γ-Selective allylation of *(E)*-alkenylzinc iodides prepared by reductive coupling of arylacetylenes with alkyl iodides

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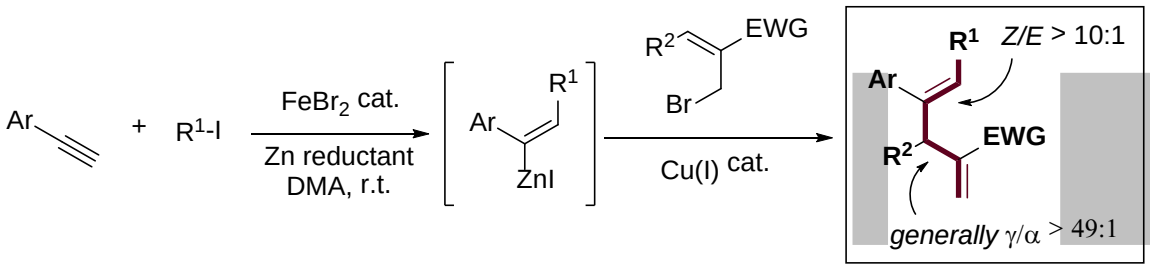
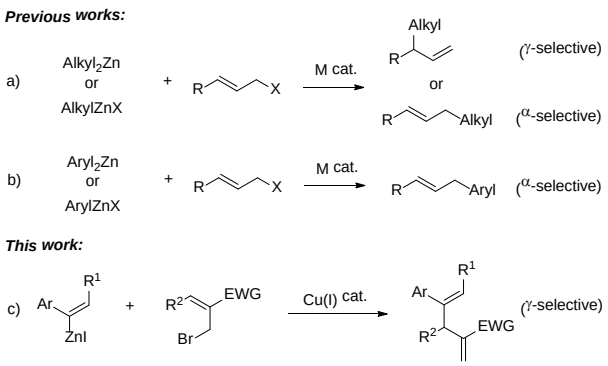


ABSTRACT: The first examples of Cu-catalyzed γ-selective allylic alkenylation using organozinc reagents are reported. *(E)*-alkenylzinc iodides were prepared by Fe-catalyzed reductive coupling of terminal arylalkynes with alkyl iodides. In the presence of a copper catalyst, these reagents reacted with allylic bromides derived from Morita-Baylis-Hillman alcohols to give 1,4-dienes in high yields. The reactions are highly γ-selective (generally γ/α > 49:1) and tolerate a wide range of functional groups such as ester, cyano, keto, and nitro.

Metal-catalyzed allylic substitution using organozinc reagents is a versatile method for C-C bond formation. Unlike alkylzinc[1-3] and arylzinc[4, 5] reagents (Scheme 1, a and b) which are widely used in these reactions, alkenylzinc reagents are rarely employed. There are only few examples of catalytic allylic alkenylation using alkenylzinc reagents to yield 1,4-dienes, which are ubiquitous in nature and represent an important class of synthetic building blocks .[5-10]

Scheme 1. Metal-catalyzed allylic substitution with organozinc reagents



Alkenylzinc compounds are commonly prepared[11] by direct Zn insertion into the carbon-halogen bond of alkenyl halides,[12, 13] or by transmetallation from alkenyl organometallic reagents.[14] Both approaches are limited by the difficulty to obtain stereochemically pure alkenyl halides.[15] Alkenylzinc reagents can also be prepared by carbozincation of alkynes with organozinc reagents.[16] This approach is potentially stereoselective, but it requires reactive organometallic reagents which can be hard to handle or can lower functional group compatibility. We have recently reported Fe-catalyzed reductive coupling of arylacetylenes with alkyl halides to form *cis*-alkenes. Mechanistic studies indicated that the reaction proceeded via formation of *(E)*-alkenylzinc intermediates (eq 1).[17,18] Thus, this reaction provides an easy access to stereochemically pure alkenylzinc reagents **1** without the need of sensitive organometallic reagents. Here we describe a Cu-based catalytic system for the reactions of these alkenylzinc reagents with allylic bromides (Scheme 1, c). To the best of our knowledge, this is the first γ-selective catalytic allylic alkenylation. The few precedents of catalytic allylic alkenylation either employed symmetrical allylic substrates[12,19-21] or were α-selective.[22,23]

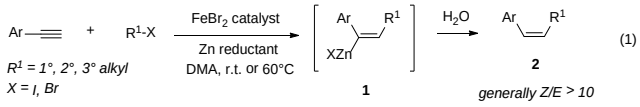
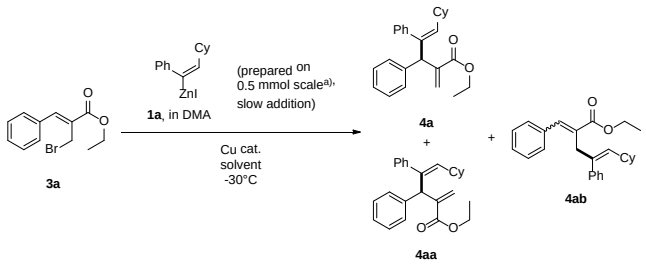


Table 1. Optimization of reaction conditions of *(E)*-alkenylzinc iodides allylation



entry	addition rate, mL/h	catalyst (mol%)	solvent (mL)	time, h	yield[b], % (4a:4ab)
1[c]	3.0	$CuBr{\cdot}SMe_2$ (10)	DCM (2)	3.5	58 (71:1)
2[c]	3.0	$(MeCN)_4CuPF_6$ (10)	DCM (2)	3.5	63 (66:1)
3[c]	3.0	$(CuOTf)_2{\cdot}C_6H_6$ (10)	DCM (2)	3.5	53 (40:1)
4[c]	3.0	CuCl·2LiCl (10)	DCM (2)	3.5	65 (45:1)
5[c]	3.0	CuCN·2LiCl (10)	DCM (2)	3.5	74 (70:1)
6[c]	3.0	CuNHC[d] (5)	DCM (2)	3.5	<1 (n.d.)
7[c]	1.0	CuCN·2LiCl (5)	DCM (2)	24	88 (56:1)
8[c]	1.0	CuCN·2LiCl (5)	THF (2)	24	77 (42:1)
9[e]	1.0	CuCN·2LiCl (5)	DCM (2)	24	93[f] (68:1)
10[e]	1.0	-	DCM (2)	24	1 (n.d.)

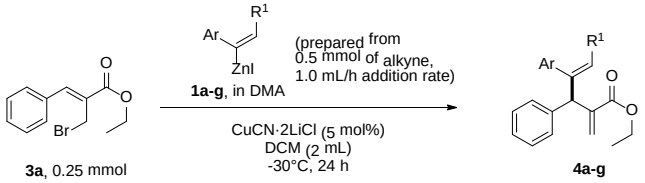
a) Phenylacetylene (0.5 mmol, 1 equiv.), iodocyclohexane (1.5 equiv.), Zn (1.5 equiv.), TMSCl (20 mol%), $FeBr_2$ (10 mol%) were stirred in DMA (1 mL) overnight (17-19 h). The resulting solution was used directly for the reactions with allylic bromides; b) Uncalibrated GC yield of the isomeric mixture (**4a** + **4aa** + **4ab**), corrected by number of carbons; c) 0.35 mmol of **3a** was used; d) Chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]copper(I) was used as catalyst; e) 0.25 mmol of **3a** was used; f) **4a**:**4aa** 12:1.

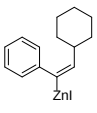
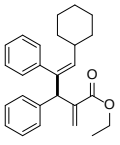
Allylic halides derived from Morita-Baylis-Hillman (MBH) alcohols were chosen because the products contain both an activated C-C double bond and an electron-withdrawing group that are prone to further transformations. A diverse number of substrates are available thanks to the large scope of MBH

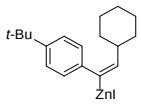
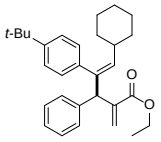
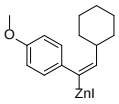
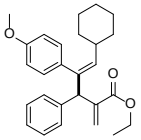
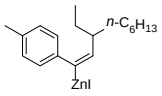
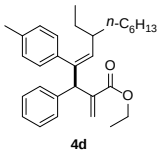
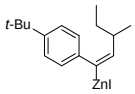
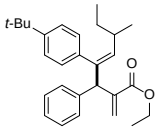
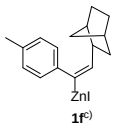
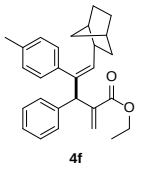
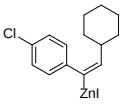
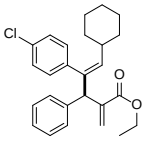
reaction.[24] Moreover, earlier works[25-27] showed that alkylation of MBH alcohols-derived allylic halides could be γ-selective. It was found that under Cu-catalysis ethyl *(Z)*-2-(bromomethyl)-3-phenylacrylate (**3a**) reacted with **1a,** prepared by Fe-catalyzed reductive coupling of phenylacetylene and iodocyclohexane, to give the corresponding γ-product **4a** with high regioselectivity (Table 1). Among various copper catalysts, CuCN·2LiCl gave the highest yield and γ-selectivity (Table 1, entries 1-6). The yield could be improved using longer reaction time (24 h) and a slower addition rate with 5 mol% of CuCN·2LiCl as catalyst (Table 1, entry 7). Replacing dichloromethane (DCM) by tetrahydrofuran (THF) as the solvent led to a lower yield (Table 1, entry 8). The highest yield was obtained using 5 mol% of CuCN·2LiCl in DCM at -30°C for 24 h with 0.25 mmol of **3a** and **1a** prepared on 0.5 mmol scale (Table 1, entry 9). Only a trace amount of product was obtained without a copper catalyst (Table 1, entry 10).

Table 2 shows the scope of this reaction with respect to *(E)*-alkenylzinc reagents. Despite the presence of a complex mixture of metal ions and unreacted organic starting materials and side-products, the desired dienes **4a-g** were obtained in high isolated yields and with high *Z/E* selectivity. In all cases the products were almost exclusively γ-regioisomers (γ/α > 49:1). Various substituents on the aryl rings of the *(E)*-alkenylzinc reagents were tolerated (**1a-1d**, **1g**). The R^1 group of the *(E)*-alkenylzinc reagents can be either cyclic (**1a**, **1f**) or acyclic (**1d**, **1e**).

Table 2. Scope of *(E)*-alkenylzinc reagent



entry	alkenylzinc iodide	product	yield[a], %	Z/E[b]
1	 1a	 4a	87	12:1

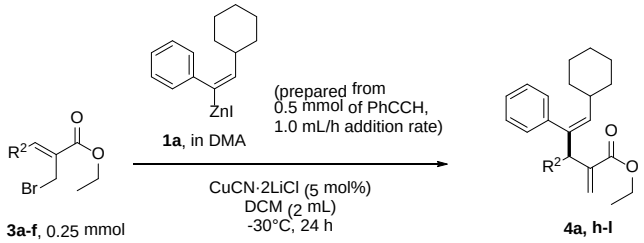
2	 **1b**	 **4b**	84	12:1
3	 **1c**	 **4c**	79	11:1
4	 **1d**	 **4d**	73	57:1
5	 **1e**	 **4e**	74	21:1
6	 **1f**[c)]	 **4f**	68	16:1
7	 **1g**	 **4g**	73	11:1

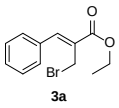
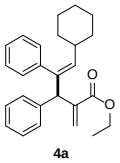
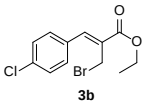
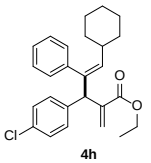
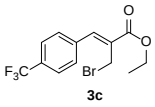
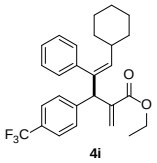
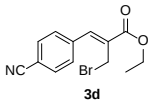
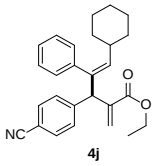
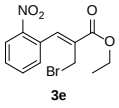
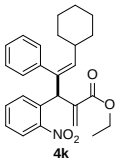
a) Isolated yields of pure products (as a mixture of isomers); b) Determined by ^{1}H NMR. Similar values were obtained by GC; c) exo/endo of the corresponding alkene is > 50:1.[17]

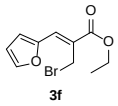
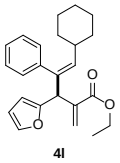
The scope of 2-(bromomethyl)acrylates is shown in Table 3. Both aryl- (**3a-e**) and heteroarylsubstituted (**3f**) substrates could be used. The reactions were again highly γ-selective (γ/α > 49:1) and Z-selective. Electron-withdrawing substituents in the aryl ring generally led to high yields, except for **4k**, which has a nitro group in *ortho*-position of the phenyl ring. The steric influence of this nitro group probably led to the modest yield (49%). An electron-rich 2-furylsubstituted substrate also reacted in a high yield (**3f**). A crystal structure of compound **4k** was determined (Figure 1) to confirm the regioselec-

tivity and diastereoselectivity of the reaction.

Table 3. Scope of aryl- and heteroarylsubstituted 2-(bromomethyl)acrylates



entry	allylic bromide	product	yield[a], %	Z/E[b]
1	 3a	 4a	87	12:1
2	 3b	 4h	90	12:1
3	 3c	 4i	84	12:1
4	 3d	 4j	92	13:1
5	 3e	 4k	49	16:1

6	 3f	 4l	75	11:1

a) Isolated yield of pure product (as a mixture of isomers). b) Determined by ^{1}H NMR (similar values were obtained by GC).

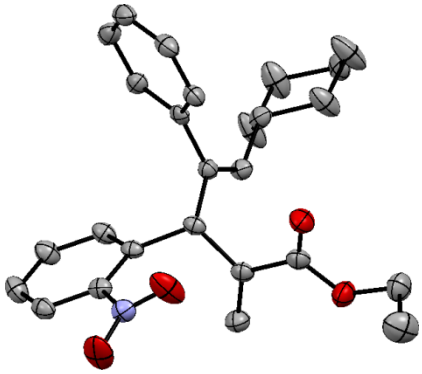
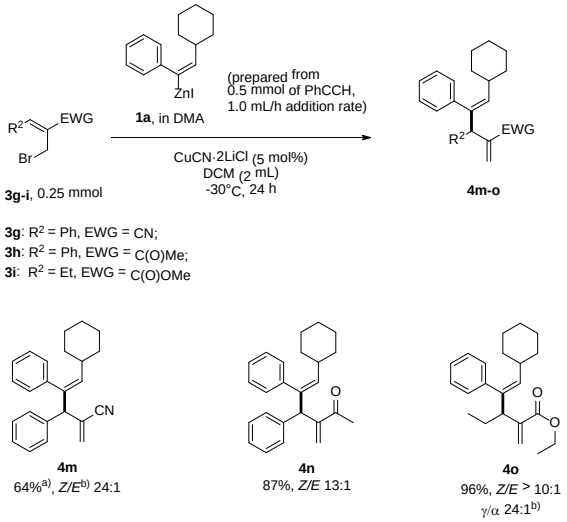


Figure 1. X-Ray structure of compound **4k**. Thermal ellipsoids are drawn at 50% probability level. Hydrogen atoms are omitted. Color code: red for O; blue for N; grey for C.

Previously allylic substitution with MBH alcohols-derived allylic bromides was limited to reactions of 3-aryl-2-(bromomethyl)acrylates.[25] In the current study, the scope of allylic bromides is increased (Scheme 2). Substrates bearing a nitrile group (**3g**) and alkyl keto group (**3h**) reacted with excellent regioselectivity (γ/α > 49:1). A substrate derived from alkyl aldehyde (**3i**) was also alkenylated with good regioselectivity (γ/α = 24:1).

Scheme 2. Scope of novel types of MBH alcohols-derived allylic bromides



a) Isolated yield of pure product (as a mixture of isomers). b) Determined by ^{1}H NMR (similar values were obtained by GC).

In summary, the first Cu-catalyzed γ-selective allylic alkenylation was developed, employing *(E)*-alkenylzinc reagents prepared by Fe-catalyzed reductive coupling of arylacetylenes with alkyl iodides and allylic bromides derived from Morita-Baylis-Hillman alcohols. The method uses a simple copper(I) catalyst and tolerates a number of important functional groups such as ester, nitrile, keto and nitro. This method provides an easy access to highly functionalized 1,4-dienes in high regio- and *Z/E*-selectivity and may be used to prepare libraries of steroid mimics and antitumor drugs, such as aromatase inhibitor tamoxifen and related compounds.[28]

EXPERIMENTAL SECTION

General Information

NMR spectra were recorded on a 400 MHz instrument at ambient temperature in $CDCl_3$ as solvent. ^{1}H NMR chemical shifts (δ, ppm) were measured relative to tetramethylsilane (TMS) signal in $CDCl_3$ (0.00 ppm) unless otherwise stated. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C NMR chemical shifts (δ, ppm) are reported relative to $CDCl_3$ signal

(77.16 ppm) unless otherwise stated. The diffraction data were measured at low temperature [100(2) K] using Mo K_α radiation on a diffractometer equipped with a kappa geometry goniometer.

Unless otherwise noted, all chemicals were commercially available and were used as received without further purifications. Solvents were purified using a two-column solid-state purification system and transferred to glove box without exposure to air by the aid of a Straus flask. Zn powder (<10µ, 98%+) was purchased from Aldrich. Anhydrous dimethylacetamide (DMA) (99.8% purity) was commercially purchased and stored under nitrogen. Iron(II) bromide ($FeBr_2$, 98% purity) was purchased from Aldrich or Acros. All the chiral starting materials and products were in form of racemic mixtures, for the products containing two stereogenic centers the corresponding diastereomeric ratio was 1:1. Silica gel (40-63 µm, 230-400 mesh) was used as stationary phase for column chromatography.

Starting materials preparation

For additional details about preparation of *(E)*-alkenylzinc reagents **1a-g** see ref. 17,18. All the substrates **3a-i** were prepared from corresponding Morita-Baylis-Hillman (MBH) alcohols by treatment with HBr/H_2SO_4[25] or PBr_3.[29] For the furylsubstituted substrate **3f** PBr_3 must be used. In order to obtain good yields in allylic substitution reactions, the crude bromides should be purified by column chromatography or (if possible) recrystallized from ether/hexane.

For the substrates **3a-e**, **3g**, the starting MBH-alcohols can be prepared by using the procedure from ref. 25. MBH-alcohols for preparation of **3f** and **3i** are synthesized using 1,4-dioxane/water 1:1 mixture as solvent, in order to accelerate the reaction.[30] In case of the alcohol that corresponds to the bromide **3h**,[31] we were unable to separate it from methylvinylketone (MVK) dimer that forms as a side-product. However, after the treatment of the product mixture by PBr_3, the resulting bromide **3h**, can be easily isolated from unreacted MVK dimer. All the bromides are obtained as *Z*-isomers,[25,31] with exception of **3g**, which was obtained as a mixture of *E*- and *Z*-isomers.[32]

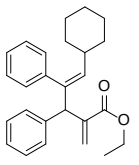
General procedures

Alkenylzinc reagent solution. Under a dry nitrogen atmosphere a 20 mL screw-cap vial, equipped with a magnetic stirring bar, was charged with Zn dust (49 mg, 0.75 mmol), DMA (1 mL) and TMSCl (11 mg, 0.1 mmol). The mixture was vigorously shaken for a while and then $FeBr_2$ (11 mg, 0.05 mmol), alkyne (0.5 mmol) and alkyl iodide (0.75 mmol) were added. The vial was then sealed and its content was allowed to stir overnight (18-20 h) at ambient temperature.

Allylic alkenylation. A 20 mL screw-cap vial, equipped with a small magnetic stirring bar (to prevent splashing the reaction mixture on the walls of the vial), was charged under a dry nitrogen atmosphere with allylic bromide (0.25 mmol, 1.0 equiv.), CuCN·2LiCl (0.13 mL of 0.1 M solution in THF, 0.013 mmol, 5 mol%) and dry degassed DCM (2 mL). The vial was sealed with a rubber septum, taped, and cooled to -30°C. Alkenylzinc reagent solution was added using a syringe pump at 1.0 mL/h rate. The resulting mixture was allowed to stir for 24 h at -30°C (counting from the beginning of organozinc reagent addition). The mixture was quenched with 1M HCl. *n*-Dodecane (57 µL, 0.25 mmol) was added, and the mixture was extracted into ca. 4 mL of diethyl ether. The ethereal layer was analyzed by GC-MS at this point. After that, the content of the vial was poured into water or 1M HCl and extracted with diethyl ether (4 x 10 mL). Combined ether extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The crude was dried *in vacuo*, and purified by column chromatography (10-15 g of SiO_2, ethyl acetate / hexane 1:99 – 10:90).

If the GC yield is less than 80-85%, to facilitate the chromatographic isolation of the product, the crude can be stirred with DABCO (0.25-0.5 mmol) in 2-4 mL of diethyl ether overnight. Then, the ether was removed *in vacuo* and the residue was taken up in a small amount of the eluent for the column chromatography purification.

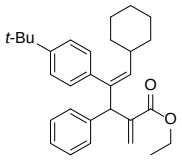
Ethyl (Z)-5-cyclohexyl-2-methylene-3,4-diphenylpent-4-enoate (**4a**)



4a

Prepared from phenylacetylene (51 mg, 0.5 mmol), iodocyclohexane (158 mg, 0.75 mmol) and bromide **3a** (67 mg, 0.25 mmol). Yellowish oil, 80.9 mg (87%). *Z/E* 12:1. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.29-7.13 (10H, m); 6.28 (1H, s); 5.24 (1H, d, *J* = 9.9 Hz); 5.08 (1H, s); 4.91 (1H, s); 4.23 (2H, q, *J* = 7.0 Hz); 2.1-2.0 (1H, m); 1.64-1.49 (5H, m); 1.30 (3H, t, *J* = 7.0 Hz); 1.17-1.03 (5H, m). ^{13}C NMR ($CDCl_3$, 101 MHz): 167.5; 144.1; 142.2; 139.8; 139.0; 136.2; 129.7; 128.6; 128.4; 128.0; 126.8; 126.6; 60.9; 55.0; 37.7; 33.6; 33.3; 26.1; 25.7; 25.7; 14.5. Anal. Calcd for $C_{26}H_{30}O_2$: C, 83.38; H, 8.07. Found: C, 83.47; H 8.18. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{30}O_2Na$ 397.2143; Found 397.2144.

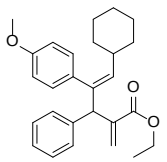
Ethyl (Z)-4-(4-(tert-butyl)phenyl)-5-cyclohexyl-2-methylene-3-phenylpent-4-enoate (**4b**)



4b

Prepared from 1-(tert-butyl)-4-ethynylbenzene (79 mg, 0.5 mmol), iodocyclohexane (158 mg, 0.75 mmol) and bromide **3a** (67 mg, 0.25 mmol). Yellowish oil, 90.3 mg (84%). Z/E 12:1. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.29-7.15 (7H, m); 7.06 (2H, d, J = 7.8 Hz); 6.27 (1H, s); 5.21 (1H, d, J = 10.0 Hz); 5.04 (1H, s); 4.92 (1H, s); 4.21 (2H, q, J = 7.0 Hz); 2.1-2.0 (1H, m); 1.68-1.50 (5H, m); 1.31-1.27 (12H, m); 1.16-1.06 (5H, m). ^{13}C NMR ($CDCl_3$, 101 MHz): 167.5; 149.1; 144.4; 140.2; 139.0; 138.5; 136.4; 129.7; 128.3; 128.1; 126.7; 126.4; 124.8; 60.9; 54.8; 37.6; 34.5; 33.7; 33.4; 31.5; 26.1; 25.7; 25.7; 14.5. Anal. Calcd for $C_{30}H_{38}O_2$: C, 83.67; H 8.89. Found: C, 83.67; H 9.13. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{30}H_{39}O_2$ 431.2945; Found 431.2946.

Ethyl (Z)-5-cyclohexyl-4-(4-methoxyphenyl)-2-methylene-3-phenylpent-4-enoate (**4c**)

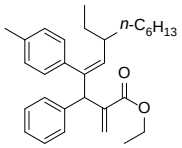


4c

Prepared from 1-ethynyl-4-methoxybenzene (66 mg, 0.5 mmol), iodocyclohexane (158 mg, 0.75

mmol) and bromide 3a (67 mg, 0.25 mmol). Yellowish oil, 80.2 mg (79%). Z/E 11:1. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.28-7.16 (5H, m); 7.06 (2H, d, J = 7.9 Hz); 6.76 (2H, d, J = 7.9 Hz); 6.27 (1H, s); 5.21 (1H, d, J = 9.9 Hz); 5.05 (1H, s); 4.88 (1H, s); 4.22 (2H, q, J = 7.1 Hz); 3.73 (3H, s); 2.1-2.0 (1H, m); 1.64-1.43 (5H, m); 1.30 (3H, t, J = 7.1 Hz); 1.19-1.02 (5H, m). ^{13}C NMR ($CDCl_3$, 101 MHz): 167.5; 158.3; 144.2; 139.9; 138.5; 136.0; 134.5; 129.7; 129.6; 128.4; 126.7; 126.4; 113.4; 60.9; 55.2; 55.1; 37.7; 33.7; 33.3; 26.1; 25.8; 25.7; 14.5. Anal. Calcd for $C_{27}H_{32}O_3$: C, 80.16; H, 7.97. Found: C, 80.06; H, 8.16.

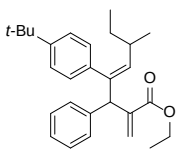
Ethyl (Z)-6-ethyl-2-methylene-3-phenyl-4-(p-tolyl)dodec-4-enoate (**4d**)



4d

Prepared from 1-ethynyl-4-methylbenzene (58 mg, 0.5 mmol), 3-iodononane (191 mg, 0.75 mmol) and bromide **3a** (67 mg, 0.25 mmol). Yellowish oil, 78.5 mg (73%). Z/E 57:1. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.29-7.18 (5H+5H, m); 7.01 (4H+4H, br.s.); 6.30 (1H+1H, s); 5.12 (1H+1H, br.s.); 5.10 (1H+1H, d, *J* = 10.7 Hz); 4.93-4.92 (1H+1H, m); 4.29-4.16 (2H+2H, m); 2.26 (3H+3H, s); 2.01 (1H+1H, br.s.); 1.34-1.05 (15H+15H, m); 0.90-0.84 (6H+3H, m), 0.72 (3H, t, *J* = 7.4 Hz). ^{13}C NMR ($CDCl_3$, 101 MHz): 167.53; 167.48; 144.02; 140.98; 140.91; 139.93; 139.46; 139.41; 135.82; 135.21; 135.16; 129.85; 129.82; 128.74; 128.72; 128.58; 128.35; 126.76; 126.74; 126.62; 126.59; 60.97; 60.96; 55.56; 40.00; 39.87; 36.06; 35.82; 32.10; 32.06; 29.74; 29.72; 29.09; 28.85; 27.71; 27.25; 22.91; 22.82; 21.26; 14.40; 14.29; 14.26; 12.33; 11.85. Anal. Calcd for $C_{30}H_{40}O_2$: C, 83.28; H, 9.32. Found: C, 83.53; H 9.40. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{30}H_{40}O_2Na$ 455.2926; Found 455.2922.

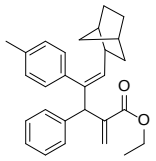
Ethyl (Z)-4-(4-(tert-butyl)phenyl)-6-methyl-2-methylene-3-phenyloct-4-enoate (**4e**)



4e

Prepared from 1-(tert-butyl)-4-ethynylbenzene (79 mg, 0.5 mmol), 2-iodobutane (138 mg, 0.75 mmol) and bromide **3a** (67 mg, 0.25 mmol). Yellowish oil, 74.4 mg (74%). *Z/E* 21:1. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.29-7.19 (7H + 7H, m); 7.07-7.03 (2H + 2H, m); 6.30-6.28 (1H + 1H, m); 5.18-5.10 (2H+1H, m); 5.03 (1H, m); 4.93 (1H, s); 4.91 (1H, s); 4.28-4.18 (2H + 2H, m); 2.21-2.10 (1H + 1H, m); 1.34-1.26 (14H + 14H, m); 0.98 (3H, d, *J* = 6.6 Hz); 0.85-0.80 (3H + 3H, m); 0.71 (3H, t, *J* = 7.4 Hz). ^{13}C NMR ($CDCl_3$, 101 MHz): 167.51; 167.49; 149.07; 149.04; 144.44; 144.06; 140.17; 140.02; 139.64; 139.48; 139.15; 139.13; 136.71; 136.29; 129.77; 129.76; 128.34; 128.19; 128.15; 126.71; 126.70; 126.57; 126.53; 124.80; 124.77; 60.96; 60.88; 55.07; 54.97; 34.80; 34.51; 34.50; 31.49; 30.45; 30.41; 21.66; 21.14; 14.45; 14.42; 12.31; 11.96. Anal. Calcd for $C_{28}H_{36}O_2$: C, 83.12; H, 8.97. Found: C, 83.17; H 9.06. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{28}H_{36}O_2Na$ 427.2613; Found 427.2614.

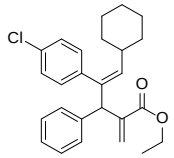
Ethyl (Z)-5-(bicyclo[2.2.1]heptan-2-yl)-2-methylene-3-phenyl-4-(p-tolyl)pent-4-enoate (**4f**)



4f

Prepared from 1-ethynyl-4-methylbenzene (58 mg, 0.5 mmol), 2-iodobicyclo[2.2.1]heptane (167 mg, 0.75 mmol) and bromide **3a** (67 mg, 0.25 mmol). Yellowish oil, 67.9 mg (68%). Z/E 16:1. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.29-7.15 (5H + 5H, m); 7.07-7.02 (4H + 4H, m); 6.27 (1H + 1H, br.s.); 5.27-5.23 (1H + 1H, m); 5.09 (1H, s); 5.06 (1H, s); 4.95-4.93 (1H + 1H, m); 4.25-4.18 (2H + 2H, m); 2.28 (3H + 3H, s); 2.20-2.08 (2H + 2H, m); 2.02 (1H, br.s.); 1.87 (1H, br.s.); 1.48-1.00 (11H + 11H, m). ^{13}C NMR ($CDCl_3$, 101 MHz): 167.49; 167.48; 144.24; 144.21; 140.14; 140.12; 139.02; 138.97; 137.89; 137.84; 136.03; 135.95; 129.72; 129.67; 128.77; 128.74; 128.64; 128.40; 128.36; 126.75; 126.71; 126.50; 126.48; 60.87; 54.74; 54.69; 43.55; 43.38; 41.29; 41.24; 40.01; 39.64; 36.76; 36.74; 36.31; 29.58; 28.94; 28.90; 21.29; 14.45; 14.43. Anal. Calcd for $C_{28}H_{32}O_2$: C, 83.96; H, 8.05. Found: C, 83.91; H, 8.18.

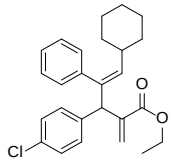
Ethyl (Z)-4-(4-chlorophenyl)-5-cyclohexyl-2-methylene-3-phenylpent-4-enoate (**4g**)



4g

Prepared from 1-chloro-4-ethynylbenzene (68 mg, 0.5 mmol), iodocyclohexane (158 mg, 0.75 mmol) and bromide **3a** (67 mg, 0.25 mmol). Yellowish oil, 74.5 mg (73%). *Z/E* 11:1. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.29-7.24 (2H, m); 7.22-7.18 (5H, m); 7.08-7.04 (2H, m); 6.29 (1H, m); 5.27 (1H, d, *J* = 9.9 Hz); 5.06 (1H, m); 4.83 (1H, s); 4.27-4.19 (2H, m); 2.0-1.9 (1H, m); 1.65-1.46 (5H, m); 1.31 (3H, t, *J* = 7.1 Hz); 1.19-1.01 (5H, m). ^{13}C NMR ($CDCl_3$, 101 MHz): 167.3; 143.8; 140.6; 139.3; 138.0; 136.5; 132.4; 129.9; 129.7; 128.5; 128.3; 127.0; 126.7; 61.0; 54.9; 37.8; 33.5; 33.1; 26.0; 25.7; 25.6; 14.5. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{26}H_{30}ClO_2$ 409.1929; Found 409.1924.

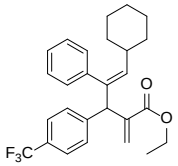
Ethyl (Z)-3-(4-chlorophenyl)-5-cyclohexyl-2-methylene-4-phenylpent-4-enoate (**4h**)



4h

Prepared from phenylacetylene (51 mg, 0.5 mmol), iodocyclohexane (158 mg, 0.75 mmol) and bromide **3b** (76 mg, 0.25 mmol). Yellowish oil, 92.1 mg (90%). *Z/E* 12:1. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.25-7.11 (9H, m); 6.30 (1H, s); 5.22 (1H, d, *J* = 9.9 Hz); 5.09 (1H, s); 4.89 (1H, s); 4.23 (2H, q, *J* = 7.1 Hz); 2.1-2.0 (1H, m); 1.65-1.42 (5H, m); 1.30 (3H, t, *J* = 7.1 Hz); 1.19-0.98 (5H, m). ^{13}C NMR ($CDCl_3$, 101 MHz): 167.2; 143.7; 141.8; 138.8; 138.4; 136.5; 132.6; 131.0; 128.6; 128.5; 128.1; 126.8; 126.7; 61.0; 54.4; 37.7; 33.6; 33.2; 26.1; 25.7; 25.7; 14.4. Anal. Calcd for $C_{26}H_{29}ClO_2$: C, 76.36; H, 7.15. Found: C, 76.46; H, 7.28.

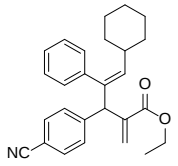
Ethyl (Z)-5-cyclohexyl-2-methylene-4-phenyl-3-(4-(trifluoromethyl)phenyl)pent-4-enoate (**4i**)



4i

Prepared from phenylacetylene (51 mg, 0.5 mmol), iodocyclohexane (158 mg, 0.75 mmol) and bromide **3c** (84 mg, 0.25 mmol). White solid, 92.8 mg (84%). *Z/E* 12:1. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.54 (2H, d, *J* = 7.8 Hz); 7.34 (2H, d, *J* = 7.9 Hz); 7.26-7.13 (5H, m); 6.33 (1H, s); 5.25 (1H, d, *J* = 10.0 Hz); 5.08 (1H, s); 5.00 (1H, s); 4.23 (2H, q, *J* = 7.0 Hz); 2.1-2.0 (1H, m); 1.66-1.48 (5H, m); 1.31 (3H, t, *J* = 7.1 Hz); 1.20-1.00 (5H, m). ^{13}C NMR ($CDCl_3$, 101 MHz): 167.1; 144.2; 143.3; 141.7; 138.4; 137.1; 130.0; 129.2 (q, $J_{C\text{-}F}$ = 32.4 Hz); 128.5; 128.2; 126.9; 126.9; 125.4 (q, $J_{C\text{-}F}$ = 3.8 Hz); 124.4 (q, $J_{C\text{-}F}$ = 272.0 Hz); 61.1; 54.7; 37.7; 33.5; 33.2; 26.1; 25.7; 25.6; 14.4. Anal. Calcd for $C_{27}H_{29}F_3O_2$: C, 73.28; H, 6.61. Found: C, 73.18; H, 6.73.

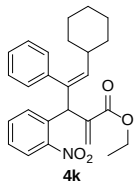
Ethyl (Z)-3-(4-cyanophenyl)-5-cyclohexyl-2-methylene-4-phenylpent-4-enoate (**4j**)



4j

Prepared from phenylacetylene (51 mg, 0.5 mmol), iodocyclohexane (158 mg, 0.75 mmol) and bromide **3d** (74 mg, 0.25 mmol). Yellowish oil, 91.7 mg (92%). *Z/E* 13:1. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.58 (2H, d, *J* = 8.2 Hz); 7.34 (2H, d, *J* = 8.2 Hz); 7.27-7.11 (5H, m); 6.35 (1H, s); 5.22 (1H, d, *J* = 10.0 Hz); 5.10 (1H, s); 5.00 (1H, s); 4.23 (2H, qd, *J* = 7.1 Hz, 2.2 Hz); 2.1-2.0 (1H, m); 1.65-1.48 (5H, m); 1.30 (3H, t, *J* = 7.1 Hz); 1.18-1.01 (5H, m). ^{13}C NMR ($CDCl_3$, 101 MHz): 166.8; 145.8; 142.7; 141.3; 138.0; 137.4; 132.3; 130.4; 128.4; 128.2; 127.0; 126.9; 118.9; 110.8; 61.2; 54.9; 37.7; 33.4; 33.1; 26.0; 25.6; 25.6; 14.4. Anal. Calcd for $C_{27}H_{29}NO_2$: C, 81.17; H, 7.32; N, 3.51. Found: C, 81.16; H, 7.39; N, 3.45.

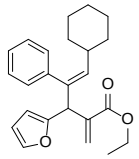
Ethyl (Z)-5-cyclohexyl-2-methylene-3-(2-nitrophenyl)-4-phenylpent-4-enoate (**4k**)



4k

Prepared from phenylacetylene (51 mg, 0.5 mmol), iodocyclohexane (158 mg, 0.75 mmol) and bromide **3e** (79 mg, 0.25 mmol). Yellowish solid, 51.9 mg (49%). *Z/E* 16:1. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.85 (1H, d, J = 8.0 Hz); 7.58-7.53 (2H, m); 7.39-7.35 (1H, m); 7.28-7.18 (5H, m); 6.42 (1H, s); 5.71 (1H, s); 5.29 (1H, s); 5.13 (1H, d, *J* = 10.0 Hz); 4.19 (2H, q, *J* = 7.0 Hz); 2.1-2.0 (1H, m); 1.62-1.49 (5H, m); 1.25 (3H, t, *J* = 7.1 Hz); 1.15-0.97 (5H, m). ^{13}C NMR ($CDCl_3$, 101 MHz): 166.5; 150.0; 141.7; 141.0; 138.2; 137.6; 134.8; 132.5; 131.2; 128.7; 128.2; 127.8; 127.3; 127.0; 125.1; 61.2; 49.6; 37.8; 33.4; 33.2; 26.0; 25.6; 14.3. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{29}NNaO_4$ 442.1994; Found 442.1994.

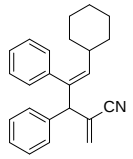
Ethyl (Z)-5-cyclohexyl-3-(furan-2-yl)-2-methylene-4-phenylpent-4-enoate (**4l**)



4l

Prepared from phenylacetylene (51 mg, 0.5 mmol), iodocyclohexane (158 mg, 0.75 mmol) and bromide **3f** (65 mg, 0.25 mmol). Yellowish oil, 68.6 mg (75%). *Z/E* 11:1. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.35-7.21 (6H, m); 6.33 (1H, br.s.); 6.28 (1H, br.s.); 6.13 (1H, m); 5.27 (1H, br.s.); 5.25 (1H, d, *J* = 10.3 Hz); 4.95 (1H, s); 4.22 (2H, q, *J* = 7.1 Hz); 2.1-2.0 (1H, m); 1.64-1.48 (5H, m); 1.28 (3H, t, *J* = 7.1 Hz); 1.11-0.99 (5H, m). ^{13}C NMR ($CDCl_3$, 101 MHz): 166.8; 154.3; 142.1; 141.5; 141.2; 136.9; 136.4; 128.7; 128.0; 126.8; 126.4; 110.2; 108.8; 60.9; 48.6; 37.6; 33.4; 33.2; 26.1; 25.7; 25.6; 14.4. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{29}O_3$ 365.2117; Found 365.2119.

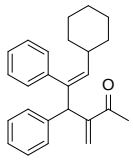
(Z)-5-Cyclohexyl-2-methylene-3,4-diphenylpent-4-enenitrile (**4m**)



4m

Prepared from phenylacetylene (51 mg, 0.5 mmol), iodocyclohexane (158 mg, 0.75 mmol) and bromide **3g** (56 mg, 0.25 mmol). Yellowish oil, 52.8 mg (64%). Z/E 24:1. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.34-7.20 (8H, m); 7.08-7.06 (2H, m); 6.00 (1H, d, *J* = 1.1 Hz); 5.41 (1H, d, *J* = 1.5 Hz); 5.39 (1H, d, *J* = 10.1 Hz); 4.48 (1H, s); 2.1-2.0 (1H, m); 1.69-1.54 (5H, m); 1.21-1.11 (5H, m). ^{13}C NMR ($CDCl_3$, 101 MHz): 140.9; 138.8; 137.5; 136.9; 132.3; 129.4; 128.8; 128.5; 128.3; 127.7; 127.0; 126.1; 118.9; 57.7; 38.0; 33.3; 33.1; 26.1; 25.7; 25.6. Anal. Calcd for $C_{24}H_{25}N$: C, 88.03; H, 7.70; N, 4.28. Found: C, 88.09; H, 7.49; N, 4.29.

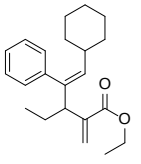
(Z)-6-Cyclohexyl-3-methylene-4,5-diphenylhex-5-en-2-one (**4n**)



4n

Prepared from phenylacetylene (51 mg, 0.5 mmol), iodocyclohexane (158 mg, 0.75 mmol) and bromide **3h** (60 mg, 0.25 mmol). Yellowish oil, 74.8 mg (87%). *Z/E* 13:1. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.28-7.15 (10H, m); 6.14 (1H, s); 5.35 (1H, d, *J* = 1.3 Hz); 5.12 (1H, d, *J* = 9.9 Hz); 5.04 (1H, s); 2.34 (3H, s); 2.05-1.95 (1H, m); 1.62-1.50 (5H, m); 1.11-0.98 (5H, m). ^{13}C NMR ($CDCl_3$, 101 MHz): 199.3; 151.9; 142.1; 140.2; 139.2; 136.3; 129.6; 128.5; 128.4; 128.0; 126.7; 126.6; 53.5; 37.6; 33.6; 33.4; 26.8; 26.1; 25.7; 25.6. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{25}H_{29}O$ 345.2213; Found 345.2204.

Ethyl (Z)-5-cyclohexyl-3-ethyl-2-methylene-4-phenylpent-4-enoate (**4o**)



4o

Prepared from phenylacetylene (51 mg, 0.5 mmol), iodocyclohexane (158 mg, 0.75 mmol) and bromide **3i** (55 mg, 0.25 mmol). Yellowish oil, 78.5 mg (96%). *Z/E* > 10:1. γ/α 24:1. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.30-7.25 (2H, m); 7.23-7.19 (1H, m); 7.09-7.07 (2H, m); 6.20 (1H, d, *J* = 0.7 Hz); 5.34 (1H, m); 5.27 (1H, d, *J* = 9.9 Hz); 4.19 (2H, q, *J* = 7.1 Hz); 3.41 (1H, t, *J* = 7.3 Hz); 1.9-1.8 (1H, m); 1.62-1.47 (7H, m); 1.29 (3H, t, *J* = 7.1 Hz); 1.11-1.02 (5H, m); 0.90 (3H, t, *J* = 7.4 Hz). ^{13}C NMR ($CDCl_3$, 101 MHz): 167.9; 142.7; 141.1; 139.3; 135.3; 129.2; 127.8; 126.4; 123.9; 60.7; 50.1; 37.7; 33.5; 33.5; 26.1; 25.7; 25.1; 14.4; 12.5. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{31}O_2$ 327.2319; Found 327.2313.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Copies of NMR spectra and table of X-Ray data for **4k** (PDF)

Crystallographic data for **4k** (CIF)

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