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THREE-COMPONENT COUPLING REACTION OF ENYNES, CARBONYLS, AND ORGANOZINC REAGENTS

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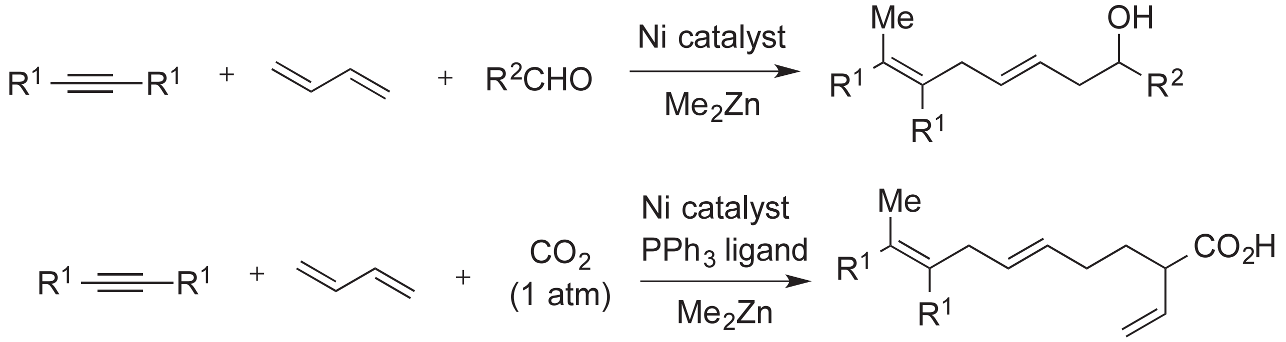
Dedicated to Prof. Dr. Isao Kuwajima on the occasion of his 77th birthday

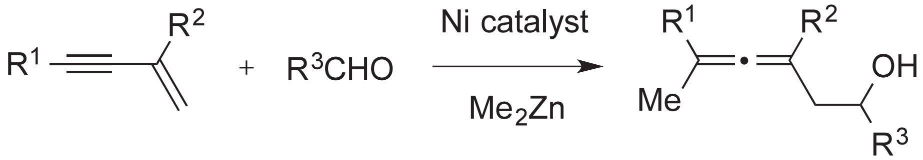
Abstract – A mixture of *t*-butylzinc halide and an aldehyde reacts with enyne to provide homopropargyl alcohol in a 1,2-addition manner. Under carbon dioxide at atmospheric pressure, three components (*t*-butylzinc halide, enyne, and carbon dioxide) combine in a 1:1:1 ratio to give allenyl carboxylic acids in a 1,4-addition manner. These products are useful for the synthesis of heterocyclic compounds such as α,β-unsaturated γ-butyrolactones.

Multi-component coupling is one of the most efficient and convenient methodologies for the construction of important and complicated molecules in modern organic synthesis.[1] Recently, we have developed Ni-catalyzed multi-component coupling of conjugated dienes, alkynes, and aldehydes in the presence of dimethylzinc to afford 3,6-octadienyl alcohols with high regio- and stereoselectivities (Scheme 1).[2] This reaction seems to take place via oxidative coupling of alkynes, conjugated dienes, and aldehydes by means of Ni(0) catalyst. Under similar catalytic conditions, carbon dioxide may be used in the coupling reaction to form 2-vinyl-5*E*,8*Z*-decadienoic acid.[3] In this case, a PPh_3 ligand is indispensable for the coupling reaction via oxidative cyclization of two equivalents of 1,3-butadiene followed by dimerization to form a σ-allyl-π-allylnickel active species. Thus, 1,3-butadiene can provide C4 and C8 carbon units for multi-component coupling reactions.



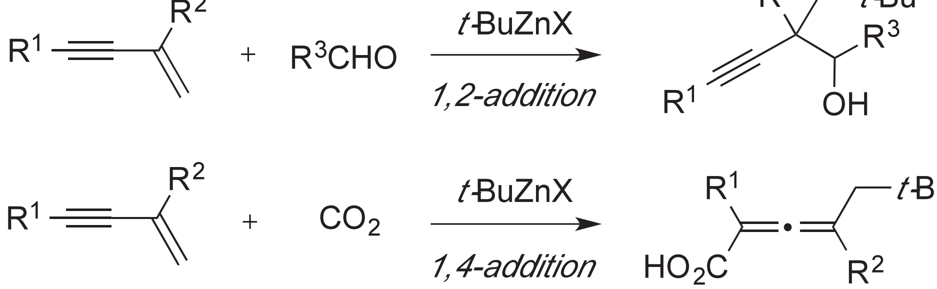
Scheme 1. Ni-Catalyzed three-component coupling of alkyne, conjugated dienes, carbonyls, and Me_2Zn

Conjugated enynes are attractive as a C4 carbon unit for C-C bond formation. In particular, transition-metal-catalyzed coupling of enynes with carbonyls is a significant synthetic method for the construction of unsaturated hydrocarbon skeletons, and it has been reported that allenic alcohols and homopropargyl alcohols are generated through allenyl and propargyl metal species.[4] Recently, we developed a Ni-catalyzed three-component coupling reaction of enyne, aldehyde, and dimethylzinc to form tetrasubstituted allenic alcohols via a propargylnickel intermediate with high regioselectivity (Scheme 2).[5]



Scheme 2. Ni-Catalyzed three-component coupling of enyne, aldehyde, and Me_2Zn

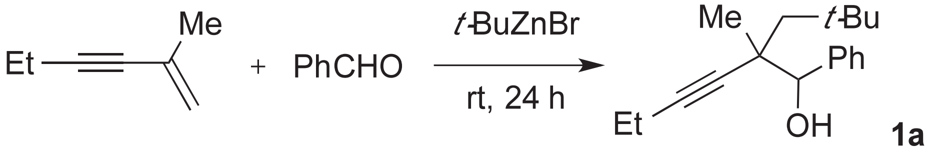
Herein, we disclose that a mixture of *t*-butylzinc halides and aldehydes reacts with enynes in a 1,2-addition manner to provide homopropargyl alcohols. Furthermore, under atmospheric pressure of carbon dioxide, the three components (*t*-butylzinc halide, enyne, and carbon dioxide) combine in a 1:1:1 ratio to give four-substituted allenyl carboxylic acids. It is notable that these coupling reactions require no Ni catalyst, and enynes can serve as a C4 unit to afford homopropargyl alcohols and allenyl carboxylic acids depending on the kinds of electrophile used.



Scheme 3. Three-component coupling of enyne, carbonyls, and *t*-butylzinc reagents

The reaction was undertaken in the presence of 2-methyl-1-hexen-3-yne, benzaldehyde, and *t*-BuZnBr solution at room temperature under a nitrogen atmosphere (Table 1). Among various solvents, THF and CH_2Cl_2 were effective in the coupling reaction to afford homopropargyl alcohol **1a** in high yields (entries 1-7, Table 1).[6] The coupling reactions proceeded with excellent regioselectivity, with the *t*-Bu group adding to the C1 position and the aldehyde adding to the C2 position. Although no transition metal catalyst was required for the reaction to proceed, these stereoselectivities were miserable, at 1.1:1 to 1.6:1, regardless of the type of solvent used. In order to improve the stereoselectivity, we examined the use of various additives, such as phosphines and amines, in the coupling reaction. However, both monodentate and bidentate phosphines impeded the reaction, resulting in a complex mixture of products (entries 8-10, Table 1). Diamines are often utilized to enhance the nucleophilicity of organozinc reagents toward carbonyl electrophiles,[7] nevertheless, our attempts were useless, improving neither yield nor stereoselectivity (entries 11-13, Table 1).

Table 1. Three-component coupling reaction of enyne, PhCHO, and *t*-BuZnBr[a]

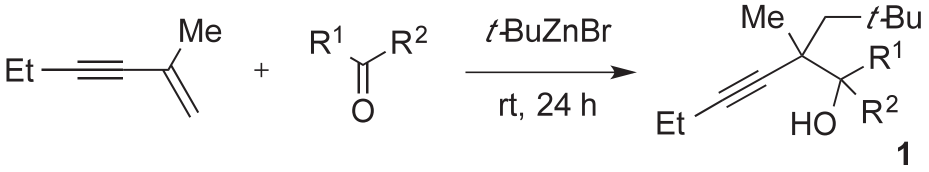


Entry	Additives	Solvent	Yield of **1a** (%) [ratio]
1	none	DMSO	87 [1.2:1]
2	none	DMA	63 [1.2:1]
3	none	Et_2O	73 [1.1:1]
4	none	CH_2Cl_2	96 [1.4:1]
5	none	THF	96 [1.6:1]
6	none	benzene	57[1.3:1]
7	none	*n*-hexane	96 [1.3:1]
8	PPh_3	THF	complex mixture
9	dppf	THF	complex mixture
10	Xantphos	THF	complex mixture
11	triethylamine	THF	46 [1.2:1]
12	TMEDA	THF	26 [1.4:1]
13	DBU	THF	58 [1.3:1]

[a] The reaction was undertaken in the presence of enyne (1 mmol), PhCHO (1 mmol), *t*-BuZnBr (1.2 mmol of 0.5 M THF solution), additives (2.4 mmol) in solvent (3 mL) at room temperature under nitrogen atmosphere.

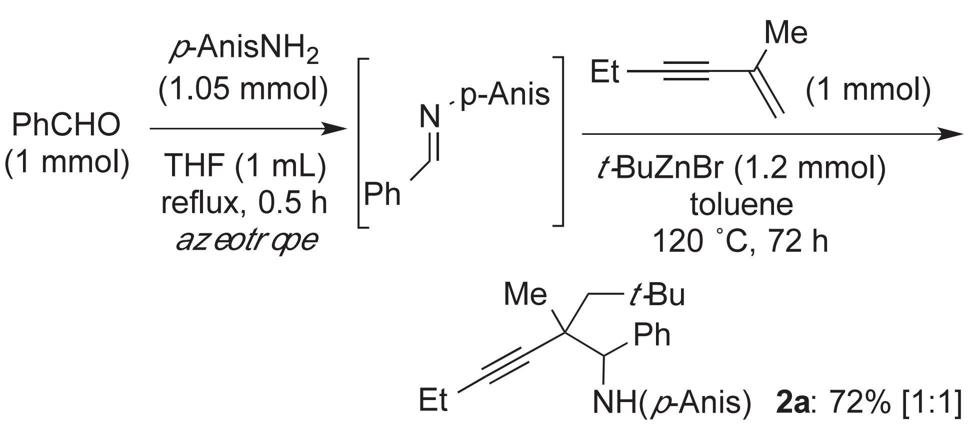
Next, we examined the coupling reaction with various aldehydes and ketones in the presence of 2-methyl-1-hexen-3-yne and *t*-BuZnBr in dry THF. The results are summarized in Table 2. Aromatic aldehydes participated in the coupling reaction in reasonable yields, providing a mixture of diastereoisomers in ratios of 1.2:1 to 1.6:1 (entries 1 and 2, Table 2). Aliphatic aldehydes provided the desired products in modest yields with a mixture of diastereoisomers (entries 3 and 4, Table 2). Although the similar coupling reaction of ketones proceeded in lower yields than that of aldehydes, high regioselectivities were observed in the case of ketones as well as aldehydes (entries 5-7, Table 2).

Table 2. Three-component coupling reaction of enyne, various carbonyls, and *t*-BuZnBr[a]



Entry	Aldehyde or Ketone (R^1, R^2)		Yield of **1** (%) [ratio]
1	R^1 = (*p*-OMe)Ph,	R^2 = H	**1b**: 83 [1.2:1]
2	R^1 = (*p*-Cl)Ph,	R^2 = H	**1c**: 83 [1.6:1]
3	R^1 = *c*-Hexyl,	R^2 = H	**1d**: 61 [1.1:1]
4	R^1 = *n*-Hexyl,	R^2 = H	**1e**: 38 [1:1]
5	R^1 = Me,	R^2 = Me	**1f**: 27
6	R^1 = Ph,	R^2 = Me	**1g**: 23 [1.3:1]
7	R^1 = Ph,	R^2 = Ph	**1h**: 46

[a] The reaction was undertaken in the presence of enyne (1 mmol), aldehyde or ketone (1 mmol), *t*-BuZnBr (1.2 mmol of 0.5 M THF solution) in dry THF (3 mL) at room temperature under nitrogen atmosphere.



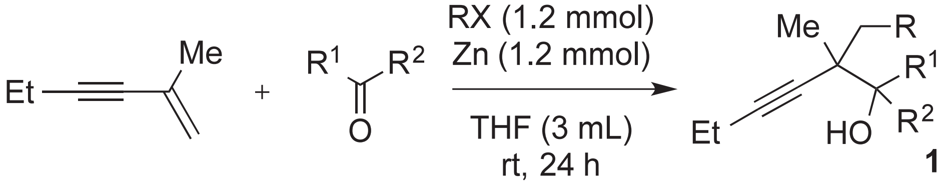
2a: 72% [1:1]

Scheme 4. Three-component coupling of enyne, aldimine, and *t*-BuZnBr

A similar coupling reaction was applied to the formation of homopropargylamine. Aldimine prepared from *p*-anisidine and benzaldehyde *via* azeotropic distillation underwent a three-component coupling reaction with enyne and *t*-BuZnBr to provide homopropargylamine **2a** in reasonable yield (Scheme 4). Although regioselectivity was completely controlled in the reaction, a mixture of stereoisomers of **2a** was observed in a 1:1 ratio.

t-BuZnI prepared from Zn dust and *t*-BuI *in situ* proved useful in a coupling reaction to provide homopropargyl alcohols **1** (Table 3).[8] *t*-BuI, enyne, and various types of aldehydes were introduced into a Zn dust suspension in dry THF solvent, and the reaction mixture was stirred at room temperature for 24 hours. Irrespective of the type of aldehydes used, the yields and steroeselectivities were almost same as for *t*-BuZnBr solution (entries 1-5, Table 3). Acetone served as an appropriate electrophile to form homopropargyl alcohols; however, acetophenone provided the expected product in modest yield (entries 6 and 7, Table 3). Isopropyl iodide and benzyl bromide took part in the three-component coupling reaction as alkylating reagents to form homopropargyl alcohols **1i** and **1j**, respectively (entries 8 and 9, Table 3).

Table 3. Three-component coupling reaction of 2-methyl-1-hexen-3-yne, carbonyls, and organozinc[a]

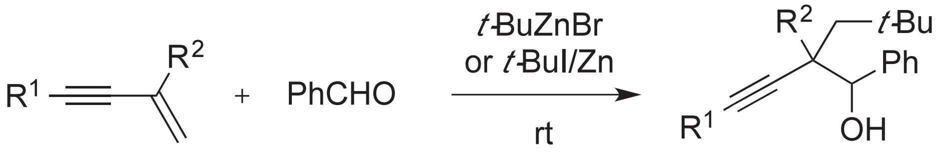


Entry	Aldehyde or Ketone (R^1, R^2)		RX	Yield of **1** (%) [ratio]
1	R^1 = Ph,	R^2 = H	*t*-BuI	**1a**: 95 [1.1:1]
2	R^1 = (*p*-OMe)Ph,	R^2 = H	*t*-BuI	**1b**: 67 [1.1:1]
3	R^1 = (*p*-Cl)Ph,	R^2 = H	*t*-BuI	**1c**: 73 [1.3:1]
4	R^1 = *c*-Hexyl,	R^2 = H	*t*-BuI	**1d**: 45 [1.1:1]
5	R^1 = *n*-Hexyl,	R^2 = H	*t*-BuI	**1e**: 47 [1:1]
6	R^1 = Me,	R^2 = Me	*t*-BuI	**1f**: 65
7	R^1 = Ph,	R^2 = Me	*t*-BuI	**1g**: 19 [1:1]
8	R^1 = Ph,	R^2 = H	*i*-PrI	**1i**: 27 [1.1:1]
9	R^1 = Ph,	R^2 = H	BnBr	**1j**: 32 [1.1:1]

[a]The reaction was undertaken in the presence of enyne (1 mmol), aldehyde or ketone (1 mmol), Zn dust (1.2 mmol), alkyl halide (1.2 mmol) in dry THF (3 mL) at room temperature under nitrogen atmosphere.

Next, we investigated the reactions of various enynes and benzaldehyde by means of *t*-BuZnBr solution or *t*-BuZnI prepared from Zn dust and *t*-BuI. The results are summarized in Table 4. The reactions were conducted in the presence of substituted enynes and benzaldehyde at room temperature in the presence of *t*-BuZnBr (condition A) and *t*-BuI/Zn (condition B). 2-Methyl-1-octen-3-yne underwent coupling with benzaldehyde to provide the desired product **1k** through attack by the *t*-Bu group on the C1 position and benzaldehyde on the C2 position under both conditions of A and B (entry 1, Table 4). An enyne possessing a terminal alkyne moiety provided only a small amount of **1l** or a complex mixture (entry 2, Table 4). 2-Methyl-4-phenyl-1-buten-3-yne provided homopropargyl alcohol **1m** in reasonable yield under condition A and in moderate yield under condition B (entry 3, Table 4). Although 4-phenyl-1-buten-3-yne (R^2 = H) was employed with the aim of improving stereoselectivities to avoid steric repulsion with neopentyl group, it had no effect at all (entry 4, Table 4). Terminal alkyne and alkene moieties seemed to result in lower yields than 2,4-disubstituted 1-buten-3-ynes.

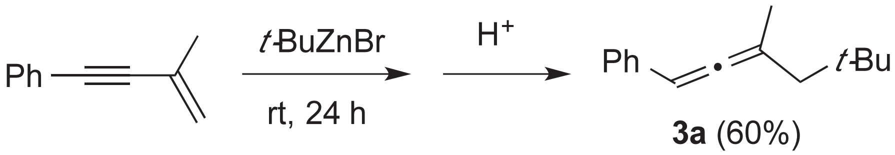
Table 4. Three-component coupling reaction of enynes, benzaldehyde, and organozinc[a]



Entry	Enyne (R^1, R^2)	Condition A (*t*-BuZnBr) Yield (%)	Condition B (*t*-BuI/Zn) Yield (%)
1	R^1 = *n*-Bu, R^2 = Me	**1k**: 36 [1.3:1]	**1k**: 31 [1:1]
2	R^1 = H, R^2 = Me	**1l**: 6 [1.3:1]	**1l**: complex mixture
3	R^1 = Ph, R^2 = Me	**1m**: 77 [1.1:1]	**1m**: 45 [1:1]
4	R^1 = Ph, R^2 = H	**1n**: 10 [1.2:1]	**1n**: 40 [1.4:1]

[a] Condition A: enyne (1 mmol), PhCHO (1 mmol), *t*-BuZnBr (1.2 mmol of 0.5 M THF solution) in dry THF (3 mL) at room temperature under nitrogen atmosphere. Condition B: enyne (1 mmol), PhCHO (1 mmol), Zn dust (1.2 mmol), *t*-BuI (1.2 mmol) in dry THF (3 mL) at room temperature under nitrogen atmosphere.

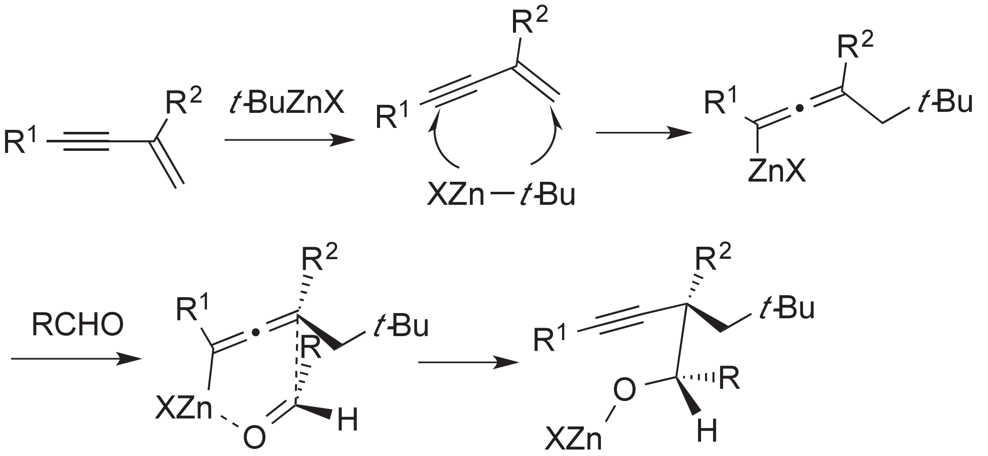
In order to elucidate the reaction mechanism, we carried out the coupling reaction of enyne and *t*-BuZnBr in the absence of carbonyl electrophiles. *t*-BuZnBr was added to a solution of 2-methyl-4-phenyl-1-buten-3-yne in THF, and the mixture was stirred at room temperature for 24 hours, followed by hydrolysis with aqueous acid solution to provide **3a** as a sole product. This result suggests that the reaction proceeds via an allenylzinc intermediate from a mixture of enyne and *t*-BuZnBr.



3a (60%)

Scheme 5. 1,4-Addition of *t*-BuZnBr toward enyne

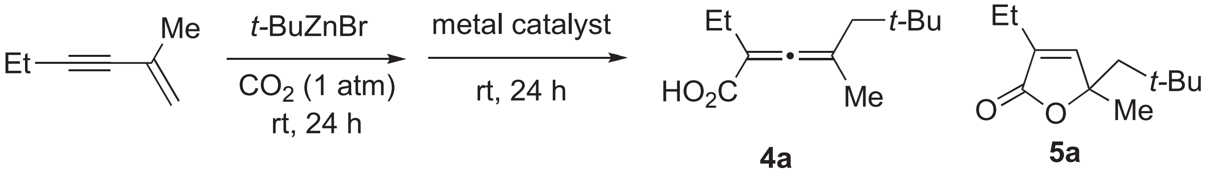
A plausible reaction mechanism for the three-component coupling reaction is shown in Scheme 6. The C-Zn bonds of *t*-BuZnBr are cleaved by homolysis to form *t*-Bu and ZnX radical spepcies, which then add to the 1,3-enyne in a 1,4-addition manner.[8] The *t*-butyl group attacks the olefinic C1 position and zinc atom attacks the acetylenic C4 position to form an allenylzinc intermediate. The carbonyl electrophile reacts at the γ-position of the allenylzinc species via a six-membered transition state and undergoes a three-component coupling reaction, resulting in the formation of a homopropargyl alcohol with a mixture of *syn* and *anti* stereoselectivity.



Scheme 6. A plausible reaction mechanism for three-component coupling of enyne, aldehyde, and *t*-butylzinc reagents

In the absence of aldehydes and ketones, carbon dioxide could also participate in the coupling reaction as a carbonyl electrophile. 2-Methyl-1-hexen-3-yne underwent a three-component coupling reaction with *t*-BuZnBr under a carbon dioxide atmosphere, providing four-substituted allenyl carboxylic acid **4a** in high yield. In contrast to the regioselectivities of aldehydes and ketones, the *t*-Bu group added to the terminal C1 position and carbon dioxide added to the C4 position. The formation of an allenyl carboxylic acid seems to suggest the reaction does not proceed through a six-membered cyclic transition state via an allenylzinc intermediate. During these investigations in the presence of transition metal catalysts, CuCl and AgOTf promoted 5-*endo-trig* cyclization of carboxylic acid **4a** at the allenic C-C double bond to provide γ-butyrolactone **5a**. These cyclizations may be utilized in synthetic methodologies for physiologically active molecules, such as α,β-unsaturated γ-butyrolactones.

Table 5. Three-component coupling reaction of enyne and *t*-BuZnBr under carbon dioxide[a]



Entry	Metal catalyst	Yield (%) **4a**	**5a**
1	none	87	0
2	CuCl	0	57
3	AgOTf	22	20
4	$NiCl_2$	0	0
5	$PdCl_2$	0	0

[a] The reaction was undertaken in the presence of enyne (1 mmol), *t*-BuZnBr (1.2 mmol of 0.5 M THF solution) in dry THF (3 mL) at room temperature under carbon dioxide atmospheric pressure for 24 hours, and then metal catalyst was added to the reaction mixture.

In summary, we developed three-component coupling reactions involving the use of a *t*-butylzinc halide with a reaction mixture of enyne and aldehyde to provide homopropargyl alcohols in a 1,2-addition manner. In the presence of carbon dioxide at atmospheric pressure, the three components (*t*-butylzinc halide, enyne, and carbon dioxide) combined in a 1:1:1 ratio to afford allenyl carboxylic acids in a 1,4-addition manner. These products may be useful in the synthesis of heterocyclic compounds such as dihydrofurans and α,β-unsaturated γ-butyrolactones.

ACKNOWLEDGEMENTS

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6. General procedure for multi-component coupling reaction (run 5, Table 1): A 25 mL of two-necked round-bottomed flask, equipped with a rubber septum and an air condenser at the top of which is attached a three-way stopcock fitted a nitrogen balloon is purged with nitrogen and the flask is charged with freshly distilled THF (3 mL). Into this solution, benzaldehyde (106 mg, 1 mmol), 2-methyl-1-hexen-3-yne (94 mg, 1 mmol), and *tert*-BuZnBr (2.4 mL of 0.5 M THF solution; 1.2 mmol) are successively added while stirring the solution with a magnetic stirrer. The stirring is continued for 24 h at room temperature. After the reaction completes, the reaction mixture is diluted with EtOAc (20 mL). The organic phase is washed with 2 M HCl (20 mL), sat. aq. $NaHCO_3$ (2 x 20 mL), and brine (2 x 20 mL), and then dried over magnesium sulfate, filtered, and concentrated. The organic phase was dried ($MgSO_4$) and concentrated in vacuo to give a brown oil, which was subjected to column chromatography over silica gel (hexane/EtOAc = 30/1 v/v) to give **1a** (248 mg, 96%).

2-Methyl-2-neopentyl-1-phenylhex-3-yn-1-ol (**1a**): (a mixture of *anti* and *syn* isomers in a ratio of 1.6:1): IR (neat) 3464 (br), 2953 (s), 2345 (w), 1454 (m), 1363 (m), 1202 (w), 1026 (m), 702 (s) cm-^{1}; ^{1}H NMR (400 MHz, $CDCl_3$, major) δ 1.01 (s, 9 H), 1.13 (d, J = 14.1 Hz, 1 H), 1.15 (t, J = 7.6 Hz, 3 H), 1.29 (s, 3 H), 1.62 (d, J = 14.1 Hz, 1 H), 2.21 (q, J = 7.6 Hz, 2 H), 2.60 (d, J = 4.0 Hz, 1 H), 4.41 (d, J = 4.0 Hz, 1 H), 7.23 (dm, J = 6.2 Hz, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$, major) δ 12.5, 13.8, 25.9, 31.4, 31.6, 40.9, 47.5, 81.8, 84.1, 86.3, 127.2, 127.3, 128.0, 139.8; ^{1}H NMR (400 MHz, $CDCl_3$, minor) δ 1.05 (s, 9 H), 1.16 (t, J = 7.6 Hz, 3 H), 1.18 (d, J = 14.1 Hz, 1 H), 1.51 (s, 3 H), 1.75 (d, J = 14.1 Hz, 1 H), 2.24 (q, J = 7.6 Hz, 2 H), 2.78 (d, J = 4.1 Hz, 1 H), 4.38 (d, J = 4.1 Hz, 1 H), 7.40 (dm, J = 6.2 Hz, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$, minor) δ 12.5, 13.8, 23.7, 31.4, 31.8, 41.2, 50.4, 81.1, 83.6, 86.9, 127.3, 127.4, 128.1, 139.7; High-resolution MS, calcd for $C_{18}H_{26}O$: 258.1984. Found *m/z* (relative intensity): 259 (M^{+}+1, 5), 258.1949 (M^{+}: 15), 243 (48), 225 (47).

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