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-Park 1, 45470, Mülheim an der Ruhr, Germany
list@kofo.mpg.de

Received: 19.06.2020
Accepted after revision: 13.07.2020
Published online: 14.08.2020
DOI: 10.1055/s-0040-1706413; Art ID: st-2020-r0356-l

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 (DSI) 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

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 transamination 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. 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 transamination, thereby potentially preventing the reductive dimerization. However, while anion-binding catalysis has shown utility in the synthesis of secondary amines,10 we expected that if N–H imine hydrochloride salts would be used instead of the free imines, the corresponding ammonium salts should not engage in the transamination, thereby potentially preventing the reductive dimerization. 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.14 (pK_a = 8.5 in CH_2CN). 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 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 (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-triethylsilyl- 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).

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.14 (pK_a = 8.5 in CH_2CN). 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 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 (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-triethylsilyl- 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

---

Table 1 Optimization of the Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Conv. (%)</th>
<th>e.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>MTBE</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>3a</td>
<td>MTBE</td>
<td>83.5:16.5</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3b</td>
<td>MTBE</td>
<td>91:9</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3c</td>
<td>MTBE</td>
<td>97.5:2.5</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3c</td>
<td>MeCy</td>
<td>75</td>
<td>99:1</td>
</tr>
<tr>
<td>6</td>
<td>3c</td>
<td>CHCl_3</td>
<td>93:7</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>3c</td>
<td>MTBE–MeCy (1:2)</td>
<td>99:1</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>3c</td>
<td>MTBE–MeCy (1:2)</td>
<td>98.5:1.5</td>
<td></td>
</tr>
</tbody>
</table>

*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.
salt afforded amine HCl salt product 4m in good yield and with an e.r. of 99:1. Interestingly, phenylthethyl-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 3c with an e.r. of 99:1. Interestingly, phenylethyl-substituted saccharin 3a 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 1H NMR in CDCl3 indeed revealed a great acceleration when comparing DSI-3a (pKₐ = 8.5) and HCl (pKₐ = 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 bisaryl disulfonimide 5a as the catalyst (pKₐ = 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 pKₐ slowly decreased the reaction rate from catalyst 5d (pKₐ = 8.2) to 5a (10.2), 5b (11.3), 5c (12.0), and saccharin 6 (14.6).

In contrast, the more acidic aryl trifluoromethyl disulfonimide 7 (pKₐ = 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 bisaryl disulfonimide 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
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.

Funding Information

Generous support from the Max-Planck-Gesellschaft, the Deutsche Forschungsgemeinschaft (Leibniz Award to B.L. and Cluster of Excellence RESOLV, Grant No. EXC 1069), and the European Research Council (Advanced Grant ‘C-H Acids for Organic Synthesis, CHAOS’) are gratefully acknowledged. C.O. also acknowledges Alexander von Humboldt Foundation and Bayer Science & Education Foundation for the Humboldt-Bayer Fellowship for Postdoctoral Researchers.

Acknowledgment

We thank the technicians of our group, and the MS, GC, HPLC, and NMR groups of the Max-Planck-Institut für Kohlenforschung, especially J. Lingnau for their excellent service. Finally, we gratefully acknowledge our lab colleagues for their suggestions via internal Crowd Reviewing, especially J. L. Kennemur.

Supporting Information

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

References and Notes


(5) For selected examples of other organocatalytic asymmetric imine reductions and reductive aminations, see: (a) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. J. Am. Chem. Soc. 2006,


(11) Reactions involving the use of dynamic kinetic resolution, see: (a) Malkov, A. V.; Stonikov, P. R. Angew. Chem. Int. Ed. 2016, 55, 15775.


$J = 6.8 \text{ Hz, } 3 \text{ H})$, 1.21 (s, 9 H). $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta = 151.8, 135.4, 126.8, 126.0, 51.5, 34.7, 31.4, 20.8$. HRMS (ESI): m/z calcd for C$_8$H$_{16}$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, $\lambda = 220$ nm, $t_{R} = 3.13$ min (minor) and $t_{R} = 4.60$ min (major). [D]$_{25}^{25} = 16.0^\circ$ ($c 0.63, \text{CH}_2\text{Cl}_2$).

(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).


(18) See the Supporting Information for NMR studies on the speciation of the catalyst with the substrates and the products under the reaction conditions.