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Preparation of (*E*)-1,3-Enyne Derivatives through Palladium Catalyzed Hydroalkynylation of Allenes

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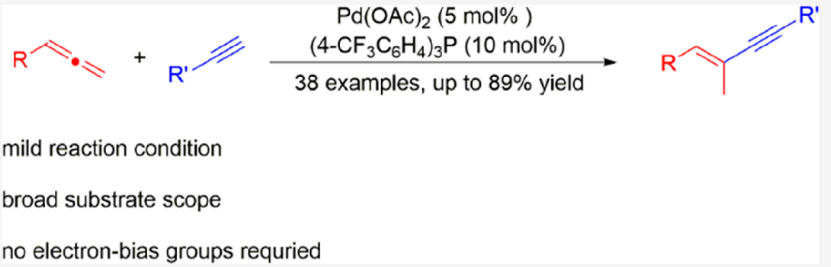
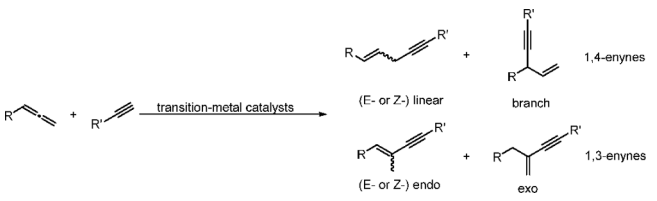


ABSTRACT: A general and efficient palladium catalyzed hydroalkynylation of allenes was developed to produce synthetically versatile (*E*)-1,3-enyne derivatives with high regio- and stereoselectivity. This catalytic system proceeded under mild conditions and was compatible with a broad range of substrates, especially for allenes without electron-bias groups. This work further broadens the synthetic potential of these scaffolds in organic synthesis and medicinal chemistry.

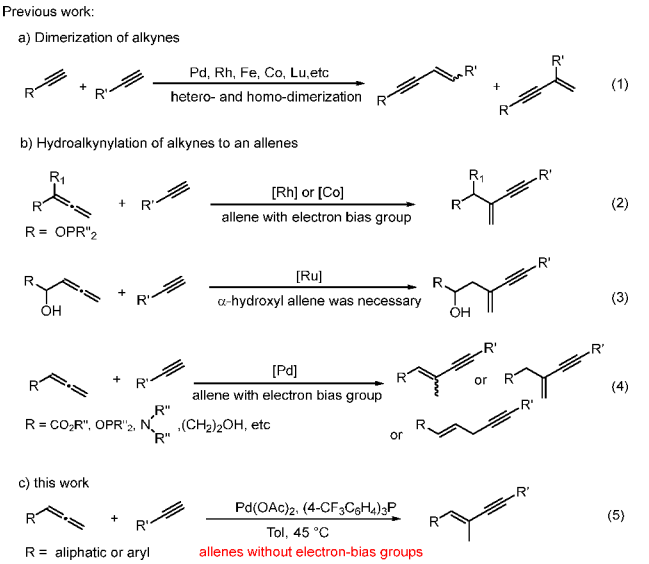
Conjugated 1,3-enynes are not only valuable structural motifs present in bioactive products,[1] but also useful synthons in a broad scope of organic synthesis.[2] Consequently, development of facile and efficient approaches toward conjugated enynes has attracted continuous attention from the literature.[3] There are several synthetic routes toward conjugated enynes, such as Sonogashira cross-coupling reactions,[4] Wittig reactions of conjugated alkynals or alkynones,[5] and the dehydrations of propargyl alcohols.[6] Besides those methods, addition of terminal alkynes to allenes is the most straightforward and atom economic method to prepare these conjugated enynes. However, the control of regio- and stereoselectivity of the process is quite difficult, as it could form 1,3- or 1,4-enynes, and the linear 1,4-enyne and endo 1,3-enyne can exist as *E*- or *Z*-isomers or mixtures (Scheme 1).

At present, transition-metal catalyzed dimerization of terminal alkynes to produce highly regio- and stereoselective 1,3-enynes has been widely reported[7] (Scheme 2, eq 1). However, there exists hetero- and homodimerization, which is

Scheme 1. Different Products of the Allene Hydroalkynylation



Scheme 2. Hydroalkynations of Terminal Alkynes to Alkynes or Allenes



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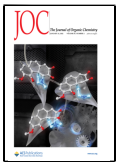

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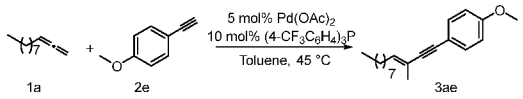
hard to control in the practical operation. In contrast, hydroalkynylation of allenes as a more flexible synthetic route is developed and catalyzed by Rh, Co, Ru, and Pd catalysts. For example, Hayashi and co-workers achieved asymmetric addition of terminal alkynes to diarylphosphinylallenes and 1,1-disubstituted allenes, which proceeded with high regioselectivity in the presence of a rhodium[8] or cobalt[9] catalyst (Scheme 2, eq 2). Yamaguchi's group reported a ruthenium-promoted[10] cross coupling reaction of hydroxyl allenes and 1-alkynes to give exo-enynes, in which α-hydroxyl allene was necessary (Scheme 2, eq 3). Besides, several groups have demonstrated palladium catalyzed[11] cross-coupling reactions of alkynes with electron-bias groups (Scheme 2, eq 4). Trost and Kottirsch reported the cross-condensation of terminal alkynes to acyl allenes afforded (*E*)-1,3-enynes.[11a] Similarly, Gevorgyan and co-workers used two types of palladium catalysts to obtain exo-enynes or endo-enynes as single products by the addition of terminal alkynes to allenylphosphine oxides.[11b] Park and co-workers subsequently developed palladium catalyzed highly efficient ligand-enabled regiodivergent hydroalkynylations of allenamide, giving (*Z*)-endo- 1,3-enyne or (*E*)-linear products.[11c] Recently, Gandon and Roulland demonstrated palladium catalyzed cross-coupling reactions of alkynes with β-alkoxy or β-hydroxyl allenes, which afforded (*E*)-stereoselectivity trisubstituted enynes in good yield.[11d] The above depicted examples of cross-coupling of terminal alkynes to allenes involved the use of special allenes bearing hydroxyl, acyl, phosphoryl, acylamino groups. Apart from the above, it is important to note that the palladium catalyzed hydroalkynylation of propadiene and allenyl heterocycles has been reported by Grigg and co-workers earlier.[11e] But it is still of great significance to develop new and general catalytic systems for hydroalkynylation of electron-unbiased allenes. Herein, we present a palladium catalyzed hydroalkynylation of allenes for the preparation of (*E*)-1,3-enyne derivatives with high regio- and stereoselectivity (Scheme 2, eq 5).

We initiated our research with 1-octylallene **1a** and 1-ethynyl-4-methoxybenzene **2e** as the model substrates. After extensive optimization, we found that 92% of the NMR yield of 1,3-enyne **3ae** could be obtained with excellent regio-/E-stereoselectivity in the presence of 5 mol % $Pd(OAc)_2$, 10 mol % $(4\text{-}CF_3C_6H_4)_3P$ in toluene at 45 °C (oil bath) after 5 h under N_2 (Table 1, entry 1). As shown in Table 1, various reaction conditions were explored. In the presence of CuCl as the additive, contrary to Gandon and Roulland's report,[11d] **3ae** was nearly not detected (Table 1, entry 2). Several palladium salts such as $PdCl_2$, $Pd(OCOCF_3)_2$ used in replacement of $Pd(OAc)_2$ showed dramatic declines of the yields (Table 1, entries 3−4). With $Pd_2(dba)_3$ as the metal catalyst, a good yield of **3ae** was detected, which indicated that Pd(0) was a reactive intermediate in this reaction (Table 1, entry 5). Furthermore, several ligands were screened, and the experimental results showed that ligands containing electron-donating group or large steric hindrance, such as $(o\text{-}OMeC_6H_4)_3P$, $(p\text{-}OMeC_6H_4)_3P$, and bisphosphine ligands, led to low conversion of 1-octylallene and poor yields of product **3ae** (Table 1, entries 6−8). The unidentified byproduct increased significantly when Johnphos was used (Table 1, entry 9). Replacing $(4\text{-}CF_3C_6H_4)_3P$ by PPh_3, $(4\text{-}FC_6H_4)_3P$ and $(2\text{-furyl})_3P$ afforded lower yields of the product (Table 1, entries 10−12). The use of THF and DMF as solvent in place of toluene decreased the yields (Table 1, entries 13−14).

Table 1. Optimization of Conditions for Hydroalkynylation of 1-Octylallene 1a with Terminal Alkyne 2e



entry	variation from standard conditions[a]	conv (%)[b]	yield of **3ae** (%)[b]
1	none	100	92
2	CuCl as additive	15	trace
3	$PdCl_2$ instead of $Pd(OAc)_2$	0	0
4	$Pd(OCOCF_3)_2$ instead of $Pd(OAc)_2$	8	trace
5[c]	$Pd_2(dba)_3$ instead of $Pd(OAc)_2$	100	72
6	$(o\text{-}OMeC_6H_4)_3P$ instead of $(4\text{-}CF_3C_6H_4)_3P$	30	10
7	$(p\text{-}OMeC_6H_4)_3P$ instead of $(4\text{-}CF_3C_6H_4)_3P$	28	18
8	xantphos instead of $(4\text{-}CF_3C_6H_4)_3P$	8	trace
9	Johnphos instead of $(4\text{-}CF_3C_6H_4)_3P$	100	10
10	PPh_3 instead of $(4\text{-}CF_3C_6H_4)_3P$	72	54
11	$(4\text{-}FC_6H_4)_3P$ instead of $(4\text{-}CF_3C_6H_4)_3P$	100	61
12	$(2\text{-furyl})_3P$ instead of $(4\text{-}CF_3C_6H_4)_3P$	100	67
13	THF instead of toluene	100	78
14	DMF instead of toluene	66	28

[a]Reaction condition: 1-octylallene **1a** (0.2 mmol), terminal alkyne **2e** (0.24 mmol), $Pd(OAc)_2$ (0.01 mmol), ligand (0.02 mmol), toluene (2 mL), N_2, 45 °C (oil bath), 5 h. [b]The yields of **3ae** were determined by ^1H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard. [c]2.5 mol % $Pd_2(dba)_3$, 5 mol % $(4\text{-}CF_3C_6H_4)_3P$.

The scope of the reaction was first explored under the optimized condition using a long-chain aliphatic 1-octylallene **1a**, which contains no electron-bias groups with different alkyne substrates. With regards to aromatic alkynes, phenyl (Scheme 3, **3aa**) as well as substituted benzenes bearing methyl (Scheme 3, **3ab**), pentyl (Scheme 3, **3ac**), *t*-Bu (Scheme 3, **3ad**), methoxy (Scheme 3, **3ae**), phenyl (Scheme 3, **3af**), and electron-withdrawing bromo (Scheme 3, **3ag**), chloro (Scheme 3, **3ah**), and ester (Scheme 3, **3ai**) groups were all found to be compatible. The respective enynes were isolated in 67−87% yields. Enynes such as **3aj** and **3ak** having heterocycle or cyclohexenyl groups were also synthesized in 72% and 70% yield, respectively. Aliphatic alkynes also underwent the cross-coupling effectively (Scheme 3, **3al**−**3an**). A TS-protected alkynol afforded the corresponding 1,3-enyne in 58% yield (Scheme 3, **3aq**), and a TBS-protected alkynol also underwent cross-coupling in good yield (Scheme 3, **3ar**). A variety of functionalities and reactive groups, including unprotected alcohols (Scheme 3, **3ao**−**3ap**), cyano (Scheme 3, **3as**), bromo (Scheme 3, **3at**), and chloro (Scheme 3, **3au**), were also compatible coupling partners in moderate to good yields. Moreover, a 10 mmol scale reaction of **1a** was performed, afforded 2.12 g **3aa** in 83% yield delightfully, and demonstrated the synthetic potential of this protocol.

Apart from the alkyne substrates, we also made an effort to investigate the possibility of changing different allenes including both aliphatic and aromatic allenes, especially for several examples of allenes containing no electron-bias groups in this hydroalkynylation with phenylacetylene **2a**. As can be seen in Scheme 4, an alkyl substituted allene without any electron-bias groups preceded well with phenylacetylene in good yield (Scheme 4, **3ba**). Cyclohexylallene was tolerated

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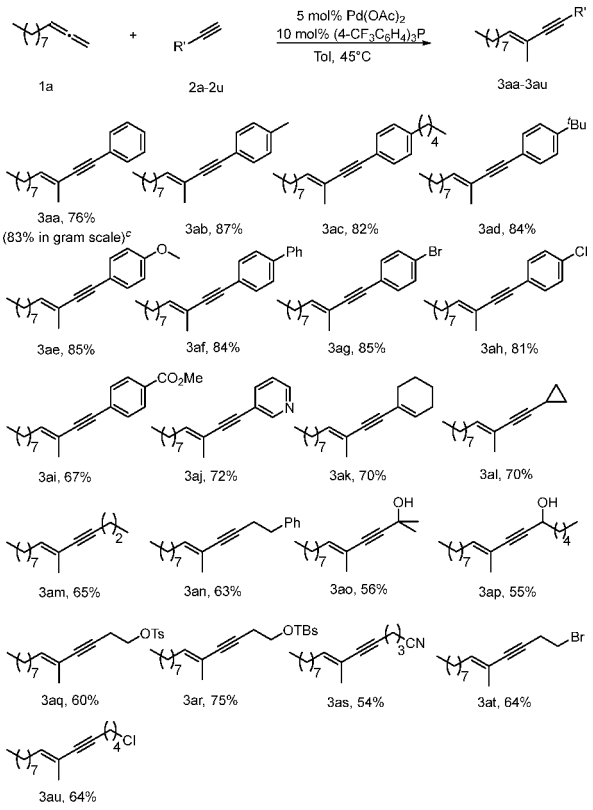
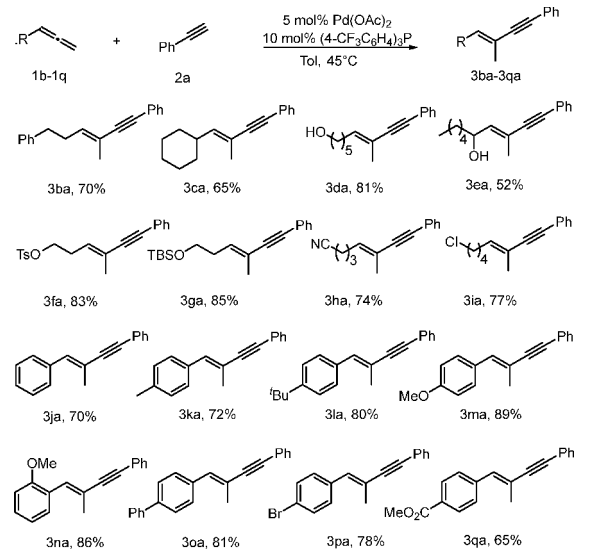
Scheme 3. Substrate Scope for Hydroalkynylation of Different Terminal Alkynes with Alkyl Allene[a,b]



[a]Reaction condition: 1-octylallene **1a** (0.3 mmol), terminal alkynes **2a−2u** (0.36 mmol), $Pd(OAc)_2$ (0.015 mmol), ligand (0.03 mmol), solvent (3 mL), 45 °C (oil bath), N_2, 5−18 h (monitored by TLC). [b]Yields of isolated products. [c]Yield of 10.0 mmol scale reaction of **1a**.

Scheme 4. Substrate Scope for Hydroalkynylation of Different Allenes[a,b]



[a]Reaction condition: allenes **1b−1q** (0.3 mmol), terminal alkyne **2a** (0.36 mmol), $Pd(OAc)_2$ (0.015 mmol), ligand (0.03 mmol), solvent (3 mL), 45 °C (oil bath), N_2, 5−18 h (monitored by TLC). [b]Yields of isolated products.

with high regioselectivity and good yield (Scheme 4, **3ca**). Furthermore, alkyl allenes containing protecting groups, such as -TS (Scheme 4, **3fa**) and -TBS (Scheme 4, **3ga**), were tested and were compatible with the reaction conditions to afford the expected products in decent isolated yields. This reaction could also tolerate a range of functionalities and reactive groups, including unprotected alcohols (Scheme 4, **3da−3ea**), cyano (Scheme 4, **3ha**), and chloro (Scheme 4, **3ia**). Several aryl substituted allenes, including electroneutral, electron-donating, and electron-withdrawing groups reacted with this alkyne to afford the (*E*)-1,3-enynes in relatively high yields (Scheme 4, **3ja−3qa**).

To gain some insights into the mechanism, some experiments were conducted. First, a Pd^0/Pd^{II} catalytic cycle might be involved because $Pd_2(dba)_3$ also showed a moderate catalytic effect (Table 1, entry 5), Next, cross-coupling reaction between **2a** and **1r** was employed to help understand the migration insertion part of the mechanism (Scheme 5). As a result, **3ra** was obtained exclusively in 80% yield and no cyclization product **3ra′** was detected. According to previous report, the **3ra′** would be obtained by trapping postulated π-allyl-Pd intermediates **E** via carbopalladation route.[12] This result implies that the formation of alkenylpalladium intermediate **D** through hydropalladation mechanism was more likely in this reaction.

On the basis of the results presented above, a plausible catalytic cycle was proposed in Scheme 6. Initially, Pd^{II} was reduction to Pd^0 species **A** by ligand.[13] Then oxidative addition with alkyne formed hydropalladium intermediate **B**. Subsequently, allene coordinated with intermediate **B** to afford intermediate **C**. According to the result in Scheme 5 and previous study of the hydroalkynylation reaction,[14] we prefer to believe that hydropalladation route is a more possible pathway to form alkenylpalladium intermediate **D**. Eventually, enynes were produced by reductive elimination of intermediate **D** and Pd^0 species **A** was regenerated.

In summary, we have devised a highly efficient palladium catalyzed hydroalkynylation of allenes with high regio- and stereoselectivity to produce (*E*)-1,3-enyne derivatives. This catalytic system proceeded under mild conditions and was compatible with a broad range of substrates, especially for alkyl or aryl allenes without electron-bias groups. This work demonstrated a facile and efficient method to prepare (*E*)-1,3-enynes and further broaden the synthetic potential of these scaffolds in organic synthesis and medicinal chemistry.

EXPERIMENTAL SECTION

General Experimental Information. The liquid-state NMR was recorded on a 400 or 500 MHz spectrometer. Chemical shifts were reported in ppm. ^1H NMR spectra were referenced to $CDCl_3$ (7.28 ppm), and $^{13}C\{^1H\}$ NMR spectra were referenced to $CDCl_3$ (77.0 ppm). All $^{13}C\{^1H\}$ NMR spectra were measured with complete proton decoupling. Peak multiplicities were designated by the following abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet; brs, broad singlet and *J*, coupling constant in Hz. Mass spectroscopy: We were grateful to the assistance of the Department of Chemistry, Xiamen University in obtaining the MS data. High resolution mass spectra (ESI HRMS) were recorded on a Micromass QTOF2 Quadruple/Time-of-Flight Tandem mass spectrometer by the instrumentation center of Department of Chemistry, Xiamen University. Unless otherwise noted, all reagents and solvents were obtained commercially and used without further purification. Allenes **1a−1b**, **1d−1r** were known compounds and were prepared according to corresponding literature procedures;[15] allene **1c** was purchased

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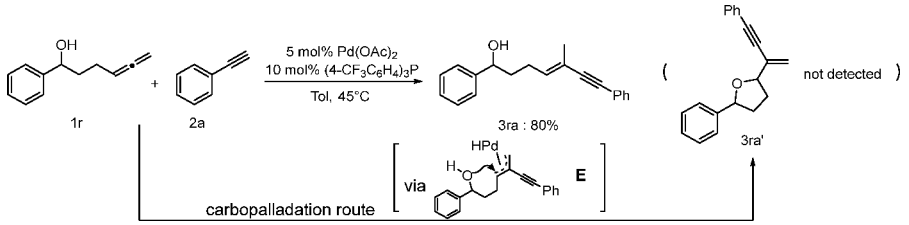
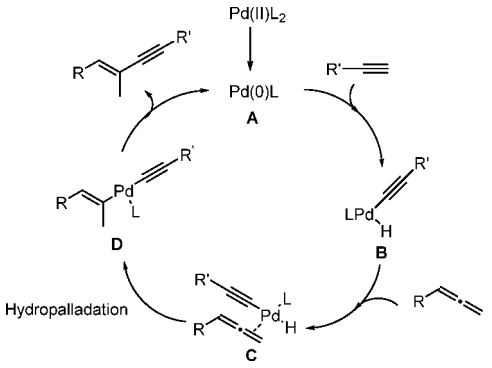
Scheme 5. Hydroalkynylation of 1-Phenylhexa-4,5-dien-1-ol with Ethynylbenzene



Scheme 6. Proposed Mechanism

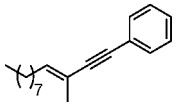


from Sigma-Aldrich and was used as received without further purification. All alkynes were obtained commercially and used without further purification.

Experimental Procedures and Spectroscopic Data. *General Synthetic Procedure for the Preparation of* ***3****.* In a nitrogen filled Schlenk tube (10 mL) charged with a magnetic stirrer bar, $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 0.05 equiv), $(4\text{-}CF_3C_6H_4)_3P$ (14.0 mg, 0.03 mmol, 0.1 equiv), and toluene (1 mL) were added, and the mixture was stirred at 45 °C (oil bath) for 10 min, and then allenes (0.3 mmol, 1 equiv) and alkynes (0.36 mmol, 1.2 equiv) in toluene (2 mL) were added under N_2. The reaction mixture was stirred at 45 °C. Upon completion (monitored by TLC), the solvent was removed by a vacuum and the crude residue was purified by silica gel column chromatography to afford the corresponding products **3**.

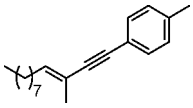
Gram Scale Synthesis of ***3aa****.* To a 250 mL of two-neck round bottomed flask charged with a magnetic stirrer bar, $Pd(OAc)_2$ (112 mg, 0.5 mmol, 0.05eq), $(4\text{-}CF_3C_6H_4)_3P$ (466 mg, 1.0 mmol, 0.1 equiv), and toluene (50 mL) were added, and the mixture was stirred at 45 °C (oil bath) for 10 min under N_2 atmosphere. Then allenes (1.52 g, 10.0 mmol 1 equiv) and alkynes (1.22 g, 12.0 mmol 1.2 equiv) in toluene (50 mL) were added, and the reaction mixture was stirred at 45 °C. Upon completion (monitored by TLC), the solvent was removed by a vacuum and the crude residue was purified by silica gel column chromatography to afford 2.12 g of **3aa** in 83% yield.

*Spectroscopic Data. ((E)-(3-Methyldodec-3-en-1-yn-1-yl)-benzene (****3aa****).*



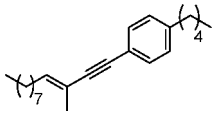
Purified by column chromatography (Eluent: petroleum ether). Isolated as a colorless liquid (76%, 57.9 mg) ^1H NMR (500 MHz, $CDCl_3$) δ 7.39−7.45 (m, 2H), 7.23−7.31 (m, 3H), 5.96 (t, J = 7.46 Hz, 1H), 2.12 (dt, apparent q, J = 7.31 Hz, 2H), 1.87 (s, 3H), 1.36−1.43 (m, 2H), 1.23−1.35 (m, 10H), 0.89 (t, J = 7.18 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 138.9, 131.4, 128.2, 127.7, 123.8, 117.6, 92.7, 85.8, 31.9, 29.5, 29.34, 29.28, 29.1, 28.6, 22.7, 17.2, 14.1. HRMS (ESI) m/z Calculated for $C_{19}H_{26}Na^+$ [M + Na^+]: 277.1932, found 277.1929.

*(E)-1-Methyl-4-(3-methyldodec-3-en-1-yn-1-yl)benzene (****3ab****).*



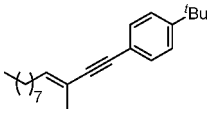
Purified by column chromatography (Eluent: petroleum ether). Isolated as a colorless liquid (87%, 69.9 mg) ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, J = 7.17 Hz, 2H), 7.27 (d, J = 7.81 Hz, 2H), 5.94 (t, J = 7.51 Hz, 1H), 2.33 (s, 3H), 2.11 (dt, apparent q, J = 7.27 Hz, 2H), 1.86 (s, 3H), 1.36−1.41 (m, 2H), 1.25−1.35 (m, 10H), 0.88 (t, J = 6.54 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ138.5, 137.7, 131.3, 129.0, 120.8, 92.5, 85.9, 55.2, 31.9, 29.5, 29.35, 29.29, 29.1, 28.6, 22.7, 21.4, 17.2, 14.1. HRMS (ESI) m/z Calculated for $C_{20}H_{28}Na^+$ [M + Na^+]: 291.2089, found 291.2085.

*(E)-1-(3-Methyldodec-3-en-1-yn-1-yl)-4-pentylbenzene (****3ac****).*



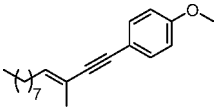
Purified by column chromatography (Eluent: petroleum ether). Isolated as a colorless liquid (82%, 76.3 mg) ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.12 Hz, 2H), 7.10 (d, J = 8.16 Hz, 2H), 5.94 (t, J = 7.49 Hz, 1H), 2.56 (t, J = 7.56 Hz, 2H), 2.12 (dt, apparent q, J = 7.26 Hz, 2H), 1.86 (s, 3H), 1.59 (m, 2H), 1.20−1.44 (m, 16H), 0.88 (m, 6H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 142.8, 138.4, 131.3, 128.3, 120.9, 117.7, 92.0, 85.9, 35.8, 31.9, 31.4, 30.9, 29.5, 29.4, 29.3, 29.1, 28.6, 22.7, 22.5, 17.2, 14.1, 14.0. HRMS (ESI) m/z Calculated for $C_{24}H_{36}Na^+$ [M + Na^+]: 347.2715, found 347.2718.

*(E)-1-(tert-Butyl)-4-(3-methyldodec-3-en-1-yn-1-yl)benzene (****3ad****).*



Purified by column chromatography (Eluent: petroleum ether). Isolated as a colorless liquid (84%, 78.1 mg) ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 8.48 Hz, 2H), 7.34 (d, J = 8.57 Hz, 2H), 5.98 (t, J = 7.49 Hz, 1H), 2.15 (dt, apparent q, J = 7.29 Hz, 2H), 1.90 (s, 3H), 1.39−1.45 (m, 2H), 1.28−1.38 (m, 19H), 0.92 (t, J = 7.05 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 150.9, 138.5, 131.1, 125.2, 120.8, 117.7, 92.0, 85.9, 34.7, 31.9, 31.2, 29.5, 29.4, 29.3, 29.1, 28.6, 22.7, 17.3, 14.1. HRMS (ESI) m/z Calculated for $C_{23}H_{34}Na^+$ [M + Na^+]: 333.2558, found 333.2562.

*(E)-1-Methoxy-4-(3-methyldodec-3-en-1-yn-1-yl)benzene (****3ae****).*



Purified by column chromatography (Eluent: petroleum ether). Isolated as a colorless liquid (85%, 71.6 mg) ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J = 8.64 Hz, 2H), 6.82 (d, J = 8.60 Hz, 2H), 5.92 (t, J = 7.24 Hz, 1H), 3.80 (s, 3H), 2.11 (dt, apparent q, J = 7.24 Hz, 2H), 1.86 (s, 3H), 1.36−1.41 (m, 2H), 1.25−1.35 (m, 10H), 0.88 (t, J = 7.01 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 159.2, 138.1, 132.8, 117.7, 116.0, 113.9, 91.3, 85.6, 55.2, 31.9, 29.5, 29.33, 29.28,

https://doi.org/10.1021/acs.joc.1c02732
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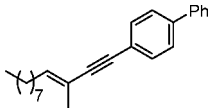
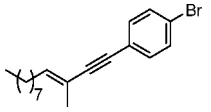
29.1, 28.6, 22.7, 17.3, 14.1. HRMS (ESI) m/z Calculated for $C_{20}H_{28}ONa^+$ [M + Na^+]: 307.2038, found 307.2033.

*(E)-4-(3-Methyldodec-3-en-1-yn-1-yl)-1,1′-biphenyl (**3af**).*



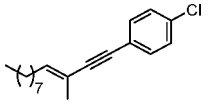
Purified by column chromatography (Eluent: petroleum ether). Isolated as a white solid (84%, 83.2 mg) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (m, 2H), 7.52 (d, J = 8.40 Hz, 2H), 7.48 (d, J = 8.43 Hz, 2H), 7.41 (m, 2H), 7.32 (m, 1H), 5.98 (t, J = 7.46 Hz, 1H), 2.13 (dt, apparent q, J = 7.41 Hz, 2H), 1.88 (s, 3H), 1.37−1.43 (m, 2H), 1.23−1.35 (m, 10H), 0.89 (t, J = 7.11 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 140.5, 140.4, 139.0, 131.9, 128.9, 127.5, 127.0, 126.9, 122.8, 117.7, 93.5, 85.8, 32.0, 29.6, 29.41, 29.36, 29.2, 28.7, 22.7, 17.2, 14.2. HRMS (ESI) m/z Calculated for $C_{25}H_{30}Na^+$ [M + Na^+]: 353.2245, found 353.2253.

*(E)-1-Bromo-4-(3-methyldodec-3-en-1-yn-1-yl)benzene (**3ag**).*



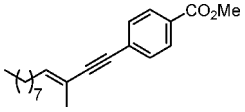
Purified by column chromatography (Eluent: petroleum ether). Isolated as a colorless liquid (85%, 84.6 mg) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, J = 8.50 Hz, 2H), 7.27 (d, J = 8.45 Hz, 2H), 5.97 (t, J = 7.49 Hz, 1H), 2.12 (dt, apparent q, J = 7.33 Hz, 2H), 1.86 (d, J = 0.75 Hz, 3H), 1.36−1.41 (m, 2H), 1.25−1.35 (m, 10H), 0.88 (t, J = 7.10 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 139.4, 132.9, 131.5, 122.9, 121.8, 117.4, 93.9, 84.8, 31.9, 29.5, 29.4, 29.3, 29.1, 28.7, 22.7, 17.1, 14.1. HRMS (ESI) m/z Calculated for $C_{19}H_{25}BrNa^+$ [M + Na^+]: 355.1037, found 355.1044.

*(E)-1-Chloro-4-(3-methyldodec-3-en-1-yn-1-yl)benzene (**3ah**).*



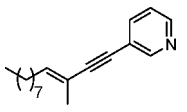
Purified by column chromatography (Eluent: petroleum ether). Isolated as a colorless liquid (81%, 70.3 mg) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, J = 8.31 Hz, 2H), 7.26 (d, J = 8.36 Hz, 2H), 5.97 (t, J = 7.52 Hz, 1H), 2.12 (dt, apparent q, J = 7.29 Hz, 2H), 1.86 (s, 3H), 1.36−1.43 (m, 2H), 1.20−1.35 (m, 10H), 0.88 (t, J = 6.91 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 139.4, 133.6, 132.6, 128.5, 122.3, 117.4, 93.7, 84.7, 31.9, 29.5, 29.34, 29.29, 29.1, 28.6, 22.7, 17.1, 14.1. HRMS (ESI) m/z Calculated for $C_{19}H_{25}ClNa^+$ [M + Na^+]: 311.1542, found 311.1537.

*Methyl (E)-4-(3-methyldodec-3-en-1-yn-1-yl)benzoate (**3ai**).*



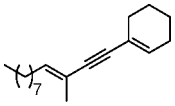
Purified by column chromatography (Eluent: 0−10% EtOAc in petroleum ether). Isolated as a yellow liquid (67%, 62.7 mg) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.49 Hz, 2H), 7.47 (d, J = 8.28 Hz, 2H), 6.01 (t, J = 7.49 Hz, 1H), 3.91 (s, 3H), 2.14 (dt, apparent q, J = 7.28 Hz, 2H), 1.88 (s, 3H), 1.24−1.43 (m, 12H), 0.89 (t, J = 6.99 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 166.6, 140.1, 131.3, 129.4, 128.9, 128.7, 117.3, 95.9, 85.2, 52.1, 31.9, 29.5, 29.34, 29.28, 29.0, 28.7, 22.7, 17.1, 14.1. HRMS (ESI) m/z Calculated for $C_{21}H_{28}O_2Na^+$ [M + Na^+]: 335.1987, found 335.1981.

*(E)-3-(3-Methyldodec-3-en-1-yn-1-yl)pyridine (**3aj**).*



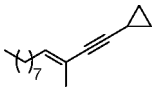
Purified by column chromatography (Eluent: 10% EtOAc in petroleum ether). Isolated as a brown liquid (72%, 55.1 mg) ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29−8.88 (m, 2H) 7.69 (d, J = 7.84 Hz, 1H), 7.18−7.29 (m, 1H), 6.01 (t, J = 7.43 Hz, 1H), 2.14 (dt, apparent q, J = 7.26 Hz, 2H), 1.88 (s, 3H), 1.21−1.46 (m, 12H), 0.89 (t, J = 7.01 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 152.1, 148.0, 140.1, 138.2, 122.9, 121.0, 117.2, 96.0, 82.4, 31.9, 29.5, 29.32, 29.27, 29.0, 28.6, 22.7, 17.0, 14.1. HRMS (ESI) m/z Calculated for $C_{18}H_{25}NNa^+$ [M + Na^+]: 278.1885, found 278.1892.

*(E)-1-(3-Methyldodec-3-en-1-yn-1-yl)cyclohex-1-ene (**3ak**).*



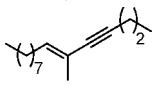
Purified by column chromatography (Eluent: petroleum ether). Isolated as a colorless liquid (70%, 54.2 mg) ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04−6.10 (m, 1H), 5.82 (t, J = 7.45 Hz, 1H), 2.02−2.18 (m, 6H), 1.79 (s, 3H), 1.53−1.68 (m, 4H), 1.19−1.41 (m, 12H), 0.88 (t, J = 6.97 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 137.7, 133.9, 120.9, 117.7, 90.0, 87.6, 31.9, 29.5, 29.4, 29.31, 29.28, 29.1, 28.5, 25.7, 22.7, 22.4, 21.6, 17.3, 14.1. HRMS (ESI) m/z Calculated for $C_{19}H_{30}Na^+$ [M + Na^+]: 281.2245, found 281.2242

*(E)-(3-Methyldodec-3-en-1-yn-1-yl)cyclopropane (**3al**).*



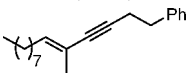
Purified by column chromatography (Eluent: petroleum ether). Isolated as a colorless liquid (70%, 45.8 mg) ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (t, J = 7.42 Hz, 1H), 2.03 (dt, apparent q, J = 7.14 Hz, 2H), 1.73 (s, 3H), 1.20−1.38 (m, 13H), 0.88 (t, J = 6.99 Hz, 3H), 0.73−0.80 (m, 2H), 0.66−0.70 (m, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 137.1, 117.7, 89.3, 79.0, 31.9, 29.5, 29.29, 29.27, 29.1, 28.4, 22.7, 17.4, 14.1, 8.4, 0.0. HRMS (ESI) m/z Calculated for $C_{16}H_{26}Na^+$ [M + Na^+]: 241.1932, found 241.1936

*(E)-6-Methylpentadec-6-en-4-yne (**3am**).*



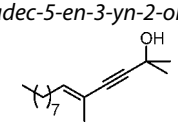
Purified by column chromatography (Eluent: petroleum ether). Isolated as a yellow liquid (65%, 42.9 mg) ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (t, J = 7.41 Hz, 1H), 2.26 (t, J = 7.08 Hz, 2H), 2.04 (dt, apparent q, J = 7.13 Hz, 2H), 1.76 (s, 3H), 1.49−1.60 (m, 2H), 1.23−1.37 (m, 12H), 0.99 (t, J = 7.37 Hz, 3H), 0.88 (t, J = 7.00 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 136.8, 117.9, 86.2, 83.8, 31.9, 29.5, 29.32, 29.27, 29.2, 28.4, 22.7, 22.4, 21.3, 17.5, 14.1, 13.5. HRMS (ESI) m/z Calculated for $C_{16}H_{28}Na^+$ [M + Na^+]: 243.2089, found 243.2087.

*(E)-(5-Methyltetradec-5-en-3-yn-1-yl)benzene (**3an**).*



Purified by column chromatography (Eluent: petroleum ether). Isolated as a colorless liquid (63%, 53.3 mg) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.32 (m, 2H), 7.18−7.24 (m, 3H), 5.76 (t, J = 7.42 Hz, 1H), 2.84 (t, J = 7.66 Hz, 2H), 2.57 (t, J = 7.60 Hz, 2H), 2.04 (dt, apparent q, J = 7.17 Hz, 2H), 1.74 (s, 3H), 1.23−1.38 (m, 12H), 0.88 (t, J = 7.04 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 140.9, 137.2, 128.5, 128.3, 126.2, 117.7, 85.5, 84.4, 35.5, 31.9, 29.5, 29.32, 29.30, 29.1, 28.4, 22.7, 21.6, 17.4, 14.1. HRMS (ESI) m/z Calculated for $C_{21}H_{30}Na^+$ [M + Na^+]: 305.2245, found 305.2249.

*(E)-2,5-Dimethyltetradec-5-en-3-yn-2-ol (**3ao**).*



Purified by column chromatography (Eluent: 10% EtOAc in petroleum ether). Isolated as a colorless liquid (56%, 39.6 mg) ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (t, J = 7.50 Hz, 1H), 2.06 (dt, apparent q, J = 7.30 Hz, 2H), 1.76 (s, 3H), 1.53 (s, 6H), 1.32−1.37 (m, 2H), 1.29−1.31 (m, 10H), 0.88 (t, J = 7.04 Hz, 3H). ^{13}C{^{1}H}

https://doi.org/10.1021/acs.joc.1c02732
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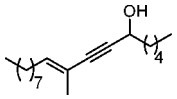
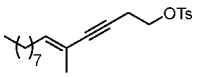
NMR (125 MHz, $CDCl_3$) δ 138.5, 116.9, 90.1, 85.2, 65.5, 31.9, 31.6, 30.9, 29.4, 29.29, 29.25, 29.0, 28.4, 22.6, 17.2, 14.1. HRMS (ESI) m/z Calculated for $C_{16}H_{28}ONa^+$ [M + Na^+]: 259.2038, found 259.2045.

*(E)-9-Methyloctadec-9-en-7-yn-6-ol (**3ap**).*



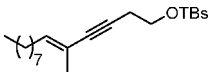
Purified by column chromatography (Eluent: 10% EtOAc in petroleum ether). Isolated as a yellow liquid (55%, 45.0 mg) ^1H NMR (400 MHz, $CDCl_3$) δ 5.85 (t, J = 7.42 Hz, 1H), 4.47 (m, 1H), 2.06 (dt, apparent q, J = 7.23 Hz, 2H), 1.93 (d, J = 5.33 Hz, 1H), 1.77 (s, 3H), 1.66−1.74 (m, 2H), 1.41−1.51 (m, 2H), 1.22−1.40 (m, 16H), 0.85−0.93 (m, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.8, 117.0, 88.0, 86.5, 63.0, 38.0, 31.9, 31.5, 29.5, 29.30, 29.27, 29.0, 28.4, 24.9, 22.7, 22.6, 17.1, 14.1, 14.0. HRMS (ESI) m/z Calculated for $C_{19}H_{34}ONa^+$ [M + Na^+]: 301.2507, found 301.2510.

*(E)-5-Methyltetradec-5-en-3-yn-1-yl 4-methylbenzenesulfonate (**3aq**).*



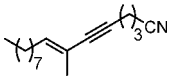
Purified by column chromatography (Eluent: 10% EtOAc in petroleum ether). Isolated as a colorless liquid (60%, 67.7 mg) ^1H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 8.04 Hz, 2H), 7.34 (d, J = 8.04 Hz, 2H), 5.75 (t, J = 7.49 Hz, 1H), 4.09 (t, J = 7.31 Hz, 2H), 2.66 (t, J = 7.17 Hz, 2H), 2.45 (s, 3H), 2.04 (dt, apparent q, J = 7.24 Hz, 2H), 1.70 (s, 3H), 1.23−1.37 (m, 12H), 0.88 (t, J = 6.74 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 144.8, 138.3, 133.0, 129.9, 128.0, 117.1, 85.9, 79.6, 68.0, 31.9, 29.5, 29.29, 29.26, 29.0, 28.4, 22.7, 21.6, 20.2, 17.1, 14.1. HRMS (ESI) m/z Calculated for $C_{22}H_{32}O_3SNa^+$ [M + Na^+]: 399.1970, found 399.1979.

*(E)-tert-Butyldimethyl((5-methyltetradec-5-en-3-yn-1-yl)oxy)-silane (**3ar**).*



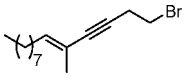
Purified by column chromatography (Eluent: 0−5% EtOAc in petroleum ether). Isolated as a colorless liquid (75%, 75.6 mg) ^1H NMR (400 MHz, $CDCl_3$) 5.77 (t, J = 7.43 Hz, 1H), 3.73 (t J = 7.24 Hz, 2H), 2.50 (t, J = 7.20 Hz, 2H), 2.04 (dt, apparent q, J = 7.14 Hz, 2H), 1.74 (s, 3H), 1.21−1.39 (m, 12H), 0.85−0.93 (m, 12H), 0.08 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 137.3, 117.6, 84.7, 82.9, 62.2, 31.9, 29.5, 29.3, 29.1, 28.4, 25.9, 23.7, 22.7, 18.4, 17.4, 14.1, −5.3. HRMS (ESI) m/z Calculated for $C_{21}H_{40}OSiNa^+$ [M + Na^+]: 359.2746, found 359.2739.

*(E)-7-Methylhexadec-7-en-5-ynenitrile (**3as**).*



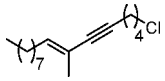
Purified by column chromatography (Eluent: 0−10% EtOAc in petroleum ether). Isolated as a colorless liquid (54%, 39.7 mg) ^1H NMR (500 MHz, $CDCl_3$) δ 5.78 (t, J = 7.44 Hz, 1H), 2.50 (t, J = 7.25 Hz, 2H), 2.47 (t, J = 6.69 Hz, 2H), 2.05 (dt, apparent q, J = 7.26 Hz, 2H), 1.88 (tt, J_1 = 6.98 Hz, J_2 = 6.98 Hz, 2H), 1.75 (s, 3H), 1.23−1.37 (m, 12H), 0.88 (t, J = 7.11 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 137.9, 119.3, 117.3, 85.6, 82.9, 31.9, 29.5, 29.31, 29.27, 29.1, 28.4, 24.8, 22.7, 18.4, 17.3, 16.2, 14.1. HRMS (ESI) m/z Calculated for $C_{17}H_{27}NNa^+$ [M + Na^+]: 268.2041, found 268.2036.

*(E)-1-Bromo-5-methyltetradec-5-en-3-yne (**3at**).*



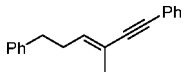
Purified by column chromatography (Eluent: petroleum ether). Isolated as a colorless liquid (64%, 54.7 mg) ^1H NMR (500 MHz, $CDCl_3$) δ 5.82 (t, J = 7.47 Hz, 1H), 3.44 (t, J = 7.43 Hz, 2H), 2.85 (t, J = 7.44 Hz, 2H), 2.05 (dt, apparent q, J = 7.33 Hz, 2H), 1.76 (s, 3H), 1.23−1.37 (m, 12H), 0.88 (t, J = 7.09 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 138.2, 117.3, 85.6, 82.6, 31.9, 29.8, 29.5, 29.30, 29.25, 29.0, 28.4, 23.8, 22.7, 17.2, 14.1. HRMS (ESI) m/z Calculated for $C_{15}H_{25}BrNa^+$ [M + Na^+]: 307.1037, found 307.1041.

*(E)-1-Chloro-7-methylhexadec-7-en-5-yne (**3au**).*



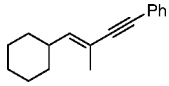
Purified by column chromatography (Eluent: petroleum ether). Isolated as a colorless liquid (64%, 51.5 mg) ^1H NMR (400 MHz, $CDCl_3$) δ 5.76 (t, J = 7.31 Hz, 1H), 3.58 (t, J = 6.62 Hz, 2H), 2.34 (t, J = 6.97 Hz, 2H), 2.05 (dt, apparent q, J = 7.28 Hz, 2H), 1.86−1.95 (m, 2H), 1.75 (s, 3H), 1.63−1.72 (m, 2H), 1.20−1.40 (m, 12H), 0.88 (t, J = 7.00 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 137.2, 117.7, 85.2, 84.3, 44.6, 31.9, 31.6, 29.5, 29.32, 29.28, 29.1, 28.4, 26.1, 22.7, 18.6, 17.5, 14.1. HRMS (ESI) m/z Calculated for $C_{17}H_{29}ClNa^+$ [M + Na^+]: 291.1855, found 291.1862.

*(E)-(3-Methylhex-3-en-1-yne-1,6-diyl)dibenzene (**3ba**).*



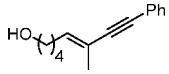
Purified by column chromatography (Eluent: petroleum ether). Isolated as a yellow liquid (70%, 51.7 mg) ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.44 (m, 2H), 7.25−7.32 (m, 5H), 7.17−7.22 (m, 3H), 6.00 (t, J = 7.44 Hz, 1H), 2.71 (t, J = 7.44 Hz, 2H), 2.45 (dt, apparent q, J = 7.72 Hz, 2H), 1.82 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 141.6, 137.3, 131.5, 128.5, 128.4, 128.3, 127.8, 126.0, 123.7, 118.5, 92.5, 86.2, 35.3, 30.5, 17.3. HRMS (ESI) m/z Calculated for $C_{19}H_{18}Na^+$ [M + Na^+]: 269.1306, found 269.1304.

*(E)-(4-Cyclohexyl-3-methylbut-3-en-1-yn-1-yl)benzene (**3ca**).*



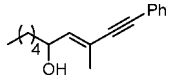
Purified by column chromatography (Eluent: petroleum ether). Isolated as a colorless liquid (65%, 43.7 mg) ^1H NMR (500 MHz, $CDCl_3$) δ 7.39−7.44 (m, 2H), 7.25−7.32 (m, 3H), 5.81 (d, J = 9.42 Hz, 1H), 2.24−2.33 (m, 1H), 1.89 (s, 3H), 1.70−1.76 (m, 2H), 1.62−1.69 (m, 3H), 1.24−1.35 (m, 2H), 1.16−1.24 (m, 1H), 1.05−1.16 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.2, 131.4, 128.2, 127.7, 123.8, 116.0, 92.8, 85.8, 37.7, 32.5, 26.0, 25.8, 17.3. HRMS (ESI) m/z Calculated for $C_{17}H_{20}Na^+$ [M + Na^+]: 247.1463, found 247.1466.

*(E)-6-Methyl-8-phenyloct-5-en-7-yn-1-ol (**3da**).*



Purified by column chromatography (Eluent: 10% EtOAc in petroleum ether). Isolated as a colorless liquid (81%, 52.0 mg) ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.45 (m, 2H), 7.24−7.33 (m, 3H), 5.96 (t, J = 7.49 Hz, 1H), 3.65 (t, J = 6.64 Hz, 2H), 2.15 (dt, apparent q, J = 7.01 Hz, 2H), 1.87 (s, 3H), 1.59 (m, 2H), 1.34−1.49 (m, 4H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.4, 131.4, 128.2, 127.7, 123.7, 117.9, 92.6, 85.9, 62.9, 32.6, 28.9, 28.5, 25.4, 17.2. HRMS (ESI) m/z Calculated for $C_{15}H_{18}ONa^+$ [M + Na^+]: 237.1255, found 237.1252.

*(E)-3-Methyl-1-phenyldec-3-en-1-yn-5-ol (**3ea**).*



Purified by column chromatography (Eluent: 10% EtOAc in petroleum ether). Isolated as a yellow liquid (52%, 37.8 mg) ^1H NMR (500 MHz, $CDCl_3$) δ 7.41−7.45 (m, 2H), 7.28−7.32 (m, 3H), 5.90 (dq, J_1 = 8.87 Hz, J_2 = 1.50 Hz, 1H), 4.44 (m, 1H), 1.94 (d, J = 1.41 Hz, 3H), 1.61−1.68 (m, 1H), 1.57 (s, 1H), 1.45−1.54 (m, 1H), 1.24−1.43 (m, 6H), 0.90 (t, J = 6.80 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 139.8, 131.5, 128.3, 128.1, 123.3, 120.1, 91.6, 87.6, 68.5, 37.2, 31.8, 24.9, 22.6, 17.8, 14.0. HRMS (ESI) m/z Calculated for $C_{17}H_{22}ONa^+$ [M + Na^+]: 265.1568, found 265.1574.

https://doi.org/10.1021/acs.joc.1c02732
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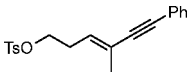
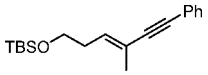
*(E)-4-Methyl-6-phenylhex-3-en-5-yn-1-yl 4-methylbenzenesulfonate (**3fa**).*



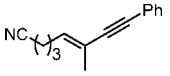
Purified by column chromatography (Eluent: 10% EtOAc in petroleum ether). Isolated as a colorless liquid (83%, 84.7 mg) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J = 8.26 Hz, 2H), 7.39−7.42 (m, 2H), 7.34 (d, J = 8.11 Hz, 2H), 7.28−7.32 (m, 3H), 5.75 (t, J = 7.40 Hz, 1H), 4.06 (t, J = 6.80 Hz, 2H), 2.49 (dt, apparent q, J = 6.91 Hz, 2H), 2.42 (s, 3H), 1.83 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 144.9, 133.0, 131.5, 130.9, 129.9, 128.3, 128.1, 127.9, 123.3, 121.5, 91.6, 87.1, 68.9, 28.4, 21.6, 17.4. HRMS (ESI) m/z Calculated for $C_{20}H_{20}O_3SNa^+$ [M + Na^+]: 363.1031, found 363.1039.

*(E)-tert-Butyldimethyl((4-methyl-6-phenylhex-3-en-5-yn-1-yl)-oxy)silane (**3ga**).*



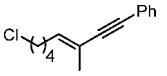
Purified by column chromatography (Eluent: 0−5% EtOAc in petroleum ether). Isolated as a brown liquid (85%, 76.5 mg) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.45 (m, 2H), 7.25−7.32 (m, 3H), 5.95 (t, J = 7.41 Hz, 1H), 3.66 (t, J = 6.82 Hz, 2H), 2.37 (dt, apparent q, J = 7.00 Hz, 2H), 1.89 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 134.4, 131.5, 128.2, 127.8, 123.7, 119.5, 92.4, 86.2, 62.2, 32.5, 26.0, 18.4, 17.4, −5.3. HRMS (ESI) m/z Calculated for $C_{19}H_{28}OSiNa^+$ [M + Na^+]: 323.1807, found 323.1810.

*(E)-6-Methyl-8-phenyloct-5-en-7-ynenitrile (**3ha**).*



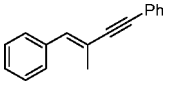
Purified by column chromatography (Eluent: 10% EtOAc in petroleum ether). Isolated as a brown liquid (74%, 46.4 mg) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.45 (m, 2H), 7.27−7.33 (m, 3H), 5.86 (t, J = 7.56 Hz, 1H), 2.36 (t, J = 7.16 Hz, 2H), 2.31 (dt, apparent q, J = 6.91 Hz, 2H), 1.91 (s, 3H), 1.77 (tt, J_1 = 7.18 Hz, J_2 = 7.18 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 135.0, 131.5, 128.3, 128.0, 123.4, 120.2, 119.5, 91.9, 86.8, 27.2, 24.9, 17.4, 16.6. HRMS (ESI) m/z Calculated for $C_{15}H_{15}NNa^+$ [M + Na^+]: 232.1102, found 232.1107.

*(E)-(8-Chloro-3-methyloct-3-en-1-yn-1-yl)benzene (**3ia**).*



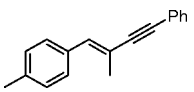
Purified by column chromatography (Eluent: petroleum ether). Isolated as a yellow liquid (77%, 53.6 mg) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.45, (m, 2H), 7.26−7.34 (m, 3H), 5.94 (t, J = 7.48 Hz, 1H), 3.55 (t, J = 6.64 Hz, 2H), 2.18 (dt, apparent q, J = 7.38 Hz, 2H), 1.88 (s, 3H), 1.77−1.86 (m, 2H), 1.52−1.62 (m, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 137.6, 131.4, 128.2, 127.8, 123.6, 118.5, 92.4, 86.1, 44.8, 32.1, 27.7, 26.3, 17.3. HRMS (ESI) m/z Calculated for $C_{15}H_{17}ClNa^+$ [M + Na^+]: 255.0916, found 255.0911.

*(E)-(2-Methylbut-1-en-3-yne-1,4-diyl)dibenzene (**3ja**).*



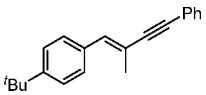
Purified by column chromatography (Eluent: in petroleum ether). Isolated as a yellow solid (70%, 45.8 mg) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46−7.50 (m, 2H), 7.29−7.38 (m, 7H), 7.23−7.27 (m, 1H), 6.94 (s, 1H), 2.16 (d, J = 1.40 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 136.9, 136.1, 131.6, 129.0, 128.33, 128.31, 128.1, 127.2, 123.5, 119.9, 93.3, 88.5, 19.3. HRMS (ESI) m/z Calculated for $C_{17}H_{14}Na^+$ [M + Na^+]: 241.0993, found 241.0997. Characterization data matched with those reported in the literature.[16]

*(E)-1-Methyl-4-(2-methyl-4-phenylbut-1-en-3-yn-1-yl)benzene (**3ka**).*



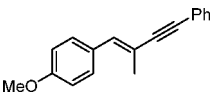
Purified by column chromatography (Eluent: petroleum ether). Isolated as a yellow solid (72%, 50.1 mg) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.49 (m, 2H), 7.27−7.34 (m, 3H), 7.22 (d, J = 8.06 Hz, 2H), 7.16 (d, J = 8.09 Hz, 2H), 6.91 (s, 1H), 2.35 (s, 3H), 2.15 (d, J = 1.35 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 137.1, 136.2, 134.1, 131.5, 129.1, 129.0, 128.3, 128.0, 123.6, 119.0, 93.6, 88.2, 21.3, 19.4. HRMS (ESI) m/z Calculated for $C_{18}H_{16}Na^+$ [M + Na^+]: 255.1150, found 255.1147.

*(E)-1-(tert-Butyl)-4-(2-methyl-4-phenylbut-1-en-3-yn-1-yl)-benzene (**3la**).*



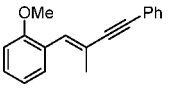
Purified by column chromatography (Eluent: petroleum ether). Isolated as a white solid (80%, 65.8 mg) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.50 (m, 2H), 7.38 (d, J = 8.36 Hz, 2H), 7.23−7.35 (m, 5H), 6.92 (s, 1H), 2.18 (d, J = 1.20 Hz, 3H), 1.33 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 150.3, 136.0, 134.1, 131.5, 128.8, 128.3, 128.0, 125.3, 123.6, 119.1, 93.6, 88.2, 34.6, 31.3, 19.4. HRMS (ESI) m/z Calculated for $C_{21}H_{22}Na^+$ [M + Na^+]: 297.1619, found 297.1615.

*(E)-1-Methoxy-4-(2-methyl-4-phenylbut-1-en-3-yn-1-yl)benzene (**3ma**).*



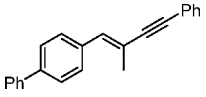
Purified by column chromatography (Eluent: petroleum ether). Isolated as a yellow solid (89%, 65.5 mg) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45−7.49 (m, 2H), 7.25−7.35 (m, 5H), 6.86−6.93 (m, 3H), 3.82 (s, 3H), 2.16 (d, J = 1.24 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 158.8, 135.8, 131.5, 130.4, 129.6, 128.3, 127.9, 123.7, 117.9, 113.8, 93.7, 87.9, 55.3, 19.3. HRMS (ESI) m/z Calculated for $C_{18}H_{16}ONa^+$ [M + Na^+]: 271.1099, found 271.1096.

*(E)-1-Methoxy-2-(2-methyl-4-phenylbut-1-en-3-yn-1-yl)benzene (**3na**).*



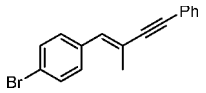
Purified by column chromatography (Eluent: petroleum ether). Isolated as a yellow liquid (86%, 64.0 mg) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46−7.49, (m, 2H), 7.29−7.34 (m, 3H), 7.24−7.29 (m, 2H), 7.06 (s, 1H), 6.95 (t, J = 7.25 Hz, 1H), 6.89 (d, J = 8.20 Hz, 1H), 3.85 (s, 3H), 2.10 (d, J = 1.45 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 157.1, 131.7, 131.6, 130.1, 128.8, 128.3, 127.9, 125.7, 123.7, 120.1, 119.7, 110.5, 93.3, 88.2, 55.5,19.3. HRMS (ESI) m/z Calculated for $C_{18}H_{16}ONa^+$ [M + Na^+]: 271.1099, found 271.1094.

*(E)-4-(2-Methyl-4-phenylbut-1-en-3-yn-1-yl)-1,1′-biphenyl (**3oa**).*



Purified by column chromatography (Eluent: petroleum ether). Isolated as a white solid (81%, 71.4 mg) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.63 (m, 4H), 7.39−7.51 (m, 6H), 7.30−7.37 (m, 4H), 6.97 (s, 1H), 2.22 (d, J = 1.32 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 140.6, 139.9, 135.9, 135.7, 131.6, 129.5, 128.9, 128.4, 128.1, 127.4, 127.02, 126.99, 123.5, 120.0, 93.5, 88.7, 19.5. HRMS (ESI) m/z Calculated for $C_{23}H_{18}Na^+$ [M + Na^+]: 317.1306, found 317.1314.

*(E)-1-Bromo-4-(2-methyl-4-phenylbut-1-en-3-yn-1-yl)benzene (**3pa**).*



Purified by column chromatography (Eluent: petroleum ether). Isolated as a white solid (78%, 69.5 mg) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.51 (m, 4H), 7.28−7.36 (m, 3H), 7.13−7.20 (m,

https://doi.org/10.1021/acs.joc.1c02732
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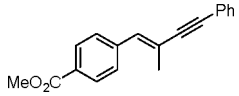
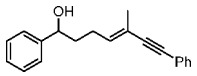
2H), 6.84 (s, 1H), 2.12 (d, J = 1.77 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 135.7, 134.8, 131.6, 131.5, 130.6, 128.4, 128.2, 123.3, 121.2, 120.7, 93.0, 89.0, 19.4. HRMS (ESI) m/z Calculated for $C_{17}H_{13}BrNa^+$ [M + Na^+]: 319.0098, found 319.0092.

*Methyl (E)-4-(2-methyl-4-phenylbut-1-en-3-yn-1-yl)benzoate (**3qa**).*



Purified by column chromatography (Eluent: 0−10% EtOAc in petroleum ether). Isolated as a white solid (65%, 53.2 mg) ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.24 Hz, 2H), 7.46−7.51 (m, 2H), 7.38 (d, J = 8.24 Hz, 2H), 7.31−7.36 (m, 3H), 6.95 (s, 1H), 3.92 (s, 3H), 2.18 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.8, 141.4, 135.0, 131.6, 129.6, 128.9, 128.6, 128.4, 128.3, 123.2, 122.2, 92.9, 89.5, 52.1, 19.5. HRMS (ESI) m/z Calculated for $C_{19}H_{16}O_2Na^+$ [M + Na^+]: 299.1048, found 299.1056.

*(E)-5-Methyl-1,7-diphenylhept-4-en-6-yn-1-ol (**3ra**).*



Purified by column chromatography (Eluent: 10% EtOAc in petroleum ether). Isolated as a colorless liquid (80%, 66.2 mg) ^1H NMR (500 MHz, $CDCl_3$) δ 7.40−7.45 (m, 2H), 7.33−7.38 (m, 4H), 7.25−7.31 (m, 4H), 5.91 (t, J = 7.41 Hz, 1H), 4.71 (dd, J_1 = 7.51 Hz, J_2 = 5.66 Hz, 1H), 2.23 (dt, apparent q, J = 7.51 Hz, 2H), 1.87−1.98 (m, 1H), 1.76−1.86 (m, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 144.5, 137.5, 131.4, 128.5, 128.2, 127.8, 127.7, 125.9, 123.7, 118.5, 92.4, 86.1, 74.0, 38.1, 25.0, 17.3. HRMS (ESI) m/z Calculated for $C_{20}H_{20}ONa^+$ [M + Na^+]: 299.1412, found 299.1416.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c02732.

Copies of the NMR spectra of all products and NOE spectra of **3ba** (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Rudi, A.; Schleyer, M.; Kashman, Y. Clathculins A and B, Two Novel Nitrogen-Containing Metabolites from the Sponge Clathrina aff. Reticulum. *J. Nat. Prod.* **2000**, *63*, 1434−1436. (b) Nicolaou, K. C.; Dai, W.-M.; Tsay, S.-C.; Estevez, V. A.; Wrasidlo, W. Designed Enediynes: A New Class of DNA-Cleaving Molecules with Potent and Selective Anticancer Activity. *Science* **1992**, *256*, 1172−1178. (c) Roulland, E.; Solanki, H.; Calabro, K.; Zubia, M.; Genta-Jouve, G.; Thomas, O. P. Stereochemical Study of Puna'auic Acid. an Allenic Fatty Acid from the Eastern Indo-Pacific Cyanobacterium Pseudanabaena sp. *Org. Lett.* **2018**, *20*, 2311−2314. (d) Kim, H.; Lee, H.; Lee, D.; Kim, S.; Kim, D. Asymmetric Total Syntheses of (+)-3-(Z)- Laureatin and (+)-3-(Z)-Isolaureatin by "Lone Pair-Lone Pair Interaction-Controlled" Isomerization. *J. Am. Chem. Soc.* **2007**, *129*, 2269−2274. (e) Yamano, Y.; Chary, M. V.; Wada, A. Stereoselective Total Synthesis of the Acetylenic Carotenoids Alloxanthin and Triophaxanthin. *Org. Biomol. Chem.* **2012**, *10*, 4103−4108. (f) Commeiras, L.; Thibonnet, J.; Parrain, J.-L. First Total Synthesis of (−)-caulerpenynol. *Org. Biomol. Chem.* **2009**, *7*, 425−427.

(2) (a) Saito, S.; Yamamoto, Y. Recent Advances in the Transition-Metal-Catalyzed Regioselective Approaches to Polysubstituted Benzene Derivatives. *Chem. Rev.* **2000**, *100*, 2901−2916. (b) Wessig, P.; Müller, G. The Dehydro-Diels-Alder Reaction. *Chem. Rev.* **2008**, *108*, 2051−2063. (c) Zhou, X.; Huang, C.; Zeng, Y.; Xiong, J.; Xiao, Y.; Zhang, J. Silver-Catalysed Tandem Hydroamination and Cyclization of 2-Trifluoromethyl-1.3-enynes with Primary Amines: Modular Entry to 4-Trifluoromethyl-3-pyrrolines. *Chem. Commun.* **2017**, *53*, 1084−1087. (d) Meng, F.-F.; Xie, J.-H.; Xu, Y.-H.; Loh, T.-P. Catalytically Asymmertic Synthesis of 1,3-Bis(silyl)propenes via Copper-Catalyzed Double Proto-Silylations of Polar Enynes. *ACS Catal.* **2018**, *8*, 5306−5312. (e) Dherbassy, Q.; Manna, S.; Talbot, F. J. T.; Prasitwatcharakorn, W.; Perry, G. J. P.; Procter, D. J. Copper-Catalyzed Functionalization of Enynes. *Chem. Sci.* **2020**, *11*, 11380−11393.

(3) (a) Liu, M.; Tang, T.; Apolinar, O.; Matsuura, R.; Busacca, C. A.; Qu, B.; Fandrick, D. R.; Zatolochnaya, O. V.; Senanayake, C. H.; Song, J. J.; Engle, K. M. Atom-Economical Cross-Coupling of Internal and Terminal Alkynes to Access 1,3-Enynes. *J. Am. Chem. Soc.* **2021**, *143*, 3881−3888. (b) Lv, Y.; Wang, Y.; Pu, W.; Zhu, X.; Wu, N.; Zhao, Y. Copper-Catalyzed 1,1-Alkynylalkylation of Alkynes: Access Toward Conjugated Enynes. *Org. Chem. Front.* **2020**, *7*, 2752−2756. (c) Jeon, H.; Ko, S.-B.; Lee, S. Palladium-Catalyzed Decarboxylative Gem-Selective Addition of Alkynoic Acids to Terminal Alkynes. *Org. Chem. Front.* **2020**, *7*, 3918−3925. (d) Zhou, Y.; Zhang, Y.; Wang, J. Recent Advances in TransitionMetal-Catalyzed Synthesis of Conjugated Enynes. *Org. Biomol. Chem.* **2016**, *14*, 6638−6650.

(4) (a) Negishi, E.; Anastasia, L. Palladium-Catalyzed Alkynylation. *Chem. Rev.* **2003**, *103*, 1979−2018. (b) Fujino, T.; Hinoue, T.; Usuki, Y.; Satoh, T. Synthesis of Difluorinated Enynes through Sonogashira-Type Coupling. *Org. Lett.* **2016**, *18*, 5688−5691.

(5) Deussen, H.-J.; Jeppesen, L.; Schärer, N.; Junager, F.; Bentzen, B.; Weber, B.; Weil, V.; Mozer, S. J.; Sauerberg, P. Process Development and Scale-Up of the PPAR Agonist NNC 61−4655. *Org. Process Res. Dev.* **2004**, *8*, 363−371.

(6) Yan, W.; Ye, X.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. 1.2.3-Triazole: Unique Ligand in Promoting Iron-Catalyzed Propargyl Alcohol Dehydration. *Org. Lett.* **2012**, *14*, 2358−2361.

(7) (a) Trost, B. M.; Masters, J. T. Transition Metal-Catalyzed Couplings of Alkynes to 1.3-Enynes: Modern Methods and Synthetic Applications. *Chem. Soc. Rev.* **2016**, *45*, 2212−2238. (b) Grenier-Petel, J.-C.; Collins, S. K. Photochemical Cobalt-Catalyzed Hydroalkynylation To Form 1,3-Enynes. *ACS Catal.* **2019**, *9*, 3213−3218.

(c) Liang, Q.; Hayashi, K.; Song, D. Catalytic Alkyne Dimerization without Noble Metals. *ACS Catal.* **2020**, *10*, 4895−4905.
(8) Nishimura, T.; Guo, X.-X.; Hayashi, T. Rhodium-Catalyzed Asymmetric Addition of Terminal Alkynes to Diarylphosphinylallenes. *Chem. - Asian J.* **2008**, *3*, 1505−1510.
(9) Sawano, T.; Ou, K.; Nishimura, T.; Hayashi, T. Cobalt-Catalyzed Asymmetric Addition of Silylacetylenes to 1,1- Disubstituted Allenes. *J. Org. Chem.* **2013**, *78*, 8986−8993.
(10) Yamaguchi, M.; Kido, Y.; Omata, K.; Hirama, M. Synthesis of Exo-enynes by Ruthenium-Catalyzed Cross Coupling Reaction of Hydroxy Allenes and 1-Alkynes. *Synlett* **1995**, *1995*, 1181−1182.
(11) (a) Trost, B. M.; Kottirsch, G. Novel Allene-Acetylene Cross-Condensation Catalyzed by Palladium Complexes. *J. Am. Chem. Soc.* **1990**, *112*, 2816−2818. (b) Rubin, M.; Markov, J.; Chuprakov, S.; Wink, D. J.; Gevorgyan, V. Highly Regiocontrolled Pd-Catalyzed Cross-Coupling Reaction of Terminal Alkynes and Allenylphosphine Oxides. *J. Org. Chem.* **2003**, *68*, 6251−6256. (c) Pradhan, T. R.; Kim, H. W.; Park, J. K. Regiodivergent Synthesis of 1.3- and 1.4-Enynes through Kinetically Favored Hydropalladation and Ligand-Enforced Carbopalladation. *Angew. Chem., Int. Ed.* **2018**, *57*, 9930−9935. (d) Jeanne-Julien, L.; Masson, G.; Kouoi, R.; Regazzetti, A.; Genta-Jouve, G.; Gandon, V.; Roulland, E. Stereoselective Access to (E)-1,3-Enynes through Pd/Cu-Catalyzed Alkyne Hydrocarbation of Allenes. *Org. Lett.* **2019**, *21*, 3136−3141. (e) Bruyere, D.; Grigg, R.; Hinsley, J.; Hussain, R. K.; Korn, S.; Orgaz De La Cierva, C.; Sridharan, V.; Wang, J. Highly regioselective palladium/copper-catalysed cross-coupling reactions of terminal alkynes and allenes. *Tetrahedron Lett.* **2003**, *44*, 8669−8672.
(12) (a) Xie, X.; Ma, S. Palladium-catalyzed asymmetric coupling cyclization of terminal c-allenols with aryl iodides. *Chem. Commun.* **2013**, *49*, 5693−5695. (b) Macsári, I.; Szabó, K. J. Palladium-Catalyzed Cyclization of Allylsilanes with Nucleophilic Displacement of the Silyl Group. *Chem. - Eur. J.* **2001**, *7*, 4097−4106. (c) Caumes, X.; Jeanne-Julien, L.; Khelifi, C.; Gandon, V.; Roulland, E. Diastereoselective synthesis of 2,5-disubstituted-3-hydroxy-tetrahydrofurans through a counterion-directed Tsuji−Trost reaction. *Org. Chem. Front.* **2016**, *3*, 1462−1466.
(13) (a) Amatore, C.; Jutand, A.; M'Barki, M. A. Evidence of the formation of zerovalent palladium from $Pd(OAc)_2$ and triphenylphosphine. *Organometallics* **1992**, *11*, 3009−3013. (b) Amatore, C.; Carré, E.; Jutand, A.; M'Barki, M. A. Rates and Mechanism of the Formation of Zerovalent Palladium Complexes from Mixtures of $Pd(OAc)_2$ and Tertiary Phosphines and Their Reactivity in Oxidative Additions. *Organometallics* **1995**, *14*, 1818−1826.
(14) (a) Villarino, L.; García-Fandiño, R.; López, F.; Mascareñas, J. L. Palladium-Catalyzed Conjugate Addition of Terminal Alkynes to Enones. *Org. Lett.* **2012**, *14*, 2996−2999. (b) Jahier, C.; Zatolochnaya, O. V.; Zvyagintsev, N. V.; Ananikov, V. P.; Gevorgyan, V. General and Selective Head-to-Head Dimerization of Terminal Alkynes Proceeding via Hydropalladation Pathway. *Org. Lett.* **2012**, *14*, 2846−2849. (c) Zatolochnaya, O. V.; Gordeev, E. G.; Jahier, C.; Ananikov, V. P.; Gevorgyan, V. Carboxylate Switch between Hydro- and Carbopalladation Pathways in Regiodivergent Dimerization of Alkynes. *Chem. - Eur. J.* **2014**, *20*, 9578−9588.
(15) (a) Kuang, J.; Ma, S. An Efficient Synthesis of Terminal Allenes from Terminal 1-Alkynes. *J. Org. Chem.* **2009**, *74*, 1763−1765. (b) Wang, Z.; Nicolini, C.; Hervieu, C.; Wong, Y.-F.; Zanoni, G.; Zhang, L. Remote Cooperative Group Strategy Enables Ligands for Accelerative Asymmetric Gold Catalysis. *J. Am. Chem. Soc.* **2017**, *139* (45), 16064−16067.
(16) Mokar, B. D.; Liu, R.-S. Regioselective hydrations of 1-aryl-3-en-1-ynes using gold and platinum catalysts: selective production of 2-en-1-ones and 3-en-1-ones. *Chem. Commun.* **2014**, *50*, 8966−8969.

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