Bifunctional Asymmetric Catalysis with Hydrogen Chloride: Enantioselective Ring Opening of Aziridines Catalyzed by a Phosphinothiourea

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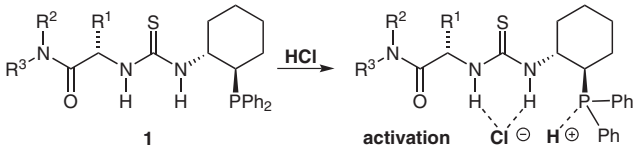
Abstract: Ring opening of aziridines with hydrogen chloride to form β-chloroamine derivatives is catalyzed by a chiral phosphinothiourea derivative in high yields and with high enantioselectivities. On the basis of ^{31}P NMR studies, activation of HCl appears to proceed via quantitative protonation of the catalyst to afford a phosphonium chloride complex.

Key words: asymmetric catalysis, halogenation, ring opening, carbocations, aziridines

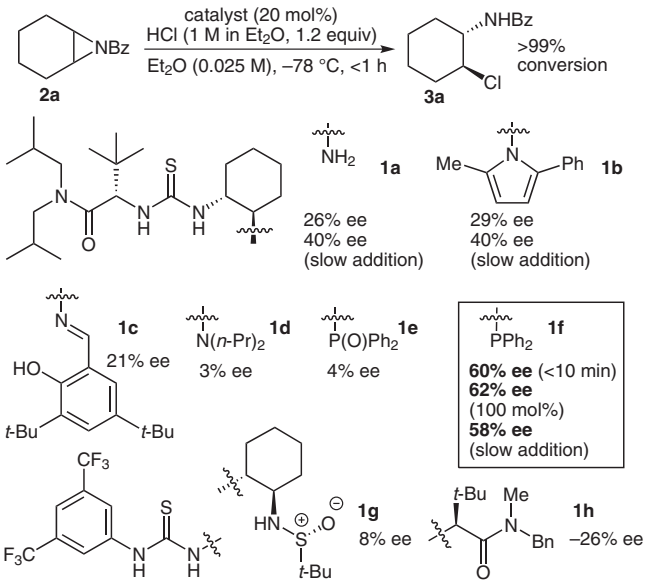
Hydrogen chloride (HCl) is a commodity chemical used in many industrial processes.[1] HCl is also a convenient and inexpensive reagent for use in laboratory-scale chemical synthesis, such as for the hydrochlorination of carbon–carbon double[2] and triple[3] bonds. However, its utility in catalytic enantioselective transformations has thus far been limited.[4] Indeed, few of the common chiral catalysts are likely to be compatible with HCl given its extremely high acidity.[5]



Scheme 1 Proposed activation mode of HCl by catalyst **1**

Over the past several years, chiral thioureas have emerged as a useful class of catalysts for a broad range of asymmetric transformations.[6] We discovered recently that chiral thiourea derivatives catalyze enantioselective additions to *N*-acyliminium/chloride ion pairs[7a–c] and α-chloro ethers.[7d] These observations have led to the proposal that thiourea catalysts engage these weakly basic electrophiles by an anion-abstraction mechanism that involves a thiourea chloride hydrogen-bonding interaction.[7b] We have found that urea and thiourea catalysts are stable to strong mineral acids,[8] suggesting that these catalysts might be amenable to productive activation of HCl. In particular, we considered the possibility that a bifunctional chiral catalyst[9] containing a basic group could undergo protonation by HCl with binding of the chloride counterion to the thiourea (Scheme 1), thereby activating the molecule to additions to polar organic electrophiles. Although many Lewis or Brønsted basic functional groups are expected to be protonated by HCl, the weak basicity of phosphines (Ph_2CyP^+H: $pK_a = 5.1$ in H_2O),[10] suggested that chiral phosphinothiourea catalysts such as **1**, originally developed in our laboratory for the [3+2] cycloaddition of allenes with imines,[11] might be particularly effective in the context of productive HCl activation. Herein, we report the use of chiral phosphinothioureas to catalyze the catalytic enantioselective addition of HCl to *N*-acylaziridines.[12]

Enantioselective desymmetrization of *meso*-epoxides with various chloride sources is a well-studied method for the preparation of optically active chlorohydrins, and many examples using stoichiometric promoters[13] as well as chiral catalysts[14] have both been reported. Interestingly, the direct use of HCl for the enantioselective variant of this transformation has not been reported.[15] In pioneering studies, Denmark reported that Lewis basic, chiral phosphoramides catalyze enantioselective opening of *meso*-epoxides with $SiCl_4$.[14a] Under the reaction conditions developed by Denmark, HCl mediates competitive, unselective epoxide ring opening, and careful distillation of $SiCl_4$ was necessary to ensure that reproducible enantioselectivity was obtained. HCl is also very reactive towards aziridines in the absence of any promoters,[16] suggesting that a



Scheme 2 Screen of thiourea catalysts

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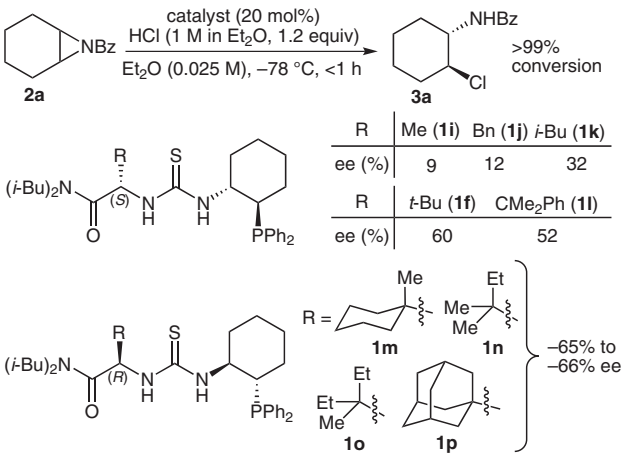
control over background reaction is necessary for achieving efficient asymmetric catalysis.

We began our study by investigating different thiourea catalysts using benzoyl protected aziridine **2a** as a model substrate (Scheme 2).[17] In the absence of a chiral catalyst, hydrochlorination of **2a** is complete within 30 minutes, even under relatively dilute reaction conditions and low temperatures (0.025 M, –78 °C), indicating that acceleration of a catalytic pathway and/or suppression of background reactivity would be necessary in order to achieve high enantioselectivities. 1,2-Diaminocyclohexane-derived catalysts **1a–d** (20 mol%) promoted formation of product **3a** with very modest enantioselectivities (3–29% ee). Slow addition of HCl (0.25 M in Et_2O) over 110 minutes led only to minor improvements (up to 40% ee for both catalysts **1a** and **1b**), suggesting that background reactivity was only partially responsible for the low ee. While phosphine oxide catalyst **1e** as well as thioureas **1g** and **1h** also led to product formation with poor enantioselectivity, phosphinothiourea catalyst **1f** promoted hydrochlorination of **2a** within 10 minutes in 60% ee.[18] In this case, neither slow addition of HCl nor increased catalyst loading had any beneficial effect on enantioselectivity, suggesting that the catalytic pathway was significantly more rapid than the background reaction. This hypothesis was confirmed by in situ IR spectroscopic experiments with cycloheptene-derived aziridine **2c**: in these studies, the initial reaction rate of hydrochlorination with catalyst **1f** (20 mol% at –40 °C) was measured to be 140 times greater than in the absence of catalyst.

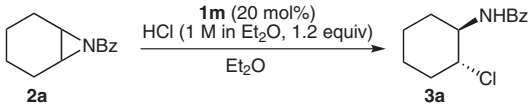


Scheme 3 Optimization of the amino acid component of the catalyst

The α-amino acid component of catalyst **1** was varied systematically in an effort to improve the enantioselectivity in the model reaction (Scheme 3). It was found that ee were responsive to increasing steric demand of the α-substituent (catalysts **1i–f**). Accordingly, highly hindered unnatural amino acids were prepared, taking advantage of recently developed thiourea-catalyzed asymmetric Strecker methodology,[19] and incorporated into the new set of phosphinothiourea derivatives **1m–p**. A measurable improvement in ee was observed with these more hindered catalysts. The amino acid used for the preparation of catalyst **1m** is readily accessible in optically pure form,[20] so **1m** was selected as the preferred catalyst for further study.

Absolute concentration has proven to be an important parameter in thiourea-catalyzed reactions, with improvements in both enantioselectivity and rate resulting in certain cases from increased dilution.[2b,21] This proved to be the case in the aziridine hydrochlorination reaction as well, with highest enantioselectivities obtained under highly dilute conditions (0.0025 M, compare entries 1–3, Table 1). However, further dilution led to significant decreases in reaction rate, necessitating higher reaction temperatures in order to achieve high conversion at the expense of ee (entries 5 and 6). Given that the racemic uncatalyzed reaction is not competitive with the catalytic pathway (entry 4),[22] it appears that the increased enantioselectivity obtained at low concentrations may be ascribed to the existence competing catalyzed pathways of varying kinetic order in catalyst and/or reactants.

Table 1 Concentration Effect

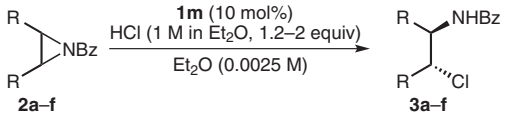


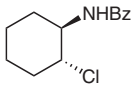
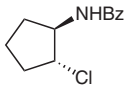
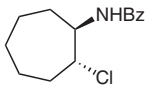
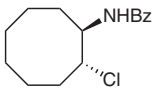
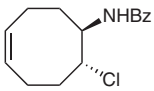
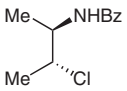
Entry	Concn (M)	Temp (°C)	Time (h)	Conv. (%)	ee (%)[a]
1	0.1	–78	<0.5	>99	35
2	0.025	–78	<0.5	>99	65
3	0.0025	–78	4	>99	81
4[b]	0.0025	–78	2	<5	–
5	0.0010	–78 to –50	3/62	99	65
6	0.0005	–78 to –50	2/45	66	59

[a] The ee values were determined by chiral HPLC analysis.
[b] Background reaction carried out in the absence of catalyst **1m**.

The optimal conditions were successfully applied to a variety of aziridines to provide β-chloroamine products with high yields and good enantioselectivities with 10–20 mol% catalyst loadings (Table 2). Cyclooctene-derived substrate **2d** (entry 4) was unreactive under highly dilute conditions (0.0025 M), but efficient hydrochlorination of this challenging substrate could be achieved at higher concentrations (0.025 M). The scope of enantioselective hydrochlorinations catalyzed by **1m** is noteworthy given that Lewis base catalyzed variants of this reaction generally afford only modest ee with cyclic substrates.[14]

Table 2 Substrate Scope



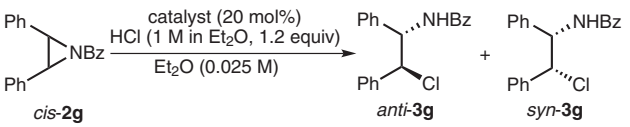
Entry	Product	Temp (°C)	Time (h)	Yield (%)[a]	ee (%)[b]
1	 **3a**	–78	4	97	83
2	 **3b**	–78	6	99	78
3[c]	 **3c**	–78 to –50	19	96	90
4[c,d]	 **3d**	–78 to –50	84	91	84
5[c]	 **3e**	–78 to –50	13	94	92
6	 **3f**	–78	1	96	70

[a] Isolated yield.
[b] Determined by chiral HPLC analysis.
[c] 20 mol% of catalyst was used.
[d] Reaction was conducted on 0.025 M.

cis-Stilbene-derived aziridine **2g** also underwent the ring opening in the presence of phosphinothiourea catalyst in reactions carried at 0.025 M (Table 3). Uncatalyzed openings of **2g** lead to mixtures of diastereomeric products, with the ratio dependent on the chloride source used: $SiCl_4$ leads to selective formation of *syn*-**3g**,[23] the result of retentive ring opening (entry 1). In contrast, HCl provides 1:1 mixture of *anti* and *syn* products (entry 2). Interestingly, *anti*-**3g**[23] was obtained in high diastereo- and enantioselectivity (up to 90% ee) in reactions promoted by chiral phosphinothiourea catalysts **1f** and **1m** (entries 4 and 5). The observation of predominantly invertive ring opening suggests an S_N2-type pathway in the catalytic reaction. Other chiral thiourea derivatives **1a** and **1h** provided lower levels of selectivity (entries 6 and 7), indicating that a bifunctional phosphinothiourea catalyst was important for this substrate as well.

The absolute configuration of **3a** (71% ee) prepared using **1f** was determined by conversion into the known *cis*-amino alcohol **5**[24] in two steps (Scheme 4).

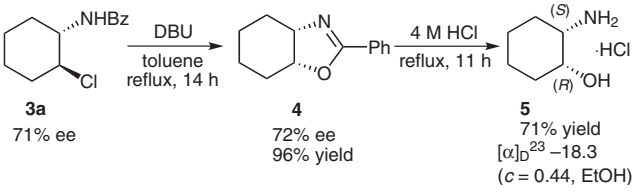
Table 3 Hydrochlorination of *cis*-Stilbene-Derived Aziridine **2g**



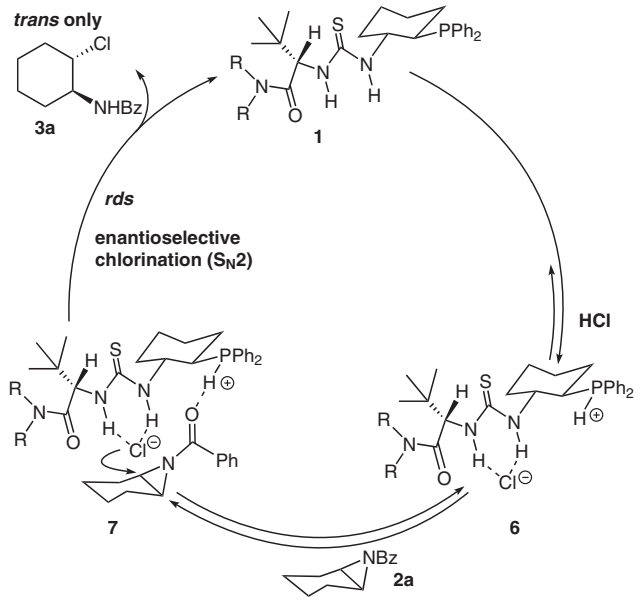
Entry	Catalyst	Temp (°C)	Time (h)	Conv. (%)	Ratio (*anti*/*syn*)[a]	ee of *anti* (%)[b]
1[c]	–	–30	1	>99	18:82	–
2	–	–78 to r.t.	19	>99	48:52	–
3	**1f**	r.t.	2	>99	74:26	50
4	**1f**	–78 to –30	20	92	94:6	90[d]
5[e]	**1m**	–78 to –30	46	>99 (85[f])	93:7	–89[d]
6	**1a**	–30	67	95	62:38	39
7	**1h**	–30	24	ca. 80	39:61	–30

[a] Diastereomeric ratios were determined by integration of ^{1}H NMR resonances.
[b] The ee values were determined by chiral HPLC analysis.
[c] $SiCl_4$ in CH_2Cl_2 was used as the chloride source.
[d] Compound *syn*-**3g** is unstable to silica gel column chromatography and undergoes cyclization to the corresponding *trans*-oxazoline. The ee was determined to be 21% with catalyst **1f** and –21% with catalyst **1m**.
[e] $[cis\text{-}\mathbf{2g}]_0$ = 0.01 M. No reaction was observed under more dilute conditions.
[f] Isolated yield of *anti*-**3g**.

In order to glean insight into the mechanism of the phosphinothiourea-catalyzed additions of HCl to aziridines, we undertook ^{31}P NMR studies of the interaction of catalyst **1f** with HCl. An anhydrous, ethereal solution of **1f** was cooled to –78 °C, and excess HCl in Et_2O (10 equiv) was added dropwise via syringe. The solution became cloudy immediately, and was stirred for 30 minutes at –78 °C. Solvent removal by gradual evaporation under reduced pressure at low temperature (–78 °C to ca. –30 °C) afforded a white solid. Analysis of this material as a $CDCl_3$ solution by ^{31}P NMR spectroscopy revealed a single resonance (δ = 4.6 ppm, J_{P-H} = 508 Hz) distinct from that of **1f** (δ = –8.0 ppm). The chemical shift and P–H coupling constant are similar to those of previously characterized protonated phosphines.[25,26] Enantioselective hydrochlorination of **2a** (0.0025 M) using the solid, protonated species without added HCl gave the ring-opened product **3a** quantitatively within one hour in 70% ee,[27] comparable to the enantioselectivity obtained under catalytic conditions (77% ee). On the basis of these results, it appears that catalytic hydrochlorinations of benzoyl azi-



Scheme 4 Determination of absolute configuration



Scheme 5 Proposed catalytic cycle for aliphatic aziridine **2a**

ridines such as **2a** catalyzed by phosphinothioureas may involve initial heterolysis of HCl to afford a phosphonium chloride complex as depicted in Scheme 1.

A proposed catalytic cycle for the ring opening of aziridine **2a** is provided in Scheme 5. Aliphatic aziridines **2a**–**f** undergo ring opening exclusively with inversion of stereochemistry to provide *trans*-addition products **3a**–**f**. Rates of invertive ring openings of epoxides and aziridines derived from medium-ring cyclic alkenes are typically highly sensitive to the steric environment defined by the ring.[28] This is observed in the present case as well, with reactions of five- and six-membered-ring substrates **2a** and **2b** being considerably more rapid than those of seven- and eight-membered substrates **2c** and **2d**. The reactivity profiles and the observation of exclusive formation of *trans* products points to an S_N2-type mechanism (Scheme 5). We propose that HCl–**1** complex **6** is generated in the first step, and that the phosphonium ion serves to activate substrate **2a** by a general acid mechanism. Chloride addition is suggested to occur from the thiourea-bound complex, resulting in a highly ordered enantiodetermining step. Although stilbene-derived aziridines are generally more prone to S_N1-type pathways, the observation of high enantioselectivity and in the predominant invertive pathway suggests a common S_N2 mechanism for all the aziridines described in this study.

In summary, we have a developed a catalytic enantioselective ring-opening reaction of *meso*-aziridines with HCl catalyzed by phosphinothioureas. A broad range of cyclic as well as acyclic substrates undergo clean addition to afford the corresponding β-chlorobenzamide derivatives in high yields and with high enantioselectivities. Investigations of other classes of acidic nucleophiles (HX) and potential electrophiles, as well as more detailed mechanistic studies are under way.

Representative Procedure for Catalytic Enantioselective Ring-Opening Reaction with HCl

To a mixture of catalyst **1m** (3.0 mg, 0.005 mmol, 10 mol%) and aziridine **2a** (10.1 mg, 0.050 mmol) in Et_2O (20 mL, 0.0025 M), HCl (1 M stock solution in Et_2O, 60 μL, 0.06 mmol, 1.2 equiv) was added at –78 °C. After 4 h, the solvent was evaporated under reduced pressure, and the residue was purified by automated column chromatography (silica gel, hexane–EtOAc, 19:1 to 3:2) to afford (1*R*,2*R*)-*N*-(2-chlorocyclohexyl)benzamide (**3a**, 11.6 mg, 0.0488 mmol) in 98% yield as colorless solid. The ee of the product was determined by HPLC analysis to be 83%.

IR (neat): 3230, 3059, 2950, 2859, 1635, 1575, 1452, 1330, 1125 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 7.6 Hz, 2 H), 7.50 (t, *J* = 7.6 Hz, 1 H), 7.44 (t, *J* = 7.6 Hz, 2 H), 6.18 (br d, *J* = 4.5 Hz, 1 H), 4.06 (ddd, *J* = 3.8, 9.3, 17.5 Hz, 1 H), 3.88 (dt, *J* = 3.8, 10.5 Hz, 1 H), 2.34–2.30 (m, 2 H), 1.84–1.74 (m, 3 H), 1.52–1.44 (m, 1 H), 1.40–1.31 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.2, 134.7, 131.4, 128.5, 127.0, 62.5, 55.6, 36.1, 32.8, 25.4, 24.2. ESI-HRMS: *m/z* calcd for $C_{13}H_{16}ClNNaO$ [M + Na^+]: 260.0813, 262.0783 (chlorine isotope); found: 260.0810, 262.0782 (chlorine isotope) $[\alpha]_D^{23}$ –54.1 (*c* 0.58, $CHCl_3$; 83% ee). HPLC (Daicel Chiralpak AD-H, 2-PrOH–hexane = 1:10, flow rate 1.0 mL/min, detection at both 210 nm and 254 nm): t_R = 13.8 min (major) and 23.4 min (minor).

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