In summary, we have developed an asymmetric Brønsted acid catalyzed reduction of N–H imine hydrochloride salts. The reaction is catalyzed by a disulfonimide catalyst, uses a Hantzsch ester as the hydrogen source, and provides facile access to several hydrochloride salts of primary amines in good yields and excellent enantioselectivities. Mechanistic studies suggest a bifunctional activation mode of our DSI catalyst. The use of iminium salts in asymmetric Brønsted acid catalyzed transformations suggests potential utility of our approach in many other useful processes.



Scheme 4 Mechanism. [a] Overall rate to 50% yield in the reduction of **1a** using catalysts with different pK_a (values in CH_3CN, see Supporting Information for further details). [b] Proposed catalytic cycle along with a stereochemical model of the transition state between the ion pair **A** and Hantzsch ester **2** (E = $CO_2{}^tBu$).

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1706413.

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(15) **General Procedure for the Asymmetric Reduction of N–H Imine Hydrochloride Salts**

An oven-dried 10 mL vial was charged with the hydrochloride salt of imine **1** (0.25 mmol), Hantzsch ester **2** (108.3 mg, 0.35 mmol, 1.4 equiv), disulfonimide DSI-**3c**, freshly activated MS 5Å (250 mg), and a magnetic stirring bar at RT. Then 7.5 mL (0.033 M) of MTBE–MeCy (MTBE–$CHCl_3$ in case of **1l**) was added under an argon atmosphere. The mixture was then subjected to the appropriate reaction time and temperature. The reaction mixture was filtered over Celite, washed with isohexane (40 mL), and isohexane–MTBE (1:1, 40 mL) to remove the neutral compounds. The hydrochloride salt of the desired amine product **4** was then collected in >99% purity (by ^{1}H NMR analysis) by washing with 3% MeOH in CH_2Cl_2 (60 mL) and evaporating the filtrate under reduced pressure. The enantiomeric ratio of products **4** was determined by HPLC after benzoylation following a standard procedure. Crude enantiomeric ratios were determined after subjecting the reaction mixture with sat. $NaHCO_3$ solution, extracting the free amine product with MTBE, followed by benzoylation and HPLC analysis.

(*S*)-1-[4-(*tert*-Butyl)phenyl]ethan-1-aminium Chloride (4b)

Prepared according to the general procedure using DSI-**3c** (7.98 mg, 2.0 mol%, 0.02 equiv) in MTBE–MeCy (1:1) at RT for 24 h and obtained as colorless solid (43.25 mg, 81%, e.r. = 99.5:0.5, crude reaction e.r. = 99.5:0.5). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.58 (br s, 3 H), 7.46–7.27 (m, 4 H), 4.30–4.20 (m, 1 H), 1.55 (d,

J = 6.8 Hz, 3 H), 1.21 (s, 9 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 151.8, 135.4, 126.8, 126.0, 51.5, 34.7, 31.4, 20.8. HRMS (ESI): *m/z* calcd for $C_{12}H_{20}N$ [M – Cl]$^+$: 178.159060; found: 178.159024. The enantiomeric ratio was determined by derivatization to the corresponding benzamide by HPLC analysis using Daicel Chiralpak OD-3, *n*-heptane–IPA = 80:20, flow rate = 1.0 mL/min, 25 °C, λ = 220 nm, t_R = 3.13 min (minor) and t_R = 4.60 min (major). $[\alpha]_D^{25}$ –16.0° (*c* 0.63, CH_2Cl_2).

(16) Additionally, when imine salt **1a** was dissolved in $CHCl_3$ and filtered through an HPLC filter to ensure complete absence of insoluble salt, reduction under completely homogeneous conditions proceeded efficiently and with high enantioselectivity (e.r. = 93:7).
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(18) See the Supporting Information for NMR studies on the speciation of the catalyst with the substrates and the products under the reaction conditions.