Catalytic Enantioselective [2,3]-Rearrangements of Allylic Ammonium Ylides: A Mechanistic and Computational Study

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ABSTRACT: A mechanistic study of the isothiourea-catalyzed enantioselective [2,3]-rearrangement of allylic ammonium ylides is described. Reaction kinetic analyses using $^3$F NMR and density functional theory computations have elucidated a reaction profile and allowed identification of the catalyst resting state and turnover-rate limiting step. A catalytically relevant catalyst-substrate adduct has been observed, and its constitution elucidated unambiguously by $^3$C and $^4$N isotopic labelling. Isotopic entrainment has shown the observed catalyst-substrate adduct to be a genuine intermediate on the productive cycle towards catalysis. The influence of HOBt as an additive upon the reaction, catalyst resting state and turnover-rate limiting step has been examined. Crossover experiments have probed the reversibility of each of the proposed steps of the catalytic cycle. Computations were also used to elucidate the origins of stereosecontrol, with a 1,5-S**O interaction and the catalyst stereodirecting group providing structure rigidification and enantioselectivity, while preference for cation-π interactions over C-H•••π is responsible for diastereoselectivity.

INTRODUCTION

The [2,3]-rearrangement of allylic ammonium ylides is a direct and elegant method towards the synthesis of α-amino acid derivatives containing multiple stereocenters.$^1$ The mechanism of this process, and that of the competitive [1,2]-Stevens rearrangement, has been much discussed and disputed within the literature. A concerted thermally allowed sigmatropic process is thought to be operative in the [2,3]-rearrangement, while a radical mechanism involving bond cleavage and recombination is usually favored for [1,2]-rearrangement (Scheme 1A).$^2$

To date, few mechanistic analyses of [2,3]-rearrangements of allylic ammonium ylides have been conducted, although Jacobsen and co-workers have recently reported a detailed mechanistic investigation into the related thiourea-catalyzed [2,3]-Wittig rearrangement.$^3$ The elegant experimental and computational work of Singleton and co-workers concerning the competitive [2,3]- and [1,2]-rearrangements of allylic ammonium ylides promoted by DBU represents the current state-of-the-art (Scheme 1B). Through $^3$C kinetic isotope effects, crossover experiments and computation, these studies demonstrate that the origin of competitive [1,2]- and [2,3]-rearrangement is the common loose transition state leading to dynamic bond cleavage.$^4$ The development of both catalytic and stereoselective variants of the [2,3]-rearrangement of allylic ammonium ylides has been a significant synthetic challenge. Tambar and co-workers have reported a tandem ammonium salt formation and diastereoselective [2,3]-rearrangement process, exploiting Pd-catalyzed allylic substitution to form the reactive ammonium salt in situ, giving (±)-anti-α-amino acid derivatives with excellent

Scheme 1. Rearrangements of allylic ammonium ylides

A) Overview of reactivity of allylic ammonium ylides

B) Singleton: Understanding of competitive [1,2]- vs [2,3]-rearrangement

C) This work:
diastereoselectivity of this [2,3]-rearrangement process, and indeed most [2,3]-rearrangements, can be rationalized through the exo- or endo- transition states 15 and 17 initially described by Houk and Marshall for the related [2,3]-Wittig rearrangement (Scheme 2B).\(^6\)

Prior to our studies within this area, only limited methods capable of imparting enantiocontrol in the [2,3]-rearrangement of allylic ammonium ylides had been developed. Sweeney first demonstrated a chiral auxiliary approach to allow access to enantiomerically enriched \(\alpha\)-amino acid derivatives,\(^7\) while the use of a superstoichiometric chiral Lewis acid promoter was subsequently reported by Somfai.\(^8\) Catalytic enantioselective variants were unknown until 2014, when our laboratory reported an isothiourea-catalyzed\(^9\) [2,3]-rearrangement of allylic quaternary ammonium salts to give \(\alpha\)-amino acid derivatives with excellent levels of diastereo- and enantiocontrol (Scheme 3).\(^10\) Treatment of quaternary ammonium salts 19 bearing an activated \(p\)-nitrophenol ester, either isolated or generated in situ, with catalytic (+)-benzotetramisole [(+)−BTM] 20, co-catalytic hydroborylation (HOBt) and iPr\(_2\)NH gave stereoselective [2,3]-rearrangement into \(\alpha\)-amino acid derivatives with excellent levels of stereoselective. This process can be performed in the absence of HOBt, however its addition provides a subtle enhancement in both diastereo- and enantioselectivity. We tentatively proposed a Lewis base catalytic cycle, initiated by nucleophiles addition of (+)-BTM 20 into the activated ester substrate to form an acyl ammonium intermediate prior to the formation of ammonium ylide 22. However, alternative mechanistic pathways using either Lewis or Brønsted base catalysis proceeding via different intermediates can be envisaged (Scheme 3). For example, assuming Lewis base catalysis is operative, the reaction could proceed through initial formation of a keten intermediate 23 en route to acyl ammonium ylide 22. Furthermore, the origin of the observed diastereo- and enantiocontrol in the rearrangement process is currently unknown.

Herein we report experimental and computational investigations into the mechanism and origins of stereoselective control in the isothiourea-catalyzed [2,3]-rearrangement of allylic ammonium ylides (Scheme 3C). In situ NMR analysis has allowed a reaction profile to be elucidated, while isotopic-labelling studies have unambiguously identified a genuine productive catalytic intermediate. Kinetic analysis has given insight into the overall process and crossover studies have provided information about the reversibility of each step. Kinetic isotope analysis has also been used to probe the stereodetermining [2,3]-rearrangement step of the process. Computational reaction coordinate modeling provides deeper insight into the catalytic cycle and transition state modelling reveals the origins of stereochemical control.

**RESULTS AND DISCUSSION**

**Mechanistic Studies.**

(i) Temporal concentration profiles. Initial studies aimed to establish the kinetics of the [2,3]-rearrangement and identify any reaction intermediate(s) or catalyst resting states. Ammonium salt 25a (34 mM) rearranges to 26a in \(d_2\)-MeCN/\(d_2\)-DMSO (9:1) at \(-20\) °C, catalyzed by (+)-BTM 20 (20 mol %) (Scheme 4). The presence of various salts in the reaction medium causes extensive line-broadening in the \(^1\)H NMR spectrum, making it unsuitable for in situ analysis of the [2,3]-rearrangement. However, the \(^{19}\)F[\(\text{H}\)] and \(^{31}\)C[\(\text{H}\)] NMR spectra were tractable, and the \(4\)-fluoro substituent in 25a allows quantitative monitoring of the process by in situ \(^{19}\)F[\(\text{H}\)] NMR (\(\delta_F = -113.1\) ppm), with PhCF\(_3\) as an internal standard.\(^3\) After an initial burst-phase (<1000 s) ammonium salt 25a is converted into 26a (≥80 % 26a, \(\delta_F = -117.6\) ppm) with pseudo-first order kinetics, vide infra, over a period of 4 hours. During the reaction evolution, a transient species (\(\delta_F = -117.0\) ppm) was detected, accumulating to a maximum concentration of ~5.2 mM in the early stages of catalysis and then

![Scheme 3](image-url)

**Scheme 3.** Catalytic enantioselective [2,3]-rearrangement

There were no significant differences in the concentration profiles obtained at 25 °C, with the following exceptions: (a) the reactions at 25 °C had a slower reaction rate (k = (1.5-2) x 10^{-4} M^{-1} s^{-1}), (b) the rate constant for the transition state (26) was ~25-fold slower at 25 °C, and (c) the reaction rate was slower at 25 °C (k = (1.5-2) x 10^{-4} M^{-1} s^{-1}).

![Scheme 4](image-url)

**Scheme 4.** System chosen for in situ \(^{19}\)F NMR study.
substrate 25a was consumed. Rearrangement in the absence of HOBt resulted in a similar reaction profile, but afforded higher concentrations of the same species (δF = -117.0 ppm), over a longer period, ascertaining in its analysis.

(ii) Identification of an on-cycle catalytic intermediate.

(a) Catalyst speciation. To determine if the transient species (δF = -117.0 ppm) involves the catalyst, a fluorinated variant, (+)-F-BTM 27, was prepared. In situ monitoring of the [2,3]-rearrangement of 25a, catalyzed by 27 (Figure 1), confirmed conversion of free (+)-F-BTM 27 (δF = -112.3 ppm) into a catalyst-derived species (δF = -113.4 ppm), which was also transient, reaching a maximum concentration of 4.6 mM at ~2500 s, and decaying as the reaction proceeds to completion (see inset graph to Figure 1). The comparable temporal intensities of the two signals (δF = -117.0 ppm and -113.4 ppm) strongly suggest they arise from a single transient intermediate containing both 25a and 27 in a formal 2:1 combination. Based on reference to isothiouronium salt 28 (δF = -113.3 ppm), the 19F chemical shift of the catalyst-derived component in transient species 29 suggested it to be an N-acylated isothiourium.

(b) Atom connectivity: 13C/15N labelling. Isotopically-labelled substrates and catalyst (1-[13C]1-25a, 1,2-[13C]1-25a, 1,2,3-[13C]1-25b (Figure 2A) and (±)-[15N]27 were prepared to deduce connectivity between various atoms in the intermediate and probe for reversibility in its generation. Rearrangement of 1,2-[13C]1-25a (34 mM) catalyzed by

Figure 1. Temporal concentration data for [2,3]-rearrangement of 25a using (+)-F-BTM 27, conditions: a) 25a (29.5 mM), (+)-F-BTM 27 (6.8 mM), iPr2NH (47 mM), d3-MeCN/d6-DMSO (9:1), -20 °C. Inset: monitoring of catalyst-derived species.

A) Isotopically-labelled substrates used (α = 13C)

B) Atom connectivity: 13C/15N labelling. Isotopically-labelled substrates and catalyst (1-[13C]1-25a, 1,2-[13C]1-25a, 1,2,3-[13C]1-25b (Figure 2A) and (±)-[15N]27 were prepared to deduce connectivity between various atoms in the intermediate and probe for reversibility in its generation. Rearrangement of 1,2-[13C]1-25a (34 mM) catalyzed by

Figure 2. A) Isotopically-labelled substrates. B) Generation of [15N, 13C]-labelled intermediate 29a. C) 13C[1H] NMR sub-spectrum (101 MHz, d3-MeCN/d6-DMSO (9:1), 273K) of the 13C=O region. Conditions, 1,2-[13C]1-25a (34 mM), (±)-[15N]-F-BTM [13C,27] (6.8 mM), iPr2NH (23.8 mM).

(±)-[15N]-27 (6.8 mM, 20 mol %) was monitored by 13C[1H] NMR (Figure 2B). Reducing the iPr2NH concentration to 23.8 mM prolonged the lifetime of the intermediate,
[\textsuperscript{[\textsuperscript{13}C,\textsuperscript{2}H]}{-29a}], allowing detailed analysis of the \textsuperscript{13}C=O region, Figure 2C. The characteristic doublets (\(J_{\text{CC}} = 58 \text{ Hz}\)) arising from the adjacent \textsuperscript{13}C labels, C(1)–C(2), in the substrate (1,2-\textsuperscript{[\textsuperscript{13}C]}{-25a}) and the product (1,2-\textsuperscript{[\textsuperscript{13}C]}{-26a}) are replaced by a doublet-doublet in [\textsuperscript{\textsuperscript{13}N, \textsuperscript{13}C]}{-29a}, (\(\delta_C = 173.1\) ppm).\textsuperscript{3} The magnitude of the C-C coupling (\(J_{\text{CC}} = 58 \text{ Hz}\)) confirms that C(2) remains sp\textsuperscript{3}-hybridized. The magnitude of the additional coupling constant (\(J_{\text{CN}} = 5.2 \text{ Hz}\))\textsuperscript{3} indicates that C(1) is directly bound to the \textsuperscript{13}N-labelled atom in the catalyst, confirming 29a to be an N-acylated isothiourea (Figure 2).

Attempts to identify the atom adjacent to C(2) in [\textsuperscript{\textsuperscript{13}N, \textsuperscript{13}C]}{-29a} from its \textsuperscript{1}H-coupled \textsuperscript{13}C NMR signal were thwarted by line broadening.\textsuperscript{3} Instead, the \textsuperscript{\textsuperscript{13}C}[\textsuperscript{\textsuperscript{1}H}] NMR spectrum of intermediate 1,2,3-\textsuperscript{[\textsuperscript{13}C]}{-29b}, generated from 1,2,3-\textsuperscript{[\textsuperscript{13}C]}{-25b}, was analysed, (Figure 3). The C(2) signal of the resulting [2,3]-rearrangement product, 1,2,3-\textsuperscript{[\textsuperscript{13}C]}{-26b} (\(\delta_C = 70.5 \text{ ppm}\)), displayed the expected doublet doublet coupling arising from C(2)-C(3) bond formation.

However, this coupling pattern was also evident in intermediate 1,2,3-\textsuperscript{[\textsuperscript{13}C]}{-29b} (\(\delta_C = 68.0 \text{ ppm}\), \(J_{\text{CC}} = 51.4 \text{ Hz}\), \(J_{\text{CN}} = 35.8 \text{ Hz}\)) with the magnitude of the C(2)-C(3) coupling indicative of sp\textsuperscript{3}-hybridization at both centres.\textsuperscript{3} Overall, the data confirms that the intermediate (29) is a catalyst-bound, post [2,3]-rearrangement, acyl ammonium salt (Figure 3).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Catalyst-bound [2,3]-rearrangement product, \textsuperscript{\textsuperscript{13}C}[\textsuperscript{\textsuperscript{1}H}] NMR sub-spectrum (101 MHz, \textsuperscript{\textsuperscript{\textsuperscript{1}H}}MeCN/d\textsubscript{6}-DMSO (9:1), 293K) of the \textsuperscript{13}C(2)-H region. Conditions: 1,2,3-\textsuperscript{[\textsuperscript{13}C]}{-25b} (34 mm), (+)-F-BTM 27 (6.8 mm), iPr\textsubscript{3}NH (23.8 mm).}
\end{figure}

\textbf{(c) Productivity of the intermediate.} The data presented so far does not discriminate between the N-acylated isothiourea species (29) being peripheral to the productive catalytic cycle (Figure 4, case A) or an integral part of it (cases B–D). The following isotopic entrainment test distinguishes these four possibilities. A catalytic reaction employing 1-\textsuperscript{[\textsuperscript{13}C]}{-25a} (17 mM), was allowed to evolve until 1-\textsuperscript{[\textsuperscript{13}C]}{-29a} had reached its maximum concentration (~5 mm). A further 1.0 equivalent (17 mm) of a differently labelled substrate, 1,2-\textsuperscript{[\textsuperscript{13}C]}{-25a}, was then rapidly added, resulting in an isotopic perturbation of the system. At the point that 1,2-\textsuperscript{[\textsuperscript{13}C]}{-25a} is added, there has been 32% net conversion of 25a ([\textsuperscript{13}C]– and [\textsuperscript{13}C]–). However, neither of the [2,3]-rearrangement products (29a and 26a) yet contain any of the [\textsuperscript{13}C]-label; all of this resides in unreacted [\textsuperscript{13}C]−25a, which comprises 0.28 [\textsuperscript{13}C] / 0.72 [\textsuperscript{13}C]. The key features are the changes in \textsuperscript{13}C-populations in the substrate 25a, intermediate 29a and product 26a, as the reaction evolves. Irrespective of the pathway (A–D) the population in the final product (26a) must ultimately rise from 0 to 50%, as dictated by the equal proportions of 1-\textsuperscript{[\textsuperscript{13}C]}{-25a} and 1,2-\textsuperscript{[\textsuperscript{13}C]}{-25a} added overall. For case A, where 29a is not productive, the isotope population in 29a will depend only on that of the final product (26a; max 50% \textsuperscript{13}C), and at all stages will be lower or equal to it. For case B, where the intermediate is productive, but is in equilibrium with 25a, the \textsuperscript{13}C-population in 25a will be reduced, in the limit from 72% to 55%. For cases C and D, where the [2,3]-rearrangement to 29a is irreversible, the isotope population in 25a is constant (72% \textsuperscript{13}C) and the \textsuperscript{13}C-content in 29a rises from 0% to a maximum of 72% as it is repopulated from 25a.\textsuperscript{4} However, for case C, equilibration of 29a with product 26a will attenuate the rise in \textsuperscript{13}C-population in 25a, in the limit to 50%. Only for case D will the \textsuperscript{13}C isotope population in 29a rise, in advance of 26a, to reach a maximum 72% \textsuperscript{13}C.\textsuperscript{4} Comparison of the predicted and experimentally determined \textsuperscript{13}C-populations as a function of net conversion (Figure 4) confirms that 26 arises from two irreversible sequential first-order inter-conversions (25 → 29 → 26) where 29 is the productive catalytic intermediate (case D).\textsuperscript{4} Kinetic modelling confirms that the impact of heavy-atom (\textsuperscript{13}C) KIEs on the isotope-entrainment are negligible.\textsuperscript{10}
Figure 4. D[C]3 Entrainment into the catalytic cycle. Conditions, 1-[D[C]3]25a (17 mM), (+)-BTM (6.8 mM), iPr_NH (47.6 mM), d5-MeCN/d6-DMSO (9:1), with 1,2-[D[C]3]25a (17 mM) added at 32% net conversion of 25a. Open circles: experimental ([C]3[H]) NMR data for D[C]3 incorporation (%) versus net conversion (%). Dashed lines: kinetic simulation where 29 is a productive intermediate in two irreversible sequential pseudo-first-order interconversions (25→29→26, Case D; with rate-ratio 0.407).11

(iii) HOBt cleavage of acyl ammonium intermediate. HOBt provides optimal diastereo- and enantiocontrol (Scheme 4), however its role within the catalytic cycle is unclear. To probe if the HOBt enhances stereocontrol via suppression of the base-mediated background reaction, the iPr_NH-mediated rearrangement of 25a was examined. Reaction of 25a with iPr_NH (47 mM) in the absence of the BTM catalyst resulted in slow formation of racemic 26a with low diastereocntrol (79:21 dr) and a kobs of 2.74 × 10−3 s−1. The addition of a catalytic amount of HOBt (6.8 mM) resulted in no change in rate (kobs 2.70 × 10−3 s−1). This rules out the role of HOBt as improving stereocontrol through direct suppression of the rate of the background reaction.

Figure 5. Addition of stoichiometric HOBt at t = 3920 s. Conditions, 25a (34 mM), (+)-BTM (6.8 mM), iPr_NH (47.6 mM), d5-MeCN/d6-DMSO (9:1), HOBt (34 mM). Total Product refers to both HOBt ester 30 and 26a.

The (+)-BTM-catalyzed rearrangement of 25a in the presence of stoichiometric HOBt (34 mM) was studied by 19F[3]H) NMR. The presence of HOBt strongly suppressed accumulation of acyl ammonium intermediate 29c ((+)-BTM replaces (+)-F-BTM) and resulted in the formation of the corresponding HOBt ester 30 (δF = −117.2 ppm, confirmed by comparison with an authentic sample), in addition to the PNPO ester product 26a. Addition of HOBt once the acyl ammonium intermediate 29c reached the pseudo-steady state (5 mM, t = 3920 s, Figure 5) resulted in immediate formation of HOBt ester 30, and consumption of acyl ammonium intermediate 29c. HOBt thus shifts the catalyst speciation to be strongly dominated by free (+)-BTM, (Figure 5). The background iPrNH-mediated reaction that converts 25 into racemic (±)-26 presumably involves the generation of ylide intermediate 24. Interception of this species by free (+)-BTM would also generate intermediate 29, thus leading to nonracemic 26. The higher the concentration of free BTM, the more effective this interception.

Scheme 5. Effect of HOBt on overall catalytic cycle

Overall, the beneficial effect of HOBt on the selectivity may arise from both a change in catalyst speciation to favour free BTM and by diversion of the background reaction onto the enantioselective pathway (Scheme 5).

(iv) Reaction kinetics, and impact of additives. Having identified, by 19F[3]H) and 13C[3]H) NMR, the major reactant-derived and catalyst-derived components pre-
sent in the reaction mixture, the empirical rate-equation
was established by analysis of the decay in substrate 25a
during the pseudo-steady-state phase of the catalysis
(Scheme 6). The standard conditions [25a (34 mM), (+)-
BTM (6.8 mM), HOBt (6.8 mM) and iPr$_2$NH (47 mM)],
afforded a pseudo-first order rate constant, $k_{obs} = 1.37 \times 10^4$
\begin{equation}
\text{s}^{-1}.
\end{equation}

**Scheme 6. Empirical rate equation**

![Scheme 6. Empirical rate equation](image)

The SKIE was measured by competition using aryl-D$_2$
C(3)-D$_2$-25a and aryl-D$_2$-C(3)-D$_2$-25a, and a double-
labelling method, in which the C(3)-D / C(3)-H ratio as a
function of fractional conversion is determined by $^{19}$F NMR
($\Delta \delta_{F} = 0.28$ ppm; aryl-D$_2$ / aryl-D$_2$). After correction for
the effect of aryl deuteration, a value of $k_{D}/k_{H} = 1.031$
was obtained. The presence of a small positive SKIE is
consistent with a product-determining [2,3]-
rearrangement transition state (Scheme 7). A linear free
energy relationship analysis of a range of C(3)-aryl-sub-
strates, against standard Hammett sigma values, showed
the C(3) position to be insensitive to electronic substitu-
ent effects.

**(vi) Crossover and reversibility studies.** We have previously demonstrated the [2,3]-rearrangement step to
be intramolecular and irreversible. To distinguish which
steps prior to the [2,3]-rearrangement are reversible, a
crossover reaction between ammonium salts 25a and 31
(1:1) bearing two distinct activated ester groups (4-
NO$_2$-C$_6$H$_4$ and 3,5-(CF$_3$)$_2$C$_6$H$_4$) and two distinct C(3)-aryl
units (4-FC$_6$H$_4$ and 3-FC$_6$H$_4$) was monitored in situ under
catalytic conditions (Scheme 8A). Complete equilibration
with ammonium salts 32 and 33 was observed, with
consistent reversible generation of non-rearranged (+)-BTA
acyl ammonium intermediates. To examine reversibility at the
deuteronation step, the [2,3]-rearrangement of a-
dideuterio ammonium salt a-[D$_2$]-25 (75% D$_2$) was monitored
in situ. The product was obtained with significantly
lower deuterium incorporation (29% D$_2$), consistent with a
reversible deprotonation step (Scheme 8B). Reaction of
ammonium salt 33 in the presence of rearrangement product 26b
(Scheme 8C) bearing distinct C(3)-aryl units and activated esters demonstrated no crossover, consistant with catalyst turnover being irreversible, confirming
the conclusions deduced from isotopic entrainment.

**Computational Studies.**

**(i) Computed catalytic cycle.** We computed all inter-
mediates, transitions structures (TSs), and possible salt
complexes involved in the mechanisms shown in Scheme 9. Exhaustive searches were performed to locate all perti-
nent conformations. Geometries and thermodynamic
corrections were computed at the Mo6-2X(6-31G(d)) level of theory. Vibrational frequencies and thermal cor-
rections to the Gibbs free energy were calculated at -20 °C
and 1 atm.
meta-GGA functional Mo6-2X is generally more robust than B3LYP at accounting for dispersion and non-bonding interactions routinely found in organocatalytic reactions. Kinetic isotope effects were calculated using the theory of Bigeleisen and Mayer along with the rigid-rotor harmonic oscillator approach (ΔHΔS). Quantum mechanical tunnelling effects were also calculated for both methods using the one-dimensional parabolic approximation. The calculation of the KIE was automated by use of the Onyx isotope effect program. While both rigid-rotor and Bigeleisen-Mayer methods agree qualitatively, the latter was consistently in better agreement with experiments, and is reported herein as the computed KIE. The catalytic cycle and the computed reaction coordinate are summarised in Scheme 9.

Direct acylation begins with BTM attack on allylic ammonium activated substrate (TS-II, ΔG‡ = 14.8 kcal·mol⁻¹) to form tetrahedral intermediate III. Release of PNPO⁻ (TS-IV, ΔG‡ = 12.0 kcal·mol⁻¹) gives dication V. Indirect acylation

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Scheme 8. Crossover studies

**A)**

Crossover observed by **in situ** NMR

**B)**

**C)**

No crossover ca. 1:1 ratio observed by **in situ** NMR

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\[ \text{Scheme 9. Proposed catalytic cycle and computed reaction coordinate} \]
through formation of the ammonium ketene III was ruled an unlikely reactive intermediate based on its high thermodynamic barrier for formation (ΔG‡ = 22.0 kcal·mol⁻¹). The small endergonicity of dication V (ΔG = 3.3 kcal·mol⁻¹) confirms the observed reversibility of catalytic acylation. Dication V is in equilibrium with ylide VII (ΔG = 1.6 kcal·mol⁻¹) through deprotonation of the α-proton of V by PNPO⁻ (ΔG‡ = 11.4 kcal·mol⁻¹), also in agreement with the experimentally-observed reversibility of the deprotonation step.⁵⁻¹

NBO analyses reveal significant enolate character of ylide intermediate VII. Intermediate VII subsequently undergoes stereoselective and turnover-rate limiting [2,3]-rearrangement (TS-VII-(2S,3S)-Major, ΔG‡ = 17.3 kcal·mol⁻¹) to yield enantio- and diastereoenriched acyl ammonium product-catalyst complex IX. Catalyst turnover is computed as stepwise and begins with PNPO⁻ attack (TS-X) and ends with catalyst and product release (TS-XII). The barrier for PNPO⁻ attack as calculated from intermediate IX (ΔG‡ = 16.9 kcal·mol⁻¹) indicates that, in the absence of HOBt, this step is highly competitive with rearrangement as turnover-rate limiting.

(ii) The effect of counterions on the theoretical KIE. The presence of counterions posed a challenge to the accuracy of DFT, and significantly increased the complexity of the conformational search and the number of relevant structures to consider.³¹ Almost all species present in the catalytic cycle prior to catalyst turnover bear a positive charge, with intermediate V being dicaticonic. Species indicated to include a counterion in Scheme 8 were optimized with the explicit ion shown. Given the charged nature of the species present, the identification of the structures that compose the free-energy span resulted from considering all possible counterion coordination combinations for all conformations of each charged species in the catalytic cycle. This exhaustive process led to the identification of acyl substrate I and TS-VIII as the most stable intermediate and turnover-rate limiting step, respectively. Rearrangement is computed as the first irreversible step of the mechanism, thereby allowing kinetic
isotopic fractionation to occur. The computed KIE depends on the vibrational frequencies of I and TS VIII. The computed KIE could then be utilized to corroborate the computed thermodynamics and barriers of this energy span.34

In a multistep reaction with highly charged and zwitterionic species, leveraging KIE prescribes a means to not only identify the structures that compose the free-energy span,33 but also which ions coordinate, the binding site of the counterion,35 and the conformation.27,36 We sought to identify the coordination state of TS-VIII by leveraging both the KIE and computed barriers for TS-VIII-F; i.e. bearing the 4-fluoro substituent used for KIE determination (Scheme 7). Coordination to TS-VIII-F, formation of byproduct salt complexes, and conformations all affect the barrier in going from I-F to TS-VIII-F. Two possible counterions, PNPO– and Br–, were considered as TS counterions, while ipr,NH3+ was evaluated as a component of the possible remaining complexes (Figure 6). No coordination to the TS (Figure 6, left) leaves H-bond complex PNPOH–···ipr,NH3+ as the lowest-energy remaining complex, giving an overall ΔG‡ = 18.3 kcal-mol–1. Bromide ion binding to the TS (TS-VIII-F-(2S,3S)–Br, Figure 7, middle) also leaves complex PNPOH–···ipr,NH3+ (ΔG‡ = 18.7 kcal-mol–1). PNPO– binding and the complexation of ipr,NH3+ and Br– gives the highest barrier (TS-VIII-F-(2S,3S)–PNPO, ΔG‡ = 22.8 kcal-mol–1). With no counterion coordination to the TS (TS-VIII-F-(2S,3S)-Major), the KIE comp of 1.028 matches well with experiment (KIE exp = 1.031). Bromide complexation, which is computed as 0.4 kcal-mol–1 higher, also matches fairly closely, giving KIE comp of 1.041.38 PNPO– complexation leads to an erroneously large magnitude of rate difference between kii/kD, yielding KIE comp of 1.050.

iii) Stereocontrol model. The computed diastereomeric [2,3]-rearrangement TSs are shown in Figure 8. All TSs feature concerted C-C bond formation and ammonium N-C bond cleavage.4,6 The four main elements that control the stereochemical outcome of the reaction are (Figure 8):

A) E vs. Z configuration of the enolate in ylide VII: NBO analysis indicates that both ylide VII and TS-VIII-(2S,3S)-Major have significant enolate character.39 Ylide VII displays a C-O bond-order of 1.39 and a C-C bond-order of 1.52 (Figure 8, bottom left inset), while TS-VIII-(2S,3S)-Major displays a C-O bond-order of 1.54 and a C-C bond-order of 1.21.39 The computed bond order of 1.52 for ylide VII suggests partial C-C double bond character leading to distinct isomeric E and Z enolate configurations prior to rearrangement with the configuration set in place by the deprotonation step. The Z-configuration is heavily favored over the

![Figure 6: Computed TSs, ions, complexes, and KIEs involving the 4-fluoro substituted substrate I-F. The computed KIE depends on the coordination state of substrate I-F and TS-VIII-F. The violet highlighted atom is the isotopic proton (H/D). All energies in kcal-mol–1. Shaded green lines represent forming/breaking bonds. Green lines represent C–H electrostatic interactions and hydrogen bonds.](image)

E, as shown in the model system Z/E-35 where the Z is favored by >16 kcal-mol–1. All stable [2,3]-rearrangement transition structures feature the Z-enolate.

B) Anti vs. syn S catalyst to O substrate orientation: In all the lowest energy conformations of the ylide-VII and rearrangement TS-VIII, the S–O relationship is syn. The syn distances (~2.7–2.8 Å) are significantly below the sum of the Van der Waals radii (3.4 Å), indicating close-contact S···O interactions (Figures 7 and 8, orange lines).40 Computed model systems show >4 kcal-mol–1 preference for the conformation which contains the 1,5-S···O interaction (anti/syn-38, Figure 8). All [2,3]-rearrangement TSs that do not bear the S···O interaction are higher by >6 kcal-mol–1. The conformational bias towards the S–O syn arrangement is proposed to result from nO to σ* C=S delocalization coupled with electrostatic attraction of the partially-positive sulfur atom and partially-negative oxygen atom.40

C) Facial selectivity of rearrangement: The S···O interaction significantly rigidifies the ylide-VII structure, leaving conformational freedom only to the substrate cinnamyl group. With rearrangement possible from either face of the planar isothiourea catalyst, the facial selectivi-
ty is controlled by the catalyst Ph stereodirecting group. The most

Figure 7. Stereodetermine [2,3]-rearrangement TSs. All energies in kcal mol\(^{-1}\) and distances in Å. Shaded grey lines represent forming/breaking bonds. Solid orange lines represent non-bonding S•••O interactions. Dashed blue lines represent aromatic interactions.

favored [2,3]-TSs favor approach opposite to this group (TS-VIII-(2S,3S)-Major and TS-VIII-(2S,3R), Figure 7). Approach on the same side as the stereodirecting Ph is disfavored by >6 kcal mol\(^{-1}\) (TS-VIII-(2R,3R) and TS-VIII-(2R,3S)).

D) Endo vs. exo [2,3]-TS: Rearrangement can occur either endo or exo with respect to the substrate C=O (Figure 9). In the simple allyl model TS, the endo/exo preference is ~1 kcal mol\(^{-1}\). This preference is ~2 kcal mol\(^{-1}\) between TS-VIII-(2S,3S)-Major and TS-VIII-(2S,3R), and additional interactions contribute to the diastereoselectivity. In major TS there is a π-cation interaction, which is favored over the π-C-H interaction found in the minor.\(^{43}\)

Truncated fully optimized model systems probing the difference in energy between these interactions in the context of cationic BTM reveal ~1 kcal mol\(^{-1}\) preference for \(38\) π-cation over \(38\) π-C-H (Figure 8, bottom right inset).\(^{11}\) These two factors contribute to the computed 2 kcal mol\(^{-1}\) preference for TS-VIII-(2S,3S)-Major over TS-VIII-(2S,3R), in good agreement with the experimental selectivity of 1.5 kcal mol\(^{-1}\).

CONCLUSIONS

The experimental and computational investigation reported herein has provided mechanistic and stereochemical insight into the enantioselective isothiourea-catalyzed [2,3]-rearrangement of allylic ammonium ylides. Kinetic analysis by \(^{19}\)F NMR has allowed reaction profiles to be established and has identified an intermediate species.

Figure 8. Computed model systems (all energies in kcal mol\(^{-1}\) and distances in Å). (A) Preference for Z over E enolate. Enolate-like character indicated by bond orders (B. O.) estimated from the Wiberg bond indices (bottom left inset). (B) Effect of S•••O interaction on acylated catalyst conformation. (C) With the acylated catalyst conformation held rigid (S•••O), the BTM stereodirecting Ph sterically biases open enolate face. (D) Endo rearrangement is favored. In the major TS, this preference is reinforced by a π-cation interaction (bottom right inset).

Isotopic labelling of catalyst (\(^{15}\)N) and substrate (\(^{13}\)C) has confirmed the constitution of the catalytic intermediate as 29/IX by \(^{13}\)C NMR. Isotopic entrainment has shown 29/IX to be an irreversibly-generated intermediate that is productive towards catalysis. A series of crossover experiments have provided detailed information regarding the reversibility of each individual step of the catalytic cycle. The turnover-rate limiting step of the process varies between product release and [2,3]-rearrangement, depending on substrate conversion, Figure 1. The effect of excess HOBt upon the reaction is to accelerate product release, thus generating a greater proportion of the free BTM catalyst, Figure 5. This may then result in more effective interception of the background racemic reaction, and thus greater diversion onto the enantioselective pathway, Scheme 5. Computational analysis has provided finer detail for the fundamental steps in the catalytic cycle as well as the key interactions that control the stereochemical outcome of the process. The insight gained into this process will have implications in a wider context, especially in the use of activated esters in Lewis base catalysis, which is currently under investigation in our laboratories.\(^{44}\)

ASSOCIATED CONTENT
Additional discussion, kinetic data, experimental procedures, characterization data, NMR spectra and HPLC chromatograms, computed geometries, energies, and vibrational frequencies. This data is available free of charge via the internet.

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• Kinetic analysis • Isotopic labelling • Computations
• Competition KIEs • Onyx KIE program • Additive effects

Productive BTM-substrate intermediate identified by $^{15}$N and $^{13}$C labelling

**Sigmatropic [2,3]**
KIE$_{exp} = 1.031$
KIE$_{comp} = 1.028$