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Synthesis of δ-Bromo γ,δ-Unsaturated Carbonyl Compounds via Palladium-Catalyzed Bromoalkylation of Alkynoates

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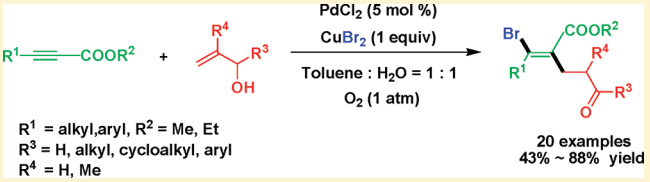
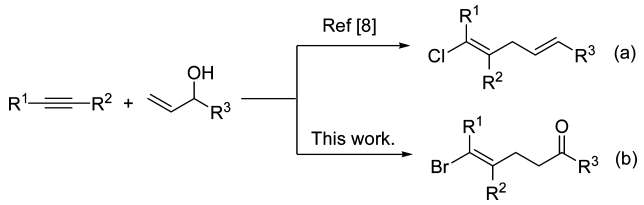
Supporting Information

ABSTRACT: Palladium-catalyzed regio- and stereoselective intermolecular tandem reaction of electron-deficient alkynes, $CuBr_2$, and allylic alcohol to synthesize δ-bromo-γ,δ-unsaturated carbonyls was developed. A mechanism involving bromopalladation of alkyne, followed by insertion of allylic alcohol and allylic hydrogen shift, is proposed. The shift of allylic hydrogen is the rate-limiting step in this reaction.



The capability to construct multiple carbon−carbon and carbon−hetero bonds in one transformation is of importance for the synthesis of vital organic molecules, and related approaches have attracted tremendous attention.[1] In particular, nucleopalladation of carbon−carbon double/triple bonds has been demonstrated to be a versatile methodology.[2,3] However, in these reported examples, only alkenes bearing electron-withdrawing groups were successfully employed to capture the vinylpalladium intermediates generated from the nucleopalladation reaction of alkynes (Scheme 1). Although

Scheme 1. (a) Reported Methods for Allylation of Alkynes and (b) the Method Presented Herein for Alkylation of Alkynes



allyl alcohols are readily available starting materials, palladium-catalyzed reactions of allyl alcohols in allylating or alkylating reactions have not been well developed.[4] The Trost group[5] first disclosed that the ruthenium-catalyzed coupling reactions of alkynes and allyl alcohols generally afford unsaturated carbonyl compounds or hydroalkoxylation products bearing no functional groups.[6] Highly functionalized carbonyl compounds are of significance since they can be readily transformed to numerous valuable synthons, yet the direct and facile synthesis of highly functionalized carbonyl compounds was still reckoned as a challenging task, and only a few examples were found in the literature. A noteworthy example was reported by Lu's group, who developed carbonyl compounds through the sequential chloropalladation of triple bonds and Heck insertion followed β-hydride elimination in a palladium(II)-catalyzed intramolecular cyclization of 4′-hydroxyl-2′-alkenyl 2-alkynoates.[2c] Other examples are Ru-catalyzed three-component coupling reaction for the synthesis of homoallyl ketones reported by Trost and co-workers[7] and Pd-catalyzed allylation of alkynes[8] and allenylation of alkynoates[9] disclosed by our groups. Herein, we report a Pd-catalyzed bromoalkylation reaction of alkynoates and allylic alcohols.

In this study, the alkylation of alkynoates with allyl alcohols was accomplished via a bimetal catalytic system, which provides a highly efficient and mild protocol for the synthesis of highly functionalized carbonyl compounds. This chemistry was initiated by the reaction of primary and secondary allylic alcohols with vinylpalladium complexes generated in situ from bromopalladation of alkynoates. Subsequently, the Pd(II) intermediate was reduced to the Pd(0) species, which is reoxidized to a Pd(II) complex by transition-metal cocatalyst and molecular oxygen. To the best of our knowledge, this catalytic cascade has not been explored in the alkylation reactions of alkynes.

The reaction of methyl oct-2-ynoate (**1a**) and prop-2-en-1-ol (**2a**) was initially piloted in the presence of 5 mol % of $PdCl_2$ and 1 equiv of $CuBr_2$ in various solvents (Table 1, entries 1−6). Apparently, the efficiency of this transformation strongly depends on the solvent used, and the reaction proceeds smoothly in the mixture of PhMe and H_2O (1:1). Plus, the most suitable reaction temperature appears to be 60 °C, and neither higher nor lower reaction temperatures were beneficial for the conversion (entries 6−9). Efforts to further optimize the reaction conditions revealed that $CuBr_2$ was the best bromide source for this reaction. When LiBr was used as the bromide source in the presence of 1.5 equiv of BQ, only a trace amount of the expected product **3aa** was detected (Table 1, entry 10). This reaction was subsequently repeated in the presence of 0.5 equiv of $CuBr_2$, and a lower yield was obtained (Table 1, entry

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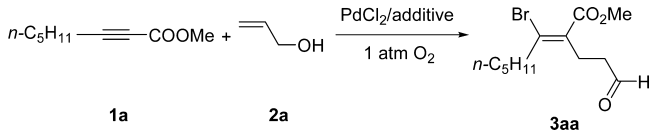
Table 1. Optimization of Reaction Conditions[a]

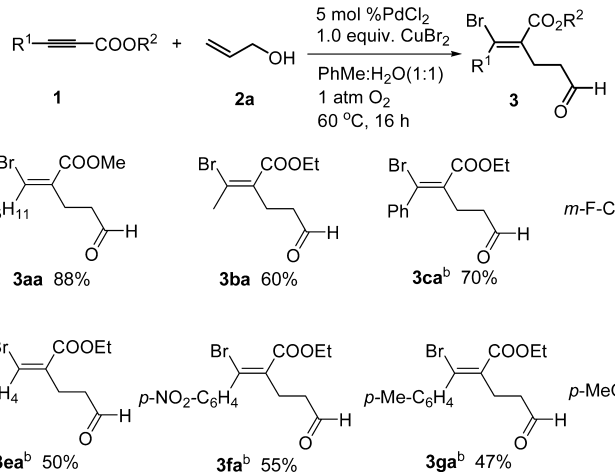


1a 2a 3aa

entry	solvent	bromide source	T (°C)	yield[b] (%)
1	DMSO/H_2O	$CuBr_2$	25	trace
2	EtOH/H_2O	$CuBr_2$	25	0
3	CH_2Cl_2/H_2O	$CuBr_2$	25	0
4	MeCN/H_2O	$CuBr_2$	25	0
5	DMF/H_2O	$CuBr_2$	25	17
6	PhMe/H_2O	$CuBr_2$	25	31
7	PhMe/H_2O	$CuBr_2$	40	37
8	PhMe/H_2O	$CuBr_2$	60	93 (88)
9	PhMe/H_2O	$CuBr_2$	80	78
10	PhMe/H_2O	LiBr/BQ[c]	60	trace
11[d]	PhMe/H_2O	LiBr/$CuBr_2$	60	66
12[e]	PhMe/H_2O	$CuBr_2$	60	15
13[f]	PhMe/H_2O	$CuBr_2$	60	78
14[g]	PhMe/H_2O	$CuBr_2$	60	36

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), $PdCl_2$ (5 mol %), and bromide source (1.0 equiv) in 1 mL of organic solvent and 1 mL of H_2O under O_2 (1 atm) for 16 h. [b]Determined by GC. Number in parentheses is yield of pure product. [c]1.5 equiv of BQ. [d]2.0 equiv of LiBr, $CuBr_2$ (10 mol %). [e]1 atm of air. [f]0.5 equiv of $CuBr_2$. [g]2.0 equiv of $CuBr_2$ and 1 atm of air.

Scheme 2. Pd-Catalyzed Alkylation of Different Alkynoates with Prop-2-en-1-ol[a]



[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), $PdCl_2$ (5 mol %), and $CuBr_2$ (1.0 equiv) in 1 mL of toluene and 1 mL of H_2O under O_2 (1 atm) for 16 h. [b]Reaction was performed at 60 °C for 28 h.

13). Moreover, a moderate yield was obtained when this reaction was conducted in the presence of air (Table 1, entries 12 and 14). It should be noted that the expected aldehyde was the only product observed, and no methyl ketone or 1,4-diene product was detected.

With the optimized reaction conditions in hand (Table 1, entry 8), we proceed to examine the scope of the alkynoates in this bromopalladation/alkylation protocol. Representative results are summarized in Scheme 2. Generally, electron-deficient alkynes gave good yields of δ-bromo-γ,δ-unsaturated carbonyls with excellent stereoselectivity, which presumably originated from the selective *trans*-bromopalladation of alkynes. The stereochemistry of **3aa** was confirmed by HMBC, HSQC, and NOESY methods. To our delight, aliphatic alkynoates afford good yields of the desired product (Scheme 2, **3aa**, **3ba**), but aromatic alkynoates appears to require longer reaction time to achieve the comparable yields (Scheme 2, **3ca**, **3da**, **3ea**, **3fa**, **3ga**, **3ha**). The electronic properties of the substituents on the aromatic alkynoates do not have significant influence on the reaction efficiency. Surprisingly, when terminal alkynoate such as ethyl propiolate was employed in this transformation, a very low yield of the desired product was obtained.

After the effect of alkynoates had been examined thoroughly, we decided to employ a series of secondary allyl alcohols **2** in this transformation (Scheme 3). Methyl-, ethyl-, hexyl-, and cyclohexyl-substituted allylic alcohols were allowed to react under the "optimal" conditions, and good to excellent yields of the desired products were obtained (Scheme 3, **3ab**, **3ac**, **3ad**, **3ae**). Subsequently, aromatic allyl alcohols bearing various substituents at the *para* position of the arenes were utilized in this reaction. Interestingly, both electron-withdrawing and electron-donating group substituted aromatic allylic alchols

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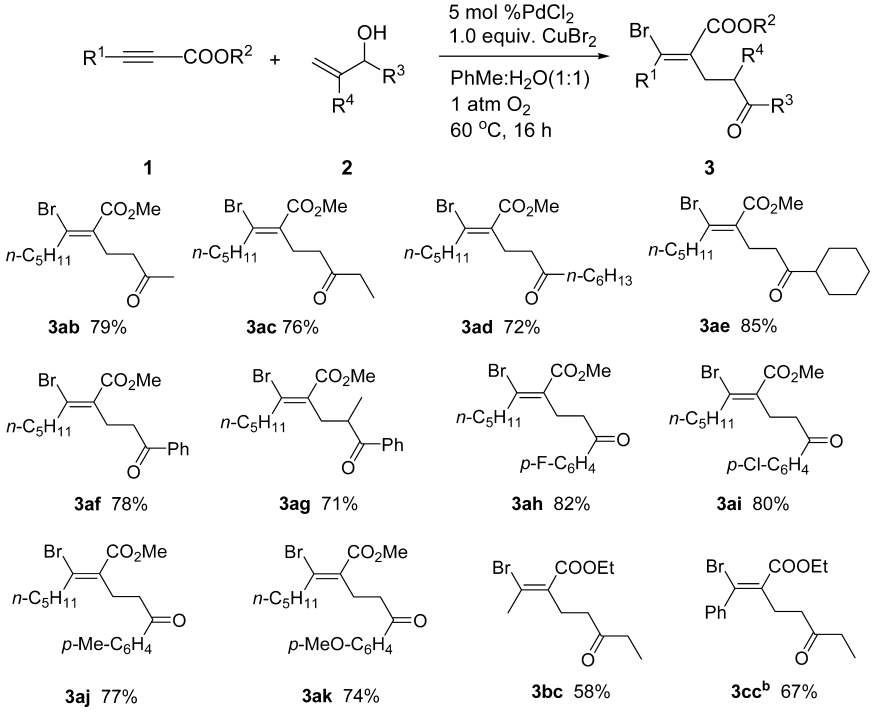
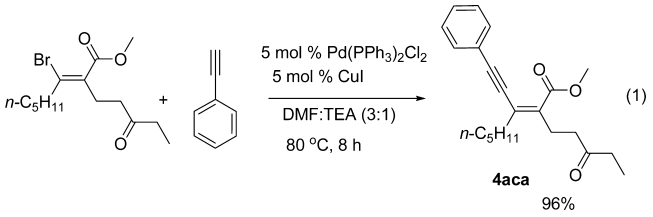
Scheme 3. Pd-Catalyzed Alkylation of Alkynoates 1 with Allyl Alcohols 2[a]



[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), $PdCl_2$ (5 mol %), and $CuBr_2$ (1.0 equiv) in 1 mL of toluene and 1 mL of H_2O under O_2 (1 atm) for 16 h. [b]Reaction was performed at 60 °C for 28 h.

afforded respectful yields of the ketone products, as expected (Scheme 3, **3ah**, **3ai**, **3aj**, **3ak**). Moreover, 2-methyl-1-phenylprop-2-en-1-ol (**2g**) also reacts with methyl oct-2-ynoate (**1a**) to produce ketone **3ag**.

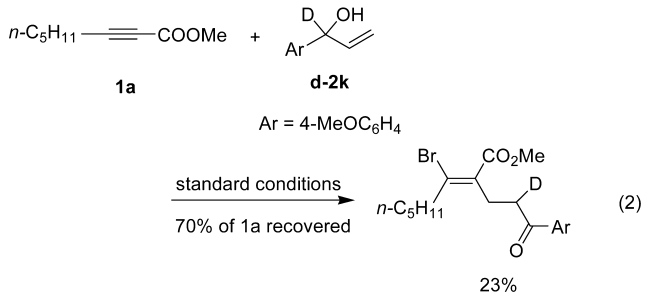
To test the synthetic utility of the products, we studied the Sonogashira coupling of δ-bromo-γ,δ-unsaturated carbonyl compounds with terminal alkynes. Treatment of (*Z*)-methyl 3-bromo-2-(3-oxopentyl)oct-2-enoate (**3ac**) with phenylacetylene under standard conditions (0.5 mmol of **3ac**, 2.0 equiv. of phenylacetylene, 5 mol % of $PdCl_2$, 10 mol % of PPh_3, 5 mol % of CuI, 1 mL of Et_3N, and 1.5 mL of DMF at 80 °C for 8 h) affords high yields of the target product (eq 1).



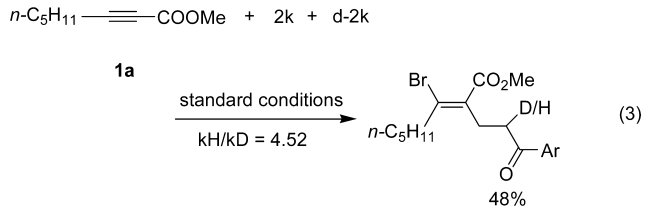
(1)

In order to understand the reaction mechanism of this unique transformation, isotope labeling experiments were performed under the standard reaction conditions. Indeed, when **1a** and **d-2k** were allowed to react, a remarkable intramolecular kinetic isotopic effects were observed (eq 2). This experiment not only indicated that an allylic hydrogen shift is involved in the rate-limiting step but also provided insightful information about the reaction mechanism. Plus, the kinetic isotope effects observed in the intermolecular (k_H/k_D = 4.52) competition experiments also suggested that the allylic hydrogen shift might be the rate-limiting step (eq 3).

On the basis of previous reports[2c−g,3b,d,10] and our experimental data, a plausible mechanism for the Pd-catalyzed



(2)



(3)

alkylation of alkynoate is illustrated in Scheme 4. This transformation presumably involves a few key steps as described below: *Trans*-selective Kaneda reaction of alkynoate **1** affords (*E*)-vinylpalladium intermediate **A**,[11] followed by Mizoroki−Heck reaction of allylic alcohol **2** inserting into the carbon−palladium bond of vinylpalladium species to form intermediate species **B**;[12] **B** undergoes β-deuterium elimination[13] to give intermediate **C**, which subsequently followed by reinsertion of palladium deuterium species into enol to generate intermediate **D**; reductive elimination reaction of intermediate **D** produces the final product **3** which is similar to a Wacker process,[14] and the Pd(II) species is regenerated in the presence of oxidizing reagents $CuBr_2$ and O_2.

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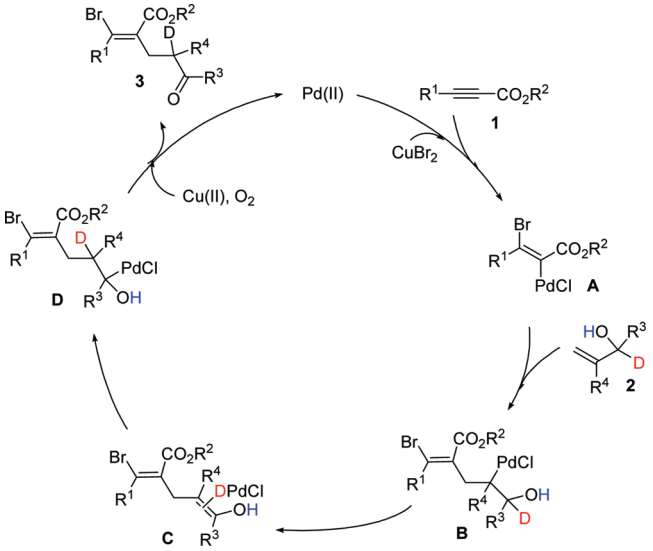
Scheme 4. Mechanistic Hypothesis for the Palladium-Catalyzed Alkylation of Alkynoates with Allyl Alcohols



In conclusion, we have discovered a novel bromoalkylation reaction of alkynoates using allylic alcohols as alkylating agents. This reaction proceeds via bromopalladation and sequential insertions of allylic alcohols. This method is highly atom efficient, regio- and stereoselective and can tolerate a broad range of functional groups. Hence, it is a comprehensive alternative for the synthesis of δ-bromo-γ,δ-unsaturated carbonyls, and this reaction will be useful in organic synthesis due to the potentials of δ-bromo-γ,δ-unsaturated carbonyls.

EXPERIMENTAL SECTION

General method. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer using $CDCl_3$ as solvent and TMS as an internal standard (NOE was recorded in a 600 MHz spectrometer).

The allyl alcohols **2f−k** and ***d*-2k** were prepared according to the literature.[15] Other reagents were purchased as reagent grade and used without further purification.

Typical Procedure for the Synthesis of δ-Bromo-γ,δ-unsaturated Carbonyls. Palladium chloride (9 mg, 0.05 mmol) and $CuBr_2$ (221 mg, 1 equiv) were mixed with toluene (1.0 mL)/H_2O (1.0 mL) in a test tube (10 mL) equipped with a magnetic stirring bar. Then, alkynoate (1.0 mmol) and allylic alcohol (1.0 mmol) were added. The mixture was stirred under an O_2 atmosphere (1 atm) at 60 °C for 16 h. The reaction mixture was taken up by in ether (10 mL) and washed with brine (10 mL). The organic layer was dried ($MgSO_4$), concentrated in vacuo, and purified by flash silica gel chromatography using petroleum ether/ethyl acetate 50:1 to give the desired products. The stereochemistry of **3aa** was further confirmed by HMBC, HSQC, NOESY methods.

*(Z)-Methyl 3-bromo-2-(2-formylethyl)oct-2-enoate (**3aa**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 3.77 (s, 3H), 2.84−2.80 (m, 4H), 2.68−2.64 (m, 2H), 1.65−1.58 (m, 2H), 1.34−1.26 (m, 4H), 0.90 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1, 166.6, 143.3, 130.5, 52.2, 42.0, 39.9, 30.8, 28.4, 27.7, 22.4, 14.0 ppm; ν_{max}(KBr)/cm^{-1} 2930, 1719, 1263; MS (EI) m/z 55, 79, 91, 107, 133, 179, 211, 290. Anal. Calcd for $C_{12}H_{19}BrO_3$: C, 49.50; H, 6.58. Found: C, 49.29; H, 6.67.

*(Z)-Ethyl 3-bromo-2-(2-formylethyl)but-2-enoat (**3ba**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 4.26−4.21 (m, 2H), 2.83 (t, J = 7.6 Hz, 2H), 2.68−2.64 (m, 5H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1, 166.0, 136.9, 131.1, 61.3, 42.0, 28.1, 27.7, 14.2 ppm; ν_{max}(KBr)/cm^{-1} 2980, 1716, 1289; MS (EI) m/z 41, 67, 95, 123, 141, 169, 248. Anal. Calcd for $C_9H_{13}BrO_3$: C, 43.39; H, 5.26. Found: C, 43.15; H, 5.34.

*(Z)-Ethyl 2-(bromo(phenyl)methylene)-4-formylbutanoate (**3ca**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.34−7.28 (m, 5H), 3.93−3.87 (m, 2H), 2.97 (t, J = 7.2 Hz, 2H), 2.80 (t, J = 7.2 Hz, 2H), 0.83 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.7, 167.0, 140.7, 134.0, 133.3, 129.0, 128.1, 61.2, 41.7, 28.1, 13.4 ppm; ν_{max}(KBr)/cm^{-1} 2980, 2934, 1716, 1276; MS (EI) m/z 77, 105, 115, 129, 157, 185, 231, 310. Anal. Calcd for $C_{14}H_{15}BrO_3$: C, 54.04; H, 4.86. Found: C, 53.81; H, 4.91.

*(E)-Ethyl 2-(bromo(3-fluorophenyl)methylene)-4-formylbutanoate (**3da**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 1H), 7.32−7.28 (m, 1H), 7.07−7.00 (m, 3H), 3.93 (q, J = 7.2 Hz, 2H), 2.95 (t, J = 7.2 Hz, 2H), 2.79 (t, J = 7.2 Hz, 2H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4, 166.5, 163.4, 142.5 (d, 8 Hz), 134.9, 131.3 (d, 2 Hz), 129.7 (d, 8 Hz), 123.9 (d, 3 Hz), 115.7 (d, 35 Hz), 115.6 (d, 79 Hz), 61.3, 41.5, 28.0, 13.4 ppm; ν_{max}(KBr)/cm^{-1} 2980, 2933, 1718, 1583, 1438, 1263; MS (EI) m/z: 123, 133, 147, 175, 203, 221, 249, 328. Anal. Calcd for $C_{14}H_{14}BrFO_3$: C, 51.08; H, 4.29. Found: C, 50.94; H, 4.34.

*(Z)-Ethyl 2-(bromo(m-tolyl)methylene)-4-formylbutanoate (**3ea**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.14−7.08 (m, 3H), 3.94−3.89 (m, 2H), 2.96 (t, J = 7.2 Hz, 2H), 2.79 (t, J = 7.6 Hz, 2H), 2.34 (s, 3H), 0.86 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.7, 167.1, 140.5, 137.8, 133.8, 133.5, 129.8, 128.7, 128.0, 125.2, 61.2, 41.7, 28.1, 21.3, 13.4 ppm; ν_{max}(KBr)/cm^{-1} 2926, 1718, 1266; MS (EI) m/z 115, 128, 143, 171, 199, 245, 324. Anal. Calcd for $C_{15}H_{17}BrO_3$: C, 55.40; H, 5.27. Found: C, 55.34; H, 5.32.

*(E)-Ethyl 2-(bromo(4-nitrophenyl)methylene)-4-formylbutanoate (**3fa**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (s, 1H), 8.23−8.19 (m, 2H), 7.48−7.44 (m, 2H), 3.95 (q, J = 7.2 Hz, 2H), 3.00 (t, J = 7.2 Hz, 2H), 2.81 (t, J = 6.8 Hz, 2H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.1, 165.7, 147.7, 146.9, 136.0, 130.5, 129.2, 123.4, 61.6, 41.5, 27.9, 13.6 ppm; ν_{max}(KBr)/cm^{-1} 2980, 1719, 1275; MS (EI) m/z 77, 117, 128, 147, 174, 277, 355. Anal. Calcd for $C_{14}H_{14}BrNO_5$: C, 47.21; H, 3.96; N, 3.93. Found: C, 47.12; H, 4.01; N, 3.98.

*(Z)-Ethyl 2-(bromo(p-tolyl)methylene)-4-formylbutanoate (**3ga**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.85 (s, 1H), 7.19 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 3.96−3.90 (m, 2H), 2.95 (t, J = 7.6 Hz, 2H), 2.79 (t, J = 7.2 Hz, 2H), 2.36 (s, 3H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.7, 167.1, 139.1, 137.8, 133.7, 133.6, 128.7, 128.1, 61.2, 41.7, 28.2, 21.3, 13.5 ppm; ν_{max}(KBr)/cm^{-1} 2981, 1719, 1273; MS (EI) m/z 115, 128, 143, 173, 199, 245, 324. Anal. Calcd for $C_{15}H_{17}BrO_3$: C, 55.40; H, 5.27. Found: C, 55.34; H, 5.32.

*(Z)-Ethyl 2-bromo-(4-methoxyphenyl)methylene)-4-formylbutanoate (**3ha**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.27−7.22 (m, 2H), 6.85−6.81 (m, 2H), 3.98−3.90 (m, 2H), 3.80 (s, 3H), 2.95−2.90 (m, 2H), 2.78−2.73 (m, 2H), 0.95−0.89 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.8, 167.3, 160.1, 133.3, 133.0, 129.7, 128.8, 113.4, 61.2, 55.4, 41.7, 28.3, 13.6 ppm; ν_{max}(KBr)/cm^{-1} 2967, 1718, 1254; MS (EI) m/z 115, 135, 145, 159, 173, 189, 215, 261, 340. Anal. Calcd for $C_{15}H_{17}BrO_4$: C, 52.80; H, 5.02. Found: C, 52.57; H, 5.06.

*(Z)-Methyl 3-bromo-2-(3-oxobutyl)oct-2-enoate (**3ab**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 2.81−2.70 (m, 4H), 2.66−2.59 (m, 2H), 2.16 (s, 3H), 1.64−1.57 (m, 2H), 1.35−1.25 (m, 4H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.5, 166.9, 142.2, 131.1, 52.1, 41.5, 39.8, 30.8, 29.8, 29.2, 28.4, 22.4, 13.9 ppm; ν_{max}(KBr)/cm^{-1} 2929, 1720, 1261; MS (EI) m/z 43, 79, 107, 193, 225, 304. Anal. Calcd for $C_{13}H_{21}BrO_3$: C, 51.16; H, 6.94. Found: C, 50.98; H, 6.99.

*(Z)-Methyl 3-bromo-2-(3-oxopentyl)oct-2-enoate (**3ac**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 2.79−2.71 (m, 4H), 2.61−2.57 (m, 2H), 2.46−2.40 (m, 2H), 1.63−1.56 (m, 2H), 1.33−1.26 (m, 4H), 1.05 (t, J = 7.2 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.1, 166.9, 142.1, 131.3, 52.1, 40.1, 39.8, 35.8, 30.8, 29.3, 28.4, 22.4, 13.9, 7.8 ppm; ν_{max}(KBr)/cm^{-1} 2939, 1720, 1267; MS (EI) m/z: 41, 57, 79, 107, 179, 207, 239, 318. Anal. Calcd for $C_{14}H_{23}BrO_3$: C, 52.67; H, 7.26. Found: C, 52.53; H, 7.31.

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*(Z)-Methyl 2-(1-bromohexylidene)-5-oxoundecanoate (**3ad**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 2.78−2.69 (m, 4H), 2.60−2.54 (m, 2H), 2.42−2.37 (m, 2H), 1.63−1.52 (m, 4H), 1.33−1.26 (m, 10H), 0.90−0.84 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.9, 166.9, 142.0, 131.3, 52.0, 42.7, 40.5, 39.8, 31.6, 30.8, 29.2, 28.9, 28.4, 23.8, 22.5, 22.4, 14.0, 13.9 ppm; ν_{max}(KBr)/cm^{-1} 2929, 1718, 1260; MS (EI) *m*/*z* 43, 85, 113, 235, 263, 295, 374. Anal. Calcd for $C_{18}H_{31}BrO_3$: C, 57.60; H, 8.32. Found: C, 57.23; H, 8.36.

*(Z)-Methyl 3-bromo-2-(3-cyclohexyl-3-oxopropyl)oct-2-enoate (**3ae**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 3H), 2.75 (t, *J* = 7.2, 2H), 2.70−2.67 (m, 2H), 2.63−2.59 (m, 2H), 2.41−2.28 (m, 1H), 1.83−1.75 (m, 4H), 1.66−1.55 (m, 4H), 1.33−1.20 (m, 8H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.7, 167.0, 141.8, 131.5, 52.0, 50.7, 39.8, 38.4, 30.8, 29.2, 28.5, 28.4, 25.8, 25.6, 22.4, 13.9 ppm; ν_{max}(KBr)/cm^{-1} 2931, 2858, 1717, 1444, 1261; MS (EI) *m*/*z* 55, 83, 107, 121, 149, 195, 293, 372. Anal. Calcd for $C_{18}H_{29}BrO_3$: C, 57.91; H, 7.83. Found: C, 57.69; H, 7.91.

*(Z)-Methyl 3-bromo-2-(3-oxo-3-phenylpropyl)oct-2-enoate (**3af**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 3.77 (s, 3H), 3.19 (t, *J* = 7.6 Hz, 2H), 2.91 (t, *J* = 8.0 Hz, 2H), 2.83 (t, *J* = 7.6 Hz, 2H), 1.67−1.60 (m, 2H), 1.36−1.26 (m, 4H), 0.91 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 167.0, 142.7, 136.7, 133.1, 131.3, 128.6, 128.1, 52.1, 39.9, 36.7, 30.9, 29.7, 28.4, 22.4, 14.0 ppm; ν_{max}(KBr)/cm^{-1} 2952, 1721, 1443, 1260; MS (EI) *m*/*z* 41, 77, 91, 105, 227, 255, 287, 366. Anal. Calcd for $C_{18}H_{23}BrO_3$: C, 58.86; H, 6.31. Found: C, 58.68; H, 6.39.

*(Z)-Methyl 3-bromo-2-(2-methyl-3-oxo-3-phenylpropyl)oct-2-enoate (**3ag**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.6 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 3.73 (s, 3H), 2.97−2.92 (m, 1H), 2.83−2.68 (m, 3H), 1.62−1.55 (m, 2H), 1.33−1.20 (m, 8H), 0.88 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.1, 167.2, 142.4, 136.3, 133.0, 130.9, 128.6, 128.4, 52.0, 40.0, 39.6, 38.0, 30.8, 28.4, 22.4, 16.9, 13.9 ppm; ν_{max}(KBr)/cm^{-1} 2935, 1722, 1686, 1449, 1275, 1230; MS (EI) *m*/*z* 77, 105, 301, 380. Anal. Calcd for $C_{19}H_{25}BrO_3$: C, 59.85; H, 6.61. Found: C, 59.64; H, 6.68.

*(Z)-Methyl 3-bromo-2-(3-(4-fluorophenyl)-3-oxopropyl)oct-2-enoate (**3ah**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03−7.99 (m, 2H), 7.15−7.10 (m, 2H), 3.77 (s, 3H), 3.18−3.14 (m, 2H), 2.92−2.89 (m, 2H), 2.83 (t, *J* = 7.6 Hz, 2H), 1.67−1.59 (m, 2H), 1.36−1.29 (m, 4H), 0.91 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 166.9, 165.8 (d, 253 Hz), 142.8, 133.1 (d, 3 Hz), 131.2, 130.7 (d, 10 Hz), 115.7 (d, 22 Hz), 52.1, 39.9, 36.6, 30.9, 29.8, 28.4, 22.4, 14.0 ppm; ν_{max}(KBr)/cm^{-1}2943, 1719, 1597, 1236, 1159; MS (EI) *m*/*z* 41, 95, 123, 305, 384. Anal. Calcd for $C_{18}H_{22}BrFO_3$: C, 56.11; H, 5.76. Found: C, 55.94; H, 5.83.

*(Z)-Methyl 3-bromo-2-(3-(4-chlorophenyl)-3-oxopropyl)oct-2-enoate (**3ai**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 3.77 (s, 3H), 3.17−3.13 (m, 2H), 2.91−2.87 (m, 2H), 2.84−2.81 (m, 2H), 1.66−1.59 (m, 2H), 1.36−1.28 (m, 4H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.7, 166.9, 142.9, 139.5, 135.0, 131.1, 129.5, 128.9, 52.1, 39.9, 36.7, 30.9, 29.7, 28.4, 22.4, 14.0 ppm; ν_{max}(KBr)/cm^{-1} 2949, 2363, 1720, 1257, 1091; MS (EI) *m*/*z* 111, 139, 321, 400. Anal. Calcd for $C_{18}H_{22}BrClO_3$: C, 53.82; H, 5.52. Found: C, 53.61; H, 5.56.

*(Z)-Methyl 3-bromo-2-(3-oxo-3-p-tolylpropyl)oct-2-enoate (**3aj**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 3.76 (s, 3H), 3.17−3.13 (m, 2H), 2.92−2.88 (m, 2H), 2.84−2.81 (m, 2H), 2.40 (s, 3H), 1.66−1.59 (m, 2H), 1.36−1.29 (m, 4H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.5, 167.0, 143.8, 142.5, 134.2, 131.4, 129.3, 128.2, 52.1, 39.9, 36.6, 30.9, 29.8, 28.4, 22.4, 21.6, 14.0 ppm; ν_{max}(KBr)/cm^{-1} 2953, 1721, 1609, 1441, 1260; MS (EI) *m*/*z* 91, 119, 301, 380. Anal. Calcd for $C_{19}H_{25}BrO_3$: C, 59.85; H, 6.61. Found: C, 59.73; H, 6.64.

*(Z)-Methyl 3-bromo-2-(3-(4-methoxyphenyl)-3-oxopropyl)oct-2-enoate (**3ak**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H), 3.77 (s, 3H), 3.15−3.11 (m, 2H), 2.91−2.81 (m, 4H), 1.67−1.59 (m, 2H), 1.35−1.28 (m, 4H), 0.91 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 167.0, 163.5, 142.4, 131.5, 130.4, 129.8, 113.7, 55.5, 52.1, 39.9, 36.4, 30.9, 29.9, 28.4, 22.4, 14.0 ppm; ν_{max}(KBr)/cm^{-1} 2930, 1721, 1678, 1602, 1267; MS (EI) *m*/*z* 77, 107, 135, 150, 317, 396; Anal. Calcd for $C_{19}H_{25}BrO_4$: C, 57.44; H, 6.34. Found: C, 57.29; H, 6.41.

*(Z)-Ethyl 2-(1-bromoethylidene)-5-oxoheptanoate (**3bc**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24−4.18 (m, 2H), 2.73 (t, *J* = 7.2 Hz, 2H), 2.60−2.51 (m, 5H), 2.45−2.40 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.05 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.2, 166.3, 135.7, 131.8, 61.2, 40.1, 35.7, 29.2, 28.0, 14.2, 7.8 ppm; ν_{max}(KBr)/cm^{-1} 2979, 1716, 1268; MS (EI) *m*/*z* 57, 151, 197, 276. Anal. Calcd for $C_{11}H_{17}BrO_3$: C, 47.67; H, 6.18. Found: C, 47.55; H, 6.21.

*(Z)-Ethyl 2-(bromo(phenyl)methylene)-5-oxoheptanoate (**3cc**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.28 (m, 5H), 3.90 (q, *J* = 7.2 Hz, 2H), 2.92−2.87 (m, 2H), 2.77−2.73 (m, 2H), 2.49 (q, *J* = 7.2 Hz, 2H), 1.09 (t, *J* = 7.2 Hz, 3H), 0.84 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.8, 167.2, 140.7, 134.8, 132.4, 128.9, 128.1, 61.1, 39.8, 35.8, 29.6, 13.4, 7.8 ppm; ν_{max}(KBr)/cm^{-1} 2979, 1712, 1449, 1272; MS (EI) *m*/*z* 57, 105, 129, 157, 185, 259, 338. Anal. Calcd for $C_{16}H_{19}BrO_3$: C, 56.65; H, 5.65. Found: C, 56.48; H, 5.67.

*(Z)-Methyl 2-(3-oxopentyl)-3-(2-phenylethynyl)oct-2-enoate (**4aca**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.44 (m, 2H), 7.36−7.33 (m, 3H), 3.78 (s, 3H), 2.92−2.88 (m, 2H), 2.66−2.63 (m, 2H), 2.59−2.55 (m, 2H), 2.44 (q, *J* = 7.2 Hz, 2H), 1.68−1.62 (m, 2H), 1.37−1.33 (m, 4H), 1.06 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.60, 168.37, 135.69, 134.13, 131.70, 128.83, 128.45, 122.78, 99.14, 88.46, 51.67, 41.47, 35.85, 33.85, 31.45, 28.54, 27.44, 22.49, 14.03, 7.86 ppm; ν_{max}(KBr)/cm^{-1} 2931, 2862, 1715, 1596, 1439, 1271, 1171, 1103, 1023, 757, 690; HRMS EI (*m*/*z*) calcd for $C_{22}H_{28}O_3$ 340.2038, found 340.2033.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectral data for all new compounds; NOE studies on the stereochemistry of **3aa**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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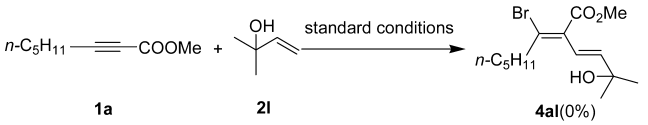

100% recovery of **1a**

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