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Structures and Reactivities of Sodiates Evans Enolates: Role of Solvation and Mixed Aggregation on the Stereochemistry and Mechanism of Alkylations

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Abstract

Oxazolidinone-based sodiated enolates (Evans enolates) were generated using sodium diisopropylamide (NaDA) or sodium hexamethyldisilazide (NaHMDS) in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA), (*R,R*)-*trans*-*N,N,N',N'*-tetramethylcyclohexanediamine [(*R,R*)-TMEDA], or (*S,S*)-TMEDA. ¹³C NMR spectroscopic analysis in conjunction with the method of continuous variations (MCV) and density functional theory (DFT) computations revealed the enolates to be octahedral *bis*-diamine-chelated monomers. Rate and computational studies of an alkylation with allyl bromide implicate a *bis*-diamine-chelated-monomer-based transition structure. The sodiated Evans enolates form mixed dimers with NaHMDS, NaDA, or sodium 2,6-di-*tert*-butylphenolate, the reactivities of which are examined. Stereoselective quaternizations, aldol additions, and azaaldol additions of sodiated Evans enolates are described.

Graphical Abstract

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Supporting Information: Spectroscopic, kinetic, and computational data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Introduction

Oxazolidinone-derived enolates—so-called Evans enolates—have been used in both academic and industrial laboratories in the development of asymmetric syntheses since they were first reported by Evans and co-workers in 1981.¹ Highly stereoselective functionalizations stemming from a wide variety of auxiliaries and counterions are legion.² Aldol additions typically rely on boron- or transition-metal-based enolates,³ whereas alkylations require the more reactive sodium and lithium enolates.^{1,4}

(1)

We previously characterized the structures of lithiated Evans enolates as tetramer–dimer mixtures in tetrahydrofuran (THF) solution,⁵ underscored potential applications in simple aldol additions,^{6,7} and demonstrated doubly diastereoselective aldol additions using lithium enolate–lithium amino alkoxide mixed tetramers.⁸ We have also examined the structures and reactivities of key intermediates in di-*n*-butylboron triflate-based aldol additions.^{9,10}

This paper examines the corresponding sodium enolates. Sodium enolate **2** in neat THF shows broad ¹H and ¹³C resonances reminiscent of the poor structural control of simple sodium enolates in THF solution.¹¹ Although the use of THF is prevalent throughout organolithium chemistry,^{12,13} could it be that the almost irresistible urge to use THF as the default medium may be suboptimal for organosodium compounds?

Structural, mechanistic, and stereochemical studies of sodiated Evans enolates generically depicted as **2** (eq 1) in toluene solutions with *N,N,N',N'*-tetramethylethylenediamine (TMEDA) and related *N,N,N',N'*-tetramethylcyclohexanediamines [(*R,R*)- and (*S,S*)-*trans*-TMEDA)] reveal octahedral monomers of general structure **4** (Chart 1). Moreover, vicinal diamines promote mixed dimers **5–7**. Studies of the structure and mechanism of alkylation are shaping our thinking about the ligand-based control of structure and selectivity in organosodium chemistry, and the results underscore the potential merits of diamine/hydrocarbon mixtures.

Results

General Methods

Sodium enolates were generated using either NaDA^{14,15} or sodium hexamethyldisilazide (NaHMDS)^{16,17} (recrystallized) dissolved in diamine/toluene solutions. Although the two bases afford similar results, NaHMDS is superior in this case owing to its ease of handling, commercial availability, and in some cases, superior role in subsequent functionalizations stemming from reversible deprotonation. Structures and reaction coordinates were examined with density functional theory (DFT) computations at the B3LYP/6–31G(d) level of theory

with single-point calculations at the MP2 level of theory.¹⁸ We refer to generic enolate **2** and the more specific monomer **4** interchangeably, depending on the context.

Enolization with either 0.10 M NaDA or 0.10 M NaHMDS in 1.0 M TMEDA/toluene is essentially instantaneous at $-78\text{ }^{\circ}\text{C}$. The IR spectra show the loss of **1** at 1783 cm^{-1} and the appearance of an absorbance at 1743 cm^{-1} . During rate studies of alkylations, however, IR spectroscopy proved to have limited value owing to mediocre resolution and distortions caused by the deposition of NaBr. Also of note, sodium enolate **2** shows none of the aggregate-derived aging effects that can plague the highly aggregated lithium enolates.^{5,6} However, **2** decomposes above $-20\text{ }^{\circ}\text{C}$, affording sodium salt **8** observed with in situ IR spectroscopy (eq 2; 1666 cm^{-1}).¹⁹ Deacylated oxazolidinone along with debris that may derive from ketene were isolated on workup.^{2b} The decomposition is approximately twofold slower in TMEDA/toluene than in THF solutions, which may be more consequential than one might suspect (*vide infra*).

(2)

Structures of Enolate Monomers

^1H and ^{13}C NMR spectroscopic studies of enolate **2** in the absence of excess NaDA or NaHMDS showed resonances corresponding to a single magnetically distinct subunit, as observed by monitoring the ^{13}C resonances of the oxazolidinone carbonyl carbon and the oxygen-bearing enolate carbon ($\delta 157.3$ and 152.7 ppm, respectively; Figure 1A). The diamine-solvated enolate was suggested to be monomeric when a synthetic racemate derived from (*S*)-**2** and (*R*)-**2** showed no resonances attributable to a heterochiral aggregate. Mixtures containing 1:1 pairs of enolate **2** with structurally analogous but spectroscopically distinct enolates **9a–d** as well as pairs containing **10** (six pairs in total) also showed no evidence of heteroaggregates (eq 3).²⁰ Emblematic ^{13}C NMR spectra of a binary mixture are shown in Figure 1B,C. Heteroaggregates were also not formed from enolate pairs solvated by either (*S,S*)-TMCDA or (*R,R*)-TMCDA.

(3)

At the outset, we presumed that the monomers were four-coordinate chelates of general structure **11**. However, binary mixtures of diamines afforded homo- and heterosolvates (eq 4) that could be resolved by ^{13}C NMR spectroscopy, as shown in Figure 2. The peak broadening in the samples containing mixed solvates is consistent with stereoisomerism delineated in the discussion. Despite the substandard spectral quality, we could use the method of continuous variations (MCV)²¹ to confirm the structure as a doubly TMEDA-chelated monomer. Varying the diamine proportions in TMEDA/(*S,S*)-TMEDA mixtures and monitoring the homo- and heterosolvates versus *measured* mole fraction of TMEDA (χ_{TMEDA}) afforded a Job plot²² with a unexpectedly good fit to the disolvate model (Figure 3).

(4)

MCV can present a dangerous trap, exemplified by the Job plot in Figure 3, that is worthy of elaboration. Using measured mole fraction—the mole fraction determined by monitoring only ligand within the ensemble of interest—eliminates distortions arising from measuring errors, impurities, and side equilibria. It also precludes the influence of binding constant on the position of maxima.²¹ By contrast, using the standard approach of plotting integration versus *intended* mole fraction—the mole fraction of the amines added within the total sample—provides the decidedly different result shown in Figure 4. It might be tempting to conclude from Figure 4 that TMEDA and (*S,S*)-TMCDA bind in a 2:1 stoichiometry. In this case, however, the skewing of the maximum to higher χ_{TMEDA} reflects the higher binding affinity of (*S,S*)-TMCDA relative to that of TMEDA.

One can (and we have²³) extracted binding constants from such Job plots. (*S,S*)-TMCDA shows a -0.5 kcal/mol (exothermic) preference for substituting the first TMEDA and an attenuated -0.2 kcal/mol preference for substituting the second TMEDA. Computations

predict -0.7 kcal/mol and -0.1 kcal/mol, respectively. Had the differential binding been more dramatic, the maximum would have been pushed even closer to the right-hand y -axis. An analogous Job plot shows that sequential substitutions of TMEDA by (*R,R*)-TMEDA are nearly thermoneutral ($+0.1$ and -0.1 kcal/mol, respectively).

Summarizing an important point, using a simple binary system in which two species, A and B, bind to each other poses no lurking risk because the relative binding constants are *by definition* identical: the maximum in the curve reflects the relative stoichiometries. If two species—ligands in this case—compete for binding to a third entity (sodium), however, differential binding eliminates the relationship of the maximum and the stoichiometry of binding. This risk has inspired one group to declare the “death of the Job plot.”²⁴ Although we think that declaration is a bit hyperbolic, such concerns should be heeded.

The veracity of the assignment of enolate **2** as the *bis*-chelated octahedral monomer **4** is supported by DFT computations showing the exothermic serial solvation of unsolvated enolate monomer **2** (eq 5). The octahedral geometry is illustrated in Figure 5 using the lowest energy stereoisomer of **4**. A more elaborate description of the stereochemistry of chelation is deferred to the discussion.

(5)

Structures of Enolate–Amide Mixed Dimers

The enolization of **1** with excess NaDA or NaHMDS generates additional enolate ^{13}C resonances manifesting amide-concentration-dependent intensities and amide-dependent chemical shifts (Figure 6). These new species are assigned as mixed dimers **5** and **6**. The 1:1 stoichiometry in **6** is shown by the quantitative formation with 1.0 equiv NaHMDS (Figure 6) as reflected in the Job plot in Figure 7. By contrast, NaDA shows qualitatively similar behavior, albeit reflecting a soft equilibrium (Figures 8 and 9). Thus, *NaHMDS shows a greater penchant than NaDA for mixed aggregation*, which is the opposite of what is observed for LDA and LiHMDS.²⁵

We attempted to confirm the number of chelating ligands on mixed dimers **5** and **6** by integrating the ^{13}C resonances of free and bound TMEDA, but we were unable to obtain the necessary resolution. Nonetheless, decreasing the TMEDA concentration promotes NaDA mixed dimer **5**, consistent with a lower per-sodium solvation (eq 6).^{15,26} DFT computations using the NaHMDS-derived mixed dimer **6** emblematically showed serial chelation by TMEDA to be exothermic for both the first and the second ligations (Scheme 1). The computed structure of the bis-chelate is illustrated in Figure 10. The planes defined by Na_2O_2 and the oxazolidinone chelated enolate are twisted by $50\text{--}60^\circ$.

(6)

Structures of Enolate–Phenolate Mixed Dimers

Hoping to exploit mixed dimers to control the selectivity of enolate functionalizations (*vide infra*), we found that insoluble sodium 2,6-di-*tert*-butylphenolate²⁷ suspended in TMEDA/toluene is solubilized by enolate **2** to form mixed dimer **7** quantitatively (Figure 11). The 1:1 enolate–phenolate stoichiometry was shown with ¹³C NMR spectroscopy. Although ligand exchange was too fast for the direct measurement of the number of coordinated TMEDA ligands, DFT computations showed exothermic double chelation and support the structure in Figure 12. The phenolate moiety shows a significant cant away from the oxazolidinone for reasons that are not obvious. The approximate planes defined by the Na₂O₂ and oxazolidinone rings are skewed by >60°.

Kinetics of Alkylation²⁸

Technical problems with using in situ IR spectroscopy to study the allylation of monomer **4** (generic enolate **2** in eq 1) prompted us to monitor the loss of allyl bromide with ¹H NMR spectroscopy. Pseudo-first-order conditions were established by maintaining standard concentrations of enolate **4** (0.050–0.50 M) and 2.0 equiv TMEDA per sodium (0.10–1.0 M) with low allyl bromide concentrations (0.010 M), all in toluene. The loss of allyl bromide follows a clean pseudo-first-order decay (Figure 13). Following an alkylation to full consumption of enolate shows no evidence of autoinhibition or autocatalysis. The other dependencies were determined using the method of initial rates.²⁹ Plotting initial rates versus enolate and TMEDA concentration revealed first and zeroth orders, respectively (Figures 14 and 15). The rate data are consistent with the idealized³⁰ rate law in eq 7 and the generic mechanism in eq 8. DFT computations suggest a massive 2000:1 preference at –20 °C (3.9 kcal/mol; eq 1) compared with the more modest 20:1 diastereoselectivity observed experimentally. The transition structures show no significant rotations about the N–C(ONa) bond compared with a 30° twist noted in the aldol additions by lithiated Evans enolates (Figure 16).⁶ The TMEDA distal to the alkylating agent shows significant Na–N bond lengthening at the transition state that, according to IRC calculations, becomes pronounced as a Na–Br contact emerges.

$$d[\text{RBr}]/dt = k_{\text{obsd}}[\text{RBr}]^1[\text{RONa}]^1[\text{TMEDA}]^0$$

(7)

(8)

Solvent- and Salt-Dependent Selectivities

The choice of diamine has no discernible effects ($\pm 10\%$) on enolization rates, alkylation rates, or diastereoselectivities. Using THF, which affords a structurally complex enolate, alkylates twofold faster but is otherwise indistinguishable.

Allylations of mixed aggregates gave mixed results. Low yields and complex mixtures from **5** and **6** suggested that the sodium amides pose problems. The alkylation of phenolate mixed aggregate **7**, by contrast, afforded a good yield but an eroded (10:1) diastereoselectivity (eq 9). The *change* in selectivity may be important (*vide infra*).

(9)

Quaternization

We examined a number of reactions of **sodium enolates** to ascertain how its structure influences selectivity. For example, Evans enolate-based quaternizations have been reported sporadically.³¹ Presumed kinetic enolization of **13** using NaDA/TMEDA and subsequent alkylation afford free auxiliary (eq 2) resulting from enolate acylation^{4a} and a more arcane decomposition of the oxazolidinone backbone.³² The enolization of **13**³³ using NaHMDS and subsequent alkylation at -20°C manifest highly solvent-dependent results (eq 10; Table 1). THF affords essentially no (<5%) quaternized product owing to facile deacylation (entry 1). By contrast, using NaHMDS in TMEDA/toluene affords a 54% yield of **14** as an 11:1 mixture of diastereomers (entry 2). Enolization and alkylation of diastereomer **15** afford the *same* 11:1 selectivity, which suggests that selectivity stems from an equilibrated *Z/E* enolate mixture (eq 11).

Curiously, accelerating the enolization merely twofold using NaHMDS/ Et_3N /toluene³⁴ increases the yield to 70% with no measurable loss in stereoselectivity (11:1; entry 4). Under such poorly solvating conditions, precomplexation of the substrate was observable with IR.³⁵ Enolization using NaHMDS/ Et_3N /toluene with *subsequent* addition of (*R,R*)-TMCD

gave identical results (entry 5). The isolated yields roughly correlate with the suppression of the deacylation. NaHMDS/(*R,R*)-TMCDa afforded improved selectivities (30:1) with a sacrificed yield (40%; entry 6), whereas NaHMDS/(*S,S*)-TMCDa gave 19:1 selectivity in 52% yield (entry 7). Adding di-*tert*-butylphenolate (possibly forming an analog of mixed dimer **7**) gave the standard 11:1 selectivity in 44% yield (entry 8).

(10)

(11)

Azaaldol Additions

A brief examination of other electrophiles afforded nothing of interest with epoxides even with assistance from BF_3 .³⁶ The azaaldol addition, however, proved productive. Simple imines are too unreactive to compete with enolate decomposition. Noting success using imines activated with strongly electron withdrawing substituents,^{37,38,39,40} we turned to highly reactive BF_3 –imine complexes⁴¹ while adding the phenethyl moiety, hoping to amplify the stereocontrol (Scheme 2).³⁹

The addition of BF_3 –imine complex **19** dissolved in toluene to enolate **2** in TMEDA/toluene at -78°C afforded adduct **16** in >30:1 selectivity and 93% yield. *Adding $\text{BF}_3\text{-Et}_2\text{O}$ to an imine/enolate mixture was considerably less effective.* The antipodal BF_3 –imine complex **20** afforded **17** in an analogously high (>30:1) selectivity and 82% yield. Hydrogenolyses of **16** and **17** both afforded adduct **22**.⁴² Thus, contrary to some 1,2-additions to phenethyl imines showing high stereochemical control,^{40,43} the stereochemistry of the phenethylimine moiety had no effect whatsoever. Benzylimine– BF_3 complex **21** afforded adduct **18** in 17:1 stereoselectivity and 87% yield. The steric demands of the phenethyl moiety may have some consequence. We hoped that even acetate-based azaaldols would be selective, but no stereocontrol was observed (eq 12).

(12)

Aldol Additions

Aldol addition to 1.0 equiv *i*-PrCHO afforded a low yield of aldol **23** owing to the formation of acetal **25** with credible stereocontrol (Scheme 3). Aldol addition in the presence of excess *i*-PrCHO afforded acetal **25** contaminated with approximately 10% total of three minor diastereomers in a non-optimized 61% isolated yield. Acetal **25** presumably forms via 1,2-adduct **24**. Treating stereochemically pure syn aldol adduct **23** sequentially with 1.0 equiv of NaHMDS (to generate the alkoxide) and *i*-PrCHO afforded **25** in an unoptimized 59% yield with no loss of syn stereoselectivity. Acetal **25** from the aldol addition-cyclization sequence was shown to be an 7:1 mixture of enantiomers reflecting the original syn:syn selectivity.⁴⁴

Discussion

Structures of TMEDA-Solvated Enolates

Our fledgling studies of sodiated enolates have produced decidedly different results than studies of their lithium counterparts (Scheme 4).¹² For example, lithium cyclohexenolate is tetrameric in THF and a doubly chelated dimer in TMEDA/toluene.⁴⁵ By contrast, sodium cyclohexenolate is intractably complex in THF and forms chelated tetramer **26** in TMEDA/toluene.¹¹ Similar bifurcated behavior is observed with Evans enolates. Lithiated Evans enolates are predominantly unsolvated tetramers in either TMEDA or THF.⁵ The sodium analogs are, once again, spectroscopically intractable in THF yet exclusively chelated monomers (**4**) in TMEDA/toluene.

The *two* chelating diamines in **4** cause highly characteristic mixed solvates in binary mixtures of TMEDA, (*R,R*)-TMEDA, and (*S,S*)-TMEDA. The details were obscured by broadened resonances and limited resolution that attest to the stereochemical complexity presented by the octahedral environment of **4** (Scheme 5). If the chelated diamines in **4** (depicted using red and blue color coding) are both TMEDA, there are two delta isomers⁴⁶ suggested by DFT computations to have nearly equal energy (0.4 kcal/mol; see Figure 5). Each delta isomer contains two magnetically inequivalent TMEDA ligands manifesting eight magnetically inequivalent methyls—16 in total. In the limit of slow conformational exchange of TMEDA, half-chair conformers that are well-documented for TMEDA–lithium chelates⁴⁷ would cause that number to spike. The stereochemical complexity doubles with mixtures of structurally distinct diamines (denoted as red and blue in Scheme 5) when delta isomerism and *positional* isomerism are superimposed. DFT computations predict the four isomers in Scheme 5 to be within <1.0 kcal/mol for the (*S,S*)-TMEDA/TMEDA mixed

solvate, for example. Thus, we were *never* going to resolve all the magnetically inequivalent resonances and consider it fortunate that we could detect and measure the total populations of the mixed and homosolvates by focusing on the enolate sp^2 carbons.

Mechanism and Stereochemistry of Alkylation

The mechanism of alkylation of monomer **4** is simple, occurring via a doubly chelated monomer (Figure 16) without any invasive structural changes. DFT computations markedly overestimate the observed 20:1 selectivity but are qualitatively consistent (eq 13). The simplicity of an observable monomer reacting as monomer contrasts with the reaction of lithium Evans enolates in THF solution, in which a kinetically generated mixture of isomeric dimers readily ages to predominantly tetramer, and with the reaction of enolate **2** in THF, which seems to exist as an ill-defined but obviously quite complex mixture of species. Owing to pre-equilibria, explicit correlations of observable structure with reactivity and selectivity are questionable. Nonetheless, years of experience have shown that high stereocontrol is often accompanied by good structural control. For the allylation in eq 1, we observed no advantages or disadvantages offered by TMEDA/toluene compared with THF, but that is not universally the case (*vide infra*).

(13)

Enolate Quaternization

There are relatively few quaternizations of Evans enolates, and they tend to be specialized cases such as those bearing sterically undemanding α -fluoro or α -alkoxy moieties.^{31,48} In our hands, the quaternization (Scheme 6 and eq 10) completely fails in THF solution owing to competitive deacylation. By contrast, TMEDA-solvated enolate—presumably a bis-chelated monomer analogous to **4**—gave 54% yield and 11:1 diastereoselectivity. The stereochemistry appeared to be dictated by a fully equilibrated *Z/E* enolate mixture. There are potentially superior protocols,³¹ but quaternizations of TMEDA-solvated Evans enolates may find a niche and certainly underscore a uniqueness of monomeric enolate **4**.

Other Electrophiles

A casual survey of electrophiles showed that TMEDA-solvated monomer **4** might find broader applications (Scheme 6). The most notable results come from additions of **4** to pre-formed imine- BF_3 complexes. 1,2-Additions of Evans enolates to activated imines are rare.³⁸ Although the addition formed adduct **16** in good yield with essentially total stereoselectivity (>30:1), the choice of phenethylimine antipode had no influence on the selectivity whatsoever; the oxazolidinone auxiliary was the dominant control element.

Equally surprising on the other end of the scale, an acetate-based addition was totally unselective irrespective of the phenethylimine antipode.

We suspect that relatively few attempts have been made to exploit sodiated Evans enolates for aldol additions; we found one report.⁴⁹ This is to be expected given the limited attention received by their lithium counterparts.⁷ Indeed, we observed low yields of addition to *i*-PrCHO, albeit with a credible stereoselectivity (Scheme 3). The major byproduct was acetal **25**, presumably formed via 1,2-adduct **24**. Using excess *i*-PrCHO affords acetal **25** in 61% yield (Scheme 3). We suspect that the diastereoselective cyclization required to control the stereochemistry at the acetal-based stereogenic center arises from reversible adduct formation and selective closure. Adduct **24** is reminiscent of the compounds exploited by Beauchemin and co-workers using aldehydes as organocatalysts (eq 14),⁵⁰ as well as the key intermediates in a tandem aldol addition and Tishchenko reaction.⁵¹ We have previously suggested that transiently and reversibly formed 1,2-adducts may be prevalent but undetected.⁶

(14)

The formation of **25** poses a number of synthetically notable possibilities. Precluding the retroaldol may be the source of the markedly increased yield relative to that of the simple aldol addition. A potentially four-pot sequence—aldol addition, alcohol protection, deacylation, and esterification—is telescoped to one in >90% yield per step. The premature removal of the auxiliary, however, causes the stereochemical refinement of adducts analogous to **23** to become a problem of refining optical purity. In the spirit of Beauchemin's results, stereochemically pure syn aldol adduct **23** can be transformed to **25** in a single step with an unoptimized 59% yield and no loss of diastereoselectivity (eq 15). This one-step replacement of what would otherwise be a three-step protocol may have some synthetic utility in polyketide synthesis.

(15)

Mixed Aggregate Structure and Reactivity

Admittedly limited studies to date have shown little evidence of mixed aggregation in NaDA/NaX mixtures,^{52,53} which is quite unlike the often-observed LDA–LiX mixed

aggregates.²⁵ We were surprised, therefore, to observe sodium enolate–sodium amide mixed dimers **5** and **6** (Scheme 7). Moreover, NaHMDS forms mixed dimer **6** quantitatively, whereas the analogous NaDA–sodium enolate mixed dimer **5** is formed in a much softer (non-quantitative) equilibrium given that the reverse is true for LiHMDS and LDA.²⁵ Even insoluble sodium di-*tert*-butylphenolate is drawn into solution to form mixed dimer **7** quantitatively.

Mixed aggregates **5–7** could impose stereochemical control over the alkylations *provided that the mixed aggregates react without dissociation to monomer 4*.^{54,55} Although alkylations of **5** and **6** gave poor results presumably owing to the nefarious reactivities of the sodium amide fragments, the phenolate-derived mixed dimer **7** showed promise: it reacted cleanly *and* altered the product distribution, albeit in the wrong direction (eq 9). Here is why we still find the experiment interesting. *If* mixed dimer **7** reacts directly without invasive structural changes, there is a stereocontrol element that is unavailable to monomer **4** (Figure 17). The monomer has a sodium and affiliated ligands in an *s*-trans orientation relative to the enolate carbon, placing potential stereochemically controlling ligands remote from the nucleophilic enolate carbon. By contrast, the dimer has an *s*-cis orientation. Despite early failures to improve the selectivity, we sense that persistence in the choice of salt (NaX) and diamine could lead to success.

Conclusion

Sodiated Evans enolates are often used for stereoselective alkylations; however, they are *not* just “lithium enolates on steroids.” TMEDA-solvated monomer **4** has good structural control compared with the analogous enolate in THF solution and offers comparable alkylation selectivities and yields, allows for quaternizations, and exhibits potentially useful reactivities toward imines and aldehydes.

The contrasting behavior of THF and TMEDA raises an important issue. The development of organometallic chemistry is a story of ligand development and optimization. Whether we are speaking of transition-metal-catalyzed couplings or organolithium-based metalations, the coordination sphere is paramount. The temptation to use THF for sodium chemistry because it works so well for lithium may be misguided. Organolithium reagents dominate organoalkali metal chemistry despite lower reactivities because of their higher selectivities. We are not convinced that this will necessarily be the case going forward. Achieving high selectivities in organosodium chemistry may stem from the development of its ligands for the larger sodium ion.

Experimental

Reagents and Solvents

THF, TMEDA, TMCDA, and toluene were distilled from solutions containing sodium benzophenone ketyl. NaDA¹⁴ and NaHMDS were prepared and purified as described previously.¹⁶ Oxazolidinones are commercially available or prepared according to literature procedures.⁵⁶ Air- and moisture-sensitive materials were manipulated under argon with standard glove box, vacuum line, and syringe techniques.

IR spectroscopic analyses

IR spectra were recorded with an in situ IR spectrometer fitted with a 30-bounce, silicon-tipped probe. The spectra were acquired in 16 scans at a gain of 1 and a resolution of 4 cm^{-1} . A representative reaction was carried out as follows: The IR probe was inserted through a nylon adapter and O-ring seal into an oven-dried, cylindrical flask fitted with a magnetic stir bar and a T-joint. The T-joint was capped with a septum for injections and a nitrogen line. After evacuation under full vacuum, heating, and flushing with nitrogen, the flask was charged with NaHMDS (101 mg, 0.55 mmol) in 1.0 M TMEDA/toluene, and cooled to $-78\text{ }^{\circ}\text{C}$. After recording a background spectrum, oxazolidinone **1** (116.5 mg, 0.50 mmol) in toluene was added. The absorbance of **1** at 1783 cm^{-1} was immediately replaced with an absorbance of enolate **2** at 1743 cm^{-1} . To this solution was added neat allyl bromide (363 mg, 3.0 mmol), causing the enolate absorbance to be replaced by the absorbance of oxazolidinone **3** (1783 cm^{-1}). IR spectra were recorded every 15 s with monitoring of the absorbance at 1783 cm^{-1} over the course of the reaction.

NMR Spectroscopy

Individual stock solutions of substrates and NaHMDS were prepared at room temperature. An NMR tube under vacuum was flame-dried on a Schlenk line, allowed to cool to room temperature, backfilled with argon, and placed in a $-78\text{ }^{\circ}\text{C}$ dry ice/acetone bath. Appropriate amounts of oxazolidinone and NaHMDS (1.1 equiv) were added sequentially via syringe. The tube was sealed under partial vacuum, vortexed 3 times on a vortex mixer for 5 s with cooling between each vortexing. Samples could be stored overnight in a $-86\text{ }^{\circ}\text{C}$ freezer. Standard ^1H and ^{13}C NMR spectra were recorded on a 500 MHz spectrometer at 500 and 125.79 MHz, respectively. The ^1H and ^{13}C resonances are referenced to CDCl_3 (7.26 and 77.16 ppm, respectively) and toluene- d_8 ($\text{C}_6\text{D}_5\text{CD}_3$ at 20.4 ppm).

NMR Reaction Kinetics

An NMR tube was charged with reagents as described above. The sample was vortexed 3 times on a vortex mixer for 5 s with cooling between each vortexing. To this solution, allyl bromide was added. The reaction was followed by ^1H NMR spectroscopy at $-20\text{ }^{\circ}\text{C}$ recording spectra at 1.0 min intervals.

Preparation of **3**

To a solution of NaHMDS (0.60 mmol, 110 mg) and TMEDA (1.2 mmol, 180 μL) in 4.5 mL toluene under argon at $-78\text{ }^{\circ}\text{C}$ was added **1** (0.50 mmol, 116.5 mg) in 0.50 mL toluene. After stirring for 30 minutes, allyl bromide (3.0 mmol, 260 μL) was injected, and the vessel was warmed to $0\text{ }^{\circ}\text{C}$. The reaction was quenched by 5.0 mL saturated NH_4Cl and extracted three times with EtOAc. The organic extracts were dried over MgSO_4 and concentrated in vacuo. Flash chromatography with 20% ethyl acetate in hexanes provided 132 mg (97% yield) shown by ^1H NMR spectroscopy to be a 20:1 diastereomeric mixture of **3** and its isomer analogous to that reported previously.³³

Preparation of **13**

To a solution of NaHMDS (3.3 mmol, 605 mg) and TMEDA (6.6 mmol, 988 μ L) in 5.0 mL toluene under argon at $-78\text{ }^{\circ}\text{C}$ was added **1** (3.0 mmol, 699 mg) in 1.0 mL of toluene. The reaction was stirred for 30 minutes, charged with benzyl bromide (20 mmol, 2.4 mL), warmed to $0\text{ }^{\circ}\text{C}$, and stirred for 0.5 h. The reaction was quenched with 5.0 mL saturated NH_4Cl and extracted three times with EtOAc. The organic extracts were dried over MgSO_4 and concentrated in vacuo. Flash chromatography with 20% ethyl acetate in hexanes afforded 825 mg of **13** (85% combined yield) displaying spectroscopic properties described previously.³³

Preparation of **14**

To a solution of NaHMDS (0.10 mmol, 18.3 mg) and TMEDA (0.20 mmol, 30 μ L) in toluene (2.0 mL) under argon was added **13** (0.070 mmol, 22.6 mg) in 0.10 mL of toluene. Reaction was stirred under argon for 1 hour at $-20\text{ }^{\circ}\text{C}$. Allyl bromide (0.40 mmol, 35 μ L) was injected and the mixture was warmed to $0\text{ }^{\circ}\text{C}$ over 2 hr. The reaction was quenched with 3.0 mL saturated NH_4Cl and extracted three times with EtOAc. The organic extracts were dried over MgSO_4 and concentrated in vacuo. Flash chromatography with 15% ethyl acetate in hexanes afforded 13.7 mg of product (54% combined yield) shown to be an 11:1 mixture of **14** and its minor diastereomer. ^1H NMR (599 MHz, CDCl_3) δ 7.34 – 7.30 (m, 2H), 7.28 – 7.24 (m, 3H), 7.23 – 7.19 (m, 5H), 5.77 (dddd, J = 16.9, 10.1, 8.0, 6.7 Hz, 1H), 5.11 (dq, J = 17.0, 1.6 Hz, 1H), 5.06 (ddt, J = 10.0, 2.0, 1.0 Hz, 1H), 4.61 (ddt, J = 10.7, 6.7, 3.3 Hz, 1H), 4.15 – 4.10 (m, 2H), 3.61 (d, J = 13.6 Hz, 1H), 3.18 (dd, J = 13.2, 3.3 Hz, 1H), 3.12 – 3.04 (m, 2H), 2.61 (dd, J = 13.2, 10.6 Hz, 1H), 2.29 (ddt, J = 14.3, 6.7, 1.4 Hz, 1H), 1.36 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 176.07, 152.77, 137.72, 135.94, 134.39, 130.58, 129.54, 129.06, 128.20, 127.38, 126.74, 118.27, 66.43, 58.32, 50.54, 42.01, 40.73, 38.01, 23.38. m/z calculated for $(\text{M}+\text{H})^+$ 364.19072, found 364.19097.

Confirming the structure of **14**

To a solution of **14** (0.050 mmol, 18 mg) in THF (0.45 mL) and water (0.15 mL) at $0\text{ }^{\circ}\text{C}$ was added H_2O_2 (30%, 40 mL) dropwise and LiOH (2.4 mg) in water (0.10 mL). The reaction was warmed to $20\text{ }^{\circ}\text{C}$ for 2 hr, cooled to $0\text{ }^{\circ}\text{C}$, and treated with Na_2SO_3 (56.8 mg) in water (0.3 mL) with stirring at $20\text{ }^{\circ}\text{C}$ for 12 hr. The reaction was concentrated in vacuo and its pH was adjusted to 13 using NaOH at $0\text{ }^{\circ}\text{C}$. The aqueous solution was extracted three times with CH_2Cl_2 and pH brought to 1 using concentrated HCl at $0\text{ }^{\circ}\text{C}$. The mixture was extracted three times with EtOAc, dried over MgSO_4 , and concentrated in vacuo to afford 7 mg of product (69% combined yield). ^1H NMR (500 MHz, CDCl_3) δ 7.30 – 7.21 (m, 3H), 7.20 – 7.14 (m, 2H), 5.82 (ddt, J = 18.5, 9.2, 7.4 Hz, 1H), 5.17 – 5.09 (m, 2H), 3.05 (d, J = 13.4 Hz, 1H), 2.78 (d, J = 13.4 Hz, 1H), 2.53 (ddt, J = 13.8, 6.9, 1.3 Hz, 1H), 2.21 (ddt, J = 13.7, 7.7, 1.2 Hz, 1H), 1.12 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 183.05, 137.33, 133.75, 130.35, 128.23, 126.77, 118.76, 47.48, 44.89, 43.33, 20.72. m/z calculated for $(\text{M}+\text{H})^+$ 205.12231, found 205.12198. $[\alpha]^{22} = +12$, c 0.35, DCM. An authentic sample was prepared using the procedure of Myers and coworkers.⁵⁷ $[\alpha]^{22} = +24$, c 0.5, CH_2Cl_2 .

Preparation of imine adduct 16

To a solution of NaHMDS (1.0 mmol, 183 mg) and TMEDA (2.0 mmol, 300 μ L) in toluene (4.5 mL) was added **1** (1.0 mmol, 233 mg) followed by stirring under argon for 30 min at -78°C . A solution of imine- BF_3 complex **19** (1.0 mmol) in toluene (0.20 mL) was injected. After stirring for 30 m, the reaction was quenched by 5.0 mL saturated NH_4Cl and extracted three times with EtOAc. The organic extracts were dried over MgSO_4 and concentrated in vacuo. The crude product was analyzed with ^1H NMR showing **16** in >30:1 selectivity. Flash chromatography (10% ethyl acetate/hexanes/3% Et_3N) afforded **16** (380 mg, 93% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.33 (dt, J = 7.6, 2.8 Hz, 4H), 7.31 – 7.25 (m, 3H), 7.25 – 7.19 (m, 3H), 4.70 (ddt, J = 10.9, 7.2, 3.4 Hz, 1H), 4.20 – 4.15 (m, 1H), 4.15 – 4.11 (m, 1H), 3.95 (p, J = 6.8 Hz, 1H), 3.86 (q, J = 6.5 Hz, 1H), 3.40 (dd, J = 13.2, 3.4 Hz, 1H), 2.88 (dd, J = 6.2, 4.8 Hz, 1H), 2.60 (dd, J = 13.1, 10.4 Hz, 1H), 1.67 (pd, J = 6.9, 4.9 Hz, 1H), 1.33 (d, J = 6.6 Hz, 3H), 1.29 (d, J = 6.9 Hz, 3H), 0.80 (d, J = 6.8 Hz, 6H). ^{13}C NMR (126 MHz, CDCl_3) δ 177.35, 153.32, 146.49, 135.64, 129.48, 129.13, 128.37, 127.46, 127.27, 127.02, 66.17, 61.44, 57.74, 55.71, 41.64, 38.38, 32.49, 24.25, 20.74, 17.86, 13.82. m/z calculated for $(\text{M} + \text{H})^+$ 409.24857, found 409.24889.

Preparation of imine adduct 17

Adduct **17** was prepared as described for adduct **16** using imine- BF_3 complex **20**. ^1H NMR spectroscopy of the crude shows **17** in >30:1 selectivity. Flash chromatography (10% ethyl acetate/hexanes/3% Et_3N) afforded **17** in 82% yield. ^1H NMR (500 MHz, CDCl_3) δ 7.37 – 7.30 (m, 4H), 7.30 – 7.24 (m, 3H), 7.22 – 7.16 (m, 3H), 4.63 (ddt, J = 10.8, 7.3, 3.4 Hz, 1H), 4.16 – 4.10 (m, 1H), 4.09 (dd, J = 9.1, 3.4 Hz, 1H), 3.96 – 3.86 (m, 2H), 3.25 (dd, J = 13.2, 3.4 Hz, 1H), 2.87 (dd, J = 6.7, 4.2 Hz, 1H), 2.52 (dd, J = 13.2, 10.3 Hz, 1H), 1.80 (pd, J = 6.9, 4.2 Hz, 1H), 1.34 (d, J = 6.5 Hz, 3H), 1.12 (d, J = 6.9 Hz, 3H), 1.07 (d, J = 6.9 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 177.23, 153.22, 146.33, 135.63, 129.48, 129.09, 128.42, 127.43, 127.16, 127.00, 66.04, 60.80, 56.84, 55.53, 40.84, 38.16, 31.84, 24.32, 20.67, 18.09, 14.15. m/z calculated for $(\text{M} + \text{H})^+$ 409.24857, found 409.24796.

Preparation of imine adduct 18

Adduct **18** was prepared as described for adduct **16** using imine- BF_3 complex **21** in 87% yield. ^1H NMR spectroscopy of the crude shows **18** and its minor diastereomer in 17:1 selectivity. Flash chromatography (10% ethyl acetate/hexanes/3% Et_3N) afforded **18** (34.3 mg, 87% yield). ^1H NMR (500 MHz, CDCl_3) δ 7.39 – 7.34 (m, 2H), 7.34 – 7.30 (m, 2H), 7.30 – 7.24 (m, 3H), 7.24 – 7.21 (m, 3H), 4.73 (ddt, J = 11.0, 7.3, 3.5 Hz, 1H), 4.20 – 4.15 (m, 1H), 4.14 (dd, J = 9.1, 3.6 Hz, 1H), 4.06 – 3.99 (m, 1H), 3.86 (d, J = 12.5 Hz, 1H), 3.81 (d, J = 12.5 Hz, 1H), 3.40 (dd, J = 13.2, 3.4 Hz, 1H), 2.90 (t, J = 6.0 Hz, 1H), 2.60 (dd, J = 13.1, 10.4 Hz, 1H), 1.81 (pd, J = 13.3, 6.7 Hz, 1H), 1.25 (d, J = 6.9 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 176.99, 153.30, 141.05, 135.60, 129.43, 129.09, 128.46, 128.28, 127.42, 127.06, 66.20, 64.67, 55.57, 55.30, 41.14, 38.33, 32.33, 20.42, 18.83, 12.57. m/z calculated for $(\text{M} + \text{H})^+$ 395.23292, found 395.23215.

Hydrogenolysis

To a solution of **17** (0.08 mmol, 33.3 mg) in methanol (2 mL) was added palladium on carbon (0.008 mmol, 8.5 mg). Reaction was stirred under 1.0 atm of H₂ for 24 hr at room temperature. After filtering through Celite and concentrating in vacuo, flash chromatography with 3% triethylamine in ethyl acetate afforded **22** (14.5 mg, 60% yield). Peak broadening presumably owing to hydrogen bonding was mitigated by warming to 60 °C. ¹H NMR (599 MHz, CDCl₃, 60 °C) δ 7.26 – 7.25 (m, 1H), 7.25 – 7.20 (m, 3H), 7.20 – 7.16 (m, 1H), 5.17 – 5.05 (m, 2H), 4.02 – 3.95 (m, 1H), 3.83 (dd, *J* = 12.0, 3.0 Hz, 1H), 3.24 (dd, *J* = 13.7, 9.7 Hz, 1H), 3.12 (dd, *J* = 13.7, 6.9 Hz, 1H), 2.66 (p, *J* = 7.0 Hz, 1H), 1.64 (pd, *J* = 14.0, 6.9 Hz, 1H), 0.97 – 0.87 (m, 3H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 171.32, 155.43, 138.18, 129.51, 128.49, 126.62, 63.85, 60.55, 55.92, 34.67, 27.90, 18.77, 18.18, 14.35, 9.89. *m/z* calculated for (M+H)⁺ 305.18597, found 305.18521.

Aldol Addition

To a solution of NaHMDS (0.3 mmol, 54.9 mg) and TMEDA (0.9 mmol, 144 μL) in toluene (3 mL) was added **1** (0.3 mmol, 69.9 mg) in 0.10 mL of toluene. After stirring under argon for 30 min at –78 °C isobutyraldehyde (0.9 mmol, 82 μL) was injected and the mixture was stirred for 1 hr at –78 °C. After quenching with 1.0 mL saturated NH₄Cl and extracted three times with EtOAc, the organic extracts were dried over MgSO₄ and concentrated in vacuo. Flash chromatography with 10% ethyl acetate in hexanes afforded 36.4 mg of **25** (61% combined yield). ¹H NMR showed a 17:1:0.7:0.4 mixture of **25** and three minor stereoisomers. ¹H NMR (599 MHz, CDCl₃) δ 5.06 (d, *J* = 4.2 Hz, 1H), 3.39 (dd, *J* = 9.0, 3.7 Hz, 1H), 2.73 (qd, *J* = 7.2, 3.7 Hz, 1H), 1.98 (hd, *J* = 6.9, 4.2 Hz, 1H), 1.84 (dh, *J* = 9.0, 6.6 Hz, 1H), 1.23 (d, *J* = 7.2 Hz, 3H), 1.01 – 0.97 (m, 9H), 0.86 (d, *J* = 6.8 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 172.94, 106.45, 82.07, 38.20, 32.71, 28.45, 18.67, 17.60, 16.17, 15.83, 11.74. *m/z* calculated for (M+H)⁺ 201.14852, found 201.14824.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References and Footnotes

1. (a) Ager DJ; Prakash I; Schaad DR Chem. Rev 1996, 96, 835. [PubMed: 11848773] (b) Wu G; Huang M Chem. Rev 2006, 106, 2596. [PubMed: 16836294] (c) Farina V; Reeves JT; Senanayake CH; Song JJ Chem. Rev 2006, 106, 2734. [PubMed: 16836298] (d) Evans DA; Shaw JT actualité Chimique 2003, 35. (e) Franklin AS; Paterson I Contemp. Org. Syn 1994, 1, 317. (f) Baiget J; Cosp A; Galvez E; Gomez-Pinal L; Romea P; Urpi F Tetrahedron, 2008, 5637. (g) Velazques F; Olivio H Curr. Org. Chem 2002, 6, 303. (h) Heravi MM; Zadsirjan V; Farajpour B RSC Adv. 2016, 6, 30498.
2. Evans DA; Bartroli J; Shih TL J. Am. Chem. Soc 1981, 103, 2127.
3. (a) "Modern Aldol Reactions", Vols. 1 and 2 (Ed.: Mahrwald R), Wiley-VCH, Weinheim, 2004. (b) Lin G-Q; Li Y-M; Chan ASC Principles and Applications of Asymmetric Synthesis, Wiley & Sons: New York, 2001; 135. (c) Palomo C; Oiari M; Garcia JM Chem. Soc. Rev 2004, 33, 65. [PubMed: 14767502] (d) Mahrwald R in "Aldol Reactions", Springer, New York, 2009.

4. (a)Evans DA; Takacs JM; McGee LR; Ennis MD; Mathre DJ; Bartroli J Pure Appl. Chem 1981, 53, 1109.(b)Evans DA; Ennis MD; Mathre DJ J. Am. Chem. Soc 1982, 104, 1737.(c)Matsumoto K; Koyachi K; Shindo M Tetrahedron 2013, 69, 1043.(d)Hansen DB; Starr M-L; Tolstoy N; Joullie MM Tetrahedron: Asymmetry 2005, 16, 3623.
5. Tallmadge EH; Collum DB J. Am. Chem. Soc 2015, 137, 13087. [PubMed: 26437278]
6. Tallmadge EH; Jermaks J; Collum DB J. Am. Chem. Soc 2016, 138, 345. [PubMed: 26639525]
7. For an attempt to assemble a comprehensive bibliography of lithium-based Evans aldol additions, see ref 6.
8. Jermaks J; Tallmadge EH; Keresztes I; Collum DB J. Am. Chem. Soc 2018, 140, 3077. [PubMed: 29457718]
9. Zhang Z; Collum DB J. Org. Chem 2017, 82, 7595. [PubMed: 28686020]
10. For other examples of physical studies of Evans enolates, see:Shinasha CB; Sunoj RB J. Am. Chem. Soc 2010, 132, 12319. [PubMed: 20707387] Sreenithya A; Sunoj RB Org. Lett 2012, 14, 5752. [PubMed: 23116155] Shinisha CB; Sunoj RB Org. Lett 2010, 12, 2868. [PubMed: 20503998] Goodman JM; Paton RSJ Chem. Soc., Chem. Commun 2007, 2124.Baringhaus KH; Matter H; Kurz MJ Org. Chem 2000, 65, 5031.Kimball DB; Michalczyk R; Moody E; Ollivault-Shiflett M; De Jesus K; Silks LA III J. Am. Chem. Soc 2003, 125, 14666. [PubMed: 14640616]
11. Tomasevich LL; Collum DB J. Am. Chem. Soc 2014, 136, 9710. [PubMed: 24915602]
12. For an interesting historical perspective on organoalkali metal chemistry, see:Seyferth D Organometallics 2006, 25, 2.Seyferth D Organometallics 2009, 28, 2.
13. Mulvey RE; Robertson SD Angew. Chem., Int. Ed 2013, 52, 11470.
14. Ma Y; Algera RF; Collum DB J. Org. Chem 2016, 81, 11312. [PubMed: 27768310]
15. Andrews PC; Barnett NDR; Mulvey RE; Clegg W; O'Neil PA; Barr D; Cowton L; Dawson AJ; Wakefield BJ J. Organomet. Chem 1996, 518, 85.
16. "Sodium hexamethyldisilazide". Watson BT; Lebel H In e-EROS Encyclopedia of Reagents for Organic Synthesis; John Wiley & Sons, New York; 2005, p 1–10.
17. (a)Ojeda-Amador AI; Martinez-Martinez AJ; Kennedy AR; Armstrong DR; O'Hara CT Chem. Commun 2017, 53, 324.(b)Henderson KW; Dorigo AE; Liu QY; Williard PG J. Am. Chem. Soc 1997, 119, 11855.(c)Kennedy AR; Mulvey RE; O'Hara CT; Robertson SD; Robertson GM Acta Crystallographica, Section E: Structure Reports Online 2012, 68, m1468.
18. Gaussian 09, Revision A.02, Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Scalmani G, Barone V, Petersson GA, Nakatsuji H, Li X, Caricato M, Marenich A, Bloino J, Janesko BG, Gomperts R, Mennucci B, Hratchian HP, Ortiz JV, Izmaylov AF, Sonnenberg JL, Williams-Young D, Ding F, Lipparini F, Egidi F, Goings J, Peng B, Petrone A, Henderson T, Ranasinghe D, Zakrzewski VG, Gao J, Rega N, Zheng G, Liang W, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Vreven T, Throssell K, Montgomery JA Jr., Peralta JE, Ogliaro F, Bearpark M, Heyd JJ, Brothers E, Kudin KN, Staroverov VN, Keith T, Kobayashi R, Normand J, Raghavachari K, Rendell A, Burant JC, Iyengar SS, Tomasi J, Cossi M, Millam JM, Klene M, Adamo C, Cammi R, Ochterski JW, Martin RL, Morokuma K, Farkas O, Foresman JB, and Fox DJ, Gaussian, Inc., Wallingford CT, 2016.
19. Evans DA; Britton TC; Ellman JA Tetrahedron Lett. 1987, 28, 6141.
20. We refer to $(\text{LiX})_n$ and $(\text{LiX})_m(\text{LiX}')_n$ as a "homoaggregate" and "heteroaggregate", respectively, and reserve the term "mixed aggregate" for $(\text{LiX})_m(\text{LiY})_n$.
21. Renny JS; Tomasevich LL; Tallmadge EH; Collum DB Angew. Chem., Int. Ed 2013, 52, 11998.
22. Job P Ann. Chim 1928, 9, 113.
23. Houghton MJ; Collum DB J. Org. Chem 2016, 81, 11057. [PubMed: 27749060]
24. Hibberta DB; Thordarson P Chem. Commun 2016, 52, 12792.
25. (a)Collum DB Acc. Chem. Res 1993, 26, 227.(b)Lucht BL; Collum DB Acc. Chem. Res 1999, 32, 1035.
26. Algera RF; Ma Y; Collum DB J. Am. Chem. Soc 2017, 139, 7921. [PubMed: 28557426]
27. (a)Boyle TJ; Velazquez AT; Yonemoto DT; Alam TM; Moore C; Rheingold AL Inorg. Chim. Acta 2013, 405, 374.(b)Calvo B; Davidson MG; Garcia-Vivo D Inorg. Chem 2011, 50, 3589. [PubMed: 21410272]

28. Collum DB; McNeil AJ; Ramírez A *Angew. Chem., Int. Ed* 2007, 46, 3002.
29. Casado J; Lopez-Quintela MA; Lorenzo-Barral FM *J. Chem. Educ* 1986, 63, 450.
30. We define the idealized rate law as that obtained by rounding the observed reaction orders to the nearest rational order.
31. For an excellent review of enolate quaterization including several examples involving oxazolidinones, see: Minko Y; Marek I *Chem. Commun* 2014, 50, 12597.
32. The back bone metalation product was obtained at a roughly 50% yield and characterized by various ¹H and ¹³C NMR correlation spectroscopies to be the structure below. It appears to derive from deprotonation of auxilliary oxygen-neighboring methylene proton followed by acylation at that position.

33. Schmidt B; Wildemann HJ *Chem. Soc., Perkin Trans 1*, 2002, 1050.
34. LiHMDS has been shown to be substantially more reactive in Et₃N/toluene than in THF solution: Zhao P; Collum DB *J. Am. Chem. Soc* 2003, 125, 14411. [PubMed: 14624589]
35. The oxazolidinone-NaHMDS complex in Et₃N/toluene shows IR absorbances at 1761 and 1711 cm⁻¹.
36. Addition of BF₃ to accelerate organolithium-based epoxide cleavages was first reported by Ganem and coworkers: Eis MJ; Wrobel JE; Ganem B *J. Am. Chem. Soc* 1984, 106, 3693.
37. Velazquez F; Olivo H *Current Org. Chem* 2002, 6, 303.
38. Azaaldol additions using Evans enolates: Bian J; Blakemore D; Warmus JS; Sun J; Corbett M; Rose CR; Bechle BM *Org. Lett* 2013, 15, 562. [PubMed: 23343056] Ma Z; Zhao Y; Jiang N; Jin X; Wang J *Tetrahedron Lett.* 2002, 43, 3209.
39. Azaaldols of alkali metal enolates to phenethylamines: Evans CD; Mahon MF; Andrews PC; Muir J; Bull SD *Org. Lett* 2011, 13, 6276. [PubMed: 22050269]
40. (a) Vemula R; Wilde NC; Goreti R; Corey EJ *Org. Lett* 2017, 19, 3883. [PubMed: 28696724]
(b) Díez R; Badorrey R; Díaz-de-Villegas MD; Gálvez JA *Eur. J. Org. Chem* 2007, 13, 2114.
(c) Kawate T; Yamada H; Yamaguchi K; Nishida A; Nakagawa M *Chem. Pharm. Bull* 1996, 44, 1776.
41. Ma Y; Lobkovsky E; Collum DB *J. Org. Chem* 2005, 70, 2335. [PubMed: 15760225]
42. The methyl stemming from the propionyl group appears as a broad 'singlet' in the ¹H NMR spectrum at room temperature. Raising the temperature causes considerable sharpening around 40 °C, affording the anticipated doublet at 60 °C. Lowering the temperature to -80 °C reveals two conformers attributed to hydrogen bonding. Despite the gamut of twodimensional ¹H and ¹³C

NMR spectroscopies, the assignment was ultimately made by derivatizing **22** as the corresponding BOC-protected methyl ester and comparing it with an authentic sample: Seebach D; Abele S; Gademann K; Guichard G; Hintermann T; Jaun B; Mathews JL; Schreiber JV *Helv. Chim. Acta* 1998, 81, 932.

43. (a)Vemula R; Wilde NC; Goreti R; Corey EJ *Org. Lett* 2017, 19, 3883. [PubMed: 28696724]
(b)Veith U; Leurs S; Jäger V *Chem. Commun* 1996, 3, 329.(c)Chandrasekhar S; Pendke M; Muththe C; Akondi SM; Mainkar PS *Tetrahedron Lett.* 2012, 53, 1292.
44. After several abortive attempts to ascertain the optical purity of **25** using HPLC and NMR shift reagents, reaction with the lithium salt of the oxazolidinone auxilliary afforded aldol adduct **23** contaminated by the other syn isomer (7:1) albeit in low (15%) yield.
45. (a)Gruver JM; Liou LR; McNeil AJ; Ramírez A; Collum DB *J. Org. Chem* 2008, 73, 7743. [PubMed: 18781812] (b)Liou LR; McNeil AJ; Ramírez A; Toombes GES; Gruver JM; Collum DB *J. Am. Chem. Soc* 2008, 130, 4859. [PubMed: 18336025]
46. (a)Ashby MT; Govindan GN; Grafton AK *Inorg. Chem* 1993, 32, 3803.(b)Barton JK; Danishefsky AT; Goldberg JM *J. Am. Chem. Soc* 1984, 106, 2172.(c)Haq I; Lincoln P; Suh D; Norden B; Chowdhry BZ; Chaires JB *J. Am. Chem. Soc* 1995, 117, 4788.
47. Bauer W; Schleyer P. v. R. "Advances in Carbanion Chemistry"; Snieckus V, ed.; JAI: New York, 1992, p 89.
48. (a)Suzuki T; Inui M; Hosokawa S; Kobayashi S *Tetrahedron Lett.* 2003, 44, 3713.(b)Hosokawa S; Sekiguchi K; Enemoto M; Kobayashi S *Tetrahedron Lett.* 2000, 41, 6429.(c)Edmonds MK; Graichen FHM; Gardiner J; Abell AD *Org. Lett* 2008, 10, 885. [PubMed: 18232705] (d)Less SL; Handa S; Millburn K; Leadlay PF; Dutton CJ; Staunton J *Tetrahedron Lett.* 1996, 37, 3515.
(e)Peddie V; Pietsch M; Bromfield KM; Pike RN; Duggan PJ; Abell AD *Synthesis* 2010, 11, 1845.
(f)Falck JR; Gao S; Prasad RN; Koduru SR *Bioorg. Med. Chem. Lett* 2008, 18, 1768. [PubMed: 18308568] (g)Murata Y; Kamino T; Hosokawa S; Kobayashi S *Tetrahedron Lett.* 2002, 43, 8121.
(h)Jacobson IC; Reddy GP *Tetrahedron Lett.* 1996, 37, 8263.(i)Minko Y; Marek I *Chem. Commun* 2014, 50, 12597 and references cited therein.
49. Fuerstner A; Fenster MDB; Fasching B; Godbout CP; Radkowski K *Angew. Chem., Int. Ed. Engl* 2006, 45, 5510. [PubMed: 16906500]
50. Li B-J; El-Nachef C; Beauchemin AM *Chem. Commun* 2017, 53, 13192.
51. (a)Koskinen AMP; Kataja AO *Org. React* 2015, 86, 105.(b)Mahrwald R in "Modern Aldol Reactions", Vol. 2 (Ed.: Mahrwald R), Wiley-VCH, Weinheim, 2004, pg 327.
52. Algera RF; Ma Y; Collum DB *J. Am. Chem. Soc* 2017, 139, 15197. [PubMed: 28946744]
53. (a)Ojeda-Amador AI; Martinez-Martinez AJ; Kennedy AR; O'Hara CT *Inorg. Chem* 2015, 54, 9833. [PubMed: 26417943] (b)For a NaHMDS-sodium enolate mixed aggregate characterized crystallographically, see: Williard PG; Hintze MJ *J. Am. Chem. Soc* 1990, 112, 8602.
54. Mixed aggregation can tip the relative contributions of competing monomer- and dimer-based toward the monomer through the net dilution of the homoaggregates: Ramírez A; Sun X; Collum DB *J. Am. Chem. Soc* 2006, 128, 10326. [PubMed: 16881665]
55. For a discussion of aggregation and cooperative effects on the aldol addition, see: Larranaga O; de Cozar A; Bickelhaupt FM; Zangi R; Cossio FP *Chem. Eur. J* 2013, 19, 13761. [PubMed: 23964002]
56. Oxazolidinone precursors to enolates **2**, **9a-e**, and **10** were prepared according to literature procedures.Mabe PJ; Zakarian A *Org. Lett* 2014, 16, 516. [PubMed: 24377351] Kretschmer M; Dieckmann M; Li P; Rudolph S; Herkommer D; Troendlin J; Menche D *Chem. Euro. J.* 2013, 19, 15993.Szostak M; Spain M; Eberhart AJ; Procter DJ *J. Am. Chem. Soc* 2014, 36, 2268.Gille A; Hiersemann M *Org. Lett* 2010, 12, 5258. [PubMed: 20973508] Bull SD; Davies SG; Jones S; Sanganee HJ *J. Chem. Soc. Perkin Trans* 1999, 4, 387.
57. Kummer DA; Chain WJ; Morales MR; Quiroga O; Myers AG *J. Am. Chem. Soc* 2008, 130, 13231. [PubMed: 18788739]

Figure 1.

Partial ^{13}C NMR spectra of a mixture (*S*)-**2** and (*R*)-**9b** (with 0.20 M total enolate titer) in 1.0 M TMEDA in toluene recorded at $-80\text{ }^{\circ}\text{C}$: (A) pure (*S*)-**2**; (B) equimolar (*S*)-**2** and (*R*)-**9b**; (C) pure (*R*)-**9b**. *Denotes the enolate–NaHMDS mixed aggregate **6**.

Figure 2. Partial ^{13}C NMR spectra of a mixture with 0.20 M enolate **2** and 1.0 M total TMEDA (L) and (*S,S*)-TMCDA (L') concentration in toluene at -80°C showing *bis*-TMEDA-solvated monomer (2L_2), *bis*-TMCDA-solvated monomer ($2\text{L}'_2$), and mixed solvated monomer ($2\text{LL}'$); see eq 4). The *intended* mole fractions for TMEDA, X_B , are as labeled.

Figure 3. Job plot showing the relative integrations of *bis*-TMEDA-solvated monomer ($2L_2$), *bis*-TMCDA-solvated monomer ($2L'_2$), and mixed solvated monomer ($2LL'$) versus the *measured* mole fraction of TMEDA for 0.20 M enolate (**2**) and TMEDA/(*S,S*)-TMCDA mixtures (1.0 M total diamine concentration) in toluene at -80°C .

Figure 4.

Job plot showing the relative integrations versus the *intended* mole fraction of TMEDA for a mixture of 0.20 M of enolate **2** and 1.0 M total diamine concentration in TMEDA/(*S,S*)-TMCDA mixtures in toluene at $-80\text{ }^{\circ}\text{C}$. The shift in the maximum to $\chi_{\text{TMEDA}} > 0.50$ reflects the stronger binding of (*S,S*)-TMCDA.

Figure 5.
Computed structure of *bis*-chelated monomer **4** as its lowest energy delta stereoisomer.

Figure 6. Partial ^{13}C NMR spectra of 0.20 M enolate **2** and 1.0 M TMEDA at various equivalents of excess NaHMDS (as indicated) in toluene at -80°C showing monomer **4** and mixed dimer **6**.

Figure 7.

Job plot showing the relative integrations of NaHMDS (red), enolate monomer **4** (black), and mixed dimer **6** (blue) versus the *measured* mole fraction of NaHMDS with various proportions of NaHMDS and enolate (0.30 M total sodium titer) in 0.60 M TMEDA/toluene at $-80\text{ }^{\circ}\text{C}$. The ratios were ascertained by following the resonances of monomer **4** (carbonyl carbon at $\delta 157.3$), mixed dimer **6** (carbonyl carbon at $\delta 155.5$ and Me_3Si carbon at $\delta 7.52$), and NaHMDS (Me_3Si carbon $\delta 6.76$ ppm).

Figure 8. Partial ^{13}C NMR spectra of 0.20 M enolate **2** and 1.0 M TMEDA with various equivalents of excess NaDA (as indicated) in toluene at -80°C . Monomer **4** and mixed dimer **5** are shown.

Figure 9.

Job plot showing the relative integrations of NaDA (red), enolate monomer **4** (black), and mixed dimer **5** (blue) versus the *measured* mole fraction of NaDA with various proportions of NaDA and enolate (0.40 M total sodium titer) in 1.0 M TMEDA/toluene at $-80\text{ }^{\circ}\text{C}$. The ratios were ascertained by following the resonances of monomer **4** (carbonyl carbon at $\delta 157.3$), mixed dimer **5** (carbonyl carbon at $\delta 155.5$ and NaDA methyne carbon at $\delta 50.4$), and NaDA (NaDA methyne carbon $\delta 50.2$ ppm).

Figure 10.
Computed structure of bis-TMEDA-chelated mixed dimer **6**.

Figure 11.

^{13}C NMR spectra of mixtures containing enolate **2** and sodium 2,6-di-*tert*-butylphenolate (0.30 M total sodium titer) in 1.0 M TMEDA/toluene at -80°C showing monomer **4** and mixed aggregate **7**. The concentrations of phenolate are 0.00, 0.10, and 0.15 (1.0 equiv), respectively.

Figure 12. Computed structure of sodium 2,6-di-*tert*-butylphenolatecontaining mixed dimer **7** solvated by TMEDA.

Figure 13.

Plot following the loss of allyl bromide (0.010 M) by enolate monomer **4** (0.40 M) in 1.0 M TMEDA/toluene at -20°C . The curve depicts a least squares fit to $y = ae^{-bx}$, such that $b = k_{\text{obsd}}^{28}$

Figure 14.

Plot of initial rates for the allylation of monomer **4** with allyl bromide (0.010 M) versus the enolate concentration at a fixed 2:1 TMEDA/enolate ratio in toluene. $y = ax^n$; $a = 0.15 \pm 0.01$; $n = 1.11 \pm 0.08$.

Figure 15.

Plot of initial rates for the allylation of monomer **4** (0.20 M) with allyl bromide (0.010 M) versus *free* (unbound) TMEDA concentration in toluene. $y = ax + b$, $a = -0.0011 \pm 0.0003$; $b = 0.0236 \pm 0.0007$.

Figure 16.
Computed lowest-energy anti transition structure **12** for the allylation of monomer **4**.

Figure 17.
Illustration of *s-cis* and *s-trans* alignments.

Scheme 1.
Serial solvation of NaHMDS to give mixed dimer **6**.

Scheme 2.1,2-Additions of enolate **2** to imine- BF_3 complexes.

Scheme 3.
Aldol addition and aldehyde-mediated deacylation.

Scheme 4.

Structures of sodium enolates in THF and TMEDA/toluene.

Scheme 5.
Positional and delta isomers of octahedral monomeric enolates.

Scheme 6.
Reactions of diamine-solvated monomeric enolate **4**.

Scheme 7.
Mixed aggregation with Evans enolates.

Chart 1.
Structures of sodiated Evans enolates solvated by diamines.

Table 1.Selectivities for quaternization of oxazolidinone **13** (eq 10).

Entry	Solvent	Yield (%)	14 (<i>S/R</i>)
1	THF	Decomp	
2	TMEDA	54	11:1
3	DME	40	11:1
4	Et ₃ N	70	11:1
5	Et ₃ N then (<i>R,R</i>)-TMCDA	71	11:1
6	(<i>R,R</i>)-TMCDA	40	30:1
7	(<i>S,S</i>)-TMCDA	52	19:1
8	7 /TMEDA	44	11:1