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Lithium Enolates Derived from Pyroglutaminol: Mechanism and Stereoselectivity of an Azaaldol Addition

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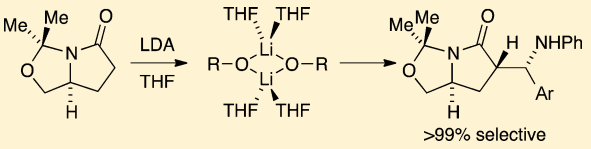
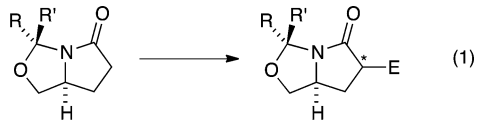
Supporting Information

ABSTRACT: A lithium enolate derived from an acetonide-protected pyroglutaminol undergoes a highly selective azaaldol addition with (*E*)-*N*-phenyl-1-[2-(trifluoromethyl)phenyl]-methanimine. The selectivity is sensitive to tetrahydrofuran (THF) concentration, temperature, and the presence of excess lithium diisopropylamide base. Rate studies show that the observable tetrasolvated dimeric enolate undergoes reversible deaggregation, with the reaction proceeding via a disolvated-monomer-based transition structure. Limited stereochemical erosion stems from the intervention of a trisolvated-monomer-based pathway, which is suppressed at low THF concentrations and elevated temperature. Endofacial selectivity observed with excess lithium diisopropylamide (LDA) is traced to an intermediate dianion formed by subsequent lithiation of the monomeric azaaldol adduct, which is characterized as both a dilithio form and a trilithio dianion–LDA mixed aggregate.



INTRODUCTION

A program at Pfizer to develop anti-inflammatory agents has focused on the functionalizations of protected pyroglutaminol (eq 1).[1] The readily available hemiaminals of pyroglutaminol

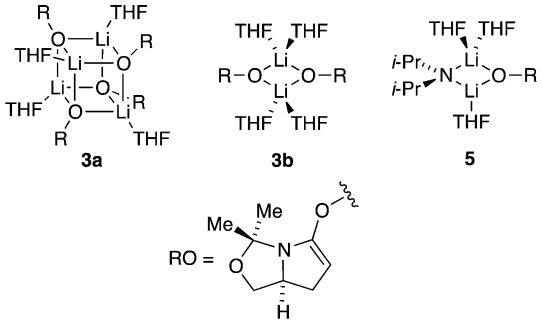


have been subjects of intense scrutiny and can be functionalized exofacially with moderate selectivity sufficient for many applications.[2] Acetonide-protected derivative **1a** shows more promise than the more popular benzylidene analog **1b**.[3] Rarely reported functionalization from the concave face relies largely on epimerization and is poorly selective.[4]

The Collum group became interested in lithium enolates in hopes of correlating their structure and solvation with the stereochemistry of their functionalizations.[5] We have previously described structural studies of a dozen enolates within the class,[3] all of which form mixtures of tetrasolvated tetramers and tetrasolvated dimers as exemplified by acetonide-derived enolates (Chart 1). These enolates are deceptively hindered, causing observable atropisomerism and slow solvent exchanges within the tetramer form.

We describe herein investigations of an azaaldol addition (Scheme 1).[6,7] Reactions of imines offer excellent templates for the study of organolithium structure–reactivity relationships, especially in conjunction with variations of hemiaminal protecting group on the enolate.[8] We are following on the heels of Moloney and co-workers,[9] who reported an azaaldol addition to tosylimines with a protected pyroglutaminol-derived enolate that proceeds with high exo selectivity but less control at the β-amino position. The optimized selectivity in our case is exceptional at both positions. We trace the stereocontrol to a dominant monomer-based pathway. Erosion of selectivity originates in a mechanistically distinct, more highly solvated form. We also show that the inherent exo selectivity can be changed to endo with excess lithium diisopropylamide (LDA) owing to the intervention of an N,O-dianion generated from the 1,2-adduct akin to that proposed by the Moloney group.[9]

Chart 1



RESULTS

Lithium enolate **3** was previously characterized as tetrasolvated tetramer **3a** and tetrasolvated dimer **3b**. Dimer **3b** is the only

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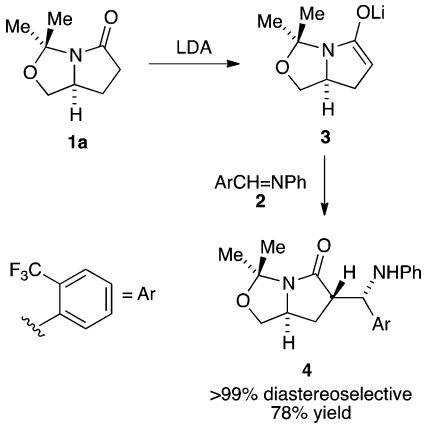
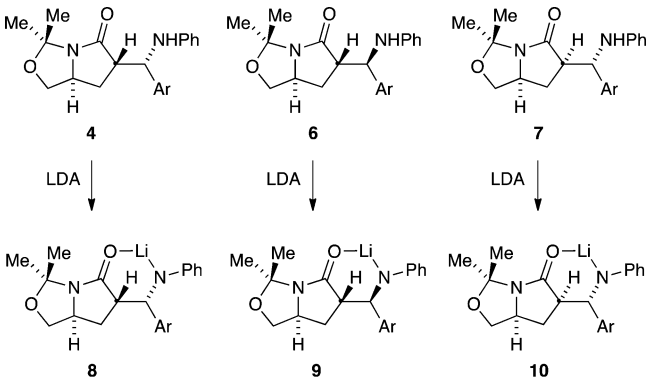
Scheme 1



observable form in 3.0−12.3 M tetrahydrofuran (THF). Similarly, mixed aggregate **5** was previously characterized with ^{6}Li and ^{15}N NMR spectroscopies[10] using [^{6}Li,^{15}N]LDA[11] and augmented by computational studies.[3] The same methods were used to characterize an intermediate dianion (vide infra). Structural and mechanistic studies were supported by density functional theory (DFT) calculations at the B3LYP/6-31G(d) level with single-point calculations at the MP2 level of theory.[12,13] Only the calculations needed to make specific points are included herein; the preponderance of the computational results are in the Supporting Information.

Azaaldol Addition: Stereoselectivity. The azaaldol addition in Scheme 1 was used to probe structure−reactivity relationships. The CF_3 moiety allowed us to exploit ^{19}F NMR spectroscopy[14] to monitor diastereoselectivities and reaction rates. Major isomer **4** and two minor isomers (**6** and **7**) from the azaaldol addition of enolate **3** were assigned by using COSY, HSQC, HMBC, and ROESY spectroscopies. The same methods provided more compelling assignments when the purified β-aminolactams were N-lithiated; **8** and **10,** which exist as conformationally constrained chelated monomers (vide infra), were characterized (Scheme 2).

Scheme 2



A quick survey of a range of hemiaminal-protected pyroglutaminols[3] showed mediocre selectivities for reaction with **2**, as evidenced by multiple resonances in the ^{19}F NMR spectra of the crude products. By contrast, mixing enolate **3** with imine **2**[15] in neat THF at −78 °C showed promising results, affording β-amino lactams **4** and **6** in 10:1 selectivity to the exclusion of other isomers (<0.5%). A number of parameters were examined to optimize the selectivity.

Mixing imine **2** and enolate **3** in neat THF solution yielded no changes in selectivity with percent conversion (0.10−1.0 equiv of imine **2**) whether monitored in situ with ^{19}F NMR spectroscopy or quenching; this result showed that mixed-aggregate-derived feedback loops (autocatalysis or autoinhibition) are inconsequential.[16,17] Maintaining the resulting lithiated adducts at elevated temperature (−40 °C) for 2.0 h before quenching resulted in no erosion of selectivity, which indicated that stereochemical scrambling owing to retro azaaldol addition was also not occurring.

THF concentration and temperature proved to be the key parameters (Table 1). *Raising* the temperature *increased* the selectivity, an unusual inverted dependence. *Decreasing* the THF concentration also *increased* the selectivity (see Table 1), which displayed a linear relationship versus THF concentration in toluene cosolvent (Figure 1). (Depiction of the reciprocal relationship, the minor−major ratio, in Figure 1 appears in the context of the rate studies described below.) Because conventional wisdom suggests that both higher temperatures and lower THF concentrations promote tetrameric enolates over dimeric enolates,[18] it might be tempting to infer the intervention of a tetramer-based mechanism, but that would be a mistake. The two dependencies *are* consistent with the stereochemical erosion deriving from a pathway that demands elevated solvation numbers. We see no dependence whatsoever of stereoselectivity on enolate concentration, which indicates that the major and minor products arise from a common aggregation state.

Table 1. Tetrahydrofuran (THF)- and Temperature-Dependent Stereoselectivities (eq 1)[a]

T (°C)	[THF] (M)	4:6
−78	12	11:1
−78	1.0	150:1
−55	12	14:1
−55	1.0	>200:1

[a]Lithium diisopropylamide = 0.10 M; imine **2** = 0.13 M.

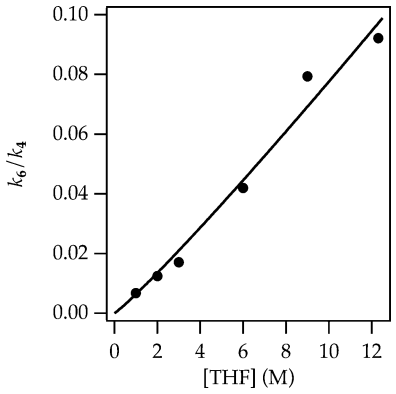


Figure 1. Plot of k_6/k_4 vs tetrahydrofuran (THF) concentration (M) as determined by carrying out the addition of lithium enolate **3** (0.10 M) with imine **2** (0.13 M) at −78 °C and monitoring the proportions of **6** and **4** in quenched aliquots with ^{19}F NMR spectroscopy. The curve depicts an unweighted least-squares fit to $y = k[\mathrm{THF}]^n$ [$k = (6.4 \pm 2.0) \times 10^{-3}$, $n = 1.09 \pm 0.13$].

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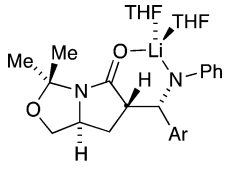
Azaaldol Addition: Structure of the Lithiated Product. To state the obvious, isolated product **4** is not the same as the initially formed lithium salt depicted generically as **8**. Monitoring the azaaldol addition of enolate **3** to imine **2** with ^{19}F NMR spectroscopy showed **8** and traces of **9**. Metalation of the purified, fully characterized β-amino lactams **4** and **6** with 1.0 equiv of LDA regenerated **8** and **9**, respectively, as expected (Scheme 2). Using [^{15}N]**4** prepared from [^{15}N]aniline, we observed a ^{6}Li doublet and ^{15}N triplet (J_{Li-N} = 6.2 Hz) consistent with the monomer substructure of **8**.[10] Mixtures of lithium amides **8** and **10** show no heteroaggregation, further supporting the monomer assignment. Chelation by the carbonyl and solvation by two THF ligands, yielding **8a**, is supported by DFT calculations: a nonchelated trisolvate was computed to be 10 kcal/mol less stable and a trisolvated chelate, although seemingly plausible based on compelling evidence of high-coordinate lithium,[19] was not computationally viable. We suspected that the aryl moiety precluded higher coordination, yet calculation with an NH rather than an NPh moiety failed to afford a minimum corresponding to a chelated trisolvate.



8a

Azaaldol Addition: Kinetics and Mechanism.[17] An equimolar mixture of enolate **3** and imine **2** under conditions in which dimer **3b** was the only observable form showed an exponential decay manifesting none of the aberrant curvatures (sigmoids or stalling) that would be expected if autocatalysis or autoinhibition were intervening. Addition at normal enolate concentration (0.10 M) in neat THF and pseudo-first-order in imine (0.005 M) followed a clean first-order decay from which pseudo-first-order rate constants (k_{obsd}) were extracted. k_{obsd} is independent of the initial concentration of imine **2**, which was also consistent with a first-order dependence on **2**.

A plot of k_{obsd} versus THF concentration using toluene as cosolvent showed a zeroth-order dependence (Figure 2). A plot of k_{obsd} versus enolate concentration showed a half-order dependence (Figure 3) consistent with a dimer–monomer pre-

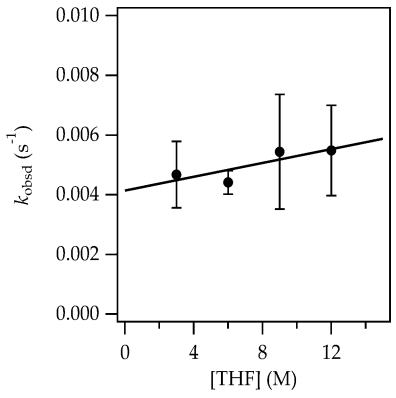


Figure 2. Plot of k_{obsd} vs THF concentration (M) in toluene cosolvent for the addition of lithium enolate **3** (0.10 M) to imine **2** (0.005 M) at −70 °C. The curve depicts an unweighted least-squares fit to $k_{obsd} = k + k'$[THF] [k = (4.1 ± 0.5) × 10^{-3}, k' = (1.2 ± 0.6) × 10^{-4}].

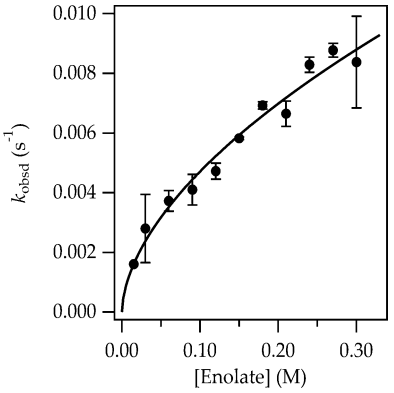


Figure 3. Plot of k_{obsd} vs concentration of enolate **3** for the addition of lithium enolate **3** to imine **2** (0.003 M) in 12.3 M THF at −70 °C. The curve depicts an unweighted least-squares fit to $y = k[\mathbf{3}]^n$ [k = 0.017 ± 0.001, n = 0.57 ± 0.05].

equilibrium. The idealized rate law[20] (eq 2) was consistent with the mechanism shown generically in eqs 3–5. Inclusion of the THF-dependent term in the rate law and the trisolvated-monomer-based pathway in eq 5 (see **12a** and **12b** below) stems from the stereochemical independence of enolate concentration and first-order dependence on THF concentration (see Figure 1).[21] This contribution is far too small to detect in the absolute rates, but it is readily discerned in the *relative* rates.

$$\mathrm{d[enolate]}/\mathrm{d}t = k[\mathrm{imine}]^1[\mathrm{enolate}]^{1/2}\{1 + k'[\mathrm{THF}]^1\} \quad (2)$$

$$\underset{\mathbf{3b}}{1/2(\mathrm{enolate})_2(\mathrm{THF})_2} + \mathrm{THF} \overset{K_{eq}}{\leftrightarrows} (\mathrm{enolate})(\mathrm{THF})_2 \quad (3)$$

$$(\mathrm{enolate})(\mathrm{THF})_2 + \underset{\mathbf{2}}{\mathrm{imine}} \overset{k_2}{\rightarrow} \underset{\mathbf{11}}{[(\mathrm{enolate})(\mathrm{THF})_2(\mathrm{imine})]^{\ddagger}} \quad (4)$$

$$(\mathrm{enolate})(\mathrm{THF})_2 + \underset{\mathbf{2}}{\mathrm{imine}} \xrightarrow{k_3[\mathrm{THF}]} \underset{\mathbf{12}}{[(\mathrm{enolate})(\mathrm{THF})_3(\mathrm{imine})]^{\ddagger}} \quad (5)$$

With clear stoichiometric guidance from the kinetics, we examined the origins of the stereochemistry by using DFT calculations. These calculations supported the experimentally observed disolvation of the transition structure and were consistent with the observed preference for transition structure **11a** (progenitor of major product **4**) over transition structure **11b** that leads to minor isomer **6**. Inspection of the three-dimensional structures (with the aid of a computer graphics interface) left us unsure of the origins of this preference. Analogous transition structures that led to endo adducts were ≥2.5 kcal/mol less stable. Stereochemical erosion was shown experimentally to stem from low contributions from *trisolvated*-monomer-based addition. Computational studies concur by showing that trisolvated transition structures **12a** and **12b** were less stable than the disolvates and displayed the opposite selectivity (Scheme 3).

Azaaldol Addition: Endo Selectivity with Excess LDA. A dominant *endo* addition appears when excess LDA is present (eq 6). Organolithium chemists may be tempted to invoke addition via previously characterized LDA–enolate mixed dimer **5**.[3] Once again, this would be wrong. An analogous endo selectivity was detected by Moloney and co-workers[9] and suggested to arise from an intervening dianion. The key observation that supported their thesis is that control at the β-

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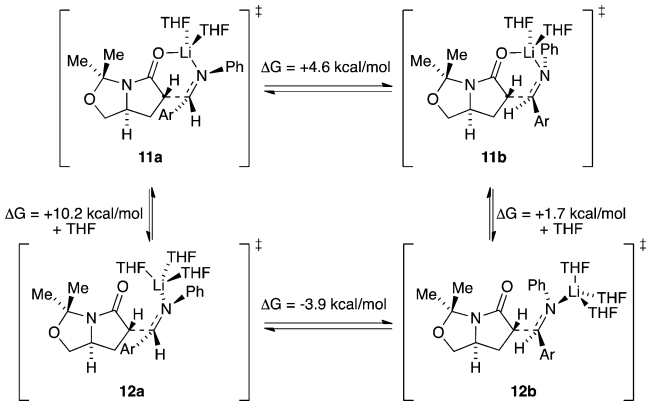
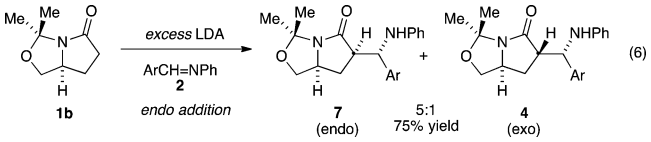
Scheme 3





amino position of the endo adducts is identical to that in the exo adducts. Indeed, we subsequently traced the selectivity to an N,O-dianion as described below.

Endo Selectivity: An N,O-Dianion. Carrying out the azaaldol addition by using excess LDA and monitoring it with ^{19}F NMR spectroscopy revealed the initial formation of adduct **8**, which was subsequently converted to two new species at −78 °C depending on the amount of LDA added (Figure 4). These

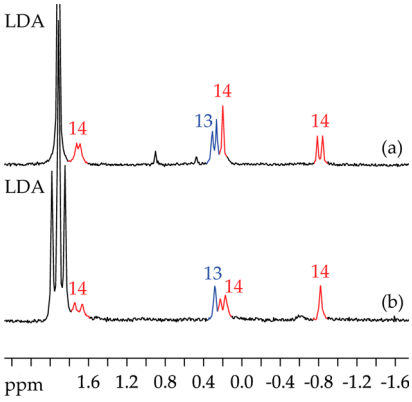
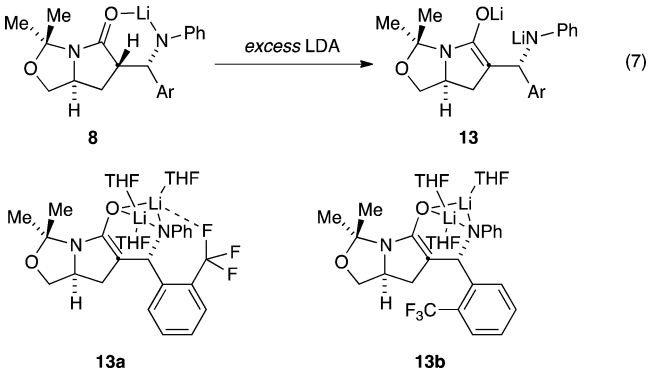


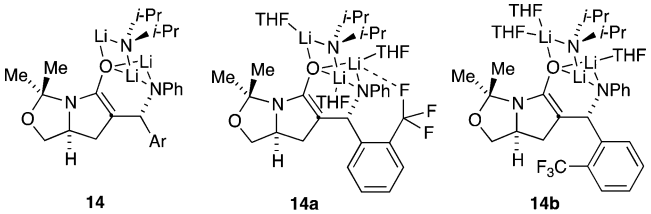
Figure 4. ^{6}Li NMR spectra of 0.10 M enolate **3** with 0.40 M excess lithium diisopropylamide (LDA) showing dianion **13** (blue) and trilithiated dianion−LDA mixed aggregate **14** (red): (a) [^{6}Li,^{15}N]**8** and [^{6}Li]LDA; (b) [^{6}Li]**8** and [^{6}Li,^{15}N]LDA.

same species could be generated from purified adduct **4** or **7** by adding LDA, with 2.0 equiv producing a new species displaying one ^{19}F resonance believed to be the dianion depicted generically as **13** (eq 7). ^{15}N-labeled **13** manifested a sharp ^{6}Li doublet (Figure 4a) and a broad, unresolved ^{15}N multiplet that collapsed to a singlet on single-frequency ^{6}Li decoupling. The spectra are consistent with a doubly bridging dianion. DFT calculations showed the most stable form and highest solvation state to be trisolvate **13a**, which displayed provocative evidence of an Li−F contact (2.03 Å).[22] Dianion **13b** showed no such Li−F interaction, however, and was 3.6 kcal/mol less stable than **13a**. In theory, **13** should have shown two distinct ^{6}Li



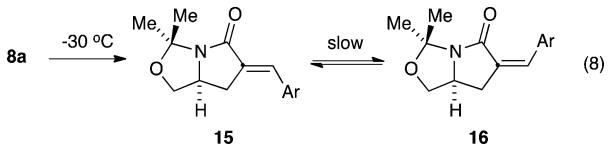
resonances, but we are untroubled that they fail to resolve or exchange rapidly.

Forming dianion **13** in the presence of excess LDA afforded a new species shown to be a trilithiated mixed aggregate of gross structure **14** with ^{6}Li and ^{15}N NMR spectroscopies aided by ^{6}Li and ^{15}N single-frequency decoupling. [^{6}Li,^{15}N]LDA showed that two of the three ^{6}Li resonances were coupled to LDA (Figure 4b). The corresponding ^{15}N spectrum displayed a broad quintet consistent with coupling to two slightly magnetically inequivalent ^{6}Li nuclei. ^{6}Li and ^{15}N spectra recorded on a sample prepared from [^{15}N]**5** showed coupling of the anilide ^{15}N to two resonances (see Figure 4a) and a broad quintet in the ^{15}N spectrum. The connectivity of **14** derives from coupling data. Computational studies of **14** uniformly showed a transannular Li−O contact in a ladder motif with three coordinated THF ligands. Evidence of a Li−F contact in **14a** is provocative but not net stabilizing. Rotation of the CF_3 away from the lithium causes the THF to migrate to give **14b**, which is also more stable by 2.4 kcal/mol. We have never witnessed (or at least noticed) such a THF migration in a simple ground-state minimization.[23]



Clearly, endo isomer **7** is derived when dianion **13** or **14** is protonated from the exo face, leaving the stereogenic center at the β carbon intact. We explored half a dozen alternative quenching protocols (by no means an exhaustive study) but found no improvements over the simple aqueous quench.

Dehydroamination. We conclude the results section with some minor housekeeping. Warming lithiated azaaldol product **8** to temperatures above −30 °C afforded complex products that appeared by mass spectrometry to be Claisen condensation products of little interest to us. We also, however, noted facile dehydroamination even at low temperatures when low THF concentrations were used (eq 8). These reactions afforded



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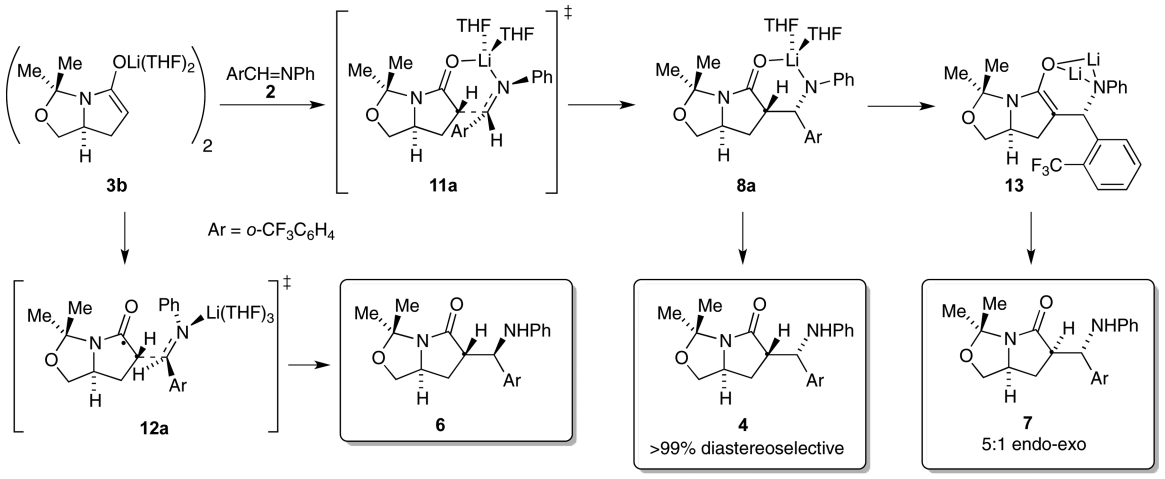
Scheme 4



benzylidene **15** exclusively as the less stable *E* isomer (shown by NOESY studies). The *E* isomer equilibrated to the *Z* isomer, **16**, on standing at 25 °C for 0.5 h. All such byproducts were excluded by keeping the temperature low and the THF concentrations at ≥1.0 M. It is not obvious why the elimination follows this pattern.

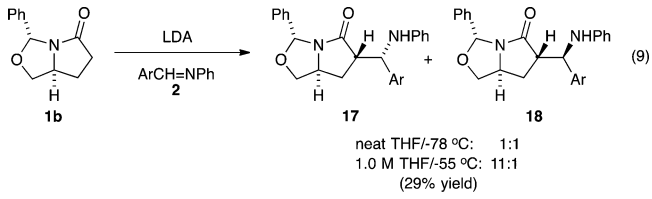
DISCUSSION

For the second paper in a two-part series, we investigated the reactivity of protected pyroglutaminol-derived lithium enolates (**3**) to better understand the origins of their reactivity and selectivity. Our collaborators in the Pfizer group are motivated by medicinal chemistry interests: the bicyclo[3.3.0] ring system is a potential source of stereocontrol needed for a program to develop anti-inflammatory agents.[1] The interest of the Collum group was piqued by the flexibility offered by the hemiaminal linkage that might be used to modify enolate structure, reactivity, and reaction mechanism. Our interest in imine chemistry in general[8] and the azaaldol addition in particular[7] stems from the versatility of the two imine appendages in modulations of structure−reactivity relationships.

The results are summarized in Scheme 4. Enolate **3** was previously shown to exist as tetrasolvated dimer **3b** over a broad range of THF concentrations. The reluctance to form tetramers except under extremely low THF concentrations was attributed to deceptively high steric congestion within the cubic tetramers. Enolate **3** undergoes addition to imine **2** with >100:1 stereocontrol via disolvated-monomer-based transition structure **11** to give essentially a single isomeric adduct, **4**, in 70−80% yield under optimal conditions (1.0 M THF-toluene and −55 °C). DFT calculations mimicked the diastereoselectivity (Scheme 3); however, the selectivity *dropped at lower temperatures and higher THF concentrations* (see Table 1). These unusual dependencies—especially the inverted temperature dependence—were traced to a minor trisolvated-monomer-based pathway and open transition structure **12**. Calculations mimicked experiment by showing that the preference for **12b** over **12a** (Scheme 3) reversed selectivity. This result is a relatively rare example of the stereocontrol of an organolithium reaction being traced to specific mechanistic events.[24] The THF concentration dependence reinforces the assertion[17] that optimizations should include changes in solvent *concentrations*, not just solvent.

In a related azaaldol addition of a pyroglutaminol hemiaminal using a toluenesulfonyl-substituted imine, Moloney and co-workers[9] observed that excess LDA inverts the stereochemistry to predominantly endo and proposed an intermediate dianion.[25,26] We observed an analogous 5:1 preference for endo isomer **10** with excess LDA. Despite the appeal of models involving mixed-aggregation-dependent selectivities, Moloney's thesis proved correct: adduct **8a** undergoes further metalation to give a dianion generically drawn as **13**, which then undergoes exofacial protonation. The 5:1 selectivity was not markedly improved by variations in the quenching agent. Dianion **13** was characterized with [^{6}Li,^{15}N]LDA and [^{15}N]**2** and DFT calculations as trisolvate **13a** or **13b** as well as LDA−dianion mixed aggregate **14a** or **14b** (see above).

We wondered whether the superior selectivities observed using acetonide-protected enolate **3** could be exploited to improve the decidedly inferior results obtained with the more commonly used benzylidene-substituted lactam **1b** (eq 9).



Could we stem stereochemical leakage? Although the selectivities are not as high, the greater selectivity at low THF concentration and elevated temperature is notable. The poor yield stems from competitive decomposition during protracted reaction times.

CONCLUSION

Several high-water marks in this study are noteworthy. The pyroglutaminol-derived enolates showed their potential as synthons for highly stereoselective functionalization and templates for the study of organolithium structure−reactivity−selectivity relationships. Given the condition-dependent selectivity, we wonder whether additional stereocontrol might be available to previously described functionalizations through judicious choice of reaction conditions. Tracing stereochemical changes to explicit mechanistic changes is also of importance to mechanistic organolithium chemists. Moreover, the character-

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ization of another dianion is noteworthy—these are complex species even by organolithium chemistry standards.[27]

EXPERIMENTAL SECTION

Reagents and Solvents. THF and toluene were distilled from solutions containing sodium benzophenone ketyl. The toluene stills contained approximately 1% tetraglyme to dissolve the ketyl. LDA, [^{6}Li]LDA, and [^{6}Li,^{15}N]LDA were prepared as described previously.[11] LDA was titrated for active base by following a literature method.[28] Air- and moisture-sensitive materials were manipulated under argon with standard glovebox, vacuum line, and syringe techniques. Pyroglutaminol derivatives **1a** and **1b** were prepared by using literature methods.[29]

NMR Spectroscopy. Individual stock solutions of substrates and LDA were prepared at room temperature, mixed in NMR tubes at −78 °C, and flame-sealed under partial vacuum. Standard ^{6}Li, ^{13}C, ^{15}N, and ^{19}F NMR spectra were recorded on a 500 MHz spectrometer at 73.57, 125.79, 50.66, and 470.35 MHz, respectively. The ^{6}Li, ^{13}C, ^{15}N, and ^{19}F resonances were referenced to 0.30 M [^{6}Li]LiCl/MeOH at −80 °C (0.0 ppm), the CH_2O resonance of THF at −90 °C (67.57 ppm), neat Me_2NEt at −90 °C (25.7 ppm), and C_6H_5F in neat THF at −80 °C (−112.0 ppm).

*(6S,7aS)-3,3-Dimethyl-6-((S)-(phenylamino)(2-(trifluoromethyl)-phenyl)methyl)tetrahydro-3H,5H-pyrrolo[1,2-c]oxazol-5-one (**4**).* Lithium diisopropylamide (35.9 mg, 0.34 mmol) was dissolved in toluene (1.079 mL) and THF (0.26 mL) and cooled to −55 °C. To this mixture was added **1a** (50 mg, 0.32 mmol) dissolved in toluene (1.34 mL) and was allowed to stir for 10 min. Imine **2** (104.4 mg, 0.42 mmol) dissolved in toluene (1.34 mL) was added. After 2 h, the reaction was quenched with pH 7 phosphate buffer (6 mL) and allowed to warm. The mixture was extracted 3 × 20 mL with Et_2O, dried over Na_2SO_4, and rotary evaporated. The resulting yellow oil was purified using flash chromatography using a gradient of ethyl acetate/hexane mixtures and rotary evaporated to yield 102 mg (78%) of white solid. R_f = 0.19 in 40% EtOAc/hexanes; mp =106.9−112.4. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 7.9 Hz, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.36 (t, J = 7.7 Hz, 1H), 7.05 (t, J = 7.8 Hz, 2H), 6.66 (t, J = 7.3 Hz, 1H), 6.53 (d, J = 8.0 Hz, 2H), 5.30 (s, 1H), 5.01 (d, J = 7.9 Hz, 1H), 4.40−4.23 (m, 1H), 4.06 (dd, J = 8.3, 5.7 Hz, 1H), 3.36 (appt, J = 8.8 Hz, 1H), 3.00 (ddd, J = 9.8, 7.5, 2.3 Hz, 1H), 2.01−1.79 (m, 2H), 1.67 (s, 3H), 1.50 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.7, 145.0, 138.5, 131.2, 128.19 (q, $^3J_{C-F}$ = 7.8 Hz), 128.15, 127.6, 127.3 (q, $^2J_{C-F}$ = 29.7 Hz), 127.0, 125.4 (q, $^3J_{C-F}$ = 5.9 Hz), 123.7 (q, $^1J_{C-F}$ = 275 Hz), 117.0, 112.8, 90.4, 69.0, 58.8, 52.9, 52.7, 25.2, 22.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ −55.5. HRMS (DART ionization, orbitrap mass analyzer) calcd for $C_{12}H_{12}FNO_2$ [M + H] 405.17899, found 405.17844.

*(6S,7aS)-3,3-Dimethyl-6-((R)-(phenylamino)(2-(trifluoromethyl)-phenyl)methyl)tetrahydro-3H,5H-pyrrolo[1,2-c]oxazol-5-one (**6**).* Lithium diisopropylamide (376 mg, 3.54 mmol) was dissolved in THF (12 mL) and cooled to −78 °C. To this mixture was added **1a** (500 mg, 3.22 mmol) dissolved in THF (10.3 mL) and was allowed to stir for 10 min. Imine **2** (104.4 mg, 0.42 mmol) dissolved in THF (10.3 mL) was added. After 2 h, the reaction was quenched with pH 7 phosphate buffer (25 mL) and allowed to warm. The mixture was extracted 3 × 60 mL with Et_2O, dried over Na_2SO_4, and rotary evaporated. The resulting yellow oil was purified using flash chromatography using a gradient of ethyl acetate/hexane mixtures and rotary evaporated to yield 91 mg (7%) of white foam. R_f = 0.22 in 40% EtOAc/hexanes. ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.77 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 7.9 Hz, 1H), 7.52 (dd, J = 8.3, 7.0 Hz, 1H), 7.36 (t, J = 7.7 Hz, 1H), 7.05 (dd, J = 8.6, 7.3 Hz, 2H), 6.66 (t, J = 7.3 Hz, 1H), 6.56−6.48 (m, 2H), 5.30 (s, 1H), 5.01 (d, J = 7.9 Hz, 1H), 4.32 (p, J = 7.2 Hz, 1H), 4.06 (dd, J = 8.3, 5.7 Hz, 1H), 3.36 (dd, J = 9.3, 8.3 Hz, 1H), 3.00 (td, J = 8.6, 7.5, 2.3 Hz, 1H), 2.00−1.78 (m, 2H), 1.67 (s, 3H), 1.50 (s, 3H). ^{13}C NMR (151 MHz, cdcl$_3$) δ 171.3, 147.4, 141.3, 135.7, 132.7, 129.1, 128.5, 127.7, 126.2, 118.3, 114.0, 92.9, 70.1, 59.9, 55.3, 55.0, 28.0, 23.5, 27.1 (carbon not directly observed). ^{19}F NMR (376 MHz, chloroform-*d*) δ −56.52. HRMS (DART ionization, orbitrap mass analyzer) calcd for $C_{12}H_{12}FNO_2$ [M + H] 405.17899, found 405.17844.

*(6R,7aS)-3,3-Dimethyl-6-((S)-(phenylamino)(2-(trifluoromethyl)-phenyl)methyl)tetrahydro-3H,5H-pyrrolo[1,2-c]oxazol-5-one (**7**).* Lithium diisopropylamide (275.9 mg, 2.6 mmol) was dissolved in THF (2.69 mL) and cooled to −78 °C. To this mixture was added **1a** (100 mg, 0.65 mmol) dissolved in THF (2.69 mL) and was allowed to stir for 10 min. Imine **2** (209 mg, 0.84 mmol) dissolved in THF (1.08 mL) was added. After 2 h, the reaction was quenched with pH 7 phosphate buffer (6 mL) and allowed to warm. The mixture was extracted 3 × 15 mL with Et_2O, dried over Na_2SO_4, and rotary evaporated. The resulting yellow oil was purified using flash chromatography with 60% diethyl Et_2O/pentane and rotary evaporated to yield 127.4 mg (49%) of yellow oil. R_f = 0.70 in 40% EtOAc/hexanes. ^{1}H NMR (599 MHz, $CDCl_3$) δ 8.01 (d, J = 8.0 Hz, 1H), 7.63 (dd, J = 7.9, 1.3 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.30 (t, J = 7.7 Hz, 1H), 7.11−7.07 (m, 1H), 6.67 (tt, J = 7.3, 1.1 Hz, 1H), 6.62−6.59 (m, 1H), 5.47 (d, J = 9.4 Hz, 1H), 4.95 (d, J = 8.9 Hz, 1H), 4.17−4.04 (m, 1H), 3.54−3.46 (m, 1H), 3.31 (ddd, J = 12.8, 7.4, 2.2 Hz, 1H), 2.38 (ddd, J = 12.4, 7.4, 5.4 Hz, 1H), 1.99 (td, J = 12.3, 8.9 Hz, 1H), 1.75 (s, 1H), 1.45 (s, 1H). ^{13}C NMR (151 MHz, cdcl$_3$) δ 170.6, 146.9, 141.2, 132.2, 129.2, 128.8, 127.2, 125.9, 118.4, 114.2, 91.6, 69.7, 58.6, 54.0, 53.4, 31.1, 23.8, 26.5 (carbon not directly observed). ^{19}F NMR (376 MHz, chloroform-*d*) δ −58.13. HRMS (DART ionization, orbitrap mass analyzer) calcd for $C_{12}H_{12}FNO_2$ [M + H] 405.17899, found 405.17844.

*(S,E)-3,3-Dimethyl-6-(2-(trifluoromethyl)benzylidene)tetrahydro-3H,5H-pyrrolo[1,2-c]oxazol-5-one (**15**).* Lithium diisopropylamide (74.3 mg, 0.70 mmol) was dissolved in toluene (2.16 mL) and THF (0.067 mL) and cooled to −55 °C. To this mixture was added **1a** (100 mg, 0.64 mmol) dissolved in toluene (1.56 mL) and was allowed to stir for 10 min. Imine **2** (210 mg, 0.83 mmol) dissolved in toluene (2.68 mL) was added. After 6 h, the reaction was quenched with pH 7 phosphate buffer (6 mL) and allowed to warm. The mixture was extracted 3 × 20 mL with Et_2O, dried over Na_2SO_4, and rotary evaporated. The resulting yellow oil was purified using flash chromatography using a gradient of diethyl ether/pentane mixtures and rotary evaporated to yield 88 mg (44%) of white solid. R_f = 0.45 in diethyl ether; mp =106.9−112.4. ^{1}H NMR ^{1}H NMR (599 MHz, $CDCl_3$) δ 7.70 (d, J = 7.8 Hz, 1H), 7.55 (s, 1H), 7.53 (t, J = 7.7 Hz, 1H), 7.42 (d, J = 7.3 Hz, 2H), 7.40 (d, J = 7.7 Hz, 1H), 4.23−4.13 (m, 2H), 3.47 (dd, J = 9.4, 7.8 Hz, 1H), 2.99 (ddd, J = 16.9, 6.7, 2.1 Hz, 1H), 2.68 (ddd, J = 17.0, 5.6, 3.6 Hz, 1H), 1.74 (s, 3H), 1.54 (s, 3H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 171.6, 142.8, 137.8, 136.7, 132.0, 128.7 (q, $^2J_{C-F}$ = 28.9 Hz), 128.2, 127.6 (q, $^3J_{C-F}$ = 9.9 Hz) 126.8, 126.2 (q, $^3J_{C-F}$ = 5.7 Hz), 124.2 (q, $^1J_{C-F}$ = 274 Hz), 119.4, 92.6, 67.1, 64.6, 29.2, 28.8, 23.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ −59.92; HRMS (DART ionization, orbitrap mass analyzer) calcd for $C_{12}H_{12}FNO_2$ [M + H] 312.12114, found 312.12059.

*(S,Z)-3,3-Dimethyl-6-(2-(trifluoromethyl)benzylidene)tetrahydro-3H,5H-pyrrolo[1,2-c]oxazol-5-one (**16**).* Lithium diisopropylamide (74.3 mg, 0.70 mmol) was dissolved in THF (2.16 mL) at −55 °C. To this mixture was added **1a** (100 mg, 0.64 mmol) dissolved in THF (1.56 mL) and was allowed to stir for 10 min. Imine **2** (210 mg, 0.83 mmol) dissolved in THF (2.68 mL) was added. After 2 h, the reaction was allowed to warm to room temp and stirred for an additional 30 min. The reaction was then quenched with pH 7 phosphate buffer (10 mL), extracted 3 × 20 mL with Et_2O, dried over Na_2SO_4, and rotary evaporated. The resulting yellow oil was purified using flash chromatography using a gradient of diethyl ether/pentane mixtures and rotary evaporated to yield 60 mg (30%) of yellow oil. R_f = 0.71 in diethyl ether. ^{1}H NMR (599 MHz, chloroform-*d*) δ 7.64 (d, J = 7.8 Hz, 1H), 7.47 (t, J = 7.5 Hz, 1H), 7.39 (d, J = 7.7 Hz, 1H), 7.33 (t, J = 7.7 Hz, 1H), 6.34 (s, 1H), 4.45 (ddd, J = 10.0, 5.9, 2.1 Hz, 1H), 4.03 (dd, J = 8.1, 6.2 Hz, 1H), 3.73 (s, 2H), 3.20 (dd, J = 9.8, 8.1 Hz, 2H), 1.67 (s, 3H), 1.54 (s, 3H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 165.3, 138.8, 131.6, 129.26 (q, $^3J_{C-F}$ = 10.0 Hz), 129.20, 129.0 (q, $^2J_{C-F}$ = 30.3 Hz), 128.2, 126.8, 126.2 (q, $^3J_{C-F}$ = 5.5 Hz), 123.9 (q, $^1J_{C-F}$ = 274 Hz), 92.2, 70.0, 58.2, 28.9, 27.1, 23.6. ^{19}F NMR (376 MHz, chloroform-*d*) δ −59.74; HRMS (DART ionization, orbitrap

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mass analyzer) calcd for $C_{12}H_{12}FNO_2$ [M + H] 312.12114, found 312.12059.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b05481.

Spectroscopic, kinetic, and computational data and authors for ref 12 (PDF)

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Notes

The authors declare no competing financial interest.

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