Synthesis of highly substituted allylic alcohols by a regio- and stereo-defined CuCl-mediated carbometallation reaction of 3-aryl-substituted secondary propargylic alcohols with Grignard reagents†

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A highly regio- and stereoselective CuCl-mediated carbometallation reaction of 3-aryl-substituted secondary propargylic alcohols with alkyl, aryl, vinyl or allyl Grignard reagents for the synthesis of fully-substituted allylic alcohols was developed. The R^2 group from the Grignard reagent was successfully introduced to the 2-position of the propargylic alcohols due to the chelation of metal atom with the hydroxyl oxygen atom forming 5-membered metallacyclic intermediates, which smoothly react with various electrophiles to afford stereodefined polysubstituted allylic alcohols. By this method, optically active allylic alcohols can be prepared from readily available optically active propargylic alcohols without obvious racemization. Five-membered lactones can also be synthesized by Pd-catalyzed carbonylation with iodoallylic alcohols.

Introduction

The stereoselective synthesis of stereodefined allylic alcohols is of current interest due to their synthetic significance,[1] and the stereoselective carbometallation of propargylic alcohols is one of the most powerful methods to afford multi-substituted stereodefined allylic alcohols.[2] Duboudin *et al.* reported that the Cu(I)-catalyzed *anti*-carbomagnesiation of primary propargylic alcohols with Grignard reagents in ether provided 2-substituted prop-2-enols with high regio- and steroselectivties.[3,4] Fleming *et al.* reported a similar reaction of 3-cyano-substituted primary alkynols with Grignard reagents affording hydroxyl-group-directed five-membered cyclic organometallic intermediates.[5] However, the Cu(I)-mediated carbometallation of secondary or tertiary propargylic alcohols afforded a mixture of two regioisomeric products.[3c,d] Recently, we achieved the controllable regio- and stereoselective Cu-mediated carbometallation of secondary or tertiary terminal propargylic alcohols with Grignard reagents in various solvents. However, the R groups of the Grignard reagents were limited to primary alkyl or phenyl groups.[6] Furthermore, when 3-substituted secondary propargylic alcohols were used the carbometallation was low-yielding and not regio- or stereochemically selective. Therefore, to the best of our knowledge, the regio- and stereoselective carbometallation of 3-aryl-substituted secondary alkynols has not been achieved to date. Herein, we wish to report the highly regio- and stereoselective CuCl-mediated carbometallation of 3-aryl-substituted secondary propargylic alcohols with Grignard reagents, affording fully substituted allylic alcohols with high regio- and stereoselectivity.

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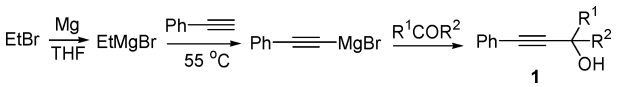
Results and discussion

The starting propargylic alcohols **1a–d** were prepared *via* the reaction of phenylethynyl magnesium bromide with corresponding aldehydes (fresh distilled) or acetone (Scheme 1).[7]



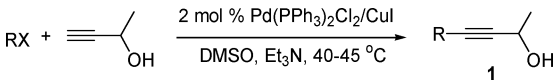
1a: $R^1 = CH_3$, $R^2 = H$, 84%, **1b**: $R^1 = n\text{-}C_5H_{11}$, $R^2 = H$, 67%
1c: $R^1 = Ph$, $R^2 = H$, 81%, **1d**: $R^1 = CH_3$, $R^2 = CH_3$, 94%

Scheme 1

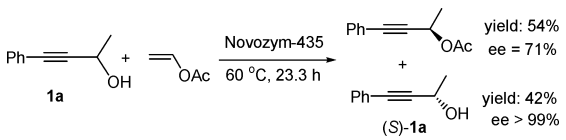
Propargylic alcohols **1e–k** were prepared by a modified procedure for Sonogashira coupling reaction of 3-butyn-2-ol with aryl iodides or bromides developed in our laboratory in 58–94% yields (Table 1).[8]

Optically active starting material (*S*)-**1a** was prepared by the Novozym-435-catalyzed kinetic resolution of the racemic **1a** with vinyl acetate in 42% yield with 99% ee (eq. 1).[9]

Table 1 The preparation of propargylic alcohols (**1e–k**)



Entry	R	X	t (h)	Isolated yield of **1** (%)
1	3-MeC_6H_4	I	10.5	89 (**1e**)
2	4-MeC_6H_4	I	10.3	91 (**1f**)
3	4-$MeOC_6H_4$	I	11.2	78 (**1g**)
4	4-ClC_6H_4	I	11.2	93 (**1h**)
5	2-Pyridinyl	I	11.5	94 (**1i**)
6	2-Thienyl	Br	15.4	58 (**1j**)
7	2-$CF_3C_6H_4$	Br	12.4	74 (**1k**)



(1)

We chose 4-phenyl-3-butyn-2-ol **1a** as a test substrate to optimize the reaction conditions. Firstly, we applied the conditions used in our reported carbometallation of secondary terminal propargylic alcohols:[6a] a solution of *n*-C_5H_{11}MgBr in THF was added dropwise to a solution of **1a** in toluene with 0.5 equiv of CuI at −78 °C. After the addition, the reaction mixture was warmed up to room temperature to afford the expected product 3-(*n*-pentyl)-4-phenylbut-3(*E*)-en-2-ol *E*-**2a**, together with its regioisomer 4-phenyl-3(*Z*)-nonen-2-ol *Z*-**3a** upon hydrolysis in 46% and 9% yields, respectively, with 33% of **1a** being recovered (entry 1, Table 2). The configurations of the carbon–carbon double bonds in *E*-**2a** and *Z*-**3a** were determined by NOE analysis (Fig. 1).

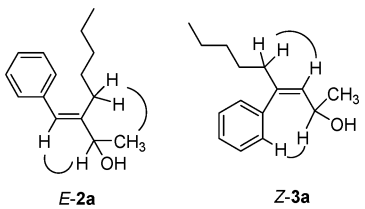
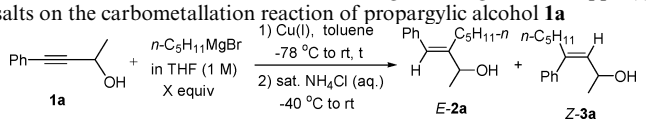


Fig. 1

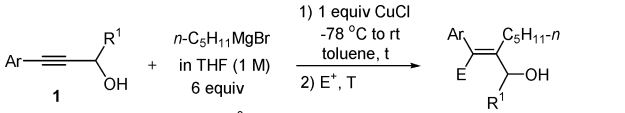
We then explored the effect of the amount of the Grignard reagent and catalyst used on the selectivity and yield. With more *n*-C_5H_{11}MgBr, both the yield and the selectivity of the reaction were improved (compare entry 2 with entry 3, Table 2) as previously observed in this group.[6a] The reaction of **1a** with 6 equiv of *n*-C_5H_{11}MgBr provided *E*-**2a** in 95% yield with high regio- and stereoselectivity (entry 4, Table 2). Using CuCl gave better result than CuBr and CuI (compare entries 4–6, Table 2), and the result with 1 equiv of CuCl was the best (compare entries 4, 7, 8 and 9, Table 2). Thus, we used as our standard conditions for further studies the reaction of 3-aryl propargylic alcohols in toluene with 6 equiv of Grignard reagents in THF solution at −78 °C, warming to room temperature (entry 4, Table 2).

Table 2 Effect of the amounts of the Grignard reagent and copper(I) salts on the carbometallation reaction of propargylic alcohol **1a**



Entry	X	Cu(I) (equiv)	t (h)	NMR yield (%) *E*-**2a**	*Z*-**3a**	Recovery of **1a**
1	3.5	CuI (0.5)	12.1	46	9	33
2	3.5	CuCl (1.0)	11.6	44	9	40
3	4.5	CuCl (1.0)	11.6	87	3	8
4	6.0	CuCl (1.0)	11.6	95	2	2
5	6.0	CuI (1.0)	12.0	70	8	8
6	6.0	CuBr (1.0)	12.0	70	10	8
7	6.0	CuCl (1.5)	13.2	95	3	5
8	6.0	CuCl (0.5)	13.2	88	4	6
9	6.0	CuCl (2.0)	13.0	85	4	13

Table 3 Carbometallation of 3-aryl substituted secondary propargylic alcohols with *n*-C_5H_{11}MgBr followed by hydrolysis or iodination[a]

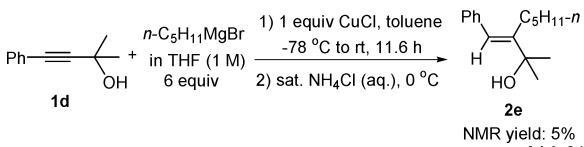


Entry	**1** Ar	R^1	t (h)	E^+	NMR yield of **2**, **4**, **5**, **6** (%)[b]
1	Ph	Me (**1a**)	8.7	I_2	85 (83) (*Z*-**4a**)
2	4-ClC_6H_4	Me (**1h**)	10	I_2	82 (78) (*Z*-**4b**)
3	3-$CF_3C_6H_4$	Me (**1k**)	11.2	I_2	83 (75) (*Z*-**4c**)
4[c]	3-MeC_6H_4	Me (**1e**)	17.3	I_2	58 (49) (*Z*-**4d**)
5	4-MeC_6H_4	Me (**1f**)	14	I_2	68 (66) (*Z*-**4e**)
6[d]	4-$MeOC_6H_4$	Me (**1g**)	13.3	I_2	55 (56) (*Z*-**4f**)
7	2-Thienyl	Me (**1j**)	10	H^+[e]	87 (83) (*E*-**2b**)
8	2-Pyridyl	Me (**1i**)	10	H^+[e]	82 (78) (*E*-**2c**)
9	Ph	Ph (**1c**)	12	H^+[e]	48 (45) (*E*-**2d**)
10	Ph	*n*-C_5H_{11} (**1b**)	12.8	I_2	32 (31) (*Z*-**4g**)[f]
11	Ph	Me (**1a**)	11.6	H^+[e]	95 (90) (*E*-**2a**)
12	Ph	Me (**1a**)	16.3	D_2O	96 (88) (*E*-**5a**)[g]
13	Ph	Me (**1a**)	16.3	NBS	54 (54) (*Z*-**6a**)

[a] The reaction was conducted with 1 mmol of propargylic alcohol, 1 equiv of CuCl, and 6 equiv of the Grignard reagent in 1.5 mL of toluene. [b] The numbers in parentheses are the isolated yields. [c] The quenching temperature was −30 °C. [d] 9 equiv of *n*-C_5H_{11}MgBr, 2 equiv of CuCl and 9 equiv I_2 were added. [e] H^+ = sat. NH_4Cl (aq.). [f] 38% of **1b** was recovered. [g] The deuterium incorporation was 99%.

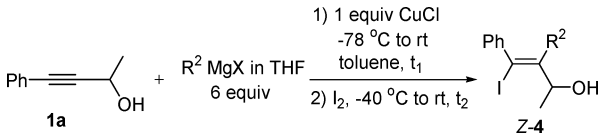
We then studied the substrate scope of the reaction. Both the electron-withdrawing groups and electron-donating groups can be introduced to the 3- or 4-positions of the phenyl group in the starting alcohols (entries 2–6, Table 3). The reaction of 4-(2-thienyl)-3-butyn-2-ol **1j** with *n*-C_5H_{11}MgBr, followed by hydrolysis, afforded 3-(*n*-pentyl)-4-(2-thienyl)-3(*E*)-buten-2-ol *E*-**2b** in 83% yield (entry 7, Table 3). A similar reaction can be conducted with 4-(2-pyridyl)-3-butyn-2-ol (**1i**) to afford 3-(*n*-pentyl)-4-(2-pyridyl)-3(*E*)-buten-2-ol *E*-**2c** in 78% yield upon protonolysis (entry 8, Table 3). When R^1 was a phenyl or *n*-pentyl group, the reaction afforded 2-(*n*-pentyl)-1,3-diphenyl-2(*E*)-propen-1-ol *E*-**2d** and 1-iodo-2-(*n*-pentyl)-1-phenyl-1(*Z*)-octen-3-ol *Z*-**4g** in 45% and 31% yields (entries 9 and 10, Table 3). By hydrolysis with sat. NH_4Cl (aq) or D_2O, the reaction of **1a** with *n*-C_5H_{11}MgBr afforded 3-(*n*-pentyl)-4-phenyl-3(*E*)-buten-2-ol *E*-**2a** in 90% yield (entry 11, Table 3) and 4-deutero-3-(*n*-pentyl)-4-phenyl-3(*E*)-buten-2-ol *E*-**5a** in 88% yield with a deuterium incorporation of 99% (entry 12, Table 3), respectively. The related reaction of **1a** quenched with NBS afforded 4-bromo-3-(*n*-pentyl)-4-phenyl-3(*Z*)-buten-2-ol *Z*-**6a** in 54% yield (entry 13, Table 3).

However, under similar conditions, the reaction of tertiary alcohol 2-methyl-4-phenyl-3-butyn-2-ol **1d** with *n*-C_5H_{11}MgBr afforded the corresponding product **2e** in only 5% yield, probably due to the steric hindrance (eq. 2).



(2)

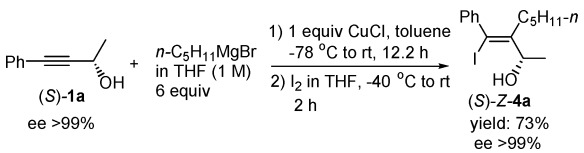
Table 4 Carbometallation of **1a** with various Grignard reagents followed by iodination[a]



Entry	R^2	X	t_1 (h)	t_2 (h)	NMR yield of *Z*-**4** (%)[b]
1	Et	Br	16.3	1.2	80 (82) (*Z*-**4h**)
2	*i*-Pr	Br	12.1	1.5	79 (83) (*Z*-**4i**)
3	Allyl	Cl	22	0.8	—[c] (49) (*Z*-**4j**)
4	Ph	Cl	14	1.0	—[c] (69) (*Z*-**4k**)
5	Ph	Br	14	1.0	58 (63) (*Z*-**4k**)
6	4-MeC_6H_4	Br	20.7[d]	1.5	86 (83) (*Z*-**4l**)
7	4-MeOC_6H_4	Br	13	1.0	80 (73) (*Z*-**4m**)

[a] The reaction was conducted with 1 mmol of propargylic alcohol, 1 equiv of CuCl, and 6 equiv of the Grignard reagent in 1.5 mL of toluene. [b] The numbers in parentheses are the isolated yields. [c] The crude yield could not be determined by NMR analysis. [d] The reaction was conducted at rt for 13.1 h, then heated at 40 °C for 7.6 h.

With optically active (*S*)-4-phenyl-3-butyn-2-ol (*S*)-**1a**, optically active allylic alcohol (*S*)-*Z*-**4a** can be prepared without obvious racemization in 73% isolated yield by quenching with I_2 (eq. 3).



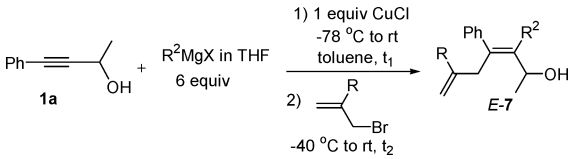
(3)

These promising results encouraged us to extend the scope of the reaction with various Grignard reagents (Table 4). Both primary and secondary alkyl Grignard reagents can react with **1a** to afford the corresponding products (entries 1 and 2, Table 4). 3-Allyl-4-iodo-4-phenyl-3(*Z*)-buten-2-ol *Z*-**4j** can be produced by the reaction of **1a** with allyl magnesium chloride (entry 3, Table 4). The reaction of **1a** with phenyl or substituted phenyl Grignard reagents afforded the 3-aryl-substituted products **4k–m** in 63–83% isolated yields (entries 4–7, Table 4). Phenylmagnesium chloride gave a better result than phenylmagnesium bromide (compare entries 4 and 5, Table 4).

Primary or secondary alkyl and vinyl Grignard reagents reacted with 4-phenyl-3-butyn-2-ol **1a** followed by the treatment with allyl bromide to afford corresponding products *E*-**7a–e** in 76–91% isolated yields (entries 1–5, Table 5). The reaction of **1a** with *n*-C_5H_{11}MgBr followed by reaction with 2-bromo-allyl bromide or 2-butyl-allyl bromide afforded corresponding products **7f** and **7g** in 48% and 79% isolated yields, respectively (entries 6 and 7, Table 5).

Further study showed that the *in situ*-formed cyclic organometallic intermediate **M1** may also undergo Pd-catalyzed Kumada-type coupling reaction directly with various aryl or vinyl iodides (Table 6). The coupling reaction of phenyl iodides containing electron-withdrawing groups or electron-donating groups at their 3- or 4-positions with the *in situ*-generated cyclic organometallic intermediate **M1** at 80 °C afforded the coupling products **8a–d** in 69–75% yields (entries 1–4, Table 6). The reaction also afforded 3-(*n*-pentyl)-4-phenyl-3(*E*),5(*E*)-decadien-2-ol (3*E*,5*E*)-**8e** from the coupling of intermediate **M1** with 1(*E*)-hexenyl iodide in 48% isolated yield (entry 5, Table 6).

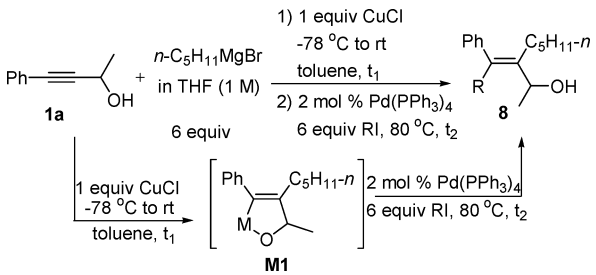
Table 5 Carbometallation of **1a** with Grignard reagents followed by treatment with allylic bromides[a]



Entry	R^2	X	t_1 (h)	t_2 (h)	Allylic bromide R	NMR yield of *E*-**7** (%)[b]
1	*n*-C_5H_{11}	Br	12.2	4.3	H	94 (85) (*E*-**7a**)
2	CH_3	Cl	18	3.0	H	92 (91) (*E*-**7b**)
3	*i*-Pr	Br	12.4	4.8	H	89 (82) (*E*-**7c**)
4	*c*-Hexyl	Cl	12	7.4	H	78 (76) (*E*-**7d**)
5	Vinyl	Cl	18	3.2	H	82 (77) (*E*-**7e**)
6	*n*-C_5H_{11}	Br	12.2	6.0	Br	54 (48) (*E*-**7f**)
7	*n*-C_5H_{11}	Br	10.3	3.3	*n*-C_4H_9	85 (79) (*E*-**7g**)

[a] The reaction was conducted with 1 mmol of **1a**, 1 equiv of CuCl, 6 equiv of the Grignard reagent, 1.5 mL of toluene, and 6 equiv of allylic bromide. [b] The numbers in parentheses are the isolated yields.

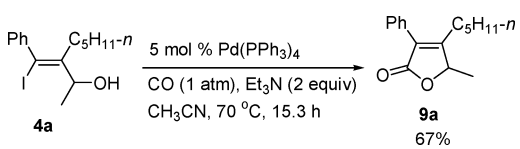
Table 6 Pd-catalyzed Kumada-type coupling reactions of organometallic intermediate **M1** with various aryl or vinyl iodides[a]



Entry	t_1 (h)	t_2 (h)	R	NMR yield of **8** (%)[b]
1	11	20	C_6H_5	80 (75) (**8a**)
2	12.2	24.3	3-MeC_6H_4	77 (75) (*Z*-**8b**)
3	12.0	12	4-MeOC_6H_4	80 (74) (*Z*-**8c**)
4	13.0	12	4-ClC_6H_4	71 (69) (*Z*-**8d**)
5	16.3	23.5	*n*-C_4H_9CH=CH (*E*)	56 (48) (*E*-**8e**)

[a] The reaction was conducted with 1 mmol of propargylic alcohol **1a**, 1 equiv of CuCl, 6 equiv of the Grignard reagent, 1.5 mL of toluene, 6 equiv of aryl or vinyl iodides, and 2 mol% $Ph(PPh_3)_4$. [b] The numbers in parentheses are the isolated yields.

In addition, 5-methyl-4-(*n*-pentyl)-3-phenyl-2(5*H*)-furanone **9a** can be prepared in 67% yield by the palladium-catalyzed carbonylation reaction of **4a** (eq. 4).[10]



(4)

Conclusions

In summary, a highly regio- and stereoselective Cu(I)-catalyzed carbometallation of 3-aryl-substituted secondary propargylic alcohols with Grignard reagents followed by treatment with various electrophiles, affording stereodefined polysubstituted allylic alcohols was developed. The alkyl, aryl, vinyl, and allyl groups from the Grignard reagents could be introduced to the 2-position of the propargylic alcohols to form 5-membered cyclic organometallic intermediates. Optically active allylic alcohol (*R*)-*Z*-**4a** may be prepared without obvious loss of enantiopurity. Further studies in this area are being conducted in our laboratory.

Experimental section

Materials

Et_2O and THF were distilled from Na/benzophenone, Et_3N was distilled from KOH, and DMSO was distilled from CaH_2. Commercially available chemicals were purchased and used without additional purification unless otherwise noted.

Synthesis of 4-phenyl-3-butyn-2-ol (1a)[7,11]. To a dry three-necked flask containing magnesium turnings (2.88 g, 0.12 mol) and I_2 (a few crystals) in THF (120 mL) were added several drops of ethyl bromide. Upon the initiation of the Grignard reaction, the remaining ethyl bromide (8.96 mL, d = 1.461 g/mL, 13.09 g, 0.12 mol) was added dropwise, which was followed by stirring until the magnesium disappeared. Phenylethyne (11.0 mL, d = 0.930 g/mL, 10.20 g, 0.10 mol) was added dropwise into the solution at 55 °C followed by stirring for 1.5 h at this temperature. Then acetaldehyde (4.0 mL, d = 0.780 g/mL, 3.12 g, 0.07 mol) was added at 55 °C and the resulting mixture was stirred at this temperature for 2 h. The reaction mixture was then quenched with an saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic layer was washed sequentially with 5% HCl, sat. $NaHCO_3$ (aq.), brine, and dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent then distillation afforded **1a** (8.72 g, 84%, 126–128 °C/2.2 mmHg). Liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.38 (m, 2 H), 7.33-7.27 (m, 3 H), 4.81-4.72 (m, 1 H), 2.24 (bs, 1 H), 1.55 (d, J = 6.6 Hz, 3 H).

Synthesis of 4-(*m*-methylphenyl)-3-butyn-2-ol 1e[8,12]. To a dry Schlenk flask were added 3-iodotoluene (1.0959 g, 5.0 mmol), 3-butyn-2-ol (0.6983 g, 9.9 mmol), CuI (0.0193 g, 0.10 mmol, 2 mol%), $Pd(PPh_3)_2Cl_2$ (0.0675 g, 0.096 mmol, 2 mol%), DMSO (12 mL), and Et_3N (10 mL). The resulting mixture was then heated at 40–45 °C. After complete conversion of the starting material as monitored by TLC, the reaction mixture was quenched with an saturated aqueous NH_4Cl, and extracted with Et_2O. The combined organic layer was washed with 5% HCl, sat. $NaHCO_3$ (aq.), brine, and dried over anhydrous Na_2SO_4. Chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10/1) of the crude product afforded the **1e** (0.7166 g, 89%). Liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.08 (m, 4 H), 4.80-4.70 (m, 1 H), 2.32 (d, J = 0.3 Hz, 3 H), 2.04-1.98 (m, 1 H), 1.55 (d, J = 6.6 Hz, 3 H).

Synthesis of optically active propargylic alcohol (*S*)-4-phenyl-3-butyn-2-ol ((*S*)-1a) from racemic propargylic alcohol 1a[9,12]. To a mixture of racemic **1a** (4.0032 g) and vinyl acetate (100 mL) was added Novozym-435 (0.7008 g). After shaking at 60 °C for 23.3 h (monitored by TLC), the reaction mixture was worked up by filtration and washing with ether. Evaporation and purification by flash chromatography on silica gel (eluent: petroleum ether/ether = 60/1 to 20/1), afforded (*S*)-4-phenyl-3-butyn-2-ol (1.6780 g, 42%, ee > 99%, HPLC conditions: Chiralcel OJ-H, *n*-hexane/*i*-PrOH = 90/10, 1 mL/min, λ = 230 nm, tr 10.121 min (major), 8.978 min (minor)), $[\alpha]^{20}_D$ = −33.0 (c = 0.94, $CHCl_3$)) and (*R*)-4-phenyl-3-butyn-2-ol acetate (2.7696 g, 54%, ee = 71%, $[\alpha]^{20}_D$ = +145.8 (c = 1.03, $CHCl_3$)), (ee value was determined after its conversion to the corresponding alcohol). Liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.39 (m, 2 H), 7.34-7.27 (m, 3 H), 4.76 (q, J = 6.6 Hz, 1 H), 2.16 (bs, 1 H), 1.56 (d, J = 6.6 Hz, 3 H).

Synthesis of 3-(*n*-pentyl)-4-phenyl-3(*E*)-buten-2-ol (*E*-2a). To a solution of **1a** (0.1477 g, 1.0 mmol) and CuCl (0.1005 g, 1.0 mmol, 1 equiv) in dry toluene (1.5 mL) under a nitrogen atmosphere was added the *n*-$C_5H_{11}MgBr$ in THF (6 mL, 1 M, 6 mmol, 6 equiv) dropwise to the reaction mixture at −78 °C in 15 min, which was followed by warming up to rt naturally. After complete conversion of the starting material as monitored by TLC, the reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL) at 0 °C, and extracted with Et_2O (15 mL × 3). The combined organic layer was washed with 5% HCl (10 mL), sat. $NaHCO_3$ (aq.) (10 mL), brine (10 mL), and dried over anhydrous Na_2SO_4. After evaporation, the NMR ratio was determined by using 1,3,5-trimethylbenzene as the internal standard (35 μL, 0.25 mmol). Chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10/1) of the crude product afforded *E*-**2a** (0.1984 g, 90%): Liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.38 (m, 2 H), 7.27-7.18 (m, 3 H), 6.56 (s, 1 H), 4.42 (q, J = 6.4 Hz, 1 H), 2.42-2.32 (m, 1 H), 2.22-2.10 (m, 1 H), 1.65-1.55 (m, 1 H), 1.55-1.43 (m, 2 H), 1.39 (d, J = 6.6 Hz, 3 H), 1.37-1.23 (m, 4 H), 0.91-0.83 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.8, 137.7, 128.5, 128.1, 126.3, 124.0, 71.7, 32.2, 28.8, 28.4, 22.5, 22.3, 14.0; IR (neat, cm^{-1}) 3357, 3056, 3024, 2957, 2929, 2868, 1649, 1599, 1493, 1464, 1368, 1284, 1165, 1114, 1071; MS (m/z): 200 (($M^+ - H_2O$), 10.73), 129 (100); Elemental analysis calcd. for $C_{15}H_{22}O$: C, 82.52, H, 10.16; Found: C, 82.86, H, 10.03.

Synthesis of 4-iodo-3-(*n*-pentyl)-4-phenyl-3(*Z*)-buten-2-ol (*Z*-4a). Following the procedure for the CuCl-mediated carbometallation of propargylic alcohols with Grignard reagents described above, the reaction was conducted using **1a** (0.1469 g, 1.0 mmol), CuCl (0.1007 g, 1.0 mmol, 1 equiv), 1.5 mL of toluene, and a solution of *n*-$C_5H_{11}MgBr$ in THF (6 mL, 1 M, 6 mmol, 6 equiv). After complete conversion of the starting material as monitored by TLC, the reaction mixture was quenched by the dropwise addition of a solution of I_2 (1.5243 g, 6.0 mmol, 6 equiv) in 5 mL of THF at −40 °C, and allowed to warm to rt over 1 h. It was then treated with a saturated aqueous $Na_2S_2O_3$ at 0 °C, and extraction with Et_2O (15 mL × 3). The combined organic layer was washed with 5% HCl (10 mL), sat. $NaHCO_3$ (aq.) (10 mL), brine (10 mL), and dried over anhydrous Na_2SO_4. After evaporation, the NMR ratio was determined by using 1,3,5-trimethylbenzene as the internal standard (35 μL, 0.25 mmol). Chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 20/1) of the crude product afforded *Z*-**4a** (0.2878 g, 83%): Liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.28 (m, 2 H), 7.28-7.15 (m, 3 H), 4.97-4.87 (m, 1 H), 2.21-1.99 (m, 2 H), 1.93 (bs, 1 H), 1.40 (d, J = 6.3 Hz, 3 H), 1.36-1.20 (m, 2 H), 1.15-0.99 (m, 4 H), 0.74 (t,

J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.3, 144.5, 128.2, 128.1, 127.6, 96.0, 77.0, 31.8, 29.8, 28.8, 22.0, 21.2, 13.8; IR (neat, cm^{-1}) 3363, 2956, 2928, 2865, 1620, 1592, 1486, 1458, 1442, 1367, 1285, 1222, 1175, 1104, 1060; MS (m/z): 344 (M^+, 0.50), 327 ($(M-H_2O)^+$, 22.04), 117 (100); HRMS calcd. for $C_{15}H_{21}OI$ (M^+): 344.0637, found: 344.0642.

Synthesis of 3-(*n*-pentyl)-4-phenylhepta-3(*E*),6-dien-2-ol (*E*-7a). Following the procedure for the CuCl-mediated carbometallation of propargylic alcohols with Grignard reagents described above, the reaction was conducted using **1a** (0.1499 g, 1.0 mmol), CuCl (0.1041 g, 1.1 mmol, 1 equiv), 1.5 mL of toluene, and a solution of n-$C_5H_{11}MgBr$ in THF (6 mL, 1 M, 6 mmol, 6 equiv). After complete conversion of the starting material as monitored by TLC, the reaction mixture was quenched by the dropwise addition of a solution of allyl bromide (0.54 mL, d = 1.398 g/mL, 0.7549 g, 6.2 mmol, 6.2 equiv) in 2 mL of THF at –40 °C, followed by warming up to rt naturally. The resulting mixture was treated with saturated aqueous NH_4Cl at 0 °C, and extracted with Et_2O (15 mL × 3). The combined organic layer was washed with 5% HCl (10 mL), sat. $NaHCO_3$ (aq.) (10 mL), brine (10 mL), and dried over anhydrous Na_2SO_4. After evaporation, the NMR ratio was determined by using 1,3,5-trimethylbenzene as the internal standard (35 μL, 0.25 mmol). Chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 20/1) of the crude product afforded *E*-**7a** (0.2250 g, 85%): Liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.27 (m, 2 H), 7.26-7.18 (m, 1 H), 7.11-7.07 (m, 2 H), 5.82-5.67 (m, 1 H), 5.05-4.89 (m, 3 H), 3.15 (qdt, J = 12.9, 6.3, and 1.5 Hz,2 H), 2.02-1.85 (m, 2 H), 1.59 (bs, 1 H), 1.38 (d, J = 6.6 Hz, 3 H), 1.35-1.19 (m, 2 H), 1.15-0.96 (m, 4 H), 0.74 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.4, 140.3, 136.0, 135.5, 128.4, 127.9, 126.2, 115.2, 67.6, 38.7, 32.2, 30.3, 28.4, 22.1, 22.0, 13.9; IR (neat, cm^{-1}) 3382, 3077, 3057, 3019, 2956, 2929, 2870, 1636, 1599, 1491, 1456, 1441, 1368, 1283, 1106, 1177, 1072, 1056; MS (m/z): 258 (M^+, 1.22), 130 (100); HRMS calcd. for $C_{18}H_{26}ONa$ (M^+ + Na): 281.1876, Found: 281.1870.

Synthesis of 3-(*n*-pentyl)-4,4-diphenyl-3-buten-2-ol (8a). Following the procedure for the CuCl-mediated carbometallation of propargylic alcohols with Grignard reagents described above, the reaction was conducted using **1a** (0.1458 g, 1.0 mmol), CuCl (0.0992 g, 1.0 mmol, 1 equiv), 1.5 mL of toluene, and a solution of Grignard reagent in THF (6 equiv, 6 mmol). After complete conversion of the starting material as monitored by TLC, $Pd(PPh_3)_4$ (0.0237 g, 0.02 mmol, 2 mol%) and a solution of PhI (1.2537 g, 6.2 mmol, 6 equiv) in THF (2 mL) were added sequentially at rt. The resulting mixture was then heated at 80 °C and monitored by TLC until the starting material disappeared. This mixture was then quenched with saturated aqueous NH_4Cl, and extracted with Et_2O (15 mL × 3). The combined organic layer was washed with 5% HCl (10 mL), sat. $NaHCO_3$ (aq.) (10 mL), brine (10 mL), and dried over anhydrous Na_2SO_4. After evaporation, the NMR yield and ratio were determined by using 1,3,5-trimethylbenzene as the internal standard (35 μL, 0.25 mmol). Chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 20/1 to 10/1) of the crude product afforded **8a** (0.2204 g, 75%). According to ^{1}H NMR analysis of crude reaction mixture before separation, product **8a** was formed in 80% yield together with 7% of protonolysis product. **8a**: Liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.20 (m, 4 H), 7.19-7.10 (m, 6 H), 4.63 (q, J = 6.6 Hz, 1 H), 2.22-2.10 (m, 2 H), 1.77 (s, 1 H), 1.52-1.33 (m, 2 H), 1.30 (d, J = 6.6 Hz, 3 H), 1.18-1.03 (m, 4 H), 0.75 (t, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.6, 142.2, 141.5, 139.9, 128.8, 128.7, 128.1, 128.0, 126.4, 126.3, 68.3, 32.2, 30.2, 27.3, 22.0, 21.9, 13.8; IR (neat, cm^{-1}) 3405, 3077, 3055, 3020, 2956, 2929, 2870, 1597, 1576, 1490, 1465, 1443, 1367, 1257, 1100, 1073, 1054, 1031, 1002; MS (m/z): 294 (M^+, 2.19), 167 (100); Elemental analysis calcd. for $C_{21}H_{26}O$: C, 85.67, H, 8.90; Found: C, 85.66, H, 8.83.

Synthesis of 5-methyl-4-(*n*-pentyl)-3-phenyl-2(5*H*)-furanone (9a). To a Schlenk tube were added $Pd(PPh_3)_4$ (0.0242 g, 0.02 mmol, 5 mol%), *Z*-**4a** (0.1372 g, 0.40 mmol), Et_3N (0.0828 g, 0.82 mmol, 2 equiv), and CH_3CN (4 mL) at rt. This mixture was degassed with CO using freeze–pump–thaw cycles and then heated at 70 °C. After complete conversion of the starting material as monitored by TLC, the reaction mixture was quenched by H_2O (5 mL) and extracted with Et_2O (20 mL × 3). The combined organic layer was washed with 5% HCl (10 mL), sat. $NaHCO_3$ (aq.) (10 mL), brine (10 mL), and dried over anhydrous Na_2SO_4. Chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 20/1) of the crude product afforded **9a** (0.0656 g, 67%). Liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.32 (m, 5 H), 5.06 (q, J = 6.7 Hz, 1 H), 2.77-2.65 (m, 1 H), 2.42-2.30 (m, 1 H), 1.60-1.40 (m, 5 H), 1.35-1.20 (m, 4 H), 0.91-0.82 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.6, 166.1, 130.0, 128.8, 128.3, 128.2, 126.4, 77.9, 31.6, 27.4, 26.7, 22.1, 18.3, 13.8; IR (neat, cm^{-1}) 2954, 2931, 2866, 1752, 1656, 1601, 1493, 1446, 1376, 1322, 1150, 1100, 1062; MS (m/z): 244 (M^+, 58.66), 91 (100); Elemental analysis calcd. for $C_{16}H_{20}O_2$: C, 78.65, H, 8.25; Found: C, 78.64, H, 8.26.

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