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Directed hydrozirconation of homopropargylic alcohols

Xiaofeng Liu, Joseph M. Ready *

Department of Biochemistry, The University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Boulevard, Dallas, TX 75390-9038, United States

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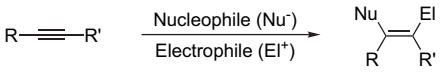
ABSTRACT

Homopropargylic alcohols undergo directed hydrozirconation with Schwartz reagent (Cp_2ZrHCl) to generate vinyl-metal species in which the metal fragment is proximal to the alkoxide. Electrophilic trapping yields tri-substituted olefins in good yields with good control of regio- and stereochemistry. Experiments with a homopropargylic ether confirmed the role of the hydroxyl group in the directed hydrometalation.

1. Introduction

Olefin synthesis remains a challenging and important endeavor. Olefins are building blocks for organic synthesis and components of natural products, pharmaceuticals, and functional molecules. Of the many strategies to generate alkenes, those based on coupling a nucleophile, an electrophile, and an alkyne offer substantial versatility (Eq. 1).[1] The ready availability of alkynes from commercial sources and standard preparations[2] adds to the attractiveness of these methods. To synthesize olefins from alkynes in a practical manner, however, three challenges must be addressed. In particular, the modest reactivity of alkynes must be overcome, and both the regiochemistry and stereochemistry of the alkene product must be controlled.

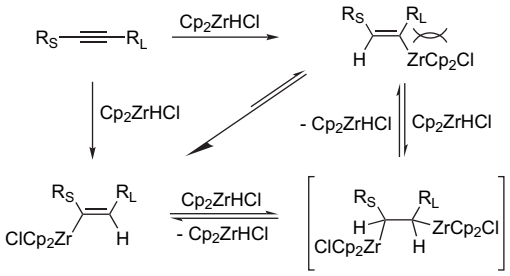


(1)

Among reagents that react with alkynes, the Schwartz reagent (Cp_2ZrHCl) is notable for its utility. The Schwartz reagent reacts with internal and terminal alkynes with predictable regioselectivity and stereospecificity to provide vinyl zirconium species.[3] This reagent is ideally suited for the synthesis of alkenes (Eq. 1, Nu=H) because the vinyl zirconium intermediates can participate in cross-coupling reactions, conjugate and nucleophilic additions, and can undergo carbonylation, halogenation or transmetalation. The wide applicability of vinyl zirconium reagents is reflected by their frequent appearance in the literature of synthetic chemistry.[4]

The regioselectivity of hydrozirconation is usually controlled by steric effects. Indeed, early elegant studies from the Schwartz group established that the least-hindered vinyl zirconium species is favored kinetically. Furthermore, this kinetic selectivity can be enhanced through an equilibration process (Scheme 1). Thus, in the presence of excess Cp_2ZrHCl, hydrozirconation of a vinyl zirconium intermediate can generate a vicinal dimetallic species. Subsequent β-hydride elimination provides a means to interconvert regioisomeric vinyl zirconium products.[5] Of note, hydrozirconation is stereospecific, so cis-addition of H–Zr is almost always observed.[6]

The identification of factors other than steric bulk for controlling the regioselectivity of hydrozirconation could create new opportunities and applications for hydrozirconation in organic synthesis.[7] If the normal regioselectivity of hydrozirconation could be reversed it might provide access to olefins with substitution patterns that are difficult to access by other methods. In this context, we have demonstrated an alkoxide-directed hydrozirconation of terminal propargylic alcohols (Eq. 2).[8] We found that under standard conditions propargylic alcohols undergo hydrozirconation with the expected sense of regioselectivity. However, in the presence of $ZnCl_2$, the lithium alkoxides of terminal propargylic alcohols react to yield the branched products exclusively.[9] As part of a broader program to exploit directing groups in alkyne functionalization reactions,[10,11] this result encouraged us to explore the hydrozirconation of homopropargylic alcohols.[12] In this regard, it is



Scheme 1. Hydrozirconation of alkynes with Schwartz reagent. R_S and R_L represent small and large substituents, respectively.

* Corresponding author.
E-mail address: joseph.ready@utsouthwestern.edu (J.M. Ready).

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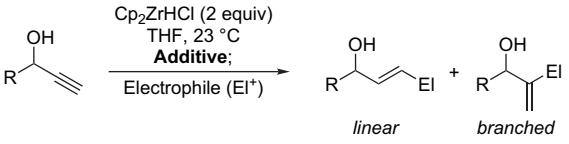
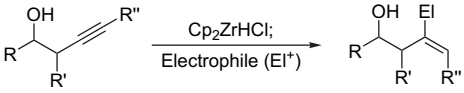
noteworthy that Hoveyda and co-workers found that homoallylic alcohols could modulate the regioselectivity of Cp_2ZrCl_2-catalyzed carobometalation.[13]

We were especially interested in the reactivity and selectivity observed with homopropargylic alcohols because these substrates can be prepared easily and in optically active form through propargylation of aldehydes[14] or addition of terminal alkynes to epoxides.[15] As described below, our studies resulted in the discovery of a simple method for directed hydrometalation of homopropargylic alcohols (Eq. 3). These transformations introduce a hydride and an electrophile cis with respect to the new olefin, with the electrophile proximal to the directing group. In this regard, both cis- and trans-selective hydrosilylations have been reported.[16,17] Similar to the protocols disclosed here, these reductions introduce the silyl group proximal to the alcohol. In contrast, hydroalumination of homopropargylic alcohols generally yields organometallic reagents with the metal fragment distal to the alcohol moiety; both cis- and trans addition of Al–H to the alkyne are possible.[18,19] Finally, hydrostannylation with $Bu_2Sn(OTf)H$ provides (*Z*)-γ-stannylated allylic alcohols with good selectivity.[20]



(2)

Additive	linear : branched
none	>50 : 1
CH_3Li (1 equiv); $ZnCl_2$ (6 equiv)	1 : >50

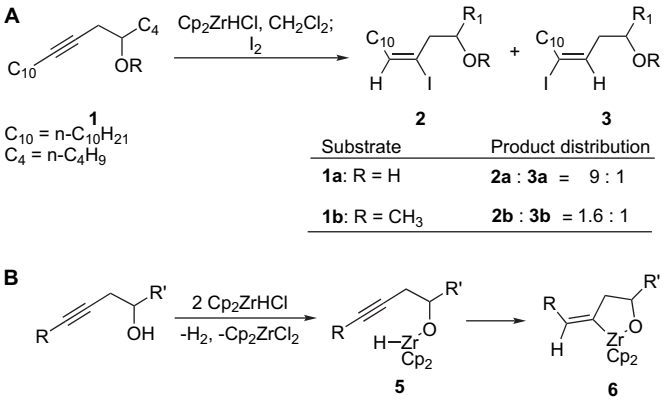


(3)

2. Results and discussion

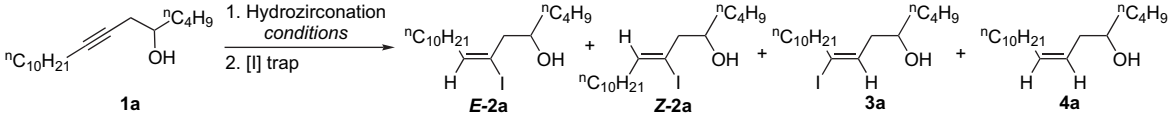
Initial experiments were performed with simple homopropargylic alcohol **1a**. Following conditions we found optimal for the branched-selective hydrozirconation of terminal propargylic alcohols,[8] **1a** was deprotonated (CH_3Li) and treated with a solution of $ZnCl_2$ and Cp_2ZrHCl in THF. Encouragingly, the regioselectivity was greater than 20:1, but conversion was modest (Table 1, entry 1). Of greater concern was the observation of substantial quantities of non-iodinated material (**4a**) and the *Z*-olefin (*Z*-**2a**) (see below). Performing the hydrozirconation at elevated temperatures or with more Schwartz reagent had only modest effects on conversion and product distribution (entries 2 and 3). As a control experiment, we omitted CH_3Li and $ZnCl_2$ and were surprised to find that hydrozirconation still proceeded with good regioselectivity. Additionally, the formation of *Z*-olefin was suppressed (entry 4). Incremental improvements in yield were observed when the iodination was carried out at a warmer temperature (entry 5), when the hydrozirconation/trapping occurred in CH_2Cl_2 (entry 6), and when I_2 was replaced with *N*-iodosuccinimide (entry 7). Compared to terminal propargylic alcohols, internal homopropargylic alcohols react more slowly, thus requiring higher concentrations of Schwartz reagent.[21] This rate difference is not surprising given the increased steric hindrance that accompanies substitution on the alkyne. However, while increased substitution decreases the reaction rate, it increases the effectiveness of the alcohol as a directing group. Accordingly, high regioselectivity is observed with homopropargylic alcohol **1a** in the absence of additives, whereas terminal propargylic alcohols require the inclusion of $ZnCl_2$ and initial generation of a lithium alkoxide (Eq. 2).

To better understand the origin of regioselectivity, we compared homopropargylic alcohol **1a** to its methyl ether, **1b** (Scheme 2A). These experiments revealed that converting the free alcohol to a methyl ether substantially attenuated the kinetic regioselectivity of the hydrozirconation. Thus alcohol **1a** provided a 9:1 ratio of regioisomers while the methyl ether **1b** showed only a modest bias for the same regioisomer. Neither ratio changed substantially upon prolonged reaction time. These results appear most easily accommodated by a model involving intramolecular hydrozirconation with an alkoxy-zirconium hydride (**5**, Scheme 2B).[7] The strong O–Zr interaction accounts for the high kinetic selectivity. The stability of



Scheme 2. Directed hydrozirconation of homopropargylic alcohols.

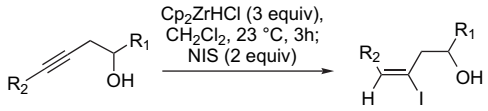
Table 1
Hydrozirconation/iodination of homopropargylic alcohol **1a**[a]



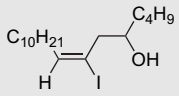
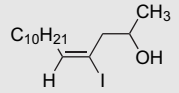
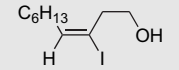
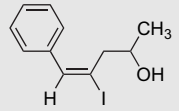
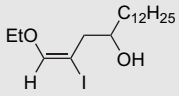
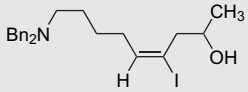
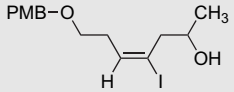
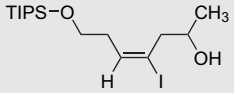
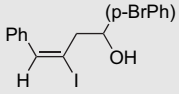
Entry	Additive	Cp_2ZrHCl (equiv)	Solvent	[I][b]/temp (°C)	NMR yields (%)				Isolated yield (**2a**)
					E-**2a**	*Z*-**2a**	**3a**	**4a**	
1	MeLi (1 equiv)/$ZnCl_2$ (6 equiv)	2	THF	I_2/−78	58	9	Trace	14	—
2	MeLi (1 equiv)/$ZnCl_2$ (6 equiv)	2 (40 °C)	THF	I_2/−78	59	13	Trace	14	—
3	MeLi (1 equiv)/$ZnCl_2$ (9 equiv)	3	THF	I_2/−78	65	17	Trace	11	—
4	—	3	THF	I_2/−78	56	—	8	23	—
5	—	3	THF	I_2/rt	70	—	12	11	61
6	—	3	CH_2Cl_2	I_2/rt	74	—	10	12	64
7	—	3	CH_2Cl_2	NIS[c]/rt	75	—	8	8	74

[a] Reactions carried out on a 0.4 mmol scale. Hydrozirconation reaction time=3 h.
[b] Two equivalents.
[c] *N*-Iodosuccinimide.

Table 2
Hydrozirconation/iodination of homopropargylic alcohols[a]



1 **2**

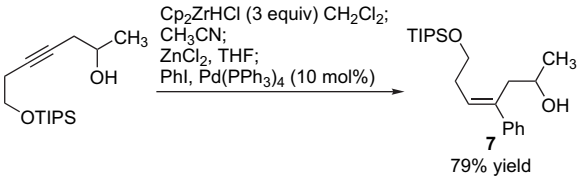
Entry	Product		Yield[b] (%)
1		**2a**	74
2		**2c**	75
3		**2d**	79
4		**2e**	72
5		**2f**	70
6		**2g**	74
7		**2h**	66
8		**2i**	76
9[c]		**2j**	68

[a] Reactions carried out on a 0.4 mmol scale; see Section 4 for details.
[b] Isolated yield of *E*-olefin.
[c] Hydrozirconation performed on the lithium alkoxide in the presence of 9 equiv $ZnCl_2$.

the five-membered chelate likely contributes to the resistance of the oxazirconacycle (**6**) to isomerization to the distal product.[22]

The scope of the directed hydrozirconation displays several noteworthy features (Table 2). Both primary and secondary alcohols effectively direct the hydrometalation. Aryl (entries 4 and 9), alkyl, and even *O*-alkyl (entry 5) substituents are tolerated on the alkyne. Furthermore, alkyl (entry 7) and silyl (entry 8) ethers as well as tertiary amines (entry 6) are accommodated by the method. In contrast to the results tabulated above, homopropargylic alcohols featuring a terminal alkyne do not provide synthetically useful yields of the vinyl iodides. Under various conditions, poor conversion, over-reduction or poor regioselectivity compromise the yield of the desired products.

Electrophilic trapping is not limited to iodination. For example, after quenching the remaining Cp_2ZrHCl with acetonitrile, transmetalation from Zr to Zn facilitated a Negishi coupling with iodobenzene (Eq. 4).[23] The coupled product was isolated as a single olefin stereoisomer in good yield.

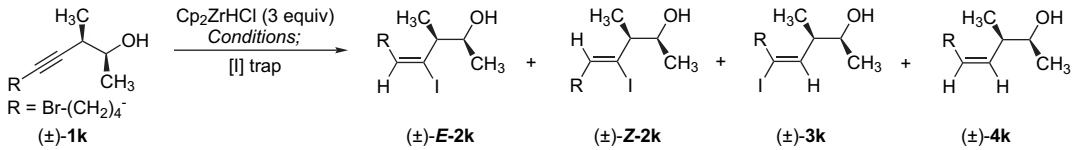


7
79% yield (4)

All of the substrates in Table 2 feature a methylene between the alkyne and the carbinol. Introducing a methyl group on the propargylic carbon expands the potential structural diversity of accessible products. However, hydrozirconation of this class of homopropargylic alcohols proved less regioselective than the reactions described above. The increased steric bulk at the propargylic position appears to counterbalance the directing effect of the hydroxyl group. In particular, treating alkynol **1k** under the conditions optimized for **1a** returned a nearly statistical distribution of regioisomers (Table 3, entry 1). In contrast and consistent with the results obtained with terminal propargylic alcohols, initial deprotonation with CH_3Li and the inclusion of $ZnCl_2$ in the reaction mixture substantially improved the regioselectivity (>38:1). Accordingly, the desired vinyl iodide was isolated in good yield (entry 2). The same procedure was found optimal for hindered homopropargylic alcohols (Table 2, entry 9).

The generation of small amounts of *Z*-vinyl iodides in the presence of Li and Zn salts (Table 1, entry 1 and Table 3, entry 2) contrasts with the usual behavior of the Schwartz reagent. Indeed, the stereospecificity of hydrozirconation contributes to its broad application in organic synthesis. This unusual loss of stereochemical integrity may result from the hydrozirconation of a vinyl zinc intermediate. In this context, Knochel and co-workers reported the hydrozirconation of vinyl zinc reagents to yield geminal heterobimetallic species.[24] In reactions of homopropargylic alcohols, directed hydrozirconation followed by transmetalation could yield a vinyl zinc intermediate (*E*-**8**, Scheme 3). Subsequent hydrozirconation would lead to a heterobimetallic compound such as **9**. Critically, β-hydride elimination could now provide either the *E* or *Z* olefin. Consistent with this proposal, the *E*/*Z* ratio was found to

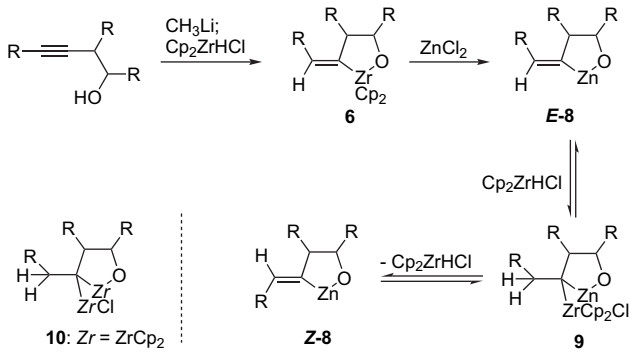
Table 3
Hydrozirconation/iodination of homopropargylic alcohol **1j**



(±)-**1k** (±)-***E*-2k** (±)-***Z*-2k** (±)-**3k** (±)-**4k**

Entry	Additive	Solvent	[I]/temp (°C)	NMR yields (%)				Isolated yield (***E*-2k**)
				***E*-2k**	***Z*-2k**	**3k**	**4k**	
1	—	CH_2Cl_2	NIS (2 equiv)/23	43	—	33	16	—
2[a]	CH_3Li (1 equiv); $ZnCl_2$ (9 equiv)	THF	I_2 (2 equiv)/−78	77	7	<2	6	69

[a] Reaction carried out on a 1.0 mmol scale; see Section 4 for details.



Scheme 3. Olefin isomerization in the presence of $ZnCl_2$.

deteriorate as the reaction progressed. The fact that single olefin stereoisomers were formed in the absence of $ZnCl_2$ indicates that hydrozirconation to yield the dizirconium species **10** is prevented, likely due to steric effects.

3. Conclusion

We have developed two procedures for hydrozirconation of homopropargylic alcohols. Substrates with a methylene group between the alkyne and the alcohol undergo stereospecific hydrozirconation with good control of regioselectivity. The reaction conditions are simple and require no additives. For more challenging substrates, such as those with substitution on the propargylic carbon, the addition of CH_3Li and $ZnCl_2$ to the reaction mixture markedly increases the regioselectivity of hydrozirconation. Coupled with prior results,[8,7] the present study suggests that factors other than sterics can dictate regioselectivity in hydrozirconation reactions. This observation should present new opportunities for organozirconium reagents in organic synthesis.

4. Experimental

4.1. General

Unless otherwise stated, reactions were performed under nitrogen atmosphere with a positive pressure using freshly purified solvents. Solvents were purified using solvent purification columns purchased from Glass Contour, Laguna Beach, CA. All reactions were monitored by ^1H NMR or thin layer chromatography with E. Merck silica gel 60 F_{254} pre-coated plates (0.25 mm). Gas chromatography (GC) was performed on an HP 6890N autosampling GC with an HP-5 capillary column and equipped with a FID detector. Flash chromatography was performed using silica gel (particle size 40–63 μm) purchased from Sorbent Technologies. ^1H and ^{13}C NMR spectra were recorded on Varian Inova-400 or Mercury-300 spectrometer. Chemical shift are reported relative to internal chloroform ($CDCl_3$: ^1H, δ=7.26, ^{13}C, δ=77.0). Coupling constants are in hertz and are reported as d (doublet), t (triplet), q (quartet), quin (quintet). Mass spectra were acquired on a Shimadzu QP5000 GC/MS using the indicated ionization method.

4.2. Materials

$Cp_2Zr(H)Cl$ was purchased from Strem Chemicals Inc. and used within 2 months. All homopropargylic alcohols were prepared by addition of appropriate terminal alkynes to epoxides,[15b] except **1d** (Table 2, entry 3, Aldrich) and **1g** (Table 2, entry 6, from the aminolysis of the corresponding 1-chloro-alkynol with dibenzyl amine[25]).

4.3. General procedure for hydrozirconation/iodination of homopropargylic alcohols with a propargylic methylene (Table 2)

A solution of homopropargylic alcohol (0.40 mmol) in CH_2Cl_2 (1.0 mL) was added in one portion to a stirred suspension of $Cp_2Zr(H)Cl$ (310 mg, 1.2 mmol) in CH_2Cl_2 (2.0 mL) at room temperature, followed by rinsing with CH_2Cl_2 (1.0 mL). The mixture was stirred for 3 h and formed a clear yellow solution. A solution of *N*-iodosuccinimide (180 mg, 0.80 mmol) in THF (2.0 mL) was added. After 0.5 h at room temperature, a mixed aqueous solution of saturated $Na_2S_2O_3$ (5 mL) in saturated aqueous $NaHCO_3$ solution (5 mL) was added to quench the reaction. After dilution with ether, the reaction mixture was separated and the aqueous layer was extracted with ether. The combined organic phases were dried over Na_2SO_4, concentrated and purified by chromatography on silica gel.

*4.3.1. (E)-7-Iodooctadec-7-en-5-ol (**E-2a**)*

Light yellow oil, 74% yield. ^1H NMR ($CDCl_3$) δ=0.87 (t, *J*=6.8, 3H), 0.92 (t, *J*=6.8, 3H), 1.18–1.56 (m, 22H), 1.64 (d, *J*=2.8, 1H), 2.00–2.16 (m, 2H), 2.40 (ddd, *J*=0.4, 3.6, 14.4, 1H), 2.62 (dd, *J*=8.8, 14.4, 1H), 3.83–3.93 (m, 1H), 6.36 (t, *J*=7.6, 1H). ^{13}C NMR ($CDCl_3$) δ=14.0, 14.1, 22.7, 27.9, 29.1, 29.1, 29.3, 29.4, 29.5, 29.6, 31.3, 31.9, 35.7, 46.3, 70.4, 98.0, 144.9. HRMS (EI^+): *m*/*z* calcd for $[C_{18}H_{35}IO]^+$: 394.1733; found: 394.1730. Regiochemical assignment was based on COSY spectra; *J*-coupling was observed between the C8 vinyl proton and the C9 allylic protons. Stereochemical assignment was based on an NOE between the C6 and C9 allylic protons and the absence of an NOE between the C8 vinyl proton and the C6 allylic proton (see *Z* isomer below). Further support is provided by comparison to a similar compound.[26]

*4.3.1.1. (Z)-7-Iodooctadec-7-en-5-ol (**Z-2a**).* Light yellow oil, ^1H NMR ($CDCl_3$) δ=0.81 (t, *J*=7.2, 3H), 0.85 (t, *J*=7.2, 3H), 1.10–1.52 (m, 22H), 2.14 (q, *J*=6.8, 2H), 2.52 (dd, *J*=8.4, 14.0, 1H), 2.63 (dm, *J*=14.0, 1H), 3.86–3.96 (m, 1H), 5.62 (t, *J*=6.4, 1H). ^{13}C NMR ($CDCl_3$) δ=14.1, 14.1, 22.7, 27.8, 28.3, 29.2, 29.3, 29.5, 29.6, 29.6, 31.9, 35.6, 36.5, 52.9, 69.5, 104.5, 138.7. HRMS (EI^+): *m*/*z* calcd for $[C_{18}H_{35}IO]^+$: 394.1733; found: 394.1732. Stereochemical assignment based on an NOE between the C8 vinyl proton and the C6 allylic proton and comparison to related compounds.[27]

*4.3.1.2. (E)-8-Iodooctadec-7-en-5-ol (**E-3a**).* Light yellow oil, ^1H NMR ($CDCl_3$) δ=0.88 (t, *J*=7.2, 3H), 0.91 (t, *J*=7.2, 3H), 1.16–1.56 (m, 22H), 2.21 (t, *J*=7.2, 2H), 2.32–2.45 (m, 2H), 3.65–3.70 (m, 1H), 6.24 (t, *J*=7.6, 1H). ^{13}C NMR ($CDCl_3$) δ=14.1, 14.1, 22.7, 22.8, 27.8, 28.4, 29.3, 29.3, 29.5, 29.6, 29.7, 29.6, 31.9, 36.5, 38.7, 71.0, 106.4, 137.0. HRMS (EI^+): *m*/*z* calcd for $[C_{18}H_{35}IO]^+$: 394.1733; found: 394.1734. Stereochemical assignment is based on an NOE between the C6 and C9 allylic protons.

*4.3.2. (E)-4-Iodopentadec-4-en-2-ol (**E-2c**)*

Light yellow oil, 75% yield. ^1H NMR ($CDCl_3$) δ=0.88 (t, *J*=7.2, 3H), 1.18–1.42 (m, 19H), 1.65 (d, *J*=3.6, 1H), 2.02–2.18 (m, 2H), 2.42 (dd, *J*=3.6, 14.4, 1H), 2.65 (dd, *J*=8.0, 14.4, 1H), 4.05–4.15 (m, 1H), 6.37 (t, *J*=8.0, 1H). ^{13}C NMR ($CDCl_3$) δ=14.1, 21.9, 22.6, 29.1, 29.1, 29.3, 29.4, 29.5, 29.5, 31.3, 31.9, 47.7, 66.8, 97.6, 144.8. HRMS (EI^+): *m*/*z* calcd for $[C_{15}H_{29}IO]^+$: 352.1263; found: 352.1261. Stereochemical assignment supported by an NOE between the C3 and C6 allylic protons.

*4.3.3. (E)-3-Iododec-3-en-1-ol (**E-2d**)*

Light yellow oil, 79% yield. ^1H NMR ($CDCl_3$) δ=0.72 (t, *J*=7.2, 3H), 1.02–1.27 (m, 8H), 1.25 (t, *J*=6.0, 1H), 1.93 (q, *J*=7.6, 2H), 2.50 (t, *J*=6.0, 2H), 3.59 (q, *J*=6.0, 2H), 6.21 (t, *J*=7.2, 1H). ^{13}C NMR ($CDCl_3$) δ=14.0, 22.5, 28.7, 29.1, 31.1, 31.6, 41.4, 61.2, 97.3, 144.8. EIMS (*m*/*z*): HRMS (EI^+): *m*/*z* calcd for $[C_{10}H_{19}IO]^+$: 282.0481; found: 282.0480.

Stereochemical assignment supported by an NOE between the C2 and C5 allylic protons.

*4.3.4. (E)-4-Iodo-5-phenylpent-4-en-2-ol (**E-2e**)*

Light yellow oil, 72% yield. ^{1}H NMR ($CDCl_3$) δ=1.26 (d, J=6.4, 3H), 1.71 (d, J=4.0, 1H), 2.51 (ddd, J=1.2, 4.0, 14.4, 1H), 2.91 (dd, J=8.8, 14.4, 1H), 4.19–4.30 (m, 1H), 7.24–7.40 (m, 5H), 7.49 (s, 1H). ^{13}C NMR ($CDCl_3$) δ=22.2, 47.8, 67.5, 103.9, 127.5, 128.3, 128.4, 137.2, 143.7. HRMS (EI$^+$): m/z calcd for $[C_{11}H_{13}IO]^+$: 288.0011; found: 288.0012. Stereochemical assignment supported by an NOE between the C3 allylic proton and the aromatic ring.

*4.3.5. (E)-1-Ethoxy-2-iodohexadec-1-en-4-ol (**E-2f**)*

Light yellow oil, 70% yield. ^{1}H NMR ($CDCl_3$) δ=0.88 (t, J=6.8, 3H), 1.18–1.40 (m, 24H), 1.41–1.58 (m, 4H), 1.79 (d, J=3.6, 1H), 2.41 (dd, J=3.6, 14.4, 1H), 2.74 (dd, J=8.4, 14.4, 1H), 3.73–3.92 (m, 3H), 6.57 (s, 1H). ^{13}C NMR ($CDCl_3$) δ=14.1, 15.3, 22.7, 25.6, 29.4, 29.6, 29.7, 29.7, 31.9, 36.3, 42.3, 68.4, 70.7, 75.1, 151.3. HRMS (EI$^+$): m/z calcd for $[C_{18}H_{35}IO_2]^+$: 410.1682; found: 410.1680.

*4.3.6. (E)-9-(Dibenzylamino)-4-iodonon-4-en-2-ol (**E-2g**)*

Yellow oil, 74% yield. ^{1}H NMR ($CDCl_3$) δ=1.22 (d, J=6.0, 3H), 1.37 (q, J=7.6, 2H), 1.50 (quin, J=7.6, 2H), 1.58 (br s, 1H), 2.00 (ddd, J=2.4, 7.2, 14.8, 2H), 2.34 (dd, J=4.4, 14.4, 1H), 2.40 (t, J=7.2, 2H), 2.56 (dd, J=8.4, 14.4, 1H), 3.54 (s, 4H), 4.02–4.12 (m, 1H), 6.29 (t, J=7.2, 1H), 7.18–7.42 (m, 10H). ^{13}C NMR ($CDCl_3$) δ=22.0, 26.3, 26.5, 30.9, 47.6, 52.8, 58.3, 66.7, 97.8, 126.8, 128.1, 128.7, 139.7, 144.5. HRMS (EI$^+$): m/z calcd for $[C_{23}H_{30}INO]^+$: 463.1372; found: 463.1373. Stereochemical assignment supported by an NOE between the C3 and C6 allylic protons.

*4.3.7. (E)-4-Iodo-7-(4-methoxybenzyloxy)hept-4-en-2-ol (**E-2h**)*

Light yellow oil, 66% yield. ^{1}H NMR ($CDCl_3$) δ=1.24 (d, J=6.0, 3H), 2.19–2.30 (m, 1H), 2.41 (dd, J=3.2, 14.4, 1H), 2.46–2.59 (m, 1H), 2.62 (d, J=3.2, 1H), 2.73 (dd, J=8.8, 14.4, 1H), 3.36–3.50 (m, 2H), 3.81 (s, 3H), 4.02–4.13 (m, 1H), 4.42 (d, J=12.0, 1H), 4.47 (d, J=12.0, 1H), 6.33 (dd, J=6.4, 9.2, 1H), 6.86–6.93 (m, 2H), 7.20–7.32 (m, 2H). ^{13}C NMR ($CDCl_3$) δ=22.3, 31.7, 48.3, 55.2, 66.2, 67.6, 72.6, 100.0, 113.7, 129.4, 129.8, 140.8, 159.2. EIMS (m/z): 332 [M−CH_3CHO]$^+$. HRMS (CI$^+$): m/z calcd for $[C_{15}H_{20}IO_3-H]^+$: 375.0458; found: 375.0459. Stereochemical assignment supported by an NOE between the C3 and C6 allylic protons.

*4.3.8. (E)-4-Iodo-7-(triisopropylsilyloxy)hept-4-en-2-ol (**E-2i**)*

Light yellow oil, 76% yield. ^{1}H NMR ($CDCl_3$) δ=1.00–1.16 (m, 21H), 1.25 (d, J=6.4, 3H), 2.12 (d, J=3.2, 1H), 2.25–2.36 (m, 1H), 2.38–2.50 (m, 2H), 2.74 (dd, J=8.4, 14.4, 1H), 3.73 (t, J=6.0, 2H), 4.02–4.13 (m, 1H), 6.40 (t, J=7.2, 1H). ^{13}C NMR ($CDCl_3$) δ=11.9, 17.9, 22.1, 34.6, 48.4, 62.0, 66.4, 99.3, 141.3. HRMS (EI$^+$): m/z calcd for $[C_{16}H_{32}IO_2Si-H]^+$: 411.1217; found: 411.1212. Stereochemical assignment supported by an NOE between the C3 and C6 allylic protons.

*4.3.9. (E)-1-(4-Bromophenyl)-3-iodo-4-phenylbut-3-en-1-ol (**E-2j**)*

Reaction was preformed following the procedure for **2k**. Light yellow viscous oil, 68% yield. ^{1}H NMR ($CDCl_3$) δ=2.06 (d, J=3.2, 1H), 2.74 (ddd, J=1.2, 4.8, 14.4, 1H), 3.12 (ddd, J=0.8, 8.8, 14.4, 1H), 5.05–5.13 (m, 1H), 7.16–7.23 (m, 3H), 7.25–7.34 (m, 4H), 7.47 (s, 1H). ^{13}C NMR ($CDCl_3$) δ=48.3, 72.9, 102.4, 121.6, 127.6, 127.7, 128.1, 128.4, 131.5, 137.0, 141.7, 144.4. MS (EI$^+$) (m/z): 428, 430 [M]$^+$. HRMS (EI$^+$): m/z calcd for $[C_{16}H_{14}IOBr]^+$: 427.9273; found: 427.9269.

4.4. Hydrozirconation/iodination of homopropargylic alcohols with substitution at the propargylic position (2k, Table 3)

Methyl lithium (0.64 mL, 1.6 M, 1.0 mmol) was added to a solution of homopropargylic alcohol **1k** (230 mg, 1.0 mmol) in THF (3.0 mL) at −78 °C. After 20 min, the solution was warmed up to room temperature. Meanwhile, $Cp_2Zr(H)Cl$ (770 mg, 3.0 mmol) and THF (2.0 mL) were added sequentially to freshly fused $ZnCl_2$ (1.2 g, 9.0 mmol). The resulting mixture was stirred until all $Cp_2Zr(H)Cl$ dissolved (about 3 min; solid $ZnCl_2$ remained suspended). The prepared solution of alkoxide was then transferred into the mixture of $ZnCl_2$ and $Cp_2Zr(H)Cl$ in THF, followed by rinsing with THF (2.0 mL). The resulting clear solution was stirred for 6 h and gave a mixture with gray precipitate. Anhydrous CH_3CN (0.52 mL, 10 mmol) was then added. After 10 min, the reaction was cooled to −78 °C and a solution of I_2 (510 mg, 2.0 mmol) in 3.0 mL of THF was added. After 1 h at this temperature, a mixed aqueous solution of saturated $Na_2S_2O_3$ (15.0 mL) and saturated aqueous $NaHCO_3$ solution (15.0 mL) was added to quench the excess I_2. After dilution with ether, the reaction mixture was separated and the aqueous layer was extracted with ether. The combined organic phases were dried over Na_2SO_4, concentrated, and purified by repetitive chromatography on silica gel to provide **2k** as a light yellow oil (247.4 mg, 69% yield). ^{1}H NMR ($CDCl_3$) δ=0.93 (d, J=6.4, 3H), 1.26 (d, J=6.4, 3H), 1.46–1.64 (m, 2H), 1.77 (d, J=2.4, 1H), 1.80–2.00 (m, 3H), 2.10–2.28 (m, 2H), 3.41 (t, J=6.4, 2H), 3.55–3.66 (m, 1H), 6.40 (t, J=7.2, 1H). ^{13}C NMR ($CDCl_3$) δ=18.3, 19.4, 27.6, 30.5, 31.9, 33.3, 45.8, 70.7, 111.5, 143.0. MS (EI$^+$) (m/z): 360, 362 [M]$^+$. HRMS (EI$^+$): m/z calcd for $[C_{10}H_{18}IOBr]^+$: 359.9586; found: 359.9585.

4.5. Hydrozirconation of homopropargylic alcohols/Negishi cross-coupling. Synthesis of 7

Hydrozirconation was carried out as described in the general procedure for substrates in Table 2. After hydrozirconation, CH_3CN (0.052 mL, 1.0 mmol) and phenyl iodide (0.140 mL, 1.2 mmol) were added. After 10 min, $Pd(PPh_3)_4$ (46 mg, 0.040 mmol) in THF (1.0 mL) was added and the reaction was stirred overnight. The reaction was quenched with aqueous $NaHCO_3$ and extracted with ether. The combined organic phases were dried over $MgSO_4$, concentrated, and purified by repetitive chromatography on silica gel to give 115 mg of product as light yellow oil (79% yield). ^{1}H NMR ($CDCl_3$) δ=1.00–1.15 (m, 21H), 1.17 (d, J=6.0, 3H), 1.90 (d, J=3.6, 1H), 2.43–2.53 (m, 1H), 2.53–2.63 (m, 1H), 2.65 (dd, J=4.4, 14.0, 1H), 2.76 (dd, J=8.0, 14.0, 1H), 3.71–3.85 (m, 1H), 3.82 (t, J=6.4, 2H), 5.84 (t, J=7.6, 1H), 7.19–7.36 (m, 5H). ^{13}C NMR ($CDCl_3$) δ=12.0, 18.0, 23.0, 32.6, 39.8, 63.0, 66.5, 126.5, 126.9, 128.3, 128.6, 138.5, 143.0 HRMS (EI$^+$): m/z calcd for $[C_{22}H_{38}O_2Si]^+$: 362.2641; found: 362.2642.

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