

# UC San Diego

## UC San Diego Previously Published Works

### Title

Nucleophilic Addition of Enolates to 1,4-Dehydrobenzene Diradicals Derived from Ene-diyne: Synthesis of Functionalized Aromatics

### Permalink

<https://escholarship.org/uc/item/2277j0kn>

### Journal

ACS Omega, 7(26)

### ISSN

2470-1343

### Authors

Shrinidhi, Annadka  
Perrin, Charles L

### Publication Date

2022-07-05

### DOI

10.1021/acsomega.2c02916

Peer reviewed

# Nucleophilic Addition of Enolates to 1,4-Dehydrobenzene Diradicals Derived from Eneidyne. Synthesis of Functionalized Aromatics

Annadka Shrinidhi<sup>†</sup> and Charles L. Perrin\*

Department of Chemistry, University of California—San Diego, La Jolla, California 92093-0358, United States

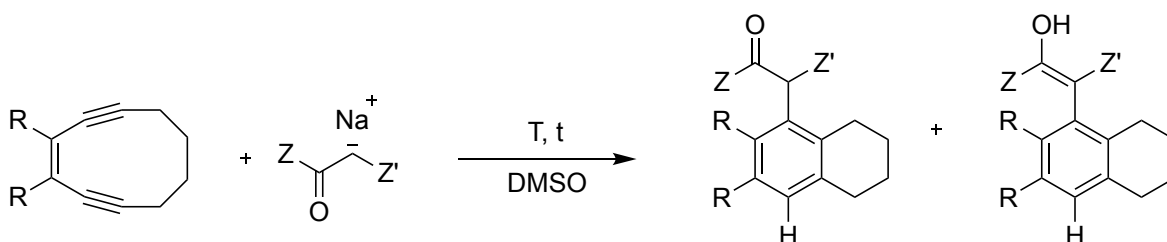
<sup>†</sup>Current address: Department of Medicinal Chemistry and Molecular Pharmacology, College of Pharmacy, Purdue University, West Lafayette, IN 47907, USA

\*Corresponding author: cperrin@ucsd.edu

## Abstract

Alkylation of aromatics and formation of a new C-C bond is usually achieved by electrophilic attack of an activated carbon species on an electron-rich aromatic ring. Herein, we report an alternative method for alkylation of aromatics via nucleophilic addition of enolates of active methylene compounds to 1,4-dehydrobenzene diradicals derived from enediynes cyclodec-1,5-diyne-3-ene, benzo[3,4]-cyclodec-1,5-diyne-3-ene, and cyclohexeno[3,4]-cyclodec-1,5-diyne-3-ene. The benzo-substituted enediyne produces slightly higher yields of alkylation products than do the other two enediynes, but the differences are not substantial. The reaction produces a new C-C bonded aromatic alkylation product, which allows the construction of complex polyfunctional structures in a few steps. Moreover, this reaction provides solely *C*-arylated products, and no *O*-arylation products were observed.

## For Table of Contents Only



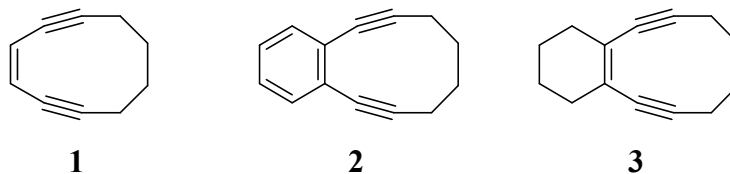
R,R (T, t) = H,H (55°C, 12 h), -(CH)<sub>4</sub>- (85°C, 72 h), -(CH<sub>2</sub>)<sub>4</sub>- (75°C, 24 h)

COZ = CN, CO<sub>2</sub>Et, COMe, and COPh      Z' = CN, CO<sub>2</sub>Et, and COMe

## Introduction

Naturally occurring compounds containing 10-membered-ring enediynes are well-known for their remarkable antibiotic and antitumor activities.<sup>1</sup> The activity of these enediyne natural products stems from their enediyne core: In the presence of chemical triggers like chromosomal DNA the enediyne moiety undergoes rearrangement to form a reactive 1,4-dehydrobenzene diradical (often called a "*p*-benzyne diradical", a designation discouraged by IUPAC, inasmuch as there is no triple bond) via a cycloaromatization known as the Bergman cyclization,<sup>2</sup> and the diradical then abstracts hydrogen atoms from the DNA backbone to cause oxidative DNA breakage and cell death.<sup>3</sup>

Therefore it has become important to understand the formation and reactivity of 1,4-dehydrobenzene diradicals. Yet even though enediyne **1** is the simplest model to study, its difficult synthesis, its volatility, and its reactivity even at room temperature limit its use in understanding cycloaromatization.<sup>4</sup> In its place benzo-fused enediyne **2** has been extensively studied because of its easy synthetic accessibility and relative stability at room temperature.<sup>5</sup> Recently we have developed cyclohexeno-fused enediyne **3** as a simple and convenient model enediyne for studying the reactivity of enediynes.<sup>6</sup>

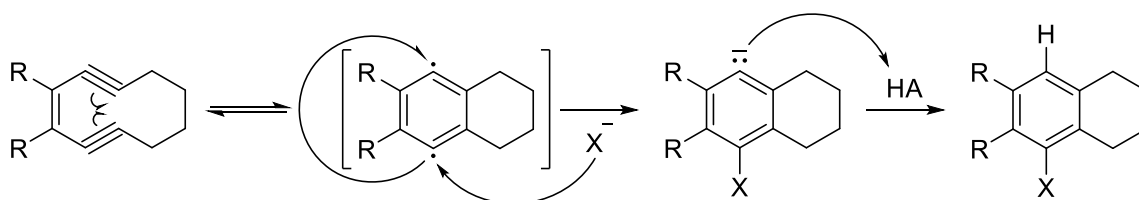


Some earlier studies involved experimental and computational evaluation of factors affecting the formation of 1,4-dehydrobenzene diradicals (or cycloaromatization), such as ring strain and geometrical effects,<sup>4a,7</sup> conformational and electronic effects,<sup>5,8</sup> and metal-ion coordination,<sup>9</sup> using enediynes **1** and **2** and related homologues. However, few studies explored their synthetic utility. Semmelhack et al reported cycloaromatization of enediyne **2** in the presence of radical trapping agents such as 1,4-cyclohexadiene, CCl<sub>4</sub>, and CBr<sub>4</sub> and obtained 1,4-dihydro-, 1,4-dichloro-, and 1,4-dibromo-tetrahydroanthracene adducts, respectively, in moderate yields.<sup>5,8a,10</sup>

In 2007 Perrin, Rodgers, and O'Connor reported nucleophilic addition of halides to the 1,4-dehydrobenzene diradical derived from enediyne **1**.<sup>11</sup> Subsequently Perrin and Reyes-

Rodriguez showed that the reaction also succeeds with other nucleophiles such as the pseudohalides cyanide, thiocyanate, and azide.<sup>12</sup>

Nucleophilic addition to 1,4-dehydrobenzenes had been a previously unexpected mode of reaction for such diradicals, which ordinarily react by radical pathways. The mechanism of halide addition is shown in Scheme 1.<sup>11</sup> Kinetic studies on enediyne **1** found that the reaction rate is simply first-order in enediyne and independent of the concentration of halide or even of which halide serves as nucleophile. Therefore the rate-limiting step is cyclization to the 1,4-dehydrobenzene diradical, which then rapidly adds halide and is protonated. Because the diradical is a singlet, with two electrons of opposite spin in two different atomic orbitals, those electrons can pair in one orbital while the electron pair coming from  $X^-$  is used to bond to the other orbital. Thermodynamic data showed that the halide additions are very exothermic. Moreover, the calculated energy of interaction between  $Cl^-$  and the diradical shows no activation barrier in the gas phase, and any experimentally detectable barrier arises from the energy required to desolvate the nucleophile.



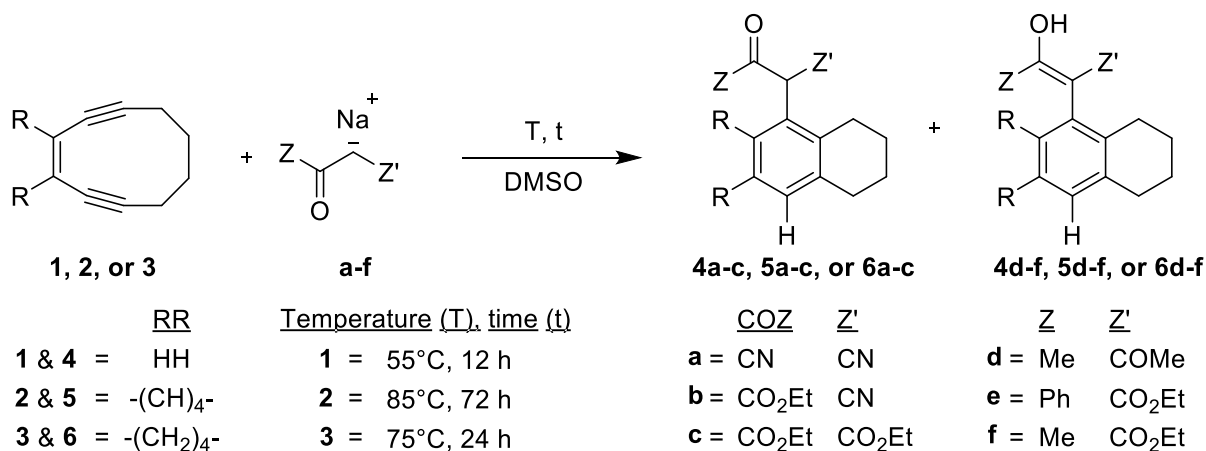
Scheme 1. Reactions of enediynes **1** ( $R = H$ ), **2** ( $RR = (CH)_4$ ), and **3** ( $RR = (CH_2)_4$ ) with halides ( $X^-$ ).

Subsequently this reaction was extended to enediynes **2**<sup>4e</sup> and **3**.<sup>6</sup> Using this strategy, Ding and Hu et al synthesized complex products via cycloaromatization of acyclic enediynes under the action of bromide ions.<sup>13</sup> Also, Basak and co-workers achieved high regioselectivity in halide addition to 1,4-dehydrobenzene or 1,4-dehydropyridine diradicals derived from unsymmetrical enediynes.<sup>14</sup>

Beyond halide addition to 1,4-dehydrobenzene diradicals, alkylation would allow the synthesis more complex structures. Such structures were obtained previously but by more roundabout procedures. Curran, Liu, and Taniguchi et al carried out borylative radical cyclizations of enediyne **2** and NHC-boranes toward their further application in  $sp^2$ - $sp^2$  C-C bond-forming

reactions such as the Suzuki–Miyaura coupling reaction.<sup>15</sup> Basak and co-workers reported a one-pot protocol for  $sp^2$ - $sp^2$  C-C bond formation in unsymmetrical aza-substituted enediynes via a regioselective halogenation of 1,4-dehydrobenzene diradicals followed by Suzuki-Miyaura coupling with aryl boronic acids.<sup>16</sup> Chen and co-workers synthesized naphthalenyl triflates via regioselective annulation of benzodiyne promoted by triflic acid.<sup>17</sup> Using these naphthalenyl triflates the authors then synthesized  $sp^2$ - $sp^3$  C-C bonded compounds by Kumada coupling,  $sp^2$ - $sp^2$  C-C bonded compounds by Suzuki and Stille coupling, and  $sp^2$ - $sp$  C-C bonded compounds by Sonogashira coupling.

However, to the best of our knowledge there are no reports of  $sp^2$ - $sp^3$  C-C bond formation by direct alkylation of 1,4-dehydrobenzene diradicals derived from enediynes. Generally, alkylation is achieved by electrophilic attack by an activated carbon species, such as a carbocation, on an electron-rich aromatic ring. In contrast to this traditional methodology we here report a new method for nucleophilic alkylation of 1,4-dehydrobenzene diradicals derived from enediynes, with the formation of a new  $sp^2$ - $sp^3$  C-C bond. In this study carbanions prepared from active methylene compounds are used as carbon nucleophiles. This reaction of enolates of active methylene compounds (**a-f**, 50-fold excess) with dehydrobenzene diradicals of enediynes (**1-3**) generated at optimized temperatures is shown in Scheme 2. For conciseness all these carbanions are designated as enolates, even though that is a misnomer for the anion derived from malononitrile, as is the abbreviation of COZ as CN.



Scheme 2. Reaction of enolates of active methylene compounds (**a-f**, 50-fold excess) with dehydrobenzene diradicals of enediynes (**1-3**) generated at optimized temperatures in DMSO.

## Results

Among enediynes **1**, **2** and **3**, enediyne **2** is the most stable toward decomposition and easiest to handle at room temperature. Therefore initial investigations were performed with enediyne **2** to explore its reactivity towards carbon nucleophiles. When enediyne **2** was heated at 85°C in anhydrous DMSO with 50 equivalents of the sodium salt of malononitrile anion (**a**), the solution turned clear and after 72 h almost all enediyne was consumed, to furnish the C-C bonded 1,4-addition product 1,2,3,4-tetrahydroanthracen-9-ylmalononitrile (**5a**) in 55% yield (Scheme 2), along with other unidentified byproducts due to competing polymerization of the enediyne or diradical. The structure of adduct **5a** was thoroughly characterized by <sup>1</sup>H, <sup>13</sup>C, <sup>1</sup>H-<sup>1</sup>H COSY NMR, and mass spectrometry.

Similarly, nucleophilic alkylation of the diradical derived by cycloaromatization of enediyne **2** with enolates of ethyl cyanoacetate (**b**), diethyl malonate (**c**), acetylacetone (**d**), and ethyl benzoylacetate (**e**) produces the corresponding C-C bonded adducts **5b-e** in 35–57% yields (Scheme 2, Table 1). In these reactions >85% of unreacted active methylene compounds could be recovered after the reaction. An exception is the reaction of ethyl acetoacetate anion (**f**) with enediyne **2**, which produces only a trace amount of **5f**, detected by mass spectrometry but not isolated. Also, after the reaction only ~70% of unreacted ethyl acetoacetate was recovered.

**Table 1.** Reaction of enolates of active methylene compounds (**a-e**, 50-fold excess) with dehydrobenzene diradicals of enediynes (**1-3**) generated at optimized temperatures in DMSO: isolated products (yields in parentheses).

Temperature, time →	55°C, 12h	85°C, 72h	75°C, 24h
Enolate ↓, Enediyne →	<b>1</b>	<b>2</b>	<b>3</b>
<b>a</b>	<b>4a</b> (29)	<b>5a</b> (55)	<b>6a</b> (46)
<b>b</b>	<b>4b</b> (25)	<b>5b</b> (57)	<b>6b</b> (44)
<b>c</b>	<b>4c</b> (19)	<b>5c</b> (51)	<b>6c</b> (37)
<b>d</b>	<b>4d</b> (24)	<b>5d</b> (54)	<b>6d</b> (43)
<b>e</b>	<b>4e</b> (trace)	<b>5e</b> (35)	<b>6e</b> (22)

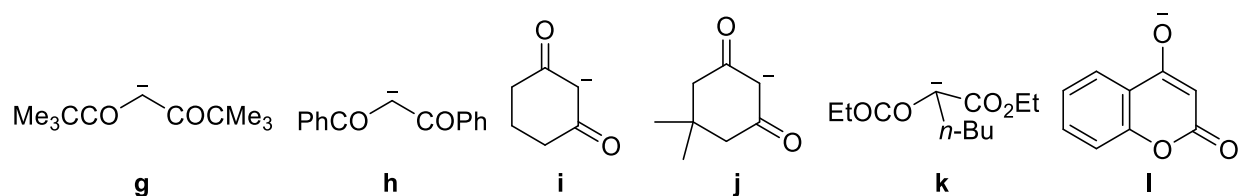
In order to find the optimum conditions for the reaction of enediynes with enolates, a series of reaction conditions was explored using enediyne **2** and an excess of enolates **a-f** to trap the diradical as soon as it forms (Table S1). Heating enediyne **2** with 100 equivalents of enolate **a** for

30 days at 75°C in DMSO produced only a very poor 2% yield of **5a**. However, on increasing the temperature to 85°C the reaction yield was increased to 57% after 3 days. At 85°C, on lowering the concentration of enolate **a** to 50 equivalents, the yield of **5a** decreases slightly to 55%. Therefore heating enediyne **2** with a 50-fold excess of enolate at 85°C in DMSO was considered as an optimum condition for the reaction. This same approach was applied to find the optimum conditions for the reactions of enediynes **1** and **3** with enolates **a-f**.

Table 1 also lists results for the alkylation of the diradicals derived from enediynes **1** and **3** with enolates of active methylene compounds **a-f**. Enediyne **1** required only 55°C for 12h and enediyne **3** required 75°C for 24h for production of their diradicals. The 1,4-dehydrobenzene diradical of enediyne **1** reacts with enolates of active methylene compounds **a-f** and forms the corresponding 1,4-addition products **4a-d** in 19–29% yield, except for **4e** and **4f**, which form in only trace amounts. The dehydrobenzene diradical from enediyne **3** reacts with enolates of active methylene compounds **a-f** and forms the corresponding C-C bonded 1,4-addition products **6a-e** in 22–46% yield, except for **6f**, which forms in only trace amount. In these reactions >85% of unreacted active methylene compounds could be recovered after the reaction, except for ethyl acetoacetate, which was recovered up to 70%.

According to <sup>1</sup>H NMR spectra, products **4a-c**, **5a-c**, and **6a-c** were isolated as their keto tautomer whereas products **4d**, **5d-e**, and **6d-e** were isolated as their enol tautomer (Scheme 2, Table 1). Since **d-f** preferentially form enolic products **4e-f**, **5f**, and **6f** are also assigned as enols, but they were not fully characterized.

Enolates of other active methylene compounds, as listed in Scheme 3, were also tested for their reactivity towards the 1,4-dehydrobenzenes from enediynes **1-3**, but no corresponding 1,4-adducts were observed, perhaps because of their steric bulk (**g-l**) or competing decomposition (**m-p**). Also, some of the anions (**h**, **j**, **l**) were not completely soluble under optimized conditions.





Scheme 3. Enolates (as Na<sup>+</sup> salts) unreactive toward enediynes **1-3** under optimized conditions.

Alkylation of enolates of active methylene compounds, especially of 1,3-dicarbonyl compounds, generally tends to afford *C*-alkylation products,<sup>18</sup> but *O*-alkylation products are also formed.<sup>19</sup> In contrast, reactions of enediyne **1-3** with enolates of active methylene compounds **a-f** selectively produce only the corresponding *C*-alkylated 1,4-addition products **4-6**, and no *O*-alkylated 1,4-addition products were detected.

## Discussion

These syntheses take advantage of nucleophilic addition to 1,4-dehydrobenzenes, a previously unexpected mode of reaction for such diradicals, which ordinarily react by radical pathways. The mechanism is considered to be the same as the nucleophilic addition of halides to the 1,4-dehydrobenzene diradical derived from enediyne **1**, as in Scheme 1.<sup>11</sup> However, these nucleophiles provide more highly functionalized products than do the previous halides.

Although the reactions of enediynes **1-3** with most halides can produce a > 75% yield of 1,4-adducts,<sup>4e,6,11</sup> and 100% with I<sup>-</sup>, the yields of 1,4-adducts with enolates **a-e** are slightly lower, only 19–55%, presumably because the enolates suffer a steric hindrance that does not impede iodide addition. Besides, yields generally decrease from **5a-e** to **6a-e** to **4a-e** (Table 1), although the variations are not substantial. Nor are the variations easy to rationalize, although they may be a consequence of the reversibility of the cycloaromatization of **2**, or of a favorable polarizability of the additional benzene ring in the alkylation of the 1,4-dehydrobenzene from **2**.

Enolates **a-e** are relatively stable under the reaction conditions, and > 85% of unreacted active methylene compounds were recovered after neutralizing workup. The observed low reactivity of the enolate of ethyl acetoacetate **f** toward enediynes **1-3** is because of the bulkiness of this enolate and also because it undergoes significant decomposition under the reaction conditions. As for the other unreactive enolates, **g-l** of Scheme 3 seem especially bulky and **m-p** are prone to decompose under the reaction conditions. Also, enolates **h, j**, and **l** are not completely soluble under the reaction conditions.



All compounds synthesized according to Scheme 2 are new except **4a** and **4e**. Nakano et al reported Cr and Co complexes of compound **4a**, but the compound itself was not fully characterized.<sup>20</sup> Liu and co-workers synthesized **4e** via ruthenium-catalyzed cycloaromatization of 1,2-diethynylcyclohexene with ethyl acetoacetate,<sup>21</sup> but this product was not isolated, owing to the rapid decomposition of enediyne **1** and to the bulkiness of enolate **e**. Liu and co-workers also tried to synthesize the corresponding dimethyl malonate derivative but obtained only a decarboxylated derivative.<sup>21</sup> In contrast, our method yields the anticipated *C*-alkylated product **4c** without any decarboxylation, although we used diethyl malonate anion instead of dimethyl malonate anion. Also we did not need any (expensive) metal catalyst. Hashmi and coworkers synthesized several hydroarylated derivatives of 1,2-bis(iodoethynyl)benzenes and 1,2-bis(iodoethynyl)cycloalkenes via Au-catalyzed cycloaromatization.<sup>22</sup> This method not only required a gold catalyst but also was restricted to terminal haloethynyl derivatives. Liu and co-workers synthesized 1-alkoxynaphthalenes via Ru-catalyzed regioselective alkoxylation of 1,2-diethynylbenzenes.<sup>21</sup> This reaction also worked well with 1,2-diethynylcycloalkenes. They also synthesized *N*-arylamino naphthalenes via Ru-catalyzed aminoarylation of 1,2-diethynylbenzenes, but this method was not regioselective and also produced *C*-arylated naphthalenes.<sup>21</sup>

We find that only the *C*-arylated products are formed in the reactions of enolates **a-f** with enediynes **1-3**. No *O*-arylated 1,4-addition products were formed. This exclusive *C*-selectivity is probably due to the fact that the diradical is a soft electrophile (owing to the polarizability of its paired electrons), which reacts at carbon, whereas a hard electrophile (with a localized electron deficiency) would react at oxygen.<sup>23</sup>

It must be acknowledged that it has not been possible to capture the aryl anion in Scheme 1 with an electrophile alternative to "HA" (presumably trace water in the solvent). Unfortunately, further functionalization of the diradical does not succeed in attaching a substituent para to the incoming nucleophile. This is a consequence of the observation that the aryl anion is formed as a "naked" anion, so poorly solvated that it reacts immediately with the surrounding solvent before any alternative electrophile can capture it.<sup>24</sup> A further drawback is the necessity for a large excess of enolate, but this is an inexpensive reagent that can be recovered if warranted.

In summary, the products shown in Scheme 2 can be synthesized by a simple procedure, in decent yield and purity, without interference from admixture of similar substances. According

to Table 1 a total of 14 different products can be obtained. Those products carry reactive functional groups that allow further conversion into a vast and diverse array of materials.

## Conclusions

We have demonstrated an alternative method for synthesis of alkylated aromatics via nucleophilic attack of enolates of active methylene compounds **a-f** on the 1,4-dehydrobenzene diradicals derived from enediynes **1-3**. The reaction produces a series of new C-C bonded aromatic alkylation products, including tetrahydronaphthalenes, tetrahydroanthracenes, and octahydroanthracenes. These highly functionalized products can then allow the construction of more complex chemical structures via addition, cyclization, or fusion in only a few additional steps. Benzo-fused enediyne **2** reacts most efficiently as compared to cyclohexeno-fused (**3**) or unsubstituted (**1**) enediynes, but all are productive. Despite the ambident reactivity of enolates of active methylene compounds this reaction provides solely the *C*-alkylation products, and no *O*-alkylation products were observed. The yields are not quantitative, but they are respectable for the preparation of such complex polyfunctional substances. Moreover, this methodology succeeds under relatively mild conditions.

## Experimental

### General Information

#### Materials

Common organic solvents and reagents were obtained from commercial suppliers and used as received. Sodium hydride (60% in mineral oil), diethyl malonate (99%), acetylacetone (99%), malononitrile (99%), and lithium hexamethyldisilazide (LiHMDS, 1M in THF) were obtained from Aldrich Chemical, Inc. and were used without further purification. Ethyl cyanoacetate (99%), and ethyl benzoylacetate (99%), were obtained from TCI Chemicals and were used without further purification. Ethyl acetoacetate (99%) was obtained from Acros Organics and was used without further purification. Chloroform-*d* (CDCl<sub>3</sub>, 99.9% D), acetonitrile-*d*<sub>3</sub> (CD<sub>3</sub>CN, 99.9% D) and dimethylsulfoxide-*d*<sub>6</sub> (DMSO-*d*<sub>6</sub>, 99.9% D) were obtained from Cambridge Isotope Laboratories, Inc. and were used without further purification.

#### Instrumentation

<sup>1</sup>H NMR spectra were obtained on JEOL ECA 500-MHz or Varian VX 500-MHz or Varian Mercury+ 400-MHz or Bruker AVA 300-MHz spectrometers. Tetramethylsilane (TMS, 0 ppm)

or residual solvent ( $\text{CHCl}_3/\text{CDCl}_3$ ,  $\text{DMSO-}d_5/\text{DMSO-}d_6$ ,  $\text{CHD}_2\text{CN}/\text{CH}_3\text{CN}$ ) was used as internal standard.  $^{13}\text{C}$  NMR spectra were obtained on a Varian VX 500-MHz FT-NMR spectrometer (125.8 MHz  $^{13}\text{C}$ ) and  $^1\text{H-}^1\text{H}$  COSY NMR spectra were obtained on a JEOL ECA500 FT-NMR spectrometer (500.2-MHz  $^1\text{H}$ ). Spectra were processed either using Bruker TopSpin 4.0, Academic Edition, or MestReNova v12.0 software. GC-EI-MS (electron ionization, EI) was obtained on an Agilent 7820A gas chromatograph coupled with a 5977B MSD detector operated in scan mode from 10 m/z to 400 m/z. HPLC-HR-ESI/APCI-MS (electrospray ionization, ESI, or atmospheric pressure chemical ionization source, APCI) was obtained on an Agilent 6230 Accurate-Mass TOFMS system using ESI/TOF-MS in a positive- or negative-ion mode.

## Synthesis and Characterization

### Synthesis of enediynes 1–3

Enediynes **1–3** were prepared according to their literature procedures. Their spectral data matched reported values.

#### Cyclodec-1,5-diyne-3-ene (**1**)<sup>4d,e</sup>

It was prepared from the reaction of 1,10-dibromodeca-2,8-diyne (5.0 g, 17.1 mmol) and 1M LiHMDS in THF (3 equiv, 51.4 mL). Pale yellow liquid (0.20 g, 9%, 0.5 M in pentane).  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{CN}$ ),  $\delta$  5.81 (s, 2H), 2.35 (m, 4H), 1.87 (m, 4H). GC-EI-MS 130.1, calculated for  $\text{C}_{10}\text{H}_{10}$   $[\text{M}]^+$ : 130.1.

#### Benzo[3,4]-cyclodec-1,5-diyne-3-ene (**2**)<sup>5</sup>

It was synthesized from 1,2-diethynylbenzene (0.5 g, 4.0 mmol) and 1,4-diiobutane (1.3 g, 4.0 mmol). White solid (0.33 g, 46%). Mp. 74–75°C (lit.<sup>7a</sup> 73.0–74.5°C).  $^1\text{H}$  NMR: (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.31 (m, 2H), 7.19 (m, 2H), 2.46 (m, 4H), 1.97 (m, 4H) ppm.  $^{13}\text{C}$  NMR (126 MHz)  $\text{CDCl}_3$ :  $\delta$  129.6, 128.2, 127.4, 100.1, 82.4, 28.7, 21.6 ppm. HPLC-APCI-MS 181.1012, calculated for  $\text{C}_{14}\text{H}_{13}$   $[\text{M}]^+$ : 181.1012.

#### Cyclohexeno[3,4]-cyclodec-1,5-diyne-3-ene (**3**)<sup>6</sup>

It was synthesized from 1,2-diethynylcyclohex-1-ene (0.5 g, 3.8 mmol) and 1,4-diiobutane (1.2 g, 3.9 mmol). White solid (0.32 g, 45%). Mp. 105–106°C (lit.<sup>6</sup> 105-106°C).  $^1\text{H}$  NMR: (300 MHz,  $\text{CDCl}_3$ )  $\delta$  2.36 (m, 4H), 2.15 (m, 4H), 1.90 (m, 4H), 1.61 (m, 4H) ppm.  $^{13}\text{C}$  NMR (126 MHz)

CDCl<sub>3</sub>:  $\delta$  129.6, 98.6, 85.4, 29.2, 28.1, 21.8, 21.6 ppm. HPLC-APCI-MS 185.1327, calculated for C<sub>14</sub>H<sub>17</sub> [M+H]<sup>+</sup>: 185.1325.

### Synthesis of active methylene enolates a–f

Active methylene enolates as their sodium salts were prepared by treating them with sodium hydride according to the reported procedure.<sup>25</sup> Sodium hydride (fresh!) in oil (60%) was washed with several portions of dry hexanes and then mixed with an equimolar amount of CH-acids in hexanes solvent under a nitrogen atmosphere. After 2h the precipitated salt was filtered off and washed with hexanes, then dried under vacuum at room temperature for 2h.

Carbanions a–f were prepared according to the literature. Their spectral data matched reported values.

#### Sodium dicyanomethanide (a)<sup>26</sup>

It was synthesized from malononitrile (0.5 g, 7.6 mmol) and NaH (7.6 mmol, 1 equiv) as a white solid (0.65 g, 82%). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  1.13 (s, 1H) ppm; <sup>13</sup>C NMR (126 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  130.4, -1.7 ppm.

#### Sodium 1-cyano-2-ethoxy-2-oxoethan-1-ide (b)<sup>27</sup>

It was synthesized from ethyl cyanoacetate (0.5 g, 4.6 mmol) and NaH (4.6 mmol, 1 equiv) as a white solid (0.45 g, 67%). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  3.72 (m, 2H), 2.33 (s, 1H), 1.02 (m, 3H) ppm; <sup>13</sup>C NMR (126 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  164.2, 119.3, 58.8, 27.4, 15.4 ppm.

#### Sodium 1,3-diethoxy-1,3-dioxopropan-2-ide (c)<sup>28</sup>

It was synthesized from diethyl malonate (0.5 g, 3.1 mmol) and NaH (3.1 mmol, 1 equiv) as a white solid (0.47 g, 76%). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  3.80 (q, *J* = 7.0 Hz, 4H), 3.59 (s, 1H), 1.06 (t, *J* = 7.1 Hz, 6H) ppm; <sup>13</sup>C NMR (126 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  167.6, 59.4, 46.8, 14.6 ppm.

#### Sodium 2,4-dioxopentan-3-ide (d)<sup>26b,29</sup>

It was synthesized from acetylacetone (0.5 g, 5.0 mmol) and NaH (5.0 mmol, 1 equiv) as a white solid (0.54 g, 78%). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  4.68 (m, 1H), 1.79 (m, 6H) ppm; <sup>13</sup>C NMR (126 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  185.2, 174.5, 29.2 ppm.

#### Sodium 1-ethoxy-1,3-dioxo-3-phenylpropan-2-ide (e)<sup>26b,30</sup>

It was synthesized from ethyl benzoylacetate (0.5 g, 2.6 mmol) and NaH (2.6 mmol, 1 equiv) as a white solid (0.51 g, 85%). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  7.74–7.60 (m, 2H), 7.35–

7.15 (m, 3H), 4.92 (s, 1H), 3.87 (q,  $J = 7.1$  Hz, 2H), 1.12 (t,  $J = 7.1$  Hz, 3H) ppm;  $^{13}\text{C}$  NMR (126 MHz, DMSO- $d_6$ )  $\delta$  179.4, 168.7, 144.8, 127.9, 127.4, 126.1, 77.7, 55.6, 15.2 ppm.

Sodium 1-ethoxy-1,3-dioxobutan-2-ide (**f**)<sup>28</sup>

It was synthesized from ethyl acetoacetate (0.5 g, 3.8 mmol) and NaH (3.8 mmol, 1 equiv) as a white solid (0.45 g, 70%).  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ )  $\delta$  4.25 (s, 1H), 3.81 (q,  $J = 7.1$  Hz, 2H), 1.59 (s, 3H), 1.07 (t,  $J = 7.0$  Hz, 3H) ppm;  $^{13}\text{C}$  NMR (126 MHz, DMSO- $d_6$ )  $\delta$  184.5, 167.9, 79.8, 55.3, 29.1, 15.2 ppm.

### Synthesis of 1,4-addition products 4-6

General procedure for the reaction of enediynes **1-3** with active methylene enolates **a-f**

Enediyne (**1**, **2** or **3**, 0.10 mmol, 5mM) was added under  $\text{N}_2$  to a solution of enolate (**a-f**, 5.0 mmol, 50 equiv., 250 mM) in anhydrous dimethyl sulfoxide (20 mL) in a 50-mL round-bottom flask and stirred at 55°C for 12 h for **1**, 85°C for 72 h for **2**, and 75°C for 24 h for **3**. The mixture was then neutralized with 0.1N HCl, followed by extraction with diethyl ether (3 x 5 mL). The combined organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated in vacuo, and the resulting crude products were purified by flash column chromatography (silica gel, 0-10% EtOAc in hexanes). About 70–90% of unreacted active methylene compounds were also recovered.

5,6,7,8-Tetrahydronaphthalen-1-ylmalononitrile (**4a**)<sup>20</sup>

It was synthesized from enediyne **1** (13.0 mg, 0.10 mmol, 200  $\mu\text{L}$ , 0.5 M in pentane) and carbanion **a** (445.3 mg, 5.00 mmol) and was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to yield **4a** (5.7 mg, 29%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.39 (d,  $J = 8.8$  Hz, 1H), 7.25–7.20 (m, 2H), 5.03 (s, 1H), 2.83 (t,  $J = 6.3$  Hz, 2H), 2.77 (t,  $J = 6.4$  Hz, 2H), 1.96–1.88 (m, 2H), 1.85–1.76 (m, 2H) ppm.  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  139.8, 134.9, 132.0, 126.9, 125.8, 124.7, 111.9, 29.9, 27.2, 26.2, 22.9, 22.3 ppm; GC-EI-MS 196.1, calculated for  $\text{C}_{13}\text{H}_{12}\text{N}_2$   $[\text{M}]^+$ : 196.1.

Ethyl  $\alpha$ -cyano-5,6,7,8-tetrahydronaphthalen-1-ylacetate (**4b**)

It was synthesized from enediyne **1** (13.0 mg, 0.10 mmol, 200  $\mu\text{L}$ , 0.5 M in pentane) and carbanion **b** (680.6 mg, 5.00 mmol) and was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to yield **4b** (6.1 mg, 25%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.29 (d,  $J = 7.3$  Hz, 1H), 7.17 (t,  $J = 7.6$  Hz, 1H), 7.12 (d,  $J = 7.6$  Hz, 1H), 4.89 (s, 1H), 4.30–4.21 (m, 2H), 2.86–2.76 (m, 3H), 2.66 (dt,  $J = 16.4, 6.3$  Hz, 1H), 1.91–1.82 (m, 2H), 1.82–1.74 (m, 2H), 1.29 (t,  $J = 7.1$  Hz, 3H) ppm.  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  165.4, 138.9, 135.2, 130.7, 129.0, 126.4, 126.2,

116.3, 63.4, 40.5, 30.1, 26.4, 23.1, 22.5, 14.1 ppm; GC-EI-MS 243.1, calculated for C<sub>15</sub>H<sub>17</sub>NO<sub>2</sub> [M]<sup>+</sup>: 243.1.

#### Diethyl 5,6,7,8-tetrahydronaphthalen-1-ylmalonate (**4c**)

It was synthesized from enediyne **1** (13.0 mg, 0.10 mmol, 200 μL, 0.5 M in pentane) and carbanion **c** (915.9 mg, 5.00 mmol) and was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to yield **4c** (5.5 mg, 19%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.19 (d, *J* = 7.7 Hz, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 7.4 Hz, 1H), 4.88 (s, 1H), 4.28–4.16 (m, 4H), 2.79 (t, *J* = 6.2 Hz, 2H), 2.68 (t, *J* = 6.3 Hz, 2H), 1.86–1.81 (m, 2H), 1.78–1.73 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 6H) ppm; <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 168.8, 138.0, 135.4, 131.8, 129.6, 126.3, 125.7, 61.9, 53.8, 30.3, 26.6, 23.4, 22.6, 14.2. ; GC-EI-MS 290.2, calculated for C<sub>17</sub>H<sub>22</sub>O<sub>4</sub> [M]<sup>+</sup>: 290.2.

#### 4-Hydroxy-3-(5,6,7,8-tetrahydronaphthalen-1-yl)pent-3-en-2-one (**4d**)

It was synthesized from enediyne **1** (13.0 mg, 0.10 mmol, 200 μL, 0.5 M in pentane) and carbanion **d** (615.6 mg, 5.00 mmol) and was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to yield **4d** (5.5 mg, 24%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 16.60 (s, 1H), 7.53 (d, *J* = 8.6 Hz, 1H), 7.35 (t, *J* = 2.1 Hz, 1H), 7.12 (dd, *J* = 8.6, 2.5 Hz, 1H), 2.88–2.77 (m, 3H), 2.49–2.44 (m, 1H), 1.79–1.76 (m, 4H), 1.33 (s, 3H), 1.28 (s, 3H) ppm. <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 190.9, 147.2, 138.2, 136.9, 128.8, 125.9, 124.1, 113.6, 31.6, 30.3, 29.6, 27.6, 23.7, 23.1 ppm; GC-EI-MS 230.1, calculated for C<sub>15</sub>H<sub>18</sub>O<sub>2</sub> [M]<sup>+</sup>: 230.1.

#### 1,2,3,4-Tetrahydroanthracen-9-ylmalononitrile (**5a**)

It was synthesized from enediyne **2** (18.0 mg, 0.10 mmol) and carbanion **a** (445.3 mg, 5.00 mmol) and purified by flash column chromatography (silica gel, 10% EtOAc in hexanes), to yield **5a** (13.6 mg, 55%) Mp. 189-190°C. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) 8.07 (d, *J* = 8.6 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.73 (s, 1H), 7.63 (t, *J* = 7.7 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 5.83 (s, 1H), 3.04 (dt, *J* = 27.7, 6.5 Hz, 4H), 1.93 (dp, *J* = 61.8, 6.3 Hz, 4H) ppm; <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 136.6, 136.1, 132.7, 131.0, 128.8, 128.8, 127.4, 126.3, 122.0, 119.3, 112.0, 30.5, 28.0, 23.2, 22.3, 21.1 ppm; HR-ESI-MS 245.1083, calculated for C<sub>17</sub>H<sub>13</sub>N<sub>2</sub><sup>+</sup> [M-H]<sup>+</sup>: 245.1084.

#### Ethyl α-cyano-1,2,3,4-tetrahydroanthracen-9-ylacetate (**5b**)

It was synthesized from enediyne **2** (18.0 mg, 0.10 mmol) and carbanion **b** (680.6 mg, 5.00 mmol) and was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to yield **5b** (16.7 mg, 57%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.99 (d, *J* = 8.5 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.64 (s, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 1H), 5.61 (s, 1H), 4.34–4.20

(m, 2H), 3.10–2.92 (m, 4H), 1.98–1.83 (m, 4H), 1.24 (t,  $J = 7.1$  Hz, 3H) ppm;  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  166.0, 136.4, 135.9, 132.5, 129.7, 129.6, 128.4, 126.5, 125.6, 123.9, 122.6, 116.0, 63.4, 37.1, 30.7, 27.9, 23.4, 22.4, 14.1 ppm; HR-ESI-MS 294.1486, calculated for  $\text{C}_{19}\text{H}_{20}\text{NO}_2^+$   $[\text{M}+\text{H}]^+$ : 294.1489.

#### Diethyl 1,2,3,4-tetrahydroanthracen-9-ylmalonate (**5c**)

It was synthesized from enediyne **2** (18.0 mg, 0.10 mmol) and carbanion **c** (915.9 mg, 5.00 mmol) and was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to yield **5c** (17.4 mg, 51%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  7.99 (d,  $J = 8.7$  Hz, 1H), 7.71 (d,  $J = 8.8$  Hz, 1H), 7.57 (s, 1H), 7.43–7.31 (m, 2H), 5.47 (s, 1H), 4.21 (q,  $J = 6.9$  Hz, 4H), 2.98 (dt,  $J = 9.2$ , 4.5 Hz, 4H), 2.01–1.81 (m, 4H), 1.30–1.20 (m, 6H) ppm;  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  169.1, 136.5, 136.3, 132.6, 131.1, 128.5, 127.9, 127.3, 125.4, 124.9, 124.6, 61.9, 52.2, 30.8, 28.0, 23.5, 22.5, 14.2 ppm; HR-ESI-MS 341.1745, calculated for  $\text{C}_{21}\text{H}_{25}\text{O}_4^+$   $[\text{M}+\text{H}]^+$ : 341.1747.

#### 4-Hydroxy-3-(1,2,3,4-tetrahydroanthracen-9-yl)pent-3-en-2-one (**5d**)

It was synthesized from enediyne **2** (18.0 mg, 0.10 mmol) and carbanion **d** (615.6 mg, 5.00 mmol) and was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to yield **5d** (15.1 mg, 54%) Mp. 148–149°C.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  16.82 (s, 1H), 7.75 (d,  $J = 7.2$  Hz, 1H), 7.65 (d,  $J = 7.6$  Hz, 1H), 7.60 (s, 1H), 7.39 (p,  $J = 6.7$  Hz, 2H), 3.01 (d,  $J = 6.0$  Hz, 2H), 2.66 (q,  $J = 5.9$ , 4.5 Hz, 2H), 1.84 (p,  $J = 3.4$  Hz, 4H), 1.67 (s, 6H) ppm;  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  191.6, 136.6, 136.3, 132.4, 131.9, 131.6, 127.7, 127.6, 125.9, 125.4, 124.5, 110.2, 30.5, 28.4, 23.5, 23.5, 23.0 ppm; HR-ESI-MS 281.1536, calculated for  $\text{C}_{19}\text{H}_{21}\text{O}_2^+$   $[\text{M}+\text{H}]^+$ : 281.1537.

#### Ethyl $\beta$ -hydroxy- $\beta$ -phenyl- $\alpha$ -(1,2,3,4-tetrahydroanthracen-9-yl)acrylate (**5e**)

It was synthesized from enediyne **2** (18.0 mg, 0.10 mmol) and carbanion **e** (1.08 g, 5.00 mmol) and was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to yield **5e** (13.0 mg, 35%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  13.92 (s, 1H), 7.73 (dd,  $J = 17.4$ , 8.7 Hz, 2H), 7.52 (s, 1H), 7.33 (p,  $J = 6.6$  Hz, 2H), 7.11 (d,  $J = 7.4$  Hz, 3H), 6.98 (t,  $J = 7.6$  Hz, 2H), 4.14 (q,  $J = 7.0$  Hz, 2H), 2.90 (q,  $J = 6.2$ , 5.5 Hz, 2H), 2.55 (ddt,  $J = 59.8$ , 16.9, 6.4 Hz, 2H), 1.69 (dddd,  $J = 30.3$ , 12.0, 8.8, 4.7 Hz, 4H), 1.06 (t,  $J = 7.1$  Hz, 3H) ppm;  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  174.0, 170.8, 136.3, 134.8, 133.0, 132.7, 132.0, 130.1, 129.9, 129.7, 128.5, 127.9, 127.7, 127.5, 127.2, 125.3, 125.2, 124.9, 99.8, 61.0, 30.4, 28.1, 23.2, 23.0, 14.3 ppm; HR-ESI-MS 373.1798, calculated for  $\text{C}_{25}\text{H}_{25}\text{O}_3^+$   $[\text{M}+\text{H}]^+$ : 373.1799.

#### 1,2,3,4,5,6,7,8-Octahydroanthracen-9-ylmalononitrile (**6a**)

It was synthesized from enediyne **3** (18.4 mg, 0.10 mmol) and carbanion **a** (445.3 mg, 5.00 mmol) and was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to yield **6a** (11.5 mg, 46%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.98 (s, 1H), 5.69 (s, 1H), 2.89 (t, *J* = 5.9 Hz, 4H), 2.69 (t, *J* = 5.9 Hz, 4H), 1.89–1.69 (m, 8H) ppm. <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 138.6, 135.3, 134.2, 134.2, 112.8, 29.9, 29.1, 28.1, 22.8, 22.7 ppm; HR-ESI-MS 249.1397, calculated for C<sub>17</sub>H<sub>17</sub>N<sub>2</sub> [M-H]<sup>+</sup>: 249.1397.

#### Ethyl α-cyano-1,2,3,4,5,6,7,8-octahydroanthracen-9-ylacetate (**6b**)

It was synthesized from enediyne **3** (18.4 mg, 0.10 mmol) and carbanion **b** (680.6 mg, 5.00 mmol) and was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to yield **6b** (13.1 mg, 44%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.88 (s, 1H), 5.21 (s, 1H), 4.33–4.24 (m, 2H), 2.89–2.52 (m, 8H), 1.90–1.69 (m, 8H), 1.31 (t, *J* = 7.1 Hz, 3H) ppm. <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 166.0, 135.7, 133.5, 131.7, 127.8, 115.8, 63.2, 37.0, 29.8, 27.1, 23.5, 22.6, 14.2 ppm; HR-ESI-MS 298.1803, calculated for C<sub>19</sub>H<sub>24</sub>NO<sub>2</sub> [M+H]<sup>+</sup>: 298.1802.

#### Diethyl 1,2,3,4,5,6,7,8-octahydroanthracen-9-ylmalonate (**6c**)

It was synthesized from enediyne **3** (18.4 mg, 0.10 mmol) and carbanion **c** (915.9 mg, 5.00 mmol) and was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to yield **6c** (12.8 mg, 37%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.86 (s, 1H), 5.04 (s, 1H), 4.23–4.17 (m, 4H), 2.63–2.54 (m, 4H), 2.42–2.34 (m, 4H), 1.93–1.80 (m, 8H), 1.21 (t, *J* = 7.2 Hz, 6H) ppm; <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 168.8, 136.5, 133.3, 132.1, 127.8, 61.9, 52.2, 28.1, 26.7, 24.2, 23.5, 14.2 ppm; HR-ESI-MS 345.2061, calculated for C<sub>21</sub>H<sub>29</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 345.2061.

#### 4-Hydroxy-3-(1,2,3,4,5,6,7,8-octahydroanthracen-9-yl)pent-3-en-2-one (**6d**)

It was synthesized from enediyne **3** (18.4 mg, 0.10 mmol) and carbanion **d** (615.6 mg, 5.00 mmol) and was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to yield **6d** (12.2 mg, 43%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 16.59 (s, 1H), 6.84 (s, 1H), 2.73 (m, 4H), 2.37 (m, 4H), 1.74 (m, 8H), 1.57 (m, 6H) ppm. <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 190.7, 135.0, 134.9, 134.0, 129.9, 111.4, 29.9, 29.8, 27.8, 23.8, 23.3, 23.2 ppm; HR-ESI-MS 285.1850, calculated for C<sub>19</sub>H<sub>25</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 285.1850.

#### Ethyl β-hydroxy-β-phenyl-α-(1,2,3,4,5,6,7,8-octahydroanthracen-9-yl)acrylate (**6e**)

It was synthesized from enediyne **3** (18.4 mg, 0.10 mmol) and carbanion **e** (1.08 g, 5.00 mmol) and was purified by flash column chromatography (silica gel, 10% EtOAc in hexanes) to



yield **6e** (8.3 mg, 22%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 13.77 (s, 1H), 7.24–7.10 (m, 5H), 6.79 (s, 1H), 4.25 (qd, *J* = 7.1, 1.1 Hz, 2H), 2.68 (dt, *J* = 15.0, 5.0 Hz, 4H), 2.51–2.23 (m, 4H), 1.76 (qd, *J* = 3.9, 1.7 Hz, 8H), 1.21 (td, *J* = 7.1, 1.0 Hz, 3H) ppm. <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 173.9, 168.8, 134.9, 134.5, 134.3, 133.2, 129.9, 129.8, 128.0, 127.8, 107.7, 100.9, 60.9, 29.7, 27.5, 23.6, 23.2, 14.6 ppm; HR-ESI-MS 377.2112, calculated for C<sub>25</sub>H<sub>29</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 377.2112.

## Associated Content

Supporting Information

Optimization of reaction conditions, <sup>1</sup>H and <sup>13</sup>C NMR spectra of **4** – **6**, and <sup>1</sup>H–<sup>1</sup>H COSY NMR spectra of **5a**.

## Acknowledgment

This research was supported by grants CHE124B, CHEFFPE, CHE63CP and CHEGDCP to C.L.P from the UCSD Department of Chemistry & Biochemistry. We sincerely thank Dr. Anthony Mrse of the NMR Facility and Dr. Yongxuan Su of the Molecular Mass Spectrometry Facility in the Department for facilitating the use of NMR and mass spectrometry.

## Author Information

### Corresponding Author

**Charles L. Perrin**, Department of Chemistry & Biochemistry, University of California San Diego, La Jolla, CA 92093-0358 USA. email cperrin@ucsd.edu.

### Author

**Annadka Shrinidhi**, Department of Chemistry & Biochemistry, University of California San Diego, La Jolla, CA 92093-0358; current address: Department of Medicinal Chemistry and Molecular Pharmacology, College of Pharmacy, Purdue University, West Lafayette, Indiana 47907, USA. email shrinidhiannadka@gmail.com.

## References

- (1) (a) Konishi, M.; Ohkuma, H.; Saitoh, K.; Kawaguchi, H.; Golik, J.; Dubay, G.; Groenewold, G.; Krishnan, B.; Doyle, T. W. Esperamicins, a Novel Class of Potent Antitumor Antibiotics. I. Physico-Chemical Data and Partial Structure. *J. Antibiot.* **1985**, *38*, 1605-1609. (b) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. Calichemicins, a Novel Family of Antitumor Antibiotics. 1. Chemistry

- and Partial Structure of Calicheamicin  $\gamma_1^I$ . *J. Am. Chem. Soc.* **1987**, *109*, 3464-3466. (c) Smith, A. L.; Nicolaou, K. C. The Eneidyne Antibiotics. *J. Med. Chem.* **1996**, *39*, 2103-2117. (d) Shen, B.; Liu, W.; Nonaka, K. Eneidyne natural products: biosynthesis and prospect towards engineering novel antitumor agents. *Curr. Med. Chem.* **2003**, *10*, 2317-2325. (e) Gredičak, M.; Jerić, I. Eneidyne Compounds - New Promises in Anticancer Therapy. *Acta Pharm.* **2007**, *57*, 133-150. (f) Nicolaou, K. C.; Das, D.; Lu, Y.; Rout, S.; Pitsinos, E. N.; Lyssikatos, J.; Schammel, A.; Sandoval, J.; Hammond, M.; Aujay, M.; Gavrilyuk, J. Total Synthesis and Biological Evaluation of Tiancimycins A and B, Yangpumicin A, and Related Anthraquinone-Fused Eneidyne Antitumor Antibiotics. *J. Am. Chem. Soc.* **2020**, *142*, 2549-2561. (g) Igarashi, M.; Sawa, R.; Umekita, M.; Hatano, M.; Arisaka, R.; Hayashi, C.; Ishizaki, Y.; Suzuki, M.; Kato, C. Sealutomicins, New Eneidyne Antibiotics from the Deep-sea Actinomycete *Nonomuraea* sp. MM565M-173N2. *J. Antibiot.* **2021**, *74*, 291-299.
- (2) (a) Jones, R. R.; Bergman, R. G. *p*-Benzyne. Generation as an Intermediate in a Thermal Isomerization Reaction and Trapping Evidence for the 1,4-Benzenediyl Structure. *J. Am. Chem. Soc.* **1972**, *94*, 660-661. (b) Sherer, E. C.; Kirschner, K. N.; Pickard, F. C.; Rein, C.; Feldgus, S.; Shields, G. C. Efficient and Accurate Characterization of the Bergman Cyclization for Several Eneidyne Including an Expanded Substructure of Esperamicin A<sub>1</sub>. *J. Phys. Chem. B* **2008**, *112*, 16917-16934.
- (3) (a) Sugiura, Y.; Shiraki, T.; Konishi, M.; Oki, T. DNA Intercalation and Cleavage of an Antitumor Antibiotic Dynemicin that Contains Anthracycline and Eneidyne Cores. *Proc. Natl. Acad. Sci.* **1990**, *87*, 3831. (b) Povirk, L. F. DNA Damage and Mutagenesis by Radiomimetic DNA-Cleaving Agents: Bleomycin, Neocarzinostatin and other Eneidyne. *Mutat. Res. - Fundam. Mol. Mech. Mutagen.* **1996**, *355*, 71-89. (c) Kraka, E.; Cremer, D. Computer Design of Anticancer Drugs. A New Eneidyne Warhead. *J. Am. Chem. Soc.* **2000**, *122*, 8245-8264. (d) Kennedy, D. R.; Ju, J.; Shen, B.; Beerman, T. A. Designer Eneidyne Generate DNA Breaks, Interstrand Cross-Links, or Both, with Concomitant Changes in the Regulation of DNA Damage Responses. *Proc. Natl. Acad. Sci.* **2007**, *104*, 17632.
- (4) (a) Nicolaou, K. C.; Ogawa, Y.; Zuccarello, G.; Schweiger, E. J.; Kumazawa, T. Cyclic Conjugated Eneidyne Related to Calicheamicins and Esperamicins: Calculations,

- Synthesis, and Properties. *J. Am. Chem. Soc.* **1988**, *110*, 4866-4868. (b) Nicolaou, K. C.; Smith, A. L. Molecular Design, Chemical Synthesis, and Biological Action of Eneidyne. *Acc. Chem. Res.* **1992**, *25*, 497-503. (c) Bunnage, M. E.; Nicolaou, K. C. Eneidyne Generation by a Retro-Diels–Alder Reaction. *Angew. Chem., Int. Ed.* **1996**, *35*, 1110-1112. (d) Jones, G. B.; Wright, J. M.; Plourde, G. W.; Hynd, G.; Huber, R. S.; Mathews, J. E. A Direct and Stereocontrolled Route to Conjugated Eneidyne. *J. Am. Chem. Soc.* **2000**, *122*, 1937-1944. (e) Reyes-Rodríguez, G. J. *Nucleophilic Additions to a para-Benzyne Derived from an Eneidyne : Exploring the Non-Radical Reactivity of a Diradical*. PhD Thesis, University of California: San Diego, 2013.
- (5) Semmelhack, M. F.; Neu, T.; Foubelo, F. Arene 1,4-Diradical Formation from *o*-Dialkynylarenes. *J. Org. Chem.* **1994**, *59*, 5038-5047.
- (6) Shrinidhi, A.; Perrin, C. L. Cyclohexeno[3,4]cyclodec-1,5-diyne-3-ene: A Convenient Eneidyne. *Org. Lett.* **2021**, *23*, 6911-6915.
- (7) (a) Darby, N.; Kim, C. U.; Salaün, J. A.; Shelton, K. W.; Takada, S.; Masamune, S. Concerning the 1,5-Didehydro[10]annulene System. *J. Chem. Soc. D* **1971**, 1516-1517. (b) Snyder, J. P. Monocyclic Eneidyne Collapse to 1,4-diyl Biradicals: a Pathway Under Strain Control. *J. Am. Chem. Soc.* **1990**, *112*, 5367-5369. (c) Magnus, P.; Fortt, S.; Pitterna, T.; Snyder, J. P. Synthetic and Mechanistic Studies on Esperamicin A<sub>1</sub> and Calichemicin  $\gamma_1$ . Molecular Strain rather than  $\pi$ -Bond Proximity Determines the Cycloaromatization Rates of Bicyclo[7.3.1]eneidyne. *J. Am. Chem. Soc.* **1990**, *112*, 4986-4987. (d) Nicolaou, K. C.; Zuccarello, G.; Riemer, C.; Estevez, V. A.; Dai, W. M. Design, Synthesis, and Study of Simple Monocyclic Conjugated Eneidyne. The 10-Membered Ring Eneidyne Moiety of the Eneidyne Anticancer Antibiotics. *J. Am. Chem. Soc.* **1992**, *114*, 7360-7371. (e) Schreiner, P. R. Cyclic Eneidyne: Relationship between Ring Size, Alkyne Carbon Distance, and Cyclization Barrier. *Chem. Commun.* **1998**, 483-484.
- (8) (a) Semmelhack, M. F.; Neu, T.; Foubelo, F. Arene 1,4-Diradical Formation from *o*-Dialkynylarenes. *Tetrahedron Lett.* **1992**, *33*, 3277-3280. (b) Nicolaou, K. C.; Dai, W. M.; Hong, Y. P.; Baldrige, K. K.; Siegel, J. S.; Tsay, S. C. Molecular Design, Chemical Synthesis, Kinetic Studies, Calculations, and Biological Studies of Novel Eneidyne Equipped with Triggering, Detection, and Deactivating Devices. Model Dynemicin A

- Epoxide and cis-Diol Systems. *J. Am. Chem. Soc.* **1993**, *115*, 7944-7953. (c) Schmittel, M.; Kiau, S. Polar Effects in the Transition State of the Bergman Cyclization. *Chem. Lett.* **1995**, *24*, 953-954. (d) Jones, G. B.; Plourde, G. W. Electronic Control of the Bergman Cycloaromatization: Synthesis and Chemistry of Chloroenediynes. *Org. Lett.* **2000**, *2*, 1757-1759. (e) Jones, G. B.; Warner, P. M. Electronic Control of the Bergman Cyclization: The Remarkable Role of Vinyl Substitution. *J. Am. Chem. Soc.* **2001**, *123*, 2134-2145. (f) Jones, G. B.; Wright, J. M.; Hynd, G.; Wyatt, J. K.; Warner, P. M.; Huber, R. S.; Li, A.; Kilgore, M. W.; Sticca, R. P.; Pollenz, R. S. Oxa-Enediynes: Probing the Electronic and Stereoelectronic Contributions to the Bergman Cycloaromatization. *J. Org. Chem.* **2002**, *67*, 5727-5732. (g) Peterson, P. W.; Shevchenko, N.; Breiner, B.; Manoharan, M.; Lufti, F.; Delaune, J.; Kingsley, M.; Kovnir, K.; Alabugin, I. V. Orbital Crossings Activated through Electron Injection: Opening Communication between Orthogonal Orbitals in Anionic C1–C5 Cyclizations of Enediynes. *J. Am. Chem. Soc.* **2016**, *138*, 15617-15628. (h) Hu, H.; Zhang, B.; Luxon, A.; Scott, T.; Wang, B.; Parish, C. A. An Extended Multireference Study of the Singlet and Triplet States of the 9,10-didehydroanthracene Diradical. *J. Phys. Chem. A* **2018**, *122*, 3688-3696.
- (9) (a) König, B.; Hollnagel, H.; Ahrens, B.; Jones, P. G. Activation of Macrocyclic Biaryl-Enediynes by Metal Ion Coordination. *Angew. Chem., Int. Ed.* **1995**, *34*, 2538-2540. (b) Coalter, N. L.; Concolino, T. E.; Streib, W. E.; Hughes, C. G.; Rheingold, A. L.; Zaleski, J. M. Structure and Thermal Reactivity of a Novel Pd(0) Metalloenediyne. *J. Am. Chem. Soc.* **2000**, *122*, 3112-3117. (c) O'Connor, J. M.; Friese, S. J.; Tichenor, M. Ruthenium-Mediated Cycloaromatization of Acyclic Enediynes and Dienynes at Ambient Temperature. *J. Am. Chem. Soc.* **2002**, *124*, 3506-3507. (d) Basak, A.; Mandal, S.; Bag, S. S. Chelation-Controlled Bergman Cyclization: Synthesis and Reactivity of Enediynyl Ligands. *Chem. Rev.* **2003**, *103*, 4077-4094. (e) O'Connor, J. M.; Friese, S. J.; Rodgers, B. L. A Transition-Metal-Catalyzed Enediyne Cycloaromatization. *J. Am. Chem. Soc.* **2005**, *127*, 16342-16343. (f) Byers, P. M.; Rashid, J. I.; Mohamed, R. K.; Alabugin, I. V. Polyaromatic Ribbon/Benzofuran Fusion via Consecutive Endo Cyclizations of Enediynes. *Org. Lett.* **2012**, *14*, 6032-6035.
- (10) Semmelhack, M. F.; Sarpong, R. Kinetic Analysis of a Reactive Model Enediyne. *J. Phys. Org. Chem.* **2004**, *17*, 807-813.

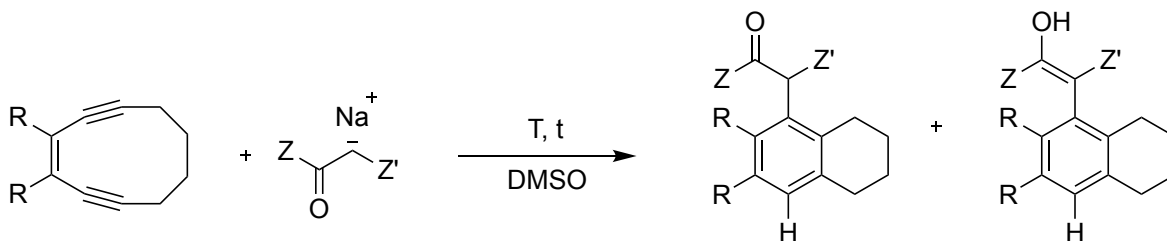
- (11) Perrin, C. L.; Rodgers, B. L.; O'Connor, J. M. Nucleophilic Addition to a *p*-Benzyne Derived from an Eneidyne: A New Mechanism for Halide Incorporation into Biomolecules. *J. Am. Chem. Soc.* **2007**, *129*, 4795-4799.
- (12) Perrin, C. L.; Reyes-Rodríguez, G. J. Reactivity of Nucleophiles Toward a *p*-Benzyne Derived from an Eneidyne. *J. Phys. Org. Chem.* **2012**, *26*, 206-210.
- (13) Chen, S.; Huang, S.; Wang, C.; Ding, Y.; Hu, A. Cycloaromatization of Eneidyne Compounds under the Action of Bromide Ions: Diradical/Zwitterionic/Anionic Pathways. *Asian J. Org. Chem.* **2017**, *6*, 1099-1103.
- (14) (a) Das, E.; Basak, S.; Anoop, A.; Basak, A. Experiment and Computational Study on the Regioselectivity of Nucleophilic Addition to Unsymmetrical *p*-Benzynes Derived from Bergman Cyclization of Eneidyne. *J. Org. Chem.* **2018**, *83*, 7730-7740. (b) Das, E.; Basak, S.; Anoop, A.; Chand, S.; Basak, A. How to Achieve High Regioselectivity in Barrier-less Nucleophilic Addition to *p*-Benzynes Generated via Bergman Cyclization of Unsymmetrical Cyclic Azaeneidyne? *J. Org. Chem.* **2019**, *84*, 2911-2921.
- (15) (a) Watanabe, T.; Geib, S. J.; Curran, D. P.; Taniguchi, T. N-Heterocyclic Carbene Boranes are Hydrogen Donors in Masamune–Bergman Reactions of Benzo[3,4]cyclodec-3-ene-1,5-diyne. *J. Org. Chem.* **2017**, *82*, 13034-13042. (b) Watanabe, T.; Hirose, D.; Curran, D. P.; Taniguchi, T. Borylative Radical Cyclizations of Benzo[3,4]cyclodec-3-ene-1,5-diyne and N-Heterocyclic Carbene-Boranes. *Chem. Eur. J.* **2017**, *23*, 5404-5409. (c) Shimoi, M.; Kevlishvili, I.; Watanabe, T.; Maeda, K.; Geib, S. J.; Curran, D. P.; Liu, P.; Taniguchi, T. The Thermal Rearrangement of an NHC-Ligated 3-Benzoborepin to an NHC-Boranorcaradiene. *Angew. Chem., Int. Ed.* **2020**, *59*, 903-909.
- (16) Das, E.; Basak, A. Regioselective Synthesis of Benzo-Fused Tetrahydroisoquinoline-Based Biaryls through a Tandem One-Pot Halogenation of *p*-Benzynes from Eneidyne and Suzuki-Miyaura Coupling. *J. Org. Chem.* **2020**, *85*, 2697-2703.
- (17) Ge, C.; Wang, G.; Wu, P.; Chen, C. Synthesis of Naphthalenyl Triflates via the Cationic Annulation of Benzodiyne with Triflic Acid. *Org. Lett.* **2019**, *21*, 5010-5014.
- (18) (a) Ono, N.; Yoshimura, T.; Saito, T.; Tamura, R.; Tanikaga, R.; Kaji, A. Alkylation and Acylation of Active Methylene Compounds Using 1,8-Diazabicyclo[5.4.0]undec-7-ene as a Base. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1716-1719. (b) Tundo, P.; Venturello, P.; Angeletti, E. Alkylation Reactions of Ethyl Malonate, Ethyl Acetoacetate, and

- Acetylacetone by Gas–Liquid Phase-Transfer Catalysis (G.L.–P.T.C.). *J. Chem. Soc., Perkin Trans. 1* **1987**, 2159-2162.
- (19) (a) Nelson, P. H.; Nelson, J. T. Synthesis of Tetra- and Pentasubstituted Benzenes from Dimedone and Derivatives. *Synthesis* **1992**, 1992, 1287-1291. (b) Mphahlele, M. J.; Modro, T. A. Reaction of Phosphonate-Stabilized Carbanions with Cyclic Enones Bearing a  $\beta$ -Leaving Group. *J. Org. Chem.* **1995**, *60*, 8236-8240. (c) Bhosale, R. S.; Bhosale, S. V.; Bhosale, S. V.; Wang, T.; Zubaidha, P. K. Iodine-Catalyzed Synthesis of  $\beta$ -Keto Enol Ethers. *Tetrahedron Lett.* **2004**, *45*, 7187-7188. (d) Yadav, J. S.; Reddy, B. V. S.; Mishra, A. K. Zinc-mediated Alkylation and Acylation of 1,3-Dicarbonyl Compounds. *Chem. Lett.* **2010**, *39*, 280-281. (e) Liu, G.-K.; Li, X.; Qin, W.-B.; Lin, W.-F.; Lin, L.-T.; Chen, J.-Y.; Liu, J.-J. Selective *O*-difluoromethylation of 1,3-Diones using *S*-(Difluoromethyl) Sulfonium Salt. *Chin. Chem. Lett.* **2019**, *30*, 1515-1518.
- (20) Nakano, Y.; Noguchi, T.; Adachi, T.; Sato, S. Ligand exchanging reactions of  $M(\text{acac})_3$  ( $M=\text{Cr}$  or  $\text{Co}$ ) in Lewis acidic conditions. *Inorg. Chim. Acta* **2003**, *343*, 202-208.
- (21) Odedra, A.; Wu, C.-J.; Pratap, T. B.; Huang, C.-W.; Ran, Y.-F.; Liu, R.-S. Ruthenium-Catalyzed Aromatization of Ene-diyne via Highly Regioselective Nucleophilic Additions on a  $\pi$ -Alkyne Functionality. A Useful Method for the Synthesis of Functionalized Benzene Derivatives. *J. Am. Chem. Soc.* **2005**, *127*, 3406-3412.
- (22) Nösel, P.; Müller, V.; Mader, S.; Moghimi, S.; Rudolph, M.; Braun, I.; Rominger, F.; Hashmi, A. S. K. Gold-Catalyzed Hydroarylation Cyclization of 1,2-Bis(2-iodoethyl)benzenes. *Adv. Synth. Catal.* **2015**, *357*, 500-506.
- (23) Pearson, R. G. Hard and Soft Acids and Bases. *J. Am. Chem. Soc.* **1963**, *85*, 3533-3539.
- (24) Perrin, C. L.; Reyes-Rodríguez, G. J. Selectivity and Isotope Effects in Hydronation of a Naked Aryl Anion. *J. Am. Chem. Soc.* **2014**, *136*, 15263-15269.
- (25) Leffek, K. T.; Tremaine, P. H. Aromatic Substitutions with Carbanion Nucleophiles. II. The Kinetics and Mechanism of the Reaction of 1-Fluoro-2,4-dinitrobenzene with the Diethyl Malonate Anion. *Can. J. Chem.* **1973**, *51*, 1659-1664.
- (26) (a) Min'ko, Y. A.; Belina, N. V.; Sushev, V. V.; Fukin, G. K.; Bubnov, M. P.; Kornev, A. N. Binuclear Titanium(III) Complex Derived from Diphenylphosphanylmalononitrile,  $[\mu^2(N,N')\text{-Ph}_2\text{PC}(\text{CN})_2\text{TiCp}_2]_2$ : Synthesis, Structure and Properties. *J. Organomet. Chem.* **2007**, *692*, 4157-4160. (b) Barchiesi, E.; Bradamante, S.; Ferraccioli, R.; Pagani, G. A.

Experimental Charge Maps in di-Activated Carbanions: Access to Charge Demands of Primary Electron-withdrawing Functionalities. *J. Chem. Soc., Perkin Trans. 2* **1990**, 375-383.

- (27) Liu, Y.-C.; Zhang, K.-D.; Liu, J.-M.; Wu, L.-M.; Liu, Z.-L. Nucleophilic Substitution Reaction of *p*-Dinitrobenzene by a Carbanion: Evidence for Electron Transfer Mechanism. *Chin. J. Chem.* **2002**, *20*, 1453-1456.
- (28) Lucius, R.; Mayr, H. Constant Selectivity Relationships of Addition Reactions of Carbanions. *Angew. Chem., Int. Ed.* **2000**, *39*, 1995-1997.
- (29) Howden, M. E. H.; Tyler, M. PMR Spectra of Sodium Enolates of Some  $\beta$ -Dicarbonyl Compounds. *Tetrahedron Lett.* **1975**, *16*, 1979-1980.
- (30) Zhang, J.; Yang, J.-D.; Zheng, H.; Xue, X.-S.; Mayr, H.; Cheng, J.-P. Exploration of the Synthetic Potential of Electrophilic Trifluoromethylthiolating and Difluoromethylthiolating Reagents. *Angew. Chem., Int. Ed.* **2018**, *57*, 12690-12695.

### TOC Graphic



R,R (T, t) = H,H (55°C, 12 h), -(CH)<sub>4</sub>- (85°C, 72 h), -(CH<sub>2</sub>)<sub>4</sub>- (75°C, 24 h)

COZ = CN, CO<sub>2</sub>Et, COMe, and CPh      Z' = CN, CO<sub>2</sub>Et, and COMe