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Multi-Ion Bridged Pathway of *N*-Oxides to 1,3-Dipole Dilithium Oxide Complexes

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and provides significant insights to guide the creation of new Noxide reagents beyond tertiary alkylamines for direct synthetic transformations. Truhlar's M06-2x functional and Møller–Plesset second-order perturbation theory with Dunning's [jul,aug]-cc-pv[D,T]z basis sets and discrete-continuum solvation models were employed to determine activation enthalpies and structures. During these mechanistic explorations, we discovered a unique multiion bridged pathway resulting from the rate-determining step, which was energetically more favorable than other alternate mechanisms. This newly proposed mechanism contains no electrophilic intermediates, strengthening the reaction potential by broadening the reagent scope and limiting the possible side reactions. This thoroughly defined general mechanism supports a more direct route for improving the use of N-oxides in generating azomethine ylide–dilithium oxide complexes with expanded functional group tolerance and breadth of chemistry.

1. INTRODUCTION

Azomethine ylides are a robust tool for the formation of cyclic nitrogen-containing ring systems¹ that serve as essential yet challenging motifs within natural products and pharmaceuticals.² Intra- and intermolecular cyclization occur via dimerization,^{3–5} Michael-type addition,^{6–10} and electrocyclization,^{11–15} but primarily through [3 + 2] cycloaddition with dipolarophiles.^{16–21} First reported by Huisgen in the early ²⁴ [3 + 2] dipolar cycloadditions are efficient and 1960s,²² regioselective methods for forming cyclic compounds, typically following Woodward-Hoffmann rules.²⁵ Moreover, Houk's theoretical and computational work into [3 + 2] cycloadditions has established a mechanistic framework for synthetic control.²⁶⁻²⁹ Strategic use of 1,3-dipolar cycloadditions has been pivotal in the synthesis of several natural products (Figure 1), including daphniphyllum 1,³⁰ stemofoline 2,³¹ daphnilactone 3^{32} pancracine 4^{33} epibatidine 5^{34} and 5-deoxymubironine 6^{35} For the synthesis of the natural products in Figure 1, and other pyrrolidine motifs of pharmaceutical interest, it is necessary to identify and efficiently synthesize the requisite dipolar azomethine ylide.

ion or a diradical intermediate. Our investigation has revealed an

alternative mechanistic pathway that explains experimental results

Many routes have been extensively studied experimentally^{36–52} and computationally^{53–60} for the synthesis of the requisite starting materials (Figure 2). For example, many of the most popular approaches, including desilylation, Nmetalation, and decarboxylation, are dependent on specific auxiliary groups, requiring additional steps along with an intrinsically decreased reaction scope.⁶¹ In contrast, 1,3-dipoles prepared from *N*-oxides represent an efficient single-step process without the need for anion-stabilizing groups.⁶² Unfortunately, there has been little follow-up exploration since Roussi's initial evaluation of the tertiary amine *N*-oxide route.¹ His initial work was on a limited set of substrates including trimethylamine,⁶³ dibenzylmethylamine,⁶² benzyldimethylamine,⁶⁴ and β -amino alcohols.^{65–67} These experiments resulted in modest yields, none higher than 66%, and lacked significant levels of regio- and/or stereoselectivity, with 36% de obtained under optimal conditions.^{62,67} However, the fundamental reaction remains attractive and shows significant promise as an efficient route to biologically relevant structures from simple precursors.

Multi-Ion

Bridge

To address the issues reported by Roussi and assess the potential of this transformation, we set out to further study the underlying mechanism with modern computational tools. Currently, a general mechanism for the *N*-oxide route is unclear, therefore elucidating that the mechanism is likely to increase both interest and inspire its practical use. Roussi et al. originally reported the *N*-oxide route to 1,3-dipoles in 1982,

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1,3-Dipole•Li₂O





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Figure 1. Natural products synthesized with 1,3-dipolar cycloadditions, with the pyrrolidine ring formed by the reaction being highlighted in red.



Figure 2. Routes for the synthesis of 1,3-dipole.

starting with dibenzylmethylamine *N*-oxide 7 and benzyldimethylamine *N*-oxide **10** (Figure 3).^{62,64} The work was eventually expanded to include trimethylamine *N*-oxide.⁶³ Treatment of these tertiary amine *N*-oxides with strong bases resulted in either dimerization or a [3 + 2] cycloaddition when in the presence of alkene dipolarophiles.^{65–67} Given the importance of the pyrrolidine motif and the need to synthesize the requisite compounds, it is surprising that the mechanism for conversion of *N*-oxides into azomethine ylide has yet to receive thorough attention.

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In his seminal papers, Roussi proposed two different mechanisms. One for dibenzylmethylamine N-oxide 7 (Figure 4), which moves through iminium intermediate 14 evident from the production of undesired Polonovski-type products benzaldehyde 17 and N-methyl phenylmethanamine 16.62 Products 16 and 17 presumably result from the nucleophilic attack of the lithium oxide onto the iminium ion 14 (Figure 4, pathway B) instead of the deprotonation path (Figure 4, pathway A), which would yield the desired 1,3-dipole 8. Alternatively, 1,3-dipole 8 can undergo protonation (Figure 4, pathway C), leading to products 16 and 17 through an orthogonal pathway. Therefore, the formation of aldehyde and secondary amine products alone do not provide proof of iminium intermediate 14. Roussi's other proposed mechanism did not reflect physical observations and was not considered in our work.⁶⁴

Similarly, a recent paper sought to further understand the mechanism of 1,3-dipole synthesis from *N*-methylmorpholine *N*-oxide (NMO).⁶⁸ However, with an oxygen contained in the ring system, NMO provided a challenging substrate, resulting in a variety of undesired side products.⁶⁸ To avoid unnecessary



Figure 3. Reactions of *N*-oxide forming 1,3-dipoles.

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Figure 4. Roussi's two mechanistic pathways (A and B) for N-oxide 1,3-dipole formation with iminium intermediate from dibenzylmethylamine N-oxide 7.

complexity, we removed excess reactive functionality from our model systems and chose to investigate tertiary alkylamine Noxides. The conclusions we draw are more broadly applicable to novel systems, and the selected framework maps well onto natural product targets. While azomethine ylide formation can be accomplished in a variety of different methods with known challenges, Roussi's work has been underutilized within the synthetic community. By uncovering the N-oxide precursor to unstabilized azomethine ylides, Roussi's work provided a versatile and simple synthesis to a wide variety of pyrrolidine motifs. However, with a suggested mechanism involving an electrophilic iminium intermediate, many synthetic chemists have avoided the reaction since such intermediates lack the control to produce high yields within complex systems. Yet, neither Roussi nor other recent workers⁶⁸ considered the formation of a multi-ion bridged intermediate, which we show is favored over the iminium intermediate. By moving through the multi-ion bridged intermediate, no electrophilic intermediate exists within the reaction path, considerably broadening the scope of compatible substrates. Furthermore, identification of the rate-determining step provides a focal point for reaction control and optimization.

2. RESULTS AND DISCUSSION

To achieve a clear and general understanding of 1,3-dipole formation from *N*-oxides, we modeled the transformation of *tert*-butyl pyrrolidine *N*-oxide **18** into its corresponding azomethine ylide **19** (Figure 5). *tert*-Butyl pyrrolidine was



Figure 5. Model reaction scheme for mechanistic evaluation of *N*-oxide route to 1,3-dipoles.

chosen due to its structural simplicity, limited reactivity, rigidity that allows for a clear stereodifferentiation between the re and si faces of the N-oxide model, and applicability to complex targets (Figure 1). Based on the proposed mechanisms given by Roussi and co-workers,^{62,64} we started our investigation by interrogating the iminium pathway, as shown in Figure 6. However, careful assessment uncovered the importance of model selection where lithium diisopropyl amide (LDA), tetrahydrofuran (THF), and diisopropylamine (DIPA) molecules were found to be intimate parts of the Noxide to azomethine ylide reaction pathway. Specifically, we have found that one LDA/THF complex is required for each deprotonation step. Consistent with the previous work by Singleton and others, it is necessary to include explicit solvent in conjunction with implicit models to elucidate organic reaction mechanisms and energy pathways.^{69,70} Consequently, our reported efforts feature the discrete-continuum solvent approximation in expanding the quantum system beyond an isolated N-oxide.

Discussion of the novel multi-ion bridged mechanism is segmented into nine sections aligned with the steps of the reaction pathway as outlined in Figure 7, where the critical factors supporting and differentiating the multi-ion bridged mechanism are addressed. The sections involve in-depth discussion on how N-oxide complexation with the first and second equivalents of the base and solvent results in a preorganized ground state for deprotonation guided by the steric congestion, rigidity, and geometric confines of such Noxide complexes (Sections 2.1 and 2.5), the syn-planar deprotonation preference (Section 2.2), the formation of a crucial four-member heterocycle (Section 2.3), the leaving of LiO⁻ for possible iminium formation (Section 2.4), the critical juncture between the breaking of the N-oxide oxygennitrogen bond defining the iminium pathway (Section 2.6) and the second deprotonation that shifts preference through the favored multi-ion bridged mechanism (Section 2.7), the geometric and energetic description of the multi-ion bridged

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Figure 6. Possible reaction pathways from N-oxide 18 to 1,3-dipole Li₂O 19_a and 1,3-dipole 19_b.



Figure 7. Reaction coordinate diagram, with ball-and-stick representation at key steps, of the *tert*-butyl pyrrolidine N-oxide formation of the 1,3-dipole- Li_2O with relative enthalpies in kcal/mol.

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structure (Section 2.8), and finally the creation of the 1,3dipole- Li_2O complex, a novel, facial-selective, cycloaddition control element (Section 2.9).

2.1. *N***-Oxide Complexation with LDA and THF.** To appreciate the flexibility of *N*-oxide **18**, a systematic search was carried out by rotating the *tert*-butyl group and probing different envelope conformations of the pyrrolidine ring. Only two conformations (Figure 8) with the pyrrolidine ring in



Figure 8. Two conformations of N-oxide 18, where 18_{endo} is 4.2 kcal/ mol higher in energy than 18_{exo} . The protons are indicated as either *syn-* (orange) or *anti-*planar (green) with respect to the N–O bond. Bond distances and nonbonded atom distances, indicated by gray lines, are given in Å.

either a destabilized endo form 18_{endo} (4.2 kcal/mol) or a lowenergy exo conformation 18_{exo} (0 kcal/mol) were located. Both envelope conformations place the N–O bond in the outof-plane position to minimize the N–O bond eclipsing with the *tert*-butyl substituent and adjacent CH bonds. No other minima could be identified, underscoring the steric congestion and rigidity of such *N*-oxides.

In 18, the α -carbons have two types of protons, referred to as syn- and anti-planar, defined with respect to the spatial orientation of the N-O bond, as shown in Figure 8. Destabilization of 18_{endo} originates from the differential positioning of its anti-planar protons (green) with respect to the tert-butyl group as compared to the syn-planar protons (orange) in 18_{exo} resulting from the pyrrolidine ring flip. Specifically, the anti-planar protons in 18_{endo} have close steric interactions of 2.00 and 2.05 Å with the tert-butyl substituent, while the $\mathbf{18}_{exo}$ syn-planar protons have an increased separation of 2.20 and 2.35 Å. Additional energetic consequences resulting from other steric interactions were examined in detail and found to mostly cancel between the two conformations, making the interactions shown the most significant. Ultimately, the positioning of the protons yields preorganized ground states for a restricted alignment yielding syn-planar selectivity, as discussed in Section 2.3, for the eventual deprotonation transition structures.

To identify the possible configurations of the *N*-oxide, LDA, and THF complexes, the systematic placement of LDA and THF around the isolated *N*-oxide **18** (both exo and endo) was carried out by considering three possible complexation modes, where each started with the lithium of LDA coordinated with the *N*-oxide oxygen of 18_{endo} and 18_{exo} as an obvious anchor point. The three geometries considered initially placed LDA over the *tert*-butyl group, over the pyrrolidine ring, or in the crevice between the pyrrolidine and tert-butyl groups. From the three starting structures, only one energy minimum complex structure between LDA and 18_{endo} or 18_{exo} was located for each conformation. THF was then added in different orientations with respect to the LDA lithium. The structures resulted with LDA in the crevice and THF

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completing the coordination sphere of the lithium from LDA, referred to as 20_{endo} and 20_{exo} , giving an enthalpy of stabilization of -23.2 kcal/mol for the 20_{exo} structure, as shown in Figure 9.



Figure 9. Two conformations of 18 complexed with LDA and THF minimized to 20_{endo} and 20_{exo} . The protons are indicated as either *syn*(orange) or *anti*-planar (green) with respect to the N–O bond. Bond distances and nonbonded atom distances, indicated by gray lines, are given in Å.

The same steric factors involving the α -carbon protons and tert-butyl group that destabilize endo over exo 18 were found to be a large part (ca. 74%) of the explanation for the unique ground-state geometries and relative energies of $\mathbf{20}_{endo}$ and $\mathbf{20}_{exo}$. The *anti*-planar protons in $\mathbf{20}_{endo}$ have close interactions of 2.04 and 2.07 Å with the tert-butyl substituent, while the 20_{exo} syn-planar protons have increased separation distances of 2.16 and 2.37 Å, relieving the steric interaction. However, the energy separation between 18_{endo} and 18_{exo} of 4.2 kcal/mol is exacerbated to 5.7 kcal/mol for 20_{endo} and 20_{exo}. Despite several additional steric interactions between the constituents within both $\mathbf{20}_{endo}$ and $\mathbf{20}_{exo}$, only the positioning of the proton to be transferred relative to the LDA nitrogen was found to be significantly different to account for the remaining 1.5 kcal/ mol energy separation of $\mathbf{20}_{endo}$ and $\mathbf{20}_{exo}$. Specifically, the distance between the base and proton along with the linearity of the LDA nitrogen, transferring proton, and α -carbon were the two parameters characterizing the remaining difference between ground states $\mathbf{20}_{\text{endo}}$ and $\mathbf{20}_{\text{exo}}.$ In both systems, where the LDA finds a steric crevice, the resulting geometry positions the basic nitrogen of LDA toward the α -carbon protons for deprotonation. In destabilized 20_{endo} (5.7 kcal/mol), the unfavorable endo conformation struggles to make the antiplanar hydrogen available for deprotonation. As shown in Figure 9, the positioning for anti-planar deprotonation is less than optimal with a N…HC^{α} distance of 2.74 Å and an \angle N– $H-C^{\alpha}$ alignment of 114° in 20_{endo}. The syn-planar proton of 20_{endo} is even further removed from LDA's nitrogen at 3.03 Å with an $\angle N-H-C^{\alpha}$ alignment of 97° and consequently less likely deprotonated. In contrast, the more stable 20_{exo} groundstate geometry provides a more natural fit to promote the synplanar deprotonation, where the N···HC^{α} syn-planar distance is decreased to 2.36 Å and the $\angle N-H-C^{\alpha}$ alignment improves to 154°.

2.2. syn-Planar Deprotonation Preference. Enlightened by the preorganization and steric congestion of the computed ground-state geometries of 20_{endo} and 20_{exo} , the commonly accepted mechanism via a concerted elimination with the hydrogen *anti*-planar to the oxygen being deprotonated seemed unlikely. However, to determine the stereoelectronic origin of *syn*-planar selectivity, both transition structures for the anti-planar $(20_{TS-endo})$ and syn-planar (20_{TS-exo}) deprotonations were computed and compared, as shown in Figure 10.



Figure 10. First deprotonation structures for both *anti*-planar $20_{TS-endo}$ and *syn*-planar 20_{TS-exo} deprotonation. The protons are indicated as either *syn*- (orange) or *anti*-planar (green) with respect to the N–O bond. Bond distances and nonbonded atom distances, indicated by gray lines, are given in Å.

A preference of 7.4 kcal/mol for deprotonation of the synplanar hydrogen (20_{TS-exo}) was computed when compared to the that of anti-planar hydrogen ($20_{TS-endo}$) transition structure, which is 3.2 kcal/mol greater than the ground-state difference between 20_{endo} and 20_{exo} . The computed 7.4 kcal/mol energy syn-planar selectivity was found to depend upon differential steric interactions, linearity of the transferring proton, and developing ring strain between the $20_{TS-endo}$ and 20_{TS-exo} transition structures.

Starting with the differential steric interactions, $20_{\text{TS-endo}}$ resulted in a shortened *anti*-planar α -carbon proton interaction distance with its *tert*-butyl substituent of 2.02 Å, whereas the lower-energy $20_{\text{TS-exo}}$ relaxed its *syn*-planar α -carbon proton interaction distance with the *tert*-butyl substituent to 2.37 Å. The steric interaction with a 0.35 Å reduction of distance was one of two significant nonbonding interactions identified as contributing to *syn*-planar selectivity. The second differential steric clash identified between the transition structures resulted with the transferring *anti*-planar proton and the *tert*-butyl group of 2.08 Å for $20_{\text{TS-exo}}$. In contrast, the lower-energy $20_{\text{TS-exo}}$ transferring *syn*-planar proton interaction with the *tert*-butyl group was relaxed by 0.13–2.21 Å, important to *syn*-planar selectivity, as shown in Figure 10.

Other differential steric clashes did not result in interaction differences between the two transition structures and consequently did not contribute to the *syn*-planar selectivity. For example, in **20**_{TS-endo}, the two β -carbon proton interactions with the *tert*-butyl substituent were 2.08 and 2.14 Å, and two isopropyl hydrogens of LDA interactions with the *tert*-butyl group had distances of 2.15 and 2.23 Å. Similarly, the lower-energy **20**_{TS-exo} with the exo pyrrolidine ring had similar β -carbon proton interactions with the *tert*-butyl substituent of 2.04 and 2.11 Å, being shorter by only 0.04 and 0.03 Å, and its two isopropyl hydrogens of LDA interactions with the *tert*-butyl group had distances of 2.16 and 2.22 Å, only different by 0.01 Å.⁷¹

The second factor for *syn*-planar selectivity involves the linearity of proton abstraction between the transition structures. In general, the linear arrangement of the three atoms involved in a transition structure for proton transfer is thought to be favored, where the assumptions of linearity are based on studies of the hydrogen bond. Specifically, in the

more frustrating 20_{endo} ground state, the $\angle N-H-C^{\alpha}$ alignment of 114° needs to expand by 45° to reach $20_{TS-endo}$ at 159°, a 31° larger change than required for the realignment of 20_{exo} to 20_{TS-exo} . Consequently, 20_{TS-exo} has an $\angle N-H-C^{\alpha}$ alignment of 168° that is 9° closer to linearity for proton abstraction than in $20_{TS-endo}$ at 159°. Thus, the geometric positioning of the *syn*-planar proton in the ground state that, in turn, facilitates access to a better-aligned transition structure concerning the linearity for proton abstraction contributes to *syn*-planar selectivity.

For the final factor for syn-planar selectivity, it is first necessary to discuss the reactants and products uniquely connected to the deprotonation transition structures $20_{TS-endo}$ and 20_{TS-exo} from IRC computations. We were surprised when IRC calculations on $20_{TS-endo}$ and 20_{TS-exo} led to unique fourmembered fused bicyclic heterocycles with the pyrrolidine ring (Figure 11) in either a *trans* 21_{endo} or *cis* 21_{exo} fashion,



Figure 11. 4,5-Heterocycle intermediates 21_{endo} and 21_{exo} from the first deprotonation step with the lowest energy 21_{exo-m} . The protons are indicated as either *syn*- (orange) or *anti*-planar (green) with respect to the N–O bond. Bond distances and nonbonded atom distances, indicated by gray lines, are given in Å.

respectively. Along both reaction paths, as the proton is abstracted, the generated carbanion collapses onto the electropositive lithium forming the four-membered heterocycle. Consequently, alignment of the developing carbanion sp³ lone pair with the coordinated lithium atom is of energetic importance in the trans 20_{TS-endo} or cis 20_{TS-exo} ring strain. Specifically, 20_{TS-endo} was found to lead to the trans fourmembered heterocycle fused to the pyrrolidine ring 21_{endo} , whereas the 20_{TS-exo} led to the more favorable *cis* fourmembered heterocycle fused to the pyrrolidine ring 21_{exo} . Specifically, the $\angle Li - C^{\alpha} - H$ angle can be used to gauge the alignment for ease of bond formation. The transition state should trend toward an angle of 110° for an unstrained acyclic bond. The $\angle \text{Li}-\text{C}^{\alpha}-\text{H}$ angle was strained at 78° for the *anti*planar deprotonation transition structure $\mathbf{20}_{TS\text{-endor}}$ 32° from a perfect tetrahedron. Comparison of the same angle (interior angle) resulted in a significant relaxation of the $\angle Li - C^{\alpha} - C^{\beta}$ alignment to 105° in $\mathbf{20}_{TS\text{-exo}}$, resulting in less strain in bond formation and contribution to syn-planar selectivity.

An additional feature regarding the influence of solvent upon activation enthalpies warrants discussion. Our model retains

THF and DIPA coordination to the lithium, maintaining ligand saturation, which is consistent with the explicit involvement of coordinating solvents, as reported by Collum and others.^{72,73} As discussed above, the syn-planar preference within the LDA and THF models is computed to be 7.4 kcal/ mol. However, a subtle but important feature of the model is the need to include explicit THF. We repeated the computations above but without THF, relying solely on PCM to model solvent interactions. Interestingly, we found that the syn-planar selectivity was virtually identical at 7.5 kcal/ mol. Consistent with the small energy difference, we computed that THF had small effects on the coordination geometry of lithium and repositioning of the proton for deprotonation. Specifically, we found that without THF, the low-energy ground-state $\mathbf{20'}_{exo}$ had a N····C^{α} distance of 3.45 Å and an $\angle N-H-C^{\alpha}$ alignment of 150°. In comparison, 20_{exo} (with THF) had a N····C^{α} distance of 3.39 Å and an \angle N-H-C^{α} alignment of 154°. Similar changes were computed for groundstate $\mathbf{20'}_{endo}$, where a N…C^{α} distance of 3.39 Å and an $\angle N$ - $H-C^{\alpha}$ alignment of 111° were computed. In 20_{endo} (with THF), a N···C^{α} distance of 3.34 Å and an \angle N-H-C^{α} alignment of 114° were computed. However, the point to note is in the computed activation enthalpies. The computed activation enthalpy of $\Delta H_{25-exo}^{\dagger}$ = 11.0 kcal/mol with THF, whereas $\Delta H^{\dagger}_{25'-exo}$ = 12.5 kcal/mol without THF. This small but important observation will be significant in the divergence between the multi-ion bridged and Roussi's iminium reaction pathways to be discussed in Section 2.5.

2.3. 4,5-Heterocycle Intermediate Formation. As discussed previously, IRC calculations on the two transition structures $20_{\text{TS-endo}}$ and $20_{\text{TS-exo}}$ did not show the concerted leaving of the lithium oxide to form the iminium intermediate, but instead, the stabilization of the carbanion via lithium, where both products led to a four-membered heterocycle, fused to the pyrrolidine ring. The last geometry of each IRC computation was taken for geometry optimization to locate the intermediates 21_{endo} and 21_{exo} .

It was immediately apparent that the nitrogen of the *N*-oxide maintained the puckered position of the envelope conformation in both 21_{endo} and 21_{exo} . The specific envelope pucker resulted in an additional torsional strain that prevented optimal alignment of the carbanion lone pair to lithium cation for both product conformations. To relieve the ring strain, other puckered envelope conformations of the pyrrolidine ring for both products were evaluated. A lower-energy minimum 21_{exo-m} (-3.9 kcal/mol compared to 21_{exo}) was identified to stabilize four-membered ring formation. A similar envelope formation could not be found for 21_{endo} since the dihedral angle between the lone pair and the oxygen in such an alignment would increase producing additional ring strain.

As discussed in Section 2.1, the five-membered pyrrolidine ring relieves strain by projecting its nitrogen out of plane to eliminate C^{α} -H eclipsing with either N-O or *t*-butyl interactions, resulting in the endo and exo conformations. For the favored *syn*-planar deprotonation intermediate **21**_{exo} predicted from the IRC computation, the four-membered heterocycle is in a *cis* orientation, with Li 1.90 Å away from oxygen and 2.18 Å away from the α carbon. This orientation aligns Li for partial orbital overlap with the carbanion sp³ lone pair, forming a bond angle between the other α -proton of 156° (Figure 11). The computed alignment between the *syn*-planar lone pair and lithium partially stabilizes the carbanion. NBO analysis of **21**_{exo} showed a charge transfer of 13.6 kcal/mol between the lone pair and the empty orbital of lithium, $LP(C^{\alpha}) \rightarrow LP^{*}(Li)$.

Despite the anion stabilization determined in $\mathbf{21}_{exo}$, the lower-energy $\mathbf{21}_{exo-m}$ conformation with the envelope pucker moved into the pyrrolidine ring provided improved *cis* alignment between the *syn*-planar lone pair and lithium. Specifically, Li was computed to be 1.87 Å away from oxygen and 2.11 Å away from the α carbon. This orientation aligns Li for a stronger orbital overlap with the carbanion sp³ lone pair, forming a bond angle between the other α -proton of 136° (Figure 11). The computed alignment between the *syn*-planar lone pair and lithium of $\mathbf{21}_{exo-m}$ stabilizes the carbanion more than that found in $\mathbf{21}_{exo-m}$ for the stronger orbital of lithium, LP(C^{α}) \rightarrow LP*(Li), or 4.8 kcal/mol more than found for $\mathbf{21}_{exo}$.

As expected, reduced stabilization of the carbanion was computed in the *anti*-planar deprotonation intermediate 21_{endo} . With the lone pair anti-planar to oxygen, the four-membered heterocycle adopts a trans alignment resulting in additional ring strain compared to the cis orientation. Consistent with the trend observed in the transition structure, lithium in 21_{endo} is positioned farther from both regions of a negative charge, 1.90 Å away from oxygen and 2.21 Å away from C5. More importantly, Li is not favorably positioned over the lone pair forming a 68° angle with carbanion and hydrogen. Consequently, NBO predicts 16.3 kcal/mol transfer of energy between the lone pair of the carbanion $(LP(C^{\alpha}))$ and the empty orbital of lithium (LP*(Li)), a decrease of 1.9 kcal/mol compared to $\mathbf{21}_{\text{exo-m}}$. Consequently, the resulting metallocycle structure (Figure 7, 21) with its fused ring provides stabilization of the carbanion, preventing a concerted electron rearrangement into the suspected iminium intermediate, a crucial step to understanding the multi-ion bridged structure mechanism.

2.4. Dissociation of N-O, Leaving of LiO⁻ for the Iminium Pathway. Despite 21_{exo-m} being 9.7 kcal/mol higher in energy than its acyclic form $\mathbf{20}_{exo}$, it provides the first opportunity for iminium formation as described by Roussi. In this specific case, the oxygen of the N-oxide is expected to dissociate with lithium as lithium monoxide anion, LiO⁻, a well-established superbase that should be an extremely poor leaving group,⁷⁴ rendering complications or even preventing iminium ion formation. Despite the undesirable features of LiO⁻ generation, we proceeded to investigate the formation of the iminium ion from 21_{exo-m} to be thorough in our mechanistic study. It is first instructive to consider the local minimum structure of 21_{exo-m} and its predisposition for Noxide nitrogen-oxygen cleavage (Figure 11). Within the fourmembered heterocycle, the coordination geometry of lithium involves simultaneous bonding with the N-oxide oxygen (Li-O = 1.87 Å) and the anionic carbon (Li–C = 2.11 Å), as well as nonbonding interactions with THF (Li…O = 1.96 Å) and DIPA (Li \cdots N = 2.06 Å). In this particular geometry, the coordination sphere of lithium is satisfied where the computed Hirshfeld charge on lithium is reduced significantly to 0.08 e from 0.51 e in LDA. However, the coordination of the departing N-oxide oxygen does not fully benefit from such stabilization (Figure 11). Specifically, the N-oxide oxygen is bound only to the lithium (Li-O = 1.87 Å) and the N-oxide nitrogen (N-O = 1.40 Å). In 21_{exo-m} , the negative charge of the N-oxide oxygen is only partially accommodated by lithium

since lithium is already complexed with THF, DIPA, and the anion. Lithium's reduced capacity to accommodate negative charge is demonstrated by the computed Hirshfeld charge of -0.38 e on the N-oxide oxygen in $21_{\rm exo-m}$ that is decreased by 0.06 e from -0.44 e in $18_{\rm exo}$ without THF, DIPA, and the anion.

Overall, the geometry for the *N*-oxide nitrogen-oxygen cleavage transition structure, 21_{TS} , shown in Figure 12, allows



Figure 12. Representation of the optimized structure for 21_{TS} with explicit THF and DIPA coordination. The protons are indicated as either *syn*- (orange) or *anti*-planar (green) with respect to the N–O bond. Bond distances and nonbonded atom distances, indicated by gray lines, are given in Å.

for the continued stabilization of lithium but results in limited stabilizing options for the departing oxygen of LiO⁻. As expected, the coordination sphere about lithium is maintained at the transition structure. Specifically, lithium develops a bond with the N-oxide oxygen (1.74 Å) and coordinates with THF (Li…O = 1.97 Å) and DIPA (Li…N = 2.09 Å). The computed Hirshfeld charge on lithium decreased slightly to 0.07 e in the transition structure from 0.08 e in ground-state 21_{exo-m} signaling that the nitrogen did not significantly stabilize the developing negative charge on the oxygen in the transition structure. In 21_{TS} , the departing N-oxide oxygen shifts toward a three-pronged pocket of protons presented by the tert-butyl group and α -proton from the pyrrolidine ring (Figure 12). Specifically, the through-space distances are $O \cdot \cdot H^{\alpha} = 2.28$ Å, $O \cdot \cdot H^{t-but} = 2.15$ Å, and $O \cdot \cdot H^{t-but'} = 2.39$ Å. The proton pocket provides some stabilization, but the lack of coordination with oxygen only magnifies the buildup of negative charge and resulting reactivity. The computed Hirshfeld charge on oxygen increased to -0.73 e, nearly twice the charge of -0.38 e in ground-state 21_{exo-my} resulting in superbase characteristics. In fact, the lack of LiO⁻ stabilization, particularly for the anionic oxygen, contributes to the large activation enthalpy, 28.2 kcal/ mol, for the leaving of LiO⁻.

The geometric changes from ground-state $2\mathbf{1}_{\text{exo-m}}$ to transition structure $2\mathbf{1}_{\text{TS}}$ indicate the development of the highly reactive iminium ion and LiO⁻. Specifically, in $2\mathbf{1}_{\text{TS}}$, the α carbon center of the developing iminium ion is only 2° out of plane, whereas the ground state is near tetrahedral at 115°. The shortened N-C^{α} of 1.31 Å reflects the delocalization of the positive charge, whereas the ground state is more localized with a N-C^{α} bond distance of 1.54 Å. The partial charge of 0.02 *e* on the α -carbon in $2\mathbf{1}_{\text{TS}}$ is significantly more positive than computed in $2\mathbf{1}_{\text{exo-m}}$. Overall, it is reasonable to expect that $2\mathbf{1}_{\text{TS}}$ should result in the formation of the iminium and LiO⁻, delivering the 1,3-dipole after a second deprotonation (Figure 6).

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Given the well-known reactivity of both the iminium ion and lithium oxide anion, further investigation was warranted into the fate of these highly reactive species in such close proximity. IRC computations reveal that the transition structure $2\mathbf{1}_{TS}$ uniquely connects to $2\mathbf{1}_{exo-m}$ in the reverse direction. However, in the forward direction, the N–O and Li–C bonds continue to fracture leading to the iminium ion and LiO⁻. Geometries were taken from several points along the IRC after $2\mathbf{1}_{TS}$, but all attempts to geometry optimize the high-energy complex failed. However, with the highly effective iminium electrophile and LiO⁻ nucleophile in such a close and constrained proximity, the location of a geometry-optimized high-energy complex should not have been expected.

Specifically, the remaining *syn*-planar α -proton on the forming iminium ion was rapidly deprotonated and with further minimization yielded 1,3-dipole **19**_C and LiOH (Figure 13). Therefore, due to the geometric and energetic character of



Figure 13. Potential energy pathway for the dissociation of the N–O toward the iminium intermediate **26**. Optimization of **26** resulted in 1,3-dipole **19**_c without a significant energy barrier. Structure **26**^{*} is a nonoptimized structure.

the products being formed, the iminium ion and LiO^- were found to be transient intermediates. The energy-minimized complex, 19_C, forms a tight ion pair that could explain iminium ion formation and observed selectivity. Ultimately, the significant 28.2 kcal/mol barrier from this transformation essentially eliminates the possibility of the reaction pathway, especially considering that these experiments are done at or below ambient temperatures. In summary, the high enthalpy of activation and reactivity of LiO⁻ release from the computations

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demonstrate that the pathway through $2{\bf 1}_{\rm TS}$ does not result in a viable pathway for iminium ion formation.

2.5. Heterocycle Complexation with Second Equivalent of LDA and THF. Confronted with the energydemanding process of iminium ion formation with a single equivalent of THF and LDA, using a second equivalent of each was considered. Complexation of both the second LDA and THF equivalents started with 21_{exo-m} since it was at least 3.9 kcal/mol lower in energy compared to the other 21 conformations identified. Specifically, LDA was added in the concave crevice of the bicyclic fused system 21_{exo-m} (see Figure 11) due primarily to the lessons learned concerning the preorganized structures and resulting energetics of the first deprotonation step and the limited options for placement from the buildup of steric bulk surrounding the N-oxide oxygen. Geometry optimization resulted with the lithium of LDA coordinated with the N-oxide oxygen and its nitrogen aligned with the α -carbon syn-planar proton. THF was then added to complete the coordination sphere of the lithium. The resulting enthalpy of stabilization resulted in -41.4 kcal/mol compared to N-oxide 18 and 2 equiv of LDA and THF (Figure 7). The choice is clear; structure $\mathbf{21}_{\text{exo-m}}$ can either become 27.8 kcal/ mol more stable through further complexation with THF and LDA to form 22 or it can overcome the 28.2 kcal/mol barrier to form the iminium ion. Once in the low-energy ground state of 22, two competing paths for either N–O dissociation to the iminium or deprotonation to the multi-ion bridged structure exist. The predisposition of 22 for both pathways is considered below.

First, the ground-state structure of **22** (Figure 14) presents a similar motif for *N*-oxide nitrogen–oxygen cleavage as that



Figure 14. Representation of the optimized structure for 22 underscoring the preorganization of the system for syn-planar deprotonation with explicit THF and DIPA coordination. The protons are indicated as either syn- (orange) or anti-planar (green) with respect to the N–O bond. Bond distances and nonbonded atom distances, indicated by gray lines, are given in Å.

discussed for $\mathbf{21}_{exo-m}$ (Section 2.3). The *N*-oxide oxygen of $\mathbf{22}$ is bound to lithium (Li···O = 1.90 Å) in the four-membered ring and directly with its *N*-oxide nitrogen (O–N = 1.41 Å) as found in $\mathbf{21}_{exo-m}$. However, the main difference in $\mathbf{22}$ is that the *N*-oxide oxygen interacts noncovalently with the Li of the second equivalent of LDA (Li···O = 1.90 Å) in a trigonal planar configuration. The benefit of the additional interaction is to reduce the computed charge on oxygen by an additional 0.06 e, to -0.32 e, as compared to $\mathbf{21}_{exo-m}$. Thus, the interaction with the second LDA actuates the reaction toward the transition structure for deprotonation.

Moreover, the computed geometry of 22 mirrored and improved upon the same preorganization advantages as found for syn-planar deprotonation in structure 20 (Figure 9).

Specifically, the resulting geometry provides an improved fit to promote *syn*-planar deprotonation as compared to 20_{exo} . The N···HC^{α} syn-planar distance was computed to be 2.40 Å with an $\angle N-H-C^{\alpha}$ alignment of 161° (Figure 14). This preorganized structure provides a basis for understanding the selectivity between iminium ion and multi-ion bridge formation.

2.6. Dissociation of N–O, Leaving of Li₂O for the Iminium Pathway. The dissociation of the N–O bond in 22 provides a second opportunity for iminium formation, as described by Roussi. In sharp contrast to the dissociation of 21_{exo-m} where superbase LiO⁻ was the leaving group (Section 2.4), dissociation of 22 involves the dissociation of lithium oxide chelated to LDA. Structure 22 is a low-energy intermediate that defines a critical juncture between the two competing mechanistic pathways depicted in Figure 6. Either the oxygen dissociates (22_{TS-A}, discussed in this section), resulting in the formation of proposed iminium ion 22 (Figure 6), or the coordinated LDA acts as a base, deprotonating the other α -carbon (22_{TS-B}, discussed in Section 2.7).

The transition structure for the N–O dissociation to the iminium ion, 22_{TS-Ay} is shown in Figure 15. In the transition



Figure 15. Representation of the optimized structure for $22_{\text{TS-A}}$ with explicit THF and DIPA coordination. The protons are indicated as either *syn-* (orange) or *anti-*planar (green) with respect to the N–O bond. Bond distances and nonbonded atom distances, indicated by gray lines, are given in Å.

structure, the forming Li₂O is bent at 144° along with unequal bond lengths of 1.83 Å and 1.77 Å, where the shorter LiO bond retains a heterocyclic character from the ground state. The breaking N–O bond is 1.89 Å, with a developing iminium planarity of $\angle N - C^{\alpha} - H - C^{\beta} = 171^{\circ}$. The coordination geometry of lithium with a heterocyclic character involves simultaneous nonbonding interactions with THF (Li…O = 2.00 Å), DIPA (Li…N = 2.08 Å), and loosely with the carbanion (Li… C^{α} = 2.65 Å). In this particular geometry, the coordination sphere of lithium is satisfied, where the computed Hirshfeld charge on lithium is reduced to 0.14 e. The coordination sphere of the other lithium is satisfied with the coordination to THF (Li···O = 2.03 Å) and DIPA (Li···N = 1.91 Å), with a partial charge of 0.10 e. Therefore, both lithiums of Li₂O receive significant stabilization from THF and DIPA. This is in sharp contrast to the charge buildup on the departing oxygen of LiO⁻, which was computed in 21_{TS} to be -0.73 e. Here, the partial charge is significantly reduced to -0.52 e within the developing Li₂O framework. The net result is that the computed activation enthalpy of 22_{TS-A} is 18.6 kcal/ mol, nearly 10 kcal/mol less than that found with 1 equiv of THF and LDA in 21_{TS} .



Figure 16. Atom distances (Å) and relative energies (kcal/mol) for the IRC calculations of 22_{TS-A} with key molecular structures highlighted along the reaction path.

To further investigate the mechanistic path of N-O dissociation, IRC calculations were performed on 22_{TS-AV} as shown in Figure 16. While we cautiously expected to observe the formation of the iminium intermediate, which could then undergo additional deprotonation forming the 1,3-dipole, the result instead showed the formation of pyrrolidinol 28. The results are different from that reported with 1 equiv of THF and LDA in Section 2.4. Figure 16 tracks the N4-O2 and O2…C5 distances, as well as the relative energy along its reaction coordinate toward products. As the N4-O2 bond elongation occurs (27_{TS-A}), N4-O2 reaches a max distance of 2.74 Å at 27. Concurrently, in 27, the electrons of the carbanion C5 shift into the empty orbital of N4, developing a partial double bond character with a distance of 1.28 Å. Up to this point, the IRC calculation is as anticipated; however, as the energy continues to decrease, the oxygen shifts over, positioning itself above the electrophilic carbon. In 27, the ∠C5-N4-O2 angle formed is 90.0°; when the reaction diagram is at 27_{TS} , the angle has shrunk to 72.5° . From this point onwards, the energy dramatically decreases, as C5 undergoes a nucleophilic attack from O2, eventually resulting in 28 with a bond between O2 and C5.

The formation of **28** was anticipated from our discussion in Section 2.4 since lithium oxide is reported as a strong nucleophile⁷⁴ and the iminium ion is a highly electrophilic intermediate. However, the magnitude of the decrease in energy resulting from this transformation was surprising, at nearly 70 kcal/mol, and we were unable to optimize an iminium intermediate where lithium oxide was included in the

calculations. With an extremely energetically favorable pseudointramolecular transition from iminium intermediate 27 to pyrrolinol 28, it is unlikely that 27 would undergo a second deprotonation to form the 1,3-dipole. Therefore, if the pathway through 22_{TS-A} occurs, then the cycloaddition products would not be expected, as shown in Figure 17. As with the first opportunity for iminium ion formation in 21_{TS} , the IRC pathway casts doubt upon iminium ion formation from the 22_{TS-A} pathway.

2.7. Second syn-Planar Deprotonation, the Multi-Ion Bridged Structure. The structural preorganization of 22 provides a basis for understanding the propensity for multi-ion bridge structure formation through $\mathbf{22}_{TS-B}$ over that of the iminium ion through 22_{TS-A} . As addressed in Section 2.5, the strongly stabilized complex 22 in the exo form results in a structure ideally suitable for the second deprotonation step. Briefly, the LDA base is locked into a close proximity of the syn-planar proton of the N-oxide to facilitate deprotonation with a N…C^{α} distance of 3.46 Å and an \angle N–H–C^{α} alignment of 161°. The corresponding transition structure for the second proton abstraction, 22_{TS-B} , is shown in Figure 18. Due to the ground-state alignment, it is not surprising to observe a high degree of geometric similarity between 22 and 22_{TS-B} , where the geometric change was isolated primarily to the transferring proton and its connecting atoms. Specifically, the transferring proton C^{α}-H distance expands by 0.46 Å to reach 1.56 Å in 22_{TS-B} . Additionally, the anchor points for the proton transfer $(N \cdots C^{\alpha} \text{ distance})$ were computed to be 2.76 Å, which is only a 0.7 Å through-space compression from ground-state 22.



Figure 17. Potential energy pathway for the dissociation of the N–O toward the iminium intermediate 27. Optimization of 27 resulted in pyrrolidinol 28 without a significant energy barrier. Structure 27^* is a nonoptimized structure.



Figure 18. Representation of the optimized structure for $22_{\text{TS-B}}$ with explicit THF and DIPA coordination. The protons are indicated as either *syn-* (orange) or *anti-*planar (green) with respect to the N–O bond. Bond lengths (Å) are indicated along the specified bonds.

Second, the $\angle N-H-C^{\alpha}$ alignment of 168° in the transition structure is likewise only 7° greater than that of the ground state. Other geometric changes were small and inconsequential. Not only are 22 and 22_{TS-B} similar, but the vibrational analysis of 22_{TS-B} results in a transition structure vibration at -930 cm⁻¹ that solely involves the motion of the transferring proton. All other atoms do not contribute significantly to the vibration. Therefore, 22 involves minimal changes in the atomic position to reach 22_{TS-A} is distinctly different, as described in Section 2.6. Briefly, a host of geometric changes to 22 are required to reach 22_{TS-A} including N–O bond elongation by 0.48–1.89 Å, breaking of the heterocycle ring where C^{α} -Li increases by 0.53-2.65 Å, and distortions of the pyrroline ring where a 7° rocking of the entire tert-butyl substituent is observed. Visualization of the computed imaginary frequency of 22_{TS-A} at -188 cm⁻¹ confirms the wide variety of atomic motions. Therefore, the higher degree of similarity between ground-state 22 and the transition structure $22_{\text{TS-B}}$ as compared with that of $22_{\text{TS-A}}$ results in a less geometric change to reach 22_{TS-B} . Implementing the principle of least motion,75 where the favored elementary reaction involves the least change in atomic position and electronic configuration, the deprotonation is expected to be favored over dissociation. In fact, the computed difference in activation enthalpies favors the formation of the multi-ion bridged structure from a second protonation by 3.8 kcal/mol. We conclude that the generation of 1,3-dipoles from tertiary amine N-oxides must pass through the multi-ion bridged pathway.

To further investigate the mechanistic path of the second deprotonation in forming the multi-ion bridged structure, an IRC calculation was performed on 22_{TS-B} . As expected, transfer of the proton occurs rapidly along the transition structure vibration yielding a deprotonated form of 22. However, with little atomic change along the imaginary frequency, other than the motion of the transferring proton motion, the IRC computation did not serve to show the full collapse of anion with the lithium cation 2.89 Å away at the end of the IRC computation. Geometry optimization starting from the end point of the IRC resulted in the collapse of the ion pair to form the multi-ion bridged structure 23. We observed a 3.8 kcal/mol

favoring of 22_{TS-B} moving through the multi-ion bridged transition state over $22_{TS-A'}$ giving pyrrolinol 28 (Figure 17). Energy decomposition analysis was performed on both ground-state 22 and the corresponding transition states 22_{TS-A} .²⁷ We noted much higher distortion energy in the ground state (117 kcal/mol), which was significantly reduced in the transition state (26.3 kcal/mol).

2.8. Multi-Ion Bridged Structure. The multi-ion bridged structure (23, Figure 19) results with placement of the second



Figure 19. Representation of the optimized structure for multi-ion bridged intermediate (23) with explicit THF and DIPA coordination. Bond lengths (Å) are indicated along the specified bonds.

lithium ion to stabilize the newly formed carbanion, as discussed for the first lithium ion in the first deprotonation step. Both lithium ions, Li1 and Li3, form two four-membered fused heterocycles on the same face of the pyrrolidine with the oxygen. The lithiums are 2.10 Å (Li1–C5) and 2.16 Å (Li3–C6) away from each carbanion, where the carbanion lone pairs were computed using NBO to transfer 12.1 kcal/mol (C5–Li1) and 13.3 kcal/mol (C6–Li3) into the empty orbitals of the coordinating lithiums. Additionally, both lithium ions stay strongly coordinated to oxygen with a distance of 1.87 Å (Li1–O) and 1.90 Å (Li3–O). The structure is completed with the inclusion of a THF and DIPA per lithium, satisfying each lithium's coordination sphere.^{72,73}

To further understand the stability of intermediate 23, we conducted a Hirshfeld charge analysis on the optimized structure. The two adjacent four-membered heterocycles are highly charged but notably symmetrical, consisting of alternating positive and negative atoms. With Li1 and Li3 charges at 0.09 e and 0.11 e, respectively, their positivity is stabilized by coordination with the -0.34 e oxygen and their respective carbanions, -0.23 e (C5) and -0.22 e (C6). Additionally, each of the carbons sharing the negative charge remains bonded to the 0.13 e nitrogen with single-bond characteristic distances of 1.55 Å (N-C5) and 1.53 Å (N-C6). While alternating charges increase the stabilization of the intermediate, there remains a preponderance of alternating charges in 23. Through breakage of the N-O bond, a further decrease in energy is achieved by allowing for a separation of charge and stabilization achieved in independent Li2O and 1,3dipolar species.

During the course of these studies, we noted that the ratedetermining step between 23_{TS} and 22 was greater than expected from the experiment (Figure 7). To address the energy difference, we tested the idea that additional equivalents of LDA, or other lithium species could coordinate to the oxygen of the N-oxide and align the computed energetics with the experiment. Since the partial charge of the oxygen in 23_{TS} (-0.50 e) is larger than in ground-state 22 (-0.32 e), an additional LDA stabilization more readily impacted 23_{TS} , pubs.acs.org/joc

lowering the requisite energy barrier from 27.7 to 17.2 kcal/ mol for the loss of lithium dioxide in an analogous fashion to that discussed earlier for 21_{TS} and 22_{TS-A} (Figure 7). This pattern reinforces that as the quantum system becomes more complete, energies and selectivities approach what we observe experimentally. Our initial observations found that the inclusion of an additional LDA resulted in an energetic difference that would be expected experimentally for the reaction and did not affect the overall mechanistic path. The inclusion of additional solvent moieties beyond the saturation of lithium should perturb the reaction path yet not alter the importance of the multi-ion bridged structure. The number of explicit, coordinating solvents used in this study represent a balance between the judicious use of available resources and computational accuracy.

2.9. 1,3-Dipole·Li₂O Complex. It is now possible to create the 1,3-dipole from the multi-ion bridged structure 23. The transition structure for the dissociation of oxygen (23_{TS}) , which forms 1,3-dipole 19, from 23, requires an activation energy of 14.5 kcal/mol. Comparatively, the dissociation of oxygen prior to the second deprotonation in $\mathbf{22}_{TS-A}$ requires 18.6 kcal/mol. The difference in energy is attributed to the dilithium oxide becoming a better leaving group after the second deprotonation. As discussed in significant detail in Section 2.2, dilithium oxide is a more stable leaving group than lithium oxide.⁷⁴ In $\mathbf{22}_{TS-A}$, the second lithium comes from an equivalent of LDA, which is also coordinated to a negatively charged nitrogen, retarding its ability to stabilize the oxygen's charge. However, after the second deprotonation, the LDA is converted into DIPA, subsequentially lowering the negative charge on nitrogen and effectively increasing the positive charge of its corresponding lithium. With a more positive lithium atom in 23_{TS} , more stability is provided to the dilithium oxide leaving group, and the activation energy is ultimately lowered.

To our surprise, the computed transition structure shown in Figure 20 reveals geometric features that were not anticipated.



Figure 20. Representation of the optimized structure for dilithium oxide-coordinated 1,3-dipole (19_a) with explicit THF and DIPA coordination. Bond distances and nonbonded atom distances, indicated by gray lines, are given in Å.

Analysis of 23_{TS} demonstrates an unsymmetrical dissociation of dilithium oxide. Structurally, lithium Li1 holds at a distance of 2.46 Å to carbanion C5, which forms a single bond at 1.38 Å with N4. Comparatively, the other carbanion C6 shares its lone pair with nitrogen forming a double bond of 1.32 Å, losing all coordination with the previously stabilizing lithium Li3, separating to a distance of 4.16 Å. Additionally, oxygen having broken its bond with nitrogen is at a distance of 3.50 Å. The impact of this dissociation is reflected in the atomic charges, where the atoms within the 1,3-dipole (C5–N–C6) have all

lowered their charges resulting in increased stabilization of the structure. In 23, negative charges of -0.23 e and -0.22 e were found on both carbanions, with the corresponding positive charge of 0.12 e on N. The dissociation of oxygen allows for the delocalization of the electrons of the C5 carbanion into the low-lying empty N orbitals, and this is reflected in the -0.10 e on C5, -0.01 e on C6, and 0.06 e on nitrogen in the structure 19_a. With a negative charge remaining on C5, the Li₂O species still coordinates strongly to the anion of the dipolar moiety and positions itself along the same face of the 1,3-dipole as it was in 23, with a dihedral angle formed between ∠O-Li1-C5-N at -0.3° . The persisting coordination of Li₂O to the 1,3-dipole does not inhibit its reactivity, as in 23, but does sterically block one face of the molecule from cycloaddition. As such, the 1,3dipole does not cleanly dissociate from Li2O but forms a complex that could provide an avenue to explain and control facial selectivity of cycloadditions. We performed energy decomposition analysis on ground-state 23 and transitionstate 23_{TS} ; we again noticed much higher distortion energy in the ground state (76.4 kcal/mol) compared to that in the transition state (1.23 kcal/mol).

With this proposed mechanism, no discrete iminium ion is formed, precluding complications arising from the nucleophilic attack. This is in agreement with the later work reported by Roussi, which cites the formation of cycloadducts, but never the secondary amine and aldehyde products resulting from the nucleophilic attack upon an iminium ion.65-67 If the nucleophilic attack occurs, resulting in pyrrolidinol 28, then this is expected to collapse into an aldehyde, secondary imine pair via a Polonovski mechanism.⁷⁶ However, only one of Roussi's reaction systems, dibenzylmethyl N-oxide, resulted in the Polonovski-type reaction products.⁶² All other systems only isolated cycloadduct- or dimerization-type products.60 Therefore, our proposed mechanism (Figure 7), which moves through a multi-ion bridged intermediate, is supported not only by our calculations but also by all other previous experimental outcomes.

3. IMPACT OF OUR NEWLY PROPOSED MECHANISM

Since the N-oxide deprotonation is predicted to move through a multi-ion bridged intermediate, instead of an iminium intermediate, there is no electrophilic species generated during the course of the reaction. Azomethine ylides, such as 31, are nucleophilic at both carbons with chemical properties much more similar to allylic anions than iminiums. This opens up more functional group compatibility than originally thought; unprotected alkoxides, amines, thiols, and carboxylates, to name a few, should pose no significant hindrance to the reaction scope. Indeed, in Roussi's later work, he was able to utilize amine oxides bearing unprotected alcohols for diastereoselective cycloaddition reactions (Figure 21).⁶⁷ If the iminium intermediate was the dominant pathway, then we would expect that oxazolidine 36 would be the major product resulting from the intramolecular nucleophilic attack of the pendant oxygen on the iminium carbon (Figure 21, pathway B). However, instead, Roussi achieved a repeatable major product of the intermolecular [3 + 2] cycloaddition reaction with trans-stilbene 32 (Figure 21, pathway A). The minor oxazolidine product 36 most likely results from partial quenching of intermediate 31, protonating the carbanion, followed by intramolecular cyclization. Our newly proposed mechanism, and Roussi's prior results, indicates that the Noxide route to 1,3-dipoles is an efficient, single-step process,



Figure 21. Roussi's 1,3-dipole synthesis from an N-oxide with unprotected alcohol with final cyclization products and yields indicated. 67

with increased flexibility to functional groups. This mechanism proceeds through what we have termed the multi-ion bridged structure 23, which is 3.9 kcal/mol lower in energy than the elimination of lithium oxide, passing through the iminium ion to the final amine alcohol 28. This critical juncture also serves as the rate-determining step, providing insight for future exploration and expanding the scope of chemistry. Specifically, it opens up the possibility of 1,3-dipoles containing unprotected alcohols, amines, thiols, and even carboxylic acids. Finally, dipolarophiles with similar unprotected functionality may be utilized without the concern of nucleophilic attack, creating undesired side products.

4. CONCLUSIONS

For the general synthesis of 1,3-dipoles from tertiary alkylamine N-oxides, our calculations show that the energetically favorable pathway moves through a multi-ion bridged intermediate instead of the previously postulated iminium ion intermediate. Therefore, no electrophilic intermediates occur along the pathway toward the azomethine ylide, significantly expanding functional group compatibilities. Additionally, inclusion of explicit solvent was critical for the accurate modeling of 1,3-dipole generation and creation of a complete quantum system. This was best demonstrated when our results showed that the oxygen-nitrogen bond requires less energy to break when oxygen is coordinated to 2 equiv of lithium and that when THF is coordinated to the lithium of LDA, the activation energy of the subsequent deprotonation is significantly lowered. This newly proposed mechanism establishes the N-oxide route as a robust and efficient approach to 1,3-dipole synthesis with increased functional group

flexibility, allowing for and further encouraging experimental exploration to expand this method for creating complex alkaloid natural products and cores for drug discovery.

5. EXPERIMENTAL METHODS

Quantum chemistry methods of metahybrid density functional theory (DFT)77 and second-order Møller-Plesset perturbation theory were carried out at the Center for Computational Sciences (CCS) at Duquesne University⁷⁹ using Gaussian 16.80 The M06-2X functional⁸¹ with Dunning's jul-cc-pVDZ basis set⁸² was used primarily to calculate electronic, enthalpic, and free energies for both ground and transition structures. M06-2X, developed by Truhlar and co-workers, has been reported to be accurate to within 1.2 kcal/mol for reaction barriers and within 0.37 kcal/mol of noncovalent interaction energies. 83,84 To verify the accuracy of M06-2X/jul-cc-pDVZ calculations, a subset of activation enthalpies were calculated using expanded basis sets and/or higher levels of theory. Using the M06-2X functional, the basis set was increased to a triple zeta (jul-cc-pVTZ) and more diffuse functions (aug-cc-pVDZ). We verified our theory level, while also using jul-cc-pVDZ, with second-order Møller-Plesset calculations (see the Supporting Information).85 Vibrational frequency calculations were used to confirm all stationary points as either minima or transition structures and to provide thermodynamic corrections for enthalpies and free energies.

Implicit solvation models were integrated into each stage of our analysis. The polarizable continuum model (PCM) was developed by Tomasi et al.⁸⁶ and reviewed elsewhere.⁸⁷ Briefly, PCM allows the model to include bulk solute electrostatic interactions that impact the stability of stationary states.⁸⁸ It has also been found that the inclusion of explicit solvent, in combination with PCM, provided an improved model,⁸⁹ essential to the base and solvent becoming part of the quantum system.⁹⁰

Intrinsic reaction coordinate (IRC) calculations using the local quadratic approximation for the predictor step were used to elucidate the reactant and product from the vibrational frequency of each transition structure.⁹¹ The theory and implementation of IRC calculations have been described elsewhere.^{92,93} In this study, the reactants and products were identified through IRC calculations by tracing the reaction path to provide the electronic energies necessary to provide both the activation energy and energy of reaction.

Natural bonding orbital analysis (NBO), both versions 3.5 and 7, was performed on several ground states to better understand orbital interactions.^{94,95} NBO has been reviewed in detail.^{96,97} Second-order perturbation theory interaction between filled and unfilled orbitals provided valuable insight into interactions influencing the structures and energies of systems. Additionally, natural population analysis (NPA),⁹⁸ electrostatic potentials using a grid-based method (CHelpG),⁹⁹ and Hirshfeld population analyses^{100–102} were utilized to calculate the charge distributions in molecules of interest. While similar trends were observed across all three analyses, the Hirshfeld method was shown previously to be most reliable.¹⁰³ Throughout the paper, calculations to determine partial charges of atoms were conducted using Hirshfeld population analysis unless otherwise noted.

All calculations discussed were carried out using M06-2X/jul-ccpDVZ within the polarizable continuum model using the dielectric constant for THF unless stated otherwise.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01047.

Information on the correlation between reported results with higher levels of theory, larger figures for each structure, and input/output files for each structure (PDF)

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Notes

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