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On the Nature of the Oxidative Heterocoupling of Lithium Enolates

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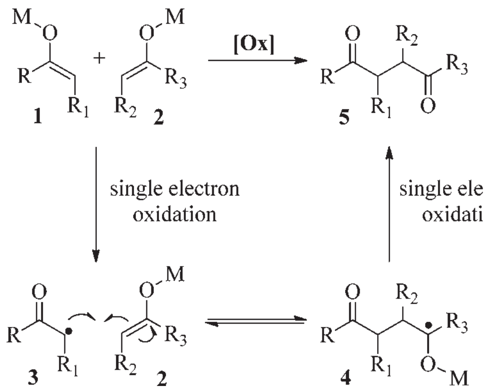
S Supporting Information

ABSTRACT: The coupling of enolates through single-electron oxidation is one of the most direct routes for generating 1,4-dicarbonyls. Recent work on the intermolecular heterocoupling of equimolar amounts of two different enolates through single-electron oxidation has shown that synthetically useful yields beyond those predicted by statistics can be obtained. To determine the underlying basis for the selective formation of heterocoupled products, kinetic, ^{7}Li NMR, and synthetic studies were performed. The collection of data obtained from these experiments shows that the selective formation of heterocoupled products is a consequence of heteroaggregation of lithium enolates.

The coupling of enolates through single-electron oxidation is the most direct route for generating 1,4-dicarbonyls, which are important precursors or structural components in a variety of natural products.[1] Cyclizations are achieved through the intramolecular coupling of enolates derived from diesters[2] and diketones[3] as well as the intramolecular oxidative cross-coupling of enolates derived from two different carbonyl precursors.[1b,d] Intermolecular homocoupling reactions of enolates are straightforward and have a long history in organic chemistry.[2−5] Conversely, bimolecular heterocoupling of equimolar amounts of two enolates through single-electron oxidation is more difficult and at best should result in a 50% yield of the product. Successful approaches for the synthesis of unsymmetric 1,4-dicarbonyls require the use of superstoichiometric amounts of one enolate relative to the other[5] or the use of silyl bis-enol ethers.[6]

Unlike other synthetic routes to 1,4-dicarbonyls, single-electron oxidative coupling of equimolar amounts of enolates can afford the same products while requiring no prefunctionalization steps. As a result, the development of efficient enolate oxidative coupling reactions has the potential to lead to improved overall atom economy in multistep syntheses. Despite previous studies on single-electron oxidation of enolates, the ability to heterocouple two different enolates selectively through single-electron oxidation remained elusive until recently, when Baran and coworkers[7] reported the intermolecular oxidative heterocoupling of enolates. In all of the reported cases, when equimolar amounts of two different enolates were oxidized with Fe(III)- or Cu(II)-based oxidants, the heterocoupled products were obtained in greater than 50% yield, and some products were obtained in >70% yield. Subsequent synthetic studies on these coupling reactions revealed that the best results were obtained in tetrahydrofuran (THF).[7b] Additionally, the presence of α-carbonyl radicals was established through radical-clock studies.[7b] While these studies demonstrated several factors important in the oxidative heterocoupling of enolates, they do not address the underlying basis for the selective formation of the heterocoupled product from an equimolar mixture of two different enolates. Herein we present spectroscopic and mechanistic data showing that the selective formation of heterocoupled products is a consequence of the heteroaggregation of lithium enolates.

Scheme 1. Selective Formation of Heterocoupled Products through Preferential Oxidation



A considerable body of mechanistic work from our group has demonstrated that selective single-electron oxidation or reduction of one component in an equimolar mixture of two unique substrates is responsible for successful cross-coupling of different functional groups.[8] In the case of enolate heterocoupling, if two enolates having different stabilities are present, one enolate may be preferentially oxidized to a radical, as shown in Scheme 1. Faster oxidation of enolate **1** leads to radical **3**. Preferential reaction of **3** with enolate **2** (as opposed to homodimerization) provides intermediate **4**. A second single-electron oxidation leads to heterodimer **5**. The oxidation of several enolates derived from the reactions of ketones, esters, and amides with lithium hexamethyldisilazide (LiHMDS) was examined with ceric tetra-*n*-butylammonium nitrate (CTAN) using stopped-flow spectrophotometry. Surprisingly, all of these reactions were too fast to monitor and occurred in the mixing time of the instrument, even at reduced temperatures. Although these experiments did not provide the expected results, the data suggested that differential rates of oxidation may not provide the basis for the selectivity observed in these oxidative enolate heterocouplings.

Careful inspection of the literature describing successful enolate coupling through oxidation reveals that in most reactions, lithium bases are employed. Lithium coordination to anions, alkoxides, and carbanions oftentimes leads to highly ordered aggregates in solution. The work of Reich,[9] Seebach,[10] and

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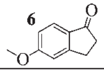
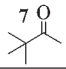
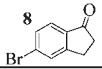
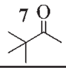
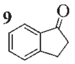
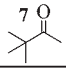
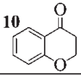
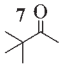
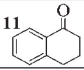
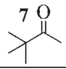
Table 1. Lithium Aggregate Distributions[a] of Equimolar Mixtures of Enolates[b]

Ketone A	Ketone B	$\frac{A_2B_2}{A_4 + B_4}$
6 	7 	15.7 : 1
8 	7 	14.7 : 1
9 	7 	14.3 : 1
10 	7 	8.5 : 1
11 	7 	4.4 : 1

[a] Distributions were obtained by integrating ^{7}Li NMR spectra at −30 °C. [b] $[A] = [B] = 0.15$ M and $[\text{LiHMDS}] = 0.304$ M in 2.0 M THF/toluene

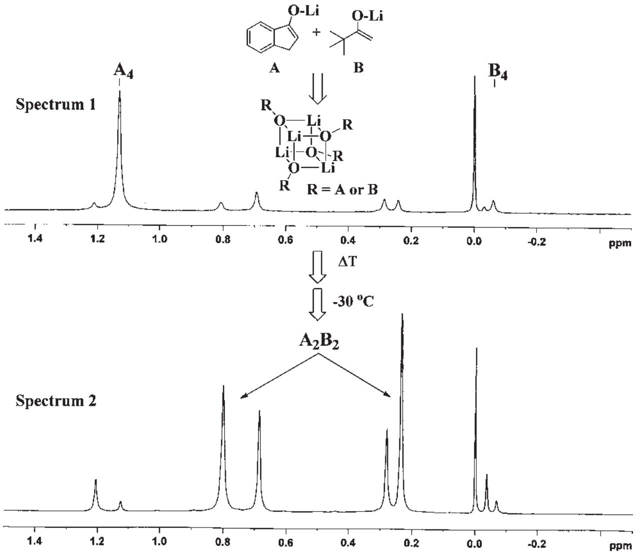


Figure 1. ^{7}Li NMR spectra of a 1:1 mixture of **7** and **9** with LiHMDS at −30 °C. Spectrum 1: **7** and **9** were enolized separately and combined at −78 °C. Spectrum 2: after warming and recooling to −30 °C.

Collum[11] has demonstrated that the unique coordination chemistry of lithium is responsible for the reactivity observed when lithium bases are employed as reagents in many bond-forming reactions. Interestingly, Collum and co-workers[12] have shown that equimolar mixtures of two different enolates in tetramethylethylenediamine (TMEDA)/toluene preferentially form heteroaggregated dimers depending on the steric congestion of the carbonyl precursors. The formation of heteroaggregated dimers is due to unfavorable steric interactions in the homodimer of the bulky carbonyl precursor.[12] These findings raised the following question: could lithium enolate aggregation play a mechanistic role in the nonstatistical formation of heterocoupled products?

Many successful oxidative couplings of enolates are performed in THF.[2−5,7] Collum's work on the impact of solvent on lithium aggregation showed that enolates are tetrameric in THF.[13] Because of the complexity of the system, we chose to study mixtures of the lithium enolate of pinacolone with equimolar amounts of lithium enolates derived from a series of cyclic ketones. Ketones with similar pK_a values were chosen to ensure that the rates of enolization and stabilities were comparable. As a consequence, the relative rates of oxidation should be similar as well.[14] Pinacolone was selected as one of the ketone partners because it is sterically bulky and has been shown previously to preferentially form lithium heteroaggregate dimers in TMEDA/toluene.[12] To determine the impact of structure on heteroaggregation of equimolar amounts of two different lithium enolates, ^{7}Li NMR experiments were performed on a series of ketone−ketone mixtures (Table 1). In each of these experiments, the lithium enolate of pinacolone was mixed with an equal amount of another lithium enolate derived from a cyclic aryl ketone.

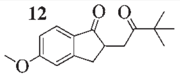
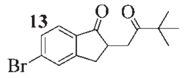
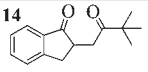
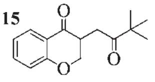
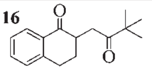
The results of the ^{7}Li NMR experiments revealed several important features of the aggregation of lithium enolates in THF. For all of the equimolar enolate mixtures of ketone−ketone partners examined, the lithium aggregates were ensembles of homoaggregated and heteroaggregated tetramers (A_4, A_3B_1, A_2B_2, A_1B_3, and B_4) consistent with those reported by Collum.[13] As illustrated in spectrum 1 in Figure 1 , when lithium enolates of **7** and **9** were generated separately and mixed at −78 °C, the homotetramer of **9** (A_4) and smaller amounts of other aggregates, including the homotetramer of **7** (B_4), were the predominant species, indicating minimal interaggregate exchange at reduced temperatures. However, after the solution was warmed and recooled, the aggregate distribution shifted dramatically to favor the heteroaggregated A_2B_2 tetramer (Figure 1, spectrum 2). This finding indicates that an energy barrier exists for rearrangement to the more thermodynamically stable enolate heteroaggregates.

To assess the impact of substrate structure on the heteroaggregate distribution of equimolar mixtures of lithium enolates, the amount of the most abundant heteroaggregate (A_2B_2) was compared with the sum of the amounts of the individual homotetramers (A_4 and B_4) for every ketone−ketone mixture. As shown in Table 1, a unique ratio was obtained for each mixture of lithium enolates. Interestingly, even the ratio for the lithium enolates derived from **7** and **11**, which was the smallest for the mixtures examined, was still larger than the statistically predicted distribution for an ensemble of tetramers.[15]

While placing substituents on the aromatic ring of ketone A (substrates **6** and **8**) did not significantly impact the lithium aggregation, increasing the size of the adjacent ring (substrates **10** and **11**) greatly reduced the amounts of heteroaggregated tetramers. These observations are consistent with the results of Collum's work on lithium heterodimers, which showed that statistically predicted aggregate distributions are obtained when both enolates are sterically bulky.[12]

With the ^{7}Li NMR data in hand, the question remains: are these nonstatistical distributions of lithium aggregates involved in the selective oxidative heterocoupling of lithium enolates? To investigate the role of heteroaggregation, optimal reaction conditions were determined for the coupling of substrates **7** and **9**. By screening several different oxidants, we found that CTAN and I_2 provided the best yields and reproducibility. Iodine was employed as the oxidant in subsequent reactions (Table 2) because it is an attractive oxidant in terms of atom economy in that 1 equiv of I_2 carries out two single-electron oxidations.[16]

Table 2. Product Distributions from the Oxidative Coupling of Lithium Enolates[a]

Ketone A	Ketone B	Heterocoupled Product	Product Ratio[b]	Yield (%)[c, d]
6	**7**	12 	13.8 : 1	62
8	**7**	13 	12.8 : 1	58
9	**7**	14 	12.4 : 1	62
10	**7**	15 	7.0 : 1	46
11	**7**	16 	3.0 : 1	47

[a] [A] = [B] = 0.12 M in THF, [LiHMDS] = 0.26 M in THF, $[I_2]$ = 0.12 M in THF. [b] Ratios (heterocoupled product:homodimer of 7) were determined by ^{1}H NMR analysis. [c] Determined by ^{1}H NMR analysis with ±3% error. [d] 15−25% of ketone A was recovered in these reactions.

Furthermore, oxidations using I_2 benefited from improved synthetic workup procedures, as the lipophilic tetra-*n*-butylammonium counterions of CTAN acted as phase-transfer reagents, complicating reaction workup.

The oxidative coupling of equimolar mixtures of two different enolates preferentially generated the heterocoupled products (Table 2). More importantly, in all cases the product ratio of heterocoupled product to homodimer of 7 was larger than the statistically predicted value of 2:1. It is interesting to note that homodimers of ketone **A** were never observed, with the starting ketones being recovered instead in all cases. While experimental observations indicate that enolates derived from these ketones are oxidized, hydrogen atom abstraction from THF coordinated to the lithium centers of the aggregates becomes a competitive pathway.[16,17]

With the synthetic studies completed, the degree of lithium enolate heteroaggregation was compared to the product ratio obtained after oxidation. As shown in Figure 2, there is a direct linear correlation between the amount of lithium enolate heteroaggregation and the formation of heterocoupled product. Furthermore, the high degree of correlation between the heteroaggregate content and the degree of heterodimer product suggests that *aggregation is the major driving force for the selective heterocoupling of two different lithium enolates.* In the predominant A_2B_2 heteroaggregate, two different enolates are tethered to one another in solution. Having these enolates in proximity transforms a bimolecular oxidative carbon−carbon bond-forming event into a unimolecular process and provides a mechanism for nonstatistical heterocoupling. As a consequence, equimolar mixtures of lithium enolates that exist predominantly as heteroaggregated enolates (A_2B_2) generate the most heterocoupled product upon oxidation.

Previous coupling reactions performed by Saegusa[5] and Baran[7] have shown that synthetically useful yields of heterocoupled products can be obtained by employing an excess of one enolate relative to another. To further demonstrate the importance of lithium aggregation in the oxidative coupling of lithium enolates, ^{7}Li NMR spectra for 1:1 and 2:1 mixtures of the enolates from substrates **10** and **7** were obtained (Figure 3). The ^{7}Li NMR spectrum for the 1:1 mixture (spectrum 1) exhibits a symmetric distribution of tetrameric aggregates. Upon oxidation, the ratio of heterocoupled product **15** to homodimer of **7** was 7:1 (Table 2). Spectrum 2 shows the ^{7}Li NMR spectrum for the 2:1 mixture. Interestingly, the lithium enolate aggregate distribution is dramatically shifted for the 2:1 mixture to favor A_2B_2 over the homotetramer of **7** (B_4). When the 2:1 mixture was oxidized with I_2, the selective formation of **15** improved to 26:1, well above the ratio expected for the use of a 1 equiv excess of **10** relative to **7**.[18] The enolate derived from **10** does not tend to homocouple upon oxidation (*vide supra*), and the amount of the homotetramer of **7** is drastically reduced in the 2:1 mixture. As a consequence, the likelihood of **7** being in proximity to **10** is significantly increased, and the presence of excess A_4 is not detrimental since **10** does not

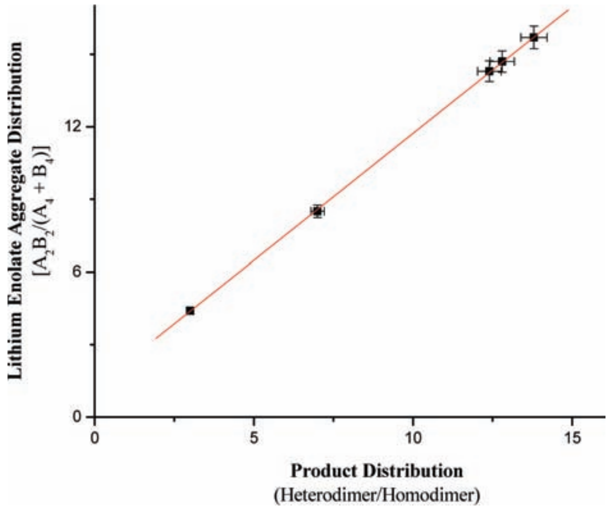


Figure 2. Impact of heteroaggregation on the oxidative heterocoupling of lithium enolates (R^2 = 0.999).

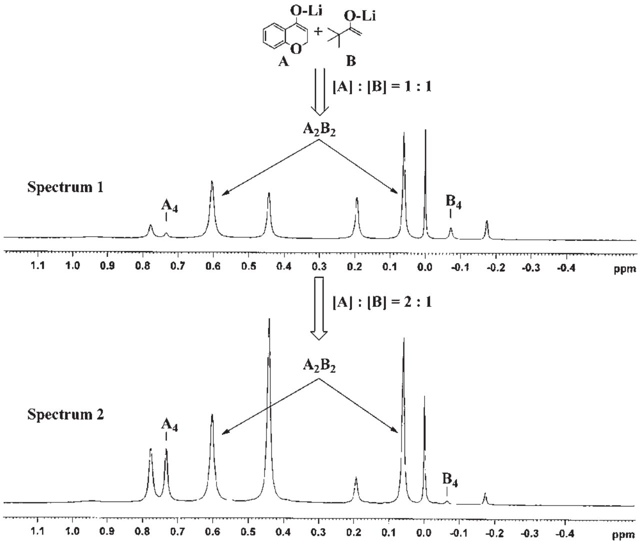


Figure 3. ^{7}Li NMR spectra for (spectrum 1) 1:1 and (spectrum 2) 2:1 mixtures of the enolates of **7** and **10** at −30 °C.

homocouple. This combination of factors leads to the increase in selectivity and yield, reaffirming the integral role that lithium aggregation plays in the oxidative coupling of enolates.

Taken together, the mechanistic experiments described herein show the following: (1) Equimolar mixtures of two different lithium enolates are ensembles of tetramers in THF. (2) The distribution of homo- and heteroaggregates is dependent on the substrate structure. (3) The major component of the mixture is heteroaggregate A_2B_2 when one enolate is sterically encumbered. (4) Single-electron oxidation of solutions predominantly containing the A_2B_2 heteroaggregate furnish the heterocoupled product selectively. (5) The ratio of heterocoupled to homocoupled products is directly related to the relative amount of heteroaggregate A_2B_2.

From a practical point of view, these data suggest that lithium aggregation may be responsible for the success (or failure) of previously reported reactions that proceed through the oxidation of enolates. In classic studies performed by Snider on oxidative cyclizations,[19] lithium enolates containing a pendant olefin dimerized instead of cyclizing to produce a five-membered ring as expected. In light of the present work, it is likely that lithium enolates tethered through an aggregate drive dimerization over the relatively fast intramolecular cyclizations. In another example, Alvarez-Ibarra and co-workers[20] showed that lithium bases provide significantly improved yields and diastereoselectivities over potassium bases in the oxidative homocoupling of enolates derived from glycine esters.

Overall, the results described herein highlight yet another example of lithium-aggregation-driven selectivity in organic reactions. The rational design of efficient syntheses is best facilitated by identifying and understanding the important mechanistic factors involved in the reaction system. Simple empirical models that discount aggregation are often insufficient to explain their role in bond-forming reactions. In view of the large body of work on lithium aggregation, it is surprising that the impact of lithium coordination chemistry in the design and mechanism of reactions is often overlooked. We are currently examining the role of lithium aggregates in more complex systems involving the oxidation of enolates derived from different carbonyl precursors (i.e., esters and amides). The results of these studies will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) On the basis of Pascal's triangle, the statistical distribution of an equimolar mixture of two enolates in an ensemble of tetramers should be 1:4:6:4:1. For this distribution, the ratio of the amount of heteroaggregate A_2B_2 to the sum of the amounts of homoaggregates A_4 and B_4 would be 3:1.

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