JOC The Journal of Organic Chemistry

Article

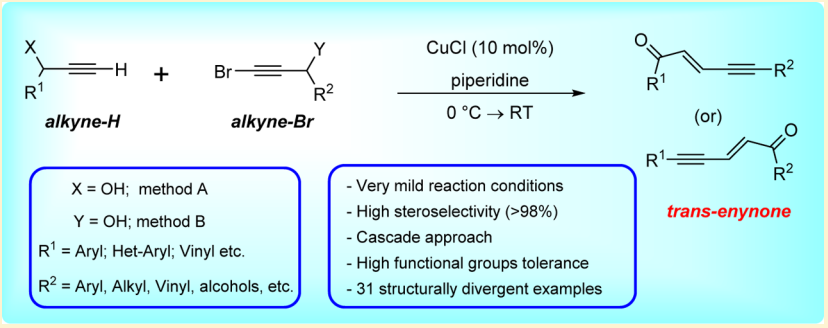
pubs.acs.org/joc

Stereoselective, Cascade Synthesis of *trans*-Enynones through Coupling-Isomerization Reaction

Bhavani Shankar Chinta and Beeraiah Baire*

Department of Chemistry, Indian Institute of Technology Madras, Chennai 600036, Tamilnadu India

Supporting Information



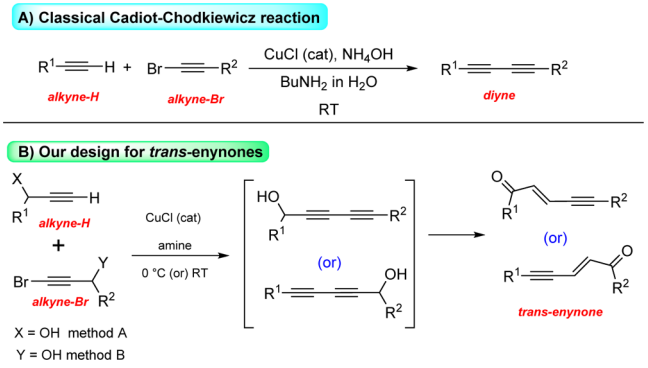
ABSTRACT: A mild, cascade methodology based on the modified Cadiot−Chodkiewicz reaction was developed for the stereoselective synthesis of *trans*-enynones. By this methodology, structurally divergent *trans*-enynones, which are embedded with sensitive functional groups, were synthesized. Control experiments suggested that the CuCl alone does not have a role in the isomerization step, whereas the CuCl−piperidine complex (formed during the cross coupling) may have a rate enhancing effect. Furthermore, additional sets of control experiments favor the involvement of unimolecular [1,2]-H shift rather than a homobimolecular proton abstraction during the isomerization step.

INTRODUCTION

From practical considerations and green chemistry point of view cascade (tandem) reactions are ideal techniques in organic synthesis for building complex structures.[1] In most cases, these approaches provide mild reaction conditions there by imparting high tolerance for many functional groups. *trans*-Enynones are very useful building blocks in organic synthesis,[2a−c] e.g., synthesis of furans,[3a] total synthesis of natural products,[3b] etc. However, very few methods[2a,b,4] have been developed for the generation of these structural units, with limited substrate scope and functional group tolerance because of the harsh reaction conditions. Therefore, developments of mild, efficient, and stereoselective protocols are very much in need for the synthesis of *trans*-enynones.

Herein we report a highly stereoselective, and mild, coupling-isomerization cascade methodology for the synthesis of *trans*-enynones, that is tolerant to many sensitive functional groups. The classical Cadiot−Chodkiewicz reaction[5] is the CuCl-catalyzed cross coupling between two terminal alkynes, one with terminal hydrogen (alkyne-H) and the other with a terminal bromide (alkyne-Br) to yield an unsymmetrical diyne unit (Scheme 1A). In principle any amine (primary, secondary, or tertiary and cyclic or acyclic) base should be able to promote this cross coupling reaction.[6] With this background, we envisioned that in the presence of a suitable amine as base in combination with CuCl in Cadiot−Chodkiewicz reaction of a terminal alkyne (alkyne-H) and an alkynyl bromide (alkyne-Br), where one of the alkyne is also a primary or secondary propargylic alcohol (Scheme 1B), it should be possible to promote a coupling-isomerization cascade to generate thermodynamically preferred *trans*-enynones with high stereoselectivity. To the best of our knowledge, no isomerization has been reported in the classical Cadiot−Chodkiewicz reaction.[7]

Scheme 1. Classical Cadiot−Chodkiewicz Reaction and Our Designed Coupling-Isomerization Cascade



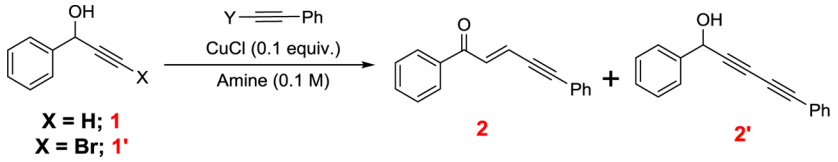
RESULTS AND DISCUSSION

To test our hypothesis, initially we have examined various amines, such as, *n*-butyl amine (primary), diisopropyl amine

Received: August 2, 2015
Published: September 23, 2015

DOI: 10.1021/acs.joc.5b01780
J. Org. Chem. 2015, 80, 10208−10217

Table 1. Screening of Various Amine Bases for Coupling-Isomerization Cascade to *trans*-Enynones



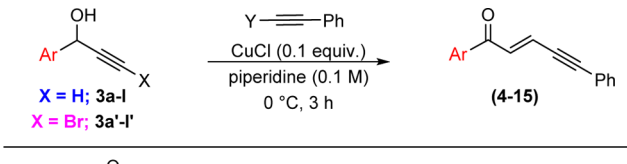
entry	X	Y	base/solvent	temperature	time (h)	yield (%) 2	yield (%) 2′
Method A							
1	H	Br	Et_3N	0 °C→RT	22	–	46
2	H	Br	pyridine	0 °C→RT	16	–	43
3	H	Br	piperidine	0 °C	3	66	–
4	H	Br	pyrrolidine	0 °C→RT	6	39	–
5	H	Br	$^{i}Pr_2NH$	0 °C→RT	22	5	57
6	H	Br	*n*-$BuNH_2$	0 °C→RT	6	5	29
Method B							
7	Br	H	Et_3N	0 °C→RT	26	–	54
8	Br	H	pyridine	0 °C→RT	16	–	77
9	Br	H	piperidine	0 °C	3	78	–
10	Br	H	pyrrolidine	0 °C	3	32	–
11	Br	H	$^{i}Pr_2NH$	0 °C→RT	26	–	64
12	Br	H	*n*-$BuNH_2$	0 °C	3	24	12

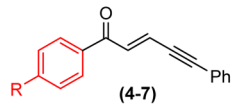
(acyclic-secondary), piperidine (cyclic-secondary), pyrrolidine (cyclic-secondary), triethyl amine (acyclic-tertiary), and pyridine (cyclic-tertiary) to identify a suitable base that can promote cross coupling as well as isomerization. The results of this study are presented in Table 1. Two complementary methods have been developed. In method A, alcohol is on the alkyne-H partner **1** (entries 1–6, Table 1), and in method B (entries 7–12, Table 1), alcohol is on the alkyne-Br partner **1′**. Phenylacetylene and its bromide were used as alkyne-H in method B and as alkyne-Br in method A, respectively. Initially, method A was investigated. When Et_3N (entry 1) was used, only the cross coupling product **2′** was obtained after stirring for 22 h at room temperature, and not even a trace amount of enynone **2** was detected. Similarly, use of pyridine also resulted in the formation of only the coupled product **2′** (entry 2). On the other hand, when piperidine and pyrrolidine were employed, *trans*-enynone **2** was isolated as the sole product (entries 3 and 4, Table 1) after 3 and 6 h, respectively. The structures of enynone **2** and diynol **2′** were confirmed by the spectroscopic data (^1H and ^{13}C NMR, IR, and HRMS). Surprisingly, $^{i}Pr_2NH$ gave very low conversion to enynone **2** (~5%) after 22 h, and the diynol **2′** was isolated in 57% yield (entry 5). In contrast, $^{n}BuNH_2$ was not at all effective either for coupling or for isomerization, as it gave only 5% of enynone **2** and 29% of **2′** after 6 h (entry 6). Hence in method A piperidine was found to be best amine for the proposed cascade to generate *trans*-enynone quickly, selectively, and efficiently.

In method B (entries 7–12, Table 1), the alcohol functional group was kept on the alkyne-Br, and the reactions were carried out using the same amines as in method A. In this method also piperidine (entry 9) was the best amine to afford the *trans*-enynone **2** selectively and efficiently. On the other hand, Et_3N, pyridine, and $^{i}Pr_2NH$ (entries 7, 8, and 11) were inert to give any trace of enynone **2**, even after long stirring at RT. In the case of *n*-$BuNH_2$ (entry 12), the formation of enynone **2** was observed but in poor yield (24%). Overall, in both methods A and B, piperidine[8] stands out to be the amine of choice for selective and efficient *trans*-enyone generation.

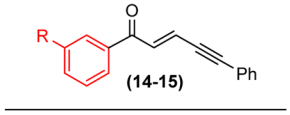
With the optimized reaction conditions in hand, we next studied the scope for various aryl propargylic alcohols **3a–l** and **3a′–l′** Table 2. Both methods A and B have been employed for majority of the substrates. All the *para*-substituted aryl propargyl alcohols **3a–d** and **3a′–d′** underwent smooth coupling-isomerization cascade with excellent (~100%) stereo-

Table 2. Scope of Various Aryl Propargylic Alcohols in the Coupling-Isomerization Cascade to *trans*-Enynones

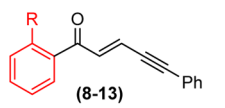




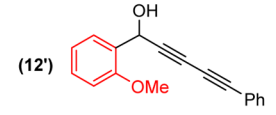
Entry	Compound	R	Yield (%) A	Yield (%) B
1	**4**	F	78	83
2	**5**	Cl	92	74
3	**6**	Br	75	79
4[a]	**7**	OMe	73	82



Entry	Compound	R	Yield (%) A	Yield (%) B
11	**14**	Br	81	93
12[a]	**15**	NO_2	36	--



Entry	Compound	R	Yield (%) A	Yield (%) B
5[a]	**8**	F	55	--
6	**9**	Br	65	55
7[a]	**10**	I	53	57
8[b]	**11**	Me	70	67
9[c]	**12**	OMe	0	0
10	**13**	NHBoc	67	--



Method A: X = H & Y = Br
Method B: X = Br & Y = H

[a]Time = 8 h. [b]Time = 16 h. [c]Only alcohol **12′** was isolated in 77 and 95% yields in methods A and B, respectively.

DOI: 10.1021/acs.joc.5b01780
J. Org. Chem. 2015, 80, 10208–10217

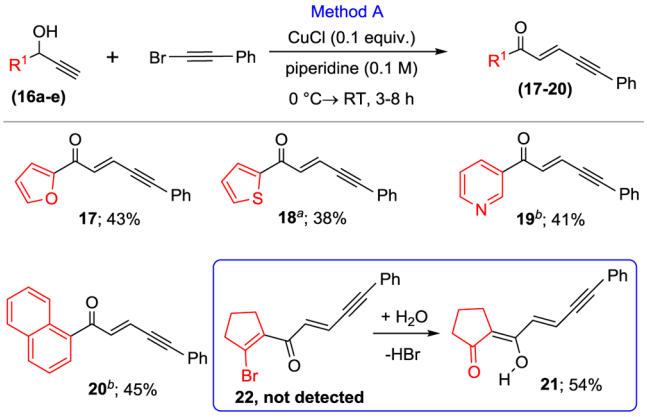
selectivity to afford the corresponding *trans*-enynones **4**−**7** (entries 1−4, Table 2) in good to excellent yields. Only in case of *p*-OMe (**3d** and **3d**′) the reaction time was longer (8 h), but there was no compromise either on the selectivity or the yield. All the *ortho*-substituted propargyl alcohols **3e**−**j** and **3e**′−**j**′ including halogens, methyl, and NHBoc substituted derivatives gave the corresponding *trans*-enynones **8**−**13** in good yields. In case of the *o*-Me derivative, isomerization was slow and took about 16 h. With *o*-OMe (entry 9, Table 2) only the coupled alcohol **12**′ was isolated, and enynone **12** was not formed even after prolonged reaction times.[10]

In addition to the spectroscopic characterization, we have also confirmed the structure of *trans*-enynone **13** by the single crystal X-ray diffraction analysis[9] of *trans*-enynone **13**′, and the ORTEP diagram is depicted in Figure 2 of the Supporting Information (SI).

The *m*-Br derivatives **3k** and **3k**′ generated the corresponding enynone **14** in excellent yield, whereas with *m*-NO_2 alcohol **3l** (entry 12, Table 2) the cascade process was relatively slow (8 h) and less efficient (36%) to give **15**. Overall, *para*-substituted derivatives were relatively faster and higher in efficiency than corresponding *ortho*-substituted counterparts. From Table 2 it is clear that both methods A and B are equally good in terms of efficiency and selectivity toward the formation of *trans*-enynone derivatives.

To extend the utility of this methodology, we have studied (Scheme 2) this cascade process with various heteroaromatics

Scheme 2. Coupling-Isomerization Cascade with Hetero-Aromatic and Cyclic Propargylic Alcohols in Method A

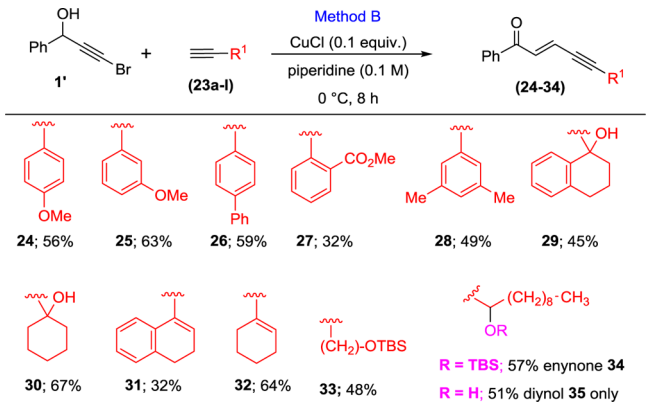


[a]In method B 56% of **18** was isolated. [b]Time = 8 h.

like 2-furanyl, 2-thienyl, 3-pyridinyl, and 1-naphthyl, and also 2-bromo-1-cyclopentenyl propargylic alcohols **16a**−**e** as alkyne-H partners in method A, using phenylacetylene bromide as the alkyne-Br partner. All these substrates smoothly underwent the coupling-isomerization cascade and gave the corresponding *trans*-enynones **17**−**20** in moderate yields. Interestingly, in case of 2-bromo-1-cyclopentenyl propargylic alcohol **16e**, we have directly isolated the 1,3-diketone **21**, instead of bromo-enynone **22**. We propose Michael addition of water to **22** followed by elimination of bromide to yield **21**. The structure of the **21** was confirmed by both spectroscopic data as well as single crystal X-ray difraction analysis,[11] and its ORTEP diagram is presented in Figure 3 of the SI.

We have also studied the scope of using various alkyne-H partners **23a**−**k** in method B (Scheme 3), keeping phenyl propargyl alcohol as the alkyne-Br partner. Various sensitive

Scheme 3. Scope of Various Alkyne-H Partners in Method B for Diverse *trans*-Enynones



functional groups like *tertiary* alcohols, OTBS-ethers, esters, and olefins were found to be stable under the reaction conditions. Several substituted aryl acetylenes **23a**−**e** were used, to generate structurally diverse *trans*-enynones **24**−**28**. In all cases yields were moderate and reactions were faster (3 h) except for **27**, which required 9 h.

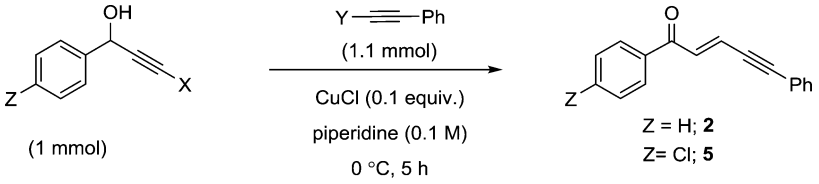
Various aliphatic alkynes **23f**−**k** have also been employed, to prepare corresponding *trans*-enynones **29**−**33** in good yields. In presence of tertiary alcohols **23f**−**g**, the cascade was smooth and generated the enynones **29** and **30**. Whereas with secondary alcohol **23l**, the first step, i.e., cross coupling was clean to give the coupled diynol **35**, but it did not undergo isomerization even after stirring the reaction mixture for prolonged period. Surprisingly, the corresponding TBS-ether **23k** underwent smooth coupling-isomerization cascade to yield the *trans*-enynone **34** in good yield.

To show the preparatory value of this cascade process, we have carried out the reaction on 1 mmol scale for substrates **1**, **1**′, **3b**, and **3b**′, in both methods A and B (Table 3). The reactions were very clean and afforded the corresponding *trans*-enynones **2** and **5** without much drop in efficiency.

After preparing structurally diverse *trans*-enynones, we have performed few control experiments (Scheme 4) in order to understand the role of CuCl and piperidine in the isomerization step. In first case (condition A, Scheme 4B), the diynol **36** was treated with CuCl (0.1 equiv) and pipyridine (0.1 M), and in second case (condition B, Scheme 4), diynol **36** was treated with pipyridine (0.1 M) alone. In both cases, the isomerization was smooth to yield the enynone **11**. Quite, surprisingly it was observed (by TLC monitoring) that the reaction time was similar, i.e., ∼48 h at RT for both conditions. In third case, when **36** was treated with CuCl alone in 1,2-dichlorobenzene, no isomerization was observed even after 48 h. These experiments clearly suggest that CuCl alone does not play a role in the isomerization step. But interestingly, the overall two stage cascade process, i.e., coupling-isomerization took about 16 h to give the enynone **11** starting from **3h** (or) **3h**′ (Scheme 4A). These observations lead us to propose that during the coupling reaction, a complex formed between CuCl and piperidine might have helped in enhancing the rate of the isomerization as compared to conditions A and B (Scheme 4B), where it is not possible to form the same complex because of absence of coupling reaction. At this stage we do not have any direct experimental evidence for the presence and structure of the complex and its interaction with coupled products, e.g., **36**.

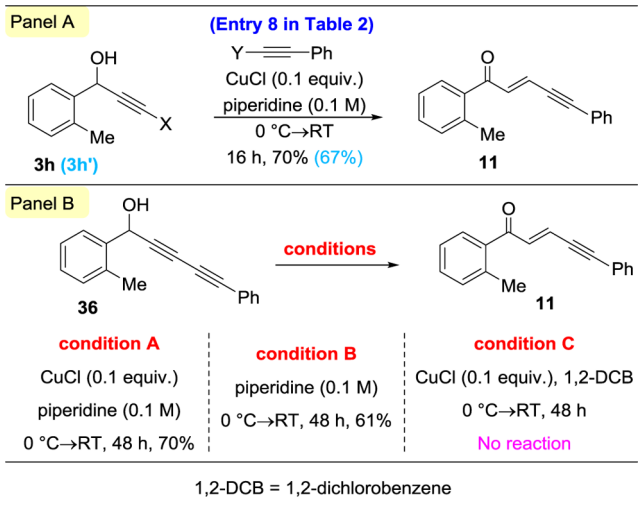
DOI: 10.1021/acs.joc.5b01780
J. Org. Chem. 2015, 80, 10208−10217

Table 3. Scale up Experiments



entry	alcohol	X	Z	Y	product	yield (%)
1	**1**	H	H	Br	**2**	62
2	**1′**	Br	H	H	**2**	68
3	**3b**	H	Cl	Br	**5**	79
4	**3b′**	Br	Cl′	H	**5**	67

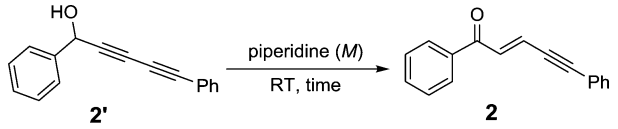
Scheme 4. Control Experiments To Understand the Role of CuCl on Isomerization Step



Based on our understanding of this cascade transformation so far, we proposed a possible mechanism in Scheme 5. In the first step, two alkyne units undergo Cadiot−Chodkiewicz cross coupling to give the diynol **37**. In the next step, **37** is transformed to the alkoxide ion **38** by piperidine. **38** is converted to **39** which is a resonance strucutre of allenyl anion **39′**, either by [1,2] proton shift or by homobimolecular proton abstraction. Upon protonation, **39′** gives an allenol-alkyne **40**, which undergoes a stereoselective enol-ketone tautomerization to give the *trans*-enynone **41**.[12]

To get some insights into the proposed mechanism, in particular to identify whether the isomerization step involves unimolecular [1,2]H shift or homobimolecular proton abstraction, we have designed and performed few control experiments using diynol **2′** as the substrate. From Table 4, it is evident that, as the concentration of the alcohol **2′** decreases (reaction dilution increases, entries 1−3), the rate of isomerization to **2** increases at any time point of the reaction (monitored by ^{1}H NMR spectroscopy, see Figure 1, Supporting

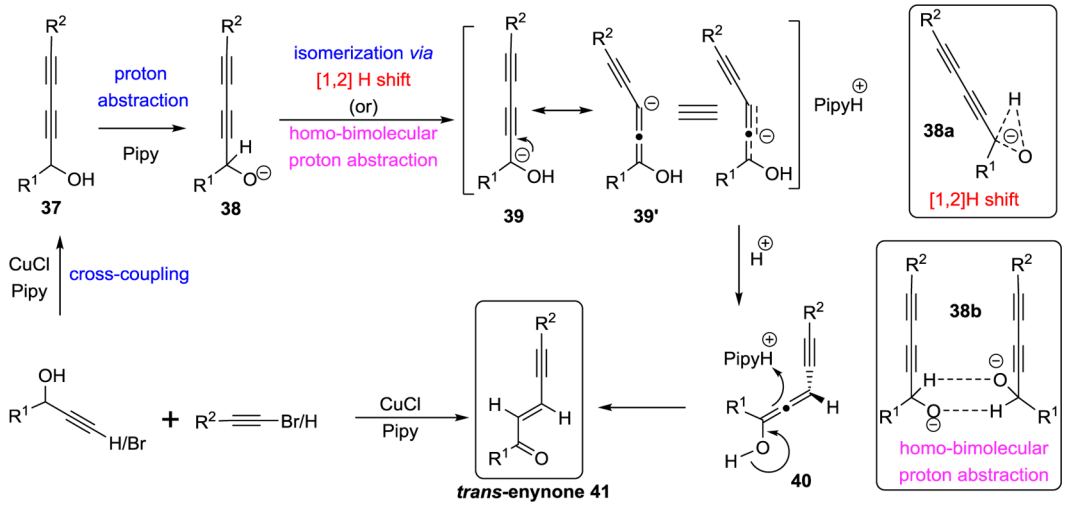
Table 4. Control Experiments to Identify the Unimolecular [1,2]H Shift vs Homobimolecular Proton abstraction



		10 min		40 min		80 min	
entry	piperidine (M)	2′	2	2′	2	2′	2
1	0.26	1	0.5	1	2.5	1[a]	100
2	0.13	1	0.8	1	4.0	1	50
3	0.04	1	6.5	1	35	0	100

[a]Time = 130 min.

Scheme 5. Proposed Mechanism For the *trans*-Enynone Formation



DOI: 10.1021/acs.joc.5b01780
J. Org. Chem. 2015, 80, 10208−10217

Information). It implies that the isomerization may be a unimolecular process dependent on alcohol concentration. On the other hand, as the concentration of the base piperidine increases (entries 1−3), the rate of isomerization is also increasing. These observations clearly support that there is an initial formation of an alkoxide **38** from alcohol **37** (this step is dependent on piperidine concentration). Next the alkoxide **38** may undergo a unimolecular process, i.e., 1,2-H shift via **38a** rather than a homobimolecular proton abstraction via **38b**, to generate a propargylic carbanion **39** then to form an allenic carbanion **39′**. If the alkoxide **38** followed the bimolecular proton abstraction process, rate of the isomerization reaction would drop as the dilution of the reaction increases, which is contrary to the observed results in Table 4. Hence we propose that the unimolecular procees might have a lower energy path.

CONCLUSIONS

In conclusion, stereoselective and cascade synthesis of *trans*-enynones has been achieved via "CuCl-piperidine" promoted, coupling-isomerization reaction. This mild methodology gave access to structurally diverse *trans*-enynones, which are embedded with various sensitive functional groups and has shown preparatory value as well. Both complementary methods A and B can be operative for all substrates. This is the first time *trans*-enynones are synthesized in a Cadiot−Chodkiewicz reaction. Control experiments suggested that CuCl alone does not have any effect on the isomerization step, but there is a rate enhancing effect of "CuCl-piperidine complex" (formed during the coupling reaction). We have also performed another set of control experiments to differentiate between two possible mechanisms for isomerization step. These experimients favor the involvement of unimolecular [1.2]-H shift rather than a homobimolecular proton abstraction for the formation of propargylic carbanion from alkoxide during the isomerization step.

EXPERIMENTAL SECTION

General Methods. Reactions were monitored by thin-layer chromatography (TLC) carried out on Merck silica plates using UV-light and anisaldehyde or potassium permanganate stains for visualization. Column chromatography was performed on silica gel (60−120 mesh) using hexanes and ethyl acetate as eluents. NMR data were recorded on 400 and 500 MHz spectrometers. ^{13}C and ^{1}H chemical shifts in NMR spectra were referenced relative to signals of $CDCl_3$ (δ 7.263 ppm for ^{1}H and 77.16 ppm for ^{13}C). Chemical shifts δ and coupling constants J are given in ppm (parts per million) and Hz (hertz), respectively. HRMS were recorded by electron spray ionization (ESI) method on a Q-TOF Micro with lock spray source. Known compounds data have been compared with the reported data, and references were given appropriately. Characterization data for new compounds are given below. ^{1}H and $^{13}C\{^{1}H\}$NMR spectra for all new compounds are given in the SI.

General Procedure for the Synthesis of Propargyl Alcohols with Terminal Hydrogen. To an ice-cold solution of aldehyde in anhydrous THF (5 mL/0.2 mmol) under nitrogen atmosphere was added ethynylmagnesium bromide (1.5 eq., 0.5 M in THF), and the reaction mixture was stirred for 2−4 h (monitored by TLC analysis) 0 °C. Reaction mixture was diluted with saturated aq. NH_4Cl (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine (10 mL) and dried over $MgSO_4$. Evaporation of the solvent and purification of the crude mixture by flash column chromatography (9:1, hexane: EtOAc) gave the corresponding propargylic alcohols in 80−95% yields.

General Procedure for the Synthesis of Bromo-Propargyl Alcohols or Bromoalkynes. To the solution of propragyl alcohol or alkyne,[13] in anhydrous acetone (2 mL/mmol) under nitrogen atmosphere, were added *N*-bromosuccinimide (NBS, 1.1 equiv) and $AgNO_3$ (0.1 equiv), and the reaction mixture was stirred for 2 h at RT. Reaction mixture was diluted with water (15 mL) and extracted with dichloromethane (CH_2Cl_2, 3 × 10 mL). The combined organic layer was washed with brine (15 mL) and dried over $MgSO_4$. Evaporation of the solvent and purification of the crude mixture by flash column chromatography (9:1, hexane:EtOAc or hexanes for alkynyl bromides) gave the corresponding bromopropargylic alcohol or alkynyl bromide in 85−97% yields.

*3-Bromo-1-(4-bromophenyl)prop-2-yn-1-ol (**3c′**).* Alkyne[14] (250 mg 1.66 mmol), *N*-bromosuccinimide (325 mg, 1.83 mmol), $AgNO_3$ (28 mg, 0.17 mmol), and acetone (7 mL) were stirred for 2 h at RT. Purification by flash chromatography (9:1; hexane:EtOAc) gave bromide **3c′** (290 mg, 1.27 mmol, 77%) as light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (2 H, d, J = 8.4 Hz), 7.35 (2 H, d, J = 8.3 Hz), 5.38 (1 H, d, J = 4.8 Hz), 3.5 (1 H, br s) ppm. $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ = 138.9, 131.8, 128.3, 122.6, 79.4, 64.7, and 47.8 ppm. IR (neat): 3352, 2923, 2922, 2853, 2211, 1593, 1409, 1054, 796, 622, and 548 cm^{-1}. GCMS: 280 and 278 (M), 209 and 211 (M-Br), 185 (M-Br and -C_2H), 157 (M-OH, -C_2H, and -Br). HRESI-MS: $[C_9H_6Br_2ONa]^+$ = $[M + Na]^+$ requires 310.8678; found 310.8669. TLC: R_f = 0.5 (4:1, Hex/EtOAc).

*3-Bromo-1-(2-bromophenyl)prop-2-yn-1-ol (**3f′**).* Alkyne[15] (300 mg 1.42 mmol), NBS (278 mg, 1.57 mmol), $AgNO_3$ (24 mg, 0.142 mmol), and acetone (8 mL) were stirred for 2 h at RT. Purification by flash chromatography (9:1; hexane:EtOAc) gave the corresponding bromide **3f′** (400 mg, 1.38 mmol, 98%) as light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (1 H, d, J = 7.6 Hz), 7.55 (1 H, d, J = 8.0 Hz), 7.35 (1 H, t, J = 7.4 Hz), 7.15 (1 H, t, J = 7.4 Hz), 5.78 (1 H, s), 3.03 (1 H, br s) ppm. $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ = 138.9, 131.8, 128.3, 122.6, 79.4, 64.7, and 47.8 ppm. IR (neat): 3355, 3070, 2922, 2854, 2211, 1600, 1508, 1416, 1227, 1160, 1051, 985, 842, and 556 cm^{-1}. GCMS: 289.9 (M), 209 and 211 (M-Br), 131 (M-Br_2), 106 (M-Br_2, M-C_2H). HRESI-MS: $[C_9H_7Br_2O]^+$ = $[M + H]^+$ requires 288.8858; found 288.8867. TLC: R_f = 0.5 (4:1, Hex/EtOAc).

*3-Bromo-1-(3-bromophenyl)prop-2-yn-1-ol (**3k′**).* Alkyne[16] (240 mg 1.14 mmol), NBS (221 mg, 1.25 mmol), $AgNO_3$ (19.3 mg, 0.114 mmol), and acetone (8 mL) were stirred for 2 h at RT. Purification by flash chromatography (9:1; hexane:EtOAc) gave the bromide **3k′** (260 mg, 0.09 mmol, 79%) as light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (1 H, s), 7.40 (2 H, m), 7.22 (1 H, t, J = 7.8 Hz), 5.40 (1 H, d, J = 4.2 Hz), 2.62 (1 H, br s) ppm. $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 142.1, 131.7, 130.3, 129.7, 125.2, 122.8, 79.3, 64.7, and 48.2 ppm. IR (neat): 3400, 2921, 2847, 2363, 2211, 1638, 1576, 1470, 1425, 1252, 1186, 1054, 992, 784, 704, and 603 cm^{-1}. GCMS: 289.9 (M), 209 and 211 (M-Br), 183 and 185 (M-Br, M-C_2H), 155 and 157 (M-OH, M-C_2H and M-Br). HRESI-MS: $[C_9H_6Br_2ONa]^+$ = $[M + Na]^+$ requires 310.8678; found 310.8684. TLC: R_f = 0.5 (4:1; Hex/EtOAc).

*3-Bromo-1-(4-chlorophenyl)prop-2-yn-1-ol (**3b′**).* Alkyne[17] (240 mg 1.45 mmol), NBS (282 mg, 1.59 mmol), $AgNO_3$ (24.5 mg, 0.144 mmol), and acetone (8 mL) were stirred at RT for 2 h. Purification by flash chromatography (6:1; hexane:EtOAc) gave the bromide **3b′** (320 mg, 1.31 mmol, 91%) as a colorless viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (2 H, d, J = 8.4 Hz), 7.30 (2 H, d, J = 8.6 Hz), 5.39 (1 H, s), 2.77 (1 H, br s) ppm. $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ = 138.4, 134.5, 128.9, 128.0, 79.5, 64.7, and 47.9 ppm. IR (neat): 3373, 2922, 2855, 2211, 1590, 1485, 1409, 1263, 1088, 1052, 984, 837, 802, 724, and 551 cm^{-1}. HRESI-MS: $[C_9H_6BrClO]^+$ = $[M + H]^+$ requires 244.9369; found 244.9368. TLC: R_f = 0.5 (4:1; Hex/EtOAc).

*3-Bromo-1-(2-iodophenyl)prop-2-yn-1-ol (**3g′**).* Alkyne[18] (200 mg 0.78 mmol), NBS (151 mg, 0.85 mmol), $AgNO_3$ (13 mg, 0.08 mmol), and acetone (7 mL) were stirred for 2 h at RT. Purification by flash chromatography (9:1; hexane:EtOAc) gave the bromide **3g′** (250 mg, 0.75 mmol, 96%) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (1 H, dd, J = 0.8 and 7.9 Hz), 7.63 (1 H, dd, J = 1.5 and 7.8 Hz), 7.32 (1 H, td, J = 0.7 and 7.7 Hz), 6.95 (1 H, td, J = 1.6 and 7.7 Hz), 5.58 (1 H, s), 2.62 (1 H, br s) ppm. $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ = 141.9, 139.8, 130.4, 128.9, 128.2, 97.9, 79.1, 69.4, and 48.0 ppm. IR (neat): 3385, 3050, 2922, 2844, 2211, 1586, 1432, 1265, 1190, 1053,

DOI: 10.1021/acs.joc.5b01780
J. Org. Chem. 2015, 80, 10208−10217

989, 752, and 607 cm^{-1}. GCMS: 336.9 (M), 257 (M-Br), 232 (M-B, M-C_2H), 203 (M-COH, M-C_2H, and M-Br). HRESI-MS: $[C_9H_6BrIONa]^+$ = $[M + Na]^+$ requires 358.8539; found 358.8524. TLC: R_f = 0.5 (4:1; Hex/EtOAc).

*3-Bromo-1-(4-methoxyphenyl)prop-2-yn-1-ol (**3d′**).* Alkyne[17] (200 mg 0.78 mmol), NBS (151 mg, 0.85 mmol), $AgNO_3$ (13 mg, 0.08 mmol), and acetone (7 mL) were stirred for 2 h at RT. Purified by flash chromatography (9:1; hexane:EtOAc) gave the bromide **3d′** (250 mg, 0.75 mmol, 96%) as light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (2 H, d, J = 8.7 Hz), 6.90 (2 H, d, J = 8.7 Hz), 5.34 (1 H, s), 3.76 (3 H, s), 2.80 (1 H, br s) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 159.7, 132.4, 128.1, 114.0, 80.1, 64.9, 55.3, and 46.9 ppm. IR (neat): 3408, 3054, 2927, 2836, 2380, 2210, 1596, 1489, 1459, 1246, 1046, 982, 753, and 610 cm^{-1}. GCMS: 241 (M), 225 and 227 (M-OH), 210 (M-OH and OCH_3), 136 (M-OH, M-C_2Br). HRESI-MS: $[C_{10}H_{10}BrO_2]^+$ = $[M + H]^+$ requires 240.9859; found 240.9853. TLC: R_f = 0.5 (4:1, Hex/EtOAc).

*3-Bromo-1-(2-methoxyphenyl)prop-2-yn-1-ol (**3i′**).* Alkyne[16] (200 mg 0.78 mmol), NBS (151 mg, 0.85 mmol), $AgNO_3$ (13 mg, 0.08 mmol), and acetone (7 mL) were stirred for 2 h at RT. Purified by flash chromatography (9:1; hexane:EtOAc) gave the bromide **3i′** (250 mg, 0.744 mmol, 96%) as a light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (1 H, d, J = 7.5 Hz), 7.27 (1 H, t, J = 8.0 Hz), 6.95 (1 H, t, J = 7.5 Hz), 6.87 (1 H, d, J = 8.3 Hz), 5.64 (1 H, s), 3.83 (3 H, s), 3.19 (1 H, br s) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ = 156.7, 129.8, 128.2, 127.8, 120.9, 111.0, 79.6, 61.9, 55.6, and 46.1 ppm. IR (neat): 3410, 3011, 2924, 2844, 2337, 2210, 1604, 1509, 1459, 1251, 1172, 1033, 829, and 567 cm^{-1}. GCMS: 241 (M), 225 and 227 (M-OH), 161 (M-Br), 135 and 137 (M-OH, M-C_2H, and M-Br). HRESI-MS: $[C_{10}H_{10}BrO_2]^+$ = $[M + H]^+$ requires 240.9859; found 240.9865. TLC: R_f = 0.5 (4:1, Hex/EtOAc).

*3-Bromo-1-(thiophen-2-yl) prop-2-yn-1-ol (**16b′**).* Alkyne[19] (200 mg, 0.76 mmol), NBS (151 mg, 0.85 mmol), $AgNO_3$ (13 mg, 0.07 mmol), and acetone (7 mL) were stirred. Purified by flash chromatography (9:1; hexane:EtOAc) gave bromide **16b′** (250 mg, 0.744 mmol, 96%) as light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (1 H, d, J = 5.0 Hz), 7.10 (1 H, d, J = 3.4 Hz), 6.93 (1 H, dd, J = 1.5 and 4.7 Hz), 3.05 (1 H, br s) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 143.7, 126.8, 126.3, 125.7, 79.2, 61.0, 47.3 ppm. IR (neat): 3403, 2921, 2855, 2363, 2210, 1595, 1459, 1413, 1367, 1120, 1036, 701, 432 cm^{-1}. GCMS: 215 (M), 203, 178, 155, 127, 102. HRESI-MS: $[C_7H_5BrOSNa]^+$ = $[M + Na]^+$ requires 238.9137; found 238.9144. TLC: R_f = 0.5 (4:1, Hex/EtOAc).

*1-(2-Bromocyclopent-1-en-1-yl) prop-2-yn-1-ol (**16e**).* Aldehyde[20] (350 mg, 2 mmol), ethynylmagnesium bromide (0.5 M in THF, 3.0 mmol, 6.0 mL), dry THF (10 mL) were stirred. Purification of the crude by flash chromatography (9:1; hexane: EtOAc) gave the alcohol **16e** (360 mg, 1.8 mmol, 90%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.30 (1 H, d, J = 1.8 Hz), 2.66 (3 H, m), 2.54 (2 H, m), 2.50 (1 H, d, J = 2.3 Hz), 1.97 (2 H, m) ppm. $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ = 138.7, 119.5, 81.9, 73.6, 59.9, 40.3, 29.9, 21.4 ppm. IR (neat): 3428, 3301, 3052, 2965, 2852, 2360, 1648, 1428, 1265, 1085, 1025, 1008, 867, 733, 546 cm^{-1}. HRESI-MS: $[C_8H_8Br]$ = [M-OH] requires 182.9809; found 182.9808. TLC: R_f = 0.5 (4:1, Hex/EtOAc).

General Procedures for Coupling-Isomerization Cascade. *Method A.* To the solution of propargyl alcohol[13] (1 equiv), and alkyne bromide[21] (1.1 equiv) in freshly degassed amine (piperidine) (1 mL/0.1 mmol) at 0 °C under nitrogen atmosphere, was added CuCl (0.1 equiv), and the reaction mixture was stirred either at 0 °C or at room temperature for several hours. Reaction mixture was diluted with EtOAc (10 mL/0.2 mmol), saturated with aq. NH_4Cl (10 mL), and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine (10 mL) and dried over $MgSO_4$. Evaporation of the solvent and purification of the crude mixture by flash column chromatography gave the corresponding *trans*-enynone.

Method B. To the solution of bromo propargyl alcohol (1 equiv), and alkyne (1.1 equiv) in freshly degassed amine (piperidine) (1 mL/0.1 mmol) at 0 °C under nitrogen atmosphere, was added CuCl (0.1 equiv), and the reaction mixture was stirred either at 0 °C or at room temperature for several hours. Reaction mixture was diluted with EtOAc (10 mL/0.2 mmol), saturated aq. NH_4Cl (10 mL), and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine (10 mL) and dried over $MgSO_4$. Evaporation of the solvent and purification of the crude mixture by flash column chromatography gave the corresponding *trans*-enynone.

*(E)-1,5-Diphenylpent-2-en-4-yn-1-one (**2**).* The enynone **2** was prepared following the method A from propargyl alcohol (30 mg, 0.23 mmol), phenyl acetylene bromide[22] (45 mg, 0.25 mmol), freshly degassed piperidene (2.2 mL), and CuCl (2 mg, 0.023 mmol) and was stirred for 3 h at 0 °C. Purification by flash column chromatography (19:1; hexane:EtOAc gave the *trans*- enynone **2** (35 mg, 0.66 mmol, 66%) as a pale yellow solid. In method B, the yield = 78%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (2 H, dd, J = 1.4 and 8.2 Hz), 7.55−7.59 (1 H, tt, J = 1.3 and 6.5 Hz), 7.45−7.52 (4 H, m), 7.40−7.44 (1 H, d, J = 15.5 Hz), 7.32−7.38 (2 H, m), 7.12 (1 H, d, J = 15.4 Hz). $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ = 189.0, 137.5, 133.3, 133.3, 132.2, 129.5, 128.9, 125.2, 122.4, 99.4, and 87.9 ppm. IR (neat): 3054, 2922, 2851, 2362, 2194, 1658, 1582, 1444, 1253, 1210, 999, 957, 756, and 691 cm^{-1}. HR ESI-MS: $[C_{17}H_{12}O]^+$ = $[M + H]^+$ requires 233.0966; found 233.0974. TLC: R_f = 0.6 (19:1, Hex/EtOAc). Mp: 86−88 °C.

*(E)-1-(4-Fluorophenyl)-5-phenylpent-2-en-4-yn-1-one (**4**).* The enynone **4** was prepared following the method A from propargyl alcohol[23] (50 mg, 0.33 mmol), phenyl acetylene bromide (66 mg, 0.36 mmol), freshly degassed piperidene (3.3 mL), and CuCl (3.3 mg, 0.33 mmol) stirred for 3 h at 0 °C. Purification by flash chromatography (19:1; hexane:EtOAc) gave *trans*-enynone **4** (64 mg, 0.26 mmol, 78%) as a yellow viscous oil. In method B yield = 83%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00−8.04 (2 H, m), 7.50 (2 H, m), 7.35−7.40 (4 H, m), 7.10−7.18 (3 H, m). $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ = 187.2, 167.1, 164.6, 133.3, 133.7, 132.6, 132.1, 129.5, 128.6, 125.4, 122.3, 116.0, 115.8, 99.6, and 87.8 ppm. IR (neat): 3054, 2922, 2851, 1657, 1592, 1322, 1249, 1002, 834, 757, 681, and 535 cm^{-1}. HR ESI-MS: $[C_{17}H_{11}FO]^+$ = $[M + H]^+$ requires 251.0872; found 251.0884. TLC: R_f = 0.6 (19:1, Hex/EtOAc).

*(E)-1-(4-Chlorophenyl)-5-phenylpent-2-en-4-yn-1-one (**5**).* The enynone **5** was prepared following the method A from propargyl alcohol[24] (50 mg, 0.301 mmol), phenyl acetylene bromide (60 mg, 0.33 mmol), freshly degassed piperidene (3 mL), and CuCl (3 mg, 0.03 mmol) stirred for 3 h at 0 °C. Purification by flash chromatography (19:1; hexane:EtOAc) gave the *trans* enynone **5** (76 mg, 0.285 mmol, 92%) as a yellow solid. In method B yield = 85%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (2 H, d, J = 8.7 Hz), 7.50 (2 H, m), 7.43 (2 H, d, J = 8.7 Hz), 7.35 (4 H, m), 7.10 (1 H, d, J = 15.4 Hz). $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ = 187.6, 139.8, 135.7, 132.6, 132.1, 130, 129.6, 129.1, 128.6, 125.7, 122.2, 99.9, and 87.8 ppm. IR (neat): 3069, 2921, 2855, 2210, 1647, 1589, 1400, 1263, 1099, 1021, 963, 815, 744, 536, and 486 cm^{-1}. HR ESI-MS: $[C_{17}H_{11}ClO]^+$ = $[M + H]^+$ requires 267.0577; found 267.0578. TLC: R_f = 0.6 (19:1, Hex/EtOAc). Mp: 88−89 °C.

*(E)-1-(4-Bromophenyl)-5-phenylpent-2-en-4-yn-1-one (**6**).* The enynone **6** was prepared following the method A from propargyl alcohol (50 mg, 0.23 mmol), phenyl acetylene bromide (47 mg, 0.26 mmol), freshly degassed piperidene (2.3 mL), and CuCl (2.3 mg, 0.023 mmol) stirred for 6 h at 0 °C. Purification by flash chromatography (19:1; hexane:EtOAc) gave *trans*-enynone **6** (53 mg, 0.17 mmol, 75%) as a yellow viscous oil. In method B yield = 79%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (2 H, d, J = 8.6 Hz), 7.60 (2 H, d, J = 8.6 Hz), 7.50 (2 H, m), 7.35 (4 H, m), 7.10 (1 H, d, J = 15.4 Hz). $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ = 187.2, 167.1, 164.6, 133.3, 133.7, 132.6, 132.1, 129.5, 128.6, 125.4, 122.3, 116.0, 115.8, 99.6, and 87.8 ppm. IR (neat): 3054, 2922, 2851, 2187, 1657, 1592, 1322, 1249, 1002, 834, 757, 681, and 535 cm^{-1}. HR ESI-MS: $[C_{17}H_{11}BrO]^+$ = $[M + H]^+$ requires 311.0072; found 311.0080. TLC: R_f = 0.7 (19:1, Hex/EtOAc).

*(E)-1-(4-Methoxyphenyl)-5-phenylpent-2-en-4-yn-1-one (**7**).* The enynone **7** was prepared following the method A from propargyl alcohol (50 mg, 0.34 mmol), phenyl acetylene bromide (68 mg, 0.38 mmol), freshly degassed piperidene (3.5 mL), and CuCl (3.3 mg,

DOI: 10.1021/acs.joc.5b01780
J. Org. Chem. 2015, 80, 10208−10217

0.034 mmol) stirred for 9 h at 0 °C. Purification by flash chromatography (19:1; hexane:EtOAc) gave the *trans*-enynone **6** (65 mg, 0.25 mmol, 73%) as a viscous yellow oil. In method B yield = 82%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (2 H, d, J = 8.8 Hz), 7.50 (2 H, m), 7.42 (1 H, d, J = 15.6 Hz), 7.35 (3 H, m), 7.10 (1 H, d, J = 15.4 Hz), 6.95 (2 H, d, J = 8.8 Hz), 3.86 (3 H, s). ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ = 187.2, 163.8, 133.2, 132.1, 131.0, 130.3, 129.4, 128.6, 124.3, 122.5, 114.1, 98.7, 88.0, and 55.6 ppm. IR (neat): 3058, 2921, 2853, 2196, 1646, 1594, 1423, 1323, 1255, 1169, 1020, 833, 755, 679, 615, and 458 cm^{-1}. HRESI-MS:$[C_{18}H_{14}O_2]^+$ = $[M + H]^+$ requires 263.1072; found 263.1078. TLC: R_f = 0.6 (9.5:0.5, Hex/EtOAc).

(E)-1-(2-Fluorophenyl)-5-phenylpent-2-en-4-yn-1-one (**8**). The enynone **8** was prepared following the method A from propargyl alcohol[25] (50 mg, 0.33 mmol), phenyl acetylene bromide (66 mg, 0.36 mmol), freshly degassed piperidene (3.3 mL), and CuCl (3.2 mg, 0.03 mmol) and was stirred for 6 h at 0 °C. Purification by flash chromatography (19:1; hexane:EtOAc) gave *trans*-enynone **8** (45 mg, 0.18 mmol, 55%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (1 H, td, J = 1.8 and 7.8 Hz), 7.50 (3 H, m), 7.35 (3 H, m), 7.25 (2 H, m), 7.10−7.15 (1 H, ddd, J = 0.8, 2.6, and 8.3 Hz), 7.03−7.07 (1 H, dd, J = 1.6 and 15.6 Hz). ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ = 187.6, 162.8, 160.3, 136.5, 134.5, 132.2, 131.1, 129.5, 128.6, 125.2, 124.7, 122.3, 116.8, 100.1, 87.8 ppm. IR (neat): 3068, 2925, 2855, 2363, 2197, 1654, 1586, 1480, 1453, 1325, 1270, 1201, 1101, 1007, 956, 755, 689, and 533 cm^{-1}. HRESI-MS: $[C_{17}H_{11}FO]^+$ = $[M + H]^+$ requires 251.0872; found 251.0867. TLC: R_f = 0.6 (19:1, Hex/EtOAc).

(E)-1-(2-Bromophenyl)-5-phenylpent-2-en-4-yn-1-one (**9**). The enynone **9** was prepared following the method A from propargyl alcohol[26] (50 mg, 0.24 mmol), phenyl acetylene bromide (47 mg, 0.26 mmol), freshly degassed piperidene (2.3 mL), and CuCl (2.3 mg, 0.024 mmol) stirred for 9 h at 0 °C. Purification by flash chromatography (19:1; hexane:EtOAc) gave the *trans*-enynone **9** (48 mg, 0.154 mmol, 65%) as a yellow viscous oil. In method B yield = 55%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (2 H, d, J = 8.6 Hz), 7.60 (2 H, d, J = 8.6 Hz), 7.50 (2 H, m), 7.35 (4 H, m), 7.10 (1 H, d, J = 15.4 Hz). ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ = 187.2, 167.1, 164.6, 133.3, 133.7, 132.6, 132.1, 129.5, 128.6, 125.4, 122.3, 116.0, 115.8, 99.6, and 87.8 ppm. IR (neat): 3058, 2922, 2852, 2195, 1644, 1589, 1401, 1262, 1115, 962, 738, 542, and 453 cm^{-1}. GCMS (method): 311.0, 281.0, 221.1, 207.0, 191.1, 147.1, 135.1, 105.1, 85.1. HRESI-MS: $[C_{17}H_{11}BrONa]^+$ = $[M + Na]^+$ requires 332.9885; found 332.9871. TLC: R_f = 0.6 (19:1 hexane:EtOAc).

(E)-1-(2-Iodophenyl)-5-phenylpent-2-en-4-yn-1-one (**10**). The enynone **10** was prepared following the method A from propargyl alcohol[27] (50 mg, 0.193 mmol), phenyl acetylene bromide (38 mg, 0.213 mmol), freshly degassed piperidine (2 mL), and CuCl (2 mg, 0.02 mmol) stirred for 9 h at 0 °C. Purification by flash chromatography (19:1; hexane:EtOAc) gave the *trans*-enynone **10** (37 mg, 0.10 mmol, 53%) as a brown oil. In method B yield = 57%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (1 H, dd, J = 0.7 and 7.8 Hz), 7.48 (2 H, dd, J = 2.0 and 7.5 Hz), 7.30−7.40 (5 H, m), 7.10−7.40 (1 H, td, J = 1.8 and 7.8 Hz), 6.92 (1 H, d, J = 16 Hz), 6.76 (1 H, d, J = 16 Hz). ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ = 194.6, 143.7, 140.3, 136.5, 132.2, 131.7, 129.7, 128.7, 128.6, 128.1, 127.3, 122.1, 101.8, 92.2, and 87.2 ppm. IR (neat): 3061, 2921, 2851, 2192, 1652, 1583, 1420, 1289, 1095, 1010, 952, 755, 681, and 620 cm^{-1}. HR ESI-MS:$[C_{17}H_{11}IO]^+$ = $[M + H]^+$ requires 358.9933; found 358.9939. TLC: R_f = 0.6 (19:1, Hex/EtOAc).

(E)-5-Phenyl-1-(o-tolyl) pent-2-en-4-yn-1-one (**11**). The enynone **11** was prepared following the method A from propargyl alcohol (50 mg, 0.342 mmol), phenyl acetylene bromide (68 mg, 0.38 mmol), freshly degassed piperidene (3.4 mL), and CuCl (3.3 mg, 0.035 mmol) stirred for 9 h at 0 °C. Purification by flash chromatography (19:1; hexane:EtOAc) gave the *trans*- enynone **11** (59 mg, 0.24 mmol, 70%) as a yellow oil. In method B yield = 67%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (3 H, m), 7.38 (4 H, m), 7.28 (2 H, m), 7.05 (1 H, d, J = 16 Hz), 6.86 (1 H, d, J = 16 Hz), 2.40 (3 H, s). ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ = 194.6, 138.0, 137.6, 137.5, 132.1, 131.6, 131.1, 129.5, 128.6, 128.5, 125.9, 125.6, 122.3, 100.3, 87.3, and 20.5 ppm. IR (neat): 3061, 2928, 2862, 2195, 1654, 1588, 1447, 1308, 1258, 1207, 1031, 757, 689, and 452 cm^{-1}. HRESI-MS: $[C_{18}H_{14}O]^+$ = $[M + H]^+$ requires 247.1123; found 247.1118. TLC: R_f = 0.6 (19:1, Hex/EtOAc).

tert-Butyl (E)-[2-(5-Phenylpent-2-en-4-ynoyl) phenyl] carbamate (**13**). The enynone **13** was prepared following the method A from propargyl alcohol[28] (160 mg, 0.65 mmol), phenyl acetylene bromide (128 mg, 0.71 mmol), freshly degassed piperidene (6.4 mL), and CuCl (6.4 mg, 0.065 mmol) and was stirred for 8 h at 0 °C. Purification by flash chromatography (19:1; hexane:EtOAc) gave trans enynone **13** (147 mg, 0.45 mmol, 67%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.8 (1 H, s), 8.47 (1 H, d, J = 8.5 Hz), 7.84 (1 H, d, J = 7.9 Hz), 7.51 (3 H, m), 7.45 (1 H, d, J = 15.4 Hz), 7.35 (3 H, m), 7.09 (1 H, d, J = 15.4 Hz), 7.02 (1 H, t, J = 7.5 Hz), 1.53 (9 H, s). ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ = 191.4, 153.1, 142.3, 135.0, 134.2, 132.1, 130.7, 129.5, 128.6, 125.4, 122.2, 121.9, 121.15, 119.5, 100.0, 87.8, 80.6, and 28.3 ppm. IR (neat): 3355, 2980, 2849, 2925, 2341, 1730, 1638, 1579, 1521, 1449, 1248, 1153, 1023,753 and 528 cm^{-1}. HR ESI-MS:$[C_{22}H_{21}NO_3]^+$ = $[M + H]^+$ requires 348.1600; found 348.1587. TLC: R_f = 0.6 (19:1, Hex/EtOAc). Mp: 82−84 °C.

(E)-1-(2-Aminophenyl)-5-phenylpent-2-en-4-yn-1-one (**13′**). To an ice-cold solution of *N*-Boc *trans*-enynone **13** (80 mg, 0.25 mmol) in dry CH_2Cl_2 under nitrogen atmosphere was added trifluoro acetic acid (TFA) (0.1 mL, 0.37 mmol), and the reaction was stirred at 0 °C for 4 h. The solvent was removed under reduced pressure, and crude was diluted with CH_2Cl_2 (10 mL) and neutralized with saturated aq. $NaHCO_3$ (10 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layer was washed with brine solution (10 mL) and dried over $MgSO_4$. Evaporation of the solvent and purification of the crude by flash chromatography (19:1; hexane:EtOAc) gave amine **13′** (45 mg, 0.182 mmol, 79%) as a brown solid. It was recrystallized from hexane-EtOAc mixture. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74−7.75 (1 H, dd, J = 1.4 and 8.6 Hz) 7.46−7.50 (3 H, m), 7.30−7.32 (3 H, m), 7.21−7.26 (1 H, m), 7.00 (1 H, d, J = 15.4 Hz), 6.60−6.65 (2 H, m), 6.30 (2 H, br s). ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ = 190.7, 151.4, 134.7, 134.5, 132.07, 131.15, 129.3, 128.6, 123.2, 122.6, 118.2, 117.4, 116.1, 98.2, 88.1 ppm. IR (neat): 3470, 2924, 2853, 2189, 1637, 1606, 1571, 1459, 1330, 1360, 1288, 1243, 1207, 1162, 1024, 988, 954, 914, 860, 751, 685, 524 cm^{-1}. TLC: R_f = 0.6 (19:1, Hex/EtOAc). GC-MS: 247.1 (M), 230.0, 218.0, 207.0, 183, 165.1, 102.1, 91.1. Mp: 85−86 °C. HRESI-MS: $[C_{17}H_{14}NO]^+$ = $[M + H]^+$ requires 248.1070; found 248.1082.

(E)-1-(3-Bromophenyl)-5-phenylpent-2-en-4-yn-1-one (**14**). The enynone **14** was prepared following the method A from propargyl alcohol[29] (60 mg, 0.28 mmol), phenyl acetylene bromide (56 mg, 0.312 mmol), freshly degassed piperidene (2.8 mL), CuCl (3 mg, 0.03 mmol) stirred for 6 h at 0 °C. Purification by flash chromatography (19:1; hexane:EtOAc) gave the *trans*-enynone **14** (70 mg, 0.225 mmol, 81%) as a yellow solid. In method B yield = 93%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (1 H, s), 7.88 (1 H, d, J = 7.7 Hz), 7.68 (1 H, d, J = 7.9 Hz), 7.50 (2 H, dd, J = 2.2 and 7.2 Hz), 7.35 (5 H, m), 7.13 (1 H, d, J = 15.4 Hz). ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ = 187.5, 139.1, 136, 132.4, 132.2, 131.6, 130.3, 129.6, 128.6, 127.1, 126.0, 123.1, 122.2, 100.2, and 87.7 ppm. IR (neat): 3072, 2923, 2855, 2363, 2194, 1660, 1584, 1419, 1320, 1252, 1205, 957, 751, and 689 cm^{-1}. HRESI-MS: $[C_{17}H_{11}BrO]^+$ = $[M + H]^+$ requires 311.0072; found 311.0075. TLC: R_f = 0.6 (19:1, Hex/EtOAc). Mp: 87−89 °C.

(E)-1-(3-Nitrophenyl)-5-phenylpent-2-en-4-yn-1-one (**15**). The enynone **15** was prepared following the method A from propargyl alcohol (50 mg, 0.28 mmol), phenyl acetylene bromide (56 mg, 0.31 mmol), freshly degassed piperidene (2.8 mL), and CuCl (2.8 mg, 0.028 mmol) and was stirred for 7 h at 0 °C. Purification by flash chromatography (19:1; hexane:EtOAc) gave *trans*-enynone **15** (28 mg, 0.10 mmol, 36%) as a brown viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.80 (1 H, s), 8.45 (1 H, d, J = 8.0 Hz), 8.35 (1 H, d, J = 7.8 Hz), 7.70 (1 H, t, J = 8.0 Hz), 7.55 (2 H, dd, J = 1.9 and 8.0 Hz), 7.40 (4 H, m), 7.23 (1 H, d, J = 15.4 Hz). ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ = 186.7, 148.6, 138.7, 134.1, 132.3, 131.7, 130.1, 129.9, 128.7, 127.5, 127.3, 123.4, 122.1, 101.3, and 87.7 ppm. IR (neat):

DOI: 10.1021/acs.joc.5b01780
J. Org. Chem. 2015, 80, 10208−10217

3079, 2924, 2849, 2355, 2193, 1655, 1582, 1528, 1441, 1349, 1251, 1211, 1093, 1020, 957, 735, 689, and 539 cm^{-1}. HRESI-MS: $[C_{17}H_{11}NO_3]^+ = [M + H]^+$ requires 278.0817; found 278.0807 TLC: R_f = 0.6 (19:1, Hex/EtOAc).

*1-(2-Methoxyphenyl)-5-phenylpenta-2,4-diyn-1-ol (**12′**).* The diynol **12′** was prepared following the method A from propargyl alcohol (50 mg, 0.31 mmol), phenyl acetylene bromide (61 mg, 0.34 mmol), freshly degassed piperidene (3 mL), and CuCl (3 mg, 0.031 mmol) stirred for 3 h at 0 °C. Purification by flash chromatography (9:1; hexane:EtOAc) gave the coupled alcohol **12′** (62 mg, 0.24 mmol, 77%) as a yellow oil. In method B yield = 95%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (1 H, dd, J = 1.6 and 7.5 Hz), 7.45 (2 H, dd, J = 1.4 and 7.9 Hz), 7.22−7.38 (4 H, m), 6.97 (1 H, dt, J = 0.9 and 7.5 Hz), 6.90 (1 H, d, J = 8.3 Hz), 5.75 (1 H, s), 3.86 (3 H, s). $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ = 156.8, 132.6, 130.0, 129.3, 128.4, 128.0, 121.6, 121.1, 111.1, 81.9, 78.9, 73.6, 70.3, 61.9, and 55.7 ppm. IR (neat): 3419, 3061, 2923, 2847, 2376, 2195, 1595, 1484, 1458, 1245, 1095, 1024, 752, 685, and 624 cm^{-1}. GC-MS: 265.1, 221.1, 207.0, 191.1, 147.1, 135.1, 105.1, 85.1. TLC: R_f = 0.4 (9:1, Hex/EtOAc).

*(E)-1-(Furan-2-yl)-5-phenylpent-2-en-4-yn-1-one (**17**).* The enynone **17** was prepared following the method A from propargyl alcohol[30] (70 mg, 0.57 mmol), phenyl acetylene bromide (114 mg, 0.63 mmol), freshly degassed piperidene (5.7 mL), and CuCl (6 mg, 0.06 mmol) stirred for 3 h at 0 °C. Purification by flash chromatography (19:1; hexane:EtOAc) gave *trans*-enynone **17** (55 mg, 0.25 mmol, 43%) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (1 H, dd, J = 0.6 and 1.6 Hz), 7.52 (2 H, dd, J = 1.8 and 6.9 Hz), 7.35−7.39 (3 H, m), 7.27−7.31 (2 H, m), 7.15 (1 H, d, J = 15.6 Hz), 6.58 (1 H, dd, J = 1.7 and 3.6 Hz). $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ = 176.7, 153.1, 147.1, 132.7, 132.1, 129.5, 128.5, 124.4, 122.3, 118.3, 112.7, 99.6, 87.8 ppm. IR (neat): 3055, 2926, 2854, 2364, 2195, 1654, 1587, 1465, 1414, 1395, 1324, 1265, 1160, 1089, 1053, 1028, 959, 912, 823, 738, and 530 cm^{-1}. HR ESI-MS: $[C_{15}H_{11}O_2]^+ = [M + H]^+$ requires 223.0754; found 223.0761. TLC: R_f = 0.6 (19:1, Hex/EtOAc). Mp: 72−74 °C.

*(E)-5-Phenyl-1-(thiophen-2-yl) pent-2-en-4-yn-1-one (**18**).* The enynone **18** was prepared following the method A from propargyl alcohol (50 mg, 0.36 mmol), phenyl acetylene bromide (72 mg, 0.4 mmol), freshly degassed piperidene (3.6 mL), and CuCl (3.5 mg, 0.037 mmol) stirred for 3 h at 0 °C. Purification by flash chromatography (19:1; hexane:EtOAc) gave *trans*-enynone **18** (33 mg, 0.14 mmol, 38%) as a brown viscous oil. In method B yield = 56%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (1 H, dd, J = 1.0 and 4.0 Hz), 7.68 (1 H, dd, J = 1.1 and 4.9 Hz), 7.50 (2 H, dd, J = 2.8 and 6.9 Hz), 7.35 (3 H, m), 7.28 (1 H, d, J = 15.4 Hz), 7.14 (2 H, m). $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ = 180.8, 144.8, 134.6, 133.0, 132.4, 132.1, 129.5, 128.6, 128.5, 124.5, 122.3, 99.6, and 87.7 ppm. IR (neat): 3054, 2979, 2926,2853, 2362, 2195, 1644, 1583, 1514, 1414, 1357, 1325, 1264, 1211, 1064, 972, 861, 809, 735, 535, 415 cm^{-1}. HRESI-MS: $[C_{15}H_{10}OS]^+ = [M + H]^+$ requires 239.0531; found 239.0523. TLC: R_f = 0.6 (19:1 hexane:EtOAc).

*(E)-5-Phenyl-1-(pyridin-3-yl)pent-2-en-4-yn-1-one (**19**).* The enynone **19** was prepared following the method A from propargyl alcohol[31] (60 mg, 0.45 mmol), phenyl acetylene bromide(89 mg, 0.5 mmol), freshly degassed piperidene (4.5 mL), and CuCl (4.4 mg, 0.045 mmol) stirred for 8 h at 0 °C. Purification by flash chromatography (6:1; hexane:EtOAc) gave *trans*-enynone **19** (41 mg, 0.18 mmol, 41%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.17 (1 H, s), 8.78 (1 H, d, J = 4.5 Hz), 8.24 (1 H, d, J = 8.0 Hz), 7.34−7.50 (7 H, m), 7.15 (1 H, d, J = 15.5 Hz). $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ = 187.6, 153.6, 149.9, 135.9, 132.7, 132.3, 132.2, 129.7, 128.6, 126.4, 123.8, 122.2, 100.7, and 87.6 ppm. IR (neat): 3054, 2923, 2854, 2357, 2197, 1657, 1583, 1421, 1316, 1260, 1004, 960, 854, 753, 683, 547, and 431 cm^{-1}. HR ESI-MS: $[C_{16}H_{11}NO]^+ = [M + H]^+$ requires 234.0919; found 234.0923; TLC: R_f = 0.5 (7:3, Hex/EtOAc); Mp: 70−71 °C.

*(E)-1-(Naphthalen-1-yl)-5-phenylpent-2-en-4-yn-1-one (**20**).* The enynone **20** was prepared following the method A from propargyl alcohol[32] (75 mg, 0.4 mmol), phenyl acetylene bromide (82 mg, 0.45 mmol), freshly degassed piperidene (4 mL), and CuCl (4 mg, 0.04 mmol) stirred for 8 h at 0 °C. Purification by flash chromatography (19:1; hexane:EtOAc) gave *trans*-enynone **20** (50 mg, 0.18 mmol, 45%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.40 (1 H, d, J = 8.3 Hz), 7.97 (1 H, d, J = 8.2 Hz), 7.88 (1 H, d, J = 7.6 Hz), 7.77 (1 H, d, J = 7.0 Hz), 7.50 (6 H, m), 7.34 (3 H, m), 7.20 (1 H, d, J = 16 Hz), 6.96 (1 H, d, J = 16 Hz). $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ = 193.8, 137.8, 136.0, 134.0, 132.4, 132.1, 130.6, 129.5, 128.6, 128.6, 127.8, 127.8, 126.7, 126.08, 125.7, 124.5, 122.3, 100.5, and 87.5 ppm. IR (neat): 3054, 2923, 2854, 2358, 2191, 1656, 1577, 1449, 1304, 1250, 1178, 1102, 964, 778, 690, and 509 cm^{-1}. HRESI-MS: $[C_{21}H_{14}O]^+ = [M + H]^+$ requires 283.1123; found 283.1117. TLC: R_f = 0.6 (19:1, Hex/EtOAc).

*(Z)-2-[(E)-1-Hydroxy-5-phenylpent-2-en-4-yn-1-ylidene]-cyclopentan-1-one (**21**).* The enynone **21** was prepared following the method A from propargyl alcohol[33] (55 mg, 0.28 mmol), phenyl acetylene bromide (54 mg, 0.3 mmol), freshly degassed piperidene (2.7 mL), CuCl (2.7 mg, 0.027 mmol) stirred for 3 h at 0 °C. Purification by flash chromatography (19:1; hexane:EtOAc) gave *trans* -enynone **21** (36 mg, 0.15 mmol, 54%) as a yellow solid. It was recrystallized from (1:1) hexane-MeOH solvent system. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 13.0 (1 H, br s), 7.48 (2 H, dd, J = 1.4 and 7.6 Hz), 7.34 (3 H, m), 6.80 (1 H, d, J = 15.6 Hz), 6.45 (1 H, d, J = 15.6 Hz), 2.67 (2 H, t, J = 7.2 Hz), 2.43 (2 H, t, J = 7.9 Hz),1.96 (2 H, m). $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ = 211.3, 161.6, 132.0, 131.9, 129.1, 128.5, 122.7, 118.9, 111.8, 98.4, 88.3, 38.2, 25.4, 20.6 ppm. IR (neat): 3455, 2923, 2852, 2371, 2189, 1645, 1610, 1568, 1488, 1443, 1360, 1227, 949, 818, 757, 693, 622, 527, 456 cm^{-1}. GC-MS (method): 239.1 (M), 218.1, 189.1, 165.1, 126.1. HRESI-MS: $[C_{16}H_{15}O_2]^+ = [M + H]^+$ requires 239.1067; found 239.1070. TLC: R_f = 0.6 (19:1, Hex/EtOAc). Mp: 90−92 °C.

*(E)-5-(4-Methoxyphenyl)-1-phenylpent-2-en-4-yn-1-one (**24**).* The enynone **24** was prepared following the method B from. terminal bromide[34] (50 mg, 0.24 mmol), alkyne[35] (41 mg, 0.26 mmol), freshly degassed piperidene (2.3 mL), and CuCl (2.35 mg, 0.024 mmol) stirred for 8 h at 0 °C. Purification by flash chromatography (19:1; hexane:EtOAc) gave *trans*-enynone **24** (35 mg, 0.134 mmol, 56%) as an yellow viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (2 H, d, J = 7.4 Hz), 7.58 (1 H, t, J = 7.4 Hz), 7.47 (4 H, m), 7.39 (1 H, d, J = 15.5 Hz), 7.13 (1 H, d, J = 15.4 Hz), 6.89 (2 H, d, J = 8.7 Hz), 3.83 (3 H, s). $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ = 189.1, 160.7, 137.6, 133.9, 133.2, 132.3, 128.8, 128.6, 125.7, 114.5, 114.3, 100.2, 87.2, and 55.5 ppm. IR (neat): 3054, 2926, 2853, 2361, 2333, 2191, 1657, 1580, 1509, 1462, 1322, 1306, 1263, 1211, 1174, 1029, 1002, 958, 834, 739, 702, and 537 cm^{-1}. HRESI-MS: $[C_{18}H_{14}O_2]^+ = [M + H]^+$ requires 263.1072; found 263.1061. TLC: R_f = 0.6 (9:1, Hex/EtOAc).

*(E)-5-(3-Methoxyphenyl)-1-phenylpent-2-en-4-yn-1-one (**25**).* The enynone **25** was prepared following the method B from terminal bromide (70 mg, 0.34 mmol), alkyne[36] (56 mg, 0.36 mmol), freshly degassed piperidene (3.3 mL), and CuCl (3.2 mg, 0.034 mmol) stirred for 8 h at 0 °C. Purification by flash chromatography (19:1 hexane:EtOAc) gave *trans*-enynone **25** (60 mg, 0.21 mmol, 63%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (2 H, d, J = 8.5 Hz), 7.57 (1 H, m), 7.48 (2 H, t, J = 7.8 Hz), 7.42 (1 H, d, J = 15.5 Hz), 7.25 (1 H, m), 7.10 (2 H, m), 7.02 (1 H, m), 6.90 (1 H, m), 3.80 (3 H, s). $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ = 189.0, 159.5, 137.4, 133.3, 131.8, 129.7, 128.8, 128.7, 125.1, 124.7, 123.3, 116.8, 116.2, 99.3, 87.6, and 55.4 ppm. IR (neat): 3050, 2923, 2851, 2362, 2341, 2194, 1658, 1597, 1463, 1423, 1329, 1267, 1210, 1175, 1039, 1006, 958, 857, 739, 692, and 477 cm^{-1}. HRESI-MS: $[C_{18}H_{14}O_2]^+ = [M + H]^+$ requires 263.1072; found 263.1081. TLC: R_f = 0.6 (9:1, Hex/EtOAc).

*(E)-5-[(1,1′-Biphenyl)-4-yl]-1-phenylpent-2-en-4-yn-1-one (**26**).* The enynone **26** was prepared following the method B from terminal bromide (50 mg, 0.24 mmol), alkyne[37] (46 mg, 0.26 mmol), freshly degassed piperidene (2.3 mL), and CuCl (2.35 mg, 0.024 mmol) stirred for 8 h at 0 °C. Purification by flash chromatography (19:1; hexane:EtOAc) gave *trans*-enynone **26** (44 mg, 0.14 mmol, 59%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (2 H, dd, J = 1.4 and 7.1 Hz), 7.55 (8 H, m), 7.45 (4 H, m), 7.35 (1 H, m), 7.12 (1 H, d, J = 15.4 Hz). $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ = 188.9, 142.2,

DOI: 10.1021/acs.joc.5b01780
J. Org. Chem. 2015, 80, 10208−10217

140.1, 137.4, 133.9, 133.3, 133.1, 133.0, 132.6, 129.0, 128.8, 128.6, 128.0, 127.2, 127.1, 125.2, 121.2, 99.4, and 88.6 ppm. IR (neat): 3065, 3033, 2922, 2855, 2362, 2341, 2187, 1653, 1580, 1455, 1399, 1317, 1256, 1117, 952, 840, 763, 690, and 457 cm^{-1}. HRESI-MS: $[C_{23}H_{16}O]^+ = [M + H]^+$ requires 309.1279; found 309.1293. TLC: R_f = 0.6 (9:1, Hex/EtOAc). Mp: 76−77 °C.

*Methyl (E)-2-(5-oxo-5-phenylpent-3-en-1-yn-1-yl) Benzoate (**27**).* The enynone **27** was prepared following the method B from terminal bromide (50 mg, 0.24 mmol), alkyne[38] (39 mg, 0.26 mmol), freshly degassed piperidene (2.3 mL), and CuCl (2.3 mg, 0.024 mmol) stirred for 8 h at 0 °C. Purification by flash chromatography (19:1; hexane:EtOAc) gave *trans*-enynone **27** (21 mg, 0.08 mmol, 32%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (3 H, m), 7.45−7.65 (7 H, m), 7.20 (1 H, d, J = 15.5 Hz), 3.90 (3 H, s). $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ = 189.0, 166.3, 137.3, 135.4, 134.5, 133.7, 133.3, 132.1, 131.9, 130.9, 130.7, 129.0, 128.8, 128.7, 125.2, 122.8, 97.7, 92.2, and 52.4 ppm. IR (neat): 3061, 2926, 2854, 2358, 2193, 1732, 1658, 1578, 1441, 1258, 1131, 1086, 1002, 955, 738, 658, and 539 cm^{-1}. HRESI-MS: $[C_{19}H_{14}O_3]^+ = [M + H]^+$ requires 291.1021; found 291.1016. TLC: R_f = 0.6 (9:1, Hex/EtOAc).

*(E)-5-(3,5-Dimethylphenyl)-1-phenylpent-2-en-4-yn-1-one (**28**).* The enynone **28** was prepared following the method B from terminal bromide (50 mg, 0.24 mmol), alkyne[39] (34 mg, 0.26 mmol), freshly degassed piperidene (2.3 mL), and CuCl (2.3 mg, 0.024 mmol) stirred for 8 h at 0 °C. Purification by flash chromatography (19:1; hexane:EtOAc) gave *trans*-enynone **28** (30 mg, 0.12 mmol, 49%) as a brown viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (2 H, dd, J = 1.4 and 8.3 Hz), 7.56−7.60 (1 H, tt, J = 1.2 & 8.0 Hz), 7.50 (2 H, m), 7.40 (1 H, d, J = 15.5 Hz), 7.15 (2 H, m), 7.12 (1 H, d, J = 15.5 Hz), 7.00 (1 H, s), 2.30 (6 H, s). $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ = 189.1, 139.4, 138.2, 137.5, 133.2, 133.0, 131.5, 129.9, 128.8, 128.6, 125.2, 122.06, 114.2, 100.1, 87.3, and 21.2 ppm. IR (neat): 3056, 2923, 2853, 2362, 2192, 1659, 1598, 1581, 1447, 1337, 1280, 1210, 1179, 1011, 956, 852, 773,738, 692, and 461 cm^{-1}. HRESI-MS: $[C_{19}H_{16}O]^+ = [M + H]^+$ requires 261.1279; found 261.1282. TLC: R_f = 0.6 (9:1, Hex/EtOAc).

*(E)-5-(1-Hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-1-phenylpent-2-en-4-yn-1-one (**29**).* The enynone **29** was prepared following the method B from terminal bromide (50 mg, 0.24 mmol), propargyl alcohol[40] (45 mg, 0.26 mmol), freshly degassed piperidine (2.3 mL), and CuCl (2.35 mg, 0.024 mmol) stirred for 8 h at 0 °C. Purification by flash chromato-graphy (9:1; hexane:EtOAc) gave *trans*-enynone **29** (36 mg, 0.10 mmol, 45%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (2 H, dd, J = 1.4 and 8.6 Hz), 7.75 (1 H, dd, J = 2.7 and 7.5 Hz), 7.57 (1 H, m), 7.48 (2 H, t, J = 7.8 Hz), 7.35 (1 H, d, J = 15.6 Hz), 7.25 (2 H, m), 7.15 (1 H, m), 6.95 (1 H, d, J = 15.6 Hz), 2.85 (2 H, m), 2.26 (2 H, t, J = 5.7 Hz), 2.29 (2 H, m), 1.60 (1 H, br s). $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ = 189.0, 138.5, 137.2, 136.2, 133.8, 133.3, 129.4, 128.8, 128.7, 128.5, 127.9, 126.8, 124.7, 114.2, 103.3, 82.5, and 68.5 ppm. IR (neat): 3436, 2923, 2851, 2365, 2341, 1655, 1588, 1447, 1327, 1288, 1210, 1078, 1011,963, 763, 695, and 542 cm^{-1}. HRESI-MS: $[C_{21}H_{18}O_2]^+ = [M + H]^+$ requires 303.1385; found 303.1371. TLC: R_f = 0.5 (9:1, Hex/EtOAc).

*(E)-5-(1-Hydroxycyclohexyl)-1-phenylpent-2-en-4-yn-1-one (**30**).* The enynone **30** was prepared following the method B from terminal bromide (100 mg, 0.48 mmol), cyclohexanol (65 mg, 0.52 mmol), freshly degassed piperidene (4.7 mL), and CuCl (4.71 mg, 0.05 mmol) stirred for 8 h at 0 °C. Purification by flash chromatography (9:1; hexane:EtOAc) gave *trans*-enynone **29** (82 mg, 0.32 mmol, 67%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (2 H, dd, J = 1.4 and 7.2 Hz), 7.58 (1 H, tt, J = 1.2 and 6.6 Hz), 7.48 (2 H, t, J = 8.0 Hz), 7.29 (1 H, d, J = 15.6 Hz), 6.93 (1 H, d, J = 15.6 Hz), 2.18 (1 H, br s), 1.97 (2 H, m), 1.54−1.74 (8 H, m). $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ = 189.0, 137.2, 133.6, 133.3, 128.8, 128.6, 124.9, 103.2, 82.4, 69.3, 39.8, 25.2, and 23.3 ppm. IR (neat): 3430 (OH), 3058, 2932, 2855, 2206, 1656, 1590, 1448, 1328, 1276, 1212, 1178, 1070, 963, 736, 696, 525, and 416 cm^{-1}. HR ESI-MS: $[C_{17}H_{18}O_2]^+ = [M + H]^+$ requires 255.1385; found 255.1374. TLC: R_f = 0.6 (4:1, Hex/EtOAc).

*(E)-5-(3,4-Dihydronaphthalen-1-yl)-1-phenylpent-2-en-4-yn-1-one (**31**).* The enynone **31** was prepared following the method B from terminal bromide (70 mg, 0.34 mmol), propargyl alcohol[41] (56 mg, 0.36 mmol), freshly degassed piperidene (3.3 mL), and CuCl (3.2 mg, 0.034 mmol) stirred for 8 h at 0 °C. Purification by flash chromatography (19:1; hexane:EtOAc) gave *trans*-enynone **31** (30 mg, 0.105 mmol, 32%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (2 H, dd, J = 1.4 and 8.5 Hz), 7.55−7.60 (2 H, m), 7.50 (2 H, m), 7.42 (1 H, d, J = 15.5 Hz), 7.18−7.24 (4 H, m), 6.60 (1 H, t, J = 5.0 Hz), 2.81 (2 H, t, J = 8.1 Hz), 2.45 (2 H, m). $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ = 189.1, 138.5, 137.5, 133.3, 133.0, 132.1, 128.8, 128.7, 128.1, 127.7, 126.9, 125.4 125.1, 121.8, 97.7, 88.9, 27.1, and 24.1 ppm. IR (neat): 3058, 3025, 2925, 2851, 2185, 1656, 1586, 1449, 1297, 1288, 1210, 1012, 957, 768, and 695 cm^{-1}. HRESI-MS: $[C_{21}H_{16}O]^+ = [M + H]^+$ requires 285.1279; found 285.1280. TLC: R_f = 0.6 (19:1, Hex/EtOAc).

*(E)-5-(Cyclohex-1-en-1-yl)-1-phenylpent-2-en-4-yn-1-one (**32**).* The enynone **32** was prepared following the method B from terminal bromide (100 mg, 0.48 mmol), alkyne (56 mg, 0.52 mmol), freshly degassed piperidene (4.7 mL), and CuCl (4.71 mg, 0.05 mmol) stirred for 22 h at 0 °C to RT. Purification by flash chromatography (19:1; hexane:EtOAc) gave *trans*-enynone **32** (72 mg, 0.31 mmol, 64%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (2 H, dd, J = 1.4 and 8.6 Hz), 7.55 (1 H, tt, J = 1.2 and 7.3 Hz), 7.45 (2 H, t, J = 7.8 Hz), 7.30 (1 H, d, J = 15.4 Hz), 7.02 (1 H, d, J = 15.4 Hz), 6.28 (1 H, m), 2.10 (4 H, m) 1.60 (4 H, m). $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ = 189.0, 138.5, 137.4, 133.1, 132.1, 128.7, 128.5, 125.8, 120.6, 102.0, 85.7, 28.9, 26.1, 22.2, and 21.3 ppm. IR (neat): 3054, 3019, 2929, 2855, 2363, 2181, 1657, 1577, 1448, 1327, 1300, 1221, 1179, 1013, 957, 917, 857, 775, 695, and 578 cm^{-1}. HRESI-MS: $[C_{17}H_{16}O]^+ = [M + H]^+$ requires 237.1279; found 237.1273. TLC: R_f = 0.6 (9:1, Hex/EtOAc).

*(E)-6-[(tert-Butyldimethylsilyl) oxy]-1-phenylhex-2-en-4-yn-1-one (**33**).* The enynone **33** was prepared following the method B from terminal bromide[42] (101 mg, 0.4 mmol), propargyl alcohol (50 mg, 0.37 mmol), freshly degassed piperidene (3.7 mL), and CuCl (3.6 mg, 0.04 mmol) stirred for 8 h at 0 °C. Purification by flash chromatography (19:1; hexane:EtOAc) gave *trans*-enynone **33** (56 mg, 0.18 mmol, 48%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (2 H, dd, J = 1.4 and 8.2 Hz), 7.55 (1 H, tt, J = 1.3 and 6.6 Hz), 7.32−7.35 (2 H, m), 7.16−7.2 (1 H, d, J = 15.6 Hz), 6.85−6.90 (1 H, dt, J = 1.9 & 15.6 Hz), 4.48 (2 H, d, J = 2.0 Hz), 0.80 (9 H, s), 0.15 (6 H, s). $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ = 189.1, 137.3, 133.6, 133.3, 128.8, 128.7, 124.8, 98.3, 83.1, 52.4, 31.7, 25.9, and 18.4 ppm. IR (neat): 3063, 2954, 2927, 2855, 2367, 2342, 1722, 1662, 1595, 1521, 1463, 1365, 1287, 1257, 1213, 1160, 1086, 1010, 837, 778, and 694 cm^{-1}. HRESI-MS: $[C_{18}H_{24}O_2Si]^+ = [M + H]^+$ requires 301.1624; found 301.1630. TLC: R_f = 0.6 (19:1, Hex/EtOAc).

*(2E)-6-[(tert-butyldimethylsilyl)oxy]-1-phenylpentadeca-2,7,9,11,13-pentaen-4-yn-1-one (**34**).* The enynone **34** was prepared following the method B from terminal bromide (50 mg, 0.24 mmol), alkyne[43] (77 mg, 0.**26** mmol), freshly degassed piperidene (2.3 mL), and CuCl (2.36 mg, 0.024 mmol) stirred for 8 h at 0 °C to RT. Purification by flash chromatography (19:1 hexane:EtOAc) gave *trans*-enynone **34** (30 mg, 0.07 mmol, 30%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (2 H, dd, J = 1.4 and 8.2 Hz), 7.41−7.45 (1 H, tt, J = 1.3 and 6.6 Hz), 7.31−7.35 (2 H, m), 7.11 (1 H, d, J = 6.0 Hz), 6.74−6.78 (1 H, dd, J = 1.8 and 15.6 Hz), 4.39 (1 H, td, J = 1.6 and 6.5 Hz), 1.56 (2 H, m), 1.28 (2 H, m), 1.13 (15 H, m), 0.75 (9 H, s), 0.01 (3 H, s), −0.02 (3 H, s). $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ = 189.2, 137.3, 133.4, 133.3, 128.9, 128.6, 125.2, 101.9, 82.4, 63.9, 38.5, 32.0, 31.7, 29.8, 29.6, 29.4, 29.3, 25.9, 25.3, 22.8, 18.4, 14.2, −4.3, and −4.8 ppm. IR (neat): 3536, 3438, 3061, 2922, 2853, 2206, 1734, 1664, 1589, 1461, 1288, 1163, 1087, 1021, 961, 835, 774, and 693 cm^{-1}. HRESI-MS: $[C_{27}H_{42}NaO_2Si]^+ = [M + Na]^+$ requires 449.2852; found 449.2860. TLC: R_f = 0.6 (9:1, Hex/EtOAc).

*1-Phenylpentadeca-2,4-diyne-1,6-diol (**35**).* The diynol **35** was prepared following the method B from terminal bromide (50 mg, 0.24 mmol), alkyne[44] (48 mg, 0.26 mmol), freshly degassed piperidene (2 mL), and CuCl (2 mg, 0.019 mmol) stirred for 9 h at 0 °C to RT.

DOI: 10.1021/acs.joc.5b01780
J. Org. Chem. 2015, 80, 10208−10217

Purification by flash chromatography (9:1; hexane:EtOAc) gave coupled alcohol **35** (38 mg, 0.12 mmol, 51%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50−7.51 (2 H, d, J = 7.0 Hz), 7.33−7.40 (3 H, m), 5.52 (1 H, s), 4.40−4.44 (1 H, t, J = 8.0 Hz), 1.68−1.72 (2 H, m), 1.41−1.43 (4 H, m), 1.25 (9 H, m), 0.86−0.89 (6 H, t, J = 6.2 Hz). ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ = 139.7, 128.9, 128.8, 126.7, 114.2, 81.5, 78.9, 70.7, 68.9, 65.1, 63.0, 37.6, 32.0, 29.8, 29.6, 29.4, 29.0, 25.1, 22.8, and 14.2 ppm. IR (neat): 3528, 3401, 3061, 2922, 2853, 2206, 1734, 1664, 1589, 1461, 1288, 1213, 1163, 1087, 1021, 961, 835, 774, 693, 630, 543, and 426 cm^{-1}. TLC: R_f = 0.5 (4:1, Hex/EtOAc). HRESI-MS: $[C_{21}H_{29}O_2]^+$ = $[M + H]^+$ requires 313.2162; found 313.2169.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01780.

^{1}H and ^{13}C{^{1}H}NMR spectra of all new compounds synthesized during this study and ORTEP diagrams for compounds **13′** and **21** (PDF)

X-ray crystallographic information (CIF) for **13′** (CIF)

X-ray crystallographic information (CIF) for **21** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

* E-mail: beeru@iitm.ac.in.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Indian Institute of Technology Madras, Chennai for the financial support through CHY/13-14/622/NFSC/BEER grant. B.S.C. thanks IIT Madras for HTRA fellowship. We thank Mr Ramkumar for single crystal X-ray analysis.

■ REFERENCES

(1) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Wasilke, J.-C.; Obrey, S. J.; Baker, T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (c) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (d) Kirsch, S. F. *Synthesis* **2008**, *2008*, 3183. (e) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993.

(2) (a) Cheng, M.; Hulce, M. *J. Org. Chem.* **1990**, *55*, 964. (b) Krause, N. *Chem. Ber.* **1991**, *124*, 2633. (c) Arndt, S.; Handke, G.; Krause, N. *Chem. Ber.* **1993**, *126*, 251. (d) Purpura, M.; Krause, N. *Eur. J. Org. Chem.* **1999**, *1999*, 267.

(3) (a) Reddy, C. R.; Reddy, M. D. *J. Org. Chem.* **2014**, *79*, 106. (b) Toshima, H.; Aramaki, H.; Ichihara, A. *Tetrahedron Lett.* **1999**, *40*, 3587.

(4) Chen, J.; Fan, G.; Liu, Y. *Org. Biomol. Chem.* **2010**, *8*, 4806.

(5) (a) Chodkiewicz, W. *Ann. Chim. Paris* **1957**, *2*, 819. (b) Cadiot, P.; Chodkiewicz, W. *In Chemistry of Acetylenes*, Viehe, H. G., Ed.; Marcel, Dekker: New York, 1969, 597. (c) Marino, J. P.; Nguyen, H. N. *J. Org. Chem.* **2002**, *67*, 6841. (d) Nishihara, Y.; Ikegashira, K.; Hirabayashi, K.; Ando, J.; Mori, A.; Hiyama, A. T. *J. Org. Chem.* **2000**, *65*, 1780. (e) Bellina, F.; Carpita, A.; Mannocci, L.; Rossi, R. *Eur. J. Org. Chem.* **2004**, *2004*, 2610. (f) Jiang, H.-F.; Wang, A.-Z. *Synthesis* **2007**, *2007*, 1649. (g) Reddy, B. V. S.; Rao, R. N.; Kumaraswamy, B.; Yadav, J. S. *Tetrahedron Lett.* **2014**, *55*, 4590. (h) Kraus, G. A.; Bae, J.; Wu, L.; Wurtele, E. *Molecules* **2006**, *11*, 758. (i) Sindhu, K. S.; Thankachan, A. P.; Sajitha, P. S.; Anilkumar, G. *Org. Biomol. Chem.* **2015**, *13*, 6891.

(6) Alami, M.; Ferri, F. *Tetrahedron Lett.* **1996**, *37*, 2763.

(7) (a) See Scheme 5, compound **10j** in Bowling, N. P.; Burrmann, N. J.; Halter, R. J.; Hodges, J. A.; McMahon, R. J. *J. Org. Chem.* **2010**, *75*, 6382. (b) Villeneuve, K.; Riddell, N.; Jordan, R. W.; Tsui, G. C.; Tam, W. *Org. Lett.* **2004**, *6*, 4543. (c) Fang, Z.; Wills, M. *Org. Lett.* **2014**, *16*, 374.

(8) We have performed the cascade reaction using low amounts of piperidine in various degassed solvents like 1,2-dichlorobenzene (S:P; 4:1), and THF (S:P; 4:1). Here we observed that the coupling was smooth and quick but the isomerization was very slow and took about 30 h for completion and gave the *trans*-enynone **2** in 50% and 55% respective yields in 1,2-dichlorobenzene and THF.

(9) Crystallographic data information for **13′** has been deposited with the Cambridge Crystallographic Data Centre with CCDC1405917. Further details were given in Figure 4 of the Supporting Information and accompanying CIF file.

(10) Even after stirring the pure diynol **12′** with piperidine for 24 h at RT, there was no formation of enynone **12**.

(11) Crystallographic data information for **21** has been deposited with the Cambridge Crystallographic Data Centre with CCDC1405918. Further details were given in Figure 5 of the Supporting Information and accompanying CIF file.

(12) Braun, R. U.; Ansorge, M.; Müller, T. J. J. *Chem. - Eur. J.* **2006**, *12*, 9081.

(13) Matsuya, Y.; Koiwai, A.; Sugimoto, D. K.; Toyooki, N. *Tetrahedron Lett.* **2012**, *53*, 5955.

(14) Xu, C.; Xu, M.; Yang, L.; Li, C. *J. Org. Chem.* **2012**, *77*, 3010.

(15) Park, J.; Yun, J.; Kim, J.; Jang, D.; Park, C. H.; Lee, K. *Synth. Commun.* **2014**, *44*, 1924.

(16) Corey, E. J.; Niimura, K.; Konishi, Y.; Hashimoto, S.; Hamada, Y. *Tetrahedron Lett.* **1986**, *27*, 2199.

(17) Xu, C.; Xu, M.; Yang, L.; Li, C. *J. Org. Chem.* **2012**, *77*, 3010.

(18) Mark, R.; Reinhard, B. *Tetrahedron Lett.* **1997**, *38*, 7353.

(19) Chena, P.; Zhua, X. *J. Mol. Catal. B: Enzym.* **2013**, *97*, 184.

(20) Pwaar, S. K.; Wang, C.; Bhunia, S.; Jadhav, A. M.; Liu, R. *Angew. Chem., Int. Ed.* **2013**, *52*, 7559.

(21) Zatalochnaya, O. V.; Gevorgyan, V. *Org. Lett.* **2013**, *15*, 2562.

(22) Ghosh, N.; Nayak, S.; Prabagar, B.; Sahoo, A. K. *J. Org. Chem.* **2014**, *79*, 2453.

(23) Chena, P.; Zhua, X. *J. Mol. Catal. B: Enzym.* **2013**, *97*, 184.

(24) Xu, C.; Xu, M.; Yang, L.; Li, C. *J. Org. Chem.* **2012**, *77*, 3010.

(25) Xu, S.; Zhuang, X.; Pan, X.; Zhang, Z.; Duan, L.; Liu, Y.; Zhang, L.; Ren, X.; Ding, K. *J. Med. Chem.* **2013**, *56*, 4631.

(26) Park, J.; Yun, J.; Kim, J.; Jang, D.; Park, C. H.; Lee, K. *Synth. Commun.* **2014**, *44*, 1924.

(27) Mark, R.; Reinhard, B. *Tetrahedron Lett.* **1997**, *38*, 7353.

(28) Seppanen, O.; Muuronen, M.; Helaja, J. *Eur. J. Org. Chem.* **2014**, *2014*, 4044.

(29) Corey, E. J.; Niimura, K.; Konishi, Y.; Hashimoto, S.; Hamada, Y. *Tetrahedron Lett.* **1986**, *27*, 2199.

(30) Singh, V. *Synth. Commun.* **2010**, *40*, 1280.

(31) Galli, U.; Ercolano, E.; Carraro, L.; Blasi, R.; Sorba, G.; Canonico, P. L.; Genazzani, A.; Tron, G. C.; Bilington, R. A. *ChemMedChem* **2008**, *3*, 771.

(32) Bhanuchandra, M.; Kuram, M. R.; Sahoo, A. K. *Org. Biomol. Chem.* **2012**, *10*, 3538.

(33) Pawar, S. K.; Wang, C.; Bhunia, S. A.; Jadhav, M.; Liu, R. *Angew. Chem., Int. Ed.* **2013**, *52*, 7559.

(34) Ghosh, N.; Nayak, S.; Prabagar, B.; Sahoo, A. K. *J. Org. Chem.* **2014**, *79*, 2453.

(35) Chang, H.; Liao, Y.; Liu, R. *J. Org. Chem.* **2007**, *72*, 8139.

(36) Nishi, M.; Kuninobu, Y.; Takai, K. *Org. Lett.* **2012**, *14*, 6116.

(37) Li, H.; Petersen, J. L.; Wang, K. *J. Org. Chem.* **2001**, *66*, 7804.

(38) Mehta, S.; Larock, R. C. *J. Org. Chem.* **2010**, *75*, 1652.

(39) Trost, B. M.; Pinkerton, A. B. *Tetrahedron Lett.* **2000**, *41*, 9627.

(40) Nandi, G. C.; Rathman, B. M.; Laali, K. *Tetrahedron Lett.* **2013**, *54*, 6258.

(41) Das, B. C.; Tang, X.; Evans, T. *Tetrahedron Lett.* **2012**, *53*, 1316.

(42) Lam, T. Y.; Wang, Y.; Danheiser, R. L. *J. Org. Chem.* **2013**, *78*, 9396.

(43) Grie, R.; Eugenekhaskin, G.; Foltz, J. L.; Schaefer, P. W.; Gries, G. *J. Chem. Ecol.* **2003**, *29*, 2201.

(44) Steven, A.; Fleming, R. *Tetrahedron Lett.* **2005**, *46*, 8095.

DOI: 10.1021/acs.joc.5b01780
J. Org. Chem. 2015, 80, 10208−10217