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# Accessing Rare α-Heterocyclic Aziridines via Brønsted Acid-catalyzed Michael Addition/Annulation: Scope, Limitations, and Mechanism

Timothy A. Hilton,[a] Andrew G. Leach,[b] Aidan P. McKay,[a] and Allan J. B. Watson*[a]

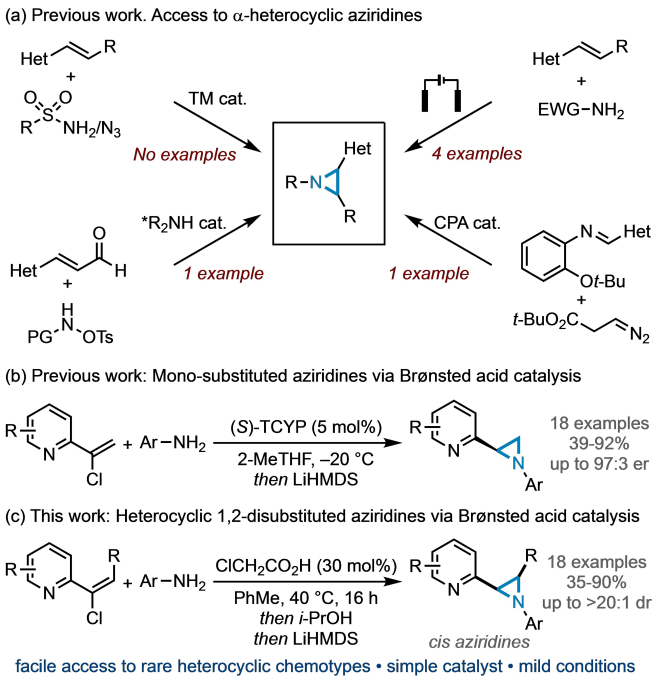
We report an approach to the diastereoselective synthesis of 1,2-disubstituted heterocyclic aziridines. A Brønsted acid-catalyzed conjugate addition of anilines to trisubstituted heterocyclic chloroalkenes provides an intermediate 1,2-chloroamine. Diastereocontrol was found to vary significantly with solvent selection, with computational modelling confirming selective, spontaneous fragmentation in the presence of trace acids, proceeding through a pseudo-cyclic, protonated intermediate and transition state. These chloroamines can then be converted to the aziridine by treatment with LiHMDS with high stereochemical fidelity. This solvent-induced stereochemical enrichment thereby enables an efficient route to rare *cis*-aziridines with high *dr*. The scope, limitations, and mechanistic origins of selectivity are also presented.

## Introduction

Aziridines are a privileged motif within natural products and organic synthesis. This ring system is electrophilic enabling reaction with a broad range of nucleophiles and access to functionalized amine products.[1] Aziridines have found extensive utility in the total synthesis of alkaloid natural products, as well as their downstream functionalization.[2] Moreover, aziridine natural product analogues have demonstrated potent antitumor,[3] antimicrobial,[4] and antiviral activity.[5] Such properties have made aziridines highly attractive structures for applications within the pharmaceutical industry, for example as covalent inhibitors.[6]

Considering their utility in medicinal chemistry,[7] it is interesting to note a general lack of diversity of aziridine structures within the literature (Scheme 1a). Aliphatic and aromatic substituents dominate this space; however, few α-heterocyclic examples have been reported, with *N*-functionalized examples particularly scarce. This is perhaps due to the requirement of 'activated' nitrogen species (bearing electron-withdrawing groups) used in these methodologies, such as nitrenes.[1a] Despite extensive development, few examples of α-heterocyclic aziridines have been reported using transition metal catalysis,[8] electrochemical[9] or flow electrochemical approaches,[10] organocatalysis,[11] or utilising substitution chemistry with sulfur ylides or imines.[12]

Previous work within our group sought to access this underexplored chemotype through a chiral phosphoric acid (CPA)-catalyzed enantioselective aza-Michael addition of aromatic amines to chlorovinyl heterocycles, followed by basic annulation (Scheme 1b).[13] This yielded chiral mono-substituted α-heterocyclic aryl aziridines with high yield and *ee*. A limitation of this approach was the lack of further substitution on the




**Scheme 1.** (a) Reported syntheses of α-heterocyclic aziridines. (b) Chiral Brønsted acid-catalyzed Michael addition/aziridination. (c) This work: Brønsted acid-catalyzed route to rare α-heterocyclic 1,2-discubstituted aziridines.

[a] *T. A. Hilton, Dr. A. P. McKay, Prof. Dr. A. J. B. Watson*
*EaStCHEM, School of Chemistry*
*University of St Andrews*
*North Haugh, St Andrews, Fife, KY16 9ST, U.K.*
*E-mail: aw260@st-andrews.ac.uk*
*Homepage: https://watsongroup.wp.st-andrews.ac.uk/*
[b] *Dr. A. G. Leach*
*School of Health Sciences*
*University of Manchester*
*Oxford Road, Manchester, M13 9PL, U.K.*

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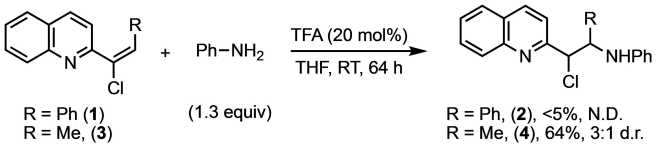
aziridine ring. We therefore sought to expand the scope of this CPA strategy by establishing a method for the synthesis of 1,2-disubsituted α-heterocyclic aryl aziridines. Here we provide a full account of this reaction development, including scope, limitations, and mechanism.

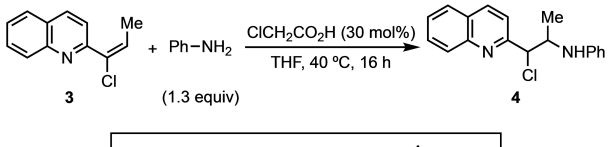
## Results and Discussion

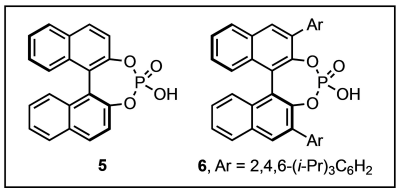
**Reaction Development: Aza-Michael Process**. To investigate the potential for this acid-catalyzed synthesis of 1,2-disubstituted aziridines, our initial benchmark system was based on stereochemically pure trisubstituted chloroalkene **1** using aniline as the nucleophile and TFA as catalyst to access the desired chloroamine product (Scheme 2). We quickly found that phenyl substitution at the 2-position of the alkene was not accommodated – product **2** was not obtained under any conditions employed (see ESI for full details). We attribute this to a steric issue and not an electronic issue based on additional observations (*vide infra*). Changing to methyl-substituted **3**, gave 64% conversion to the desired chloroamine **4** in approx. 3:1 d.r. under equivalent conditions. Accordingly, **3** was selected for further optimization (Table 1).[14]




**Scheme 2.** Initial benchmark reactions.

**Table 1.** Reaction development.




| Entry | Deviation | Yield **4** [%] (d.r.)[a] |
|---|---|---|
| 1 | none | 61 (4:1) |
| 2 | **5** instead of $ClCH_2CO_2H$ | 35 (4:1) |
| 3 | **6** instead of $ClCH_2CO_2H$[b] | 37 (5:1)[c] |
| 4 | **6** instead of $ClCH_2CO_2H$, 0 °C[b,d] | 50 (9:1)[e] |
| 5 | PhMe instead of THF | 83 (1.1:1) |
| 6 | *i*-PrOH instead of THF, RT | 48 (>20:1) |
| 7 | *i*-PrOH:PhMe (1:4) instead of THF | 45 (5:1) |
| 8 | *i*-PrOH:PhMe (1:1) instead of THF | 24 (19:1) |

[a] Yield and d.r. determined by $^1$H NMR using TCE as an internal standard; [b] 64 h; [c] 51:49 e.r.; [d] PhMe as solvent; [e] 66:34 e.r.

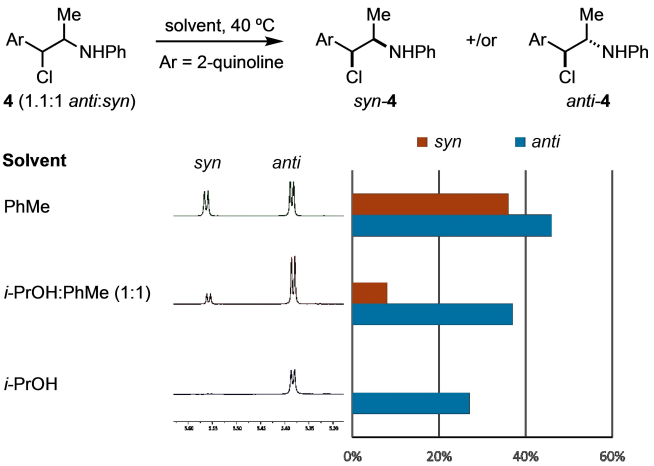
Following a preliminary assessment of reaction variables (see ESI for full details), the desired conjugate addition product **4** was obtained in 61% NMR yield and ca. 4:1 d.r. using chloroacetic acid as a catalyst (entry 1). Based on this, we explored the use of chiral phosphoric acid catalysts **5** and **6** to induce enantioselective bond formation (entries 2–4); however, despite similar d.r. to entry 1, levels of asymmetric induction were poor. Enantioselectivity could not be improved despite broad screening (see ESI). This lack of enantioenrichment is in agreement with previous studies, where 2,3-disubsituted heterocyclic cores could not induce enantioselectivity due to increased allylic strain.[13a]

Despite this, promising diastereoselectivity was observed using simple carboxylic acid catalysts (e.g., entry 1). We therefore sought to develop a diastereoselective approach to the rare disubstituted aziridine products. Performing the reaction in aromatic solvents, such as PhMe (entry 5) gave improved yields; however, at the expense of diastereocontrol. In contrast, excellent diastereoselectivity was obtained using polar protic solvents such as *i*-PrOH (entry 6), but at lower yield. Mixtures of *i*-PrOH and PhMe gave results in between the extremes of the pure solvents (entries 7 and 8). No further improvements to reaction conditions could be made.

The significant impact of these solvents compelled further investigation (Scheme 3).

Suspension of **4** (1.1:1 d.r., racemic) in mixtures of *i*-PrOH and PhMe led to selective degradation of *syn*-**4** with increasing alcohol content (see ESI for full details). The same degradation of *syn*-**4** was observed on column chromatography.

**Computational Calculations of the Aza-Michael Process and Solvent Effects**. In order to understand these observations, we turned to density functional theory calculations (MN15/6-31+G**-SMD). These employed **3** and $PhNH_2$ as representative substrates, with AcOH as a model for the $ClCH_2CO_2H$. The free-energy profile obtained for the essentially unselective formation of *syn*-**4** and *anti*-**4** is shown in Figure 1. Complexation of the quinoline nitrogen of **3** to AcOH precedes addition of the $PhNH_2$. This addition is concerted with proton transfer of one of




**Scheme 3.** Solvent-induced diastereoenrichment of **4**. Yield and d.r. determined by $^1$H NMR using TCE as an internal standard.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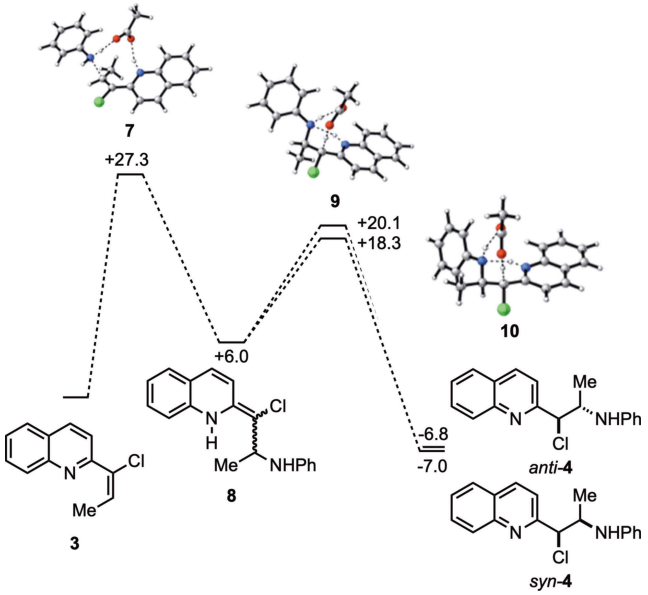



**Figure 1.** Computed transition states and intermediates for the AcOH-catalyzed Michael addition of $PhNH_2$ to chloroalkene **3**.

the NH protons to the acid which in turn protonates the quinoline nitrogen. This occurs through transition states like **7**, computed to correspond to a barrier of 27.3 kcal/mol in toluene. The enamine **8** that forms can undergo rapid rotation to relieve the steric clashing imposed by the double bond in **3**. A second, subsequent process mediated by AcOH sees protonation of the enamine **8** concerted with deprotonation of its NH through transition states like **9** and **10**. At first glance, the modelling appears to suggest a significant kinetic preference for formation of *syn*-**4**, in contradiction to the experimentally observed non-selective process. Experiment and theory are in agreement when the barriers for the back reaction are considered. The reversions to **8** by the two stereoisomers have barriers of 25.3 and 26.9 kcal/mol; these are lower than the rate-limiting barrier leading to **8** and thus reversion of **4** and equilibration of the two isomers is to be expected. The initial emergence of a modest excess of *anti*-**4** (see ESI for details) is consistent with this isomer having the higher barrier for reversion. The calculations support a thermodynamically controlled preference, and suggest any energy difference between the *syn* and *anti* isomers is below the limit of what can be accurately computed, supportive of the non-stereoselective formation observed.

Turning to the stereoselective degradation of **4**, it was assumed that this depends on trace Lewis or Brønsted acid that can complex the quinoline nitrogen of **4**, hence the reaction proceeding in the presence of both *i*-PrOH and silica. Further computational studies used a concentration of $1\times10^{-18}$ M of protonated *i*-PrOH, **4**, and settings for solvation by *i*-PrOH to model these conditions.

Protonation of **4** promotes fragmentation with computed barriers of 26.6 kcal/mol for fragmentation of *syn*-**4** and 28.1 kcal/mol for *anti*-**4**. This is consistent with the direction and degree of stereoselectivity observed and with catalysis by trace acid. The origin of the stereoselectivity can be understood by considering the effect of protonating the quinoline nitrogen. This creates a cationic aromatic surface (Figure 2) that makes a strong interaction with the electron rich aniline ring, rendering the system pseudo-cyclic. A further stabilizing influence is a through-space interaction between the electron-rich belt around the Cl and the nearby $NH^+$. In the *syn*-**11** structure (shown looking down the fragmenting bond in Figure 2), it is clear that the aniline-π cation interaction and Cl-NH interaction can be comfortably retained while permitting the methyl group to be anti-periplanar to the quinoline. Inversion to give *anti*-**11** might require loss of the Cl-NH interaction or the methyl clashing with the quinoline. Instead, the preferred structure retains these features but in doing so requires the pseudo-cyclic structure held together by the aniline-π cation interaction to be boat-like. Thus, *syn*-**4** is more readily protonated and fragments more rapidly than *anti*-**4**, accounting for the high diastereoselectivity observed upon exposure to *i*-PrOH or silica gel chromatography.

**Reaction Development: Aziridination**. With a greater understanding of this degradation process, we utilized this pathway in order to access 1,2-chloroamines with high d.r., followed by a base-mediated $S_Ni$ to enable access to the desired 1,2-disubstituted aziridine targets (Scheme 4).

**Reaction Scope Assessment**. We sought to explore the scope of this process with regards to the heterocyclic chloroalkene and aniline nucleophile components (Scheme 5).

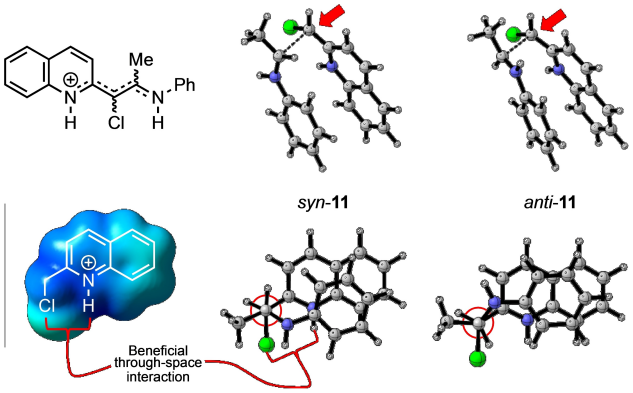
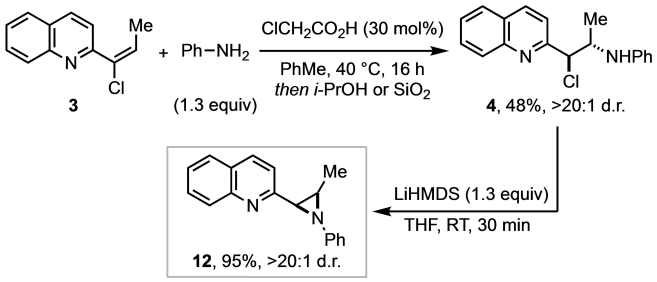



**Figure 2.** Transition states (**11**) for the fragmentation of **4** and the electrostatic potential of protonated quinoline, showing the beneficial through-space interaction for *syn*-**11**.




**Scheme 4.** Optimized method for diastereoselective synthesis of α-heterocyclic 1,2-aziridine products.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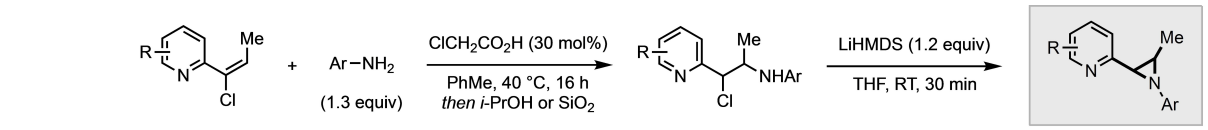


(a) Choroamine products

*Heterocycle scope*

**4** (4 mmol scale)
85%, 1.5:1 d.r.[a]
43%, >20:1 d.r.[b]

**13**
79%, 1:1 d.r.[a]
46%, >20:1 d.r.[b]

**14**
77%, 1.5:1 d.r.[a]
30%, >20:1 d.r.[b]

**15**
70%, 1.5:1 d.r.[a]
25%, >20:1 d.r.[b]

**16**
48%, 3:1 d.r.[a]
32%, >20:1 d.r.[b]

**17**
32%, 1:1 d.r.[a]
16%, 2:1 d.r.[b]

*Aniline scope*

R = OMe, **18** 73%, 2:1 d.r.[a] 50%, >20:1 d.r.[b]
R = Bpin, **19** 84%, 1.5:1 d.r.[a] 61%, 3.5:1 d.r.[b]
R = $CF_3$, **20** 29%, 1.5:1 d.r.[a] 13%, >20:1 d.r.[b]

R = Me, **21** 71%, 2:1 d.r.[a] 43%, 9:1 d.r.[b]
R = Br, **22** 90%, 1:1 d.r.[a] 35%, >20:1 d.r.[b]
R = I, **23** 90%, 1:1 d.r.[a] 50%, 12:1 d.r.[b]

R = *i*-Pr, **24** 47%, 3:1 d.r.[a] 32%, >20:1 d.r.[b]
R = F, **25** 44%, 2:1 d.r.[a] 31%, >20:1 d.r.[b]
R = Br, **26** 79%, 1:1 d.r.[a] 32%, 10:1 d.r.[b]
R = $OCF_3$, **27** 87%, 1:1 d.r.[a] 39%, >20:1 d.r.[b]
R = SH, **28** 91%, 1:1 d.r.[a] 50%, >20:1 d.r.[b]

**29**
68%, 1.5:1 d.r.[a]
41%, >20:1 d.r.[b]

**30**
54%, 2:1 d.r.[a]
35%, >20:1 d.r.[b]

**31**
87%, 1.1:1 d.r.[a]
50%, >20:1 d.r.[b]

(b) Aziridine products

*Heterocycle scope*

**12** (1.5 mmol scale)
94%, >20:1 d.r.[b]

*Aniline scope*

R = OMe, **37**, 95%, >20:1 d.r.[b]
R = Bpin, **38**, 87%, 4:1 d.r.[b]

R = Me, **39**, 99%, >20:1 d.r.[b]
R = Br, **40**, 98%, 19:1 d.r.[b]
R = I, **41**, 97%, >20:1 d.r.[b]

R = *i*-Pr, **42**, 96%, >20:1 d.r.[b]
R = Br, **43**, 80%, >20:1 d.r.[b]
R = $OCF_3$, **44**, 74%, >20:1 d.r.[b]
R = SH, **45**, 81%, >20:1 d.r.[b]

**32**
71%, >20:1 d.r.[b]

**33**
98%, >20:1 d.r.[b]

**34**
83%, >20:1 d.r.[b]

**46**
91%, >20:1 d.r.[b]

**35**
74%, >20:1 d.r.[b]

**36**
95%, 3:1 d.r.[a]

**47**
77%, >20:1 d.r.[a]

**48**
98%, >20:1 d.r.[b]

**49**
89%, 3:1 d.r.[b]

(c) Limitations

*Heterocycles*

R = H, Br, $CF_3$

*Anilines/amines*

R = CN, $CO_2H$, $CO_2R$ $CH_2OH$, OH

R = H, $CO_2H$

**Scheme 5.** Scope and limitations. (a) Chloroamine products. (b) Aziridine products. (c) Limitations. Reaction conditions. Chloroamine synthesis: chloroalkene (0.2 mmol), aniline (1.3 equiv), chloroacetic acid (0.3 equiv), PhMe (0.4 M), 40 °C, 16 h. Aziridination: chloroamine (0.1 mmol), LiHMDS (1.3 equiv), THF (0.2 M), RT, 30 min. [a] Yield and d.r. determined by $^1$H NMR using TCE as an internal standard. [b] Isolated yield, d.r. determined by $^1$H NMR. See ESI for full details.


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For the conjugate addition process (Scheme 5a), the most practical approach was to perform the reaction in toluene to give the crude product as a mixture of diastereomers. Diastereomeric enrichment could be achieved either by suspending the crude product in *i*-PrOH or exposing to silica chromatography.

In most cases this delivered the *anti*-chloroamine product as a single diastereomer. The *anti*-chloroamine could then be treated with LiHMDS to deliver the desired *cis*-aziridine with complete stereochemical fidelity (Scheme 5b).

Regarding the generality of the two-step process, a range of heterocycles and aromatic amines were compatible. For the conjugate addition step (Scheme 5a), modification of the azaheterocycle was possible, with substituted quinoline cores achieving moderate to excellent yields (**13**–**16**, **29**). In general, more electron-rich systems, such as those bearing electron-donating groups (**16**) or benzothiazole (**17**) were less reactive. Under the PhMe-based conditions, product ratio does not vary greatly from 1.2:1; however, except for benzothiazole **17**, the enrichment process generally delivered >20:1 d.r.

A broad range of anilines was accommodated, with efficiency varying in line with electronic parameters. Electron-rich anilines (e.g., 2-OMe, **18**) were generally more efficient, due to enhanced nucleophilicity. Conversely, anilines bearing electron-withdrawing groups (e.g., 2-$CF_3$, **20**) performed poorly for the same reason. The incorporation of synthetic handles, such as halogens (**22**, **23**, **26**, **29**) or Bpin (**19**) was also tolerated with good yields.

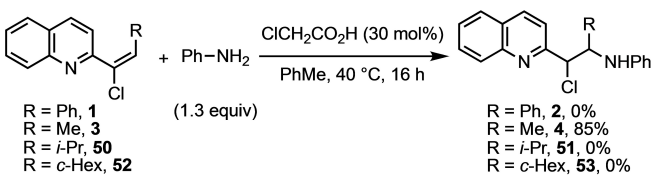
Scalability of this first step was demonstrated in a 4 mmol reaction of the benchmark reaction to give 0.45 g of **4** as a single diastereomer.

The chloroamine products underwent smooth conversion to the desired cis-aziridines in generally excellent yields. Confirmation of stereochemistry was obtained through single crystal X-ray structures of **12** and **45**. Scalability was also demonstrated in the benchmark reaction to give 0.37 g of **12** as a single diastereomer.

There are some limitations to the route outlined, as shown in Scheme 5c (see ESI for full details).

Alternative heterocycles, such as pyridine, pyrimidine, or benzimidazole systems were unreactive. The reaction was highly sensitive to amine nucleophilicity, with more nucleophilic amines (*e.g.*, alkylamines) resulting in catalyst deactivation. In addition, anilines with strong electron-withdrawing groups, such as nitrile or ester, were also unreactive.

Derivatization of the alkene substituent was also challenging (Scheme 6). Changing from Me (**3**) to Ph (**1**), *i*-Pr (**50**), or *c*-Hex (**52**) was not accommodated. Increasing catalyst loading, temperature, aniline equivalents, or reaction time failed to enable the conjugate addition process using these chloroalkenes.




**Scheme 6.** Substitution tolerance on the chloroalkene component. Yield determined by $^1$H NMR using TCE as an internal standard.

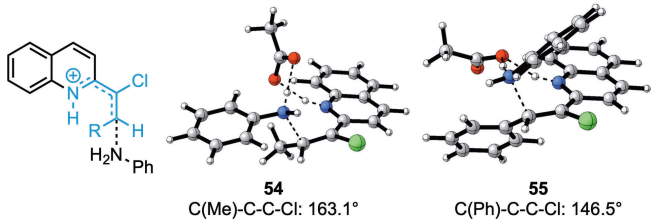



**Figure 3.** Calculated transition states from **1** and **3**.

**Understanding Scope Limitations via Computational Calculations**. To rationalize these observations, we once again turned to DFT calculations, using the solvation parameters for toluene. Having already established that the rate-limiting step is the initial addition, the reactants and transition states for the different substituted examples were obtained. These revealed that whereas the computed barrier for **3** is 27.3, the barriers for **1**, **50**, and **52** are 30.7, 27.5, and 29.2 kcal/mol, respectively. In general, a deactivating effect by larger groups is observed. Comparing the transition state for **3** (**54**) with that for **1** (**55**) reveals a significant difference between the two (Figure 3). In this process, the double bond shifts along one carbon atom and in the transition state there are therefore two adjacent partial double bonds that would ideally have the three atoms involved and all of their substituents co-planar (substructure highlighted in blue in Figure 3). For the reaction of **54**, this can be tolerated and the C(Me)-C–C-Cl dihedral angle is 163°. However, co-planarity in the reaction of **1** would entail the Ph group clashing with the quinoline. To avoid this clash, the C(Ph)-C–C-Cl dihedral angle must reduce to 147° in transition state **55**, and this species corresponds to a higher barrier than for **54**.

## Conclusions

In summary, an operationally simple synthesis of rare α-heterocyclic aziridines has been developed *via* the Brønsted acid-catalyzed Michael addition of anilines to chloroalkenes. Degradation of the *syn*-diastereomer of the chloroamine products by trace acid allows the isolation of a single *anti*-diastereomer, which has been rationalized by computational modelling. The *anti*-chloroamine products can then be readily converted to the corresponding *cis*-aziridines with complete stereochemical fidelity. The scope of this transformation has been demonstrated, and despite some limitations, this approach offers a solution to a considerable gap in this area of chemical space that cannot currently be accessed by alternative synthetic methodologies, which may be helpful in the generation of compound libraries.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## Experimental Section

### General experimental procedure for preparing cis-aziridines (e.g., 12)

**3** (40.7 mg, 0.2 mmol, 1.0 equiv) and chloroacetic acid (5.7 mg, 0.06 mmol, 30 mol%) were added to a dry microwave vial, which was capped, purged, and filled with $N_2$. PhMe (500 μL, 0.4 M) was added, and the mixture was stirred at 40 °C for 15 min prior to the addition of aniline (24 μL, 0.26 mmol, 1.3 equiv). The reaction was stirred at 40 °C for 16 h, before being quenched by the addition of saturated $NaHCO_3$ solution. The mixture was extracted with EtOAc, dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure.

The residue was resuspended in *i*-PrOH (1 mL, 0.2 M) and stirred at 40 °C for 4 h (or until a single diastereomer was present by $^1$H NMR), and then concentrated under reduced pressure. The resulting product was suspended in dry THF (500 μL, 0.4 M) and stirred at RT for 2 min prior to the dropwise addition of LiHMDS (0.26 mmol, 1.3 equiv). The reaction was stirred at RT for 30 min, quenched with saturated $NH_4Cl$ solution, and extracted with EtOAc. The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 0–5% EtOAc in hexane) to yield the desired *cis*-aziridine **12** as a yellow oil (25 mg, 48%).

### Computational information

Calculations employed the MN15 density functional and the 6–31 + G** basis set.[15] Solvation was incorporated via the SMD continuum solvation model.[16] All geometries were optimised and confirmed as minima or transition states by frequency calculation in Gaussian16.[17] Free energies were computed with the goodvibes software with concentration of 1 M, temperature of 298 K and a frequency cutoff of 20 $cm^{-1}$ and the Grimme quasi-harmonic approach for low frequency vibrations.[18] Systematic conformational sampling of all minima was undertaken with low energy conformations subjected to redundant internal coordinate scanning to obtain corresponding transition states. Electrostatic potential was computed in GaussView using default settings and molecular structure visualizations created in CYLview2.[19]

## Supporting Information

The authors have cited additional references within the Supporting Information.[13a,15–18,20–40]

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## Conflict of Interests

The authors declare no conflict of interest.

## Data Availability Statement

The research data supporting this publication can be accessed at https://doi.org/10.17630/4c1267fc-fdc2-47f8-9a0d-a03bdb8247f0. Deposition Number(s) 2309019 (for **12**), 2309020 (for **46**) contain(s) the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

**Keywords:** Annulation · Aziridine · Diastereoselectivity · Heterocycles · Mechanism · Organocatalysis

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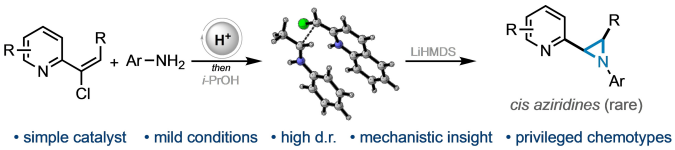


We report an approach to the diastereoselective synthesis of rare 1,2-disubstituted heterocyclic aziridines. Our approach utilizes an inherent degradation of 1,2-chloroamines in the presence of trace acid, followed by annulation to give a diverse array of *cis*-aziridines which are not captured by alternative synthetic methodologies. The scope, limitations, and mechanistic insights into the selectivity are presented.

*T. A. Hilton, Dr. A. G. Leach, Dr. A. P. McKay, Prof. Dr. A. J. B. Watson**

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**Accessing Rare α-Heterocyclic Aziridines via Brønsted Acid-catalyzed Michael Addition/Annulation: Scope, Limitations, and Mechanism**

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