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# Copper(I)-Mediated Highly Stereoselective *syn*-Carbometalation of Secondary or Tertiary Propargylic Alcohols with Primary Grignard Reagents in Toluene with a High Linear Regioselectivity

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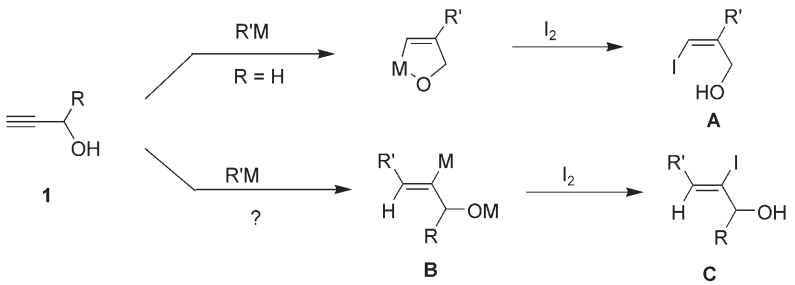
**Abstract:** A highly regio- and stereoselective *syn*-carbometalation of terminal secondary or tertiary propargylic alcohols with primary alkyl Grignard reagents in toluene or phenylmagnesium bromide in $Et_2O$ was developed, in which the alkyl or phenyl group from the Grignard reagents is introduced into the terminal position of the alcohols. The organometallic intermediate formed may be used directly for the coupling reaction with organic halides. Upon treatment with $I_2$ after the carbometalation, iodides may be obtained, which may undergo Sonogashira coupling reaction and highly stereoselective Novozym-435-catalyzed kinetic resolution to afford the optically active products.

**Keywords:** C–C coupling; copper; Grignard reagents; kinetic resolution; propargyl alcohols; regioselectivity

## Introduction

Hydro- or carbometalation of propargylic alcohols is an attractive reaction for organic chemists since propargylic alcohols are easily available[1–3] and the products are of synthetic importance due to the highly loaded functionalities.[4] In the hydro- or carbometalation reaction of primary propargylic alcohols, the alkyl or H group from the organometallic reagent was highly regio- and stereoselectively introduced into the 2-position of propargylic alcohols probably due to the favorable formation of the 5-membered metallacyclic intermediate affording the 3-iodo-2(*E*)-propenols **A** upon quenching with $I_2$ (Scheme 1).[5,6] However, for secondary or tertiary alcohols the carbometalation afforded regioisomeric mixtures of isomers **A** (branched) and **C** (linear) depending on the reaction conditions.[7] In this paper we report a highly stereoselective *syn*-carbometalation of secondary or tertiary propargylic alcohols with linear regioselectivity, which




**Scheme 1.**

led to the formation of the corresponding *syn*-carbometalation products **C** upon quenching with $I_2$.[8]

## Results and Discussion

When CuI (2 equivs.) was used, the reaction of 3-butyn-2-ol with *n*-$C_5H_{11}MgBr$ (6 equivs.) in ether[5] afforded a mixture of 3-iodo-3(*Z*)-nonen-2-ol **2a** and 4-iodo-3-(*n*-pentyl)-3-buten-2-ol **3a** in 74% combined yield with the ratio of **2a**/**3a** being 62:38 upon reaction with $I_2$ (entry 1, Table 1).[7] However, after some screening we observed that if the toluene solution of *n*-$C_5H_{11}MgBr$, *prepared in $Et_2O$ first followed by the addition of toluene and heating at 120 °C for 0.5 h*, was used, to our surprise, the carbometalation reaction of a toluene solution of **1a** at −40 °C to 0 °C afforded the products **2a** and **3a** in 71% yield with a **2a**/**3a** ratio as high as 95:5 after quenching with $I_2$ (entry 2, Table 1). The reaction can also be conducted using 1 equiv. of CuI (entry 3, Table 1). When the carbometalation reaction was conducted with 3.5 equivs. of the Grignard reagent, the yield was similar with a slightly lower selectivity (entry 4, Table 1). This was used as the standard procedure for this study. The same reaction with 2 equivs. of the Grignard reagent afforded the products in very low yield (entry 5, Table 1); the reaction at −40 °C for 2 h also provided the products in low yields (entry 6, Table 1). With 10 mol% of CuI, both the yield and the regioselectivity were poor (entry 7, Table 1).

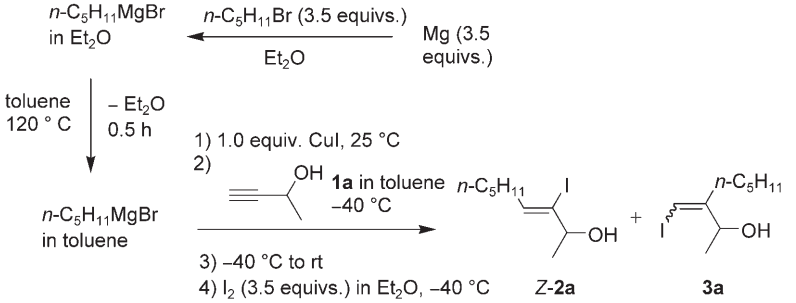
With this protocol in hand (entry 4, Table 1) we demonstrated the scope of this reaction with the typical results summarized in Table 2.

The following points are noteworthy: (1) The regioselectivity is, in most cases, high (≥ 90/10, Table 2); (2) *Z*-**2** was formed highly stereoselectively in this reaction indicating a *syn*-carbometalation process;[9] (3) Both secondary (entries 1–10, Table 2) and tertiary alcohols (entry 11, Table 2) can be used; (4) $R^2$ can be an alkyl (entries 1–7, Table 2), aryl (entries 8 and 9, Table 2), or heteroaryl group (entry 10, Table 2); (5) $R^1$ can be a primary alkyl or aryl group. No reaction was observed with *c*-$C_6H_{11}MgX$ (X=Br, Cl) or *t*-BuMgBr, and only trace reaction was observed with *o*-MeO-$C_6H_4MgBr$; (6) The configuration of **2** was determined by an NOE study of the compound **2a** and the coupling constants of the olefinic protons in the protonation product **2Hd** (Scheme 2).

Based on the structure of the products *Z*-**2**, the **B**-type intermediate **D** was proposed, which may undergo coupling reaction with allyl bromide[5a,10] or PhI (catalyzed by $Pd(PPh_3)_4$)[11] to afford the corresponding coupling products **4a** and **6a** smoothly in 55% and 56% isolated yields, respectively (Scheme 3).

Iodide **2a** can undergo the Sonogashira coupling reaction[12] with terminal alkynes in DMSO[12f] to afford **8a**. This racemic alcohol **2a** can also be efficiently resolved *via* the Novozym-435-catalyzed kinetic resolution[13,14] with vinyl acetate to afford *S*-(−)-**2a** and *R*-(+)-**9a** in excellent yields and enantiopurity (Scheme 4). The absolute configuration of (−)-**2a** was assigned to be *S* by comparing the specific rotation

**Table 1.** Optimization of the reaction conditions for the CuI-mediated carbometalation of 3-butyn-2-ol with *n*-$C_5H_{11}MgBr$.

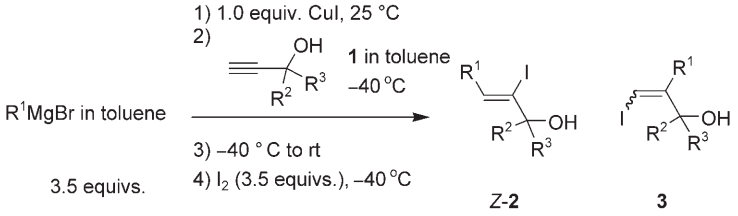



| Entry | *n*-$C_5H_{11}MgBr$:CuI:**1a**[a] | Solvent | Yield of (**2a**+**3a**) [%][b] | **2a**:**3a** |
|---|---|---|---|---|
| 1 | 6:2:1 | $Et_2O$ | 74 | 62:38 |
| 2 | 6:2:1 | toluene | 71 | 95:5 |
| 3 | 6:1:1 | toluene | 67 | 96:4 |
| 4 | 3.5:1:1 | toluene | 75 | 93:7 |
| 5 | 2:1:1 | toluene | 7 | 54:46 |
| 6[c] | 3.5:1:1 | toluene | 31 | 92:8 |
| 7 | 3.5:0.1:1 | toluene | 18 | 92:8 |

[a] Molar ratio.
[b] Yield determined from the $^1H$ NMR spectra using 1,3,5-trimethylbenzene as the internal standard.
[c] The reaction mixture was kept at −40 °C for 2 h and quenched at this temperature with $I_2$.

**Table 2.** The CuI-mediated carbometalation of propargylic alcohols with a toluene solution of Grignard reagents.[a]

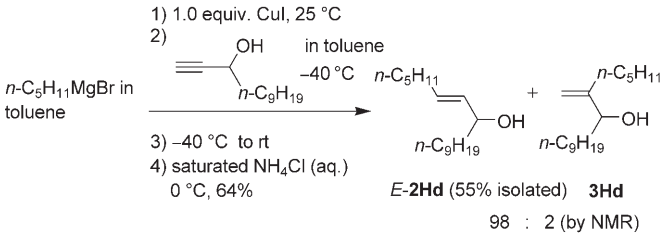



| Entry | $R^1$ | $R^2$ | $R^3$ | **2:3** | NMR yield of **2** [%] (isolated) |
|---|---|---|---|---|---|
| 1 | $n$-$C_5H_{11}$ | $CH_3$ | H | 93:7 (**2a**:**3a**) | 67 (67) |
| 2 | $n$-$C_5H_{11}$ | $C_2H_5$ | H | 96:4 (**2b**:**3b**) | 56 (50) |
| 3 | $n$-$C_5H_{11}$ | $n$-$C_3H_7$ | H | 96:4 (**2c**:**3c**) | 54 (53) |
| 4 | $n$-$C_5H_{11}$ | $n$-$C_9H_{19}$ | H | 99:1 (**2d**:**3d**) | 54 (48) |
| 5 | $n$-$C_7H_{15}$ | $CH_3$ | H | 95:5 (**2e**:**3e**) | 66 (62) |
| 6 | $n$-$C_7H_{15}$ | $n$-$C_3H_7$ | H | 98:2 (**2f**:**3f**) | 53 (51) |
| 7 | $n$-$C_7H_{15}$ | $n$-$C_5H_{11}$ | H | 97:3 (**2g**:**3g**) | 56 (55) |
| 8 | $n$-$C_5H_{11}$ | Ph | H | 93:7 (**2h**:**3h**)[b] | 66 (60) |
| 9 | $n$-$C_5H_{11}$ | $p$-$MeC_6H_4$- | H | 93:7 (**2i**:**3i**)[b] | 73 (62) |
| 10 | $n$-$C_5H_{11}$ | 2-thienyl | H | 95:5 (**2j**:**3j**)[b] | 68 (63) |
| 11 | $n$-$C_5H_{11}$ | $CH_3$ | $CH_3$ | >99:1 (**2k**:**3k**) | 68 (63) |
| 12 | Ph[c] | $CH_3$ | H | 90:10 (**2l**:**3l**) | - (64) |

[a] The reaction was conducted using Mg (20 mmol, 3.5 equivs.), $n$-$C_5H_{11}Br$ (21 mmol, 3.5 equivs.), CuI (5.7 mmol, 1 equiv.), propargylic alcohol (5.7 mmol, 1.0 equiv.) and $I_2$ (20 mmol, 3.5 equivs.), see Supporting Information for a detailed procedure.

[b] $Z$-**2**:$E$-**2** > 97:3.

[c] A solution of PhMgBr in $Et_2O$ was used instead of that in toluene.

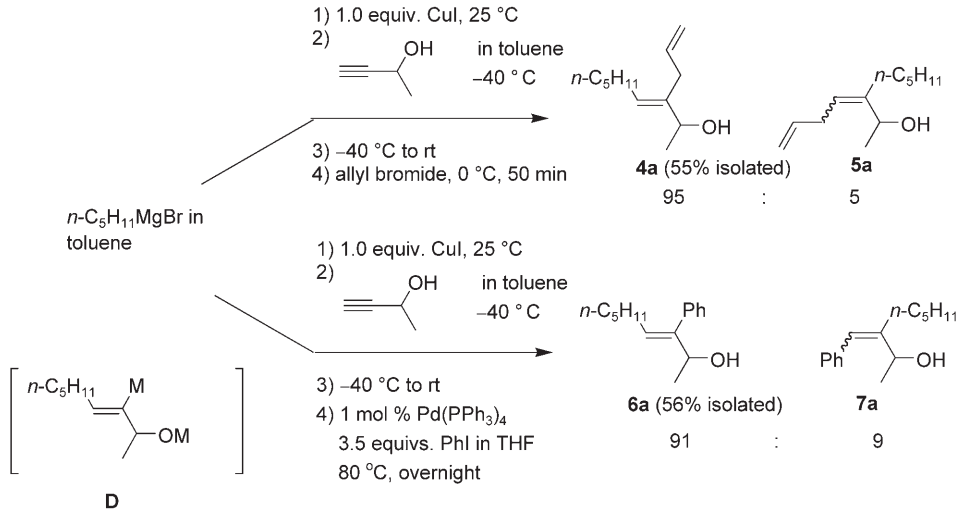



**Scheme 2.**

with $R$-(+)-**2a**, which was prepared via the CuI-mediated *syn*-carbometalation of $R$-**1a**[15] without obvious loss of the chirality (Scheme 5).

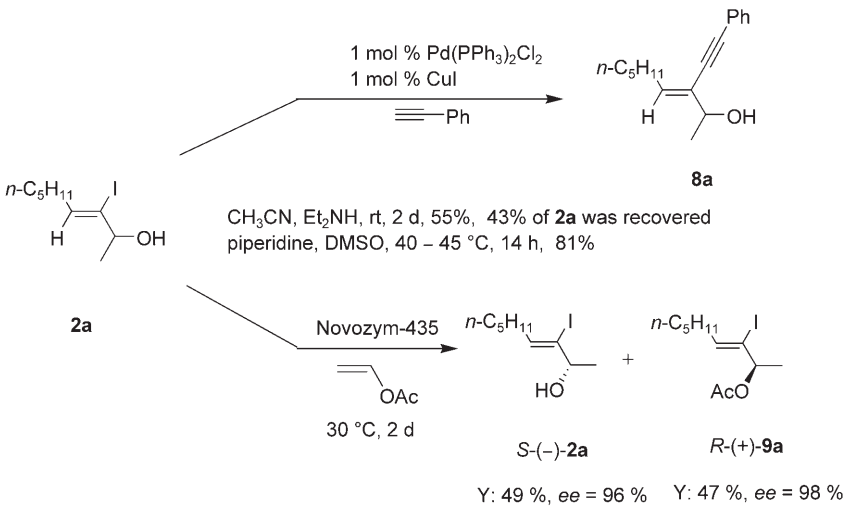
## Conclusions

In conclusion, we have developed a highly stereoselective *syn*-carbometalation of terminal secondary or

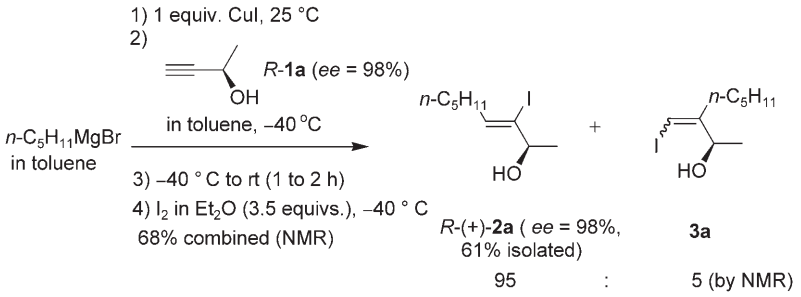



**Scheme 3.**




**Scheme 4.**




**Scheme 5.**

tertiary propargylic alcohols with a high linear regioselectivity based on a new way for the preparation of primary alkyl Grignard reagent in toluene. The intermediate formed may be used directly for the coupling reaction with allyl bromide or phenyl iodide. The iodides thus prepared can undergo coupling reaction and highly stereoselective Novozym-435-catalyzed kinetic resolution to afford the optically active products. Due to the easily available of the Grignard reagents, propargylic alcohols, and CuI as well as the synthetic potential of the stereodefined iodo-substituted allylic alcohols, this method will be useful in organic synthesis. Further studies in this area are being carried out in our laboratory.

## Experimental Section

### General Procedure for the Copper(I)-Mediated Carbometalation of Secondary and Tertiary Propargylic Alcohols with Grignard Reagents in Toluene

Several drops of an alkyl bromide were added to a mixture of magnesium turnings (20 mmol) and $I_2$ (a few crystals) in $Et_2O$ (15 mL) under a nitrogen atmosphere. Upon the initiation of the Grignard reaction, the remaining alkyl bromide (21 mmol) was added dropwise, which was followed by stirring for 2 h at room temperature. Then toluene (20 mL) was added and the mixture was heated at 120 °C (oil bath temperature) for 0.5 h to get rid of $Et_2O$. Then CuI (5.7 mmol) was added at 25 °C. Right after the addition the color of the mixture turned black and the mixture was cooled to −40 °C immediately. A solution of the alcohol (5.7 mmol) in toluene (4 mL) was added dropwise slowly to the reaction mixture at −40 °C, which was followed by warming up to room temperature naturally within 2 h. After complete conversion of the starting material as monitored by TLC, the reaction was quenched subsequently with dropwise addition of a solution of $I_2$ (20 mmol) in $Et_2O$ (40 mL) or THF (40 mL) at −40 °C for 0.5 h and 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 using 1,3,5-trimethylbenzene as the internal standard (140 μL, 1 mmol). Chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 40/1–20/1) afforded the products.

### (*Z*)-3-Iodonon-3-en-2-ol (2a)

The reaction of Mg turnings (0.4832 g, 20 mmol), *n*-$C_5H_{11}Br$ (2.6 mL, 3.17 g, 21 mmol), CuI (1.0731 g, 5.7 mmol), **1a** (0.4002 g, 5.7 mmol), and $I_2$ (5.08 g, 20 mmol) afforded pure

**2a**; yield: 1.0318 g (67%); liquid; $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 5.89$ (t, $J = 6.8$ Hz, 1H), 3.93 (q, $J = 6.3$ Hz, 1H), 2.18–2.11 (m, 2H), 1.98 (bs, 1H), 1.45–1.35 (m, 2H), 1.35–1.23 (m, 7H), 0.88 (t, $J = 6.8$ Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta = 135.2$, 117.0, 74.4, 35.5, 31.3, 27.8, 23.8, 22.5, 14.0; MS: $m/z = 268$ ($M^+$, 46.60), 71 (100); IR (neat): $\nu =$ 3356, 2927, 2857, 1638, 1456, 1369, 1120, 1068 $cm^{-1}$; HR-MS: $m/z$ = 268.0326, calcd. for $C_9H_{17}IO$: 268.0324.

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