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

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ABSTRACT: A mechanistic study of the isothiurea-catalyzed enantioselective [2,3]-rearrangement of allylic ammonium ylides is described. Reaction kinetic analyses using ¹⁹F 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 ¹³C and ¹⁵N 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 stereocontrol, with a 1,5-S...O interaction and the catalyst stereodirecting group providing transition structure rigidification and enantioselectivity, while preference for cation- π interactions over C-H... π is responsible for diastereoselectivity.

INTRODUCTION

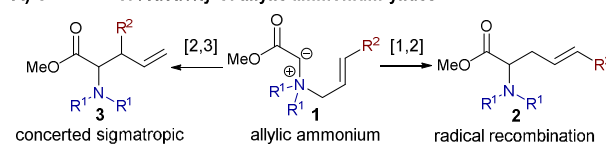
The [2,3]-rearrangement of allylic ammonium ylides is a direct and elegant method towards the synthesis of α -amino acid derivatives containing multiple stereocenters.¹ The mechanism of this process, and that of the competitive [1,2]-Stevens rearrangement, has been much discussed and disputed within 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 ¹³C 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

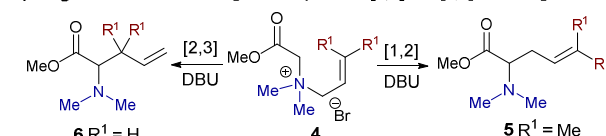
have reported a tandem

Scheme 1. Rearrangements of allylic ammonium ylides

A) Overview of reactivity of allylic ammonium ylides

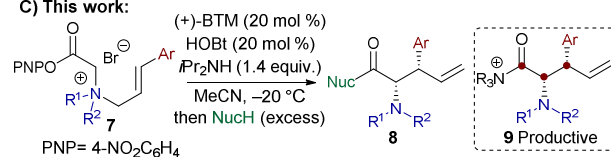


B) Singleton: Understanding of competitive [1,2]- vs [2,3]-rearrangement



• Natural Abundance ¹³C KIE • Computational Modelling
• Crossover Experiments

C) This work:



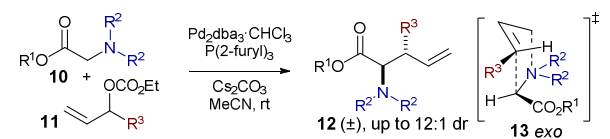
• Kinetic Analysis • Identification of Productive Catalytic Intermediate
• Computational Modelling • Competition KIEs
• Crossover Experiments • Additive Effects

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

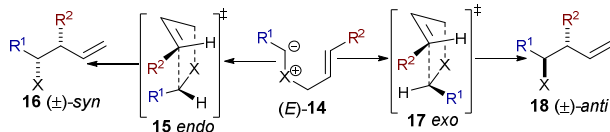
diastereocontrol via proposed transition state **13** (Scheme 2A).⁵ The

Scheme 2. Stereochemical models for [2,3]-rearrangements

A) Tambar: *in-situ* ylide generation and diastereoselective rearrangement



B) General stereochemical model for [2,3]-rearrangements



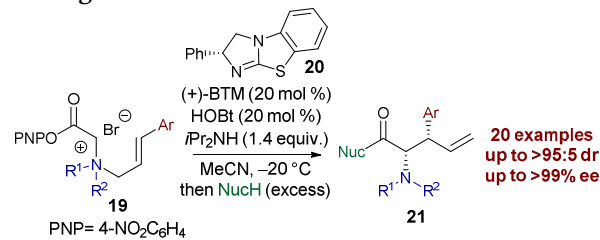
observed diastereoselectivity of this [2,3]-rearrangement process, and indeed most [2,3]-rearrangements, can be rationalized through the *exo*- or *endo*- transition states **15** and **17** initially described by Houk and Marshall for the related [2,3]-Wittig rearrangement (Scheme 2B).⁶

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 α -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 isothioureacatalyzed⁹ [2,3]-rearrangement of allylic quaternary ammonium salts to give *syn*- α -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 hydroxybenzotriazole (HOBt) and *i*Pr₂NH gave stereoselective [2,3]-rearrangement into *syn*- α -amino acid derivatives with excellent levels of stereocontrol. 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 nucleophilic 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 ketene 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.

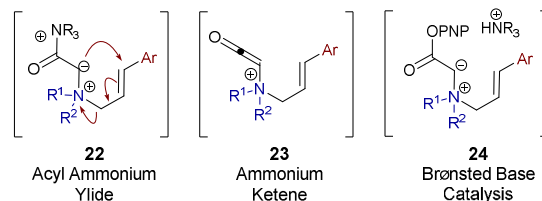
Herein we report experimental and computational investigations into the mechanism and origins of stereocontrol in the isothioureacatalyzed [2,3]-rearrangement of

allylic ammonium ylides (Scheme 1C). *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

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



Possible Reactive Intermediates:



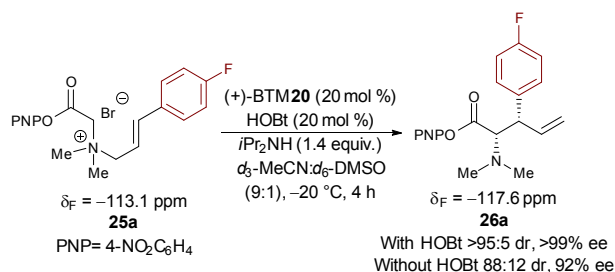
has given insight into the overall process and crossover studies have provided information about the reversibility of each step. Kinetic isotope analysis has also been used to probe the stereodetermining [2,3]-rearrangement step of the process. Computational reaction coordinate modelling provides deeper 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*₃-MeCN/*d*₆-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 ¹H NMR spectrum, making it unsuitable for *in situ* analysis of the [2,3]-rearrangement. However, the ¹⁹F{¹H} and ¹³C{¹H} NMR spectra were tractable, and the 4-fluoro substituent in **25a** allows quantitative monitoring of the process by *in situ* ¹⁹F{¹H} NMR ($\delta_F = -113.1$ ppm), with PhCF₃ as an internal standard.¹¹ 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 depleting

Scheme 4. System chosen for *in situ* ¹⁹F 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 ($\delta_F = -117.0$ ppm), over a longer period, assisting in its analysis.

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

(a) Catalyst speciation. To determine if the transient species ($\delta_F = -117.0$ ppm) involves the catalyst, a fluorinated variant,¹² (+)-F-BTM **27**, was prepared.¹¹ *In situ* monitoring of the [2,3]-rearrangement of **25a**, catalyzed by **27** (Figure 1), confirmed conversion of free (+)-F-BTM **27** ($\delta_F = -123.3$ ppm) into a catalyst-derived species ($\delta_F = -113.4$ 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 ($\delta_F = -117.0$ ppm and -113.4 ppm) strongly suggest they arise from a single transient intermediate containing both **25a** and **27** in a formal 1:1 combination. Based on reference to isothiuronium salt **28** ($\delta_F = -113.3$ ppm), the ¹⁹F chemical shift of the catalyst-derived component in transient species **29** suggested it to be an *N*-acylated isothiurea.

(b) Atom connectivity: ¹³C/¹⁵N labelling. Isotopically-labelled substrates and catalyst (1-¹³C]-**25a**, 1,2-¹³C]-**25a**, 1,2,3'-¹³C]-**25b** (Figure 2A) and (±)-¹⁵N]-**27**) were prepared¹¹ to deduce connectivity between various atoms in the intermediate and probe for reversibility in its generation. Rearrangement of 1,2-¹³C]-**25a** (34 mM) catalyzed by

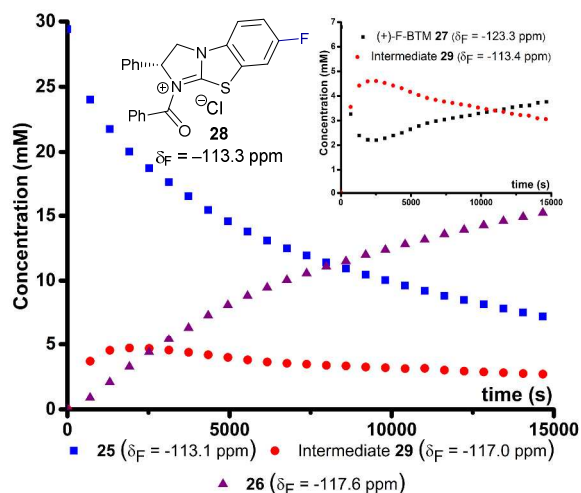
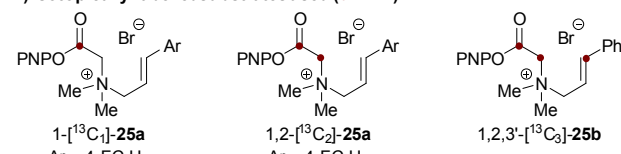
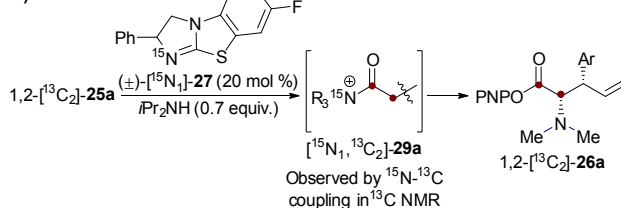


Figure 1. Temporal concentration data for [2,3]-rearrangement of **25a** using (+)-F-BTM **27**, conditions: **25a** (29.5 mM), (+)-F-BTM **27** (6.8 mM), *i*Pr₂NH (47 mM), d₃-MeCN/d₆-DMSO (9:1), -20 °C. Inset: monitoring of catalyst-derived species.

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



B)



C) ¹³C=O region of ¹³C{¹H} NMR

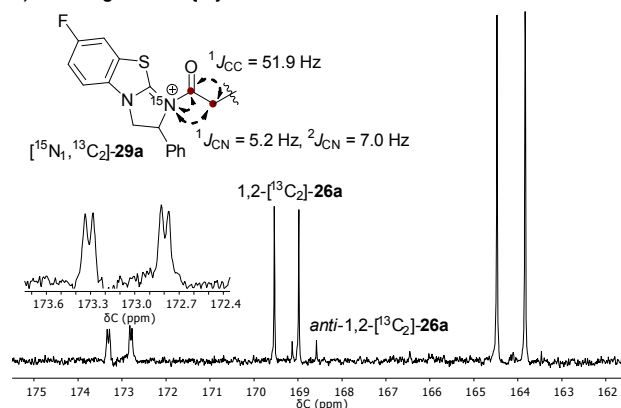


Figure 2. A) Isotopically-labelled substrates. B) Generation of [¹⁵N₁, ¹³C₂]-labelled intermediate **29a**. C) ¹³C{¹H} NMR sub-spectrum (101 MHz, d₃-MeCN/d₆-DMSO (9:1), 273K) of the ¹³C=O region. Conditions, 1,2-¹³C]-**25a** (34 mM), (±)-¹⁵N-F-BTM [¹⁵N]-**27** (6.8 mM), *i*Pr₂NH (23.8 mM).

(±)-¹⁵N]-**27** (6.8 mM, 20 mol %) was monitored by ¹³C{¹H} NMR (Figure 2B). Reducing the *i*Pr₂NH concentration to 23.8 mM prolonged the lifetime of the intermediate,

[^{15}N , $^{13}\text{C}_2$]-**29a**, allowing detailed analysis of the $^{13}\text{C}=\text{O}$ region, Figure 2C. The characteristic doublets ($J_{\text{CC}} = 52 \text{ Hz}$) arising from the adjacent ^{13}C labels, C(1)-C(2), in the substrate (1,2- $^{13}\text{C}_2$)-**25a** and the product (1,2- $^{13}\text{C}_2$)-**26a** are replaced by a double-doublet in [^{15}N , $^{13}\text{C}_2$]-**29a**, ($\delta_{\text{C}} = 173.1 \text{ ppm}$).¹³ The magnitude of the C-C coupling ($J_{\text{CC}} = 52 \text{ Hz}$) confirms that C(2) remains sp^3 -hybridized. The magnitude of the additional coupling constant ($J_{\text{CN}} = 5.2 \text{ Hz}$)¹³ indicates that C(1) is directly bound to the ^{15}N -labelled atom in the catalyst, confirming **29a** to be an *N*-acylated isothiurea (Figure 2).

Attempts to identify the atom adjacent to C(2) in [^{15}N , $^{13}\text{C}_2$]-**29a** from its ^1H -coupled ^{13}C NMR signal were thwarted by line broadening.¹³ Instead, the $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of intermediate 1,2,3- $^{13}\text{C}_3$]-**29b**, generated from 1,2,3'- $^{13}\text{C}_3$]-**25b**, was analysed, (Figure 3). The C(2) signal of the resulting [2,3]-rearrangement product 1,2,3- $^{13}\text{C}_3$]-**26b** ($\delta_{\text{C}} = 70.5 \text{ ppm}$) displayed the expected double-doublet coupling arising from C(2)-C(3) bond formation. However, this coupling pattern was also evident in intermediate 1,2,3- $^{13}\text{C}_3$]-**29b** ($\delta_{\text{C}} = 68.0 \text{ ppm}$, $J_{\text{CC}} 51.4 \text{ Hz}$, $J_{\text{CC}} 35.8 \text{ Hz}$) with the magnitude of the C(2)-C(3) coupling indicative of sp^3 -hybridization at both centres.¹³ Overall the data confirms that the intermediate (**29**) is a catalyst-bound, post [2,3]-rearrangement, acyl ammonium salt (Figure 3).

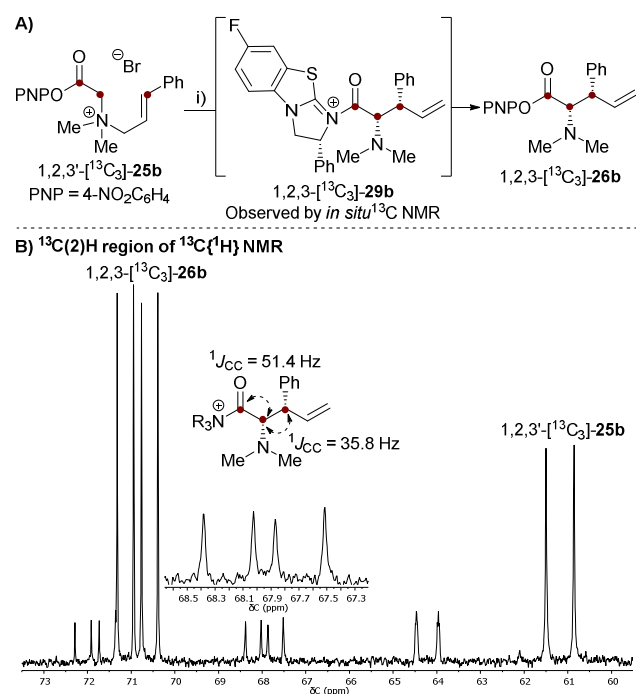


Figure 3. Catalyst-bound [2,3]-rearrangement product, $^{13}\text{C}\{^1\text{H}\}$ NMR sub-spectrum (101 MHz, d_3 -MeCN/ d_6 -DMSO (9:1), 293K) of the $^{13}\text{C}(2)$ -H region. Conditions: 1,2,3'- $^{13}\text{C}_3$]-**25b** (34 mM), (+)-F-BTM **27** (6.8 mM), $i\text{Pr}_2\text{NH}$ (23.8 mM).

(c) Productivity of the intermediate. The data presented so far does not discriminate between the *N*-acylated isothiurea 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- $^{13}\text{C}_1$]-**25a** (17 mM), was allowed to evolve until 1- $^{13}\text{C}_1$]-**29a** had reached its maximum concentration ($\sim 5 \text{ mM}$). A further 1.0 equivalent (17 mM) of a differently labelled substrate, 1,2- $^{13}\text{C}_2$]-**25a**, was then rapidly added, resulting in an isotopic perturbation of the system. At the point that 1,2- $^{13}\text{C}_2$]-**25a** is added, there has been 32% net conversion of **25a** ($^{13}\text{C}_1$ - and $^{13}\text{C}_2$ -). However, neither of the [2,3]-rearrangement products (**29a** and **26a**) yet contain any of the $^{13}\text{C}_2$ -label: all of this resides in unreacted $^{13}\text{C}_{1,2}$]-**25a**, which comprises 0.28 $^{13}\text{C}_1$ / 0.72 $^{13}\text{C}_2$. The key features are the changes in $^{13}\text{C}_2$ -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- $^{13}\text{C}_1$]-**25a** and 1,2- $^{13}\text{C}_2$]-**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% $^{13}\text{C}_2$) 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 $^{13}\text{C}_2$ -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% $^{13}\text{C}_2$ -) and the $^{13}\text{C}_2$ -content in **29a** rises from 0 % to a maximum of 72 % as it is repopulated from **25a**.¹⁴ However, for case C, equilibration of **29a** with product **26a** will attenuate the rise in $^{13}\text{C}_2$ -population in **29a**, in the limit to 50%. Only for case D will the $^{13}\text{C}_2$ isotope population in **29a** rise, in advance of **26a**, to reach a maximum 72% $^{13}\text{C}_2$.¹⁴ Comparison of the predicted and experimentally determined $^{13}\text{C}_2$ -populations as a function of net conversion (Figure 4) confirms that **26** arises from two irreversible sequential first-order interconversions (**25**→**29**→**26**) where **29** is the productive catalytic intermediate (case D).¹⁴ Kinetic modelling confirms that the impact of heavy-atom ($^{12}\text{C}/^{13}\text{C}$) KIEs on the isotope-entrainment are negligible.¹¹

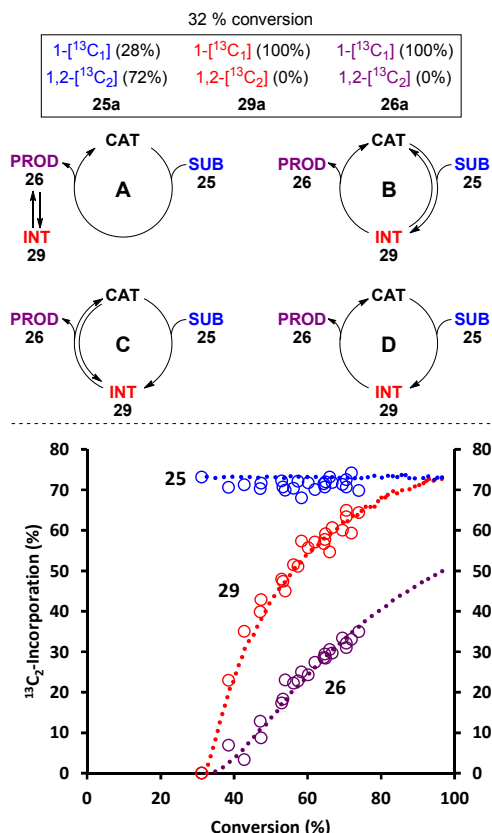


Figure 4. $^{13}\text{C}_2$ Entrainment into the catalytic cycle. Conditions, 1- $^{13}\text{C}_1$ -**25a** (17 mM), (+)-BTM (6.8 mM), $i\text{Pr}_2\text{NH}$ (47.6 mM), d_3 -MeCN/ d_6 -DMSO (9:1), with 1,2- $^{13}\text{C}_2$ -**25a** (17 mM) added at 32% net conversion of **25a**. Open circles: experimental ($^{13}\text{C}\{^1\text{H}\}$ NMR) data for $^{13}\text{C}_2$ -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).¹⁴

(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 $i\text{Pr}_2\text{NH}$ -mediated rearrangement of **25a** was examined. Reaction of **25a** with $i\text{Pr}_2\text{NH}$ (47 mM) in the absence of the BTM catalyst resulted in slow formation of racemic **26a** with low diastereocontrol (79:21 dr) and a k_{obs} of $2.74 \times 10^{-5} \text{ s}^{-1}$. The addition of a catalytic amount of HOBt (6.8 mM) resulted in no change in rate (k_{obs} $2.70 \times 10^{-5} \text{ s}^{-1}$). This rules out the role of HOBt as improving stereocontrol through direct suppression of the rate of the background reaction.

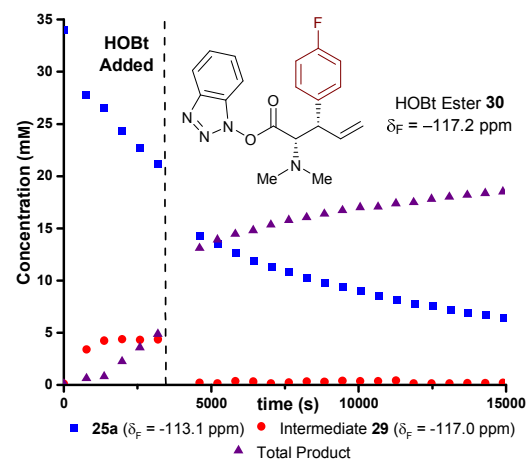
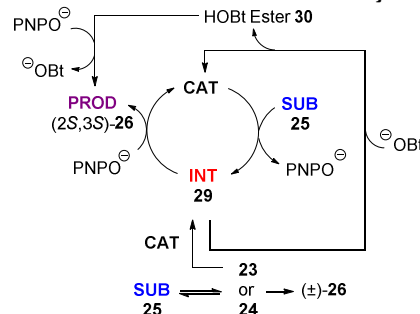


Figure 5. Addition of stoichiometric HOBt at $t = 3920 \text{ s}$. Conditions, **25a** (34 mM), (+)-BTM (6.8 mM), $i\text{Pr}_2\text{NH}$ (47.6 mM), d_3 -MeCN/ d_6 -DMSO (9:1), HOBt (34 mM). Total Product refers to both HOBt ester **30** and **26a**.

The (+)-BTM-catalyzed rearrangement of **25a** in the presence of stoichiometric HOBt (34 mM) was studied by $^{19}\text{F}\{^1\text{H}\}$ 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** ($\delta_F = -117.2 \text{ ppm}$, confirmed by comparison with an authentic sample),¹¹ in addition to the PNPO ester product **26a**. Addition of HOBt once the acyl ammonium intermediate **29c** reached the pseudo-steady state (5 mM, $t = 3920 \text{ s}$, 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 $i\text{Pr}_2\text{NH}$ -mediated reaction that converts **25** into racemic (\pm)-**26** presumably involves the generation of ylide intermediate **24**. Interception of this species by free (+)-BTM would also generate intermediate **29**, thus leading to non-racemic **26**. The higher the concentration of free BTM, the more effective this interception.

Scheme 5. Effect of HOBt on overall catalytic cycle

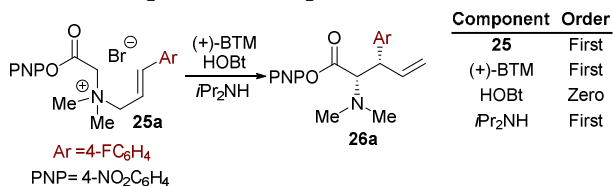


Overall, the beneficial effect of HOBt on the selectivity may arise from both a change in catalyst speciation to favour free BTM and by diversion of the background reaction onto the enantioselective pathway (Scheme 5).

(iv) **Reaction kinetics, and impact of additives.** Having identified, by $^{19}\text{F}\{^1\text{H}\}$ and $^{13}\text{C}\{^1\text{H}\}$ 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).¹⁵ The standard conditions [**25a** (34 mM), (+)-BTM (6.8 mM), HOBT (6.8 mM) and *i*Pr₂NH (47 mM)], afforded a pseudo-first order rate constant, $k_{\text{obs}} = 1.37 \times 10^{-4} \text{ s}^{-1}$.

Scheme 6. Empirical rate equation^a

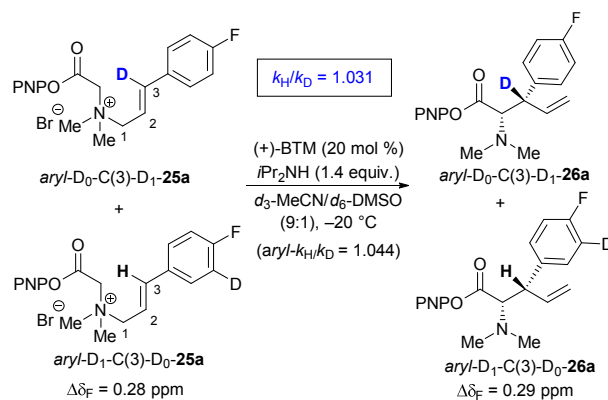


^a Conditions: **25a** (17 – 68 mM), (+)-BTM (1.7 – 13.6 mM), HOBT (0 – 34 mM), *i*Pr₂NH (23.8 – 95.2 mM), *d*₃-MeCN/*d*₆-DMSO (9:1), 253 K, 4 h.

There was a linear relationship between the enantiopurity of (+)-BTM and product **26a**, consistent with predominant or exclusive speciation of the catalyst in an active, monomeric, form.¹¹ Systematic variation of the concentration of the reaction components afforded first-order dependencies on (+)-BTM (1.7–13.6 mM) and diisopropylamine (23.8–95.2 mM), and with no rate-impact from the HOBT (0–34 mM). Addition of *n*-Bu₄N 4-nitrophenoxide (27.2 mM) in the absence of HOBT resulted in a large increase in rate ($k_{\text{obs}} = 2.42 \times 10^{-4} \text{ s}^{-1}$) and reduced the accumulation of the [2,3]-rearrangement acyl ammonium intermediate **29c** ($\leq 2 \text{ mM}$). Control studies showed that *n*-Bu₄NBr (27.2 mM) resulted in a similar rate enhancement ($k_{\text{obs}} = 2.35 \times 10^{-4} \text{ s}^{-1}$) but did not suppress the accumulation of **29c** (5 mM). The observed increase in k_{obs} may be rationalized by an increase in ionic strength of the medium.¹¹ The *n*-Bu₄N 4-nitrophenoxide thus promotes catalyst turnover of acyl ammonium **29c** into product **26a** and (+)-BTM. Addition of 4-nitrophenol (0–34 mM) resulted in a decrease in rate, with a negative first-order dependency. Overall, this suggests that 4-nitrophenoxide or benzotriazololate are required for efficient turnover of acyl ammonium **29c** into products **26a** / **30** and (+)-BTM.

(v) Secondary Kinetic Isotope Effect (SKIE). Although it is clear that the [2,3]-rearrangement to generate **29** is irreversible, it is not evident whether this is the product-determining step, i.e. the *first* irreversible step in the cycle. During the [2,3]-rearrangement step, the carbon that becomes C(3)-H in **29** undergoes rehybridization from sp² to sp³. The process to generate a C(3)-D isotopologue of **29** would be thus expected to exhibit a ³H-SKIE. Alternatively, if deprotonation at C(2)-H to generate an allylic ammonium ylide (Scheme 3) was the product-determining step, there would not be any significant SKIE, as C(3)-D is remote.

Scheme 7. C(3) SKIE competition experiment

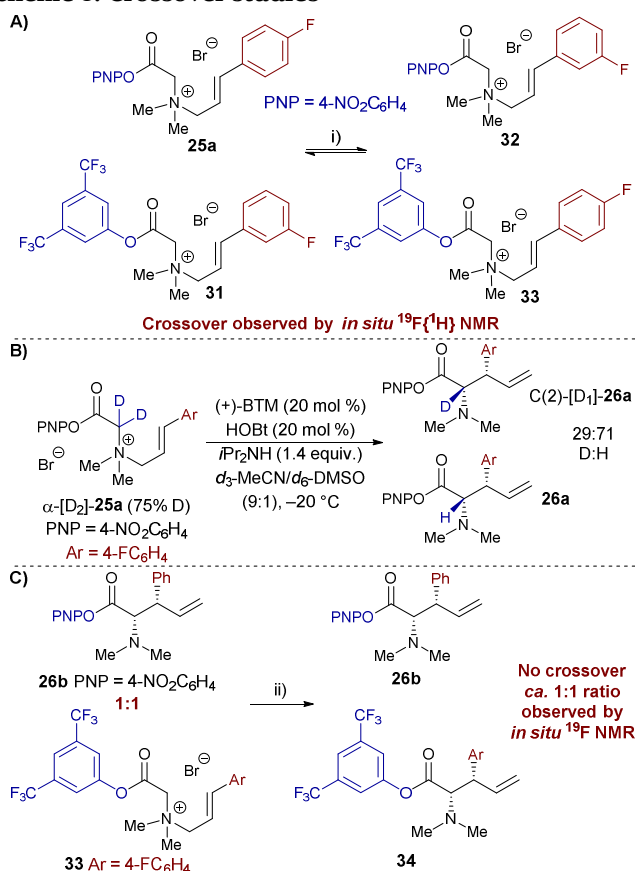


The SKIE was measured by competition using *aryl*-D₁-C(3)-D₀-**25a** and *aryl*-D₀-C(3)-D₁-**25a**, and a double-labelling method,¹⁶ in which the C(3)-D / C(3)-H ratio as a function of fractional conversion is determined by ¹⁹F NMR ($\Delta\delta_{\text{F}} = 0.28 \text{ ppm}$; *aryl*-D₀ / *aryl*-D₁). After correction for the effect of aryl deuteration,^{17,18} a value of $k_{\text{H}}/k_{\text{D}} = 1.031$ 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 substrates, against standard Hammett sigma values, showed the C(3) position to be insensitive to electronic substituent effects.¹¹

(vi) Crossover and reversibility studies. We have previously demonstrated the [2,3]-rearrangement step to be intramolecular and irreversible.¹⁰ 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-NO₂C₆H₄ and 3,5-(CF₃)₂C₆H₃) and two distinct C(3)-aryl units (4-FC₆H₄ and 3-FC₆H₄) was monitored *in situ* under catalytic conditions (Scheme 8A). Complete equilibration with ammonium salts **32** and **33** was observed,¹¹ consistent with reversible generation of non-rearranged (+)-BTM acyl ammonium intermediates. To examine reversibility at the deprotonation step, the [2,3]-rearrangement of α -dideuterio ammonium salt α -[D₂]-**25** (75% D₂) was monitored *in situ*. The product was obtained with significantly lower deuterium incorporation (29% D), consistent with a reversible deprotonation step (Scheme 8B).¹⁹ 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, consistent with catalyst turnover being irreversible, confirming the conclusions deduced from isotopic entrainment.

Computational Studies.

i) Computed catalytic cycle. We computed all intermediates, transition structures (TSs), and possible salt complexes involved in the mechanisms shown in Scheme 9. Exhaustive searches were performed to locate all pertinent conformations. Geometries and thermodynamic corrections were computed at the Mo6-2X²⁰/6-31G(d)²¹ level of theory.²² Vibrational frequencies and thermal corrections to the Gibbs free energy were calculated at –20 °C and 1 atm

Scheme 8. Crossover studies^a

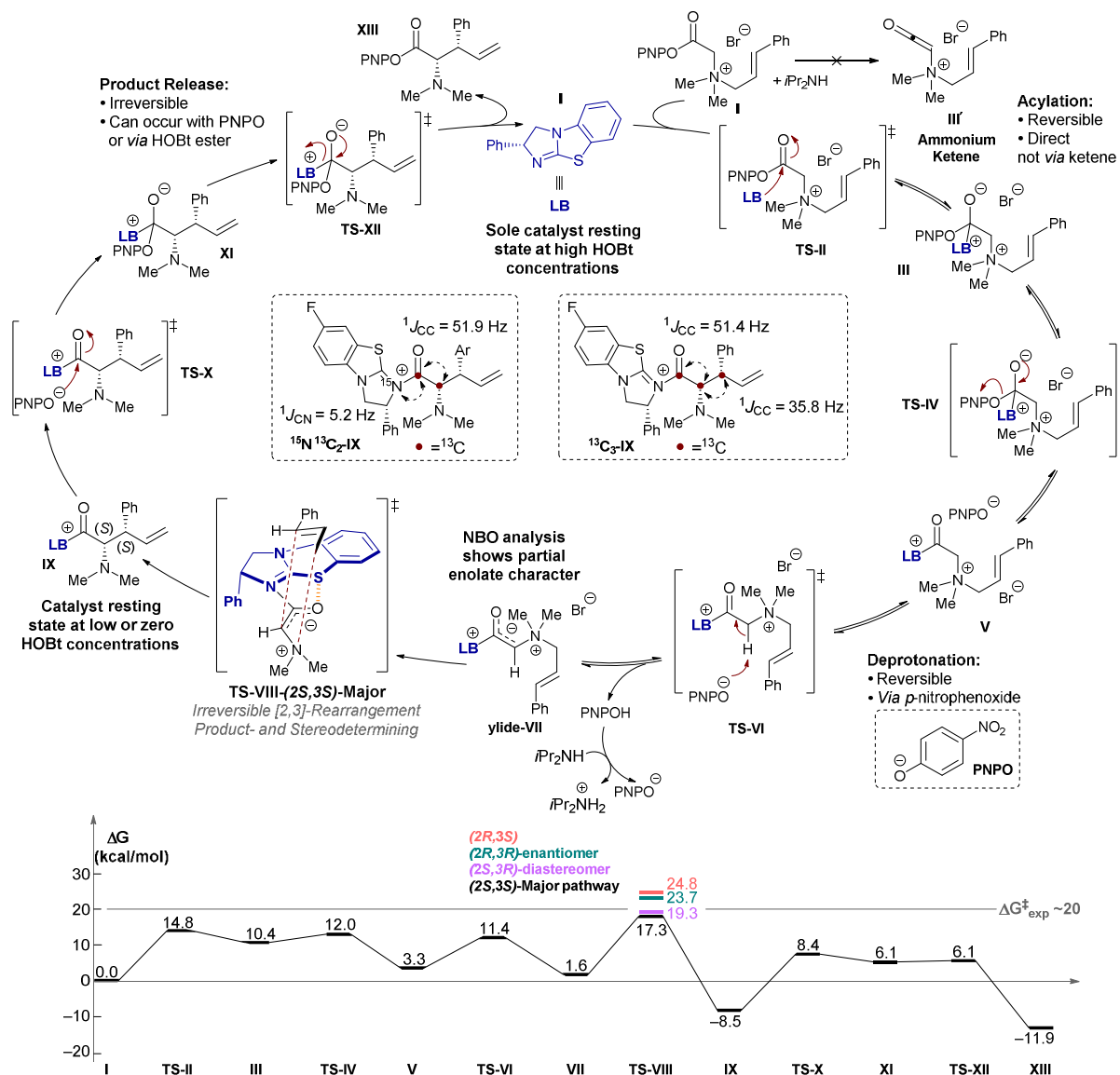
^a i) (+)-BTM (20 mol %), iPr₂NH (1.4 equiv.), 25a (0.5 equiv.), 31 (0.5 equiv.), d₃-MeCN/d₆-DMSO (9:1), 253 K, 4 h. ii) (+)-BTM (20 mol %), HOBt (20 mol %), iPr₂NH (1.4 equiv.), 26b (0.5 equiv.), 33 (0.5 equiv.), MeCN, 253 K

to match the experimental conditions. Further energy refinements were completed using Mo6-2X/6-311++G(2df,p).²³ Implicit solvation corrections were applied using the polarized continuum model (PCM)²⁴ with UFF radii for acetonitrile in both the geometry optimizations and the single-point energy refinements. The hybrid

Scheme 9. Proposed catalytic cycle and computed reaction coordinate

meta-GGA functional Mo6-2X is generally more robust than B₃LYP at accounting for dispersion and non-bonding interactions routinely found in organocatalytic reactions.²⁵ Kinetic isotope effects were calculated using the theory of Bigeleisen and Mayer²⁶ along with the rigid-rotor harmonic oscillator approach (ΔHΔS).²⁷ Quantum mechanical tunnelling effects were also calculated for both methods using the one-dimensional parabolic approximation.²⁸ The calculation of the KIE was automated by use of the Onyx isotope effect program.²⁹ 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



through formation of the ammonium ketene **III'** was ruled an unlikely reactive intermediate based on its high thermodynamic barrier for formation ($\Delta G^\ddagger = 22.0$ kcal·mol⁻¹). The small endergonicity of dication **V** ($\Delta G^\ddagger = 3.3$ kcal·mol⁻¹) confirms the observed reversibility of catalyst acylation. Dication **V** is in equilibrium with **ylide VII** ($\Delta G = 1.6$ kcal·mol⁻¹) through deprotonation of the α -proton of **V** by PNPO⁻ ($\Delta G^\ddagger = 11.4$ kcal·mol⁻¹), also in agreement with the experimentally-observed reversibility of the deprotonation step.^{30,31}

NBO analyses reveal significant enolate character of **ylide VII**. Intermediate **VII** subsequently undergoes stereoselective and turnover-rate limiting [2,3]-rearrangement (**TS-VIII**-(2*S*,3*S*)-Major, $\Delta G^\ddagger = 17.3$ 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** ($\Delta G^\ddagger = 16.9$ 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.³² Almost all species present in the catalytic cycle prior to catalyst turnover bear a positive charge, with intermediate **V** being dicationic. 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 span³³ 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 specific binding site of the counterion,³⁵ and the conformation.^{27b,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 $i\text{Pr}_2\text{NH}_2^+$ was evaluated as a component of the possible remaining complexes (Figure 6). No coordination to the TS (Figure 6, left) leaves H-bond complex $\text{PNPOH}\cdots i\text{Pr}_2\text{NH}$ as the lowest-energy remaining complex, giving an overall $\Delta G^\ddagger = 18.3$ kcal·mol⁻¹. Bromide ion binding to the TS (**TS-VIII-F-(2S,3S)···Br**, Figure 7, middle) also leaves complex $\text{PNPOH}\cdots i\text{Pr}_2\text{NH}$ ($\Delta G^\ddagger = 18.7$ kcal·mol⁻¹). PNPO^- binding and the complexation of $i\text{Pr}_2\text{NH}_2^+$ and Br^- gives the highest barrier (**TS-VIII-F-(2S,3S)···PNPO**, $\Delta G^\ddagger = 22.8$ 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 ($\text{KIE}_{\text{exp}} = 1.031$). 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 $k_{\text{H}}/k_{\text{D}}$, 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 1.21.¹¹ 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

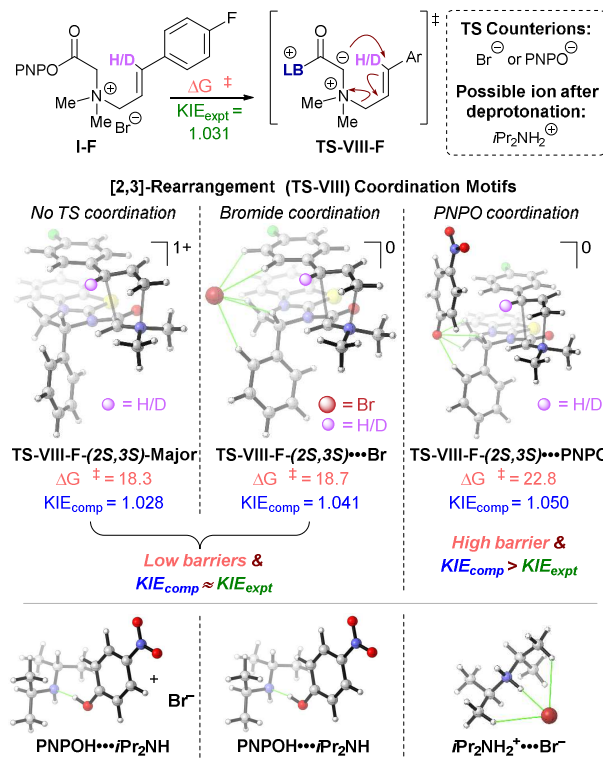


Figure 6. Computed TSs, ions, complexes, and KIEs involving the 4-fluoro substituted substrate **I-F**. The computed KIE depends on the coordination state of substrate **I-F** and **TS-VIII-F**. The violet highlighted atom is the isotopic proton (H/D).³⁷ All energies in kcal·mol⁻¹. Shaded grey lines represent forming/breaking bonds. Green lines represent C-H electrostatic interactions and hydrogen bonds.

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 $\text{S}\cdots\text{O}$ 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 $\text{S}\cdots\text{O}$ 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- $\text{S}\cdots\text{O}$ interaction (*anti/syn-38*, Figure 8). All [2,3]-rearrangement TSs that do not bear the $\text{S}\cdots\text{O}$ interaction are higher by >6 kcal·mol⁻¹.¹¹ The conformational bias towards the *S-O syn* arrangement is proposed to result from n_{O} to $\sigma_{\text{C-S}}^*$ delocalization coupled with electrostatic attraction of the partially-positive sulfur atom and partially-negative oxygen atom.⁴¹

C) Facial selectivity of rearrangement: The $\text{S}\cdots\text{O}$ 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 selectivity

ty is controlled by the catalyst Ph stereodirecting group. The most

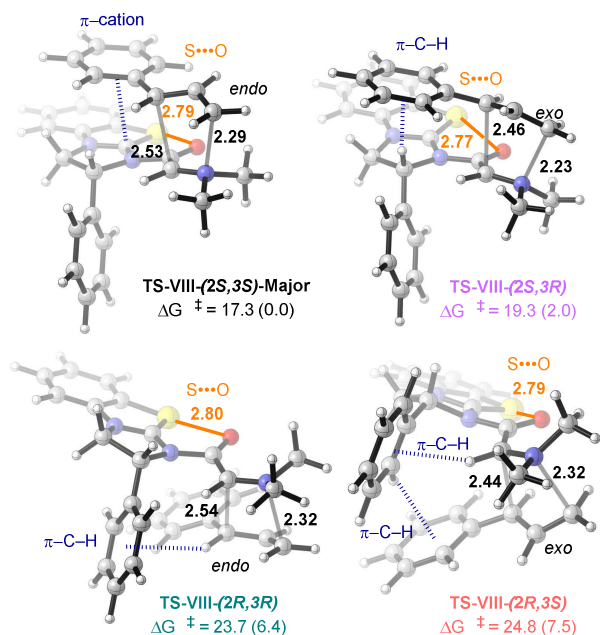


Figure 7. Stereodetermining [2,3]-rearrangement TSs.³⁴ All energies in kcal·mol⁻¹ and distances in Å. Shaded grey lines represent forming/breaking bonds. Solid orange lines represent non-bonding S...O interactions. Dashed blue lines represent aromatic interactions.

favorable [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,⁴² 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 isothioureacatalyzed [2,3]-rearrangement of allylic ammonium ylides. Kinetic

analysis by ¹⁹F NMR has allowed reaction profiles to be established and has identified an intermediate species.

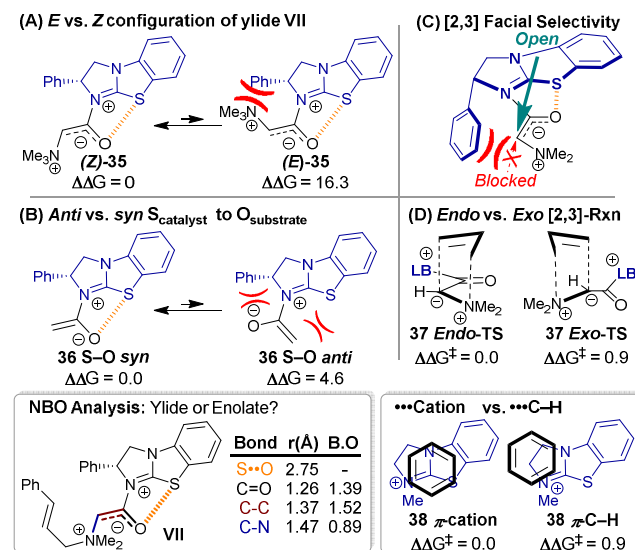


Figure 8. Computed model systems (all energies in kcal·mol⁻¹ and distances in Å). (A) Preference for Z over E enolate. Enolate-like character indicated by bond orders (B. O.) estimated from the Wiberg bond indices (bottom left inset). (B) Effect of S...O interaction on acylated catalyst conformation. (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 (¹⁵N) and substrate (¹³C) has confirmed the constitution of the catalytic intermediate as **29/IX** by ¹³C 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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REFERENCES

- (a) Sweeney, J. B. *Chem. Soc. Rev.* **2009**, 38, 1027-1038. (b) West, T. H.; Spoehrle, S. S. M.; Kasten, K.; Taylor, J. E.; Smith, A. D. *ACS Catal.* **2015**, 5, 7446-7479.
- Clark, J. S. Nitrogen, Oxygen, and Sulfur Ylide Chemistry: A Practical Approach in Chemistry; Oxford University Press: New York, **2002**.
- Kennedy, C. R.; Guidera, J. A.; Jacobsen, E. N. *ACS Cent. Sci.* **2016**, 2, 416-423.
- Biswas, B.; Collins, S. C.; Singleton, D. A. *J. Am. Chem. Soc.* **2014**, 136, 3740-3743.
- (a) Soheili, A.; Tambar, U. K. *J. Am. Chem. Soc.* **2011**, 133, 12956-12959. (b) Nash, A.; Soheili, A.; Tambar, U. K. *Org. Lett.* **2013**, 15, 4770-4773. (c) Soheili, A.; Tambar, U. K. *Org. Lett.* **2013**, 15, 5138-5141.
- Wu, Y. D.; Houk, K. N.; Marshall, J. A. *J. Org. Chem.* **1990**, 55, 1421-1423.
- Workman, J. A.; Garrido, N. P.; Sançon, J.; Roberts, E.; Wessel, H. P.; Sweeney, J. B. *J. Am. Chem. Soc.* **2005**, 127, 1066-1067.
- (a) Blid, J.; Panknin, O.; Somfai, P. *J. Am. Chem. Soc.* **2005**, 127, 9352-9353. (b) Blid, J.; Panknin, O.; Tuzina, P.; Somfai, P. *J. Org. Chem.* **2007**, 72, 1294-1300.
- Isothiouras have been widely explored as Lewis base catalysts across a range of organocatalytic processes. For a seminal report, see: Birman, V. B.; Guo, L. *Org. Lett.* **2006**, 8, 4859-4861. For reviews on isothiouras catalysis, see: (a) Taylor, J. E.; Bull, S. D.; Williams, J. M. *J. Chem. Soc. Rev.* **2012**, 41, 2109-2121. (b) Merad, J.; Pons, J.-M.; Chuzel, O.; Bressy, C. *Eur. J. Org. Chem.* **2016**, 2016, 5589-5610.
- West, T. H.; Daniels, D. S. B.; Slawin, A. M. Z.; Smith, A. D. *J. Am. Chem. Soc.* **2014**, 136, 4476-4479.
- See the supporting information for details.
- (+)-F-BTM **27** (20 mol %), HOBt (20 mol %) gave comparable reactivity and stereocontrol (68% yield, 92:8 dr, 97% ee) to the reaction using (+)-BTM **20** under the same conditions.
- Typical range for one bond carbon-carbon coupling constants: sp^2-sp^2 J_{CC} 75 – 80 Hz, sp^2-sp^3 J_{CC} 35 – 60 Hz, sp^3-sp^3 J_{CC} 25-55 Hz, Hansen, P. E.; Wray, V. *Org. Magn. Resonance* **1981**, 15, 102-103. The magnitude of observed J_{CN} and $^2J_{CN}$ coupling constants are consistent with the literature; Freyer, V. W. *Z. Chem.* **1981**, 21, 47-58; see supporting information for select examples. A $^2J_{CH}$ value of ~1-2 Hz would be expected for coupling between C(2) and C(3)H in the intermediate if the [2,3]-rearrangement has taken place. The presence or absence of this coupling could not be unambiguously established.
- The maximum $^{13}C_2$ population attainable in the intermediate is dictated by the relative rate of build-up and decay of the intermediate. The simulation used in Figure 4 employs a rate ratio for step 1 vs step 2 (k_1/k_2) of 0.407 leading to a maximum 6 mM concentration of the intermediate, analogous to that found experimentally under catalytic conditions.
- An initial drop in substrate concentration is observed and after ~3000 s **25a** decays with good pseudo-first order kinetics.
- Direct competition experiment analysed by 1H NMR was not possible due to significant line broadening. To allow ^{19}F NMR to be used, a double-labeling experiment was employed.
- Gonzalez, J. A.; Ogba, O. M.; Morehouse, G. F.; Rosson, N.; Houk, K. N.; Leach, A. G.; Cheong, P. H. Y.; Burke, M. D.; Lloyd-Jones, G. C. *Nat. Chem.* **2016**, 8, 1067-1075.
- (a) Perrin, C. L.; Dong, Y. *J. Am. Chem. Soc.* **2007**, 129, 4490-4497. (b) Pehk, T.; Kiirend, E.; Lippmaa, E.; Ragnarrsson, U.; Grehn, L. *J. Chem. Soc. Perk., Trans 2* **1997**, 445-450.
- Re-treatment of the PNP ester products under the reaction conditions resulted in no epimerization of the products.
- Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, 120, 215-241
- Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, 56, 2257-2261.
- Frisch, M. J. *et al.* Gaussian 09 (Gaussian, Inc., Wallingford CT, **2009**). See supporting information for full citation.
- Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, 28, 213-222.
- Miertuš, S.; Scrocco, E.; Tomasi, J. *Chem. Phys.* **1981**, 55, 117-129.
- (a) Wheeler, S. E.; Seguin, T. J.; Guan, Y.; Doney, A. C. *Acc. Chem. Res.* **2016**, 49, 1061-1069. (b) Sunoj, R. B. *Acc. Chem. Res.* **2016**, 49, 1019-1028. (c) Walden, D. M.; Ogba, O. M.; Johnston, R. C.; Cheong, P. H.-Y. *Acc. Chem. Res.* **2016**, 49, 1279-1291. (d) Gould, E.; Walden, D. M.; Kasten, K.; Johnston, R. C.; Wu, J.; Slawin, A. M. Z.; Mustard, T. J. L.; Johnston, B.; Davies, T.; Cheong, P. H.-Y. and Smith, A. D. *Chem. Sci.*, **2014**, 5, 3651-3658.
- Bigeleisen, J.; Mayer, M. G. *J. Chem. Phys.* **1947**, 15, 261-267.

- (27) (a) Fong, A.; Meyer, M. P.; O'Leary, D. J. *Molecules* **2013**, *18*, 2281–2296. (b) O'Leary, D. J.; Rablen, P. R.; Meyer, M. P. *Angew. Chem. Int. Ed.* **2011**, *50*, 2564–2567.
- (28) (a) Northrop, D. B. *J. Am. Chem. Soc.* **1999**, *121*, 3521–3524. (b) Bell, R. P. *The Tunnel Effect in Chemistry*. New York: Chapman and Hall; **1980**. (c) Bell, R. P. *Chem. Soc. Rev.* **1974**, *4*, 513–544.
- (29) Kinetic isotope effects calculated using the Onyx program: Brueckner, A. C.; Cevallos, S. L.; Ogba, O. M.; Walden, D. M.; Meyer, M. P.; O'Leary, D. J.; Cheong, P. H.-Y. *Onyx*, version 1.0; Oregon State University: Corvallis, OR, USA, **2016**.
- (30) Deprotonation by $i\text{Pr}_2\text{NH}$ was also computed, but gave a much higher barrier of 20.5 kcal·mol⁻¹. See supporting information for structural details.
- (31) The presence of an ylide intermediate has been confirmed in the closely related [1,2]-Stevens rearrangement of ammonium acetophenones: Capobianco, A.; Caruso, T.; Palombi, L.; Peluso, A. *Electrochim. Acta* **2013**, *92*, 446–451.
- (32) Bedin, M.; Karim, A.; Reitti, M.; Carlsson, A.-C. C.; Topić, F.; Cetina, M.; Pan, F.; Havel, V.; Al-Ameri, F.; Sindelar, V.; Rissanen, K.; Gräfenstein, J.; Erdélyi, M. *Chem. Sci.* **2015**, *6*, 3746–3756.
- (33) Free energy span is the energetic counterpart of turnover frequency: (a) Rohmann, K.; Hölscher, M.; Leitner, W. *J. Am. Chem. Soc.* **2016**, *138*, 433–443. (b) Yu, Z.-X.; Cheong, P. H.-Y.; Liu, P.; Legault, C. Y.; Wender, P. A.; Houk, K. N. *J. Am. Chem. Soc.* **2008**, *130*, 2378–2379. (c) Kozuch, S.; Shaik, S. *J. Am. Chem. Soc.* **2006**, *128*, 3355–3365.
- (34) Plata, R. E.; Singleton, D. A. *J. Am. Chem. Soc.* **2015**, *137*, 3811–3826.
- (35) Świderek, K.; Paneth, P. *Chem. Rev.* **2013**, *113*, 7851–7879.
- (36) Hirschi, J. S.; Takeya, T.; Hang, C.; Singleton, D. A. *J. Am. Chem. Soc.* **2009**, *131*, 2397–2403.
- (37) Structure images generated using the CylView molecular visualization program: Legault, C. Y. *CYLview*, version 1.0b; Université de Sherbrooke: Quebec, Canada, **2009**; <http://www.cylview.org>.
- (38) Bromide coordination to the TS is likely weak, as evidenced by the minor difference in energy between bromide coordinated TS and uncoordinated TS (0.4 kcal·mol⁻¹ favoring no counterion, Figure 6). This suggests a Boltzmann-weighted distribution of KIEs contributes to the experimentally observed KIE. The Boltzmann averaged KIE from the static TSs matches the observed KIE. However, the flexibility and energetic accessibility of conformers and complexes indicates that explicit solvation and dynamics also play a role.
- (39) Computed bond orders using NBO analysis indicated enolate character for ylide VII. TS-VIII lies in between dication V and ylide VII in terms of enolate-like character. See SI for details.
- (40) For S^{••}O interactions as control elements in isothiourea catalysis, see: (a) Robinson, E. R. T.; Walden, D. M.; Fallan, C.; Greenhalgh, M. D.; Cheong, P. H.-Y.; Smith, A. D. *Chem. Sci.* **2016**, *7*, 6919–6927. (b) Abbasov, M. E.; Hudson, B. M.; Tantillo, D. J.; Romo, D. *J. Am. Chem. Soc.* **2014**, *136*, 4492–4495. (c) Liu, P.; Yang, X.; Birman, V. B.; Houk, K. N. *Org. Lett.* **2012**, *14*, 3288–3291. (d) Birman, V. B.; Li, X.; Han, Z. *Org. Lett.* **2007**, *9*, 37–40. For an alternative use of non-bonded S^{••}O interactions in asymmetric synthesis see Nagao, Y.; Miyamoto, S.; Miyamoto, M.; Takeshige, H.; Hayashi, K.; Sano, S.; Shiro, M.; Yamaguchi, K.; Sei, Y. *J. Am. Chem. Soc.* **2006**, *128*, 9722–9729.
- (41) NBO calculation by Romo and Tantillo suggest a number of orbital interactions responsible for the conformational preference. See 35b. For additional discussions on the origin of the S^{••}O interaction, see: (a) Beno, B. R.; Yeung, K.-S.; Bartberger, M. D.; Pennington, L. D.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 4383–4438. (b) Zhang, X.; Gong, Z.; Li, J.; Lu, T. *J. Chem. Inf. Model.* **2015**, *55*, 2138–2153. Fairlie has suggested electrostatic attraction and dipole minimization. See: (c) Reid, R. C.; Yau, M.-K.; Singh, R.; Lim, J.; Fairlie, D. P. *J. Am. Chem. Soc.* **2014**, *136*, 11914–11917.
- (42) (a) Wheeler, S. E.; Bloom, J. W. *J. Phys. Chem. A* **2014**, *118*, 6133–6147. (b) Yang, X.; Liu, P.; Houk, K. N.; Birman, V. B. *Angew. Chem. Int. Ed.* **2012**, *51*, 9638–9642. (c) Yang, X.; Bumbu, V. D.; Birman, V. B. *Org. Lett.* **2011**, *13*, 4755–4757. (d) Yamada, S.; Fossey, J. S. *Org. Biomol. Chem.* **2011**, *9*, 7275–7281. (e) Wheeler, S. E.; Houk, K. N. *J. Am. Chem. Soc.* **2009**, *131*, 3126–3127. (f) Zhao, Y.; Cotellet, Y.; Sakai, N.; Matile, S. *J. Am. Chem. Soc.* **2016**, *138*, 4270–4277. (g) Kennedy, C. R.; Lin, S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2016**, *55*, 12596–12624.
- (43) Krenske, E. H.; Houk, K. N. *Acc. Chem. Res.* **2013**, *46*, 979–989.
- (44) The research data underpinning this publication can be found at DOI: <http://dx.doi.org/10.17630/odbeff98-db91-4051-803c-24e46c073f22>.

TOC Graphic

