

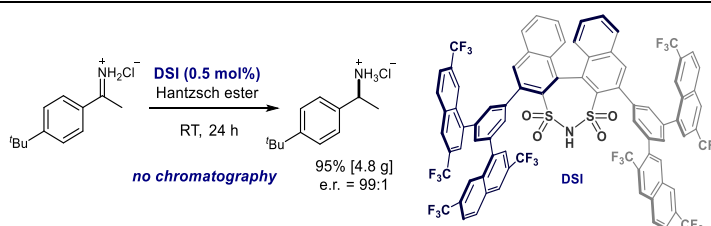


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Chiral Brønsted Acids Catalyze Asymmetric Additions to Substrates that are Already Protonated: Highly Enantioselective Disulfonimide Catalyzed Hantzsch Ester Reductions of NH–Imine Hydrochloride Salts

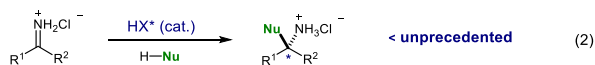
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Abstract While imines are frequently used substrates in asymmetric Brønsted acid catalysis, their corresponding salts are generally considered unsuitable reaction partners. Such processes are challenging because they require the successful competition 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.

Chiral Brønsted acids are powerful organocatalysts for a great variety of asymmetric nucleophilic additions to imines (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 (eq 2).



< competition of catalytic enantiopure anion vs. stoichiometric chloride

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 (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 C2-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 CH₃CN) 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	cat	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	Full	99:1
8 ^e	3c	MTBE:MeCy 1:2	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 SI.

^d 5 h.

^e 2 mol% of catalyst. 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 CH₃CN). 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 3–4) 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)phenylsubstituent, 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 enantiomeric ratio 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/*iso*-hexane, 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/CH₂Cl₂ in >99% purity (based on ¹H 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 (Table 2).¹⁵

Table 2 Exploration of the substrate scope^a

4a 93%, e.r. = 99:1	4b 81%, e.r. = 99.5:0.5	4c 74%, e.r. = 97.5:2.5 ^{b,c}
4d 95%, e.r. = 99.5:0.5	4e 85%, e.r. = 98:2	4f 88%, e.r. = 99.5:0.5 ^d
4g 94%, e.r. = 98.5:1.5	4h 83%, e.r. = 97:3 ^b	4i 93%, e.r. = 99:1
4j 73%, e.r. = 97:3	4k 92%, e.r. = 99:1 ^e	4l 85%, e.r. = 97.5:2.5 ^{b,e,f}
4m 87%, e.r. = 99:1	4n 85%, e.r. = 97.5:2.5 ^{g,h}	4o 83%, e.r. = 98:2 ^{b,e}

^a 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.

^b 5 mol% of catalyst.

^c Slower addition of imine HCl salt **1c** in MeCy, at 15 °C, 8 h.

^d 48 h.

^e 96 h.

^f Reaction was performed in MTBE:CHCl₃.

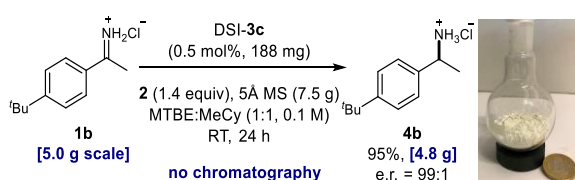
^g 72 h.

^h At 10 °C.

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–4j**). *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 salt afforded amine HCl salt product **4m** in good yield and with an e.r. of 99:1. Interestingly, phenyl ethyl-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 1). Catalyst DSI-**3c** can be recovered in 76% yield via flash column chromatography followed by acidification.



Scheme 1 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 (Table 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 ^1H NMR in CDCl_3 indeed revealed a great acceleration when comparing DSI-**3a** ($pK_a = 8.5$) and HCl ($pK_a = 10.3$) (Figure 1a). 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 bis-aryldisulfonimide **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).

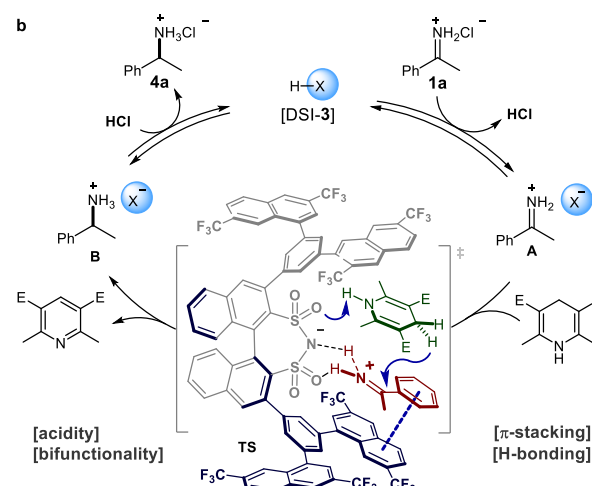
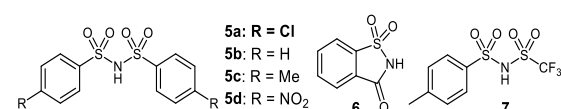
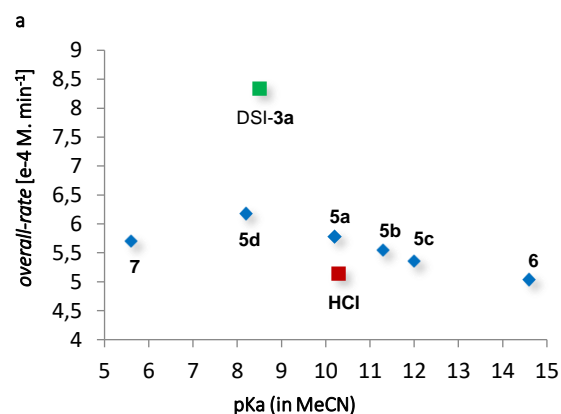


Figure 1 Mechanism. ^a Overall rate to 50% yield in the reduction of **1a** using catalysts with a pK_a (values in CH_3CN , see SI for further details). ^b Proposed catalytic cycle along with a stereochemical model of the transition state between the ion pair **A** and Hantzsch ester **2** ($\text{R} = \text{CO}_2^t\text{Bu}$)

In contrast, the more acidic aryl trifluoromethylidisulfonimide **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 bis-aryldisulfonimide **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 (Figure 1b), 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.

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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 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 molecular sieve 5Å (250 mg) and a magnetic stirring bar at RT. Then 7.5 mL (0.033 M) of MTBE:MeCy (in the case of **11** used MTBE:CHCl₃) was added under argon atmosphere. The mixture was then introduced to the desired temperature for the reaction. The reaction mixture was filtered over Celite, washed with *iso*-hexane (40 mL), and *iso*-hexane:MTBE (1:1, 40 mL) to remove the neutral compounds, followed by the hydrochloride salt of amine product was collected by washing with 3% MeOH in CH₂Cl₂ (60 mL) and the filtrate was evaporated under reduced pressure to afford the desired hydrochloride salt of amine products **4** in >99% purity (by ¹H NMR). The hydrochloride salt of amine product **4** (0.01 mmol) was benzoylated following a standard procedure to determine the enantiomeric ratio by HPLC.
- To determine the crude reaction enantiomeric ratio, following the general procedure using hydrochloride salt of imine **1** (0.03 mmol scale), the reaction was quenched with sat. NaHCO₃ solution and the amine product was extracted with MTBE and benzoylated following a standard procedure.
- (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 white solid (43.25 mg, 81%, e.r. = 99.5:0.5, crude reaction e.r. = 99.5:0.5). ¹H NMR (500 MHz, CDCl₃): δ 8.58 (bs, 3H), 7.46–7.27 (m, 4H), 4.30–4.20 (m, 1H), 1.55 (d, *J* = 6.8 Hz, 3H), 1.21 (s, 9H). ¹³C NMR (126 MHz, CDCl₃): δ 151.8, 135.4, 126.8, 126.0, 51.5, 34.7, 31.4, 20.8. HRMS (ESI) calculated for C₁₂H₂₀N [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). [α]_D²⁵ = –16.0° (*c* 0.63, CH₂Cl₂).
- (16) Additionally, when imine salt **1a** was dissolved in CHCl₃ 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).
- (17) (a) Nelson, H. M.; Patel, J. S.; Shunatona, H. P.; Toste, F. D. *Chem. Sci.* **2015**, *6*, 170. (b) Phipps, R. J.; Hamilton, G. L.; Toste, F. D. *Nat. Chem.* **2012**, *4*, 603.
- (18) See SI for NMR studies on the speciation of the catalyst with the substrates and the products under the reaction conditions.