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Anion Radical [2 + 2] Cycloaddition as a Mechanistic Probe: Stoichiometry- and Concentration-Dependent Partitioning of Electron-Transfer and Alkylation Pathways in the Reaction of the Gilman Reagent $Me_2CuLi{\cdot}LiI$ with Bis(enones)

Jingkui Yang, David F. Cauble, Adam J. Berro, Nathan L. Bauld,* and Michael J. Krische*

Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, Texas 78712

bauld@mail.utexas.edu; mkrische@mail.utexas.edu

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Exposure of easily reduced aromatic bis(enones) **1a**−**1e** to the methyl Gilman reagent $Me_2CuLi{\cdot}$LiI at 0 °C in tetrahydrofuran solvent provides the products of tandem conjugate addition−Michael cyclization, **2a**−**2e**, along with the products of [2 + 2] cycloaddition, **3a**−**3e**. Complete partitioning of the Gilman alkylation and [2 + 2] cycloaddition pathways may be achieved by adjusting the loading of the Gilman reagent, the rate of addition of the Gilman reagent, and the concentration of the reaction mixture. The Gilman alkylation manifold is favored by the rapid addition of excess Gilman reagent at higher substrate concentrations, while the [2 + 2] cycloaddition manifold is favored by slow addition of the same Gilman reagent at lower concentrations and loadings. Notably, [2 + 2] cycloaddition to form **3a**−**3e** is catalytic in Gilman reagent. Kinetic data reveal that the ratio of **2a** and **3a** changes such that the cycloaddition pathway becomes dominant upon increased consumption of Gilman reagent. These data suggest a concentration-dependent speciation of the Gilman reagent and differential reactivity of the aggregates present at higher and lower concentrations. While the species present at higher concentration induce Gilman alkylation en route to products **2a**−**2e**, the species present at lower concentration provide products of catalytic [2 + 2] cycloaddition, **3a**−**3e**. Moreover, upon electrochemical reduction of the bis(enones) **1a**−**1e**, or chemically induced single-electron transfer from arene anion radicals, the very same [2 + 2] cycloadducts **3a**−**3e** are formed. The collective data suggest that [2 + 2] cycloadducts **3a**−**3e** arising under Gilman conditions may be products of anion radical chain cyclobutanation that derive via electron transfer (ET) from the $Me_2CuLi{\cdot}LiI$ aggregate(s) present at low concentration. These observations provide a link between the Gilman alkylation reaction and related ET chemistry and suggest these reaction paths are mechanistically distinct. This analysis is made possible by the recent observation that easily reduced bis(enones) are subject to intramolecular [2 + 2] cycloaddition upon cathodic reduction or chemically induced ET from arene anion radicals, and is herewith showcased as a novel method of testing for the intermediacy of enone anion radicals.

Introduction

An electron-transfer (ET) mechanism was originally proposed for the alkylation of conjugated enones by Gilman reagents (formally lithium dialkylcuprates).[1] However, much of the data once believed to support the intermediacy of enone anion radicals in the Gilman conjugate addition have been subject to debate and in some instances refuted.[2] For example: (a) *E*/*Z* isomerization of enones upon exposure to $Me_2CuLi{\cdot}LiI$, initially attributed to the formation of anion radical intermediates, is catalyzed by lithium iodide at temperatures as low as −78 °C.[3] (b) Although a correlation between enone reduction potential and the ability to undergo conjugate addition using $Me_2CuLi{\cdot}LiI$ has been made,[4] subsequent studies reveal this correlation to be superficial, thus disqualifying rate-determining electron transfer.[5] (c) A large number of studies involving the use of chemical probes were considered to corroborate the intermediacy of anion radicals.[6−9] Specifically, upon exposure to Gilman reagents, enones possessing γ-heteroatom substitution afford products of elimination,[6] enones possessing leaving groups at the δ-position afford products of

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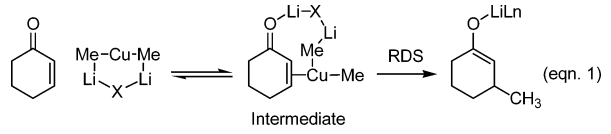
internal substitution,[6a,7] and γ,δ-cyclopropyl enones are subject to alkylative ring opening.[8] While products of ring cleavage could potentially arise via intermediacy of a cyclopropylcarbinyl radical, the nucleophilic ring opening of cyclopropyl esters and ketones using Gilman reagents is known.[9] Moreover, elegant studies by Casey demonstrate stereospecific alkylative ring opening, which appears incompatible with anion radical intermediates.[10] This result was initially interpreted as evidence for direct nucleophilic addition to the cyclopropane. Related studies by Bertz suggest that alkylative ring opening actually occurs through stereospecific rearrangement of an initially formed β-cuprio adduct.[11] Indeed, for all the aforementioned chemical probes, reactivity once deemed "diagnostic" of the presence of anion radicals is perhaps better attributed to the action of β-cuprio intermediates. (d) Finally, attempted spectroscopic detection of anion radicals using electron spin resonance (ESR) and chemically induced dynamic nuclear polarization (CIDNP) was unsuccessful.[12]

It is now generally believed that the reaction of the Gilman reagent $Me_2CuLi{\cdot}LiI$ with conjugated enones involves reversible formation of a Cu-complexed intermediate followed by rate-determining C−C reductive elimination (eq 1). Rate-determining reductive elimination is supported by kinetic isotope effects.[13] Additionally, kinetic studies performed by Krauss and Smith reveal reversible formation of an intermediate that is subject to irreversible rate-determining conversion to product.[14] While Cu-complexed enone intermediates have been directly observed using low-temperature NMR spectroscopy,[15] the precise nature of such enone complexes is subject to debate. The available theoretical data suggest their structure resides between the limiting, and perhaps mesomeric, forms represented by unsymmetrical π-complexes and oxy-π-allyls, enyls ($\sigma + \pi$), and β-cuprio adducts.[16] Studies by Boche suggest the Cu-complexed intermediate is a contact ion pair (CIP), rather than a solvent-separated ion pair (SSIP), even in cases when the latter predominate in solution.[17]



Despite strong evidence against the intermediacy of enone anion radicals in many Gilman-type conjugate additions, the ET properties of Gilman reagents have been clearly demonstrated in cases involving easily reduced substrates. These include (a) additions to doubly activated olefins,[18] (b) addition to bromonaphthoquinone,[19] (c) polyaddition to fullerenes, as well as the (d) ketyl anion radical formation and pinacolization of fluorenone.[20] Hence, the formation of anion radicals in a preequilibrium preceding the rate-determining step of the Gilman reaction remains a possibility, especially for easily reduced systems.

Our recent observation that easily reduced bis(enones) are subject to intramolecular [2 + 2] cycloaddition upon cathodic reduction or chemically promoted ET provides a hitherto unavailable means of detecting anion radical intermediates.[21] As such, it became of interest to utilize these anion radical probes in an examination of the mechanism of the Gilman alkylation of conjugated enones. Here, we disclose that upon exposure of bis(enones) **1a**−**1e** to the methyl Gilman reagent $Me_2CuLi{\cdot}LiI$ at 0 °C in THF, both the products of tandem conjugate addition−Michael cyclization, **2a**−**2e**, and [2 + 2] cycloaddition, **3a**−**3e**, are generated. Partitioning of these reaction pathways is achieved by modulating the concentration and loading of the Gilman reagent. While the aggregate(s) present at higher concentration induce typical Gilman alkylation en route to products **2a**−**2e**, the aggregate(s) present at lower concentration provide products of catalytic [2 + 2] cycloaddition, **3a**−**3e**. These studies suggest a concentration-dependent speciation of the Gilman reagent and differential reactivity of the aggregates present at higher and lower concentrations. On the basis of these data, along with our prior studies involving chemically and electrochemically induced anion radical cyclobutanation of the very same bis(enones),[21] the [2 + 2] cycloadducts **3a**−**3e** arising under Gilman conditions appear to be products of anion radical chain cyclobutanation that derive via ET from the $Me_2CuLi{\cdot}LiI$ aggregate(s) present at low concentration (Scheme 1).

Results and Discussion

Anion Radical Probe Reaction. In connection with ongoing studies toward the development of catalysts for alkene [2 + 2] cycloaddition,[21,22] the belief that Gilman reagents might serve as ET agents prompted us to

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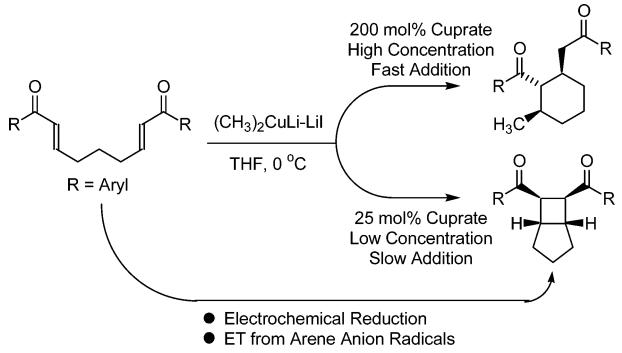
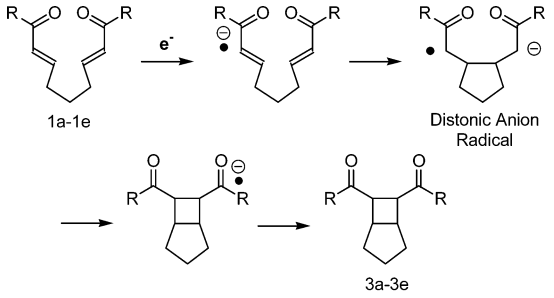
SCHEME 1. Stoichiometry- and Concentration-Dependent Partitioning of ET and Alkylation Pathways in the Reaction of the Gilman Reagent $Me_2CuLi·LiI$ with Bis(enones)



SCHEME 2. Postulated Stepwise Mechanism for Anion Radical Cyclobutanation

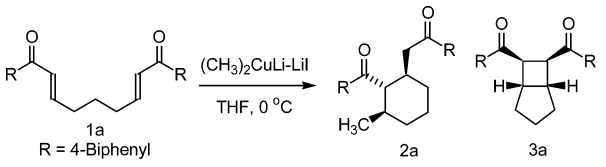


1a, R = 4-Biphenyl, 1b, R = 2-naphthyl, 1c, R = 4-Cl-Ph, 1d, R = 3,4-Cl_2-Ph, 1e, R = Ph

examine their capacity to induce anion radical chain cyclobutanation of bis(enone) substrates. The bis(enone) substrates **1a**−**1e** have been shown in this laboratory to undergo intramolecular cyclobutanation via enone anion radical intermediates formed initially either by ET from the chrysene anion radical or by cathodic reduction.[21] The available evidence strongly supports a stepwise cycloaddition mechanism involving the formation of a distonic anion radical intermediate which then cyclizes to form the anion radical of the cyclobutane product **3**, which should be localized upon the aroyl moiety. Exergonic ET to the more easily reducible substrate **1** then initiates an anion radical chain reaction (Scheme 2). Since the 4-biphenoyl moiety of **1a** more effectively stabilizes the anion radical moiety than does the benzoyl moiety of **1e**, the former has been found to be a substantially more efficient anion radical probe than the latter. Consequently, bis(enone) **1a** was used in the most extensive series of probe experiments in the present work. The prototypical Gilman reagent $Me_2CuLi·LiI$, generated through the addition of methyllithium to a THF solution of copper(I) iodide, was selected as the specific Gilman reagent for this study.

Organocuprate-Catalyzed [2 + 2] Cycloaddition. Toward this end, variable quantities of the methyl Gilman reagent were added to a THF solution (0.01 M) of the 4-biphenyl-substituted bis(enone) **1a** at 0 °C. Using 2 equiv of the Gilman reagent, an 85% yield of the tandem conjugate addition−Michael cyclization product **2a** is obtained (Table 1, entry 1). Upon use of 1 equiv of the methyl Gilman reagent, both **2a** and the [2 + 2] cycloadduct **3a** are obtained in 64% and 13% yields,

TABLE 1. Effect of Cuprate Loading, Concentration, and Rate of Addition on Partitioning of the Alkylation and Cycloaddition Pathways[a−c]



entry	[$(CH_3)_2CuLi$], mol %	[**1a**]	**1a** recov,[f] %	**2a** yield,[f] %	**3a** yield,[f] %
1	200[d]	0.01 M	5	85	–
2	100[d]	0.01 M	5	64	13
3	50[d]	0.01 M	–	38	40
4	25[d]	0.01 M	–	13	84
5	25[e]	0.01 M	3	–	91
6	10[d]	0.01 M	16	7	72
7	100[d]	1.25 mM	–	10	60

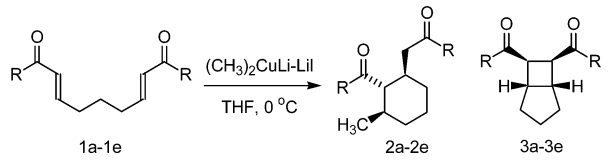
[a] See the Experimental Section for further experimental details. [b] The structural assignment of compound **2a** is corroborated by X-ray diffraction analysis of **2e**. [c] For entries 3, 4, 5, and 7 trace quantities of the product of intramolecular hetero-Diels−Alder cycloaddition were obtained. [d] A 0.5 M solution of the Gilman reagent in THF is added over 5 s. [e] A 0.5 M solution of the Gilman reagent in THF is added over 60 s. [f] Isolated yields after chromatographic separation.

respectively (Table 1, entry 2). A further decrease in the loading of the Gilman reagent was found to favor the cycloaddition pathway. Using 0.5 equiv of the Gilman reagent, **2a** and the [2 + 2] cycloadduct **3a** are produced in 38% and 40% yields, respectively (Table 1, entry 3), and upon use of 0.25 equiv of the Gilman reagent, **2a** and the [2 + 2] cycloadduct **3a** are produced in 13% and 84% yields, respectively (Table 1, entry 4). Notably, when 0.25 equiv of the Gilman reagent is added more slowly (60 s), the cyclobutanation manifold is favored to the exclusion of **2a**, providing the cycloadduct **3a** in 91% yield as a single diastereomer (Table 1, entry 5). A further decrease in loading of the Gilman reagent results in incomplete consumption of **1a** (Table 1, entry 6). Finally, use of 1 equiv of the Gilman reagent at 0.00125 M rather than 0.01 M concentration inverts the proportion of alkylation product **2a** and cyclobutanation product **3a**. The yields of **2a** and **3a** change from 64% and 13% to 10% and 60%, respectively (Table 1, entry 7). These results demonstrate that, when suitably dilute, the Gilman reagent becomes ineffective at methylation, and instead serves as a catalyst for cyclobutanation.

To explore the scope of this partitioning phenomenon, optimum Gilman alkylation and anion radical cyclobutanation conditions were applied to related bis(enones) (Table 2). Gratifyingly, complete partitioning of the alkylation and cyclobutanation manifolds was achieved in most cases. Interestingly, the parent phenyl-substituted bis(enone) **1e** is more resistant to cyclobutantion, suggesting the Gilman reagent only catalyzes the cycloaddition of easily reduced bis(enones).

Kinetic Studies. Rapid injection of a THF solution of $Me_2CuLi·LiI$ (0.01 M, 25 mol %) to a solution of **1a** (0.037 M, 100 mol %) leads to nearly exclusive formation of **2a** at the onset of the reaction. However, after the majority of the Gilman reagent is consumed through the conversion of **1a** to **2a**, the formation of **3a** begins and continues to develop. Ultimately, cycloaddition becomes the domi-

TABLE 2. Partitioning Conjugate Addition and Electron-Transfer Pathways across a Range of bis(enones), 1a−1e[a]



substrate	R	conditions	**2** yield,[b] %	**3** yield,[b] %
1a	4-biphenylyl	A	91	−
		B	−	91
1b	2-naphthyl	A	89	−
		B	−	90
1c	4-chlorophenyl	A	93	−
		B	−	80
1d	3,4-dichlorophenyl	A	85	−
		B	4	70
1e	phenyl	A	90	−
		B	12	43

[a] Conditions A employ rapid addition (5 s) of Me_2CuLi (200 mol %) to a solution of substrate (100 mol %) in THF at 0 °C. Conditions B employ slow addition (60 s) of Me_2CuLi (25 mol %) to a solution of substrate (100 mol %) in THF at 0 °C. See the Experimental Section for further details. [b] Isolated yields after chromatographic separation. The ratio of *cis* to *trans* diastereomers for **3a**, **3b**, **3c**, **3d**, and **3e** is >99:1, 44:1, 9:1, 13:1, and 17:1, respectively.

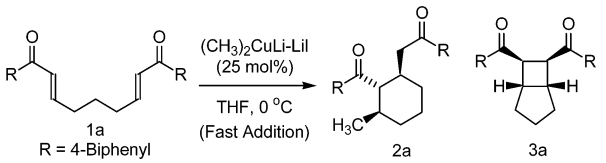
nant reaction pathway. The implications of these results will be discussed.

Mechanistic Proposal. It is evident from the results presented in Table 1 that the cyclobutanation reaction is indeed a catalytic or chain process, but that chain lengths are rather short (ca. 2−3). These experiments also suggest a concentration-dependent speciation of the Gilman reagent, as demonstrated by differential reactivity at high and low concentration. The aggregates present at high concentration favor alkylation, while the aggregates present at low concentration favor cycloaddition. A corollary to this hypothesis requires that variation of concentration at constant loading of the Gilman reagent should modulate the ratio of alkylation and cyclobutanation products. Indeed, the yields of **2a** and **3a** change from 64% and 13% to 10% and 60%, respectively, when 1 equiv of the Gilman reagent is used at 0.00125 M rather than 0.01 M concentration.

Studies of the time evolution of products **2a** and **3a** provide further insights into the mechanistic dichotomy observed in this work (Table 3). The alkylation product **2a** is formed rapidly early in the reaction, whereas only small amounts of **3a** are generated at this stage. However, after the concentration of the Gilman reagent is lowered through its consumption, the cycloaddition pathway becomes dominant. These results again suggest that the composition of the Gilman reagent is concentration dependent, and that the species present at low concentration are relatively ineffective methyl-transfer agents, but are effective agents for chain cycloaddition in the case of easily reduced bis(enones).

A further important consequence of the kinetic studies is the conclusion that lithium halide, which is present at constant concentration throughout the reaction period, is not differentially involved in the competition between methylation and cyclobutanation. This conclusion was

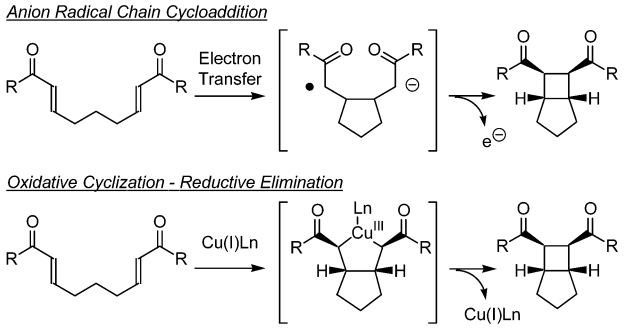
TABLE 3. Ratio of 2a and 3a over Time Reveals Dominance of the Cycloaddition Pathway upon Initial Consumption of Gilman Reagent[a]



entry	time, s	[**1a**],[b] mol %	[**2a**],[b] mol %	[**3a**],[b] mol %
1	0	100	0	0
2	10	76.3	16.3	5.1
3	30	66.7	19.0	11.7
4	60	63.4	20.3	12.7
5	180	42.0	18.6	33.2
6	480	33.4	20.2	43.2
7	1200	24.3	22.0	54.7

[a] See the Experimental Section for further details. [b] Conversion was determined by ^1H NMR analysis, and the values given are the average of two runs. Total values are under 100 mol % as small quantities of hetero-Diels−Alder cycloadduct are produced.

SCHEME 3. Alternative Cyclobutanation Mechanisms

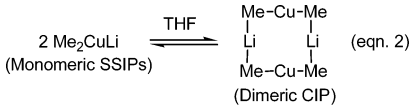


further substantiated by carrying out a reaction in which 100 mol % lithium iodide was included with the substrate, and 100 mol % Gilman reagent was added in slow fashion. Instead of favoring the methylation, the results were essentially the same as when the lithium iodide was omitted. The nature of the termination step of the anion radical chain process is not currently known, but coupling of two anion radicals is a possibility.

A paramount question relates to whether the cycloadducts **3a**−**3e** are products of anion radical chain cycloaddition or instead derive from Cu(I)-catalyzed oxidative cyclization−reductive elimination (Scheme 3). In the latter case, the Gilman intermediate, be it a π-complex, oxy-π-allyl, enyl ($\sigma + \pi$), or β-cuprio adduct, is required to insert the appendant enone. Here, it is especially noteworthy that the 4-biphenyl-derived bis(enone) **1a** is much more efficiently converted to **3a** than the related benzoyl-substituted bis(enone) **1e** is to **3e**. This same reactivity order has been observed in authenticated anion radical reactions involving ET from chrysene anion radical,[21] and is attributed to the more facile generation of the 4-biphenoyl-type anion radical moiety, as opposed to a benzoyl-type anion radical moiety, in the second cyclization step to close the cyclobutane ring. Since the comparison of **1a** and **1e** should not involve a significant difference in polar effects (phenyl vs 4-biphenyl), the enhancement associated with **1b** is presumed to be a

conjugative effect, as would be present in the delocalization of an anion radical moiety. Further, authenticated anion radical cyclobutanations involving cathodic reduction typically proceed through short chains, in the same manner as the currently observed cyclobutanations. Finally, when the same solvent (THF) is involved, chemically initiated anion radical cyclobutanation of substrate **1a** affords exclusively the *exo*,*cis*-cyclobutane product **3a**, as observed in the present work. As demonstrated in our earlier work, the *exo*,*cis*-isomer is less stable than the corresponding *trans*-isomer. The high levels of stereoselectivity evident in the formation of **1a** suggest the anion radical intermediates derived from **1a** exist as highly organized CIPs.

A second important question concerns the composition of the reactive species at high and low concentration. It has been established that, in THF solution, the methyl Gilman reagent exists primarily as solvent-separated ion pairs ($Li^+//CuMe_2^-$), which are in rapid equilibrium with the cyclic dimer of lithium dimethylcuprate ($[Me_2CuLi]_2$).[17] Extensive evidence suggests that the latter dimer is much more reactive than the former with respect to Gilman methylation. Neither monomer nor dimer is intimately associated with the lithium halide, which is consistent with our own observation that the product distribution is insensitive to added lithium iodide (eq 2).



(eqn. 2)

Since the equilibrium between the dimer and the monomer would be even further shifted to the monomer upon dilution, it is reasonable to suggest that the monomeric solvent-separated ion pairs, which are known to be relatively unreactive toward methylation, may be the species responsible for initiating electron transfer, while the dimer is the species responsible for methylation. This proposal would explain why electron-transfer chemistry appears to dominate when the Gilman reagent is very dilute, but methylation dominates when the reagent is more concentrated. Because products derived via anion radical intermediates may be formed to the exclusion of methylation products, it appears that these anion radical intermediates are not subject to Gilman methylation. Hence, the Gilman alkylation and cycloaddition pathways are mechanistically distinct.

The possibility that small amounts of extraneous impurities could be responsible for the initiation of the anion radical chemistry observed in the present work has been extensively considered, and the following reagents (acting alone, under the typical conditions of the reaction) have been shown not to initiate anion radical chemistry in the case of **1a** or any of the substrates of this study: MeLi, MeCu, and LiI. Further, the reagent lithium trimethyldicuprate reacts in essentially the same manner as lithium dimethylcuprate. This reagent was specifically considered because it could be generated from lithium dimethylcuprate and methylcopper, which is released upon Gilman methylation.

Conclusion

The now well-established intramolecular anion radical chain cyclobutanation reactions of 1,7-bisaroyl-1,6-heptadienes have been employed as anion radical probes in the reactions of these enones with the Gilman reagent. When the Gilman reagent is present in the reaction solution at low concentrations, either via slow addition of the reagent to a solution of the bis(enone), or by use of a substoichiometric amount of the reagent (25 mol %), the [2 + 2] intramolecular cycloaddition products are formed in good yield. In contrast, when a stoichiometric (or greater) amount of the reagent is added rapidly to a solution of the enone, tandem Gilman methylation−intramolecular Michael addition occurs in high yield. Under suitable conditions, complete partitioning of the anion radical and conventional Gilman methylation pathways is observed. These results indicate that anion radical intermediates are generated in competition with Gilman methylation products and that the anion radical mechanism is independent of the methylation mechanism. That is, under ideal anion radical conditions (low concentration of the Gilman reagent), no methylation is observed, and conversely, under ideal methylation conditions (high concentration and an excess of the Gilman reagent), no anion radical products are formed. The powerful dependence of the competition between ET chemistry and Gilman methylation upon the concentration of the Gilman reagent, coupled with the generally acknowledged greater methylation reactivity of the dimeric, rather than monomeric, Gilman reagent, suggests that the species responsible for methylation is probably the CIP dimer, while the species responsible for electron transfer is probably the Gilman monomer, which is present in tetrahydrofuran solutions as the solvent-separated ion pair (eq 2).

Experimental Section

Bis(enones) 1a−1e were prepared according to known procedures.[21b]

Lithium dimethylcuprate−lithium iodide ($Me_2CuLi\cdot LiI$) was prepared by adding 200 mol % MeLi (1.6 M in Et_2O) to a suspension of 100 mol % CuI in 0 °C THF. Stirring for approximately 30 min at 0 °C resulted in a homogeneous solution.

Table 1 data were obtained using the following procedure: $Me_2CuLi\cdot LI$ reagent solution (0.5 M in Et_2O/THF) was added at the indicated rate to a solution of bis(enone) **1a** (0.25 mmol) in 25 mL of 0 °C THF. The reaction mixture was allowed to stir at 0 °C for 25 min, at which point several drops of saturated aqueous NH_4Cl solution were added. The reaction mixture was partitioned between ether and brine, and the aqueous layer was extracted with ether. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The resulting residue was purified by silica gel chromatography, eluting with a mixture of ethyl acetate and hexane, to afford the Gilman methylation product **2a** and the cycloaddition product **3a**.

Table 2 data were obtained using the following representative procedures. Conditions A: $Me_2CuLi\cdot LiI$ (15.7 mL, 0.0032 M in Et_2O/THF, 200 mol %) was added over 5 s to a solution of substrate (0.26 mmol, 100 mol %) in 5 mL of THF at 0 °C. Stirring was maintained for 25 min, at which point the reaction mixture was worked up and the residue purified as described above. Conditions B: $Me_2CuLi\cdot LiI$ (0.125 mL, 0.5 M in Et_2O/THF, 25 mol %) was added over 60 s to a solution of substrate (0.25 mmol, 100 mol %) in 25 mL of THF at 0 °C.

Stirring was maintained for 25 min, at which point the reaction mixture was worked up and the residue purified as described above.

Table 3 data represent measurements from separate, parallel reactions, conducted using the following procedure: $Me_2CuLi{\cdot}LiI$ (0.98 mL, 0.034 M in Et_2O/THF, 25 mol %) was added over 5 s to a solution of substrate (0.1316 mmol, 100 mol %) in 3.5 mL of 0 °C THF. Stirring was maintained for the indicated time before workup and purification as described above.

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Supporting Information Available: Spectral data for all new compounds, including scanned images of ^1H and ^{13}C NMR spectra (PDF), and crystallographic data for **2e** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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