JOC The Journal of Organic Chemistry

Note

Access to Functionalized Quaternary Stereocenters via the Copper-Catalyzed Conjugate Addition of Monoorganozinc Bromide Reagents Enabled by N,N-Dimethylacetamide

Tyler Fulton, Phebe L. Alley, Heather R. Rensch, Adriana M. Ackerman, Cameron B. Berlin, and Michael R Krout

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b02201 • Publication Date (Web): 30 Oct 2018

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Access to Functionalized Quaternary Stereocenters via the Copper-Catalyzed Conjugate Addition of Monoorganozinc Bromide Reagents Enabled by *N,N*-Dimethylacetamide

Tyler J. Fulton,[†] Phebe L. Alley,[‡] Heather R. Rensch,[§] Adriana M. Ackerman,[‡] Cameron B. Berlin,[‡] Michael R. Krout[‡,*]

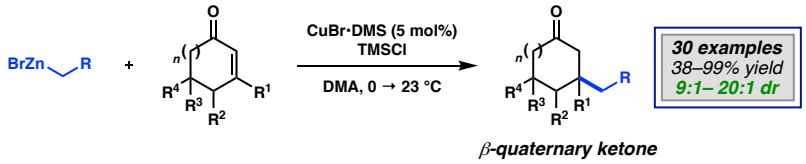
[†]Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

[§]Research and Development, Bimax, Inc., Glen Rock, Pennsylvania 17327, United States

[‡]Department of Chemistry, Bucknell University, Lewisburg, Pennsylvania 17837, United States

michael.krout@bucknell.edu

Abstract Image



Abstract

Monoorganozinc reagents, readily obtained from alkyl bromides, display excellent reactivity with β,β-disubstituted enones and TMSCl in the presence of Cu(I) and Cu(II) salts to synthesize a variety of cyclic functionalized β-quaternary ketones in 38–99% yields and 9:1–20:1 diastereoselectivities. The conjugate addition features a pronounced improvement in DMA using monoorganozinc bromide reagents. A simple one-pot protocol that harnesses in situ generated monoorganozinc reagents delivers comparable product yields.

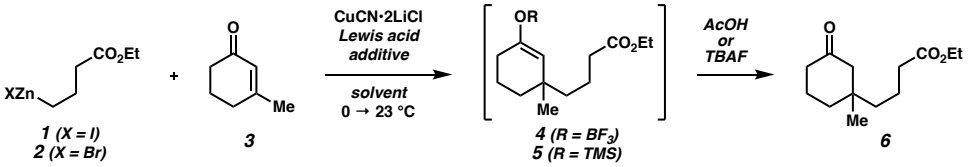
The metal-catalyzed formation of C–C bonds with organometallics represents a versatile technology in organic synthesis. Organozinc reagents comprise an important class of

organometallics that have earned widespread use due to their outstanding functional group compatibility while maintaining sufficient reactivity.[1,2,3,4] This enhanced chemoselectivity coupled with reagent accessibility facilitates applications in the construction of highly functionalized organics for complex molecule synthesis. Strategies have been developed to modulate the reactivity of mild organozinc species when engaged with challenging substrates, as demonstrated in their conjugate addition to β,β-disubstituted α,β-unsaturated carbonyls. The application of sensitive diorganozinc[5,6,7] or mixed diorganozinc[8] reagents has enabled the synthesis of β-quaternary carbonyls that include recent enantioselective achievements.[9,10,11] Monoorganozinc reagents, however, have been underutilized despite the appeal of their simplified preparation via the direct insertion of zinc into a carbon–halogen bond. Examples that leverage the addition of monoorganozinc reagents to sterically demanding β,β-disubstituted α,β-unsaturated carbonyls are surprisingly limited and require stoichiometric cyanocuprate reagents.[12,13,14] Moreover, a single example demonstrating minimal catalyst turnover has been reported.[15] Our interest in this transformation came from a desire to prepare functionalized β-quaternary ketones for synthesis applications. A key goal in this endeavor was to harness mild, functionalized organometallics that are both economical and trivial to access. To this end, we have developed a simple and efficient Cu-catalyzed addition of alkyl monoorganozinc bromide (RZnBr) reagents to cyclic α,β-unsaturated ketones augmented by the polar solvent *N,N*-dimethylacetamide (DMA).

We began our studies with monoorganozinc iodide reagent **1** (RZnI) and 3-methylcyclohexenone (**3**) as our model substrates. A variety of conditions were examined that comprised CuCN•2LiCl in combination with Lewis acids in order to establish a baseline of reactivity for the production of β-quaternary ketone **6**. The conjugate addition of **1** promoted by stoichiometric CuCN•2LiCl with BF_3[13] afforded only a modest yield of **6** (Table 1, entry 1). Employing sub-stoichiometric copper failed to produce **6**, although measurable quantities could be realized with TMSCl upon acid or fluoride-mediated hydrolysis of an intermediate silyl enol ether (entries 2 and 3). HMPA has been established as a beneficial component for conjugate additions with TMSCl,[15,16,17,18] and indeed the use of this polar additive improved the catalyst efficiency and yield of **6** to 73% (entry 4). While there is an advantage with HMPA, the use of

alternative non-carcinogenic Lewis bases is desirable.[17] To this end, various polar, aprotic solvents were considered for their compatibility with organozinc reagents.[19,20,21] We were pleased to find that the inclusion of DMA as an additive doubled the reaction efficiency compared to no polar additive, generating **6** in 49% yield (entry 5). Further utilizing DMA as the reaction solvent with **1** (solution in DMA) yielded a modest increase in **6** to 56% (entry 6). Organozinc iodide preparation is aided by the relative ease of zinc insertion into the weaker C–I bond, although this limits application with respect to the modest options of commercial alkyl iodides ostensibly due to their instability. Organozinc bromides are accessible from ubiquitous alkyl bromides,[19,20,22] including Huo's convenient method of preparing stable[23] solutions of RZnBr reagents in polar, aprotic solvents. Gratifyingly, RZnBr reagent **2** performed exceptionally in this conjugate addition to provide **6** in up to 90% yield with 5 mol% catalyst (entries 7 and 8). The proficiency of this Cu-catalyzed conjugate addition for the synthesis of β-quaternary ketone **6** is remarkable considering the use of simple RZnBr reagents in DMA, and it is arguably superior to HMPA in terms of feasibility and chemical safety. Although further investigation is necessary to ascertain to role of the halide (Br) and DMA in this transformation, we posit that both components augment the reactivity of the monoorganozinc to facilitate transmetalation to the Cu-catalyst. Recent studies have demonstrated similar halide effects in polar solvents for both Cu-catalyzed[24] and Pd-catalyzed[25,26] Negishi cross-couplings. Amidic solvents have also been hypothesized to increase the reactivity of organozinc reagents through coordination to the zinc center.[27]

Table 1. Optimization of the Cu-Catalyzed Conjugate Addition of Monoorganozinc Reagents.



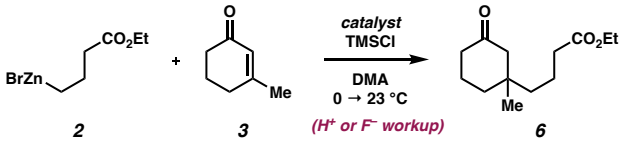
entry[a]	*RZnX*	*Cu (mol%)*	*Lewis acid*	*solvent*	*additive (equiv)*	*yield (%)*[b]
1	**1**	122	BF_3•Et_2O	THF/Et_2O	–	56
2	**1**	10	BF_3•Et_2O	THF/Et_2O	–	0
3	**1**	10	TMSCl	THF/Et_2O	–	25
4	**1**	10	TMSCl	THF/Et_2O	HPMA (2.4)	73

5	**1**	10	TMSCl	THF/Et_2O	DMA (2.4)	49
6	**1**	10	TMSCl	DMA	–	56
7	**2**	10	TMSCl	DMA	–	89
8	**2**	5	TMSCl	DMA	–	90

[a] 1.00 mmol **3**, 1.4–2.0 equiv **1** or **2**, and 2.4 equiv Lewis acid for up to 24 h. [b] Isolated yields.

Our identification of DMA as an optimal solvent with RZnBr reagents (i.e., **2**) led to further examination of the reaction catalyst and conditions. A brief survey of common catalysts revealed that a number of Cu(I) and Cu(II) salts are effective in the production of **6** (Table 2). It is noteworthy that LiCl is no longer necessary for the solvation of CuCN, affording **6** in comparable yield (cf. entries 1 and 2). Halide and carboxylate salts of Cu(I) and Cu(II) are generally efficacious for this transformation (entries 3–6 and 8–10), whereas copper oxides (entries 7 and 11) and $Ni(acac)_2$[5] (entry 12) are substantially less effective. Although various copper salts could be utilized in this transformation, we chose to advance our study with CuBr•DMS given the convenience and reproducibility of this catalyst. Lowering the CuBr•DMS loading to 2 mol% resulted in a diminished yield of **6** due to the incomplete conversion of **3** (cf. entries 3 and 13). Further analysis of TMSCl and **2** revealed that lowering the equivalence to 1.2 also decreased the product yield due to incomplete conversion (entries 14 and 15). No product was formed in the absence of either Cu-catalyst or TMSCl (entries 16 and 17). It is plausible that DMA can also enhance enone silylation through activation of TMSCl.[7]

Table 2. Conjugate Addition Catalyst Survey.



2 3 6

entry[a]	*catalyst (mol%)*	*yield (%)*[b]
1	CuCN•2LiCl (5)	90
2	CuCN (5)	87
3	CuBr•DMS (5)	92
4	CuCl (5)	90
5	CuI (5)	90

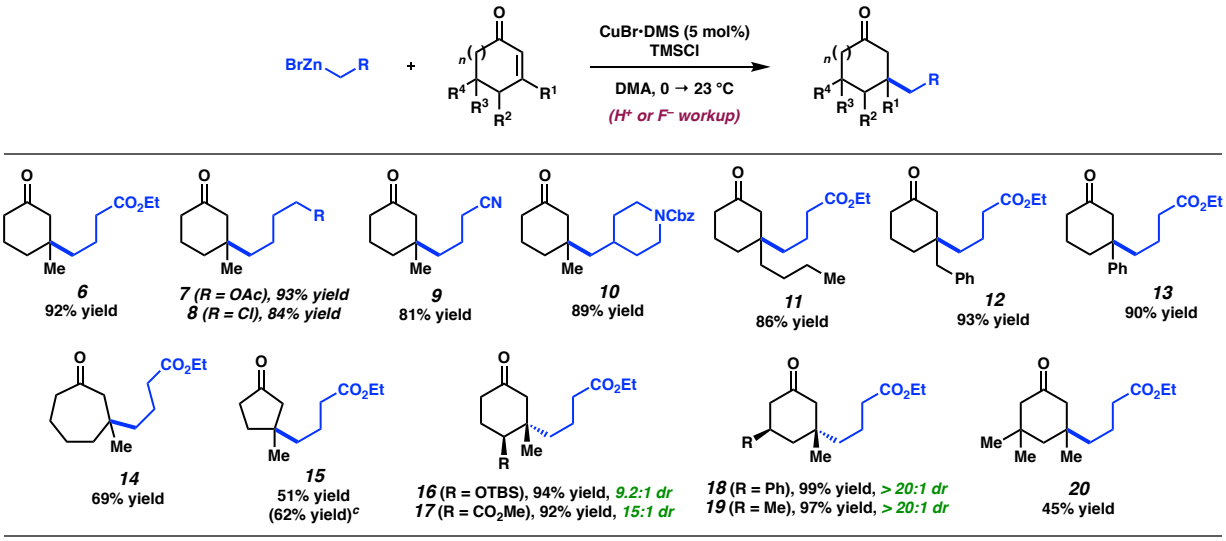
6	CuTC (5)[c]	82
7	Cu_2O (10)	35
8	$CuBr_2$ (5)	92
9	$CuCl_2$ (5)	92
10	$Cu(OAc)_2$ (5)	92
11	CuO (10)	11
12	$Ni(acac)_2$ (10)	0
13	CuBr•DMS (2)	78
14	CuBr•DMS (5)	81[d]
15	CuBr•DMS (5)	67[e]
16	CuBr•DMS (5)	0[f]
17	–	0

[a] 1.00 mmol **3**, 2 equiv **2**, and 2.4 equiv TMSCl for up to 24 h. [b] Isolated yields. [c] TC = thiophene-2-carboxylate. [d] 1.2 equiv **2**. [e] 1.2 equiv TMSCl. [f] No TMSCl.

With optimized conditions in hand, we examined the scope of monoorganozinc and α,β-unsaturated ketones (enones; Scheme 1). A variety of functional monoorganozinc reagents proved effective in this reaction, affording β-quaternary ketones that incorporate ester (**6** and **7**), chloro (**8**), nitrile (**9**), and carbamate (**10**) groups in high yields. The cyclic enones could also possess alternative β-functionality, with *n*-butyl (**11**), benzyl (**12**), and phenyl (**13**) groups well-tolerated. The absence of examples of quaternary center formations with monoorganozinc additions to enones of various ring sizes led us to survey five- and seven-membered ring substrates. Both systems were effective in this reaction, demonstrated by the formation of cycloheptenone 14 in 69% yield and cyclopentenone **15** in 51% yield. The yield of **15** could be improved to 62% by increasing the catalyst loading, although the enone conversion remained incomplete presumably due to the poor overlap of the conjugated system. The stereoselectivity of the addition reaction with a variety of γ- and δ-substituted enones was also investigated. We were pleased to find that the Cu-catalyzed reactions of simple monoorganozinc reagents proceeds with excellent efficiencies and high diastereoselectivities (**16**–**19**). Isophorone was used to examine the steric constraints of this reaction based on the highly methylated core of this enone.[28] Addition product **20** was obtained in a modest 45% yield due to incomplete conversion.

Importantly, this positive result highlights the feasibility and potential of Cu-catalyzed additions of monoorganozinc reagents to sterically demanding substrates.

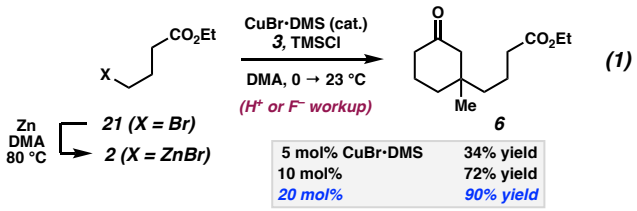
Scheme 1. Substrate Scope of the Cu-Catalyzed Conjugate Addition of Moonorganozinc Reagents to Enones[a,b]



[a] 1.00 mmol enone, 2 equiv RZnBr, and 2.4 equiv TMSCl for up to 24 h. [b] Yields represent isolated analytically pure products. [c] 10 mol% CuBr•DMS.

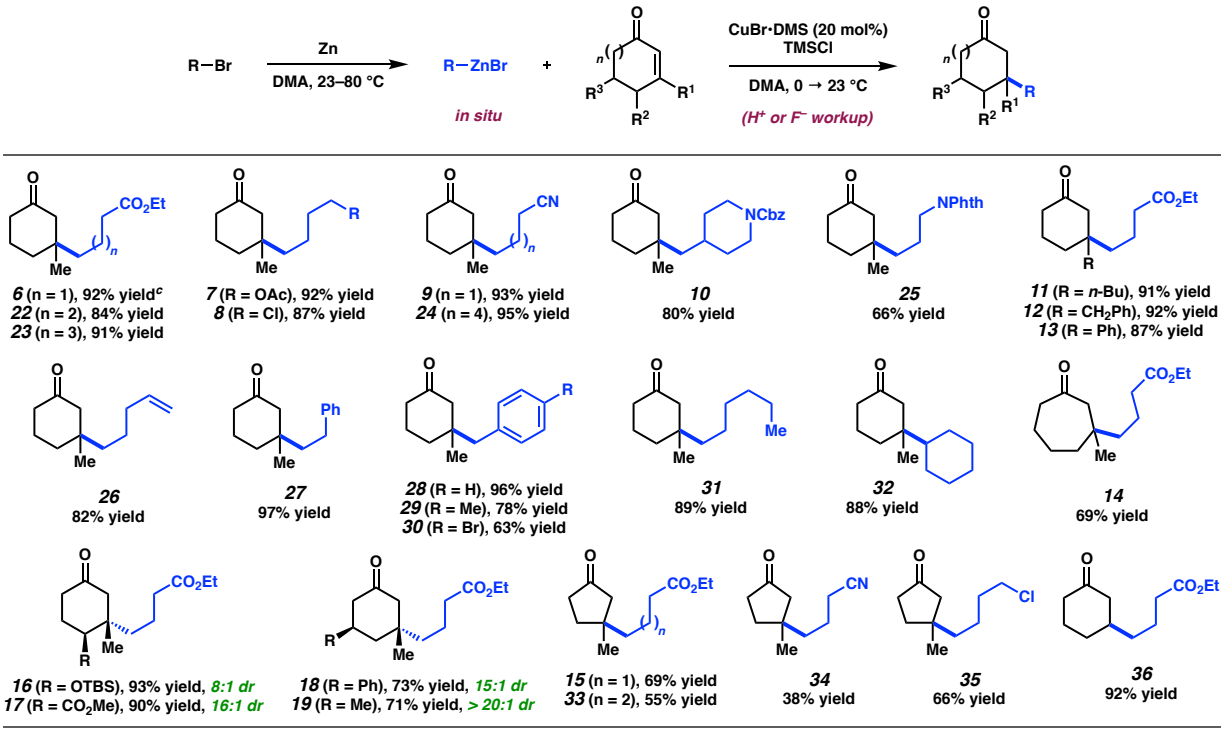
The use of isolated monoorganozinc reagents in this transformation motivated our development of a practical one-pot procedure to leverage in situ generated monoorganozincs in a sequential addition reaction. This simplified protocol would minimize reagent manipulation, and moreover, has the potential to facilitate expedient access to a more diverse collection of products considering the accessibility and stability of 1° and 2° organobromides. The monoorganozinc reagent was obtained by the direct insertion of zinc into organobromides (e.g., **21**) at elevated temperature in DMA.[21] Upon completion, the reagent was cooled to 0 °C followed by addition of CuBr•DMS, TMSCl and enone **3** to produce **6** in 34% yield (Equation 1). We surmised that the remaining zinc and related insoluble salts may impact the catalyst efficiency, and accordingly observed improved yields using higher catalyst loadings. Comparable yields were realized using 20 mol% catalyst, and we proceeded with these conditions as our standard one-pot procedure to explore a broad substrate scope (Scheme 2). Monoorganozinc reagents that incorporate ester functionality at various chain lengths afford addition products in high yields (**7**, **22**, and **23**), including **6** in 92% yield on 5.0 mmol scale. Nitrogen-containing monoorganozincs were well

tolerated to afford nitrile (**9** and **24**), carbamate (**10**), and phthalimide (**25**) products in good yields. The addition reaction was efficient with various β-substituted cyclohexenones (**11**–**13**) and cycloheptenone (**14**). Homoallyl (**26**), homobenzyl (**27**), and benzyl (**28**) monoorganozinc reagents provide high yields of addition products, including *para* substituted benzyl-containing products (**29** and **30**). The introduction of alkyl groups is facile (**31**), highlighted by use of a 2° monoorganozinc reagent to afford **32** in 87% yield. Cyclopentenone substrates remained a challenge, affording modest and variable yields with the incorporation of ester (**15** and **33**), nitrile (**34**), and chloro (**35**) functionality with our conditions. Cyclohexenone substrates with γ- and δ-substitution proceeded in high yields and diastereoselectivities for the one-pot additions (**16**–**19**). Cyclohexenone is among the most utilized substrates for this type of conjugate addition reaction, and the expected 3° product (**36**) was formed in excellent yield.[12,14,15,29]



(1)

Scheme 2. Substrate Scope for the One-Pot Synthesis and Conjugate Addition of Monoorganozinc Reagents[a,b]



[a] 1.00 mmol enone, 2 equiv RBr, 20 mol% CuBr·DMS, and 2.4 equiv TMSCl for up to 24 h. [b] Yields represent isolated analytically pure products. [c] 5.00 mmol enone.

The efficient one-pot procedure enabled us to demonstrate a broad scope of the monoorganozinc bromide reagents in the addition reaction with a few exceptions. Stabilized monoorganozincs, such as enolate **37**, homoenolate **38**,[30] and allyl (**39**) did not yield any addition products (Figure 1). Benzylic monoorganozincs appear to deviate from this trend (**28**–**30**), although electronic tuning by a withdrawing *p*-ester group (**40**) resulted in a failed addition. Monoorganozincs that contain β- or γ-NHBoc groups (**41** and **42**) did not provide addition products despite their reported use with less demanding electrophiles.[31] The conjugate addition was also found to be sensitive to organozinc sterics, indicated by unsuccessful additions with *ortho* substituted (**43**) or β-quaternary (**44**) organozincs.

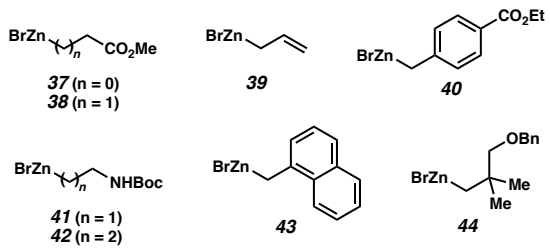
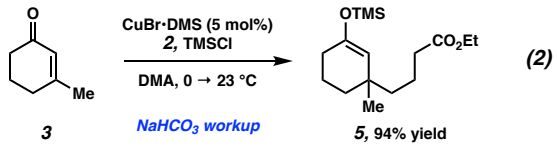


Figure 1. Unreactive Monoorganozinc Reagents in Conjugate Additions.

The standard reaction conditions and one-pot procedure both provide facile access to a variety of chiral β-quaternary ketones. The addition products shown in Scheme 1 and Scheme 2 are obtained via the hydrolysis of an intermediate silyl enol ether. Importantly, these reactive intermediates poised for subsequent functionalization[32,33,34] are moderately stable[35] and can be isolated in high yield using a modified workup (Equation 2).



We have established a general and practical reaction protocol for the Cu-catalyzed conjugate addition of simple monoorganozinc reagents to form diverse functionalized β-quaternary ketones with excellent efficiency. In contrast to the limited known examples, this method is highlighted by a significant positive influence of the solvent DMA with RZnBr reagents, facilitating access to five-, six-, and seven-membered ring products in high yields and diastereoselectivities. Efforts to expand the unsaturated carbonyl substrate scope, clarify the nature of the reagent enhancement, as well as further applications are under investigation.

Experimental Section

General Methods. *Reactions, Reagents and Solvents.* Unless otherwise noted, all reactions were performed in flame-dried Schlenk glassware under an argon or nitrogen atmosphere using dry solvents. Solvents were dried by passage through an activated alumina column under nitrogen and stored over activated 3 Å MS. Molecular sieves were activated by microwave

irradiation and cooled under vacuum. All starting materials were purchased from commercial sources and used as received, unless otherwise stated. A 1 M solution of CuCN•2LiCl in THF was prepared according to Knochel[12] and stored in a sealed tube. Liquids and solutions were transferred via syringe or positive-pressure cannulation. Brine solutions refer to saturated aqueous sodium chloride solutions. Zinc dust was activated over 1 M HCl. The following liquids were refluxed over CaH_2 and stored in a Straus flask over 3 Å molecular sieves prior to use: toluene, HMPA, DMF, Et_3N. TMSCl was cannulated into a sealed tube and stored under nitrogen. Reagent grade acetone was stored over $CaSO_4$. MeOH was refluxed over Mg turnings, distilled and stored over 3 Å molecular sieves. Unless stated otherwise, all reactions were stirred with a magnetic stir bar and monitored by gas chromatography (GC) with an FID or thin layer chromatography (TLC).

Instruments, Purification and Analysis. Thin-layer chromatography was performed using 6.5 x 2.2 cm EMD Milipore 60 g F_{254} precoated plates (9.5–11.5 μm particle size) and visualized by UV fluorescence quenching and *p*-anisaldehyde staining. Column or flash chromatography (silica) was performed with the indicated solvents using SiO_2 (VWR, 60 Å pore size, 40–63 μm particle size; or Biotage KP-Sil, 60 Å pore size, 40–60 μm particle size). Automated flash chromatography was performed on a Biotage Isolera One with UV/VIS detection (254, 280, 200–400 nm), unless otherwise noted. All crude samples were dissolved in a minimal amount of Et_2O or CH_2Cl_2 and loaded onto a Biotage dry load vessel (DLV) packed with SiO_2 (generally 10–25 g). A reduced pressure was then used to pull the sample onto the DLV and remove excess solvent. The DLV was then used with the Biotage Isolera One pre-packed SiO_2 columns as indicated. Infrared spectra were obtained on a Thermo Nicolet 4700 FT-IR with a Pike GladiATR ATR using a diamond cell and are reported in wavenumbers (cm^{-1}). ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded on a Varian 400 MHz (400 and 101 MHz, respectively) or an Oxford 600 MHz (600 and 151 MHz, respectively). Chemical shifts (δ) are reported relative to internal Me_4Si (^1H and $^{13}C\{^1H\}$, δ 0.00 ppm), chloroform (^1H, δ 7.26 ppm, $^{13}C\{^1H\}$ 77.16 ppm) or benzene (^1H, δ 7.16 ppm, $^{13}C\{^1H\}$ 128.06 ppm). High-resolution mass spectra were acquired using a Thermo Exactive Orbitrap mass spectrometer with an IonSense ID-Cube DART source in APCI ionization mode. Melting point measurements are uncorrected.

General Procedure. To a 25 mL Schlenk tube charged with CuBr•DMS (10.3 mg, 0.050 mmol, 0.050 equiv) and DMA (0.3 M; volume adjusted to account for RZnX) at 0 °C was added a solution of the RZnX (2.00 mmol, 2.0 equiv). After 10 min, TMSCl (305 μL, 2.40 mmol, 2.4 equiv) and enone (1.00 mmol, 1.0 equiv) were added. The solution was allowed to warm to 23 °C after ca. 1 h and stirred until consumption of the enone by TLC analysis, or 24 h. The reaction was quenched with glacial acetic acid (290 μL, 5.0 mmol, 5.0 equiv) and stirred until hydrolysis of the silyl enol ether was observed by TLC. In some cases, the addition of TBAF (0.5–1.1 mL of a 1.0 M solution in THF) was required for complete hydrolysis of the silyl enol ether. The reaction was then added HCl (5 mL, 1 M aq) and transferred to a separatory funnel with Et_2O (5 mL) and H_2O (5 mL). The layers were mixed, separated, and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organics were washed with $NaHCO_3$ (5 mL), brine (5 mL), and then dried over anhydrous $MgSO_4$, filtered, and concentrated to provide a crude oil. Purification by automated flash column chromatography on SiO_2 afforded the conjugated addition products.

Organozinc Reagents. DMA solutions of the organozinc bromide reagents employed in Table 1, Table 2 and Scheme 1 were prepared according to Huo[21] and Fu,[36] as represented by the preparation of **2**. To a 100 mL sealed reaction tube was added zinc dust (4.908 g, 75.07 mmol, 1.25 equiv), I_2 (760 g, 2.99 mmol, 0.05 equiv) and DMA (25.0 mL, 2.4 M). The contents were stirred vigorously until the color faded (ca. 1–5 min), and to this gray suspension was added ethyl 4-bromobutyrate (**21**; 8.60 mL, 60.1 mmol, 1.0 equiv). The reaction tube was sealed, immersed in an 80 °C oil bath and monitored by GC analysis for consumption of the organohalide (NH_4Cl aliquot quench; Et_2O extraction; required 6–10 h depending on scale). Upon completion of the organozinc formation, the reaction is cooled to ambient temperature and the stirring is ceased to allow the solids to settle for 12–24 h. The partially separated suspension was slowly filtered into a dry disposable syringe equipped with a 0.45 μm PTFE syringe filter, the needle was exchanged and the reagent was then transferred to a dry sealed storage tube. The resulting clear, dark red orange solution of **2** was quantified using iodometric titration to give concentrations in the range of 1.3–1.5 M.[37] It is recommended to perform the first titration past the end point due to the varied color of organozinc solutions. We have observed only minor changes in the titer (< 0.05–0.1 M) over a period of at least 6 months for the RZnBr solutions used in this study. Organozinc iodide reagent **1** required warming the ethyl 4-iodobutyrate to 40–50 °C.

General One-Pot Procedure. To a 25 mL Schlenk tube charged with zinc dust (163.5 mg, 2.50 mmol, 2.5 equiv) and iodine (25.4 mg, 0.10 mmol, 0.10 equiv) was added DMA (1.2 mL). The contents were stirred vigorously until the color faded (ca. 1–5 min), and to this gray suspension was added organohalide (2.0 mmol, 2.0 equiv). The reaction tube was immersed in an 80 °C oil bath and monitored by GC analysis for consumption of the organohalide (NH_4Cl aliquot quench; Et_2O extraction). Upon completion of the organozinc formation, the reaction was cooled to 0 °C and was added CuBr•DMS (41.1 mg, 0.200 mmol, 0.20 equiv) and DMA (2.1 mL, 0.3 M total). After 10 min, TMSCl (305 μL, 2.40 mmol, 2.4 equiv) and enone (1.00 mmol, 1.0 equiv) were added. The solution was allowed to warm to 23 °C after ca. 1 h and stirred until consumption of the enone by TLC analysis, or 24 h. The reaction was then quenched, worked up and purified according to the General Procedure.

Enol ether isolation. Upon completion of the reaction as described in the General Procedure, $NaHCO_3$ (5 mL) is slowly added with vigorous stirring. The reaction was then transferred to a separatory funnel with Et_2O and H_2O (10 mL). The layers were mixed, separated, and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organics were washed with brine (5 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to provide a crude oil. Purification by automated flash column chromatography on SiO_2 afforded the silyl enol ether product.

Initial Screening Procedure of 1. To a 25 mL sealed reaction tube[38] charged with zinc dust (94.8 mg, 1.45 mmol, 1.45 equiv) was added 1,2-dibromoethane (3.5 μL, 0.04 mmol, 0.04 equiv) and THF (1.0 mL, 1.4 M with respect to **1**). The reaction tube was sealed and the gray suspension was heated for approximately 20 seconds with a heat gun until a slight reflux of THF was observed, and then cooled to room temperature. To this was added TMSCl (5.1 μL, 0.04 mmol, 0.04 equiv) and ethyl 4-iodobutyrate (338.9 mg, 1.40 mmol, 1.4 equiv), and the reaction tube was sealed and immersed in a 40 °C oil bath. The reaction was monitored by GC analysis for consumption of **1** (NH_4Cl aliquot quench), and cooled to 0 °C upon completion. A solution of CuCN•2LiCl (110 μL, 0.10 mmol, 0.10 equiv or 1.3 mL, 1.22 mmol, 1.22 equiv of a 0.92 M solution in THF) and the polar additive (2.4 mmol, 2.4 equiv) were added. [*Note:* when 110 μL of CuCN•2LiCl solution was used, an additional 1.1 mL of THF was also added.] After 10 min, a solution of **3** (113 μL,

1.00 mmol, 1.0 equiv) and Lewis acid (2.40 mmol, 2.4 equiv) in Et_2O (1.0 mL, 0.30 M overall; solution prepared in a 5 mL sealed tube) were added via syringe transfer. The solution was allowed to warm to 23 °C overnight and stirred until consumption of the enone by TLC analysis, or 24 h. The reaction was then quenched, worked up and purified according to the General Procedure.

Ethyl 4-(1-methyl-3-((trimethylsilyl)oxy)cyclohex-2-en-1-yl)butanoate (5). Purification: 25 g SiO_2, 3 → 25% EtOAc in hexanes; General Procedure: isolated 280.9 mg (0.9410 mmol, 94 % yield) of a clear, colorless oil. R_f = 0.48 (6:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, C_6D_6): δ 4.75 (s, 1H), 3.97 (q, J = 7.1 Hz, 2H), 2.13 (t, J = 7.3 Hz, 2H), 1.98 (td, J = 6.4, 1.2 Hz, 2H), 1.62 (dt, J = 16.4, 7.9 Hz, 2H), 1.57–1.51 (m, 2H), 1.32 (ddd, J = 13.0, 8.3, 4.8 Hz, 1H), 1.27–1.13 (m, 3H), 0.98 (t, J = 7.1 Hz, 3H), 0.95 (s, 3H), 0.20 (s, 9H); ^{13}C{^{1}H} NMR (101 MHz, C_6D_6): δ 172.9, 150.1, 113.7, 60.0, 43.3, 35.1, 34.79, 34.75, 30.4, 28.4, 20.4, 20.0, 14.4, 0.5; IR (ATR): 2954, 2938, 1737, 1662, 1365, 1251, 1186, 842, 7545; HRMS (DART+) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{31}O_3Si$ 299.2037, found 299.2028.

Ethyl 4-(1-methyl-3-oxocyclohexyl)butanoate (6). Purification: 25 g SiO_2, 5 → 25% EtOAc in hexanes; General Procedure: isolated 208.4 mg (0.9208 mmol, 92% yield) as a clear, colorless oil; One-Pot Procedure: isolated 1.0372 g (4.583 mmol, 92% yield; 5.00 mmol scale). R_f = 0.21 (4:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.13 (q, J = 7.1 Hz, 2H), 2.32–2.23 (m, 4H), 2.15 (ABq, $\Delta\delta_{AB}$ = 0.06, J_{AB} = 13.5 Hz, 2H), 1.87 (quintet, J = 6.4 Hz, 2H), 1.60 (dtt, J = 23.3, 15.4, 7.6 Hz, 4H), 1.34–1.21 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H), 0.94 (s, 3H). All other spectral data are consistent with reported values.[39]

4-(1-Methyl-3-oxocyclohexyl)butyl acetate (7). Purification: 25 g SiO_2, 8 → 50% EtOAc in hexanes; General Procedure: isolated 211.5 mg (0.9345 mmol, 93% yield) as a clear, colorless oil; One-Pot Procedure: isolated 208.8 mg (0.9226 mmol, 92% yield). R_f = 0.31 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.06 (t, J = 6.7 Hz, 2H), 2.29–2.26 (m, 2H), 2.15 (ABq, $\Delta\delta_{AB}$ = 0.07, J_{AB} = 13.5 Hz, 2H), 2.05 (s, 3H), 1.89–1.85 (m, 2H), 1.63–1.52 (m, 4H), 1.32–1.24 (m, 4H), 0.92 (s, 3H). All other spectral data are consistent with reported values.[9]

3-(4-Chlorobutyl)-3-methylcyclohexan-1-one (8). Purification: 25 g SiO_2, 5 → 25% EtOAc in hexanes; General Procedure: isolated 170.5 mg (0.8411 mmol, 84% yield) as a clear, colorless oil; One-Pot Procedure: isolated 175.7 mg (0.8667 mmol, 87% yield). R_f = 0.28 (4:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.55 (t, J = 6.6 Hz, 2H), 2.28 (app t, J = 6.8 Hz, 2H), 2.15 (ABq, $\Delta\delta_{AB}$ = 0.06, J_{AB} = 13.4, 2H), 1.87 (tt, J = 8.8, 4.5 Hz, 2H), 1.78–1.71 (m, 2H), 1.64 (dt, J = 13.4, 6.6 Hz, 1H), 1.56 (dt, J = 13.5, 6.6 Hz, 1H), 1.45–1.38 (m, 2H), 1.30–1.24 (m, 2H), 0.93 (s, 3H). All other spectral data are consistent with reported values.[8]

4-(1-Methyl-3-oxocyclohexyl)butanenitrile (9). Purification: 25 g SiO_2, 13 → 50% EtOAc in hexanes; General Procedure: isolated 145.0 mg (0.8089 mmol, 81% yield) as a clear, colorless oil; One-Pot Procedure: isolated 166.7 mg (0.9299 mmol, 93% yield). This compound has been reported but characterization data was not included.[15] R_f = 0.33 (1:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.36 (td, J = 7.0, 1.8 2H), 2.29 (app t, J = 6.8 Hz, 2H), 2.17 (ABq, $\Delta\delta_{AB}$ = 0.06 , J_{AB} = 13.4, 2H), 1.92–1.85 (m, 2H), 1.67–1.55 (m, 4H), 1.47–1.35 (m, 2H), 0.95 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 212.3, 173.5, 60.4, 52.3, 41.2, 40.9, 36.91, 36.74, 34.7, 33.8, 25.1, 23.4, 21.7, 18.6, 14.34, 14.14; IR (ATR): 2942, 2875 2244, 1706, 1459, 1425, 1313, 1292, 1229, 508; HRMS (DART+) *m/z*: $[M + H]^+$ calcd for $C_{11}H_{18}NO$ 180.1383, found 180.1379.

Benzyl 4-((1-methyl-3-oxocyclohexyl)methyl)piperidine-1-carboxylate (10). Purification: 25 g SiO_2, 13 → 50% EtOAc in hexanes; General Procedure: isolated 305.0 mg (0.8880 mmol, 89% yield) as a clear, viscous colorless oil; One-Pot Procedure: isolated 273.4 mg (0.7960 mmol, 80% yield). R_f = 0.40 (1:1 hexanes/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35–7.30 (m, 5H), 5.12 (br s, 2H), 4.10 (br s, 2H), 2.79 (br s, 2H), 2.31–2.24 (m, 2H), 3.24 (ABq, $\Delta\delta_{AB}$ = 0.11, J_{AB} = 13.4, 2H), 1.87 (dq, J = 12.3, 6.4 Hz, 2H), 1.66–1.50 (m, 4H), 1.23 (d, J = 4.8 Hz, 2H), 1.19 (br s, 2H), 0.96 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 211.8, 155.2, 136.9, 128.4, 127.9, 127.8, 66.9, 54.0, 48.3, 44.2, 40.9, 39.3, 36.5, 34.4, 31.6, 25.4, 22.1; IR (ATR): 2917, 2851, 1692, 1427, 1283, 1223, 1111, 1072, 731, 697; HRMS (DART+) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{30}NO_3$ 344.2220, found 344.2210.

Ethyl 4-(1-butyl-3-oxocyclohexyl)butanoate (11). Purification: 25 g SiO_2, 6 → 25% EtOAc in hexanes; General Procedure: isolated 230.1 mg (0.8573 mmol, 86% yield) as a clear, colorless oil; One-Pot Procedure: isolated 259.4 mg (0.9057 mmol, 91% yield). R_f = 0.35 (3:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.13 (q, J = 7.1 Hz, 2H), 2.33–2.22 (m, 4H), 2.17 (app t, J =13.5 Hz, 2H), 1.84 (dt, J = 12.6, 6.4 Hz, 2H), 1.61 (dd, J = 6.3, 5.7 Hz, 2H), 1.57–1.49 (m, 2H), 1.32–1.13 (m, 11H), 0.90 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 212.3, 173.5, 60.4, 52.3, 41.2, 40.9, 36.9, 36.7, 34.7, 33.8, 25.1, 23.4, 21.7, 18.6, 14.3, 14.1; IR (ATR): 2932, 2871, 1731, 1708, 1458, 1372, 1175, 1033; HRMS (DART+) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{29}O_3$ 269.2111, found 269.2109.

Ethyl 4-(1-benzyl-3-oxocyclohexyl)butanoate (12). Purification: 25 g SiO_2, 6 → 25% EtOAc in hexanes; General Procedure: isolated 281.8 mg (0.9318 mmol, 93% yield) as a clear, pale yellow oil; One-Pot Procedure: isolated 278.5 mg (0.9209 mmol, 92% yield). R_f = 0.29 (3:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.21 (m, 3H), 7.10 (d, J = 6.8 Hz, 2H), 4.13 (q, J = 7.1 Hz, 2H), 2.62 (ABq, $\Delta\delta_{AB}$ = 0.07, J_{AB} = 13.4 Hz, 2H), 2.30–2.16 (m, 5H), 2.10 (d, J = 13.6 Hz, 1H), 1.99–1.91 (m, 1H), 1.88–1.79 (m, 1H), 1.76–1.54 (m, 4H), 1.27–1.13 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 212.2, 173.5, 137.4, 130.7, 128.2, 126.5, 60.5, 51.5, 44.5, 42.2, 40.9, 36.0, 34.6, 32.8, 21.7, 18.8, 14.4; IR (ATR): 2939, 2873, 1728, 1706, 1453, 1265, 1178, 1031, 731, 702; HRMS (DART+) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{27}O_3$ 303.1955, found 303.1952.

Ethyl 4-(3-oxo-1-phenylcyclohexyl)butanoate (13). Purification: 25 g SiO_2, 5 → 25% EtOAc in hexanes; General Procedure: isolated 258.9 mg (0.8977 mmol, 90% yield) as a clear, colorless oil that solidifies over time; One-Pot Procedure: isolated 249.8 mg (0.8662 mmol, 87% yield). R_f = 0.32 (2:1 hexanes/EtOAc); white waxy solid, mp 54–57 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.25 (m, 4H), 7.21–7.18 (m, 1H), 4.06 (q, J = 7.1 Hz, 2H), 2.92 (d, J = 14.2 Hz, 1H), 2.45 (d, J = 14.3 Hz, 1H), 2.31–2.28 (m, 2H), 2.20–2.13 (m, 1H), 2,14 (t, J = 7.2 Hz, 2H), 2.01 (ddd, J = 13.6, 10.1, 4.3 Hz, 1H), 1.84 (dtd, J = 16.8, 6.3, 3.2 Hz, 1H), 1.75 (td, J = 13.0, 4.5 Hz, 1H), 1.66–1.54 (m, 2H), 1.44–1.33 (m, 1H), 1.26–1.15 (m, 1H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 211.2, 173.3, 144.8, 128.6, 126.4, 126.3, 60.3, 51.2, 46.1, 42.5, 41.1, 36.4,

34.4, 21.5, 19.2, 14.3; IR (ATR): 2943, 2902, 2869, 1717, 1707, 1364, 1201, 1177, 1096, 700; HRMS (DART+) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{25}O_3$ 289.1798, found 289.1797.

Ethyl 4-(1-methyl-3-oxocycloheptyl)butanoate (14). Purification: 25 g SiO_2, 6 → 25% EtOAc in hexanes; General Procedure: isolated 164.9 mg (0.6861 mmol, 69% yield) as a clear, pale yellow oil; One-Pot Procedure: isolated 166.7 mg (0.6936 mmol, 69% yield). R_f = 0.28 (3:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.13 (q, J = 7.1 Hz, 2H), 2.52 (d, J = 12.1 Hz, 1H), 2.42–2.38 (m, 3H), 2.26 (td, J = 7.4, 4.1 Hz, 2H), 1.80–1.48 (m, 8H), 1.32-1.20 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H), 0.92 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 213.8, 173.5, 60.2, 54.7, 44.0, 42.3, 41.7, 35.2, 34.7, 26.0, 24.6, 24.1, 19.1, 14.3; IR (ATR): 2930, 1730, 1693, 1457, 1374, 1249, 1179, 1033; HRMS (DART+) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{25}O_3$ 241.1798, found 241.1797.

Ethyl 4-(1-methyl-3-oxocyclopentyl)butanoate (15). Purification: 25 g SiO_2, 5 → 33% EtOAc in hexanes; General Procedure: isolated 131.7 mg (0.6204 mmol, 62% yield) as a clear, colorless oil; One-Pot Procedure: isolated 147.3 mg (0.6939 mmol, 69% yield). R_f = 0.37 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.14 (q, J = 7.1 Hz, 2H), 2.33–2.27 (m, 4H), 2.06 (ABq, $\Delta\delta_{AB}$ = 0.04, J_{AB} = 17.7 Hz, 2H), 1.86–1.76 (m, 2H), 1.72–1.57 (m, 2H), 1.45–1.41 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H), 1.07 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 219.8, 173.5, 60.5, 52.3, 41.3, 39.6, 36.9, 35.2, 34.8, 25.0, 20.5, 14.4; IR (ATR): 2957, 1730, 1374, 1180, 1155, 1025, 499; HRMS (DART+) *m/z*: $[M + NH_4]^+$ calcd for $C_{12}H_{24}O_3N$ 230.1751, found 230.1750.

Ethyl 4-(2-((tert-butyldimethylsilyl)oxy)-1-methyl-5-oxocyclohexyl)butanoate (16). Purification: 25 g SiO_2, 6 → 25% EtOAc in hexanes; General Procedure: isolated 333.6 mg (0.9356 mmol, 94% yield, 9.2:1 dr) as a clear, colorless oil; One-Pot Procedure: isolated 317.0 mg (0.9254 mmol, 93% yield, 8:1 dr). The diastereomer ratio was measured by ^{1}H NMR integration of the –C**H**(OTBS)– absorption at δ 3.72 (major) and δ 3.68 (minor). Relative stereochemical assignment based upon literature precedent.[40] R_f = 0.44 (3:1 hexanes/EtOAc); *major diastereomer:* ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.12 (q, J = 7.1 Hz, 2H), 3.72 (dd, J = 5.0, 2.7 Hz, 1H), 2.55–2.50 (m, 1H), 2.50 (d, J = 13.1 Hz, 1H), 2.30–2.17 (m, 3H), 2.03–1.97 (m, 1H), 2.01 (d, J = 13.7 Hz, 1H), 1.91–1.86 (m, 1H), 1.61–1.52 (m, 2H),1.27–1.17 (m, 2H),1.25 (t, J = 7.1 Hz, 3H), 0.95 (s, 3H), 0.92 (s, 9H), 0.101(s, 3H), 0.097 (s, 3H); ^{13}C{^{1}H} NMR (151

MHz, $CDCl_3$): δ 211.7, 173.3, 72.4, 60.3, 49.1, 43.1, 38.4, 36.4, 34.7, 29.6, 25.9, 21.8, 18.7, 18.1, 14.3, -4.2, -4.8; *minor diastereomer (selected peaks):* ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.68 (dd, *J* = 3.5, 3.5 Hz, 0.9H), 0.86 (s, 0.24H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 211.7, 173.4, 72.5, 60.3, 49.1, 43.0, 37.6, 36.3, 34.9, 29.6, 25.9, 22.5, 18.9, 18.2, 14.3, -4.1, -5.0; IR (ATR): 2953, 2929, 2856, 1733, 1713, 1472, 1463, 1251, 1176, 1077, 835, 773; HRMS (DART+) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{37}O_4Si$ 357.2456, found 357.2453.

Methyl 2-(4-ethoxy-4-oxobutyl)-2-methyl-4-oxocyclohexane-1-carboxylate (17). Purification: 25 g SiO_2, 8 → 50% EtOAc in hexanes; General Procedure: isolated 261.7 mg (0.9203 mmol, 92% yield, 15.5:1 dr) as a clear, colorless oil; One-Pot Procedure: isolated 257.0 mg (0.9038 mmol, 90% yield, 16:1 dr). The diastereomer ratio was measured by ^{1}H NMR integration of the 4° $-CH_3$ at δ 1.02 (minor) and δ 0.99 (major). Relative stereochemical assignment based upon literature precedent.[41] R_f = 0.24 (2:1 hexanes/EtOAc); *major diastereomer:* ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.12 (q, *J* = 7.1 Hz, 2H), 27.1 (s, 3H), 2.73 (dd, *J* = 8.5, 34.7 Hz, 1H), 2.57 (dtd, *J* = 14.5, 6.2, 1.4 Hz, 1H), 2.43 (dd, *J* = 13.8, 1.5 Hz, 1H), 2.32–2.22 (m, 4H), 2.15–2.04 (m, 2H), 10.73–1.66 (m, 1H), 1.60–1.53 (m, 1H), 1.36 (td, *J* = 13.0, 4.6 Hz, 1H), 1.31 (td, *J* = 12.6, 4.7 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.99 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 210.4, 174.3, 173.3, 60.5, 51.7, 47.7, 40.6, 40.3, 38.9, 34.6, 24.9, 22.0, 18.9, 14.4; *minor diastereomer (selected peaks):* ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.72 (s, 0.21H), 1.02 (s, 0.21H) ; $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 60.5, 50.8, 48.6, 40.3, 38.2, 37.9, 34.8, 25.1, 24.8; IR (ATR): 2954, 1724, 1434, 1368, 1156, 1025, 757; HRMS (DART+) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{25}O_5$ 285.1696, found 285.1693.

Ethyl 4-(1-methyl-3-oxo-5-phenylcyclohexyl)butanoate (18). Purification: 25 g SiO_2, 6 → 25% EtOAc in hexanes; General Procedure: isolated 299.2 mg (0.9894 mmol, 99% yield, > 20:1 dr) as a clear, viscous colorless oil; One-Pot Procedure: isolated 296.6 mg (0.9808 mmol, 73% yield, 8:1 dr; 1.34 mmol scale). The minor diastereomer was not observed by ^{1}H NMR. Relative stereochemistry is assigned by analogy to product **17**. R_f = 0.35 (3:1 hexanes/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35–7.32 (m, 2H), 7.25–7.23 (m, 3H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.11 (tt, *J* = 13.0, 3.9 Hz, 1H), 2.55 (ddd, *J* = 13.8, 4.2, 2.0 Hz, 1H), 2.45 (app t, *J* = 13.4 Hz, 1H), 2.35–2.24 (m, 4H), 1.95 (dt, *J* = 13.8, 1.6 Hz, 1H), 1.74 (app t, *J* = 13.4 Hz, 1H), 1.60 (dq, *J* = 9.7, 7.3 Hz,

2H), 1.41–1.36 (m, 1H), 1.26 (t, J = 7.1 Hz, 3H), 1.27–1.22 (m, 1H), 1.08 (s, 3H); $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): δ 210.9, 173.4, 144.2, 128.8, 126.84, 126.72, 60.4, 53.9, 48.1, 43.7, 39.6, 37.8, 37.0, 34.5, 28.3, 19.1, 14.4; IR (ATR): 2955, 1730, 1710, 1454, 1372, 1184, 1028, 754, 700; HRMS (DART+) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{27}O_3$ 303.1955, found 303.1951.

Ethyl 4-(1,3-dimethyl-5-oxocyclohexyl)butanoate (19). Purification: 25 g SiO_2, 6 → 25% EtOAc in hexanes; General Procedure: isolated 232.0 mg (0.9653 mmol, 97% yield, > 20:1 dr) as a clear, colorless oil; One-Pot Procedure: isolated 170.0 mg (0.7073 mmol, 71% yield, > 20:1 dr). Relative stereochemistry of the cis-methyl relationship is assigned by ^{1}H chemical shift comparison to analogous compounds.[8,42] R_f = 0.35 (3:1 hexanes/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.12 (q, J = 7.1 Hz, 2H), 2.33 (dt, J = 13.4, 2.0 Hz, 1H), 2.29–2.19 (m, 2H), 2.13 (ABq, $\Delta\delta_{AB}$ = 0.02, J_{AB} = 13.6 Hz, 2H), 1.99–1.93 (m, 1H), 1.88 (app t, J = 13.0 Hz, 1H), 1.74 (dt, J = 13.8, 1.5 Hz, 1H), 1.59–1.49 (m, 2H), 1.25 (t, J =7.1 Hz, 3H), 1.26–1.19 (m, 2H), 1.13 (td, J = 12.9, 5.0 Hz, 1H), 1.01 (d, J = 6.2 Hz, 3H), 1.01 (s, 3H); $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$): δ 211.9, 173.6, 60.5, 53.8, 49.4, 44.7, 37.8, 37.3, 34.7, 29.2, 28.4, 22.7, 19.2, 14.4; IR (ATR): 2954, 2871, 1731, 1711, 1456, 1375, 1271, 1177; HRMS (DART+) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{25}O_3$ 241.1798, found 241.1791.

Ethyl 4-(1,3,3-trimethyl-5-oxocyclohexyl)butanoate (20). Purification: 25 g SiO_2, 5 → 25% EtOAc in hexanes; General Procedure: isolated 113.7 mg (0.4470 mmol, 45% yield) as a clear, colorless oil. R_f = 0.21 (4:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.13 (q, J = 7.1 Hz, 2H), 2.27 (app t, J = 7.4 Hz, 2H), 2.15 (ABq, $\Delta\delta_{AB}$ = 0.06, J_{AB} = 13.2 Hz, 4H), 1.65–1.58 (m, 2H), 1.57 (ABq, $\Delta\delta_{AB}$ = 0.09, J_{AB} = 15.9 Hz, 2H), 1.38 (td, J = 11.5, 6.8 Hz, 1H), 1.30-1.22 (m, 1H), 1.26 (t, J = 7.1 Hz, 3H), 1.05 (s, 3H), 1.04 (s, 3H), 1.02 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 212.2, 173.5, 60.3, 54.3, 53.1, 48.9, 44.2, 38.7, 36.1, 34.7, 32.3, 30.6, 27.3, 19.5, 14.3; IR (ATR): 2954, 2908, 1732, 1711, 1462, 1368, 1280, 1181, 1030; HRMS (DART+) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{27}O_3$ 255.1955, found 255.1946.

Ethyl 5-(1-methyl-3-oxocyclohexyl)pentanoate (22). Purification: 25 g SiO_2, 3 → 25% EtOAc in hexanes; One-Pot Procedure: isolated 201.9 mg (0.8400 mmol, 84% yield) as a clear, pale yellow oil. R_f = 0.17 (4:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.13 (q, J = 7.1

Hz, 2H), 2.29 (dt, J = 12.4, 6.5 Hz, 4H), 2.14 (ABq, $\Delta\delta_{AB}$ = 0.07, J_{AB} = 13.5 Hz, 2H), 1.86 (quintet, J = 6.4 Hz, 2H), 1.65–1.50 (m, 4H), 1.34–1.24 (m, 4H), 1.25 (t, J = 7.1 Hz, 3H), 0.91 (s, 3H); $^{13}C\{^1H\}$ NMR (400 MHz, $CDCl_3$): δ 212.3, 173.7, 60.4, 53.9, 41.4, 41.2, 38.7, 35.9, 34.4, 25.7, 25.1, 23.1, 22.3, 14.4; IR (ATR): 2937, 2870, 1731, 1710, 1462, 1170, 1031; HRMS (DART+) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{25}O_3$ 241.1798, found 241.1793.

Ethyl 6-(1-methyl-3-oxocyclohexyl)hexanoate (23). Purification: 25 g SiO_2, 5 → 25% EtOAc in hexanes; One-Pot Procedure: isolated 231.4 mg (0.9097 mmol, 91% yield) as a clear, colorless oil. R_f = 0.20 (4:1 hexanes/EtOAc); ^1H NMR (400 MHz, $CDCl_3$): δ 4.13 (q, J = 7.1 Hz, 2H), 2.28 (q, J = 6.9 Hz, 4H), 2.14 ($\Delta\delta_{AB}$ = 0.07 , J_{AB} = 13.5 Hz, 2H), 1.86 (quintet, J = 6.4 Hz, 2H), 1.66–1.50 (m, 4H), 1.30–1.24 (m, 6H), 1.26 (t, J = 7.1 Hz, 3H), 0.91 (s, 3H); $^{13}C\{^1H\}$ NMR (400 MHz, $CDCl_3$): δ 212.4, 173.9, 60.3, 53.9, 41.6, 41.2, 38.7, 36.0, 34.4, 29.9, 25.19, 25.05, 23.2, 22.3, 14.4; IR (ATR): 2933, 2870, 1731, 1710, 1463, 1176, 1031; HRMS (DART+) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{27}O_3$ 255.1955, found 255.1948.

7-(1-Methyl-3-oxocyclohexyl)heptanenitrile (24). Purification: 25 g SiO_2, 4 → 25% EtOAc in hexanes; One-Pot Procedure: isolated 211.1 mg (0.9537 mmol, 95% yield) as a clear, colorless oil. R_f = 0.27 (2:1 hexanes/EtOAc); ^1H NMR (400 MHz, $CDCl_3$): δ 2.35 (t, J = 7.1 Hz, 2H), 2.27 (t, J = 6.8 Hz, 2H), 2.14 (ABq, $\Delta\delta_{AB}$ = 0.07, J_{AB} = 13.4 Hz, 2H), 1.86 (quintet, J = 6.4 Hz, 2H), 1.69–1.42 (m, 6H), 1.30–1.26 (m, 6H), 0.91 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 212.2, 119.7, 53.7, 41.3, 41.0, 38.5, 35.8, 29.4, 28.5, 25.3, 25.0, 23.0, 22.1, 17.0; IR (ATR): 2931, 2859, 2245,1706, 1457, 1424, 1227, 731, 510; HRMS (DART+) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{24}ON$ 222.1852, found 222.1851.

2-(3-(1-Methyl-3-oxocyclohexyl)propyl)phthalimide (25). Purification: 25 g SiO_2, 12 → 50% EtOAc in hexanes; One-Pot Procedure: isolated 198.9 mg (0.6641 mmol, 66% yield) as a clear, viscous colorless oil. R_f = 0.44 (1:1 hexanes/EtOAc); ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (dd, J = 5.3, 3.0 Hz, 2H), 7.73 (dd, J = 5.3, 3.0 Hz, 2H), 3.66 (t, J = 7.2 Hz, 2H), 2.32–2.24 (m, 2H), 2.14 (ABq, $\Delta\delta_{AB}$ = 0.08, J_{AB} = 13.6 Hz, 2H), 1.86 (dq, J = 12.0, 6.3 Hz, 2H), 1.71–1.53 (m, 4H), 1.36–1.32 (m, 2H), 0.91 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 211.7, 168.3, 133.9, 132.1, 123.2, 53.6, 41.0, 38.9, 38.42, 38.35, 35.7, 24.6, 22.8, 22.1; IR (ATR): 2941, 2873, 2843,

1770, 1702, 1395, 1359, 717; HRMS (DART+) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{22}O_3N$ 300.1592, found 300.1591.

3-(But-3-en-1-yl)-3-methylcyclohexan-1-one (26). Purification: 25 g SiO_2, 5 → 25% EtOAc in hexanes; One-Pot Procedure: isolated 136.3 mg (0.8198 mmol, 82% yield) as a clear, colorless oil. R_f = 0.42 (4:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.79 (ddt, J = 17.0, 10.3, 6.6 Hz, 1H), 5.01 (dd, J =17.2, 1.3 Hz, 1H), 4.94 (dt, J = 10.1, 0.5 Hz, 1H), 2.28 (t, J = 6.8 Hz, 2H), 2.16 (ABq, $\Delta\delta_{AB}$ = 0.08, J_{AB} = 13.5 Hz, 2H), 2.05–1.99 (m, 2H), 1.91–1.84 (m, 2H), 1.68–1.53 (m, 2H), 1.38–1.34 (m, 2H), 0.94 (s, 3H); IR (ATR): 2935, 2851, 1709, 1640, 1452, 1427, 1312, 1227, 995, 908, 507; HRMS (DART+) *m/z*: $[M + H]^+$ calcd for $C_{11}H_{19}O$ 167.1430, found 167.1430. All other spectral data are consistent with reported values.[43]

3-Methyl-3-phenethylcyclohexan-1-one (27). Purification: 25 g SiO_2, 5 → 25% EtOAc in hexanes; One-Pot Procedure: isolated 210.7 mg (0.9740 mmol, 97% yield) as a clear, pale yellow oil. R_f = 0.31 (4:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (app t, J = 7.4 Hz, 2H), 7.16 (app t, J = 7.4 Hz, 3H), 2.56 (td, J = 8.6, 3.2 Hz, 2H), 2.32–2.27 (m, 2H), 2.21 (ABq, $\Delta\delta_{AB}$ = 0.08, J_{AB} = 13.4 Hz, 2H), 1.92–1.85 (m, 2H), 1.73–1.55 (m, 4H), 1.01 (s, 3H). All other spectral data are consistent with reported values.[44]

3-Benzyl-3-methylcyclohexan-1-one (28). Purification: 25 g SiO_2, 5 → 25% EtOAc in hexanes; One-Pot Procedure: isolated 194.4 mg (0.9634 mmol, 96% yield) as a clear, viscous pale yellow oil. R_f = 0.31 (4:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.23 (m, 3H), 7.12 (d, J = 6.9 Hz, 2H), 2.59 (ABq, $\Delta\delta_{AB}$ = 0.05, J_{AB} = 13.2 Hz, 2H), 2.34–2.20 (m, 3H), 2.08 (dt, J = 13.4, 1.4 Hz, 1H), 2.03–1.81 (m, 2H), 1.70–1.54 (m, 2H), 0.91 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 212.0, 137.4, 130.6, 127.9, 126.2, 52.8, 48.3, 40.8, 39.7, 35.7, 24.8, 22.0. All other spectral data are consistent with reported values.[45]

3-Methyl-3-(4-methylbenzyl)cyclohexan-1-one (29). Purification: 25 g SiO_2, 8 → 50% EtOAc in hexanes; One-Pot Procedure: isolated 168.9 mg (0.7808 mmol, 78% yield) as a clear, colorless oil. R_f = 0.47 (2:1 hexanes/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.09 (d, J = 7.6 Hz, 2H), 7.00 (d, J = 7.8 Hz, 2H), 2.54 (ABq, $\Delta\delta_{AB}$ = 0.05, J_{AB} = 13.3 Hz, 2H), 2.33 (s, 3H), 2.30–2.20

(m, 3H), 2.07 (d, J = 13.4 Hz, 1H), 1.99–1.94 (m, 1H), 1.89–1.81 (m, 1H), 1.64 (td, J = 11.8, 3.8 Hz, 1H), 1.56–1.54 (m, 1H), 0.90 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 212.4, 135.8, 134.4, 130.6, 128.7, 53.0, 48.0, 41.0, 39.8, 35.7, 25.0, 22.2, 21.1; IR (ATR): 2920, 1707, 1513, 1455, 1227, 811, 508; HRMS (DART+) *m/z*: $[M + NH_4]^+$ calcd for $C_{15}H_{24}ON$ 234.1852, found 234.1846.

3-(4-Bromobenzyl)-3-methylcyclohexan-1-one (30). Purification: 25 g SiO_2, 5 → 25% EtOAc in hexanes; One-Pot Procedure: isolated 177.0 mg (0.6295 mmol, 63% yield) as a clear, colorless oil. R_f = 0.28 (4:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, J = 8.3 Hz, 2H), 6.99 (d, J = 8.3 Hz, 2H), 2.54 (ABq, $\Delta\delta_{AB}$ = 0.06, J_{AB} = 13.3, 2H), 2.34–2.21 (m, 3H), 2.07 (d, J = 13.4 Hz, 1H), 2.02–1.81 (m, 2H), 1.67–1.54 (m, 3H), 0.89 (s, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$): δ 211.8, 136.5, 132.4, 131.1, 120.4, 52.8, 47.6, 40.9, 39.8, 35.9, 25.0, 22.1;IR (ATR): 2935, 2875, 2848, 1706, 1487, 1456, 1422, 1227, 1142, 1071, 1011, 840, 770, 729, 645, 506; HRMS (DART+) *m/z*: $[M + NH_4]^+$ calcd for $C_{14}H_{21}ONBr$ 298.0801, found 298.0797.

3-Hexyl-3-methylcyclohexan-1-one (31). Purification: 25 g SiO_2, 5 → 25% EtOAc in hexanes; One-Pot Procedure: isolated 175.4 mg (0.8934 mmol, 89% yield) as a clear, colorless oil. R_f = 0.44 (4:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.27 (t, J = 6.8 Hz, 2H), 2.14 (ABq, $\Delta\delta_{AB}$ = 0.08, J_{AB} = 13.5 Hz, 2H), 1.86 (quintet, J = 6.5 Hz, 2H), 1.63 (dt, J = 13.5, 6.6 Hz, 1H), 1.53 (dt, J =12.7, 5.8 Hz, 1H), 1.32–1.21 (m, 10H), 0.91 (s, 3H), 0.88 (t, J = 6.9 Hz, 3H). All other spectral data are consistent with reported values.[46]

1-Methyl-[1,1'-bi(cyclohexan)]-3-one (32). Purification: 25 g SiO_2, 5 → 25% EtOAc in hexanes; One-Pot Procedure: isolated 170.3 mg (0.8764 mmol, 88% yield) as a clear, pale yellow oil. R_f = 0.47 (4:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.30–2.24 (m, 3H), 2.08 (d, J =13.4 Hz, 1H), 1.92–1.52 (m, 9H), 1.24–1.08 (m, 4H), 1.01–0.91 (m, 2H), 0.82 (s, 3H); IR (ATR): 2924, 2851, 1706, 1449, 1226, 520. All other spectral data are consistent with reported values.**Error! Bookmark not defined.**

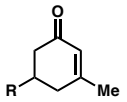
Ethyl 5-(1-methyl-3-oxocyclopentyl)pentanoate (33). Purification: 25 g SiO_2, 5 → 25% EtOAc in hexanes; One-Pot Procedure: isolated 122.6 mg (0.5417 mmol, 54% yield) as a clear,

colorless oil. R_f = 0.18 (4:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.13 (q, J = 7.1 Hz, 2H), 2.33–2.26 (m, 4H), 2.04 (ABq, $\Delta\delta_{AB}$ = 0.04, J_{AB} = 17.9 Hz , 2H), 1.84–1.72 (m, 2H), 1.63 (quintet, J = 7.3 Hz, 2H), 1.45–1.30 (m, 4H), 1.26 (t, J = 7.1 Hz, 3H), 1.04 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 220.0, 173.7, 60.4, 52.4, 41.6, 39.6, 36.9, 35.4, 34.4, 25.7, 25.1, 24.5, 14.4; IR (ATR): 2937, 2870, 1730, 1405, 1175, 1031, 501; HRMS (DART+) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{23}O_3$ 227.1647, found 227.1637.

4-(1-Methyl-3-oxocyclopentyl)butanenitrile (34). Purification: 25 g SiO_2, 12 → 100% EtOAc in hexanes; One-Pot Procedure: isolated 62.3 mg (0.3770 mmol, 38% yield) as a clear, yellow oil. R_f = 0.31 (1:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.38 (m, 2H), 2.32 (td, J = 7.9, 3.1 Hz, 2H), 2.12–2.03 (app s, 2H), 1.82 (t, J = 7.9 Hz, 2H), 1.74–1.55 (m, 4H), 1.08 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 218.9, 119.5, 52.0, 40.8, 39.2, 36.6, 35.1, 24.7, 21.1, 17.7; IR (ATR): 2953, 2875, 2245, 1733, 1457, 1404, 1160, 1160, 497; HRMS (DART+) *m/z*: $[M + H]^+$ calcd for $C_{10}H_{16}ON$ 166.1226, found 166.1227.

3-(4-Chlorobutyl)-3-methylcyclopentan-1-one (35). Purification: 25 g SiO_2, 5 → 25% EtOAc in hexanes; One-Pot Procedure: isolated 124.5 mg (0.6598 mmol, 66% yield) as a clear, colorless oil. R_f = 0.29 (4:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.56 (t, J = 6.6 Hz, 2H), 2.32–2.27 (m, 2H), 2.06 (ABq, $\Delta\delta_{AB}$ = 0.04, J_{AB} = 17.8 Hz, 2H), 1.83–1.77 (m, 4H), 1.56–1.43 (m, 4H), 1.07 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 219.8, 52.3, 45.0, 41.1, 39.6, 36.9, 35.3, 33.2, 25.1, 22.3; IR (ATR): 2953, 2670, 1745, 1457, 1404, 1287, 1154; HRMS (DART+) *m/z*: $[M + H]^+$ calcd for $C_{10}H_{18}OCl$ 189.1041, found 189.1041.

ethyl 4-(3-oxocyclohexyl)butanoate (36). Purification: 25 g SiO_2, 5 → 25% EtOAc in hexanes; One-Pot Procedure: isolated 195.4 mg (0.9158 mmol, 92% yield) as a clear, pale yellow oil. R_f = 0.32 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.13 (q, J = 7.1 Hz, 2H), 2.43 (ddt, J = 13.7, 4.0, 1.9 Hz, 1H), 2.38–2.33 (m, 1H), 2.31–2.21 (m, 3H), 2.08–1.98 (m, 2H), 1.94–1.88 (m, 1H), 1.84–1.73 (m, 1H), 1.70–1.59 (m, 3H), 1.43–1.29 (m, 3H), 1.26 (t, J = 7.1 Hz, 3H). All other spectral data are consistent with reported values.[47]



45 (R = Me)
46 (R = Ph)

δ-Substituted enones 3,5-dimethylcyclohex-2-en-1-one (45) and 5-methyl-1,6-dihydro-[1,1'-biphenyl]-3(2H)-one (46). Enones **45** and **46** were prepared using the same method,[48] as represented by the following procedure for **46**. To a round-bottom flask was added methyl 3-methyl-5-oxo-1,2,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate (1.009 g, 4.130 mmol, 1.0 equiv), DMSO (14.7 mL), H_2O (6 mL; 2.5:1 DMSO/H_2O, 0.2 M) and LiCl (700 mg, 16.5 mmol, 4 equiv). A condenser was affixed to the flask and the contents were warmed to 145 °C until consumption by TLC analysis. The reaction was then cooled to ambient temperature and the contents were transferred to a separatory funnel with Et_2O (125 mL). The contents were mixed, separated, and the organic layer was washed with H_2O (6 x 20 mL). The combined aq layers were extracted with Et_2O (4 x 20 mL), and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by manual flash chromatography (2.5 x 17 cm SiO_2, 1:1 pet. ether/Et_2O) afforded **46** (739.0 mg, 3.969 mmol, 96% yield) as a pale orange/brown oil that partially solidifies upon refrigeration. R_f = 0.23 (3:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (t, J = 7.3 Hz, 2H), 7.28–7.24 (m, 3H), 5.98 (s, 1H), 3.37–3.29 (m, 1H), 2.66 (dd, J = 16.1, 4.1 Hz, 1H), 2.59–2.51 (m, 3H), 2.01 (s, 3H). All other spectral data were consistent with reported values.[49]

Supporting Information

Additional preliminary reaction screen and compound spectra (^{1}H and ^{13}C{^{1}H}) are available in the Supporting Information.

Acknowledgements

The authors thank the American Chemical Society (ACS) Petroleum Research Fund Undergraduate New Investigator Program (Award No. 58488-UNI1), the ACS and Pfizer (research fellowship to T.J.F.), Bucknell University (research fellowships to H.R.R. and T.J.F.) and the Department of Chemistry (research fellowships to P.L.A, A.M.A. and C.B.B.) for generous support of this work. Dr. Peter M. Findeis and Brian Breczinski are acknowledged for experimental and instrumentation assistance.

References and Endnotes

[1] Knochel, P.; Leuser, H.; Cong, L.-Z.; Perrone, S.; Kneisel, F. F. Polyfunctional Zinc Organometallics for Organic Synthesis. In *Handbook of Functionalized Organometallics*; Wiley-VCH Verlag GmbH: Weinheim, Germany, 2005; pp 251–346.

[2] Dagousset, G.; François, C.; León, T.; Blanc, R.; Sansiaume-Dagousset, E.; Knochel, P. Preparation of Functionalized Lithium, Magnesium, Aluminum, Zinc, Manganese-, and Indium Organometallics From Functionalized Organic Halides. *Synthesis* **2014**, *46*, 3133–3171.

[3] Kim, J. H.; Ko, Y. O.; Bouffard, J.; Lee, S.-G. Advances in Tandem Reactions with Organozinc Reagents. *Chem. Soc. Rev.* **2015**, *44*, 2489–2507.

[4] Benischke, A. D.; Ellwart, M.; Becker, M. R.; Knochel, P. Polyfunctional Zinc and Magnesium Organometallics for Organic Synthesis: Some Perspectives. *Synthesis* **2016**, *48*, 1101–1107.

[5] Luche, J. L.; Petrier, C.; Lansard, J. P.; Greene, A. E. Ultrasound in organic synthesis. 4. A Simplified Preparation of Diarylzinc Reagents and Their Conjugate Addition to α-Enones. *J. Org. Chem.* **1983**, *48*, 3837–3839.

[6] Nakamura, E.; Kuwajima, I. Copper-Catalyzed Acylation and Conjugate Addition of Zinc Homoenolate. Synthesis of 4- and 5-Oxo Esters. *J. Am. Chem. Soc.* **1984**, *106*, 3368–3370.

[7] Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, I. Carbon-Carbon Bond-Forming Reactions of Zinc Homoenolate of Esters. A Novel Three-Carbon Nucleophile with General Synthetic Utility. *J. Am. Chem. Soc.* **1987**, *109*, 8056–8066.

[8] Lipshutz, B. H.; Wood, M. R.; Tirado, R. Michael Additions of Functionalized Organozinc Reagents Mediated by Catalytic Quantities of Copper(I). *J. Am. Chem. Soc.* **1995**, *117*, 6126–6127.

[9] Hird, A. W.; Hoveyda, A. H. Catalytic Enantioselective Alkylations of Tetrasubstituted Olefins. Synthesis of All-Carbon Quaternary Stereogenic Centers Through Cu-Catalyzed Asymmetric Conjugate Additions of Alkylzinc Reagents to Enones. *J. Am. Chem. Soc.* **2005**, *127*, 14988–14989.

[10] Lee, K.-S.; Brown, M. K.; Hird, A. W.; Hoveyda, A. H. A Practical Method for Enantioselective Synthesis of All-Carbon Quaternary Stereogenic Centers Through NHC-Cu-Catalyzed Conjugate Additions of Alkyl- and Arylzinc Reagents to B-Substituted Cyclic Enones. *J. Am. Chem. Soc.* **2006**, *128*, 7182–7184.

[11] Brown, M. K.; May, T. L.; Baxter, C. A.; Hoveyda, A. H. All-Carbon Quaternary Stereogenic Centers by Enantioselective Cu-Catalyzed Conjugate Additions Promoted by a Chiral N-Heterocyclic Carbene. *Angew. Chem. Int. Ed.* **2007**, *46*, 1097–1100.

[12] Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. Synthesis and Reactivity Toward Acyl Chlorides and Enones of the New Highly Functionalized Copper Reagents RCu(CN)ZnI. *J. Org. Chem.* **1988**, *53*, 2390–2392.

[13] Yeh, M. C. P.; Knochel, P.; Butler, W. M.; Berk, S. C. 1,4-Additions of the Highly Functionalized Copper Reagents RCu(CN)ZnI • 2 BF_3 to Trisubstituted Enones. A New BF_3 Promoted Cyclization Reaction. *Tetrahedron Lett.* **1988**, *29*, 6693–6696.

[14] Knochel, P.; Chou, T. S.; Chen, H. G.; Yeh, M. C. P.; Rozema, M. J. Nucleophilic Reactivity of Zinc and Copper Carbenoids. Part II. *J. Org. Chem.* **1989**, *54*, 5202–5204.

[15] Tamaru, Y.; Tanigawa, H.; Yamamoto, T.; Yoshida, Z. I. Copper(I)-Promoted Michael-Addition Reaction of Organozincs of Esters, Nitriles, and α-Amino Acids. *Angew. Chem. Int. Ed.* **1989**, *28*, 351–353.

[16] Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. Me_3SiCl/HMPA Accelerated Conjugate Addition of Catalytic Copper Reagent. Stereoselective Synthesis of Enol Silyl Ether of Aldehyde. *Tetrahedron Lett.* **1986**, *27*, 4025–4028.

[17] Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. Me_3SiCl Accelerated Conjugate Addition of Stoichiometric Organocopper Reagents. *Tetrahedron Lett.* **1986**, *27*, 4029–4032.

[18] Matsuzawa, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. Chlorosilane-Accelerated Conjugate Addition of Catalytic and Stoichiometric Organocopper Reagents. *Tetrahedron* **1989**, *45*, 349–362.

[19] Tamaru, Y.; Ochiai, H.; Nakamura, T.; Tsubaki, K.; Yoshida, Z. I. Generation of 2-Carboethoxyethylzinc Iodide and 3-Carboethoxypropylzinc Iodide and Their Application to the Synthesis of γ- and δ-Keto Esters. *Tetrahedron Lett* **1985**, *26*, 5559–5562.

[20] Jubert, C.; Knochel, P. Preparation of New Classes of Aliphatic, Allylic, and Benzylic Zinc and Copper Reagents by the Insertion of Zinc Dust Into Organic Halides, Phosphates, and Sulfonates. *J. Org. Chem.* **1992**, *57*, 5425–5431.

[21] Huo, S. Highly Efficient, General Procedure for the Preparation of Alkylzinc Reagents From Unactivated Alkyl Bromides and Chlorides. *Org. Lett.* **2003**, *5*, 423–425.

[22] Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. Efficient Synthesis of Functionalized Organozinc Compounds by the Direct Insertion of Zinc Into Organic Iodides and Bromides. *Angew. Chem. Int. Ed.* **2006**, *45*, 6040–6044.

[23] Son, S.; Fu, G. C. Nickel-Catalyzed Asymmetric Negishi Cross-Couplings of Secondary Allylic Chlorides with Alkylzincs. *J. Am. Chem. Soc.* **2008**, *130*, 2756–2757.

[24] Thapa, S.; Kafle, A.; Gurung, S. K.; Montoya, A.; Riedel, P.; Giri, R. Ligand-Free Copper-Catalyzed Negishi Coupling of Alkyl-, Aryl-, and Alkynylzinc Reagents with Heteroaryl Iodides. *Angew. Chem. Int. Ed.* **2015**, *54*, 8236–8240.

[25] Hunter, H. N.; Hadei, N.; Blagojevic, V.; Patschinski, P.; Achonduh, G. T.; Avola, S.; Bohme, D. K.; Organ, M. G. Identification of a Higher-Order Organozincate Intermediate Involved in

Negishi Cross-Coupling Reactions by Mass Spectrometry and NMR Spectroscopy. *Chem. Eur. J.* **2011**, *17*, 7845–7851.

[26] Achonduh, G. T.; Hadei, N.; Valente, C.; Avola, S.; O'Brien, C. J.; Organ, M. G. On the Role of Additives in Alkyl–Alkyl Negishi Cross-Couplings. *Chem. Commun.* **2010**, *46*, 4109–4111.

[27] Jensen, A. E.; Knochel, P. Nickel-Catalyzed Cross-Coupling Between Functionalized Primary or Secondary Alkylzinc Halides and Primary Alkyl Halides. *J. Org. Chem.* **2002**, *67*, 79–85.

[28] Isophorone has been shown to engage an RZnI via conjugate addition with the aid of stoichiometric CuCN and HMPA; see Reference 15.

[29] Hill, C. L.; McGrath, M.; Hunt, T.; Grogan, G. A Generic and Reproducible Route to Homo- and Heteroannular Bicyclic β-Diketones via Knochel-Type 1,4-Conjugate Additions to α,β-Unsaturated Cycloalkenones. *Synlett* **2006**, 309–311.

[30] The diorganozinc of this homoenolate has been employed in conjugate addition reactions to disubstituted enones; see References 6 and 7.

[31] Suárez, R. M.; Pérez Sestelo, J.; Sarandeses, L. A. Diastereoselective Conjugate Addition to Chiral α,β-Unsaturated Carbonyl Systems in Aqueous Media: an Enantioselective Entry To α- And γ-Hydroxy Acids And α-Amino Acids. *Chem. Eur. J.* **2003**, *9*, 4179–4187.

[32] Knopff, O.; Alexakis, A. Tandem Asymmetric Conjugate Addition−Silylation of Enantiomerically Enriched Zinc Enolates. Synthetic Importance and Mechanistic Implications. *Org. Lett.* **2002**, *4*, 3835–3837.

[33] Fleming, I.; Barbero, A.; Walter, D. Stereochemical Control in Organic Synthesis Using Silicon-Containing Compounds. *Chem. Rev.* **1997**, *97*, 2063–2192.

[34] Dilman, A. D.; Ioffe, S. L. Carbon−Carbon Bond Forming Reactions Mediated by Silicon Lewis Acids. *Chem. Rev.* **2003**, *103*, 733–772.

[35] The increased stability of the silyl enol ether intermediate is likely due to the β-quaternary substitution pattern.

[36] Son, S.; Fu, G. C. Nickel-Catalyzed Asymmetric Negishi Cross-Couplings of Secondary Allylic Chlorides with Alkylzincs. *J. Am. Chem. Soc.* **2008**, *130*, 2756–2757.

[37] Krasovskiy, A.; Knochel, P. Convenient Titration Method for Organometallic Zinc, Magnesium, and Lanthanide- Reagents. *Synthesis* **2006**, 890–891.

[38] Sealed tubes were required to mitigate evaporative loss of THF during prolonged zinc insertions.

[39] Gu, X.; Dai, Y.; Guo, T.; Franchino, A.; Dixon, D. J.; Ye, J. A General, Scalable, Organocatalytic Nitro-Michael Addition to Enones: Enantioselective Access to All-Carbon Quaternary Stereocenters. *Org. Lett.* **2015**, *17*, 1505–1508.

[40] Polla, M.; Frejd, T. Synthesis of Optically Active Cyclohexenol Derivatives via Enzyme Catalyzed Ester Hydrolysis of 4-Acetoxy-3-Methyl-2-Cyclohexenone. *Tetrahedron* **1991**, *47*, 5883–5894.

[41] Yue, G.; Yang, L.; Yuan, C.; Jiang, X.; Liu, B. Total Synthesis of (±) -Chloranthalactone A. *Org. Lett.* **2011**, *13*, 5406–5408.

[42] Yamada, K.; Fukuyama, T.; Fujii, S.; Ravelli, D.; Fagnoni, M.; Ryu, I. Cooperative Polar/Steric Strategy in Achieving Site-Selective Photocatalyzed C(sp^3)−H Functionalization. *Chem. Eur. J.* **2017**, *23*, 8615–8618.

[43] Martin, D.; Kehrli, S.; d'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. Copper-Catalyzed Asymmetric Conjugate Addition of Grignard Reagents to Trisubstituted Enones. Construction of All-Carbon Quaternary Chiral Centers. *J. Am. Chem. Soc.* **2006**, *128*, 8416–8417.

[44] Totleben, M. J.; Curran, D. P.; Wipf, P. Conjugate Addition Reactions of Organosamarium Species via in Situ Transmetalation to Copper(I) Salts. *J. Org. Chem.* **1992**, *57*, 1740–1744.

[45] Shi, X.; Miller, B. Bridgehead-Substituted Bicyclo[3.3.1]Nonenes and Their Benzo and Dibenzo Derivatives. *J. Org. Chem.* **1995**, *60*, 5714–5716.

[46] Sidera, M.; Roth, P. M. C.; Maksymowicz, R. M.; Fletcher, S. P. Formation of Quaternary Centers by Copper-Catalyzed Asymmetric Conjugate Addition of Alkylzirconium Reagents. *Angew. Chem. Int. Ed.* **2013**, *52*, 7995–7999.

[47] Jones, P.; Reddy, C. K.; Knochel, P. Conjugate Michael Additions with Mixed Diorganozincs. *Tetrahedron* **1998**, *54*, 1471–1490.

[48] Majetich, G.; Allen, S. The Use of Hagemann's Esters to Prepare Highly Functionalized Phenols and Benzenes. *ARKIVOC* **2010**, *iv*, 104–124.

[49] Buzas, A.; Gagosz, F. Gold(I) Catalyzed Isomerization of 5-en-2-Yn-1-Yl Acetates: an Efficient Access to Acetoxy Bicyclo[3.1.0]Hexenes and 2-Cycloalken-1-Ones. *J. Am. Chem. Soc.* **2006**, *128*, 12614–12615.