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On the Nature of the Oxidative Heterocoupling of Lithium Enolates

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Abstract

The coupling of enolates through single electron oxidation is one of the most direct routes to 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 statistically predicted 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 show that the selective formation of heterocoupled products is a consequence of heteroaggregation of lithium enolates.

Keywords

Lithium enolate; aggregation; single electron oxidation; oxidative coupling

The coupling of enolates through single electron oxidation is the most direct route to generating 1,4-dicarbonyls that 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 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, the 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 the single electron oxidation of enolates, the ability to selectively heterocouple two different enolates through single electron oxidation remained elusive until recently, when Baran *et al.* reported the intermolecular oxidative heterocoupling of enolates.[7] In all 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% yields with some products being obtained in greater than

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SUPPORTING INFORMATION AVAILABLE Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

70% yields. Subsequent synthetic studies on these coupling reactions revealed that best results were obtained in THF.[7b] Additionally, the presence of α-carbonyl radicals was established through radical clock studies.[7b] While these studies demonstrate several factors important in the oxidative heterocoupling of enolates, they do not address the underlying basis for the selective formation of 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.

A considerable body of mechanistic work in 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 of 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 the intermediate **4**. A second single electron oxidation leads to heterodimer **5**. The oxidation of several enolates derived from the reaction of ketones, esters, and amides with lithium hexamethyldisilazide (LiHMDS) was examined with ceric tetra-*n*-butylammonium nitrate (CTAN) using stopped flow spectrophotometry. Surprisingly, all 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 often times leads to highly ordered aggregates in solution. The work of Reich,[9] Seebach,[10] and 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 *et al.* have shown that equimolar mixtures of two different enolates in tetramethylethylenediamine (TMEDA)/toluene preferentially formed heteroaggregated dimers depending on the steric congestion of the carbonyl precursors.[12] The formation of heteroaggregated dimers is due to unfavorable steric interactions in the homodimer of the bulky carbonyl precursor.[12] Based on these findings, could lithium enolate aggregation play a mechanistic role in the non-statistical 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 shows that enolates are tetrameric in THF.[13] Given the complexity of the system, we chose to study the lithium enolate of pinacolone with an equimolar amount of lithium enolates derived from a series of cyclic ketones. Ketones with similar pK_a values were chosen so that 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 since 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 mixture of two different lithium enolates, ^{7}Li NMR experiments were performed on a series of ketone-ketone mixtures (Table 1). In these experiments, the lithium enolate of pinacolone was mixed with an equal amount of another lithium enolate derived from cyclic aryl ketones.

The results of the ^{7}Li NMR experiments revealed several important features of the aggregation of lithium enolates in THF. For all the equimolar enolate mixtures of ketone-

ketone partners examined, the lithium aggregates were ensembles of homoaggregated and heteroaggregated tetramers ($A_4 : A_3B_1 : A_2B_2 : A_1B_3 : B_4$) consistent with those reported by Collum *et al.*[13] As illustrated in Figure 1 (Spectrum 1), when lithium enolates of **7** and **9** were generated separately and mixed at 1−78 °C, the homotetramer of **9** (A_4) as well as smaller amounts of other aggregates including the homotetramer of **7** (B_4) were the predominant species indicating minimal inter-aggregate exchange at reduced temperatures. However, upon warming and recooling the solution, 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 ratio between the most abundant heteroaggregate (A_2B_2) was compared to 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 lowest of the mixtures examined, was still above 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 amount of heteroaggregated tetramers. These observations are consistent with Collum's work on lithium heterodimers which showed that statistically predicted aggregate distributions were obtained when both enolates were sterically bulky.[12]

With the ^{7}Li NMR data in hand, the question remains: are these non-statistical 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) since it is an attractive oxidant in terms of atom economy in that one equivalent of I_2 carries out two single electron oxidations.[16] Furthermore, oxidations using I_2 benefited from improved synthetic work up procedures since the tetra-*n*-butylammonium counterions of CTAN are lipophilic and act 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 better than statistically predicted (2 : 1). It is interesting to note that the homodimers of ketone **A** were never observed and instead the starting ketones were recovered 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 ratios 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 non-statistical heterocoupling. As a consequence, equimolar mixtures of lithium enolates that exist predominantly as heteroaggregated enolates (A_2B_2) generate the most heterocoupled product when oxidized.

Previous coupling reactions performed by both Saegusa and Baran have shown that synthetically useful yields of heterocoupled products can be obtained by employing an excess of one enolate relative to another.[5, 7] To further demonstrate the importance of lithium aggregation in the oxidative coupling of lithium enolates, the ^{7}Li NMR spectra for a 1 : 1 and a 2 : 1 mixture of enolates from substrates **10** and **7** were obtained (Figure 3). Spectrum 1 containing equimolar amounts of enolates derived from **7** and **10** exhibits a symmetric distribution of tetrameric aggregates. When oxidized, the heterocoupled product **15** to homodimer of **7** ratio was 7 : 1 (Table 2). Spectrum 2 shows the ^{7}Li NMR spectrum of a 2 : 1 ratio of enolates derived from **10** and **7**. Interestingly, the lithium enolate aggregate distribution dramatically shifts 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 from employing a one equivalent excess of **10** relative to **7**.[18] The enolate derived from **10** does not tend to homocouple upon oxidation (*vide supra*), and 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 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: (1) Equimolar mixtures of two different lithium enolates are ensembles of tetramers in THF. (2) The distribution of homoand heteroaggregates is dependent on 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 containing predominantly heteroaggregate A_2B_2 furnish the heterocoupled product selectively. (5) A direct correlation exists between the amount of heteroaggregate A_2B_2 and the ratio of heterocoupled to homocoupled products.

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 on oxidative cyclizations, Snider found that lithium enolates containing a pendant olefin dimerized and did not cyclize to produce a 5-membered ring as expected.[19] In light of the present work, it is likely that lithium enolates tethered through an aggregate drive dimerization even over relatively fast intramolecular cyclizations. In another example, Alvarez-Ibarra and coworkers showed that lithium bases provided significantly improved yields and diastereoselectivities over potassium bases in the oxidative homocoupling of enolates derived from glycine esters.[20]

Overall, the results described herein highlight yet another example of lithium aggregation driving 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. Given the large body of work on lithium aggregation, it is surprising the impact of lithium coordination chemistry in the design and mechanism of reactions is often over-looked. 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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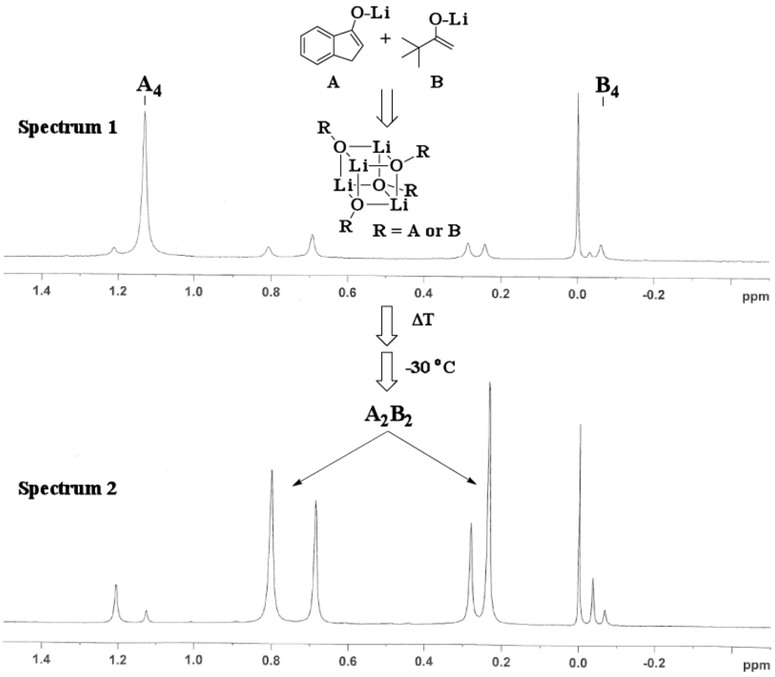


Figure 1.

^{7}Li NMR at −30 °C of 1 : 1 mixture of **7** and **9** with LiHMDS. Enolized separately and combined at −78 °C (Spectrum 1). Warming and recooling to −30 °C (Spectrum 2).

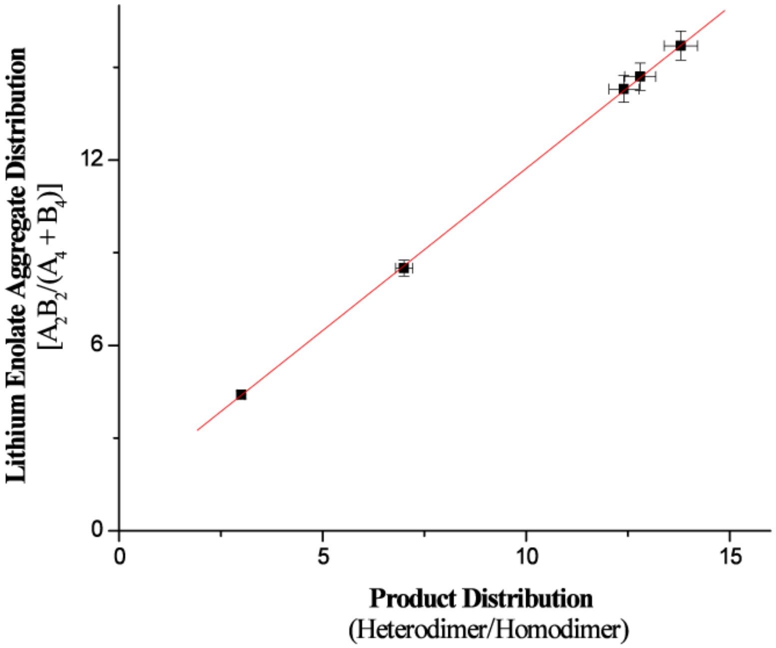


Figure 2.

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

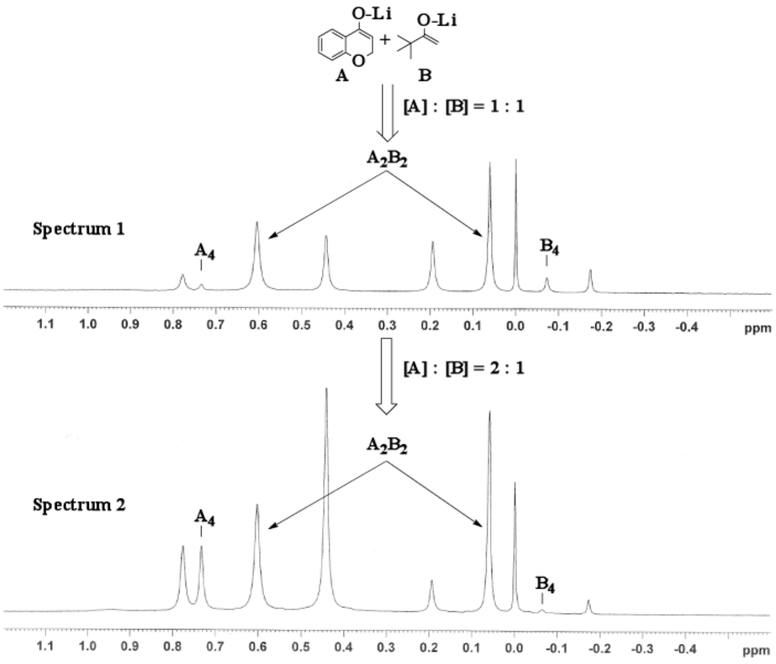
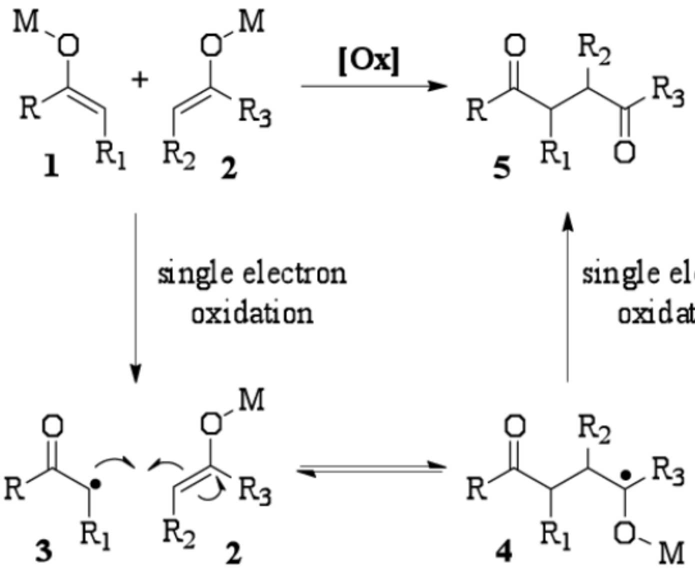


Figure 3.

^{7}Li NMR at −30 °C for 1 : 1 enolate mixture of **7** and **10** (Spectrum 1) and 2 : 1 mixture (Spectrum 2).

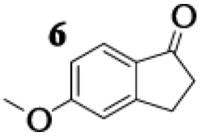
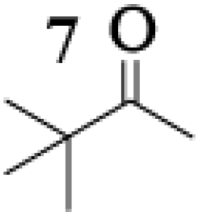
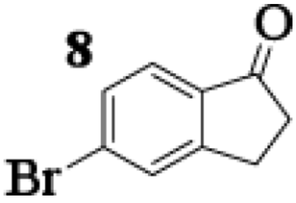
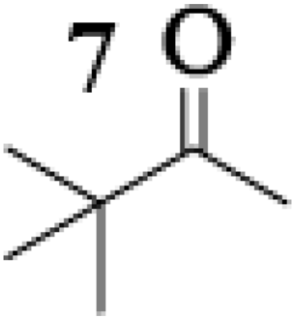
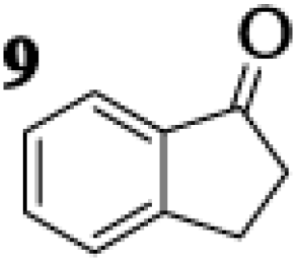
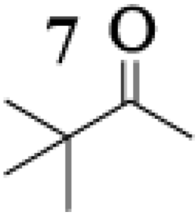
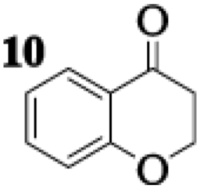
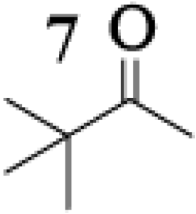
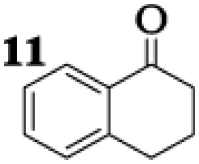
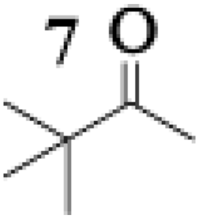


Scheme 1.

Selective formation of heterocoupled products through preferential oxidation.

Table 1

Lithium aggregate distributions[a] of equimolar mixtures of enolates[b]

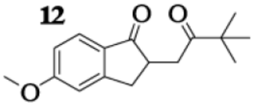
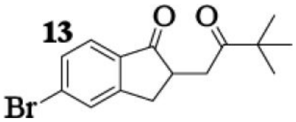
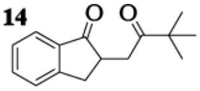
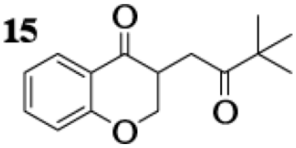
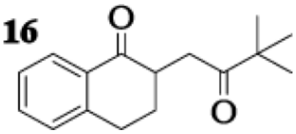
Ketone A	Ketone B	$\frac{A_2B_2}{A_4 + B_4}$
 **6**	 **7**	15.7 : 1
 **8**	 **7**	14.7 : 1
 **9**	 **7**	14.3 : 1
 **10**	 **7**	8.5 : 1
 **11**	 **7**	4.4 : 1

[a] Distributions obtained by integrating ^{7}Li NMR spectra at −30 °C.

[b] [A] = [B] = 0.15 M and [LiHMDS] = 0.304 M in 2.0 M THF:Toluene

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.

[c] Determined by ^{1}H NMR with ± 3 % error.

[d] 15–25% of ketone A was recovered in these reactions.