JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

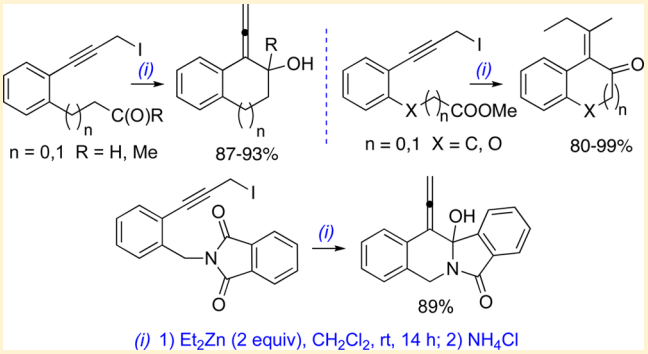
Intramolecular Trapping of Allenylzincs by Carbonyl Groups

Suribabu Jammi, Julien Maury, Jean-Simon Suppo, Michèle P. Bertrand,* and Laurence Feray*

Aix-Marseille Université, CNRS, Institut de Chimie Radicalaire UMR 7273, Equipe CMO, 13397 Cedex 20 Marseille, France

Supporting Information

ABSTRACT: Allenylzinc formed via oxygen-promoted zinc/iodine exchange between propargyl iodides and diethylzinc can be trapped by intramolecular reaction with various electrophiles such as aldehydes, ketones, esters, carbamates, and imides. Potentially useful building blocks were obtained in high yields.



INTRODUCTION

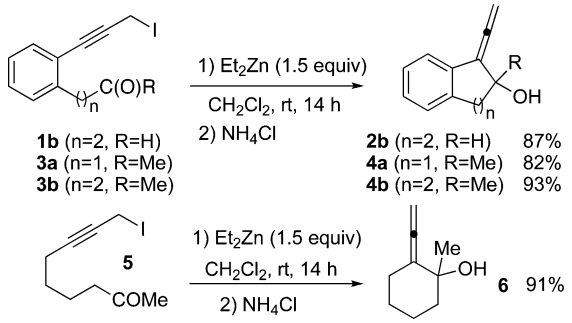
The reaction of allenylmetals with different types of electrophiles has widely been investigated.[1] Whereas examples of intramolecular reactions are documented in the case of allenylsilanes, allenylstannanes,[1c,2] and allenylindium,[3] little is known about the intramolecular trapping of nucleophilic allenylzinc reagents.[1c,d] Our interest in reactions involving oxygen-promoted zinc/iodine exchange and in subsequent tandem radical/polar reactions,[4,5] recently led us to investigate the mechanism of formation of allenylzincs from propargyl iodides and diethylzinc.[6,7] Our attention was focused on the reactivity of chelated allenylzinc species with regard to carbonyl groups.[7]

In the continuity of these studies, the reactivity of structurally related allenylzincs bearing an internal electrophilic partner was explored. We report herein, the results of intramolecular trapping of allenylzincs with classical partners such as aldehydes and ketones. Acylation was observed when using esters and carbamates, which are not usual electrophilic partners for organozinc compounds. This reactivity was exploited in tandem processes for the synthesis of more complex structures.

RESULTS AND DISCUSSION

The reactivity of aldehyde **1b** and ketones **3a**,**b** was investigated first. As expected, the corresponding cyclic secondary (**2b**) and tertiary (**4a**,**b**) allenyl alcohols were isolated in high yields (Scheme 1). All reactions were performed at room temperature, under argon atmosphere, but in nondegassed dichloromethane, so that a free radical zinc/iodine exchange could be promoted.[6,7] As discussed later on in Scheme 3, the allenylzinc formed in this process evolved through regioselective nucleophilic addition to the carbonyl group. It is worth noting that substrates bearing a more flexible aliphatic substrate like ketone **5** behaved similarly (Scheme 1). This outcome is very similar to the outcome of related allenylindiums.[3]

Scheme 1. Reactivity of aldehyde 1b, and ketones 3a,b and 5



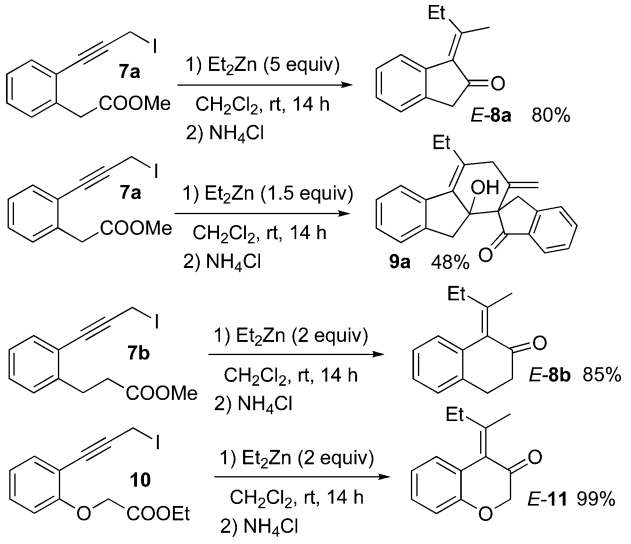
The metallotropic exchange between allenyl and propargyl zinc species was shown to be rather fast with respect to bimolecular nucleophilic addition to carbonyl groups.[7] It is largely admitted that allenylation proceeds through a six-membered transition state involving the propargylzinc tautomer (S_E2'). The structures of the starting iodides can easily accommodate such formally polycyclic transition structures.

The behavior of esters **7a** and **7b** was more interesting since esters are not commonly used as electrophilic partners for organozinc reagents (Scheme 2). Ester **7a** led exclusively to ketone **8a** when the reaction was performed in the presence of more than a 5-fold excess of diethylzinc. Conversely when only 1.5 equiv of diethylzinc was used, **7a** led to aldol **9a** which was isolated after workup as a single diastereomer in 48% yield. (The yield was calculated with respect to **7a**; **8a** was formed in trace amount according to the ^{1}H NMR spectrum of the crude mixture.)

As shown in Scheme 3, in all likelihood, ketone **12a** results from the displacement of ethylzinc methoxide from the fastly

Received: October 7, 2013
Published: November 19, 2013

Scheme 2. Reactivity of esters 7a,b and 10



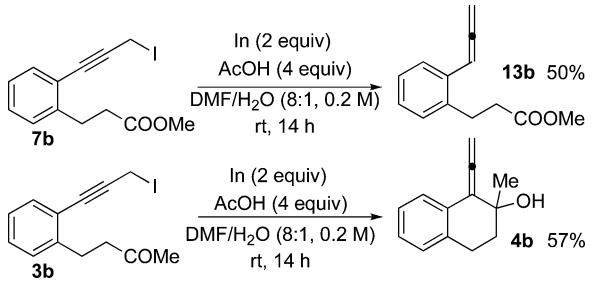
interconverting intermediates **B** and **C**. Owing to the reactivity of the conjugated allenyl moiety, ketone **12a** cannot be isolated, and the reaction with another equivalent of diethylzinc generates **E**. In nondegassed medium, the mechanism rather proceeds via ethyl radical addition followed by homolytic substitution at zinc. Direct nucleophilic conjugate addition of diethylzinc, which is not represented for the sake of clarity, cannot be excluded. Enolate **E** is protonated upon workup to give **8a** when the reaction is performed in the presence of a large excess of diethylzinc. When only 1.5 equiv is used, **12a** is not rapidly consumed by the assumed ethyl radical addition, and enolate **E** adds to **12a** to give the dimeric product **9a** via conjugate addition followed by intramolecular aldol condensation.

No dimer was formed in the reaction of ester **7b** with diethylzinc under the same experimental conditions, as if the conjugated allene **12b** was a better radical acceptor than **12a** (Scheme 3).[8] Ketone **8b** was isolated as the only product in 85% (the yield was optimized by increasing the amount of Et_2Zn up to 2 equiv) (Scheme 2). Ester **10** reacted similarly to give ketone **11** in quantitative yield according to the same mechanism (Scheme 2).[9]

The exclusive formation of the *E*- isomer[10] might result from the fast equilibration between the zinc enolate and its chelated tautomer possessing a carbon−zinc bond.[11]

It is worth noting that the behavior of the intermediate allenylmetal derivative is specific to its mode of formation.

Scheme 4. In-mediated reactions



No cyclization was observed when iodide **7b** was reacted with In(0). Allene **13b** was isolated as the only product in 50% yield (Scheme 4).

The absence of nucleophilic reactivity of the intermediate allenylindium with regard to the ester carbonyl group might be considered as surprising since the C−In bond should be more polar than the C−Zn bond according to the Pauling electronegativity scale (1.78 for In; 1.65 for Zn), but the protic medium is likely to be responsible for this anomalous reactivity. Conversely, even in the presence of AcOH, the allenylindium derived from ketone **3b** led to alcohol **4b** in 57% yield (Scheme 4). Zinc Barbier reactions should lead to similar results. They were not investigated because these reactions are typically performed in aqueous medium in the presence of NH_4Cl.[12]

These results emphasize that esters react far slower than aldehydes with allenyl metals. The absence of cyclization products when **7a** and **7b** were reacted with Et_2Zn in the presence of 2 equiv of benzaldehyde is consistent with this statement.[7]

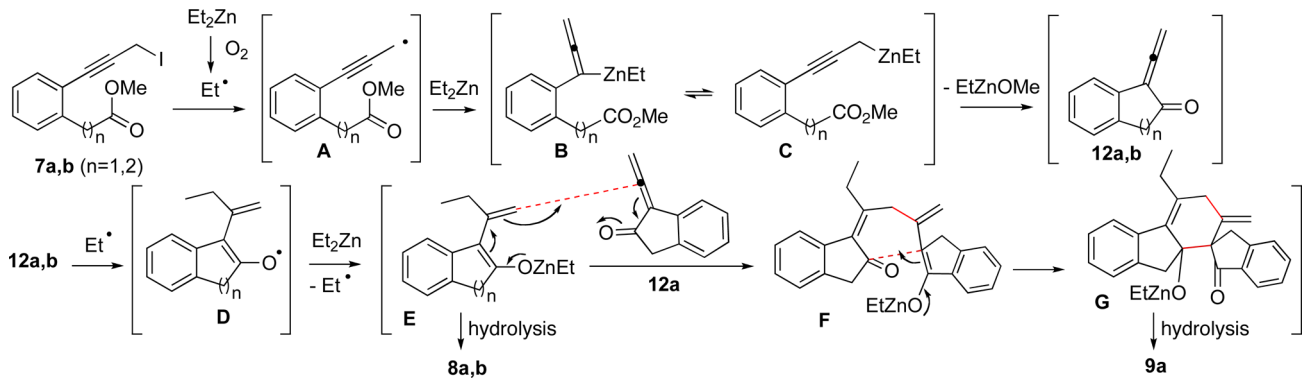
In order to delineate the scope and limitation of these cyclization processes regarding the nature of electrophilic carbonyl groups that could be used as internal traps for allenylzinc reactive intermediates, the series of substrates was completed with carbamates **16a−c** and imide **24**. The results are reported in Schemes 5, 6 and 8.

Bis-carbamate **16a** was electrophilic enough to undergo nucleophilic substitution by the corresponding intermediate allenylzinc. It led to lactam **17** in quantitative yield in the presence of a 5-fold excess of Et_2Zn (Scheme 5).[13]

The comparative reactivity of carbamate **16b** deserves being discussed. No cyclization was observed. This behavior might be rationalized as follows:

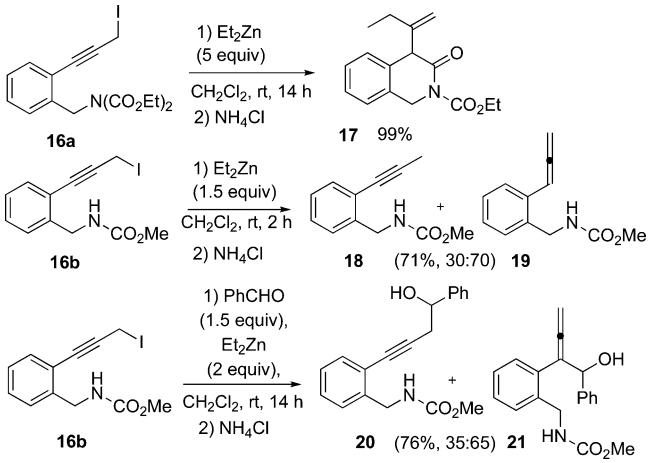
– Zinc/iodine exchange should be fast in all cases. In the case of **16b**, subsequent intramolecular proton transfer from the NH group would prevent further cyclization and explain the formation of **18** and **19** after hydrolysis.

Scheme 3. Mechanistic proposal for the formation of 9a from 7a

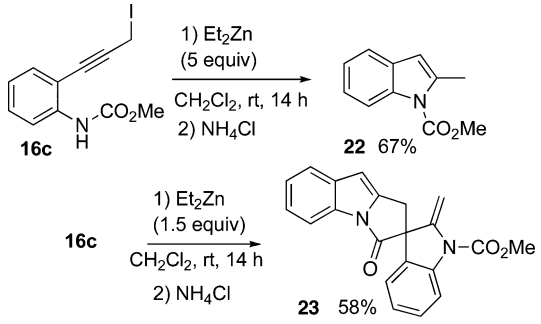


dx.doi.org/10.1021/jo4022293 | J. Org. Chem. 2013, 78, 12566−12576

Scheme 5. Reactivity of carbamates 16a,b



Scheme 6. Reactivity of carbamate 16c



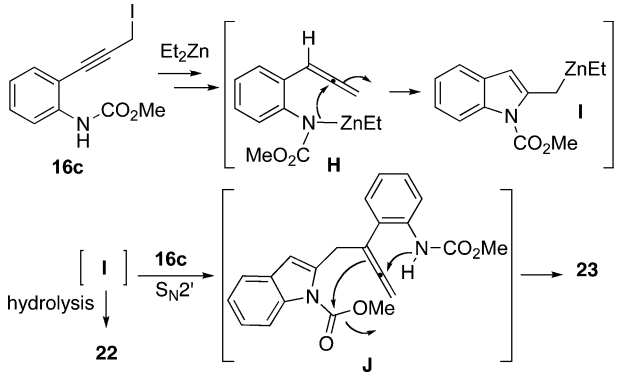
The activation of intramolecular transfer upon chelation was recently discussed in the reaction of diethylzinc with silazanes.[14]

- The formation of a mixture of homopropargyl alcohol **20** and allenyl alcohol **21** in the presence of benzaldehyde proved that the expected allenylzinc was formed in the medium. Thus, proton migration is necessarily slower than intermolecular addition of the metalated species to benzaldehyde.
- In the absence of benzaldehyde, no cyclized product was detected from **16b**, even after waiting 14h before quenching the reaction. This means that even if deprotonation is not operative, the electrophilicity of the carbamate unit cannot be compared to that of the carboxylate.

Carbamate **16c** presents a different chemoselectivity. In the presence of an excess of diethylzinc, indole **22** was formed as the only product (Scheme 6).[15] When only 1.5 equiv of diethylzinc was used, the consumption of the starting material was slow enough to enable the formation of the spiranic dimer **23**.

A possible rationale for the formation of products **22** and **23** is depicted in Scheme 7. Substrate **16c** is more acidic than its homologue **16b**. Internal proton transfer would generate intermediate **H**. Subsequent nucleophilic addition of the metalated carbamate onto the allene[16] would lead to the nucleophilic indolic species **I** which itself would give **22** after hydrolysis, when the reaction is performed in the presence of a large excess of diethylzinc. In the presence of only 1.5 equiv of diethylzinc, the consumption of iodide **16c** would be slowed down, and product **23** would originate from nucleophilic attack

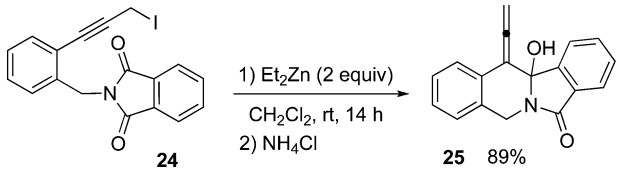
Scheme 7. Mechanistic proposal for the formation of 22 and 23



of intermediate **I** on iodide **16c** (or its conjugated base) via S_N2' mechanism.

Eventually, intramolecular addition to the carbonyl group of the imide function in **24** was achieved. It led to the one pot formation of product **25** in 89% yield. The latter possesses the skeleton of tetrahydroisoquinolinone alkaloids (Scheme 8).[17]

Scheme 8. Reactivity of imide 24



CONCLUSION

In summary, the intramolecular trapping of allenylzincs by electrophilic carbonyl groups was shown to open a route to a large variety of polycyclic scaffolds ranging from bicyclic allenyl alcohols, to bicyclic conjugated ketones, up to tetracyclic alkaloids. Owing to the great reactivity of conjugated allenes in nondegassed medium, cascade radical/polar reactions are plausible pathways. The trapping by carbamates, which are not currently used as electrophilic partners for organozinc derivatives, strongly depends on the presence and the position of acidic protons on the nitrogen atom of the carbamoyl group. These preliminary results delineate how the various parameters can influence the outcome of the reaction. Further investigations will be reported in due course. Simple phthalimido derivatives were shown to provide a very simple route to tetrahydroisoquinoline alkaloids scaffolds.

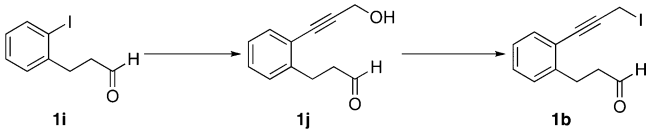
EXPERIMENTAL SECTION

General. Commercially available dichloromethane (synthesis grade - stabilized with ethanol 0.1−0.4% m/m) was stored on molecular sieves and used without further purification. The commercially available diethylzinc solutions were 1 M in heptane. Analytical thin layer chromatography was performed on precoated silica gel plates. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C) using $CDCl_3$ as the solvent. Chemical shifts (δ) are reported in ppm. Signals of the residual protonated solvent or of the deuterated solvent served as the internal standard to calibrate the spectra (^{1}H NMR, $CHCl_3$, 7.26 ppm; ^{13}C NMR, $CDCl_3$, 77.16 ppm). Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), hept (heptuplet), m (multiplet), br (broad). The *J* values are given in Hz. High resolution MS

dx.doi.org/10.1021/jo4022293 | J. Org. Chem. 2013, 78, 12566−12576

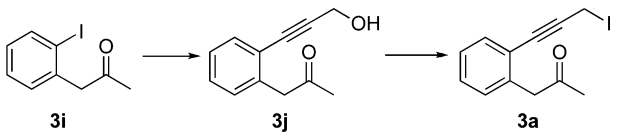
experiments were performed with a mass spectrometer equipped with an electrospray ionization source operated in the positive ion mode. In this hybrid instrument, ions were measured using an orthogonal acceleration time-of-flight mass analyzer.

Synthesis of Substrates. *3-(2-(3-Iodoprop-1-ynyl)phenyl)-propanal (**1b**).* To a solution of 3-(2-iodophenyl)propanal **1i** (1 g,



3.84 mmol, 1 equiv) in dry tetrahydrofuran/triethylamine (20/10 mL), was added $Pd(PPh_3)_4$ (0.132 g, 0.115 mmol, 0.03 equiv) followed by CuI (0.043 g, 0.23 mmol, 0.06 equiv) and propargyl alcohol (0.645 g, 11.52 mmol, 3 equiv), under argon atmosphere. The solution was stirred at 40 °C, and the reaction was monitored by TLC. After completion, the reaction mixture was concentrated in vacuo, and the crude residue was dissolved in diethylether and filtered through a short pad of silica gel column chromatography using diethylether as the eluent. The filtrate was concentrated to obtain the residue containing 3-(2-(3-hydroxyprop-1-ynyl)phenyl)propanal **1j** (0.70 g, 61%). To a light-protected solution (covered with an aluminum foil) of residue containing 3-(2-(3-hydroxyprop-1-ynyl)phenyl)propanal (0.70 g, 2.34 mmol, 1 equiv) in dry CH_2Cl_2 (20 mL) under argon atmosphere at 0 °C were added imidazole (0.239 g, 3.52 mmol, 1.5 equiv), triphenylphosphine (0.393 g, 3.52 mmol, 1.5 equiv), and iodine (0.379 g, 3.52 mmol, 1.5 equiv). The reaction mixture was stirred at 0 °C and monitored by TLC. After completion, the excess of iodine was removed by washing with sat. aqueous $Na_2S_2O_3$, and the organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was quickly purified through flash column chromatography using pentane/diethylether (9/1) as the eluent to give **1b** as a yellow oil (0.40 g, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.74 (t, J = 7.5, 2H), 3.00 (t, J = 7.5, 2H), 3.90 (s, 2H), 7.05−7.20 (m, 3H), 7.31 (d, J = 7.5, 1H), 9.77 (t, J = 1.3, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: −17.4 (CH_2), 27.2 (CH_2), 44.6 (CH_2), 83.9 (≡C), 90.5 (≡C), 121.9 (═C), 126.5 (═CH), 129.1 (2×═CH), 123.5 (═CH), 143.0 (═C), 201.7 (HC═O). HRMS (ESI): m/z: calcd for $[M + Na]^+$ $C_{12}H_{11}OINa^+$: 320.9747; found: 320.9745.

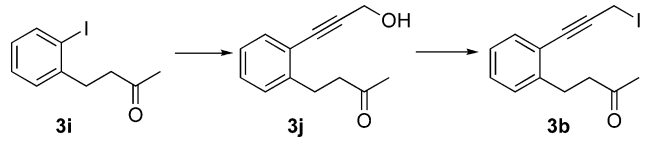
*1-(2-(3-Iodoprop-1-ynyl)phenyl)propan-2-one (**3a**). 1-(2-(3-Hydroxyprop-1-ynyl)phenyl)propan-2-one (**3j**).* To a solution of



1-(2-iodophenyl)propan-2-one (2.2 g, 8.49 mmol, 1 equiv) in dry tetrahydrofuran/triethylamine (60/30 mL), was added $Pd(PPh_3)_4$ (0.293 g, 0.25 mmol, 0.03 equiv) followed by CuI (0.096 g, 0.50 mmol, 0.06 equiv) and propargyl alcohol (1.42 g, 25.5 mmol, 3 equiv), under argon atmosphere. The solution was stirred at 40 °C, and the reaction was monitored by TLC. After completion, the reaction mixture was concentrated in vacuo, and the crude residue was purified through flash column chromatography using pentane/diethylether (1/1) as the eluent, to obtain the product as a yellow oil (1.4 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.08 (s, 3H), 2.97−3.31 (br s, 1H), 3.78 (s, 2H), 4.39 (s, 2H), 7.09−7.24 (m, 3H), 7.36 (d, J = 7.5, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.5 (CH_3), 49.7 (CH_2), 51.2 (CH_2), 83.5 (≡C), 92.4 (≡C), 123.0 (═C), 127.2 (═CH), 128.8 (═CH), 130.1 (═CH), 132.3 (═CH), 136.7 (═C), 207.2 (C═O). HRMS (ESI): m/z: calcd for $[MNa]^+$ $C_{12}H_{12}NaO_2^+$: 211.0730; found: 211.0729.

*1-(2-(3-Iodoprop-1-ynyl)phenyl)propan-2-one (**3a**).* To a light-protected solution (covered with an aluminum foil) of 1-(2-(3-hydroxyprop-1-ynyl)phenyl)propan-2-one (1.3 g, 7.44 mmol, 1 equiv) in dry CH_2Cl_2 (50 mL) under argon atmosphere at 0 °C, were added imidazole (0.75 g, 11.16 mmol, 1.5 equiv), triphenylphosphine (2.92 g, 11.16 mmol, 1.5 equiv), and iodine (2.82 g, 11.16 mmol, 1.5 equiv). The reaction mixture was stirred at 0 °C and monitored by TLC. After completion, the excess of iodine was removed by washing with sat. aqueous $Na_2S_2O_3$, and the organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was quickly purified through flash column chromatography using pentane/diethylether (9/1) as the eluent to give **3a** as a yellow oil (quantitative). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.15 (s, 3H), 3.81 (s, 2H), 3.90 (s, 2H), 7.09−7.26 (m, 3H), 7.37 (d, J = 7.3, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: −17.8 (CH_2), 29.8 (CH_3), 49.3 (CH_2), 83.9 (≡C), 90.5 (≡C), 122.7 (═C), 127.2 (═CH), 129.1 (═CH), 130.1 (═CH), 132.2 (═CH), 137.2 (═C), 205.7 (C═O). HRMS (ESI): m/z: calcd for $[MNa]^+$ $C_{12}H_{11}INaO^+$: 320.9747; found: 320.9746.

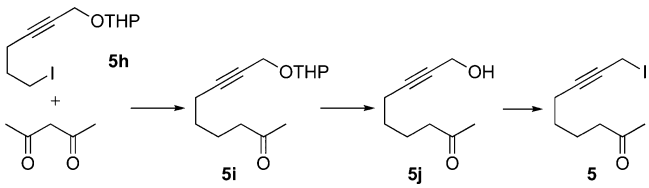
*4-(2-(3-Iodoprop-1-ynyl)phenyl)butan-2-one (**3b**). 4-(2-(3-Hydroxyprop-1-ynyl)phenyl)butan-2-one (**3j**).* To a solution of



4-(2-iodophenyl)butan-2-one **3i** (2.2 g, 8 mmol, 1 equiv) in dry tetrahydrofuran/triethylamine (40/20 mL), was added $Pd(PPh_3)_4$ (0.277 g, 0.24 mmol, 0.03 equiv) followed by CuI (0.091 g, 0.48 mmol, 0.06 equiv) and propargyl alcohol (1.344 g, 24 mmol, 3 equiv), under argon atmosphere. The solution was stirred at 40 °C, and the reaction was monitored by TLC. After completion, the reaction mixture was concentrated in vacuo, and the crude residue was purified through flash column chromatography using pentane/diethylether (1/1) as the eluent, to give the title product as a yellow oil (1.4 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.16 (s, 3H), 2.79 (t, J = 7.5, 2H), 2.82−2.99 (br s, 1H), 3.04 (t, J = 7.5, 2H), 4.52 (s, 2H), 7.12−7.27 (m, 3H), 7.40 (d, J = 7.5, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.9 (CH_2), 30.1 (CH_3), 44.2 (CH_2), 51.5 (CH_2), 83.8 (≡C), 91.9 (≡C), 122.1 (═C), 126.3 (═CH), 128.7 (═CH), 128.8 (═CH), 132.4 (═CH), 143.1 (═C), 209.1 (C═O). HRMS (ESI): m/z: calcd for $[MNa]^+$ $C_{13}H_{14}NaO_2^+$: 225.0885; found: 225.0886.

*4-(2-(3-Iodoprop-1-ynyl)phenyl)butan-2-one (**3b**).* To a light-protected solution (covered with an aluminum foil) of 4-(2-(3-hydroxyprop-1-ynyl)phenyl)butan-2-one (1.36 g, 6.73 mmol, 1 equiv) in dry CH_2Cl_2 under argon atmosphere at 0 °C were added imidazole (0.686 g, 10.09 mmol, 1.5 equiv), triphenylphosphine (2.64 g, 10.09 mmol, 1.5 equiv), and iodine (2.55 g, 10.09 mmol, 1.5 equiv). The reaction mixture was stirred at 0 °C and monitored by TLC. After completion, the excess of iodine was removed by washing with sat. aqueous $Na_2S_2O_3$, and the organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was quickly purified through flash column chromatography using pentane/diethylether (9/1) as the eluent to give the title product as a yellow oil (quantitative). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.20 (s, 3H), 2.82 (t, J = 7.5, 2H), 3.04 (t, J = 7.3, 2H), 4.01 (s, 2H), 7.14−7.28 (m, 3H), 7.40 (d, J = 7.5, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: −17.2 (CH_2), 28.7 (CH_2), 30.2 (CH_3), 44.5 (CH_2), 84.1 (≡C), 90.2 (≡C), 121.8 (═C), 126.2 (═CH), 129.0 (═CH), 129.1 (═CH), 132.4 (═CH), 143.6 (═C), 207.9 (C═O). HRMS (ESI): m/z: calcd for $[MH]^+$ $C_{13}H_{14}IO^+$: 313.0084; found: 313.0082.

*9-Iodonon-7-yn-2-one (**5**). 9-(Tetrahydro-2H-pyran-2-yloxy)non-7-yn-2-one (**5i**).* A mixture of 2-(6-iodohex-2-ynyloxy)tetrahydro-2H-



pyran **5h** (5 g, 16.2 mmol, 1 equiv), pentane-2,4-dione (1.78 g, 17.8 mmol, 1.1 equiv), potassium carbonate (2.45 g, 17.8 mmol, 1.1 equiv), and ethanol (50 mL) was heated at reflux for 24 h. Ethanol was

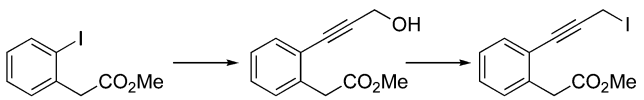
dx.doi.org/10.1021/jo4022293 | J. Org. Chem. 2013, 78, 12566−12576

evaporated, and the residue was dissolved in dichloromethane and washed with water. The combined organic layers were dried over $MgSO_4$ and filtered, and the filtrate was concentrated under vacuo. The residue was purified through flash column chromatography with pentane/Et_2O (1/1 mixture) to give the title compound as a colorless liquid (3.0 g, 80%). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.45−1.89 (m, 10H), 2.13 (s, 3H), 2.19−2.26 (m, 2H), 2.43 (t, J = 7.3, 2H), 3.46−3.56 (m, 1H), 3.77−3.89 (m, 1H), 4.23 (AB pattern, J = 15.3, $\Delta\upsilon$ = 35, 2H), 4.78 (t, J = 3.2, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.8 (CH_2), 19.2 (CH_2), 23.1 (CH_2), 25.5 (CH_2), 28.1 (CH_2), 30.0 (CH_3), 30.4 (CH_2), 43.3 (CH_2), 54.7 (CH_2), 62.1 (CH_2), 76.33 (≡C), 86.1 (≡C), 96.8 (CH), 208.8 (C═O). HRMS (ESI): m/z: calcd for $[MNH_4]^+$ $C_{14}H_{26}NO_3^+$: 256.1907; found: 256.1906.

*9-Hydroxynon-7-yn-2-one (**5j**).* To a solution of 9-(tetrahydro-2*H*-pyran-2-yloxy)non-7-yn-2-one **5i** (1.4 g, 5.88 mmol, 1 equiv) in ethanol (50 mL) was slowly added pyridinium *p*-toluenesulfonate (1.47 g, 5.88 mmol, 1 equiv) at room temperature over 30 min. After addition completion, the reaction mixture was heated at 50 °C for 12 h. Ethanol was evaporated, and the residue was purified through flash column chromatography to give the title product as a colorless liquid (0.74 g, 82%). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.50 (quint, J = 7.0, 2H), 1.67 (quint, J = 7.2, 2H), 1.79−1.95 (br s, 1H), 2.13 (s, 3H), 2.18−2.27 (m, 2H), 2.44 (t, J = 7.3, 2H), 4.23 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.7 (CH_2), 23.0 (CH_2), 28.1 (CH_2), 30.0 (CH_3), 43.2 (CH_2), 51.4 (CH_2), 79.0 (≡C), 85.9 (≡C), 209.0 (C═O). HRMS (ESI): m/z: calcd for $[MNa]^+$ $C_9H_{14}NaO_2^+$: 177.0886; found: 177.0886.

*9-Iodonon-7-yn-2-one (**5**).* To a light-protected solution (covered with an aluminum foil) of 9-hydroxynon-7-yn-2-one (0.74 g, 4.8 mmol, 1 equiv) in dry CH_2Cl_2 (50 mL) under argon atmosphere at 0 °C, were added imidazole (0.489 g, 7.2 mmol, 1.5 equiv), triphenylphosphine (1.88 g, 7.2 mmol, 1.5 equiv), and iodine (1.82 g, 7.2 mmol, 1.5 equiv). The reaction mixture was stirred at 0 °C and monitored by TLC. After completion, the excess of iodine was removed by washing with sat. aqueous $Na_2S_2O_3$, and the organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was quickly purified through flash column chromatography using pentane/diethylether (4/1) as the eluent to give the title product as a yellow oil (quantitative). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.45−1.52 (m, 2H), 1.62−1.69 (m, 2H), 2.13 (s, 3H), 2.18−2.22 (m, 2H), 2.44 (t, J = 7.3, 2H), 3.68 (t, J = 2.3, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: −16.8 (CH_2), 19.1 (CH_2), 23.0 (CH_2), 27.9 (CH_2), 30.0 (CH_3), 43.2 (CH_2), 77.6 (≡C), 86.2 (≡C), 208.2 (C═O). HRMS (ESI): m/z: calcd for $[M + H]^+$ $C_9H_{14}IO^+$: 265.0084; found: 265.0084.

*Methyl 2-(2-(3-Iodoprop-1-ynyl)phenyl)acetate (**7a**). Methyl 2-(2-(3-Hydroxyprop-1-ynyl)phenyl)acetate (**7j**).* To a solution of methyl

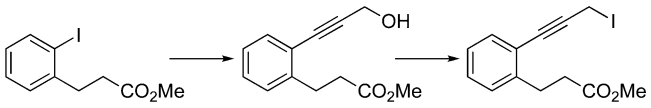


7i **7j** **7a**

2-(2-iodophenyl)acetate **7i** (1 g, 3.63 mmol, 1 equiv) in dry tetrahydrofuran/triethylamine (20/10 mL), was added $Pd(PPh_3)_4$ (0.125 g, 0.108 mmol, 0.03 equiv) followed by CuI (0.041 g, 0.217 mmol, 0.06 equiv) and propargyl alcohol (0.6 g, 10.89 mmol, 3 equiv), under argon atmosphere. The solution was stirred at 40 °C, and the reaction was monitored by TLC. After completion, the reaction mixture was concentrated in vacuo, and the crude residue was purified through flash column chromatography using pentane/diethylether (1/1) as the eluent, to obtain the title product as a yellow oil (0.650 g, 87%). ^1H NMR (400 MHz, $CDCl_3$) δ: 1.94 (br s, 1H), 3.70 (s, 3H), 3.82 (s, 2H), 4.49 (s, 2H), 7.32−7.21 (m, 3H), 7.43 (d, J = 7.5, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 40.3 (CH_2), 51.7 (CH_2), 52.3 (CH_3), 83.9 (≡C), 92.4 (≡C), 123.0 (═C), 127.3 (═CH), 128.9 (═CH), 130.0 (═CH), 132.1 (═CH), 136.5 (═C), 172.1 (O═C). HRMS (ESI): m/z: calcd for $[MNH_4]^+$ $C_{12}H_{16}NO_3^+$: 222.1125; found: 222.1125.

*Methyl 2-(2-(3-Iodoprop-1-ynyl)phenyl)acetate (**7a**).* To a light-protected solution (covered with an aluminum foil) of methyl 2-(2-(3-hydroxyprop-1-ynyl)phenyl)acetate (0.63 g, 3.08 mmol, 1 equiv) in dry CH_2Cl_2 (15 mL) under argon atmosphere at 0 °C, were added imidazole (0.25 g, 3.69 mmol, 1.2 equiv), triphenylphosphine (0.96 g, 3.69 mmol, 1.2 equiv), and iodine (0.93 g, 3.69 mmol, 1.2 equiv). The reaction mixture was stirred at 0 °C and monitored by TLC. After 2 h, the excess of iodine was removed by washing with sat. aqueous $Na_2S_2O_3$, and the organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was quickly purified through flash column chromatography using pentane/diethylether (4/1) as the eluent to give **7a** as a yellow oil (0.75 g, 80%). ^1H NMR (400 MHz, $CDCl_3$) δ: 3.73 (s, 3H), 3.82 (s, 2H), 3.97 (s, 2H), 7.32−7.21 (m, 3H), 7.43 (d, J = 7.5, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: −17.8 (CH_2), 39.8 (CH_2), 52.3 (CH_3), 83.6 (≡C), 90.8 (≡C), 122.9 (═C), 127.3 (═CH), 129.1 (═CH), 130.0 (═CH), 132.4 (═CH), 136.7 (═C), 171.6 (O═C). HRMS (ESI): m/z: calcd for $[MH]^+$ $C_{12}H_{12}IO_2^+$: 314.9877; found: 314.9871.

*Methyl 3-(2-(3-Iodoprop-1-ynyl)phenyl)propanoate (**7b**). Methyl 3-(2-(3-Hydroxyprop-1-ynyl)phenyl)propanoate (**7l**).* To a solution

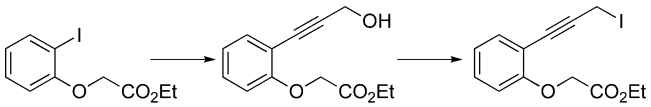


7k **7l** **7b**

of methyl 3-(2-iodophenyl)propanoate **7k** (1.20 g, 4.13 mmol, 1 equiv) in dry tetrahydrofuran/triethylamine (20/10 mL), was added $Pd(PPh_3)_4$ (0.147 g, 0.123 mmol, 0.03 equiv) followed by CuI (0.047 g, 0.247 mmol, 0.06 equiv) and propargyl alcohol (0.68 g, 12.39 mmol, 3 equiv), under argon atmosphere. The solution was stirred at 40 °C, and the reaction was monitored by TLC. After completion, the reaction mixture was concentrated in vacuo, and the crude residue was purified through flash column chromatography using pentane/diethylether (1/1) as the eluent, to obtain the title product as a yellow oil (0.820 g, 91%). ^1H NMR (400 MHz, $CDCl_3$) δ: 2.20 (br s, 1H), 2.66 (t, J = 8.0, 2H), 3.10 (t, J = 7.8, 2H), 3.68 (s, 3H), 4.52 (s, 2H), 7.27−7.15 (m, 3H), 7.40 (d, J = 7.5, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.3 (CH_2), 35.0 (CH_2), 51.7 (CH_2), 51.9 (CH_3), 83.9 (≡C), 92.0 (≡C), 122.2 (═C), 126.5 (═CH), 128.8 (═CH), 128.9 (═CH), 132.3 (═CH), 142.7 (═C), 174.0 (O═C). HRMS (ESI): m/z: calcd for $[MNH_4]^+$ $C_{13}H_{18}NO_3^+$: 236.1281; found: 236.1281.

*Methyl 3-(2-(3-Iodoprop-1-ynyl)phenyl)propanoate (**7b**).* To a light-protected solution (covered with an aluminum foil) of methyl 3-(2-(3-hydroxyprop-1-ynyl)phenyl)propanoate (0.80 g, 3.66 mmol, 1 equiv) in dry CH_2Cl_2 (15 mL) under argon atmosphere at 0 °C, were added imidazole (0.37 g, 5.50 mmol, 1.5 equiv), triphenylphosphine (1.40 g, 5.50 mmol, 1.5 equiv), and iodine (1.40 g, 5.50 mmol, 1.5 equiv). The reaction mixture was stirred at 0 °C and monitored by TLC. After 2 h, the excess of iodine was removed by washing with sat. aqueous $Na_2S_2O_3$, and the organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was quickly purified through flash column chromatography using pentane/diethylether (4/1) as the eluent to give the title product as a yellow oil (0.75 g, 56%). ^1H NMR (400 MHz, $CDCl_3$) δ: 2.68 (t, J = 8.3, 2H), 3.08 (t, J = 7.5, 2H), 3.68 (s, 3H), 3.99 (s, 2H), 7.27−7.14 (m, 3H), 7.39 (d, J = 7.8, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: −17.4 (CH_2), 29.9 (CH_2), 34.9 (CH_2), 51.8 (CH_3), 83.9 (≡C), 90.4 (≡C), 122.0 (═C), 126.5 (═CH), 129.0 (═CH), 129.1 (═CH), 132.5 (═CH), 143.1 (═C), 173.4 (O═C). HRMS (ESI): m/z: calcd for $[MH]^+$ $C_{13}H_{14}IO_2^+$: 329.0033; found: 329.0025.

*Ethyl [2-(3-Iodoprop-1-yn-1-yl)phenyl]methyl Carbonate (**10**). Ethyl (2-Iodophenyl)methyl carbonate:*[18] ^1H NMR (400 MHz,



10i **10j** **10**

$CDCl_3$) δ: 1.31 (3H, t, J = 7.0), 4.28 (2H, q, J = 7.0), 4.70 (2H, s), 6.69−6.81 (2H, m), 7.23−7.36 (1H, m), 7.78−7.85 (1H, m).

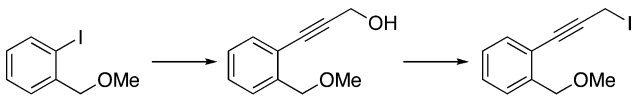
dx.doi.org/10.1021/jo4022293 | J. Org. Chem. 2013, 78, 12566−12576

^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.3 (CH_3), 61.6 (CH_2), 66.6 (CH_2), 86.6 (=C), 112.6 (=CH), 123.7 (=CH), 129.5 (=CH), 140.0 (=CH), 156.9 (=C), 168.4 (C=O).

*Ethyl [2-(3-Hydroxyprop-1-yn-1-yl)phenyl]methyl Carbonate (**10j**).* To a solution of ethyl (2-iodophenyl)methyl carbonate **10i** (2 g, 4.23 mmol, 1 equiv) in dry tetrahydrofuran/triethylamine (30/30 mL), was added $Pd(PPh_3)_4$ (196 mg, 0.17 mmol, 0.04 equiv) followed by CuI (65 mg, 0.34 mmol, 0.08 equiv) and propargyl alcohol (0.94 mL, 12.7 mmol, 3 equiv), under argon atmosphere. The solution was stirred at 40 °C during 2 h. After completion, the layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. After purification by flash chromatography on silica gel (pentane/Et_2O from 100/0 to 60/40) ethyl [2-(3-hydroxyprop-1-yn-1-yl)phenyl]methyl carbonate was isolated as a solid (333 mg, 34%). Mp (°C) = 61.7−62.7. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.29 (3H, t, J = 7.0), 2.21 (1H, br s), 4.26 (2H, q, J = 7.0), 4.52 (2H, s), 4.69 (2H, s), 6.72−6.80 (1H, m), 6.92−6.99 (1H, m), 7.22−7.30 (1H, m), 7.38−7.46 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.3 (CH_3), 51.9 (CH_2), 61.6 (CH_2), 66.3 (CH_2), 81.7 (≡C), 92.2 (≡C), 112.7 (=CH), 112.9 (=C), 121.8 (=CH), 129.9 (=CH), 133.9 (=CH), 158.6 (=C), 168.9 (C=O). HRMS (ESI): m/z: calcd for [MNa^+] $C_{13}H_{14}NaO_4^+$: 257.0784; found: 257.0783.

*Ethyl [2-(3-Iodoprop-1-yn-1-yl)phenyl]methyl Carbonate (**10**).* To a light-protected solution (covered with an aluminum foil) of ethyl [2-(3-hydroxyprop-1-yn-1-yl)phenyl]methyl carbonate (290 mg, 1.24 mmol, 1 equiv) in dry CH_2Cl_2 (8.5 mL) under argon atmosphere at 0 °C were added imidazole (101 mg, 1.49 mmol, 1.2 equiv), triphenylphosphine (390 mg, 1.49 mmol, 1.2 equiv), and iodine (377 mg, 1.49 mmol, 1.2 equiv). The reaction mixture was stirred at 0 °C during 1 h. After completion, the excess of iodine was removed by washing with sat. aqueous $Na_2S_2O_3$, and the organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. After purification by flash chromatography on silica gel (pentane/AcOEt from 100/0 to 90/10), ethyl [2-(3-iodoprop-1-yn-1-yl)phenyl]methyl carbonate was isolated (290 mg, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30 (3H, t, J = 7.0), 4.01 (2H, s), 4.27 (2H, q, J = 7.0), 4.70 (2H, s), 6.71−6.80 (1H, m), 6.91−7.01 (1H, m), 7.19−7.30 (1H, m), 7.37−7.44 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: −16.9 (CH_2), 14.3 (CH_3), 61.6 (CH_2), 66.5 (CH_2), 81.5 (≡C), 90.8 (≡C), 112.6 (=C), 113.0 (=CH), 121.9 (=CH), 130.1 (=CH), 134.1 (=CH), 158.8 (=C), 168.8 (C=O). HRMS (ESI): m/z: calcd for [MNH_4]$^+$ $C_{13}H_{17}INO_3^+$: 362.0248; found: 362.0250.

*1-(3-Iodoprop-1-ynyl)-2-(methoxymethyl)benzene (**14**). 3-(2-(Methoxymethyl)phenyl)prop-2-yn-1-ol (**14j**).* To a solution of

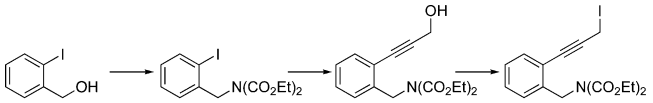


14i **14j** **14**

1-iodo-2-(methoxymethyl)benzene (3.20 g, 13.00 mmol, 1 equiv) in dry tetrahydrofuran/triethylamine (60/30 mL) was added $Pd(PPh_3)_4$ (0.45 g, 0.39 mmol, 0.03 equiv) followed by CuI (0.15 g, 0.78 mmol, 0.06 equiv) and propargyl alcohol (2.18 g, 39.00 mmol, 3 equiv), under argon atmosphere. The solution was stirred at 40 °C, and the reaction was monitored by TLC. After completion, the reaction mixture was concentrated in vacuo, and the crude residue was purified through flash column chromatography using pentane/diethylether (1/1) as the eluent, to obtain the title product as a yellow oil (2 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.41 (br s, 1H), 3.43 (s, 3H), 4.52 (d, J = 5, 2H), 4.62 (s, 2H), 7.24 (t, J = 7.5, 1H), 7.33 (t, J = 7.5, 1H), 7.43 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 51.7 (CH_2), 58.5 (CH_3), 72.8 (CH_2), 83.3 (≡C), 92.0 (≡C), 121.5 (=C), 127.5 (=CH), 127.8 (=CH), 128.8 (=CH), 132.4 (=CH), 140.0 (=C). HRMS: Calcd for $C_{11}H_{12}O_2Na^+$ (MNa)$^+$ 199.0729, Found 199.0729.

*1-(3-Iodoprop-1-ynyl)-2-(methoxymethyl)benzene (**14**).* To a light-protected solution (covered with an aluminum foil) of 3-(2-(methoxymethyl)phenyl)prop-2-yn-1-ol (2.00 g, 11.36 mmol, 1 equiv) in dry CH_2Cl_2 (60 mL) under argon atmosphere at 0 °C were added imidazole (1.60 g, 22.80 mmol, 2 equiv), triphenylphosphine (6 g, 22.80 mmol, 2 equiv), and iodine (5.75 g, 22.80 mmol, 2 equiv). The reaction mixture was stirred at 0 °C during 1 h. After completion, the excess of iodine was removed by washing with sat. aqueous $Na_2S_2O_3$, and the organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. After purification by flash chromatography on silica gel (pentane/AcOEt from 100/0 to 90/10), **14** was isolated (3 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.47 (s, 3H), 4.00 (s, 2H), 4.61 (s, 2H), 7.23 (dt, J = 1.0, 7.5, 1H), 7.34 (dt, J = 1.3, 7.5, 1H), 7.42 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: −17.5 (CH_2), 58.7 (CH_3), 72.6 (CH_2), 83.3 (≡C), 90.7 (≡C), 121.2 (=C), 127.4 (=CH), 127.7 (=CH), 129.0 (=CH), 132.2 (=CH), 140.7 (=C). HRMS: Calcd for $C_{11}H_{15}INO$ (MNH_4)$^+$ 304.0192, Found 304.0192.

*Ethyl N-(Ethoxycarbonyl)-N-{[2-(3-iodoprop-1-yn-1-yl)phenyl]-methyl}carbamate (**16a**). Ethyl N-(Ethoxycarbonyl)carbamate:*[19]



16i **16j** **16a**

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.29 (6H, t, J = 7.0), 4.23 (4H, q, J = 7.0), 4.50−4.74 (1H, br s).

*Ethyl N-(Ethoxycarbonyl)-N-[(2-iodophenyl)methyl]carbamate (**16i**).* To a solution of 2-iodobenzyl alcohol (2.9 g, 12.4 mmol, 1 equiv) and triphenylphosphine (3.6 g, 13.64 mmol, 1.1 equiv) in dry THF (206 mL) was added ethyl *N*-(ethoxycarbonyl)carbamate (2 g, 12.4 mmol, 1 equiv). The reaction mixture was cooled to 0 °C, and DEAD (2.5 mL, 13.64 mmol, 1.1 equiv) was added dropwise. The mixture was stirred for 18 h. The organic layer was diluted with ether and successively washed with water and brine. The ethereal layer was dried over $MgSO_4$, filtered, and concenterd under reduced pressure. After purification by flash chromatography on silica gel (pentane/AcOEt from 100/0 to 50/50), *N*-(ethoxycarbonyl)-*N*-[(2-iodophenyl)-methyl]carbamate was isolated as an oil (1.5 g, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.25 (6H, t, J = 7.0), 4.25 (4H, q, J = 7.0), 4.88 (2H, s), 6.90−6.98 (1H, m), 7.03−7.10 (1H, m), 7.27−7.33 (1H, m), 7.80−7.86 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.3 (CH_3), 54.9 (CH_2), 63.5 (CH_2), 97.3 (=C), 126.1 (=CH), 128.5 (=CH), 128.8 (=CH), 139.5 (=CH), 139.6 (=C), 153.6 (C=O). HRMS (ESI): m/z: calcd for [MH^+] $C_{13}H_{17}INO_4^+$: 378.0197; found: 378.0197.

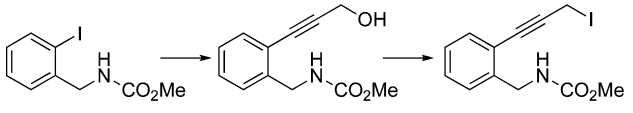
*Ethyl N-(Ethoxycarbonyl)-N-{[2-(3-hydroxyprop-1-yn-1-yl)-phenyl]methyl}carbamate (**16j**).* To a solution of ethyl *N*-(ethoxycarbonyl)-*N*-[(2-iodophenyl)methyl]carbamate (2.5 g, 6.02 mmol, 1 equiv) in dry tetrahydrofuran/triethylamine (29:29 mL) was added $Pd(PPh_3)_4$ (280 mg, 0.24 mmol, 0.04 equiv) followed by CuI (92 mg, 0.48 mmol, 0.08 equiv) and propargyl alcohol (1.3 mL, 18.1 mmol, 3 equiv), under argon atmosphere. The solution was stirred at 40 °C during 2 h. After completion, the layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. After purification by flash chromatography on silica gel (pentane/AcOEt from 100/0 to 50/50) ethyl *N*-(ethoxycarbonyl)-*N*-{[2-(3-hydroxyprop-1-yn-1-yl)phenyl]methyl}carbamate was isolated as a solid (1.5 g, 82%). Mp (°C) = 74.0−74.2. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.25 (6H, t, J = 7.3), 4.25 (4H, q, J = 7.3), 4.33 (1H, s), 4.50 (2H, s), 5.07 (2H, s), 7.16−7.31 (3H, m), 7.39−7.45 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.3 (CH_3), 48.6 (CH_2), 51.8 (CH_2), 63.4 (CH_2), 83.4 (≡C), 92.5 (≡C), 121.0 (=C), 126.5 (=CH), 127.1 (=CH), 128.8 (=CH), 132.6 (=CH), 139.5 (=C), 154.0 (C=O). HRMS (ESI): m/z: calcd for [MNa^+] $C_{16}H_{19}NNaO_5^+$: 328.1155; found: 328.1155.

*Ethyl N-(Ethoxycarbonyl)-N-{[2-(3-iodoprop-1-yn-1-yl)phenyl]-methyl}carbamate (**16a**).* To a light-protected solution (covered with an aluminum foil) of ethyl *N*-(ethoxycarbonyl)-*N*-{[2-(3-hydroxyprop-1-yn-1-yl)phenyl]methyl} carbamate (1.5 g, 4.91 mmol, 1 equiv) in dry CH_2Cl_2 (33 mL) under argon atmosphere at 0 °C were added imidazole (400 mg, 5.90 mmol, 1.2 equiv), triphenylphosphine

dx.doi.org/10.1021/jo4022293 | J. Org. Chem. 2013, 78, 12566−12576

(1.55 g, 5.90 mmol, 1.2 equiv), and iodine (1.50 g, 5.90 mmol, 1.2 equiv). The reaction mixture was stirred at 0 °C during 1 h. After completion, the excess of iodine was removed by washing with sat. aqueous $Na_2S_2O_3$, and the organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. After purification by flash chromatography on silica gel (pentane/AcOEt from 100/0 to 80/20), ethyl *N*-(ethoxycarbonyl)-*N*-{[2-(3-iodoprop-1-yn-1-yl)phenyl]methyl}carbamate was isolated as a solid (1 g, 49%). Mp (°C) = 39−40. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.26 (6H, t, J = 7.3), 4.00 (2H, s), 4.25 (4H, q, J = 7.3), 5.06 (2H, s), 7.11−7.43 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: −17.7 (CH_2), 14.3 (CH_3), 48.0 (CH_2), 63.4 (CH_2), 83.1 (≡C), 91.3 (≡C), 120.8 (=C), 125.4 (=CH), 126.9 (=CH), 129.1 (=CH), 132.4 (=CH), 140.2 (=C), 153.8 (C=O). HRMS (ESI): m/z: calcd for [MH^+] $C_{16}H_{19}INO_4^+$: 416.0353; found: 416.0354.

*Methyl N-{[2-(3-Iodoprop-1-yn-1-yl)phenyl]methyl}carbamate (**16b**). Methyl N-[(2-Iodophenyl)methyl]carbamate (**16k**).*[20] To a



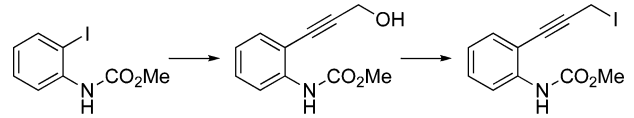
16k **16l** **16b**

solution of (2-iodophenyl)methanamine (2.75 g, 11.8 mmol, 1 equiv) were added K_2CO_3 (3.6 g, 25.96 mmol, 2.2 equiv) and methyl chloroformate (34 mL) at 0 °C. The reaction mixture was stirred at 0 °C during 1 h. After completion, the layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. Methyl *N*-[(2-iodophenyl)methyl]carbamate was isolated as an oil (3.0 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.69 (3H, s), 4.38 (2H, d, J = 6.3), 5.11−5.33 (1H, br s), 6.93−7.03 (1H, m), 7.28−7.42 (2H, m), 7.79−7.86 (1H, m).

*Methyl N-{[2-(3-Hydroxyprop-1-yn-1-yl)phenyl]methyl}-carbamate (**16l**).* To a solution of methyl *N*-[(2-iodophenyl)methyl]-carbamate (1.7 g, 5.84 mmol, 1 equiv) in dry tetrahydrofuran/triethylamine (28/28 mL) was added $Pd(PPh_3)_4$ (270 mg, 0.23 mmol, 0.04 equiv) followed by CuI (89 mg, 0.47 mmol, 0.08 equiv) and propargyl alcohol (1.3 mL, 17.5 mmol, 3 equiv), under argon atmosphere. The solution was stirred at 40 °C during 2 h. After completion, the layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. After purification by flash chromatography on silica gel (pentane/AcOEt from 100/0 to 40/60), methyl *N*-{[2-(3-hydroxyprop-1-yn-1-yl)phenyl]methyl}carbamate was isolated as an oil (1.1 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.01−3.12 (1H, br s), 3.61 (3H, s), 4.37−4.47 (4H, m), 5.07−5.18 (1H, br s), 7.13−7.27 (3H, m), 7.33−7.38 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 44.2 (CH_2), 51.5 (CH_2), 52.5 (CH_3), 83.4 (≡C), 92.8 (≡C), 122.4 (=C), 127.8 (=CH), 128.7 (=CH), 128.8 (=CH), 132.3 (=CH), 140.4 (=C), 157.5 (C=O). HRMS (ESI): m/z: calcd for [MNa^+] $C_{12}H_{13}NNaO_3^+$: 242.0787; found: 242.0788.

*Methyl N-{[2-(3-Iodoprop-1-yn-1-yl)phenyl]methyl}carbamate (**16b**).* To a light-protected solution (covered with an aluminum foil) of methyl *N*-{[2-(3-hydroxyprop-1-yn-1-yl)phenyl]methyl}-carbamate (1.1 g, 5 mmol, 1 equiv) in dry CH_2Cl_2 (33 mL) under argon atmosphere at 0 °C were added imidazole (410 mg, 6 mmol, 1.2 equiv), triphenylphosphine (1.58 g, 6 mmol, 1.2 equiv), and iodine (1.53 g, 6 mmol, 1.2 equiv). The reaction mixture was stirred at 0 °C during 1 h. After completion, the excess of iodine was removed by washing with sat. aqueous $Na_2S_2O_3$ and the organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. After purification by flash chromatography on silica gel (pentane/AcOEt from 100/0 to 70/30), methyl *N*-{[2-(3-iodoprop-1-yn-1-yl)phenyl]methyl}-carbamate was isolated as a solid (1.1 g, 67%). Mp (°C) = 69.3−70.3. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.69 (3H, s), 3.99 (2H, s), 4.48 (2H, d, J = 6.3), 5.12−5.29 (1H, br s), 7.19−7.26 (1H, m), 7.28−7.44 (3H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: −17.7 (CH_2), 43.8 (CH_2), 52.4 (CH_3), 83.3 (≡C), 91.2 (≡C), 121.6 (=C), 127.6 (=CH), 128.5 (=CH), 129.2 (=CH), 132.5 (=CH), 140.9 (=C), 157.2 (C=O). HRMS (ESI): m/z: calcd for [MH^+] $C_{12}H_{13}INO_2^+$: 329.9985; found: 329.9984.

*Methyl N-[2-(3-Iodoprop-1-yn-1-yl)phenyl]carbamate (**16c**). Methyl N-[2-Iodophenyl]carbamate (**16m**):*[21] ^{1}H NMR (400 MHz,



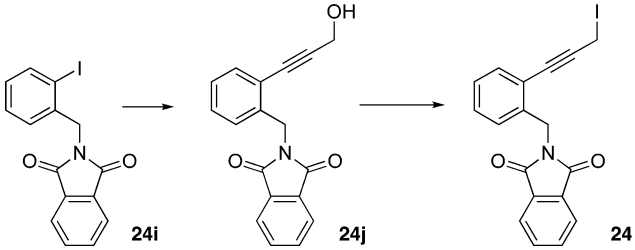
16m **16n** **16c**

$CDCl_3$) δ: 3.81 (3H, s), 6.72 (1H, dt, J = 1.5 and 7.8), 6.95 (1H, br s), 7.28 (1H, dt, J = 1.5 and 7.8), 7.75 (1H, dd, J = 1.5 and 8.0), 8.04 (1H, d, J = 8.0). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 52.7 (CH_3), 89.0 (=C), 120.4 (=CH), 125.3 (=CH), 129.4 (=CH), 138.5 (=C), 139.0 (=CH), 154.0 (C=O).

*Methyl N-[2-(3-Hydroxyprop-1-yn-1-yl)phenyl]carbamate (**16n**).* To a solution of methyl *N*-[2-iodophenyl]carbamate (1 g, 3.61 mmol, 1 equiv) in dry tetrahydrofuran/triethylamine (15/15 mL), was added $Pd(PPh_3)_4$ (166 mg, 0.144 mmol, 0.04 equiv) followed by CuI (55 mg, 0.288 mmol, 0.08 equiv) and propargyl alcohol (0.8 mL, 10.83 mmol, 3 equiv), under argon atmosphere. The solution was stirred at 40 °C during 2 h. After completion, the layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. After purification by flash chromatography on silica gel (pentane/AcOEt from 100/0 to 50/50) methyl *N*-[2-(3-hydroxyprop-1-yn-1-yl)phenyl]-carbamate was isolated as an oil (650 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.80 (1H, br s), 3.80 (3H, s), 4.57 (2H, s), 6.98 (1H, dt, J = 1 and 7.6), 7.31 (1H, dt, J = 1 and 7.6), 7.36 (1H, dd, J = 1.5 and 7.8), 7.36 (1H, br s), 8.12 (1H, d, J = 7.8). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 51.7 (CH_2), 52.6 (CH_3), 81.0 (≡C), 94.5 (≡C), 110.9 (=C), 118.0 (=CH), 122.7 (=CH), 130.1 (=CH), 132.2 (=CH), 139.3 (=C), 153.8 (C=O). HRMS (ESI): m/z: calcd for [MNa^+] $C_{11}H_{11}NNaO_3^+$: 228.0631; found: 228.0631.

*Methyl N-[2-(3-Iodoprop-1-yn-1-yl)phenyl]carbamate (**16c**).* To a light-protected solution (covered with an aluminum foil) of methyl *N*-[2-(3-hydroxyprop-1-yn-1-yl)phenyl]carbamate (1 g, 4.88 mmol, 1 equiv) in dry CH_2Cl_2 (65 mL) under argon atmosphere at 0 °C were added imidazole (400 mg, 5.85 mmol, 1.2 equiv), triphenylphosphine (1.53 g, 5.85 mmol, 1.2 equiv), and iodine (1.48 g, 5.85 mmol, 1.2 equiv). The reaction mixture was stirred at 0 °C during 1 h. After completion, the excess of iodine was removed by washing with sat. aqueous $Na_2S_2O_3$ and the organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. After purification by flash chromatography on silica gel (pentane/AcOEt from 100/0 to 80/20), methyl *N*-[2-(3-iodoprop-1-yn-1-yl)-phenyl]carbamate was isolated as an oil (1.09 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.81 (3H, s), 4.00 (2H, s), 6.97 (1H, t, J = 7.5), 7.29−7.36 (3H, m), 8.11 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: −18.4 (CH_2), 52.7 (CH_3), 80.8 (≡C), 93.5 (≡C), 110.8 (=C), 118.1 (=CH), 122.8 (=CH), 130.4 (=CH), 132.2 (=CH), 139.7 (=C), 153.9 (C=O). HRMS (ESI): m/z: calcd for [MH^+] $C_{11}H_{11}INO_2^+$: 315.9829; found: 315.9829.

*2-{[2-(3-Iodoprop-1-yn-1-yl)phenyl]methyl}-2,3-dihydro-1H-isoindole-1,3-diione (**24**). 2-[(2-Iodophenyl)methyl]-2,3-dihydro-1H-*



24i **24j** **24**

*isoindole-1,3-diione (**24i**).* To a solution of 2-iodobenzyl alcohol (2 g, 8.55 mmol, 1 equiv) and triphenylphosphine (2.69 g, 10.3 mmol, 1.2 equiv) in dry THF (25 mL) and dichloromethane (5 mL) was added phthalimide (1.5 g, 10.3 mmol, 1.2 equiv). The reaction mixture

dx.doi.org/10.1021/jo4022293 | J. Org. Chem. 2013, 78, 12566−12576

was cooled to 0 °C, and DEAD (1.6 mL, 10.3 mmol, 1.2 equiv) was added dropwise. The reaction mixture was stirred for 18 h. The organic layer was diluted with ether and successively washed with water and brine. The ethereal layer was dried over $MgSO_4$, filtered, and concenterd under reduced pressure. After purification by flash chromatography on silica gel (pentane/AcOEt from 100/0 to 90/10), 2-[(2-iodophenyl)methyl]-2,3-dihydro-1*H*-isoindole-1,3-diione was isolated as an oil (1.1 g, 38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.89 (2H, s), 6.95 (1H, td, J = 7.8 and 1.5), 7.06 (1H, dd, J = 7.8 and 1.6), 7.25 (1H, td, J = 7.8 and 1.0), 7.71−7.77 (2H, m), 7.84 (1H, dd, J = 7.8 and 1.0), 7.86−7.92 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 46.7 (CH_2), 97.7 (=C), 123.6 (2 = CH), 127.3 (=CH), 128.5 (=CH), 129.2 (=CH), 132.0 (=C), 134.3 (2 = CH), 137.9 (=C), 139.7 (=CH), 167.9 (C=O). HRMS (ESI): m/z: calcd for $[MH^+]$ $C_{15}H_{11}INO_2^+$: 363.9829; found: 363.9828.

*2-{[2-(3-Hydroxyprop-1-yn-1-yl)phenyl]methyl}-2,3-dihydro-1H-isoindole-1,3-diione (**24j**).* To a solution of 2-[(2-iodophenyl)methyl]-2,3-dihydro-1*H*-isoindole-1,3-diione (1.1 g, 3.03 mmol, 1 equiv) in dry tetrahydrofuran/triethylamine (15:15 mL) was added $Pd(PPh_3)_4$ (140 mg, 0.12 mmol, 0.04 equiv) followed by CuI (46 mg, 0.24 mmol, 0.08 equiv) and propargyl alcohol (0.66 mL, 9.09 mmol, 3 equiv), under argon atmosphere. The solution was stirred at 40 °C during 2 h. After completion, the layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. After purification by flash chromatography on silica gel (pentane/AcOEt from 100/0 to 60/40) 2-{[2-(3-hydroxyprop-1-yn-1-yl)phenyl]methyl}-2,3-dihydro-1*H*-isoindole-1,3-diione was isolated as a solid (0.55 g, 62%). Mp (°C) = 116−117. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.34 (1H, s), 4.49 (2H, s), 5.03 (2H, s), 7.20−7.34 (2H, m), 7.39−7.43 (1H, m), 7.48−7.53 (1H, m), 7.69−7.75 (2H, m), 7.81−7.89 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 41.1 (CH_2), 51.8 (CH_2), 83.7 (≡C), 93.2 (≡C), 122.2 (=C), 123.5 (2 = CH), 128.0 (=CH), 128.7 (=CH), 130.1 (=CH), 132.0 (=C), 132.4 (=CH), 134.3 (2 = CH), 137.7 (=C), 168.4 (C=O). HRMS (ESI): m/z: calcd for $[MNa^+]$ $C_{18}H_{13}NNaO_3^+$: 314.0788; found: 314.0786.

*2-{[2-(3-Iodoprop-1-yn-1-yl)phenyl]methyl}-2,3-dihydro-1H-isoindole-1,3-diione (**24**).* To a light-protected solution (covered with an aluminum foil) of 2-{[2-(3-hydroxyprop-1-yn-1-yl)phenyl]methyl}-2,3-dihydro-1H-isoindole-1,3-diione (530 mg, 1.89 mmol, 1 equiv) in dry CH_2Cl_2 (13 mL) under argon atmosphere at 0 °C were added imidazole (154 mg, 2.27 mmol, 1.2 equiv), triphenylphosphine (594 mg, 2.27 mmol, 1.2 equiv), and iodine (575 mg, 2.27 mmol, 1.2 equiv). The reaction mixture was stirred at 0 °C during 1 h. After completion, the excess of iodine was removed by washing with sat. aqueous $Na_2S_2O_3$, and the organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. After purification by flash chromatography on silica gel (pentane/AcOEt from 100/0 to 90/10), 2-{[2-(3-iodoprop-1-yn-1-yl)phenyl]methyl}-2,3-dihydro-1*H*-isoindole-1,3-diione was isolated as a solid (620 mg, 82%). Mp (°C) = 150.5−151.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.01 (2H, s), 5.03 (2H, s), 7.17−7.30 (3H, m), 7.38−7.47 (1H, m), 7.69−7.77 (2H, m), 7.84−7.92 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: −17.5 (CH_2), 40.4 (CH_2), 83.0 (≡C), 92.0 (≡C), 121.6 (=C), 123.6 (2 = CH), 123.7 (=C), 127.6 (=CH), 127.9 (=CH), 129.0 (=CH), 132.3 (=C), 132.7 (=CH), 134.2 (2 = CH), 138.2 (=C), 168.4 (C=O). HRMS (ESI): m/z: calcd for $[MH^+]$ $C_{18}H_{13}INO_2^+$: 401.9986; found: 401.9988.

General Procedure for Radical Reactions with Diethylzinc. *Reactions of Propargyl Iodides with Diethylzinc.* A light-protected round-bottom flask (covered with an aluminum foil) was loaded with ortho-substituted 3-phenylalkynyl iodide (0.5 mmol, 1 equiv) and dry CH_2Cl_2 (2.5 mL, 0.2 M) under argon atmosphere. Diethylzinc (0.75 mL, 1.5 equiv) (1 M solution in heptane) was added to the solution, and the resulting mixture was stirred at room temperature. After completion, the reaction was quenched with saturated aqueous NH_4Cl. The two layers were separated, the aqueous layer was extracted twice with dichloromethane (2 × 5 mL), and the combined organic layers were evaporated in vacuo. The crude residue was purified through flash column chromatography using pentane/diethylether as the eluent to give the products.

*1,2,3,4-Tetrahydro-1-vinylidenenaphthalen-2-ol (**2b**).* 3-(2-(3-Iodoprop-1-ynyl)phenyl)propanal, **1b** (0.298 g, 1 mmol, 1 equiv), diethylzinc (1.5 mL, 1.5 mmol, 1.5 equiv), and dichloromethane (5 mL, 0.2 M) were kept under general procedure for 14 h to obtain the title compound as a colorless liquid (0.15 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.93−2.06 (br s superimposed, 1H), 1.90−2.05 (m, 1H), 2.06−2.18 (m, 1H), 2.83 (ddd, J = 5.3, 8.3 and 16.6, 1H), 3.02 (ddd, J = 5.3, 7.0 and 16.8, 1H), 4.57−4.65 (m, 1H), 5.25−5.45 (m, 2H), 7.21−7.11(m, 3H), 7.47 (d, J = 7.0, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.3 (CH_2), 30.7 (CH_2), 67.7 (CH), 82.2 (=CH_2), 107.1 (=C), 126.4 (=CH), 127.1 (=CH), 127.4 (=CH), 129.0 (=CH), 129.4 (=C), 135.5 (=C), 205.6 (=C=). HRMS (ESI): m/z: calcd for $[MH]^+$ $C_{12}H_{13}O^+$: 173.0961; found: 173.0961.

*2,3-Dihydro-2-methyl-1-vinylidene-1H-inden-2-ol (**4a**).* 1-(2-(3-Iodoprop-1-ynyl)phenyl)propan-2-one, **3a** (0.298 g, 1 mmol, 1 equiv), diethylzinc (1.5 mL, 1.5 mmol, 1.5 equiv), and dichloromethane (5 mL, 0.2 M) were reacted under the conditions described in the general procedure for 14 h to obtain the title compound as a colorless liquid (0.14 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.48 (s, 3H), 2.00 (br s, 1H), 3.07 (AB pattern, J = 16.6, $\Delta\upsilon$ = 16, 2H), 5.28 (AB pattern, J = 13, $\Delta\upsilon$ = 8.6, 2H), 7.22−7.10 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 27.9 (CH_3), 47.6 (CH_2), 79.7 (C), 83.2 (=CH_2), 115.7 (=C), 123.3 (=CH), 125.3 (=CH), 127.4 (=CH), 128.2 (=CH), 136.8 (=C), 140.2 (=C), 203.2 (=C=). HRMS (ESI): m/z: calcd for $[MNa]^+$ $C_{12}H_{12}NaO^+$: 195.0780; found: 195.0780.

*1,2,3,4-Tetrahydro-2-methyl-1-vinylidenenaphthalen-2-ol (**4b**).* 4-(2-(3-Iodoprop-1-ynyl)phenyl)butan-2-one, **3b** (0.156 g, 0.5 mmol, 1 equiv), diethylzinc (0.75 mL, 0.75 mmol, 1.5 equiv), and dichloromethane (2.5 mL, 0.2 M) were reacted under the conditions described in the general procedure for 14 h to obtain the title compound as a colorless liquid. (0.086 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.47 (s, 3H), 1.85−1.97 (br s superimposed, 1H), 1.91 (ddd, J = 5.5, 8.5 and 13.3, 1H), 2.04 (ddd, J = 5.3, 6.8 and 13.1, 1H), 2.81 (ddd, J = 6.2, 6.3 and 16.8, 1H), 3.06 (ddd, J = 5.5, 8.3 and 16.8, 1H), 5.34 (s, 2H), 7.13−7.20 (m, 3H), 7.47 (d, J = 7.6, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.5 (CH_2), 28.5 (CH_3), 36.3 (CH_2), 69.2 (C), 82.5 (=CH_2), 110.6 (=C), 126.4 (=CH), 126.9 (=CH), 127.6 (=CH), 129.0 (=CH), 129.8 (=C), 135.1 (=C), 205.3 (=C=). HRMS (ESI): m/z: calcd for $[MNa]^+$ $C_{13}H_{14}NaO^+$: 209.0937; found: 209.0937.

*1-Methyl-2-vinylidenecyclohexanol (**6**).* 9-Iodonon-7-yn-2-one 5 (0.132 g, 0.5 mmol, 1 equiv), diethylzinc (0.75 mL, 0.75 mmol, 1.5 equiv), and dichloromethane (2.5 mL, 0.2 M) were submitted to the conditions described in the general procedure for 14 h to give the title compound as a colorless liquid (quantitative). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35 (s, 3H), 1.45−1.82 (m, 7H), 2.08−2.22 (m, 1H), 2.30−2.44 (m, 1H), 4.74−4.82 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.9 (CH_2), 26.7 (CH_2), 28.1 (CH_3), 28.7 (CH_2), 40.8 (CH_2), 69.8 (C), 77.1 (=CH_2), 108.7 (=C), 201.7 (=C=). HRMS (ESI): m/z: calcd for $[MNa]^+$ $C_9H_{14}NaO^+$: 161.0937; found: 161.0937

*(E)-1-(Butan-2-ylidene)-1H-inden-2(3H)-one (**8a**).* Methyl 2-(2-(3-iodoprop-1-ynyl)phenyl)acetate, **7a** (0.314 g, 1 mmol, 1 equiv), diethylzinc (5 mL, 5 mmol, 5 equiv), and dichloromethane (5 mL, 0.2 M) were reacted under the conditions described in the general procedure for 2 h to give the title compound as a colorless oil. (0.149 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.28 (t, J = 7.7, 3H), 2.47 (s, 3H), 2.64 (q, J = 7.7, 2H), 3.50 (s, 2H), 7.24−7.36 (m, 3H), 7.60 (d, J = 7.6, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.3 (CH_3), 21.2 (CH_3), 30.8 (CH_2), 43.2 (CH_2), 124.0 (=CH), 125.2 (=CH), 127.3 (=CH), 127.4 (=CH), 130.7 (=C), 136.9 (=C), 140.3 (=C), 155.6 (=C), 205.5 (C=O). HRMS (ESI): m/z: calcd for $[MH^+]$ $C_{13}H_{15}O^+$: 187.1123; found: 187.1121.

*(E)-1-(Butan-2-ylidene)-3,4-dihydronaphthalen-2(1H)-one (**8b**).* Methyl 3-(2-(3-iodoprop-1-ynyl)phenyl)propanoate, **7b** (0.163 g, 0.5 mmol, 1 equiv), diethylzinc (1.1 mL, 1.1 mmol, 2.2 equiv), and dichloromethane (2.5 mL, 0.2 M) were reacted under the conditions described in the general procedure for 14 h to obtain the title compound as a colorless oil. (0.085 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.09 (t, J = 7.4, 3H), 2.10 (s, 3H), 2.24 (q, J = 7.6, 2H),

dx.doi.org/10.1021/jo4022293 | J. Org. Chem. 2013, 78, 12566−12576

2.41 (t, J = 6.9, 2H), 2.80 (t, J = 6.5, 2H), 7.07−7.17 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.3 (CH_3), 20.1 (CH_3), 27.9 (CH_2), 29.6 (CH_2), 38.5 (CH_2), 126.2 (=CH), 127.0 (=CH), 127.1 (=CH), 128.7 (=CH), 133.4 (=C), 135.5 (=C), 138.6 (=C), 149.5 (=C), 204.5 (C=O). HRMS (ESI): m/z: calcd for $[MH]^+$ $C_{14}H_{17}O^+$: 201.1273; found: 201.1274.

*4-Ethyl-9a-hydroxy-2-methylidene-1′,2,3,3′,9,9a-hexahydrospiro[fluorine-1,2′-indene]-3′-one (**9a**).* Methyl 2-(2-(3-iodoprop-1-ynyl)phenyl)acetate **7a** (0.314 g, 1 mmol, 1 equiv), diethylzinc (1.5 mL, 1.5 mmol, 1.5 equiv), and dichloromethane (5 mL, 0.2 M) were reacted under the conditions described in the general procedure for 24 h to give the product as light-pink gummy foam. (0.60 g, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.32 (t, J = 7.8, 3H), 2.45−2.57 (m, 1H), 2.67 (AB parttern, J_{AB} = 16.0, $\Delta\nu$ = 26.6, 2H), 2.70 (superimposed m, 1H), 3.66 (d, A part of an AB pattern, J = 21.7, 1H), 3.88 (d, B part of an AB pattern, J = 22.6, 1H), 4.84 (m, 2H), 5.09 (m, 1H), 7.09−7.19 (m, 4H), 7.19−7.25 (m, 2H), 7.34 (d, J = 7.5, 1H), 7.62 (d, J = 8.0, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.0 (CH_3), 26.2 (CH_2), 36.7 (CH_2), 41.8 (CH_2), 44.5 (CH_2), 65.4 (C), 82.9 (C), 111.7 (CH_2), 124.6 (=CH), 125.3 (=CH), 125.7 (=CH), 125.8 (=CH), 126.9 (=CH), 127.5 (=CH), 127.9 (=CH), 128.3 (=CH), 135.9 (=C), 136.7 (=C), 136.8 (=C), 138.5 (=C), 142.2 (=C), 143.1 (=C), 144.5 (=C), 221.9 (C=O). HRMS (ESI): m/z: calcd for $[MNa]^+$ $C_{24}H_{22}NaO_2^+$: 365.1512; found: 365.1512.

*4-(But-1-en-2-yl)-3,4-dihydro-2H-1-benzopyran-3-one (**11**).* Ethyl [2-(3-iodoprop-1-yn-1-yl)phenyl]methyl carbonate **10** (100 mg, 0.29 mmol, 1 equiv), diethylzinc (0.58 mL, 2 equiv), and dichloromethane (1.45 mL, 0.2 M) were reacted under the conditions described in the general procedure for 14 h to give 4-(but-1-en-2-yl)-3,4-dihydro-2H-1-benzopyran-3-one, isolated as an oil (58 mg, quantitative). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.24 (3H, t, J = 7.5), 2.28 (3H, s), 2.40 (2H, q, J = 7.5), 4.42 (2H, s), 7.03−7.12 (2H, m), 7.20−7.29 (2H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.2 (CH_3), 20.6 (CH_3), 30.2 (CH_2), 73.9 (CH_2), 118.0 (=CH), 122.8 (=CH), 125.4 (=C), 127.3 (=C), 128.7 (=CH), 129.0 (=CH), 153.5 (=C), 155.3 (=C), 201.1 (C=O). HRMS (ESI): m/z: calcd for $[MH^+]$ $C_{13}H_{15}O_2^+$: 203.1066; found: 203.1061.

*Methyl 3-(2-(propa-1,2-dienyl)phenyl)propanoate (**13b**).* Methyl 3-(2-(3-iodoprop-1-ynyl)phenyl)propanoate **7b** (0.082 g, 0.25 mmol, 1 equiv), In (0.057 g, 0.5 mmol, 2 equiv), and acetic acid (0.060, 1 mmol, 4 equiv) were stirred at room temperature for 14 h in a DMF/H_2O mixture (1 mL/0.125 mL). After this time, the reaction mixture was filtered, and the filtrate was evaporated. The residue was purified through flash column chromatography to give the title product as a colorless oil. (25 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.60 (t, J = 8.3, 2H), 3.03 (t, J = 7.8, 2H), 3.7 (s, 3H), 5.13 (d, J = 6.9, 2H), 6.37 (t, J = 6.9, 1H), 7.10−7.25 (m, 3H), 7.41 (d, J = 7.3, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.6 (CH_2), 35.3 (CH_2), 51.8 (CH_3), 78.3 (=CH_2), 90.8 (=CH), 126.9 (=CH), 127.3 (=CH), 128.0 (=CH), 129.8 (=CH), 131.9 (=C), 137.4 (=C), 173.4 (C=O), 210.7 (=C=). HRMS (ESI): m/z: calcd for $[MH]^+$ $C_{13}H_{15}O_2^+$: 203.1066; found: 203.1066.

*1,7-bis[2-(methoxymethyl)phenyl]-4-propylhepta-1,6-diyn-4-ol (**15**).* Light-protected round-bottom flask (covered with an aluminum foil) was loaded with 1-(3-iodoprop-1-yn-1-yl)-2-(methoxymethyl)-benzene, **14** (143 mg, 0.5 mmol, 1 equiv), ethyl butanoate (290 mg, 2.5 mmol, 5 equiv), and dry CH_2Cl_2 (2.5 mL, 0.2 M) under argon atmosphere. Diethylzinc (1.1 mL, 2.2 equiv) (1 M solution in heptane) was added to the solution, and the resulting mixture was stirred at room temperature for 14 h. After that time, the reaction was quenched with saturated aqueous NH_4Cl. The two layers were separated, the aqueous layer was extracted twice with dichloromethane, and the combined organic layers were evaporated in vacuo. 1,7-Bis[2-(methoxymethyl)-phenyl]-4-propylhepta-1,6-diyn-4-ol was isolated as an oil (60 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.92 (3H, t, J = 7.3), 1.39−1.53 (2H, m), 1.68−1.76 (2H, m), 2.75 (4H, AB pattern, J = 16.6, $\Delta\nu$ = 15.4), 3.04−3.13 (1H, br s), 3.32 (6H, s), 4.55 (AB pattern, J = 12.6, $\Delta\nu$ = 7.8, 4H), 7.12−7.26 (4H, m), 7.28−7.40 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8 (CH_3), 17.0 (CH_2), 31.1 (2×CH_2), 41.2 (CH_2), 58.2 (2×CH_3), 73.2 (2×CH_2), 74.0 (C), 81.3 (2×≡C), 91.0 (2×≡C), 122.7 (2×=C), 127.7 (2×=CH), 128.1 (2×=CH), 128.2 (2×=CH), 132.3 (2×=CH), 139.9 (2×=C). HRMS (ESI): m/z: calcd for $[MNH_4]^+$ $C_{26}H_{34}NO_3^+$: 408.2533; found: 408.2532.

*Ethyl 4-(But-1-en-2-yl)-3-oxo-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (**17**).* Ethyl N-(ethoxycarbonyl)-N-{[2-(3-iodoprop-1-yn-1-yl)phenyl]methyl}carbamate, **16a** (100 mg, 0.24 mmol, 1 equiv), diethylzinc (1.2 mL, 5 equiv), and dichloromethane (1.2 mL, 0.2 M) were reacted under the conditions described in the general procedure for 14 h to give ethyl 4-(but-1-en-2-yl)-3-oxo-1,2,3,4-tetrahydroisoquinoline-2-carboxylate, **17**, isolated as an oil (65 mg, quantitative). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.01 (3H, t, J = 7.3), 1.29 (3H, t, J = 7.3), 2.07 (2H, q, J = 7.3), 4.25 (1H, s), 4.27 (2H, q, J = 7.3), 4.42 (1H, d, J = 1.3), 4.59 (1H, d, J = 15.6), 4.90 (1H, d, J = 1.3), 4.98 (1H, d, J = 15.6), 7.03−7.11 (1H, m), 7.14−7.29 (3H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.3 (CH_3), 14.3 (CH_3), 27.2 (CH_2), 48.2 (CH_2), 58.0 (CH), 63.5 (CH_2), 111.9 (=CH_2), 125.9 (=CH), 127.5 (=CH), 128.0 (=CH), 128.3 (=CH), 132.3 (=C), 134.6 (=C), 145.3 (=C), 153.8 (C=O), 169.7 (C=O). HRMS (ESI): m/z: calcd for $[MH^+]$ $C_{16}H_{20}NO_3^+$: 274.1438; found: 274.1437.

*Methyl N-{[2-(prop-1-yn-1-yl)phenyl]methyl}carbamate (**18**) and Methyl N-{[2-(propa-1,2-dien-1-yl)phenyl]methyl}carbamate (**19**).* Methyl N-{[2-(3-iodoprop-1-yn-1-yl)phenyl]methyl}carbamate (**16b**) (100 mg, 0.3 mmol, 1 equiv), diethylzinc (0.45 mL, 1.5 equiv), and dichloromethane (1.5 mL, 0.2 M) were reacted under the conditions described in the general procedure for 14 h to give, after purification by flash chromatography on silica gel (pentane/AcOEt from 100/0 to 50/50), a mixture of methyl N-{[2-(propa-1,2-dien-1-yl)phenyl]-methyl}carbamate, **19**, and methyl N-{[2-(prop-1-yn-1-yl)phenyl]-methyl}carbamate, **18**, isolated in a 70:30 ratio as an oil (0.043 g, 71% overall yield). HRMS (ESI): m/z: calcd for $[MH^+]$ $C_{12}H_{14}NO_2^+$: 204.1019; found: 204.1019.

18: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.09 (3H, s), 3.68 (3H, s), 4.48 (2H, d, J = 6.0), 5.05−5.25 (1H, br s), 7.14−7.46 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 4.6 (CH_3), 44.0 (CH_2), 52.3 (CH_3), 84.8 (≡C), 91.0 (≡C), 125.7 (=C), 128.2 (=CH), 129.6 (=CH), 132.4 (2×=CH), 134.7 (=C), 156.9 (C=O).

19: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.67 (3H, s), 4.42 (2H, d, J = 5.52), 4.85−5.03 (1H, br s), 5.13 (2H, d, J = 6.8), 6.38 (1H, t, J = 6.8), 7.14−7.46 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 43.2 (CH_2), 52.3 (CH_3), 78.3 (=CH_2), 90.6 (=CH), 125.7 (=C), 127.3 (=CH), 127.4 (=CH), 128.1 (=CH), 128.2 (=CH), 140.1 (=C), 156.9 (C=O), 210.7 (=C=).

*Methyl N-{[2-(4-Hydroxy-4-phenylbut-1-yn-1-yl)phenyl]methyl}-carbamate (**20**) and Methyl N-{[2-(1-Hydroxy-1-phenylbuta-2,3-dien-2-yl)phenyl]methyl}carbamate (**21**).* To a light-protected round-bottom flask (covered with an aluminum foil), loaded with methyl N-{[2-(3-iodoprop-1-yn-1-yl)phenyl]methyl}carbamate, **16b** (100 mg, 0.3 mmol, 1 equiv), and dry CH_2Cl_2 (1.5 mL, 0.2 M) under argon atmosphere was added benzaldehyde (61 μL, 0.6 mmol, 2 equiv). Diethylzinc (0.45 mL, 1.5 equiv) was added to the solution, and the resulting mixture was stirred at room temperature for 14 h. After that time, the reaction was quenched with saturated aqueous NH_4Cl. The two layers were separated, the aqueous layer was extracted twice with dichloromethane, and the combined organic layers were evaporated in vacuo After purification by flash chromatography on silica gel (pentane/AcOEt from 100/0 to 90/10), a mixture of methyl N-{[2-(1-hydroxy-1-phenylbuta-2,3-dien-2-yl)phenyl]-methyl}carbamate, **21**, and methyl N-{[2-(4-hydroxy-4-phenylbut-1-yn-1-yl)phenyl]methyl}carbamate, **20**, was isolated in a 61:35 ratio as an oil (0.074 g, 76% overall yield). HRMS (ESI): m/z: calcd for $[MNa^+]$ $C_{19}H_{19}NNaO_3^+$: 332.1257; found: 332.1255.

20: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.86 (2H, d, J = 6.0), 3.61 (3H, s), 4.32−4.40 (2H, m), 4.87−4.97 (1H, m), 5.57−5.66 (1H, br s), 7.02−7.45 (10H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.5 (CH_2), 44.1 (CH_2), 52.5 (CH_3), 72.8 (CH), 80.7 (≡C), 91.6 (≡C), 122.9 (=C), 125.9 (=CH), 127.7 (=CH), 128.1 (=CH), 128.4 (=CH), 128.9 (=CH), 129.4 (=CH), 134.2 (=C) 140.7 (=C), 157.4 (C=O).

21: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.01−3.39 (1H, br s), 3.61 (3H, s), 4.13−4.31 (2H, m), 4.88 (2H, s), 4.99−5.10 (1H, br s), 5.45 (1H, s), 7.02−7.45 (10H, m). ^{13}C NMR (100 MHz, $CDCl_3$)

δ: 42.7 (CH_2), 52.3 (CH_3), 75.3 (CH), 78.2 (=CH_2), 107.3 (=C), 126.7 (2=CH), 127.6 (=CH), 128.0 (=CH), 128.2 (=CH), 128.4 (=CH), 128.7 (2=CH), 129.5 (=CH), 137.4 (=C), 141.9 (=C), 143.1 (=C), 157.5 (C=O), 205.8 (=C=).

*Methyl 2-Methyl-1H-indole-1-carboxylate (**22**).* Methyl *N*-[2-(3-iodoprop-1-yn-1-yl)phenyl]carbamate, **16c** (100 mg, 0.32 mmol, 1 equiv), diethylzinc (1.6 mL, 5 equiv), and dichloromethane (1.6 mL, 0.2 M) were reacted under the conditions described in the general procedure for 14 h to give methyl 2-methyl-1*H*-indole-1-carboxylate, isolated as an oil (41 mg, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.61 (3H, bd, J = 1.0), 4.04 (3H, s), 6.35 (1H, br s), 7.17−7.28 (2H, m), 7.41−7.49 (1H, m), 8.10 (1H, d, J = 8.0). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.8 (CH_3), 53.5 (CH_3), 108.7 (=CH), 115.6 (=CH), 119.7 (=CH), 123.1 (=CH), 123.5 (=CH), 129.7 (=C), 136.5 (=C), 137.9 (=C), 152.8 (C=O). HRMS (ESI): m/z: calcd for $[MH]^+$ $C_{11}H_{12}NO_2^+$: 190.0863; found: 190.0863.

*Methyl 2′-Methylidene-3-oxo-1,1′,2′,3′-tetrahydrospiro[benzo-[b]pyrrolizine-2,3′-indole]-1′-carboxylate (**23**).* Methyl *N*-[2-(3-iodoprop-1-yn-1-yl)phenyl]carbamate **16c** (100 mg, 0.32 mmol, 1 equiv), diethylzinc (0.48 mL, 1.5 equiv) in dichloromethane (1.6 mL, 0.2 M) were reacted under the conditions described in the general procedure for 14 h to give methyl 2′-methylidene-3-oxo-1,1′,2′,3′-tetrahydrospiro-[benzo[*b*]pyrrolizine-2,3′-indole]-1′-carboxylate, isolated as an oil (32 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.62 (2H, AB pattern, J = 17.3, $\Delta\upsilon$ = 25.0), 3.99 (3H, s), 4.69 (1H, d, J = 2.0), 5.86 (1H, d, J = 2.0), 6.46 (1H, s), 6.96−7.12 (2H, m), 7.27−7.39 (3H, m), 7.53−7.62 (1H, m), 7.86−7.92 (1H, m), 7.12−8.13 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 39.2 (CH_2), 53.3 (CH_3), 62.6 (C), 96.3 (=CH_2), 101.9 (=CH), 114.2 (=CH), 116.4 (=CH), 121.0 (=CH), 122.6 (=CH), 124.0 (=CH), 124.6 (=CH), 124.9 (=CH), 129.8 (=CH), 130.5 (=C), 131.3 (=C), 135.6 (=C), 139.9 (=C), 142.4 (=C), 148.7 (=C), 153.0 (C=O), 170.0 (C=O). HRMS (ESI): m/z: calcd for $[MH]^+$ $C_{21}H_{17}N_2O_3^+$: 345.1234; found: 345.1232.

*12-Ethenelidene-12a-hydroxy-5H,7H,12H,12aH-isoindolo[2,1-b]-isoquinolin-5-one (**25**).* 2-{[2-(3-Iodoprop-1-yn-1-yl)phenyl]methyl}-2,3-dihydro-1*H*-isoindole-1,3-diione, **24** (100 mg, 0.25 mmol, 1 equiv), diethylzinc (0.50 mL, 2 equiv), and dichloromethane (1.3 mL, 0.2 M) were reacted under the conditions described in the above general procedure for 14 h to give, after purification by flash chromatography on silica gel (pentane/AcOEt from 100/0 to 50/50), 12-ethenelidene-12a-hydroxy-5*H*,7*H*,12*H*,12a*H*-isoindolo[2,1-*b*]isoquinolin-5-one, **25**, isolated as an oil (61 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.29 (1H, br s), 4.44 (1H, d, J = 16.8), 5.12 (1H, d, J = 16.8), 5.15 (1H, d, J = 12.8), 5.40 (1H, d, J = 13.0), 7.21−7.29 (3H, m), 7.39−7.50 (2H, m), 7.54−7.63 (2H, m), 7.77−7.84 (1H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 38.6 (CH_2), 83.4 (=CH_2), 85.5 (C), 103.3 (=C), 123.3 (=CH), 124.2 (=CH), 126.5 (=CH), 127.3 (=C), 127.4 (=CH), 127.5 (=CH), 127.6 (=CH), 129.6 (=CH), 130.4 (=C), 130.7 (=C), 131.9 (=CH), 145.9 (=C), 165.7 (C=O), 207.6 (=C=). HRMS (ESI): m/z: calcd for $[MH^+]$ $C_{18}H_{14}NO_2^+$: 276.1019; found: 276.1018.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

■ AUTHOR INFORMATION

Corresponding Authors

*michele.bertrand@univ-amu.fr

*laurence.feray@univ-amu.fr

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the ANR (D2R2 project) for financial support and Aix-Marseille Université for the postdoctoral grant of S.J.

■ REFERENCES

(1) For reviews, see: (a) Yamamoto, Y. In *Comprehensive Organic Synthesis*; Trost, B. M, Ed.; Pergamon Press: Oxford, 1991, *2*, 81−98. (b) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163. (c) Marshall, J. A.; Gung, B. W.; Grachan, M. L. Synthesis and Reactions of Allenyl Compounds. In *Modern Allene Chemistry*; Krause, N.; Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004; pp 493−592. (d) Marshall, J. A. In *The Chemistry of Organozinc Compounds*; Rappoport, Z.; Marek, I., Eds.; Wiley: New-York, 2006, Vol. *1*, pp 421−455. (e) Botuha, C.; Chemla, F.; Ferreira, F.; Perez-Luna, A.; Roy, B. *New J. Chem.* **2007**, *31*, 1552.

(2) For selected examples see: (a) Tanino, K.; Honda, H.; Miyashita, M. *Tetrahedron Lett.* **2000**, *41*, 9281. (b) Schinzer, D. *Synthesis* **1988**, 263. (c) Hiemstra, H.; Fortgens, P.; Speckamp, W. N. *Tetrahedron Lett.* **1984**, *25*, 3115. (d) Weinreb, S. M.; Smith, D. T.; Jin, J. *Synthesis* **1998**, 509.

(3) Kang, H.-Y.; Kim, Y.-T.; Yu, Y.-K.; Cha, J. H.; Cho, Y. S.; Koh, H. Y. *Synlett* **2004**, 45.

(4) (a) Bazin, S.; Feray, L.; Vanthuyne, N.; Siri, D.; Bertrand, M. P. *Tetrahedron* **2007**, *63*, 77. (b) Maury, J.; Feray, L.; Perfetti, P.; Bertrand, M. P. *Org. Lett.* **2010**, *12*, 3590. (c) Maury, J.; Feray, L.; Bertrand, M. P. *Org. Lett.* **2011**, *13*, 1884. (d) Maury, J.; Mouysset, D.; Feray, L.; Marque, S. R. A.; Siri, D.; Bertrand, M. P. *Chem.—Eur. J.* **2012**, *18*, 3241 and previous references cited therein.

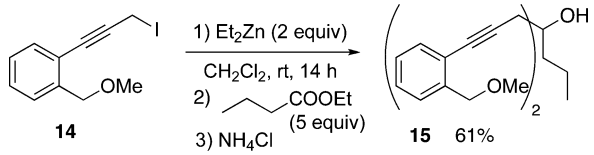
(5) For reviews on organozincs radical chemistry, see: (a) Bazin, S.; Feray, L.; Bertrand, M. P. *Chimia* **2006**, *60*, 260. (b) Akindele, T.; Yamada, K.-I.; Tomioka, K. *Acc. Chem. Res.* **2009**, *42*, 345. (c) Knochel, P. *Synlett* **1995**, 393.

(6) Maury, J.; Jammi, S.; Vibert, F.; Marque, S. R. A.; Siri, D.; Feray, L.; Bertrand, M. P. *J. Org. Chem.* **2012**, *77*, 9081.

(7) Jammi, S.; Mouysset, D.; Siri, D.; Bertrand, M. P.; Feray, L. *J. Org. Chem.* **2013**, *78*, 1589.

(8) Alternatively, the nucleophilic addition leading to intermediate **F** might be slowed down in case b.

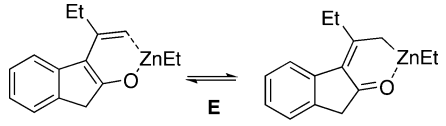
(9) It is worth noting that the allenylzinc resulting from Zn/I exchange between Et_2Zn and propargyl iodide **14** was shown to react like a classical Grignard reagent with ethyl butanoate. It led to the tertiary bis-homopropargylic alcohol **15**. For pioneering studies, with contradictory observation, see: Couffignal, R.; Gaudemar, M. *Bull. Soc. Chim.* **1969**, 3157.



14 **15** 61%

(10) The configuration of the double bond in **8a**, **8b**, and **11** was assigned from NOESY experiments showing cross-peaks between the signals of the proton of the ethyl group and the signals of the aromatic protons (see: Supporting Information).

(11) Tautomeric forms of enolate **E**



(12) (a) Bieber, L. W.; Da Silva, M. F.; Da Costa, R. C.; Silva, L. O. S. *Tetrahedron Lett.* **1998**, *39*, 3655. (b) Jögi, A.; Mäeorg, U. *Molecules* **2001**, *6*, 964.

(13) It was necessary to use an excess of diethylzinc for the reaction to be completely chemoselective.

(14) Colquhoun, V. P.; Unkelbach, C.; Strohmann, C. *Chem. Commun.* **2012**, *48*, 5034.

(15) For recent review on indole synthesis, see: (a) Taber, D. F.; Tirunahari, P. K. *Tetrahedron* **2011**, *67*, 7195. (b) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2011**, *111*, PR215.

(16) Ma, S. In *Modern Allene Chemistry*; Krause, N., Hashmi, S. K., Eds.; Wiley-VCH: Weinheim, 2004, Vol. 2, p 595.
(17) See: Selvakumar, J.; Ramanathan, C. R. *Org. Biomol. Chem.* **2011**, *9*, 7643 and references cited therein.
(18) Portscheller, J. L.; Malinakova, H. C. *Org. Lett.* **2002**, *4*, 3679.
(19) Takeuchi, Y.; Nabetani, M.; Takagi, K.; Hagi, T.; Koizumi, T. *J. Chem. Soc., Perkin Trans. 1* **1991**, 49.
(20) Chrich, D.; Krishnamurthy, V. *Tetrahedron* **2006**, *62*, 6830.
(21) Chakraborty, A.; Sinha, S. *Tetrahedron Lett.* **2011**, *52*, 6635.