JOC The Journal of Organic Chemistry

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γ-Selective Allylation of (*E*)-Alkenylzinc Iodides Prepared by Reductive Coupling of Arylacetylenes with Alkyl Iodides

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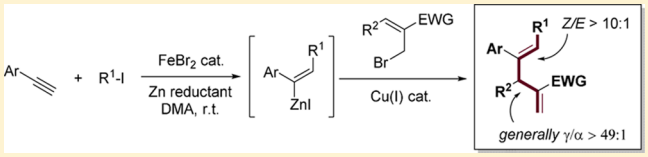
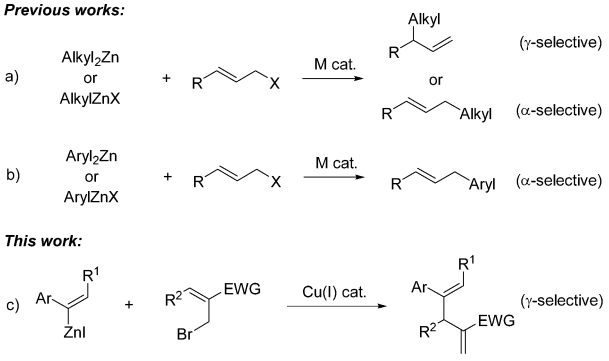
Supporting Information

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.

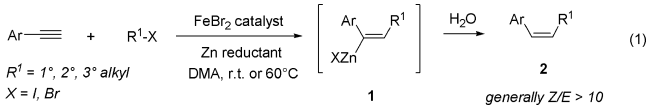


Metal-catalyzed allylic substitution using organozinc reagents is a versatile method for C−C bond formation. Unlike alkylzinc[1−3] and arylzinc[4,5] reagents (Scheme 1, a and b) which are widely used in these reactions, alkenylzinc reagents are rarely employed. There are only a few examples of catalytic 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 transmetalation 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



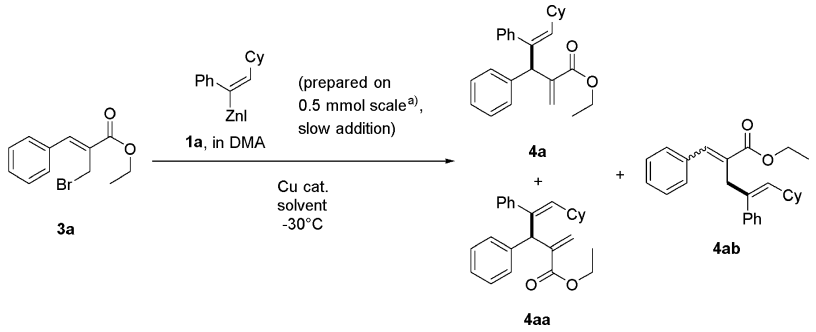
alkenylzinc reagents **1** without the need for sensitive organometallic reagents. Here we describe a Cu-based catalytic system for the reactions of these alkenylzinc reagents with allylic bromides (Scheme 1c). To the best of our knowledge, this is the first γ-selective catalytic allylic alkenylation. The few precedents of catalytic allylic alkenylation either employed symmetrical allylic substrates[12,19−21] or were α-selective.[22,23]

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 reactions.[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-phenyl acrylate (**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 a longer reaction time (24 h) and a slower addition rate with 5 mol % of CuCN·2LiCl as the 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

Received: May 31, 2016
Published: June 10, 2016

DOI: 10.1021/acs.joc.6b01306
J. Org. Chem. 2016, 81, 5795−5802

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 %), and $FeBr_2$ (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.

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**).

The scope of 2-(bromomethyl)acrylates is shown in Table 3. Both aryl- (**3a**−**e**) and heteroaryl-substituted (**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 regio- and diastereoselectivity of the reaction.

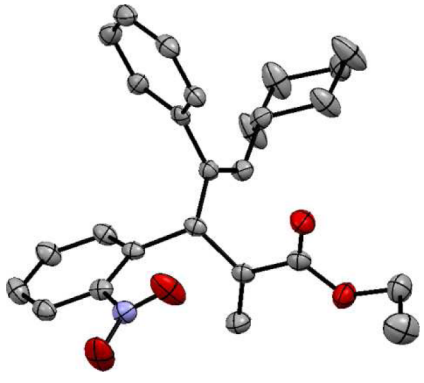
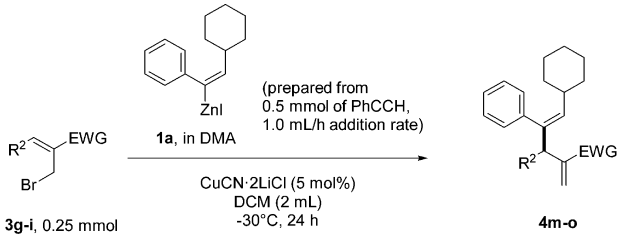
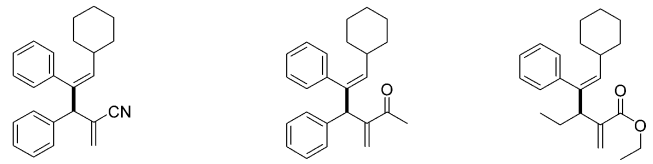


Figure 1. X-ray structure of compound **4k**. Thermal ellipsoids are drawn at 50% probability level. Hydrogen atoms are omitted. Color code: red for O; blue for N; gray for C.

Scheme 2. Scope of Novel Types of MBH Alcohols-Derived Allylic Bromides



3g: R^2 = Ph, EWG = CN;
3h: R^2 = Ph, EWG = C(O)Me;
3i: R^2 = Et, EWG = C(O)OMe



4m
64%[a], *Z*/*E*[b] 24:1

4n
87%, *Z*/*E* 13:1

4o
96%, *Z*/*E* > 10:1
γ/α 24:1[b]

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

DOI: 10.1021/acs.joc.6b01306
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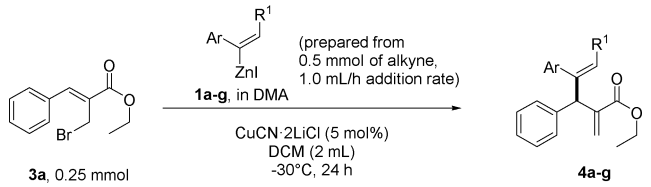
Table 2. Scope of (*E*)-Alkenylzinc Reagent



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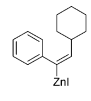
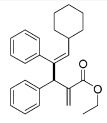
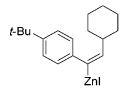
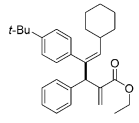
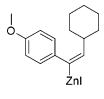
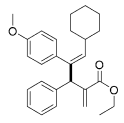
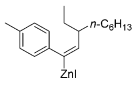
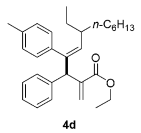
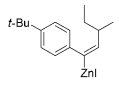
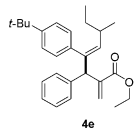
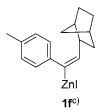
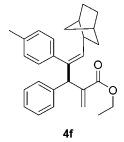
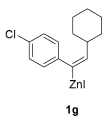
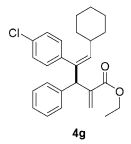
1	 1a	 4a	87	12:1
2	 1b	 4b	84	12:1
3	 1c	 4c	79	11:1
4	 1d	 4d	73	57:1
5	 1e	 4e	74	21:1
6	 1f[c]	 4f	68	16:1
7	 1g	 4g	73	11:1

[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]

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).

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]

DOI: 10.1021/acs.joc.6b01306
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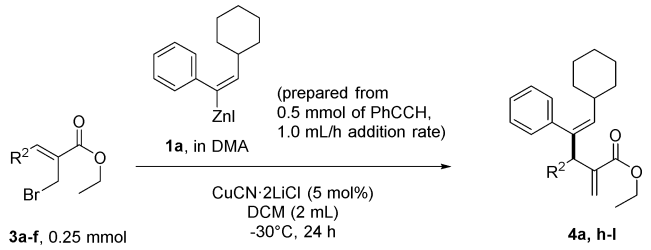
Table 3. Scope of Aryl- and Heteroaryl-Substituted 2-(Bromomethyl)acrylates



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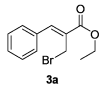
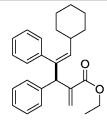
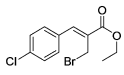
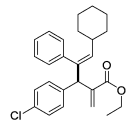
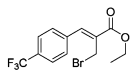
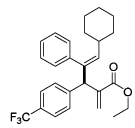
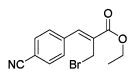
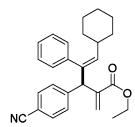
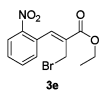
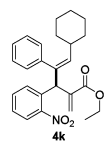
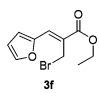
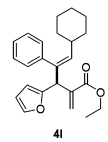
1	 3a	 4a	87	12:1
2	 3b	 4h	90	12:1
3	 3c	 4i	84	12:1
4	 3d	 4j	92	13:1
5	 3e	 4k	49	16:1
6	 3f	 4l	75	11:1

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

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 the 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 the $CDCl_3$ 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 glovebox without exposure to air by the aid of a Straus flask. Zn powder (<10 μ, 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 the 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 the stationary phase for column chromatography.

Starting Materials Preparation. For additional details about the preparation of (*E*)-alkenylzinc reagents **1a−g**, see refs 17 and 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 furyl-substituted 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

DOI: 10.1021/acs.joc.6b01306
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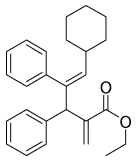
preparation of **3f** and **3i** are synthesized using a 1,4-dioxane/water 1:1 mixture as solvent, in order to accelerate the reaction.[30] In the case of the alcohol that corresponds to the bromide **3h**,[31] we were unable to separate it from the methylvinylketone (MVK) dimer that forms as a side product. However, after treatment of the product mixture by PBr_3, the resulting bromide **3h** can be easily isolated from the unreacted MVK dimer. All the bromides are obtained as *Z*-isomers,[25,31] with the 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 1 M 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. Afterward, the content of the vial was poured into water or 1 M HCl and extracted with diethyl ether (4 × 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.

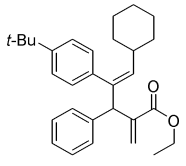
*Ethyl (Z)-5-Cyclohexyl-2-methylene-3,4-diphenylpent-4-enoate (**4a**).* Prepared from phenylacetylene (51 mg, 0.5 mmol),



4a

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.

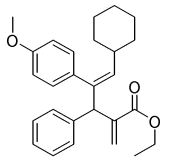
*Ethyl (Z)-4-(4-(tert-Butyl)phenyl)-5-cyclohexyl-2-methylene-3-phenylpent-4-enoate (**4b**).* Prepared from 1-(*tert*-butyl)-4-ethynylbenzene (79 mg, 0.5 mmol), iodocyclohexane (158 mg, 0.75 mmol), and bromide **3a** (67 mg, 0.25 mmol). Yellowish oil, 90.3 mg (84%).



4b

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.

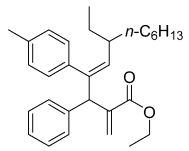
*Ethyl (Z)-5-Cyclohexyl-4-(4-methoxyphenyl)-2-methylene-3-phenylpent-4-enoate (**4c**).* Prepared from 1-ethynyl-4-methoxybenzene



4c

(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.

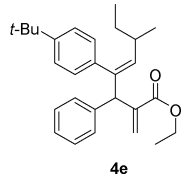
*Ethyl (Z)-6-Ethyl-2-methylene-3-phenyl-4-(p-tolyl)dodec-4-enoate (**4d**).* Prepared from 1-ethynyl-4-methylbenzene (58 mg,



4d

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**).* Prepared from 1-(*tert*-butyl)-4-ethynylbenzene



4e

(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,

DOI: 10.1021/acs.joc.6b01306
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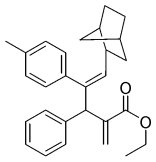
J = 6.6 Hz); 0.85−0.80 (3H + 3H, m); 0.71 (3H, t, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$, 101 MHz): 167.51; 167.49; 149.07; 149.04; 144.44; 144.06; 140.17; 140.02; 139.64; 139.48; 139.15; 139.13; 136.71; 136.29; 129.77; 129.76; 128.34; 128.19; 128.15; 126.71; 126.70; 126.57; 126.53; 124.80; 124.77; 60.96; 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.

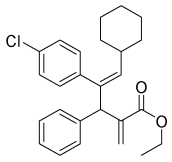
*Ethyl (Z)-5-(Bicyclo[2.2.1]heptan-2-yl)-2-methylene-3-phenyl-4-(p-tolyl)pent-4-enoate (**4f**).* Prepared from 1-ethynyl-4-methylbenzene



4f

(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.

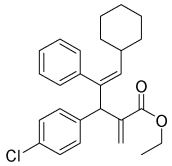
*Ethyl (Z)-4-(4-Chlorophenyl)-5-cyclohexyl-2-methylene-3-phenylpent-4-enoate (**4g**).* Prepared from 1-chloro-4-ethynylbenzene (68 mg,



4g

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.

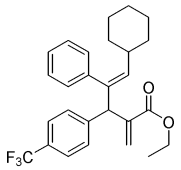
*Ethyl (Z)-3-(4-Chlorophenyl)-5-cyclohexyl-2-methylene-4-phenylpent-4-enoate (**4h**).* Prepared from phenylacetylene (51 mg, 0.5 mmol),



4h

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.

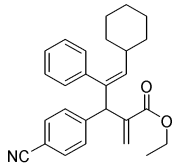
*Ethyl (Z)-5-Cyclohexyl-2-methylene-4-phenyl-3-(4-(trifluoromethyl)phenyl)pent-4-enoate (**4i**).* Prepared from phenylacetylene



4i

(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-F} = 32.4 Hz); 128.5; 128.2; 126.9; 126.9; 125.4 (q, J_{C-F} = 3.8 Hz); 124.4 (q, J_{C-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.

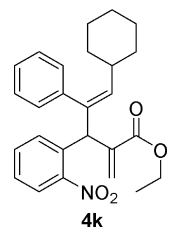
*Ethyl (Z)-3-(4-Cyanophenyl)-5-cyclohexyl-2-methylene-4-phenylpent-4-enoate (**4j**).* Prepared from phenylacetylene (51 mg, 0.5 mmol),



4j

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**).* Prepared from phenylacetylene (51 mg, 0.5 mmol),



4k

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**).* Prepared from phenylacetylene (51 mg, 0.5 mmol), iodocyclohexane (158 mg, 0.75 mmol), and bromide **3f** (65 mg,

DOI: 10.1021/acs.joc.6b01306
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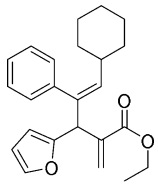
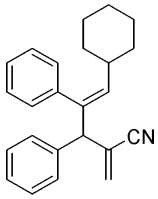


4l

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.

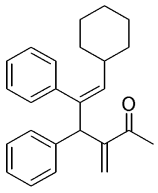
*(Z)-5-Cyclohexyl-2-methylene-3,4-diphenylpent-4-enenitrile (**4m**).* Prepared from phenylacetylene (51 mg, 0.5 mmol), iodo-



4m

cyclohexane (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.

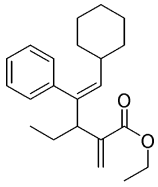
*(Z)-6-Cyclohexyl-3-methylene-4,5-diphenylhex-5-en-2-one (**4n**).* Prepared from phenylacetylene (51 mg, 0.5 mmol), iodocyclohexane



4n

(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**).* Prepared from phenylacetylene (51 mg, 0.5 mmol),



4o

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 at DOI: 10.1021/acs.joc.6b01306.

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

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

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Dr. Rosario Scopelliti (EPFL) for the X-ray analysis of **4k**. This work is supported by the European Research Council through a starting grant (No. 257096).

■ REFERENCES

(1) Falciola, C. A.; Alexakis, A. *Eur. J. Org. Chem.* **2008**, *2008*, 3765.

(2) Ji, J.-X.; Chan, A. S. C.; Helmchen, G.; Kazmaier, U.; Förster, S.; Ojima, I.; Kaloko, J. J.; Chaterpaul, S. J.; Teng, Y.-H. G.; Lin, C.-F.; Mikami, K.; Aikawa, K.; Hoveyda, A. H.; Malcolmson, S. J.; Meek, S. J.; Zhugralin, A. R. Asymmetric Carbon−Carbon Bond-Forming Reactions. In *Catalytic Asymmetric Synthesis*; John Wiley & Sons, Inc.: 2010; pp 437−770.

(3) Sekiya, K.; Nakamura, E. *Tetrahedron Lett.* **1988**, *29*, 5155.

(4) Dunet, G.; Knochel, P. *Synlett* **2007**, *2007*, 1383.

(5) Matsushita, H.; Negishi, E. *J. Am. Chem. Soc.* **1981**, *103*, 2882.

(6) Denmark, S. E.; Guagnano, V.; Dixon, J. A.; Stolle, A. *J. Org. Chem.* **1997**, *62*, 4610.

(7) Jie, M. S. F. L. K.; Pasha, M. K.; Syed-Rahmatullah, M. S. K. *Nat. Prod. Rep.* **1997**, *14*, 163.

(8) Macklin, T. K.; Micalizio, G. C. *Nat. Chem.* **2010**, *2*, 638.

(9) Roulet, J.-M.; Deguin, B.; Vogel, P. *J. Am. Chem. Soc.* **1994**, *116*, 3639.

(10) Xu, S.; Zhu, S.; Shang, J.; Zhang, J.; Tang, Y.; Dou, J. *J. Org. Chem.* **2014**, *79*, 3696.

(11) Mejuch, T.; Marek, I. *Science of Synthesis: Cross Coupling and Heck-Type Reactions*; Thieme Chemistry: 2013; Vol. *1*, p 767.

(12) Sämann, C.; Schade, M. A.; Yamada, S.; Knochel, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 9495.

(13) Bhanu Prasad, A. S.; Knochel, P. *Tetrahedron* **1997**, *53*, 16711.

(14) Klement, I.; Rottländer, M.; Tucker, C. E.; Majid, T. N.; Knochel, P.; Venegas, P.; Cahiez, G. *Tetrahedron* **1996**, *52*, 7201.

(15) For examples of (*E*)-iodoalkenes preparation see DeBerardinis, A. DeBerardinis, A. M.; Turlington, M.; Pu, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 2368.

(16) Lorthiois, E.; Meyer, C. Carbozincation of Alkenes and Alkynes. In *The Chemistry of Organozinc Compounds*; John Wiley & Sons, Ltd.: 2007; pp 863−978.

(17) Cheung, C. W.; Zhurkin, F. E.; Hu, X. *J. Am. Chem. Soc.* **2015**, *137*, 4932.

(18) Cheung, C. W.; Hu, X. *Chem. - Eur. J.* **2015**, *21*, 18439.

DOI: 10.1021/acs.joc.6b01306
J. Org. Chem. 2016, 81, 5795−5802

(19) Knochel, P.; Janakiram Rao, C. *Tetrahedron* **1993**, *49*, 29.
(20) Maezaki, N.; Sawamoto, H.; Suzuki, T.; Yoshigami, R.; Tanaka, T. *J. Org. Chem.* **2004**, *69*, 8387.
(21) Tan, B.-H.; Dong, J.; Yoshikai, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 9610.
(22) Ichitsuka, T.; Takanohashi, T.; Fujita, T.; Ichikawa, J. *J. Fluorine Chem.* **2015**, *170*, 29.
(23) The only example of γ-selective allylic alkenalytion with organozinc is the reaction of the stoichiometric divinylzinc−CuCN complex with a sophisticated secondary allylic chloride (Yoshimura, F.; Kowata, A.; Tanino, K. *Org. Biomol. Chem.* **2012**, *10*, 5431). The reaction gives a low yield (30%).
(24) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.
(25) Biswas, K.; Börner, C.; Gimeno, J.; Goldsmith, P. J.; Ramazzotti, D.; So, A. L. K.; Woodward, S. *Tetrahedron* **2005**, *61*, 1433.
(26) Goldsmith, P. J.; Teat, S. J.; Woodward, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 2235.
(27) Xu, L.-H.; Kündig, E. P. *Helv. Chim. Acta* **1994**, *77*, 1480.
(28) Lesuisse, D.; Gouvest, J.-F.; Benslimane, O.; Canu, F.; Delaisi, Ch.; Doucet, B.; Hartmann, C.; Lefrançois, J.-M.; Tric, B.; Mansuy, D.; Philibert, D.; Teutsch, G. *J. Med. Chem.* **1996**, *39*, 757.
(29) Lühr, S.; Holz, J.; Zayas, O.; Wendisch, V.; Börner, A. *Tetrahedron: Asymmetry* **2012**, *23*, 1301.
(30) Latorre, A.; Saez, J. A.; Rodriguez, S.; Gonzalez, F. V. *Tetrahedron* **2014**, *70*, 97.
(31) de Paula, B. R. S.; Zampieri, D. S.; Rodrigues, J. A. R.; Moran, P. J. S. *Tetrahedron: Asymmetry* **2013**, *24*, 973.
(32) Beltaïef, I.; Hbaïeb, S.; Besbes, R.; Amri, H.; Villiéras, M.; Villiéras, J. *Synthesis* **1998**, *1998*, 1765.

DOI: 10.1021/acs.joc.6b01306
J. Org. Chem. 2016, 81, 5795−5802