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Azaaldol Condensation of a Lithium Enolate Solvated by *N,N,N′,N′*-Tetramethylethylenediamine: Dimer-Based 1,2-Addition to Imines

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Supporting Information

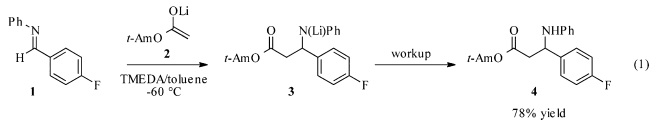
ABSTRACT: The lithium enolate of *tert*-amylacetate solvated by *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) is shown to be a doubly chelated dimer. Adding the dimeric enolate to 4-fluorobenzaldehyde-*N*-phenylimine affords an N-lithiated *β*-amino ester shown to be monomeric using ^{6}Li and ^{15}N NMR spectroscopies. Rate studies using ^{19}F NMR spectroscopy reveal reaction orders consistent with a transition structure of stoichiometry $[(ROLi)_2(TMEDA)_2(imine)]^{‡}$. Density functional theory computations explore several possible dimer-based transition structures with monodentate and bidentate coordination of TMEDA. Supporting rate studies using *trans-N,N,N′,N′*-1,2-tetramethylcyclohexanediamine showing analogous rates and rate law suggest that TMEDA is fully chelated.

INTRODUCTION

Lithium enolates are of undeniable importance to synthetic chemists[1] yet pose particularly onerous mechanistic challenges owing to complex aggregation phenomena. Solid-state structural studies initiated by Seebach with significant contributions by Williard have grown into a considerable body of work.[2] Much less is known about the structures of enolates in solution[3] and how solvation and aggregation influence reactivity.[4−8] The seminal spectroscopic and mechanistic studies were those of Jackman and co-workers.[4] The preponderance of progress in untangling the contributions of equilibrating aggregates and monomers to enolate reactivity comes from Streitwieser and co-workers.[6] Most recently, Reich and co-workers have focused on measuring relative reactivities of aggregates and monomers under *nonequilibrium* conditions.[7]

The present study of 1,2-additions of metal enolates to imines (so-called azaaldol condensations) dovetails a long-standing program aimed at understanding 1,2-additions[9] and lithiations[10] of imines with an emergent interest in structures and reactivities of lithium enolates.[1,2,11−13] Azaaldol condensations are of particular importance in the synthesis of biologically and medicinally significant *β*-amino esters, *β*-lactams, and 1,3-amino alcohols.[14−16] The flexibility of imines that synthetic chemists find appealing[16]—the capacity to vary the substituents on the imine moiety—has proven to be equally important in untangling organolithium structure−reactivity relationships.

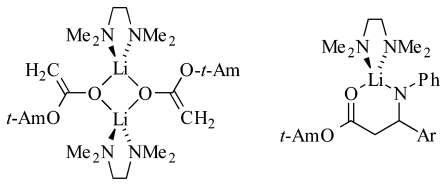
Herein we describe rate and mechanistic studies of the azaaldol addition of *tert*-amyl acetate **2** (*t*-Am = $C(CH_3)_2Et$) to imine **1** (eq 1) mediated by *N,N,N′,N′*-tetramethylethylenediamine (TMEDA).[8] The reaction is clean, proceeds at tractable rates without complicating lactamization,[17] and is readily monitored with ^{19}F NMR spectroscopy.[18] A combination of



structural, rate, and computational studies revealed an enolate dimer-based mechanism.

RESULTS

Solution Structures. Previous studies of TMEDA-solvated enolates using the method of continuous variation (the method of Job) have shown enolate **2** to be doubly chelated dimer **2a**.[19] Adduct $[^{6}Li,^{15}N]$**3** prepared from $[^{15}N]$**1** and $[^{6}Li]$LDA.[20] was shown using ^{6}Li and ^{15}N NMR spectroscopies[21−23] to be monomer **3a**. The ^{6}Li spectrum shows a 1:1 ^{6}Li doublet (J = 6.6 Hz) and 1:1:1 ^{15}N triplet J = 6.9 Hz).[24] No mixed aggregates are formed. Treatment of *β*-amino ester **4** with 1.0 equiv of $[^{6}Li]$LDA in the presence of TMEDA regenerates **3a**.



Kinetics. Adding 1.0 equiv of imine **1** to enolate **2** in 0.65 M TMEDA/toluene at −60 °C and monitoring with in situ IR spectroscopy revealed an overall second-order decay (Figure 1),

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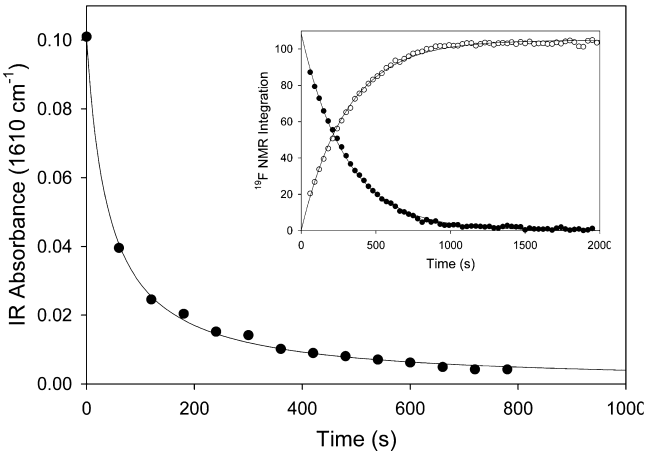


Figure 1. Curve fitting for the condensation of the lithium enolate of *tert*-amyl acetate enolate **2** (0.10 M)[26] with equimolar imine **1** (0.10 M) in 0.65 M TMEDA/toluene at −60 °C. The curve depicts an unweighted least-squares fit to the second-order function: $y = [A]_0/(1 + [A]_0kt)$ ($[A]_0 = 0.101 \pm 0.001$ M, $k = 0.24 \pm 0.01$ M^{-1} s^{-1}). The inset shows the loss of **1** and formation of **3** using lithium enolate **2** (0.10 M), imine **1** (0.005 M), and 0.55 M TMEDA/toluene at −60 °C (pseudo-first-order conditions). Imine **1** is represented by the symbol ● and the product **3** by ○. The curves depict unweighted least-squares fits to $y_{S2} = y_0e^{-bt}$ ($y_0 = 108.6 \pm 0.1$, $b = 3.32 \pm 0.03 \times 10^{-3}$ s^{-1}) and $y_{S3} = y_0(1 - e^{-bt})$ ($y_0 = 104.9 \pm 0.1$, $b = 3.28 \pm 0.03 \times 10^{-3}$ s^{-1}).

offering no evidence of autocatalysis or other mixed aggregation effects.[25] To conduct detailed rate studies under pseudo-first-order conditions we turned to ^{19}F NMR spectroscopy. Injecting imine **1** (resulting in 0.005 M **1**) into a solution of enolate **2** and TMEDA afforded clean first-order decays and affiliated values of k_{obsd} (Figure 1 inset). A standard control experiment confirmed the absence of autocatalysis: sequential injections of imine **1** (0.005 M) into a solution of enolate and TMEDA afforded indistinguishable values of k_{obsd} (within 10%). Monitoring k_{obsd} versus enolate concentration[26] revealed a first-order dependence consistent with a dimer-based addition (Figure 2). An analogous plot of k_{obsd} versus TMEDA concentration revealed a zeroth-order dependence (Figure 3). The idealized rate law[27] described by eq 2 implicates the transition structure of stoichiometry shown in eq 3.[28]

$$-\mathrm{d[imine]}/\mathrm{d}t = k[\mathrm{imine}][\mathrm{TMEDA}]^0[\mathrm{enolate}] \quad (2)$$

$$(\mathrm{ROLi})_2(\mathrm{TMEDA})_2 + \mathrm{imine} \rightarrow [(\mathrm{ROLi})_2(\mathrm{TMEDA})_2(\mathrm{imine})]^{\ddagger} \quad (3)$$

Computations. Density functional theory (DFT) computations at the B3LYP/6-31G(d) level[29] evaluated dimer-based pathways including cyclic dimers, open dimers,[30] and triple ions.[31−34] We modeled the *tert*-amyl group with a methyl. The reported energies correspond to the calculated free energies of activation at −60 °C and to fully balanced equilibria. Intrinsic reaction coordinate (IRC) calculations were performed to confirm the validity of the transition structures.[35] Figure 4 shows the computed structures in order of increasing free energy. A number of configurations were calculated including open and closed dimers with combinations of mono- and bidentate TMEDA ligands (**5a**−**5f**).[36] Structure **5g** manifests an imine nitrogen bridging two lithiums. The structure of the lowest energy form, **5a**, is an open dimer with both mono- and bidentate TMEDA. Triple ion **5h** with an $(\eta^2\text{-TMEDA})_2Li^+$ counterion is energetically ridiculous; DFT routinely fails with

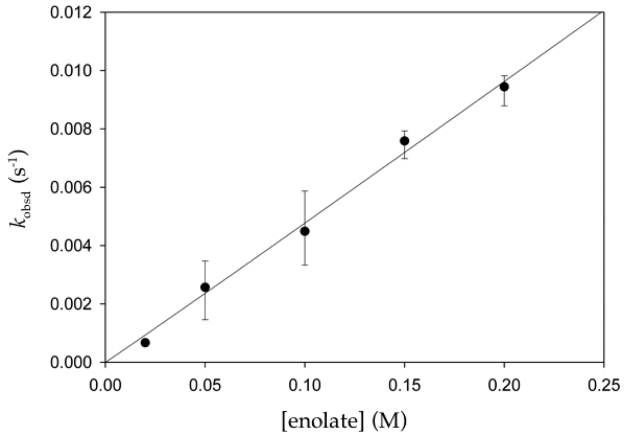


Figure 2. Plot of k_{obsd} versus concentration of enolate **2** for the condensation of imine **1** (0.005 M) with lithium enolate **2** in 0.55 M TMEDA/toluene at −60 °C. The curve depicts the unweighted least-squares fit to $k_{obsd} = k[\mathbf{2}]^b$ ($k = 0.049 \pm 0.007$, $b = 1.01 \pm 0.08$).

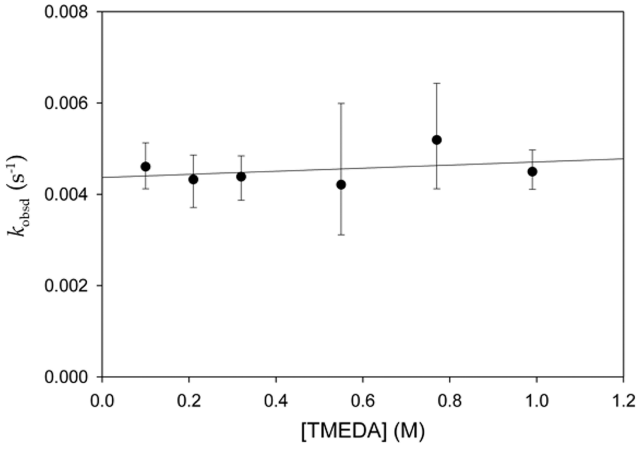
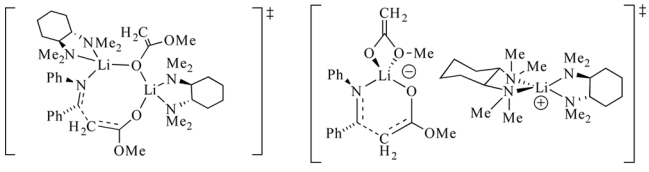


Figure 3. Plot of k_{obsd} versus free TMEDA concentration[26] in toluene cosolvent for the condensation of lithium enolate **2** (0.10 M) with imine **1** (0.005 M) at −60 °C. The curve depicts the unweighted least-squares fit to $k_{obsd} = k + k'[\mathrm{TMEDA}]_{free}$ ($k = 0.0044 \pm 0.0003$, $k' = 0.0003 \pm 0.0005$).

such fully ionized forms.[37,38] We do, however, believe that **5h** is worthy of further consideration.

Kinetics Revisited: Enolate-TMCDA. To resolve the ambiguity about whether TMEDA is functioning as a mono- or bidentate ligand we investigated *N,N,N′,N′*-tetramethylcyclohexane-diamine (TMCDA).[39] The notion was simple: TMCDA is a surrogate of TMEDA but is more strongly chelating[40] and displays no tendency to bind as a monodentate ligand.[41] Cursory examination of azaaldol condensation of enolate **2** revealed rates that were nearly indistinguishable ($k_{TMCDA}/k_{TMEDA} = 0.9$)[42] and provided an analogous rate law (Supporting Information). Computations offered transition



7a $\Delta G^{\ddagger} = 9.6$ kcal/mol

7b $\Delta G^{\ddagger} = 105.1$ kcal/mol

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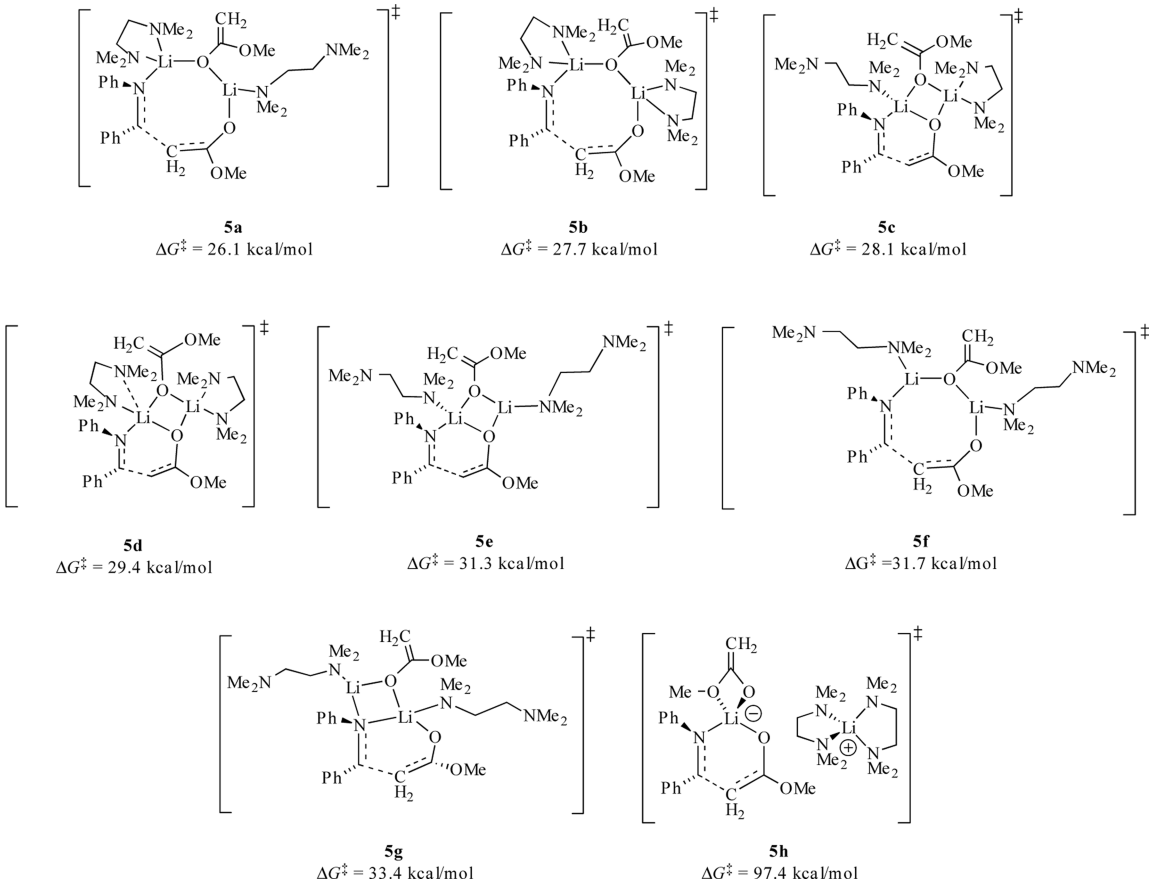
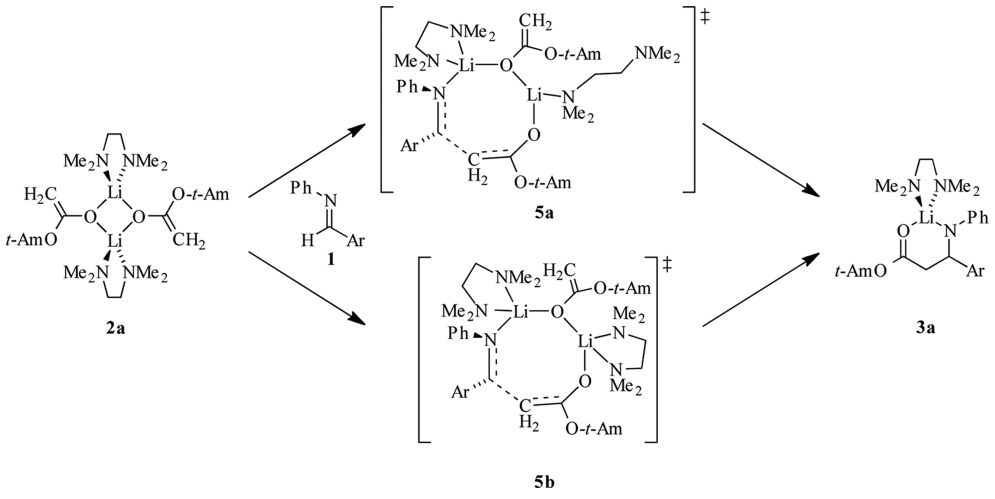


Figure 4. Computed transition structures of stoichiometry $[(ROLi)_2(TMEDA)_2(imine)]^{‡}$.

Scheme 1



structures **7a** and **7b**. The $(\eta^2$-TMCDA$)_2$Li$^+$ counterion in **7b** has crystallographic support.[43] Despite considerable effort, we found no closed dimer analogous to **5d**.

DISCUSSION

Using a combination of ^{6}Li and ^{15}N NMR spectroscopies we have shown that *tert*-amyl acetate enolate **2** is disolvated dimer **2a** in the presence of TMEDA.[12] Rate studies using ^{19}F NMR spectroscopy revealed that there is no autocatalysis and that the addition of **2a** to fluorinated imine **1** is first order in imine, first order in enolate dimer **2a**, and zeroth order in TMEDA. The rate law (eq 2) is consistent with reaction via a bis-TMEDA-solvated enolate dimer as depicted generically in eq 3.

The experimentally elusive details of the dimer-based transition structure were examined using DFT computations, revealing a number of candidates (Figure 4). The two most viable pathways are summarized in Scheme 1. Dimer-based transition structure **5a**, containing both η^1- and η^2-bound TMEDA ligands, was predicted to be the lowest energy form. We would be reckless, however, to distinguish them using calculated $\Delta G^{‡}$'s alone. For example, we found doubly chelating structure **5b** is very plausible. Consequently, we

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investigated TMCDA as a strongly chelating surrogate for TMEDA. We know of no evidence, experimental or computational, that TMCDA can coordinate as a monodentate ligand. The basal assumption, therefore, is that the rates and mechanisms using TMCDA and TMEDA diverge only if TMEDA is functioning as a nonchelating ligand somewhere along the reaction coordinate. Experimentally indistinguishable rates and rate laws for the two diamines cast the deciding vote for **5b** as the most logical transition structure. We hasten to add, however, that despite the enormous computed barrier (DFT is notoriously incapable of modeling ionization energies[38]) triple ion **5h** has considerable appeal. Triple ions, including those derived from lithium enolates,[32] are well precedented.[31,32] The $(\eta^2\text{-TMEDA})_2Li^+$ counterion has been observed,[37] and the $(\eta^2\text{-TMCDA})_2Li^+$ cation has been documented as well.[43] The bidentate interaction of the ester enolate in **5h** also has structural precedent.[44]

CONCLUSION

The azaaldol addition of a disolvated dimeric lithium enolate to an aryl imine occurs through a transition structure consisting of a disolvated dimeric enolate. Although some of the details of the transition structure remain unresolved, calculations slightly favor an open dimer (1.6 kcal/mol) with only one of the two TMEDA molecules chelating.

The dimer-based reaction is interesting in light of dominant beliefs in the earlier days of organolithium chemistry that monomers are the central fleeting intermediate. Streitwieser has wrestled with this question for a number of years and concludes that monomers are often key intermediates. Similarly, Reich has found that in nonequilibrating mixtures of monomers and dimers the monomers are almost always more reactive. That is not to say, however, that when dimers or tetramers are the observable form in solution the most favorable pathway necessarily proceeds via energetically costly deaggregations.[45] A number of groups have endorsed the notion of aggregate-based enolate reactivity. Enolates are a very broad class of intermediate. Throw into the debate the huge roles of solvent, temperature, concentration, and choice of electrophile, and considerable mechanistic variation is to be expected.

EXPERIMENTAL SECTION

Reagents and Solvents. TMEDA, TMCDA, 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.[23] Solutions of LDA were titrated for active base using a literature method.[46] Air- and moisture-sensitive materials were manipulated under argon using standard glovebox, vacuum line, and syringe techniques. Imine **1** was prepared using a literature procedure.[47]

NMR Techniques. All NMR samples were prepared using stock solutions and 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, and ^{15}N resonances are externally referenced to 0.30 M [^{6}Li]LiCl/MeOH at −90 °C (0.0 ppm), the CH_2O resonance of THF at −90 °C (67.57 ppm), and neat Me_2NEt at −90 °C (25.7 ppm), respectively.

Kinetics. Samples for NMR kinetics were prepared from stock solutions at room temperature: (1) *tert*-amyl acetate in toluene, (2) imine **1** and fluorobenzene internal standard in toluene, and (3) LDA/TMEDA in toluene. The NMR tube was capped with a septum, evacuated, flushed several times with argon, flame-dried, and put under argon. A length of 25 μm i.d. flexible capillary tubing was inserted into the tube and flushed with argon for several minutes before the end was capped with a syringe containing 100 μL of a stock solution of imine **1** in toluene. The NMR tube was then cooled in a dry ice/acetone bath, charged sequentially with the LDA/TMEDA (400 μL) and *tert*-amyl acetate/fluorobenzene standard (100 μL) stock solutions, and vortexed for 10s. The tubing was adjusted to reach the curved portion of the tube. The stock solutions were prepared to give final concentrations of 0.005 M each of **1** and fluorobenzene standard, 0.11 M LDA, and 0.10 M *tert*-amyl acetate upon completion of the final injection of imine **1**. The NMR tube was then inserted into the pre-cooled NMR probe and equilibrated at −60 °C. Stock solutions of LDA (400 mL) and ester (100 mL) were injected by standard syringe (not via the tubing). A collection array at 30 s intervals was initiated, and a 100 μL stock solution of imine was injected into the tube giving 10 s to thermally equilibrate before spectral acquisition. The loss of **1** (δ −107.4 ppm) and formation of **3** (δ −117.2 ppm) were monitored relative to a fluorobenzene internal standard (0.007 M, δ −112.96 ppm). The decay of **1** was followed to beyond five half-lives. In processing, the integral area was normalized relative to the fluorobenzene standard. The rate constant was obtained by fitting the decay for each run to the first-order function, $f(x) = ae^{bx}$.

Aminoester 4. Lithium diisopropylamide (218 mg, 2.04 mmol) was dissolved in toluene (16.0 mL) and TMEDA (2.0 mL, 13.3 mmol) in a 50 mL round-bottom flask and cooled to −60 °C. To this mixture was added *tert*-amyl acetate (330 μL, 2.22 mmol) with stirring for 5 min to ensure full enolization. Then imine **1** (307 mg, 1.53 mmol) dissolved in toluene (2.5 mL) was added. After 2 h, the reaction was quenched with methanol (4 mL), allowed to warm to room temperature, and acidified with saturated aq NH_4Cl (4 mL). The organic layer was washed with water (8 mL), dried over Na_2SO_4, and rotary evaporated. The resulting yellowish oil was recrystallized from hot methanol (3.5 mL), yielding 399 mg of white needles (78% yield) with mp = 89−90.5 °C. 2-Methyl-2-butyl 3-(4-fluorophenyl)-3-phenylamino-propanoate (**4**): analytical thin layer chromatography (TLC) on K6F silica gel 60 Å, 4:1 hexanes/EtOAc, R_f = 0.39. IR (neat, cm^{-1}) 3380, 2975, 2922, 1703, 1603, 1507. ^{1}H NMR: δ 7.34 (1H, **A**A′BB′Y, $J_{A\text{-}A'}$ = 2.2 Hz, $J_{A\text{-}B}$ = 8.7 Hz, $J_{A\text{-}X}$ = 5.0 Hz), 7.34 (1H, AA′BB′Y, $J_{A\text{-}A'}$ = 2.2 Hz, $J_{A'\text{-}B'}$ = 8.7 Hz, $J_{A'\text{-}X}$ = 5.0 Hz), 7.09 (2H, dd, J = 8.2, 7.3 Hz), 6.99 (1H, AA′**B**B′Y, $J_{B\text{-}B'}$ = 2.5 Hz, $J_{A\text{-}B}$ = 8.7 Hz, $J_{B\text{-}X}$ = 8.7 Hz), 6.99 (1H, AA′B**B**′Y, $J_{A'\text{-}B'}$ = 8.7 Hz, $J_{B'\text{-}B}$ = 2.5 Hz, $J_{B'\text{-}X}$ = 8.7 Hz), 6.67 (1H, t, 7.3 Hz), 6.52 (2H, d, 8.2 Hz), 4.75 (1H, AB**M**X, $J_{A\text{-}M}$ = 5.8 Hz, $J_{B\text{-}M}$ = 7.2 Hz, $J_{M\text{-}X}$ = 6.1 Hz), 4.61 (1H, ABM**X**, $J_{M\text{-}X}$ = 6.1 Hz), 2.71 (1H, **A**BMX, $J_{A\text{-}B}$ = 14.6 Hz, $J_{A\text{-}M}$ = 5.8 Hz), 2.69 (1H, **A**BMX, $J_{A\text{-}B}$ = 14.6 Hz, $J_{B\text{-}M}$ = 7.2 Hz), 1.70 (2H, q, J = 7.5 Hz), 1.34 (6H, s), 0.78 (3H, t, J = 7.5 Hz). ^{13}C NMR: δ 170.4, 162.2 (d, J_{C-F} = 245 Hz), 146.9, 138.1 (d, J_{C-F} = 3 Hz), 129.3, 128.1 (d, J_{C-F} = 8 Hz), 117.9, 116.7 (d, J_{C-F} = 21 Hz), 113.7, 84.1, 54.7, 44.2, 33.6, 25.6, 25.6, 8.3. ^{19}F NMR: δ −115.6. Molecular ion calculated for $C_{20}H_{24}FNO_2$: 329.1791; EIMS found m/z = 329.1793. ^{1}H NMR ABMX and AA′BB′Y couplings were identified using spin simulation in MestReNova 7.1.1.

Aminoester [^{15}N]4. Prepared as above using [^{15}N]**S2**, made from commercially available ^{15}N-aniline. ^{1}H NMR: δ 7.34 (2H, app dd), 7.10 (2H, dd, J = 8.3, 7.3 Hz), 6.99 (2H, app t), 6.67 (1H, t, J = 7.3 Hz), 6.52 (2H, d, J = 7.8 Hz), 4.75 (1H, app q), 4.61 (1H, app d), 2.75−2.65 (2H, app m), 1.70 (2H, q, J = 7.5 Hz), 1.34 (6H, s), 0.78 (3H, t, J = 7.5 Hz). ^{13}C NMR: δ 170.4, 162.2 (d, J_{C-F} = 245 Hz), 146.9 (d, J_{C-N} = 13 Hz), 138.1 (d, J_{C-F} = 3 Hz), 129.4, 128.1 (dd, J_{C-F} = 8, 1 Hz), 118.0, 115.7 (d, J_{C-F} = 21 Hz), 113.7 (d, J_{C-N} = 2 Hz), 84.1, 54.7 (d, J_{C-N} = 10 Hz), 44.2, 33.6, 25.6, 25.6, 8.3. ^{19}F NMR: δ −115.6. ^{15}N NMR: δ 73.2. Molecular ion calculated for $C_{20}H_{24}F^{15}NO_2$: 330.1761; EIMS found m/z = 330.1759.

Azaaldol Adduct [^{6}Li,^{15}N]3. Individual stock solutions of imine [^{15}N]**1** (0.22 M in toluene) and [^{6}Li]LiHMDS (0.20 M in TMEDA/toluene) were prepared at room temperature. An NMR tube was flame-dried under vacuum and allowed to come to room temperature. It was then backfilled with argon and placed in a −78 °C dry ice/acetone bath. Base (300 μL of stock solution) and imine [^{15}N]**1** (300 μL of stock solution) were added sequentially via syringe. The tube was sealed under partial vacuum, vortexed for approximately 10 s at room temperature, and cooled to −78 °C. ^{6}Li NMR spectra were

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recorded at −60 °C on a 500 MHz spectrometer with and without broadband ^{15}N decoupling. Chemical shifts are reported relative to a 0.30 M ^{6}LiCl/MeOH standard at the reported probe temperature. ^{15}N NMR spectra were recorded using the INEPT pulse sequence at −60 °C on a 500 MHz spectrometer with and without broadband ^{6}Li decoupling. ^{6}Li NMR: δ 1.54 (J_{Li-N} = 6.6 Hz). ^{19}F NMR: δ −117.1. ^{15}N NMR: δ 123.9 (t, J_{Li-N} = 6.6 Hz).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR and computational data, experimental protocols, and complete ref 29. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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