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Highly Regio- and Stereoselective Copper(I) Chloride-Mediated Carbometallation of 2,3-Allenols with Grignard Reagents

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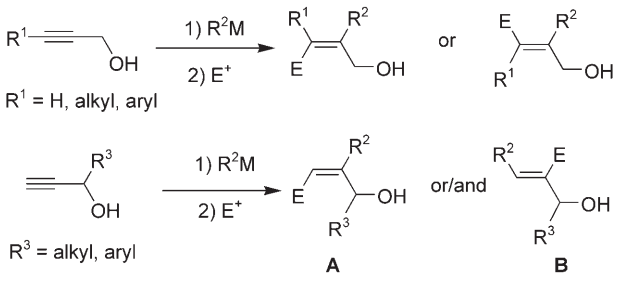
Abstract: An efficient highly regio- and stereoselective copper(I) chloride-mediated carbometallation of differently substituted 2,3-allenols with primary or secondary alkyl or aromatic Grignard reagents followed by iodination to synthesize fully-substituted allylic alcohols has been developed. This protocol introduces the R^4 group from the Grignard reagent to the terminal position of the 2,3-allenols.

Keywords: 2,3-allenols; carbometallation; coupling; Grignard reagents; iodination

Introduction

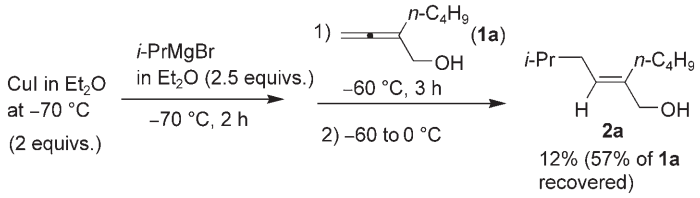
Stereoselective syntheses of allylic alcohols are of current interest due to their synthetic significance.[1] Carbometallation of primary propargylic alcohols is one of the most powerful stereoselective methods to afford multi-substituted allylic alcohols.[2] However, carbometallation of secondary terminal propargylic alcohols usually encounters the problem of the regioselectivity affording a mixture of the branched and linear products **A** and **B**.[3] Furthermore, in some case the stereoselectivity is not excellent.[3a,b] There is also a limitation referring to the Grignard reagent, i.e., only primary alkyl Grignard reagents can undergo this reaction.[3c] In addition, to the best of our knowledge, the regio- and stereoselective carbometallation of secondary non-terminal 2-alkynols has not been realized (Scheme 1).[4] On account of the higher reactivity of allenes,[5] we have a strong interest in the related carbometallation reaction of 2,3-allenols,[6] which may afford fully substituted allylic alcohols with excellent regio- and stereoselectivity. Richey and Szucs reported one example in which allylmagnesium chloride added to 2,3-butadien-1-ol to afford 2-allyl-1,3-butadiene.[6d] The addition of primary or secondary alkyl and phenyl Grignard reagents with 2,3-butadien-1-ol afforded allylic alcohols in 37–59% yield upon hydrolysis or in 33–44% yield with iodination;[7a–c] Furthermore, there is one report that describes the related reaction of 2-substituted primary 2,3-allenols, however, when we ran the same reaction reported by Gelin and Albrand[7d] in our laboratory, product **2a** was formed in very low yield with most of the substrate **1a** remaining unchanged (57%) (Scheme 2). Thus, the reported reaction conditions may be not so easy to control. Herein, we report a highly regio- and stereoselective CuCl-mediated carbometallation of primary, secondary or tertiary 2,3-allenols with primary or secondary alkyl and aromatic Grignard reagents to afford fully substituted 3-iodo-2-alkenols with excellent regio- and stereoselectivity.



Scheme 1.

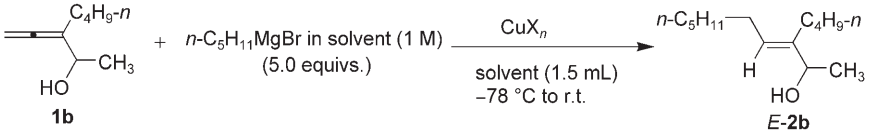
Results and Discussion

The starting allenol **1a** was prepared by the CuBr-catalyzed reaction of 4-chlorobut-2-ynol and *n*-C_4H_9MgBr in 61% yield; allenols **1b–f** were prepared



Scheme 2.

Table 1. Optimization of reaction conditions for copper-mediated addition of n-$C_5H_{11}MgBr$ with 3-(n-butyl)-penta-3,4-dien-2-ol.



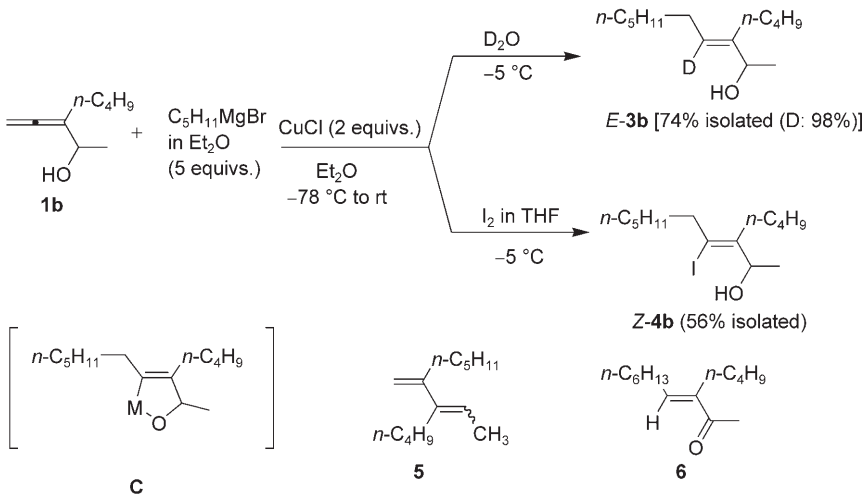
Entry	CuX_n (equivs.)	Solvent	Time [h]	Yield of **2b** [%]	Recovery of **1b** [%]
1	CuI (2)	Et_2O	11.5	33	41
2	CuI (2)	THF	12	6	78
3	CuCl (2)	toluene	18	71	-
4	CuCl (2)	Et_2O	11.5	80	3
5	$CuCl_2$ (2)	Et_2O	11.5	-	77
6	CuCl (1)	Et_2O	11	71	9
7	CuCl (0.5)	Et_2O	11	54	20
8	$PdCl_2$ (0.05)	Et_2O	11.5	-	83
9	$Pd(PPh_3)_2Cl_2$ (0.05)	Et_2O	11.5	-	68

by the reaction of propargylic bromide and aldehyde in the presence of NaI and $SnCl_2$ in DMF in 40–67% yields;[8] allenols **1g** and **1h** were prepared by the Crabbé reaction in 60–64% yields.[9] *S*-**1b** was prepared by the Novozym-435-catalyzed kinetic resolution of the racemic **1b** with vinyl acetate in 31% yield.[8]

Since the reaction of secondary alcohols is our main objective, **1b** was chosen as the model substrate. A solution of n-$C_5H_{11}MgBr$ in Et_2O was added dropwise to a solution of **1b** in Et_2O with 2 equivs. of CuI at −78 °C. After the addition, the reaction mixture was warmed up to room temperature, the expected product **2b** was formed upon hydrolysis in 32% yield with 41% of **1b** recovered (Table 1, entry 1). The reaction in THF was even slower (Table 1, entry 2), but the reaction in toluene was complete after 18 h and afforded **2b** in 71% yield (Table 1, entry 3). However, by using 2 equivs. of CuCl, the reaction in Et_2O afforded **2b** in 81% yield upon hydrolysis (Table 1, entry 4). The difference between CuI and CuCl may be due to the ligand effect of the halide anion, which has been reported in the literature.[10] No reaction occurred with $CuCl_2$ (Table 1, entry 5).[10c] With 0.5 or 1 equiv. of CuCl, the reaction was not complete (Table 1, entries 6 and 7). When $PdCl_2$ or $Pd(PPh_3)_2Cl_2$ was used instead of copper catalysis, most of the starting allenol **1b** was recovered (Table 1, entries 8 and 9).

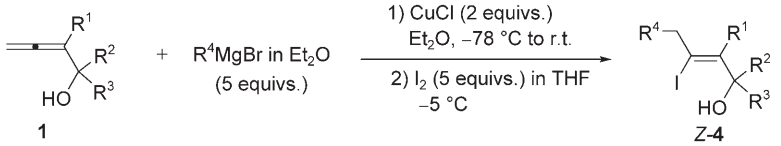
Treatment of the carbometallation mixture with D_2O afforded *E*-**3b** in 74% yield with 98% D incorporation, indicating the C-type of metallacyclic intermediate (Scheme 3).[2e,f,4] Furthermore, if iodination was applied, the corresponding iodide *Z*-**4b** can be isolated in 56% yield. Based on the analysis of the crude reaction mixture, compounds **5** and **6** may be formed to the extent of 3~4%, if any; The formation of *E*-**4b** or *Z*-**3b** was not observed indicating the excellent regio- and stereoselectivity. It is believed that the reaction may possibly proceed *via* the regioselective carbometallation of the organometallic reagent formed from the Grignard reagent and CuCl with the terminal C=C bond in 2,3-allenols. The Z-stereochemistry in products is determined by the formation of C-type cyclic intermediate.[2e,f,4]

The scope of this reaction was then studied using the established standard conditions (entry 4, Table 1). The results shown in Table 2 indicated that *Z*-3-iodoallylic alcohols (*Z*-**4**) were formed highly regio- and stereoselectively. When the optically active (*S*)-**1b** was applied, optically active (*S*)-**4b** can be prepared in 81% isolated yield without obvious racemization (Table 2, entry 2). R^1 can be alkyl, phenyl, allyl or H. Not only secondary alcohols (Table 2, entries 2–7, 9–



Scheme 3.

Table 2. The CuCl-mediated addition of Grignard reagents with 2,3-allenols.[a]



Entry	R^1	R^2	R^3	R^4	Time [h]	Yield of **4** [%]
1[b]	n-C_4H_9	H (**1a**)	H	n-C_5H_{11}	10	70 (**4a**)
2[c]	n-C_4H_9	CH_3 (*S*-**1b**)	H	n-C_5H_{11}	15	81 (*S*-**4b**)
3	n-C_7H_{15}	CH_3 (**1c**)	H	n-C_5H_{11}	17	74 (**4c**)
4	Ph	CH_3 (**1d**)	H	n-C_5H_{11}	16	80 (**4d**)
5	allyl	CH_3 (**1e**)	H	n-C_5H_{11}	17	60 (**4e**)
6	n-C_4H_9	Ph (**1f**)	H	n-C_5H_{11}	19	59 (**4f**)
7	H	Ph (**1g**)	H	n-C_5H_{11}	17	72 (**4g**)
8	H	Ph (**1h**)	Me	n-C_5H_{11}	11.5	71 (**4h**)
9[d]	n-C_4H_9	CH_3 (**1b**)	H	Cy	17	84 (**4i**)
10[d]	n-C_4H_9	Ph (**1f**)	H	Cy	17	64 (**4j**)
11	n-C_4H_9	CH_3 (**1b**)	H	*i*Bu	13	59 (**4k**)
12	n-C_4H_9	CH_3 (**1b**)	H	Ph	16	67 (**4l**)
13	n-C_4H_9	CH_3 (**1b**)	H	p-MeC_6H_4	12	60 (**4m**)

[a] The reaction was conducted using 1 mmol of allenol, 5 equivs. of Grignard reagent (1 M), and 2 equivs. of CuCl in 1.5 mL of Et_2O at −78 °C, then warmed up to room temperature (about 25–30 °C) followed by the addition of 5 equivs. of I_2 in THF at −5 °C.

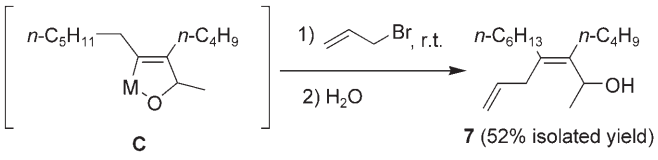
[b] 4 equivs. of I_2 in THF were applied at −78 °C.

[c] The *ee* value of *S*-**1b** is 98% as determined after its conversion to the corresponding acetate by GC with a chiral Dex-CB (Varian) column and the *ee* value of the product *S*-**4b** is 98% as determined by HPLC with a chiral AS-H column.

[d] 8 equivs. of the Grignard reagent were applied.

13) but also primary (Table 2, entry 1) and tertiary alcohols (Table 2, entry 8) can undergo this reaction with R^2 being H, methyl or phenyl. Different Grignard reagents, such as primary (Table 2, entries 1–8), secondary alkyl (Table 2, entries 9–11), phenyl (Table 2, entry 12), or substituted phenyl (Table 2, entry 13) Grignard reagents, can be used to give the carbometallation-iodination products. The configuration of **4** was determined by the NOE studies of the compounds **4b** and **4e**. It should be noted that no reaction was observed with 3-butyl-3,4-pentadienol under the same reaction conditions.

The *in-situ* formed C-type cyclic organometallic intermediate may also undergo a coupling reaction with allyl bromide[2b,7a,b] to afford the corresponding coupling product **7** smoothly in 52% isolated yield (Scheme 4).



Scheme 4.

Iodide **4b** can easily undergo the Sonogashira coupling reaction[11] with terminal alkynes in DMSO[11f] to afford **8a** and **b**, respectively. The lactone **9** can be prepared in 84% yield by the palladium-catalyzed carbonylation reaction[12] with **4b** (Scheme 5).

Conclusions

In summary, we have developed an efficient regio- and stereospecific CuCl-mediated carbometallation of differently substituted 2,3-allenols with alkyl or aromatic Grignard reagents followed by iodination to synthesize fully-substituted allylic alcohols. Further studies in this area are being conducted in our laboratory.

Experimental Section

Materials

Et_2O and THF were distilled from Na/benzophenone. The allenols were prepared easily according to the known procedure (see the text). The other commercially available chemicals were purchased and used without additional purification unless noted otherwise.

General Procedure for the CuCl-Mediated Carbometallation of 2,3-Allenols with Grignard Reagents and Iodination (Procedure I)

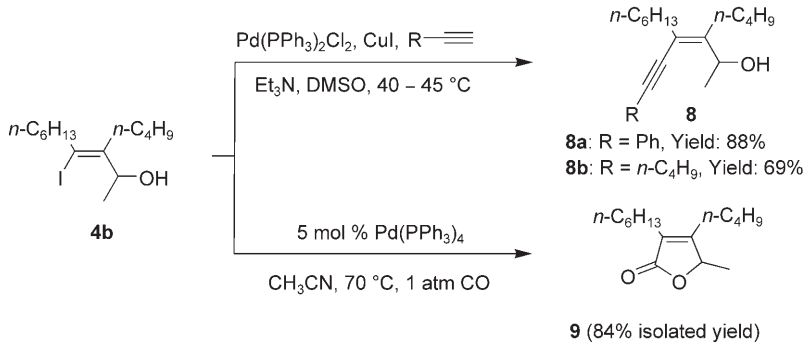
To a Schlenk tube containing CuCl (2.0 mmol, 2 equivs.) were added sequentially 2,3-allenol (1.0 mmol) and anhydrous diethyl ether (1.5 mL) under a nitrogen atmosphere at room temperature. The requisite Grignard reagent (5 equivs., 1 M in Et_2O, 5.0 mmol) was then added dropwise to the reaction mixture at −78 °C, which was followed by warming up to room temperature (about 25–30 °C) naturally. The reaction was monitored by TLC. After 10–19 h, the reaction mixture was cooled to −5 °C (for **1a**: at −78 °C), quenched with a solution of I_2 (5.0 mmol, 5 equivs.) in anhydrous THF (8 mL). After being stirring at this temperature for 1 h, the reaction mixture was treated with a saturated aqueous solution of $Na_2S_2O_3$ at −5 °C (for **1a**: at −78 °C). After extraction with diethyl ether (3 × 30 mL), the organic layer was washed subsequently with a saturated aqueous solution of $Na_2S_2O_3$, dilute HCl (5% aqueous), a saturated aqueous solution of $NaHCO_3$, brine, and dried over anhydrous Na_2SO_4. Evaporation and column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 60/1–20/1) afforded the desired product.

(*Z*)-3-Iodo-2-butylnon-2-enol (Z-4a)

The reaction of CuCl (0.1974 g, 2.0 mmol), **1a** (0.1244 g, 1.0 mmol), Et_2O (1.5 mL), a solution of *n*-$C_5H_{11}MgBr$ in Et_2O (5.0 mL, 5 equivs., 5.0 mmol), and I_2 (1.0 g, 4 equivs., 4.0 mmol) afforded *Z*-**4a** as a liquid after standard purification; yield: 0.2254 g (70%). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.22$ (s, 2H), 2.54 (t, $J = 7.6$ Hz, 2H), 2.30 (t, $J = 8.0$ Hz, 2H), 1.68 (bs, 1H), 1.57–1.47 (m, 2H), 1.43–1.27 (m, 10H), 0.95–0.85 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 143.0$, 107.6, 71.8, 41.2, 31.7, 31.0, 30.7, 29.2, 28.5, 22.5, 22.4, 14.0 (2C); MS (*m*/*z*) 324 (M^+, 41.04), 197 (M^+-I, 26.88), 55 (100); IR (neat): $\nu = 3329$, 2957, 2927, 2857, 1625, 1461, 1378, 1008 cm^{-1}; HR-MS: *m*/*z* = 324.0952, calcd. for $C_{13}H_{25}OI$: 324.0945.

CuCl-Mediated Carbometallation of 2,3-Allenol with Grignard Reagent Followed by Quenching with D_2O Affording (*E*)-4-Deutero-3-butyldec-3-en-2-ol (*E*-3b)

To a Schlenk tube containing CuCl (0.1981 g, 2 equivs., 2.0 mmol) were added sequentially anhydrous diethyl ether (1.5 mL) and **1b** (0.1435 g, 1.0 mmol) under a nitrogen atmosphere at room temperature. The requisite Grignard reagent (5.0 mL, 5 equivs., 1 M in Et_2O, 5.0 mmol) was then added dropwise to the reaction mixture at −78 °C, which was followed by warming up to room temperature naturally. The reaction was monitored by TLC. After 11 h, the reaction mixture was quenched with dropwise addition of D_2O (0.5 mL) *via* a syringe at −5 °C and then stirred for 1 h. After the treatment with water (5 mL), the resulting mixture



Scheme 5.

was extracted with diethyl ether (3×30 mL), washed sequentially with dilute HCl (5% aqueous), saturated aqueous solution of $NaHCO_3$, and brine, and dried over anhydrous Na_2SO_4. Evaporation and column chromatography on silica gel (eluent: petroleum ether/ethyl acetate=30/1) afforded *E*-**3b** as a liquid; yield: 0.1616 g (74%, D: 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.38 (t, J=7.2 Hz, 0.02H), 4.19 (q, J=6.1 Hz, 1H), 2.10–1.90 (m, 4H), 1.63 (bs, 1H), 1.40–1.18 (m, 15H), 0.97–0.80 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=143.0, 125.0 ($J_{C,D}$=22.6 Hz), 72.0, 32.1, 31.7, 29.7, 29.0, 27.3, 27.2, 23.1, 22.6, 22.2, 14.0, 13.9; MS: m/z=213 (M^+, 15.01), 72 (100); IR (neat): ν=3355, 2957, 2926, 2857, 1652, 1456, 1378, 1060 cm^{-1}; HR-MS: m/z=213.2195, calcd. for $C_{14}H_{27}OD$: 213.2197.

Coupling Reaction of Allyl Bromide with the Organometallic Intermediate C Formed *via* the CuCl-Catalyzed Carbometallation of 1b and *n*-$C_5H_{11}MgBr$; Synthesis of (*Z*)-4-Allyl-3-butyldec-3-en-2-ol (Z-7)

To a Schlenk tube containing CuCl (0.2007 g, 2 equivs., 2.0 mmol) were added sequentially anhydrous diethyl ether (1.5 mL) and **1b** (0.1427 g, 1.0 mmol) under a nitrogen atmosphere at room temperature. The requisite Grignard reagent (5.0 mL, 5 equivs., 5.0 mmol) was then added dropwise to the reaction mixture at −78 °C, which was followed by warming up to room temperature naturally. The reaction was monitored by TLC. After 10 h, allyl bromide (0.43 mL, 0.6 g, 5 mmol) was added dropwise *via* a syringe at room temperature, then the reaction mixtutre was stirred at room temperature for 16 h. After the treatment with water and dilute HCl (5% aqueous), the resulting mixture was extracted with diethyl ether (3×30 mL), washed with saturated aqueous solution of $NaHCO_3$, and brine, and dried over anhydrous Na_2SO_4. Evaporation and column chromatography on silica gel (eluent: petroleum ether/ethyl acetate=40/1) afforded *Z*-**7** as a liquid; yield: 0.1339 g (52%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.83–5.72 (m, 1H), 5.04–4.93 (m, 2H), 4.75 (q, J=6.4 Hz, 1H), 2.92–2.76 (m, 2H), 2.16–1.96 (m, 4H), 1.53–1.26 (m, 13H), 1.23 (d, J=6.4 Hz, 3H), 0.96–0.83 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=137.9, 137.4, 133.5, 114.6, 67.5, 35.3, 33.7, 32.7, 31.7, 29.7, 28.5, 26.8, 23.5, 22.6, 21.7, 14.1, 13.9; MS: m/z=252 (M^+, 0.37), 237 (M^+-CH_3, 43.58), 43 (100); IR (neat): ν=3364, 2926, 2858, 1635, 1457, 1054 cm^{-1}; HR-MS: m/z=237.2217, calcd. for $C_{16}H_{29}O^+$(M^+-CH_3): 237.2213; anal. calcd. for $C_{17}H_{32}O$: C 80.88, h 12.78; found: C 80.96, H 12.70.

Procedure for the Sonogashira Coupling Reaction of the Carbon-Iodine Bond in 4b with Terminal Alkynes; Synthesis of (*Z*)-3-Butyl-4-hexyl-6-phenylhex-5-yn-3-en-2ol (Z-8a) (Procedure II)

A mixture of **4b** (0.0843 g, 0.25 mmol), Et_3N (1 mL), phenylacetylene (0.0541 g, 0.50 mmol), $Pd(PPh_3)_2Cl_2$ (0.0038 g, 2 mol%), and CuI (0.0012 g, 2 mol%) in DMSO (1 mL) was heated at 40–45 °C over a period of 48 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 5 mL of water. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3×30 mL). The combined organic layer was dried over Na_2SO_4. Evaporation and column chromatography on silica gel (eluent: petroleum ether/ethyl acetate=60/1) afforded *Z*-**8a** as an oil; yield: 0.0684 g (88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.44–7.40 (m, 2H), 7.36–7.28 (m, 3H), 5.14 (q, J=6.4 Hz, 1H), 2.23–2.14 (m, 4H), 1.80 (bs, 1H), 1.64–1.56 (m, 2H), 1.46–1.30 (m, 13H), 0.94 (t, J=7.0 Hz, 3H), 0.90 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=150.6, 131.2 (2C), 128.3 (2C), 127.8, 123.7, 119.0, 94.1, 88.7, 70.5, 32.7, 31.9, 31.8, 29.0, 28.6, 27.3, 23.4, 22.6, 21.6, 14.1, 13.9; MS: m/z=312 (M^+, 18.42), 255 (100); IR (neat): ν=3378, 2928, 2858, 2196, 1595, 1490, 1466, 1097, 1059 cm^{-1}; HR-MS: m/z=312.2449, calcd. for $C_{22}H_{32}O$: 312.2448.

Procedure for the Palladium-Catalyzed Carbonylation Reaction of 4b Affording 3-Hexyl-4-butyl-2(5*H*)-furanone (9)

$Pd(PPh_3)_4$ (0.0117 g, 5 mol%), **4b** (0.0690 g, 0.2 mmol), and CH_3CN (1 mL) were added sequentially to potassium carbonate (0.0598 g, 0.4 mmol) under an atmosphere of carbon monoxide. The mixture was then heated at 70 °C with a CO balloon for 20 h. After complete conversion of the starting materials as monitored by TLC, the reaction mixture was cooled to room temperature and quenched with 5 mL of water. The mixture was diluted with diethyl ether (50 mL). The organic layer was washed with brine and dried over Na_2SO_4. Evaporation and column chromatography on silica gel (eluent: petroleum ether/ethyl acetate=20/1) afforded **9** as a liquid; yield: 0.0410 g (84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.85 (q, J=6.7 Hz, 1H), 2.50–2.40 (m, 1H), 2.25–2.15 (m, 3H), 1.53–1.30 (m, 9H), 1.30–1.23 (m, 6H), 0.92 (t, J=7.2 Hz, 3H), 0.85 (t, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ=174.2, 164.4, 127.0, 78.0, 31.5, 30.0, 29.1, 28.1, 26.1, 23.6, 22.7, 22.5, 18.4, 14.0, 13.7; MS: m/z=238 (M^+, 60.27), 126 (100); IR (neat): ν=2931, 2860, 1756, 1668, 1456, 1325, 1121, 1058 cm^{-1}; HR-MS: m/z=238.1932, calcd. for $C_{15}H_{26}O_2$: 238.1927.

Supporting Information

The characterization data of compounds **4b–m** and **8b**, and ^{1}H and ^{13}C NMR spectra of all the products are given in the Supporting Information.

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