JOC*Article*

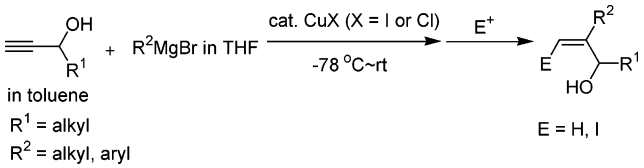
Studies on the Cu(I)-Catalyzed Regioselective *anti*-Carbometallation of Secondary Terminal Propargylic Alcohols

Zhan Lu[†] and Shengming Ma*[,†,‡]

Laboratory of Molecular Recognition and Synthesis, Department of Chemistry, Zhejiang University, Hangzhou 310027, Zhejiang, People's Republic of China, and State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, People's Republic of China

masm@mail.sioc.ac.cn

Received November 21, 2005



A highly regioselective Cu(I)-catalyzed *anti*-carbometallation of secondary terminal propargylic alcohols with 1° alkyl or aryl Grignard reagents affording 2-substituted allylic alcohols was developed. By using this method, optically active allylic alcohols can be prepared from the optically active propargylic alcohols without obvious loss of the enantiopurity. The cyclic organometallic intermediate formed may undergo an iodination or a Pd(0)-catalyzed coupling reaction to afford stereo-defined allylic alcohols.

Introduction

As a result of the presence of the carbon−carbon triple bond and the hydroxyl group, as well as the easy availability of propargylic alcohols,[1] their synthetic potentials have been extensively demonstrated.[2] Duboudin et al. reported that the Cu(I)-catalyzed carbomagnesiation of primary propargyl alcohol with Grignard reagents in ether leads to the highly selective formation of 2-substituted prop-2-enols via the hydroxyl-group controlled *anti*-carbomagnesiation.[3,4] It was also noted that the reaction of secondary propargylic alcohols afforded a mixture of two regioisomeric products, while the reaction of tertiary propargylic alcohols afforded the linear products as the major.[3c,d]

In one of our ongoing projects, we need to prepare the highly loaded secondary allylic alcohols. However, when we ran the similar reaction of 3-butyn-2-ol with *n*-C_5H_{11}MgBr in ether under the catalysis of 10 mol % CuI at −10 °C to room temperature,[3] a mixture of 3-methyleneoctan-2-ol (**2a**) and 3-nonen-2-ol (**3a**) in 32% yield and with a ratio of 19:81 was formed upon hydrolysis. In this reaction, 3-nonen-2-ol (**3a**) was the major product (entry 1, Table 1). Thus, detailed studies were performed to optimize the regioselectivity for this Cu(I)-catalyzed carbometallation of secondary propargylic alcohols, with the aim to prepare **2a**-type products with high selectivity. In this paper, we wish to disclose these results.

Results and Discussion

When a solution of *n*-C_5H_{11}MgBr in THF was used instead of that in Et_2O, the ratio of **2a**/**3a** was reversed to 87:13, with a combined yield of 42% (entry 2, Table 1). When THF was applied throughout the whole reaction process, the reaction afforded **2a** and **3a** in combined 43% yield with a ratio of **2a**/**3a** as high as 93:7 (entry 3, Table 1). Similar results were

* Corresponding author. Fax: (+86) 21-64167510.
† Zhejiang University.
‡ Chinese Academy of Sciences.

(1) For reviews on the synthesis of chiral propargylic alcohols, see: (a) Frantz, D. E.; Fassler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373. (b) He, Q.; Ma, S. *Chin. J. Org. Chem.* **2002**, *22*, 375. (c) Pu, L. *Tetrahedron* **2003**, *59*, 9873.

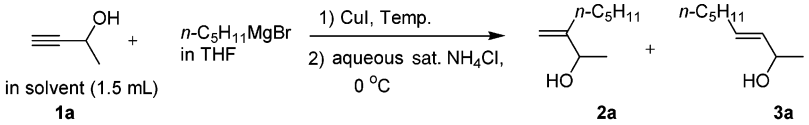
(2) (a) Nakamura, M.; Liang, C.; Nakamura, E. *Org. Lett.* **2004**, *6*, 2015. (b) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2002**, *124*, 4178. (c) Trost, B. M.; Oi, S. *J. Am. Chem. Soc.* **2001**, *123*, 1230. (d) Ma, S.; Wu, B.; Zhao, S. *Org. Lett.* **2003**, *5*, 4429. (e) Trost, B. M.; Ball, Z. T.; Joge, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 3415. (f) Nishibayashi, Y.; Inada, Y.; Yoshikawa, M.; Hidai, M.; Uemura, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1495. (g) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Milton, M. D.; Hidai, M.; Uemura, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 2681. (h) Nishibayashi, Y.; Inada, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2003**, *125*, 6060.

(3) (a) Duboudin, J. G.; Jousseaume, B. *Synth. Commun.* **1979**, *9*, 53. (b) Duboudin, J. G.; Jousseaume, B. *J. Organomet. Chem.* **1979**, *168*, 1. For carbometallation of propargylic alcohols affording regioisomeric mixtures, see: (c) Normant, J. F.; Alexakis, A.; Villieras, J. *J. Organomet. Chem.* **1973**, *57*, C99. (d) Alexakis, A.; Normant, J. F.; Villieras, J. *J. Mol. Catal.* **1975/76**, *1*, 43.

(4) (a) Tessier, P. E.; Nguyen, N.; Clay, M. D.; Fallis, A. G. *Org. Lett.* **2005**, *7*, 767. (b) Tessier, P. E.; Penwell, A. J.; Souza, F. E. S.; Fallis, A. G. *Org. Lett.* **2003**, *5*, 2989.

10.1021/jo0524021 CCC: $33.50
Published on Web 03/02/2006

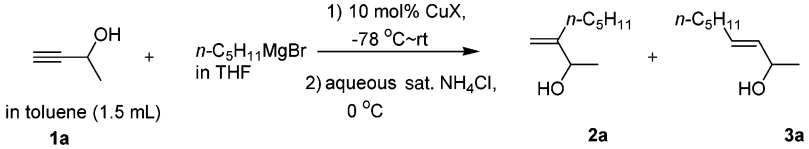
TABLE 1. Optimization of Reaction Conditions for CuI-Catalyzed Addition of *n*-C_5H_{11}MgBr with 3-Butyn-2-ol



entry	solvent	temp	catalyst (mol %)	time (h)	**2a**/**3a**	yield of **2a** + **3a**[b] (%)
1[a]	Et_2O	−10 °C∼rt	10	17	19:81	32
2	Et_2O	−10 °C∼rt	10	5	87:13	42
3	THF	−10 °C∼rt	10	5	93:7	43
4	1,4-dioxane	−10 °C∼rt	10	5	88:12	42
5	benzene	−10 °C∼rt	10	5	92:8	52
6	toluene	−10 °C∼rt	10	5	92:8	44
7	benzene	−78 °C∼rt	10	5	93:7	44
8	THF	−78 °C∼rt	10	5	93:7	19
9	toluene	−78 °C∼rt	10	5	93:7	46
10	toluene	−78 °C∼rt	20	5	91:9	63
11	toluene	−78 °C∼rt	50	5	93:7	75
12	toluene	−78 °C∼rt	100	5	87:13	70
13	toluene	0 °C	50	5	89:11	76
14	toluene	−10 °C	50	10	86:14	73
15	toluene	−20 °C	50	5.5	91:9	67
16	toluene	−30 °C	50	12	91:9	66
17	toluene	−40 °C	50	7	91:9	57

[a] A solution of *n*-C_5H_{11}MgBr in Et_2O was used. [b] Combined yield determined by ^{1}H NMR spectra using 1,3,5-trimethylbenzene as the internal standard.

TABLE 2. Effect of Catalyst on the Addition of *n*-C_5H_{11}MgBr with 3-Butyn-2-ol



entry	CuX	time (h)	yield of **2a** + **3a**[a] (%)	**2a**:**3a**
1	CuI	5	46	93:7
2	CuCl	17.5	43	95:5
3	CuBr	17.5	47	94:6
4	$CuCl_2$	7	29	91:9
5	$CuBr_2$	7	32	91:9

[a] Combined yield determined by ^{1}H NMR spectra using 1,3,5-trimethylbenzene as the internal standard.

observed when a solution of 3-butyn-2-ol in 1,4-dioxane, benzene, or toluene was treated with a THF solution of *n*-C_5H_{11}MgBr at −10 °C to rt (entries 4−6, Table 1). When the reaction was performed at −78 °C to rt, the yields were lower (entries 7 and 8, Table 1). When the amount of CuI was increased to 20 or 50%, the yields were higher, with a similar regioselectivity (entries 9−11, Table 1). With 100 mol % of CuI, both the yield and the ratio were poorer (compare entry 11 with entry 12, Table 1). With 50 mol % of CuI, the effect of temperature was also studied (entries 14−17, Table 1). Thus, we concluded conditions A (entry 11, Table 1) for Table 4 should be 10 mmol of alcohol in 15 mL of toluene, 50 mol % CuI, 3.5 equiv of Grignard reagents, and at a temperature of −78 °C to rt.

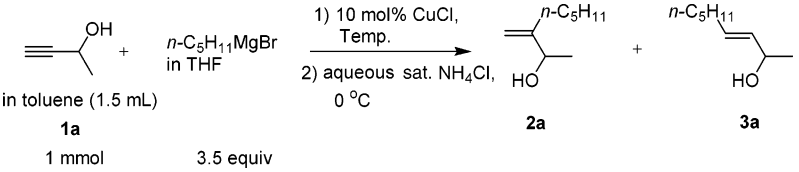
The effect of different Cu(I) or Cu(II) catalysts was also studied (Table 2), implying that the results of the Cu(I)-catalyst (entries 1−3, Table 2) are better than those with Cu(II)-catalysts (entries 4 and 5, Table 2).

It should be noted that the 10 mol % CuCl-catalyzed reaction afforded the products in slightly better regioselectivity than the reaction catalyzed by CuI (compare entry 2 with entry 1, Table 2). Thus, the conditions for the CuCl-catalyzed reaction of **1a** with the THF solution of *n*-C_5H_{11}MgBr in toluene were also optimized (Table 3). The best results were observed when the reaction was conducted at −78 °C to rt (entry 3, Table 3).

With conditions A and B (conditions B for Table 4: 10 mmol of alcohol in 15 mL of toluene, 10 mol % CuCl, 3.5 equiv of Grignard reagents, and −78 °C to rt) in hand, the scope of the Cu(I)-catalyzed carbometallation of a THF solution of R^2MgBr with different secondary propargylic alcohols in toluene was studied with some typical results summarized in Table 4. From the results in Table 4, the following points should be noted: (1) The yields under conditions A are usually higher than conditions B, while the regioselectivity for the reaction catalyzed by CuCl is, in most cases, higher than that with CuI. (2) For the substrates with R^1 and R^2 being alkyl, the regioselectivity is R^1-dependent: the regioselectivity for R^1 being Me is much higher than that with R^1 being Et (**1b**), *n*-Pr (**1c**), or *n*-C_5H_{11} (**1d**) (compare entries 1−10 with entries 13−22, Table 4). (3) The results of R^2 = phenyl were very poor (entries 11 and 12, Table 4). (4) The two products **2** and **3** can be easily separated by chromatography on silica gel.

If iodination was applied instead of protonation, 4-iodo-3-(*n*-pentyl)-3(*Z*)-buten-2-ol **4a** can be isolated in 66% yield, which may undergo Sonogashira coupling with terminal alkynes

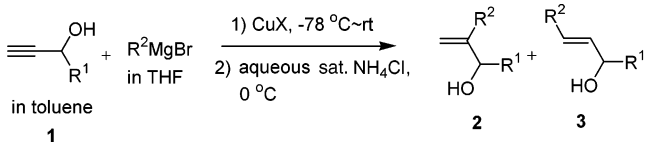
TABLE 3. Optimization of Reaction Conditions for CuCl-Catalyzed Addition of *n*-C_5H_{11}MgBr with 3-Butyn-2-ol



entry	temp	time (h)	**2a**:**3a**	yield of **2a** + **3a**[a] (%)
1	−10 °C∼rt	15	87:13	39
2	−30 °C∼rt	20.5	93:7	28
3	−78 °C∼rt	17.5	95:5	43

[a] Combined yield determined by ^{1}H NMR spectra using 1,3,5-trimethylbenzene as the internal standard.

TABLE 4. CuX-Catalyzed Addition of Grignard Reagents with Terminal Propargylic Alcohols



entry	R^1	R^2	conditions[a]	time (h)	**2**:**3**[b]	yield of **2**[c] (%)	yield of **3**[c] (%)
1	Me	*n*-C_5H_{11}	A	5	93:7 (**2a**:**3a**)	70	5
2	Me	*n*-C_5H_{11}	B	18	94:6 (**2a**:**3a**)	43	3
3	Me	*n*-C_6H_{13}	A	18	90:10 (**2b**:**3b**)	62	7
4	Me	*n*-C_6H_{13}	B	18	92:8 (**2b**:**3b**)	39	4
5	Me	*n*-C_7H_{15}	A	18	90:10 (**2c**:**3c**)	77	8
6	Me	*n*-C_7H_{15}	B	18	93:7 (**2c**:**3c**)	45	4
7	Me	*n*-C_8H_{17}	A	18	88:12 (**2d**:**3d**)	73	10
8	Me	*n*-C_8H_{17}	B	18	91:9 (**2d**:**3d**)	29	3
9	Me	*n*-C_4H_9	A	18	92:8 (**2e**:**3e**)	65	4
10	Me	*n*-C_4H_9	B	18	94:6 (**2e**:**3e**)	37	1
11	Me	Ph	A	18	41:59 (**2f**:**3f**)	20	30
12	Me	Ph	B	18	42:58 (**2f**:**3f**)	18	24
13	Et	*n*-C_5H_{11}	A	5	80:20 (**2g**:**3g**)	58	13
14	Et	*n*-C_5H_{11}	B	17	85:15 (**2g**:**3g**)	17	2
15	Et	*n*-C_6H_{13}	A	17	86:14 (**2h**:**3h**)	61	8
16	Et	*n*-C_6H_{13}	B	17	83:17 (**2h**:**3h**)	18	4
17	Et	*n*-C_8H_{17}	A	22	79:21 (**2i**:**3i**)	75	21
18	Et	*n*-C_8H_{17}	B	18	82:18 (**2i**:**3i**)[c]	18	4
19	*n*-C_3H_7	*n*-C_5H_{11}	A	18	77:23 (**2j**:**3j**)	50	14
20	*n*-C_3H_7	*n*-C_5H_{11}	B	15	86:14 (**2j**:**3j**)	24	3
21	*n*-C_5H_{11}	*n*-C_5H_{11}	A	19	83:17 (**2k**:**3k**)	59	12
22	*n*-C_5H_{11}	*n*-C_5H_{11}	B	19	88:12 (**2k**:**3k**)	19	3

[a] Conditions A: 10 mmol of alcohol, 3.5 equiv of Grignard reagents (1 M), 50 mol % CuI, 15 mL of toluene, and −78 °C∼rt. Conditions B: 10 mmol of alcohol, 3.5 equiv of Grignard reagents, 10 mol % CuCl, 15 mL of toluene, and −78 °C∼rt. [b] Determined by NMR analysis. [c] Isolated yield.

and Kumada-type coupling with PhMgBr to afford the corresponding coupling products **6a**−**c** and **7a**, respectively(Scheme 1).[5] The coupling reaction with $PhB(OH)_2$ or *n*-C_4H_9ZnBr gave very poor yields of the protonation product **2a** as the major byproduct.

The in-situ formed cyclic organometallic intermediate **A** may also undergo a Pd-catalyzed Kumada-type coupling reaction directly with PhI to afford **7a** and **8a** in 70% combined yield with a ratio of 92:8 by NMR (Scheme 2).[4,6] After chromatographic separation, pure **7a** was isolated easily in 62% yield.

With optically active (*R*)-3-butyn-2-ol ((*R*)-**1a**),[7,8] optically active allylic alcohols (*R*)-**2a** and (*R*)-**4a** can be prepared without an obvious loss of the enantiopurity either by protonation or by iodination in 63 or 59% isolated yields, respectively (Scheme 3). The absolute configurations of (*R*)-(+)-**2a** and (*R*)-(+)-**4a** was tentatively assigned on the basis of the assumption that no reaction occurred to the chiral center in (*R*)-**1a**.

In conclusion, a highly regio- and stereoselective Cu(I)-catalyzed carbometallation of secondary propargylic alcohols with alkyl Grignard reagents affording 2-substituted allylic alcohols was developed upon reacting with H^+ or I^+. The **A**-type cyclic organometallic intermediate formed may undergo iodination or a Pd(0)-catalyzed coupling reaction to afford stereodefined allylic alcohols. The iodide formed by iodination may

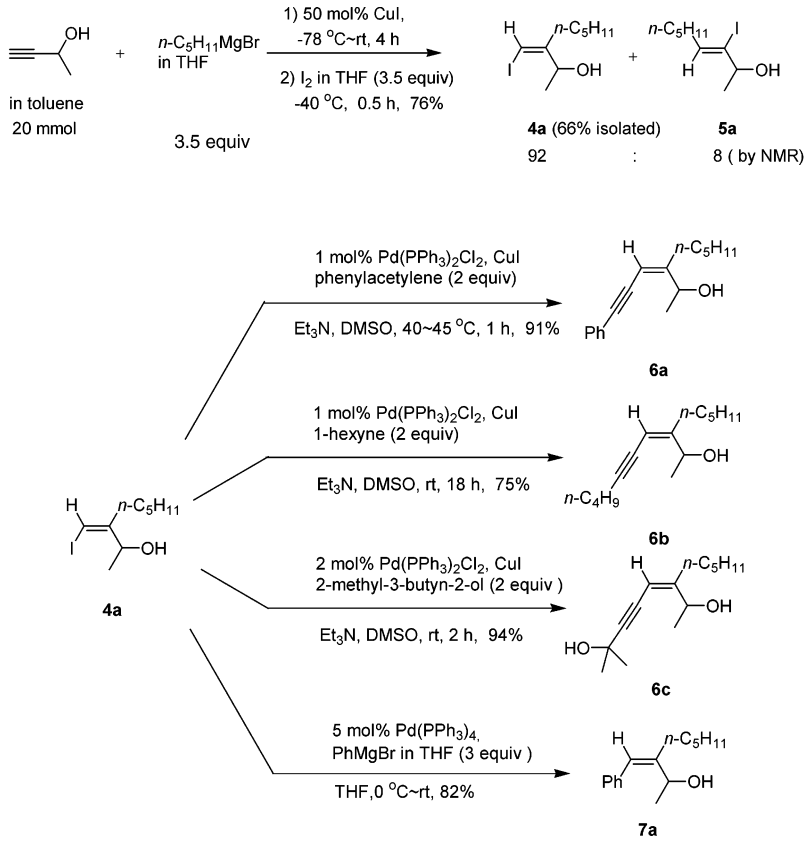
(5) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Kollhofer, A.; Pullmann, T.; Plenio, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1056. (c) Tykwinski, R. *Angew. Chem., Int. Ed.* **2003**, *42*, 1566. (d) Gelman, D.; Buchwald, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 5993. (e) Sakai, N.; Annaka, K.; Konakahara, T. *Org. Lett.* **2004**, *6*, 1527. (f) Ma, S.; Ren, H.; Wei, Q. *J. Am. Chem. Soc.* **2003**, *125*, 4817. (g) Shi, M.; Liu, L.; Tang, J. *J. Org. Chem.* **2005**, *70*, 10420.

(6) (a) Duboudin, J. G.; Jousseaume, B.; Bonakdar, A. *J. Organomet. Chem.* **1979**, *168*, 227. (b) Duboudin, J. G.; Jousseaume, B. *J. Organomet. Chem.* **1979**, *168*, 233. (c) Negishi, E.; Zhang, Y.; Cederbaum, F. E.; Webb, M. B. *J. Org. Chem.* **1986**, *51*, 4080. (d) Fallis, A. G.; Forgione, P. *Tetrahedron* **2001**, *57*, 5899.

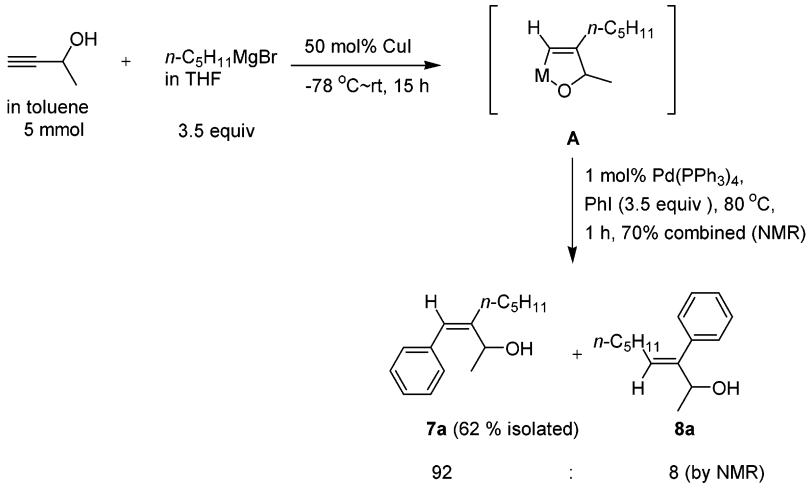
(7) Gallagher, W. P.; Maleczka, R. E. *J. Org. Chem.* **2003**, *68*, 6775.

(8) The sample used in this study was purchased from Acros Organics.

SCHEME 1



SCHEME 2



undergo a Sonogashira or Kumada-type coupling reaction. Although the exact nature of the solvent effect is not clear, the difference in regioselectivity may be explained by the easy formation of the cyclic metalacyclic intermediate **A** in a medium containing THF. Further studies in this area are being conducted in our laboratory.

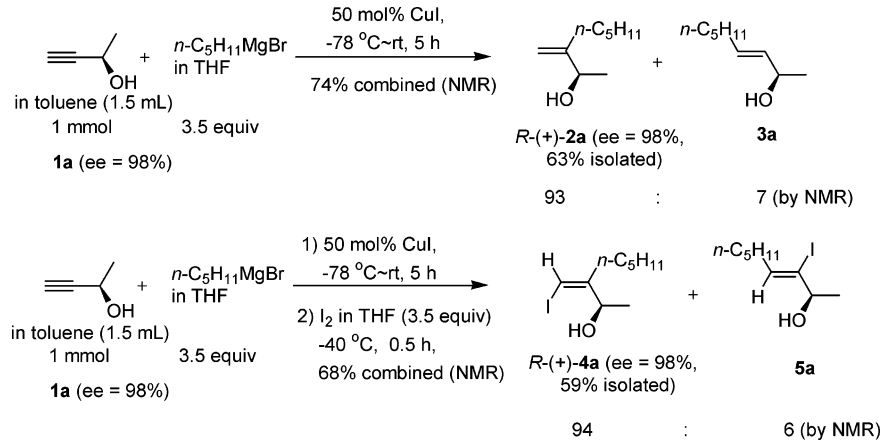
Experimental Section

Starting Materials. Racemic 3-butyn-2-ol **(1a)**[9] and (*R*)-**1a** are commercially available and used as is.

General Procedure I for the Synthesis of Propargylic Alcohols. Several drops of ethyl bromide were added to a mixture of magnesium turnings (120 mmol) and I_2 (a few crystals) in THF under a nitrogen atmosphere. Upon the initiation of the Grignard reaction, the remaining ethyl bromide (120 mmol) was added dropwise, which was followed by stirring for 2 h at room temperature. A stream of acetylene was bubbled at −20 °C (not above 10 °C) for 45 min. Then an aldehyde (100 mmol) was added at less than −30 °C, which was followed by a natural warming to room temperature. After the complete conversion of the starting material, as monitored by TLC, the reaction mixture was cooled to 0 °C, quenched with saturated NH_4Cl, extracted with diethyl ether, and dried over anhydrous Na_2SO_4. The evaporation of the solvent and the distillation afforded the propargylic alcohols.

(9) Jacobs, T. L.; Petty, W. L.; Teach, E. G. *J. Am. Chem. Soc.* **1960**, *82*, 4094.

SCHEME 3



Synthesis of 1-Pentyn-3-ol (1b).[9] Yield = 50% (62 °C/42 mmHg; lit. 52.4−52.6 °C/35 mmHg). Liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33−4.17 (m, 1H), 2.44 (s, 1H), 2.34−2.20 (br s, 1H), 1.77−1.60 (m, 2H), 1.00 (t, J = 7.4 Hz, 3H).

General Procedure II for the Cu(I)-Catalyzed Carbometalation of Propargylic Alcohols and the Subsequent Protonation. Conditions A: To a solution of propargylic alcohol (10.0 mmol) in dry toluene (15 mL) under a nitrogen atmosphere was added CuI (5.0 mmol, 50 mol %) at room temperature. The requisite Grignard reagent (3.5 equiv, 1 M in THF, 35 mmol) was then added dropwise to the reaction mixture at less than −70 °C, which was followed by a natural warming to room temperature. After complete conversion of the starting material, as monitored by TLC, the reaction mixture was cooled to 0 °C, quenched with saturated NH_4-Cl, extracted with diethyl ether (3 × 30 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 (140 μL, 1.0 mmol). Chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 20/1∼40/1) of the crude product afforded the desired product.

Conditions B: To a solution of propargylic alcohol (10.0 mmol) in dry toluene (15 mL) under a nitrogen atmosphere was added CuCl (1.0 mmol, 10 mol %) at room temperature. The requisite Grignard reagent (3.5 equiv, 1 M in THF, 35 mmol) was then added dropwise to the reaction mixture at less than −70 °C, which was followed by a natural warming to room temperature. After complete conversion of the starting material, as monitored by TLC, the reaction mixture was cooled to 0 °C, quenched with saturated NH_4-Cl, extracted with diethyl ether (3 × 30 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 (140 μL, 1.0 mmol). Chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 20/1∼40/1) of the crude product afforded the desired product.

3-Methyleneoctan-2-ol (2a) and 3-(*E*)-Nonen-2-ol (3a). Conditions A: The reaction of **1a** (0.7016 g, 10.0 mmol), CuI (0.9489 g, 5.0 mmol, 50 mol %), and n-$C_5H_{11}MgBr$ in THF (1 M, 35 mL, 35 mmol) afforded **2a** (1.0012 g, 75%) and **3a** (0.0681 g, 5%).

Conditions B: The reaction of **1a** (0.7022 g, 10.0 mmol), CuCl (0.0990 g, 1.0 mmol, 10 mol %), and n-$C_5H_{11}MgBr$ in THF (1 M, 35 mL, 35 mmol) afforded **2a** (0.6098 g, 43%) and **3a** (0.0408 g, 3%).

2a:[10] Liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99 (s, 1H), 4.76 (s, 1H), 4.24−4.16 (m, 1H), 2.11−1.92 (m, 3H), 1.49−1.39 (m, 2H), 1.38−1.20 (m, 7H), 0.87 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.5, 107.8, 70.8, 31.7, 31.6, 27.7, 22.5, 22.1, 14.0; MS (m/z) 142 (M^+, 1.35), 71 (100); IR (neat, cm^{-1}) 3361, 2930, 2861, 1647, 1458.

3a:[11] Liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61 (dt, J_1 = 15.5 Hz, J_2 = 7.0 Hz, 1H), 5.48 (dd, J_1 = 15.5 Hz, J_2 = 6.6 Hz, 1H), 4.28−4.18 (m, 1H), 1.99 (q, J = 7.1 Hz, 2H), 1.70 (br s, 1H), 1.38−1.26 (m, 6H), 1.23 (d, J = 6.4 Hz, 3H), 0.87 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 134.0, 131.1, 68.9, 32.0, 31.3, 28.8, 23.3, 22.5, 14.0; MS (m/z) 142 (M^+, 1.65), 71 (100); IR (neat, cm^{-1}) 3354, 2927, 1670, 1458.

Procedure for the Cu(I)-Catalyzed Carbometalation of Propargylic Alcohols and Iodination. Synthesis of (*Z*)-3-Iodomethyleneoctan-2-ol (4a). To a solution of **1a** (1.4001 g, 20.0 mmol) in dry toluene (30 mL) was added CuI (1.8977 g, 10.0 mmol, 50 mol %) at room temperature under a nitrogen atmosphere. A solution of n-$C_5H_{11}MgBr$ in THF (70 mL, 3.5 equiv, 1 M in THF) was then added dropwise to the reaction mixture at less than −70 °C. After the addition, the mixture was warmed gradually to room temperature and monitored by TLC. After complete conversion of the starting material, the reaction was quenched subsequently with the dropwise addition of a solution of I_2 (18.0031 g, 3.5 equiv, 70 mmol) in THF (50 mL) at −40 °C. After being warmed to 0 °C for 0.5 h, the reaction mixture was treated with a saturated aqueous solution of $Na_2S_2O_3$ at 0 °C. After extraction with diethyl ether (3 × 30 mL), drying over anhydrous Na_2SO_4, and evaporation, the NMR yields were determined by NMR analysis using 1,3,5-trimethylbenzene as the internal standard (140 μL, 1 mmol) (**4a**/**5a** = 92:8, combined yield of **4a** and **5a**: 76%). Chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 20/1) afforded **4a** (3.5792 g, 66%).

Liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (s, 1H), 4.78 (q, J = 6.4 Hz, 1H), 2.30−2.15 (m, 2H), 1.86−1.74 (br s, 1H), 1.53−1.42 (m, 2H), 1.37−1.29 (m, 4H), 1.27 (d, J = 6.8 Hz, 3H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.1, 74.0, 73.1, 31.9, 31.6, 28.2, 22.4, 20.7, 14.0; MS (m/z) 268 (M^+, 5.14), 71 (100); IR (neat, cm^{-1}) 3356, 2928, 2859, 1603, 1459. HRMS calcd for $C_9H_{17}OI$: 268.0324. Found: 268.0348.

Procedure for the Sonogashira Coupling Reaction of 4a with Terminal Alkynes. (*Z*)-3-Pentyl-6-phenylhex-5-yn-3-en-2-ol (6a). A mixture of $Pd(PPh_3)_2Cl_2$ (0.0017 g, 1 mol %, 0.0025 mmol), CuI (0.0007 g, 1.4 mol %, 0.0035 mmol), **4a** (0.0679 g, 0.25 mmol), phenylacetylene (0.0518 g, 0.50 mmol), and Et_3N (1 mL) in DMSO (1 mL) was heated at 40−45 °C over a period of 1 h under nitrogen. After complete conversion of the starting materials, as monitored by TLC, the reaction mixture was cooled to room temperature and quenched with 3 mL of water. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic layer was dried over Na_2SO_4. Evaporation

(10) Vykhrestyuk, N. I.; Bagatchenko, G. S.; Gordash, T.; Yu, T.; Tikhonov, V. P.; Tkachenko, D. A.; Chernyshev, I. A. *Zh. Prikl. Spektrosk.* **1977**, *26*, 526.

(11) Fuller, J. C.; Stangeland, E. L.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett.* **1993**, *34*, 257.

and column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 30/1) afforded **6a** (0.0557 g, 92%). Liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.40 (m, 2H), 7.37−7.30 (m, 3H), 5.55 (s, 1H), 5.10 (q, J = 6.7 Hz, 1H), 2.30−2.15 (m, 2H), 2.15−2.10 (br s, 1H), 1.57−1.46 (m, 2H), 1.42−1.30 (m, 7H), 0.93 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.6, 131.2, 128.3, 128.0, 123.4, 104.1, 94.4, 86.0, 68.9, 31.7, 30.6, 28.0, 22.5, 21.5, 14.0; MS (*m*/*z*) 242 (M^+, 79.57), 43 (100); IR (neat, cm^{-1}) 3361, 2928, 2858, 2197, 1595, 1450. HRMS calcd for $C_{17}H_{22}O$: 242.1671. Found: 242.1662.

(*Z*)-3-Pentyldec-3-en-5-yn-2-ol (6b). A mixture of $Pd(PPh_3)_2Cl_2$ (0.0018 g, 1 mol %, 0.0025 mmol), CuI (0.0007 g, 1.4 mol %, 0.0035 mmol), **4a** (0.0681 g, 0.25 mmol), 1-hexyne (0.0421 g, 0.50 mmol), and Et_3N (1 mL) in DMSO (1 mL) was stirred over a period of 18 h under nitrogen at room temperature. After complete conversion of the starting materials, as monitored by TLC, the reaction mixture was quenched with 3 mL of water. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic layer was dried over Na_2SO_4. Evaporation and column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 40/1) afforded **6b** (0.0421 g, 75%). Liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.28 (s, 1H), 4.88 (q, J = 6.7 Hz, 1H), 2.33 (t, J = 7.0 Hz, 2H), 2.18−2.02 (m, 3H), 1.55−1.37 (m, 6H), 1.37−1.23 (m, 7H), 0.94−0.83 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.7, 104.5, 95.7, 76.9, 68.9, 31.7, 30.90, 30.86, 28.1, 22.5, 22.0, 21.4, 19.2, 14.0, 13.6; MS (*m*/*z*) 222 (M^+, 34.29), 43 (100); IR (neat, cm^{-1}) 3374, 2929, 2212, 1640, 1465. HRMS calcd for $C_{15}H_{26}O$: 222.1984. Found: 222.1969.

(*Z*)-2-Methyl-6-pentyloct-3-yn-5-en-2,7-diol (6c). A mixture of $Pd(PPh_3)_2Cl_2$ (0.0036 g, 2 mol %, 0.005 mmol), CuI (0.0013 g, 2.6 mol %, 0.0068 mmol), **4a** (0.0654 g, 0.24 mmol), 2-methyl-3-butyn-2-ol (0.0438 g, 0.50 mmol), and Et_3N (1 mL) in DMSO (1 mL) was stirred over a period of 2 h under nitrogen at room temperature. After complete conversion of the starting materials, as monitored by TLC, the reaction mixture was quenched with 3 mL of water. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic layer was dried over Na_2SO_4. Evaporation and column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 3/1) afforded **6c** (0.0515 g, 94%). Liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29 (s, 1H), 4.89 (q, J = 6.7 Hz, 1H), 2.38 (br s, 2H), 2.20−2.03 (m, 2H), 1.53 (s, 6H), 1.49−1.38 (m, 2H), 1.36−1.26 (m, 7H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.4, 103.6, 99.0, 78.6, 68.7, 65.6, 31.6, 31.40, 31.37, 27.9, 22.5, 21.3, 14.0; MS (*m*/*z*) 224 (M^+, 0.13), 206 ($M^+ - H_2O$, 66.59), 43 (100); IR (neat, cm^{-1}) 3346, 2929, 2860, 2216, 1624, 1456, 1362, 1244, 1166. HRMS calcd for $C_{14}H_{22}O$ ($M^+ - H_2O$): 206.1671. Found: 206.1664.

Procedure for the Kumada Coupling Reaction of 4a with PhMgBr. Synthesis of (*Z*)-3-Benzylideneoctan-2-ol (7a). To a solution of **4a** (0.0641 g, 0.24 mmol) in dry THF (1 mL) under a nitrogen atmosphere was added $Pd(PPh_3)_4$ (0.0140 g, 5 mol %, 0.012 mmol) at room temperature. A solution of PhMgBr in THF (0.75 mL, 1 M, 0.75 mmol) was then added dropwise to the reaction mixture at 0 °C, which was followed by a natural warming to room temperature. After complete conversion of the starting materials, as monitored by TLC, the reaction was quenched with a saturated aqueous solution of NH_4Cl at 0 °C. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic layer was dried over Na_2SO_4. Evaporation and column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 40/1) afforded **7a** (0.0430 g, 82%). Liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.31 (m, 2H), 7.27−7.17 (m, 3H), 6.38 (s, 1H), 4.91 (q, J = 6.5 Hz, 1H), 2.36−2.27 (m, 2H), 1.70−1.53 (m, 3H), 1.46−1.32 (m, 7H), 0.98−0.90 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.2, 137.5, 128.7, 128.1, 126.4, 125.9, 65.9, 32.0, 29.8, 29.1, 22.6, 21.6, 14.1; MS (*m*/*z*) 218 (M^+, 2.86), 147 (100); IR (neat, cm^{-1}) 3356, 2928, 2859, 1599. HRMS calcd for $C_{15}H_{22}O$: 218.1671. Found: 218.1664.

Pd-Catalyzed Kumada-Type Coupling Reaction of the Organometallic Intermediate A with PhI. Synthesis of (*Z*)-3-Benzylideneoctan-2-ol (7a). To a solution of **1a** (0.3517 g, 5.0 mmol) in dry toluene (8 mL) was added CuI (0.4777 g, 2.5 mmol, 50 mol %) at room temperature under a nitrogen atmosphere. A solution of *n*-$C_5H_{11}MgBr$ in THF (18 mL, 3.5 equiv, 1 M in THF, 18 mmol) was then added dropwise to the reaction mixture at less than −70 °C. Then the mixture was warmed gradually to room temperature and monitored by TLC. After complete conversion of the starting material, a solution of $Pd(PPh_3)_4$ (0.0584 g, 1 mol %, 0.05 mmol) and PhI (3.5911 g, 3.5 equiv, 18 mmol) in THF (5 mL) was added with a syringe to the reaction mixture. After the addition, the reaction mixture was stirred under reflux for 1 h and quenched with the saturated NH_4Cl at 0 °C. After extraction with diethyl ether (3 × 30 mL), drying over anhydrous Na_2SO_4, and evaporation, the NMR yields were determined by NMR analysis using 1,3,5-trimethylbenzene as the internal standard (140 μL, 1 mmol; **7a**/**8a** = 92:8, combined yield of **7a** and **8a**, 70%). Chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 20/1) afforded **7a** (0.6748 g, 62%).

Procedure for the Synthesis of (*R*)-(+)-2a. To a solution of (*R*)-**1a** (0.0704 g, 1.0 mmol) in dry toluene (1.5 mL) under a nitrogen atmosphere was added CuI (0.5 mmol, 50 mol %) at room temperature. The requisite Grignard reagent (3.5 equiv, 1 M in THF, 3.5 mmol) was then added dropwise to the reaction mixture at less than −70 °C, which was followed by a natural warming to room temperature. After complete conversion of the starting material, as monitored by TLC, the reaction mixture was cooled to 0 °C, quenched with saturated NH_4Cl, extracted with diethyl ether (3 × 10 mL), and dried over anhydrous Na_2SO_4. The NMR ratio of **2a**/**3a** (93:7) 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) afforded (*R*)-(+)-**2a** (0.0894 g, 63%, ee = 98%, determined after its conversion to the corresponding acetate); $[\alpha]^{20}_D$ = +8.0 (c 1.17, $CHCl_3$). The data of compound (*R*)-(+)-**2a** are the same as that for racemic **2a**.

Procedure for the Synthesis of (*R*)-(+)-4a. To a solution of **1a** (0.0704 g, 1.0 mmol) in dry toluene (1.5 mL) was added CuI (0.0950 g, 0.5 mmol, 50 mol %) at room temperature under a nitrogen atmosphere. A solution of *n*-$C_5H_{11}MgBr$ in THF (3.5 mL, 3.5 equiv, 1 M in THF) was then added dropwise to the reaction mixture at less than −70 °C. Then the mixture was warmed gradually to room temperature and monitored by TLC. After complete conversion of the starting material, the reaction was quenched subsequently with the dropwise addition of a solution of I_2 (0.8900 g, 3.5 equiv, 3.5 mmol) in THF (5 mL) at −40 °C, and then the reaction mixture was warmed to 0 °C for 0.5 h and treated with a saturated aqueous solution of $Na_2S_2O_3$ at 0 °C. After extraction with diethyl ether (3 × 30 mL), drying over anhydrous Na_2SO_4, and evaporation, the NMR ratio of **4a**/**5a** (94:6) was determined by NMR analysis 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) afforded (*R*)-(+)-**4a** (0.1597 g, 59%, ee = 98%; HPLC conditions: Chiralcel AS−H, hexane/*i*-PrOH = 90/10, 0.8 mL/min, n = 230 nm, t_R 4.8 (minor), 5.1 (major)); $[\alpha]^{20}_D$ = +10.4 (*c* 1.80, $CHCl_3$). The data of compound (*R*)-(+)-**4a** are the same as that for racemic **4a**.

Acknowledgment. Financial support from the National Natural Science Foundation of China (No. 20420130645), and Cheung Kong Scholar Program is greatly appreciated. S.M. is jointly appointed by Zhejiang University and Shanghai Institute of Organic Chemistry. This work was conducted at Zhejiang University.

Supporting Information Available: Experimental details for all the products not listed in the text and ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0524021