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Zirconium-Promoted Epoxide Rearrangement−Alkynylation Sequence

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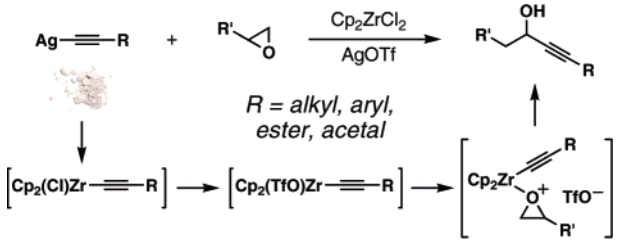
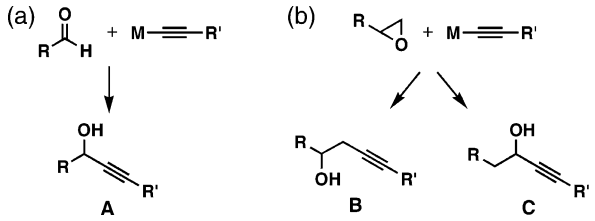


Additions of terminal alkynes to electrophiles are important transformations in organic chemistry. Generally, activated terminal alkynes react with epoxides in an S_N2 fashion to form homopropargylic alcohols. We have developed a new synthetic method to form propargylic alcohols from epoxides and terminal alkynes via 1,2-shifts. This method involves cationic zirconium acetylides as both the activator of epoxides and nucleophiles. Due to the mild conditions to pre-activate alkynes with silver nitrate, this synthetic method is useful for both electron-rich and electron-deficient alkynes with other acid- and base-sensitive functional groups.

Introduction

Alkynylation is an important transformation to add multiple functionalizable carbons to electrophiles. For example, the addition of a metal acetylide toward an aldehyde affords propargylic alcohol **A** (Scheme 1). To generate the nucleophilic metal acetylide, a terminal acetylene is treated with a strong base such as *n*-BuLi.[1] The lithium acetylide either can be used directly or transformed into other metal acetylides[2] before the addition to aldehydes. More recently, Zn[3] and Au[4] acetylides were generated directly from terminal acetylenes and used as nucleophiles toward aldehydes and iminium ions.

SCHEME 1. Formations of Propargylic and Homopropargylic Alcohols



Couplings of epoxides with terminal alkynes are widely used to prepare homopropargylic alcohols **B**.[2a,5] Such couplings are achieved by using highly basic lithium acetylides and highly acidic $BF_3{\cdot}OEt_2$.[5b] There are scarce examples for the transformation of an epoxide to propargyl alcohol **C**.[6] This scarcity is surprising because the acid-promoted rearrangements of epoxides to aldehydes are often used in combination with various nucleophiles.[7] Here, we report that zirconium acetylides[8] can be applied to the transformation of epoxide to **C**.

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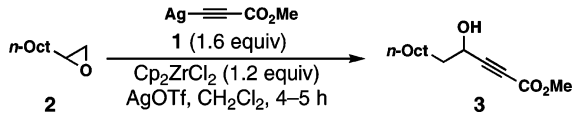
TABLE 1. Epoxide Opening



entry	AgOTf (equiv)	temp (°C)	yield (%)[a]
1	0.2	23	44
2	0.2	40	57
3	0.5	23	58
4	1.0	23	43

[a] Isolated yields. BORSM = based on recovered starting material.

Results and Discussion

At the outset of this study, we chose methyl propiolate as a model alkyne because it contains three functionalizable carbons and the reaction would produce highly versatile γ-hydroxy-α,β-acetylenic esters.[9] Silver acetylide **1** (Table 1), after extensive washing with water and drying under high vacuum, can be stored at an ambient temperature for many months in the dark without any precaution to avoid moisture.[10] If **1** is not washed thoroughly, the resulting material decomposes within a week. Despite a safety concern in the recent literature[11a] a falling hammer test on **1** was negative, indicating that **1** can be handled without extraordinary precautions (Figure S1, Supporting Information).[11b]

Under the alkynylation reaction conditions, **2** was transformed to alcohol **3** in 44% yield (79% based on recovered **2**; Table 1, entry 1). We were surprised by this result not only because this reaction afforded the unexpected bond connectivity, but also because the product may be more electrophilic than the substrate. To improve the conversion efficiency further, this reaction was heated to 40 °C in CH_2Cl_2, which afforded the same product in 57% yield (entry 2). We could also use more AgOTf (0.5 equiv) at 23 °C for essentially the same efficiency (58%; entry 3). Further addition of AgOTf (1.0 equiv) generated **3** albeit in 43% yield (entry 4). From this study, this reaction was found to be effective at 23 °C using substoichiometric AgOTf and stoichiometric Cp_2ZrCl_2.

1-Oxaspiro[2.5]octane reacted with **1** in the presence of 1.2 equiv of Cp_2ZrCl_2 and 0.2 equiv of AgOTf to form **4** in 54% yield (Table 2, entry 1). Acetylide **1** reacted with 1,2-epoxy-5-hexene less efficiently, providing **5** in 33% yield, but this epoxide reacted smoothly with electron-rich alkyne **6** to give **7** in 59% yield (entries 2 and 3). Styrene oxide reacted with **1** to afford **8** in 64% yield using only 0.05 equiv of AgOTf (entry 4). Unstable allylic epoxide **9** reacted with **6** to give **10** in 53% yield (entry 5). Interestingly, when 1,2-epoxy-3-phenoxypropane was subjected to the same reaction conditions, we obtained chlorohydrin **11** in 88% yield (entry 6). This unexpected result may be due to the inductive effect of the aryloxy group that destabilizes the necessary carbocation-like intermediate to facilitate the 1,2-hydride shift. Epoxide **12** reacts with **1** and **6** to generate **13** and **14** in 46% and 52% yields, respectively, demonstrating that additional oxygen substituents are tolerated on the epoxide molecule (entries 7 and 8). We also found that more hindered epoxides such as cyclohexene oxide and cyclopentene oxide generated intractable mixtures under the reaction conditions.

The next step was to determine the scope of this method with respect to alkynes. Epoxide **2** was treated with **6** under the reaction conditions, providing **15** in 69% isolated yield (entry 9). The phenylacetylene derivative **16** reacted with **2** to give **17** in 82% yield (entry 10). We coupled **2** and THP ether **18** (entry 11), and **19** was isolated in 82% yield. The similarly acid-sensitive diethyl acetal **20** also reacted with **2** to afford alcohol **21** in 81% yield (entry 12). These results indicate that acid-sensitive functional groups such as acetals are compatible.

One of the benefits of our alkynylation method is the specific C−H activation of terminal alkynes in the presence of similarly acidic hydrogens. To demonstrate this concept in a synthetically useful context, we treated propargyl acetate $HC{\equiv}CCH_2OAc$ with $AgNO_3$ in NH_4OH to give **22** in 97% yield despite the very similar pK_a values of terminal alkynes and esters in general (both ~25). When this acetylide was coupled with **2**, compound **23** was generated in 57% yield (entry 13). This compound is of high synthetic value as demonstrated by the Carreira group.[12] Selenide **24** reacted with **2** to form alcohol **25** in 52% yield (entry 14). These alkynes used in the epoxide openings should be readily applicable for additions to aldehydes.

To determine the stereochemical relationship between epoxides and products, we subjected *cis*- and *trans*-stilbene oxides to the reaction conditions (entries 15 and 16); in both cases, the phenyl group migrated and produced alcohol **26** in 86−88% yields. Thus, it appears that the migratory aptitude is a predominant factor in determining a migrating group. Finally, the enantioriched epoxide **27** (e.r., >40:1)[13] was reacted with **16**, forming alcohol **28** as a 1:1 diastereomeric mixture in 63−79% yields (entry 17). The HPLC and NMR analyses of the corresponding Mosher esters revealed that the enantiomeric ratios of *syn*-**28** and *anti*-**28** were both 9:1, indicating that the 1,2-hydride shift proceeded with good stereospecificity. The tentative stereochemistry assignment at the tertiary stereocenter

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(11) (a) Persson, T.; Nielsen, J. *Org. Lett.* **2006**, *8*, 3219−3222. (b) When compound **1** on aluminum foil was hit with a hammer, there was no sign of a spark or explosive nature of **1**. This material was also heated to 150 °C, and we did not observe any alarming phenomena except for slow decomposition. Although more extensive studies may be needed, the silver acetylides shown in this paper were prepared multiple times without an accident. Also, we safely performed the Cp_2ZrCl_2/AgOTf-promoted alkynylation in the following papers on 140 mmol scale as part of the FR901464/meayamycin synthesis: Albert B. J.; Sivaramakrishnan, A.; Naka, T.; Czaicki, N. L.; Koide, K., *J. Am. Chem. Soc.* **2007**, *129*, 2648−2659; Albert, B. J.; Sivaramakrishnan, A.; Naka, T.; Koide, K. *J. Am. Chem. Soc.* **2006**, *128*, 2792−2793.

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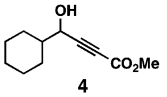
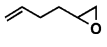
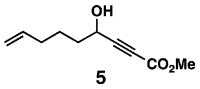
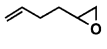
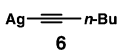
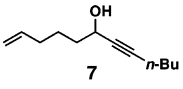
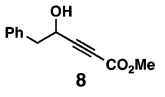
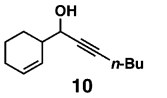
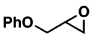
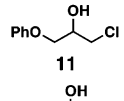
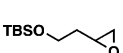
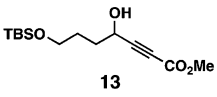
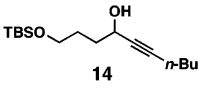
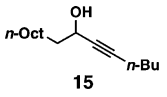
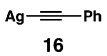
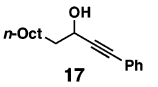
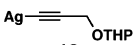
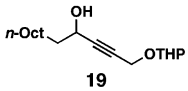
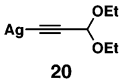
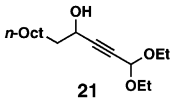
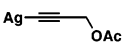
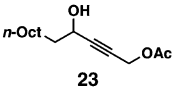
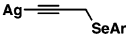
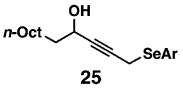
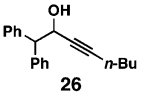
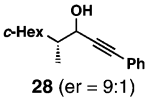
TABLE 2. Epoxide Opening[e]

entry	epoxide	alkyne (1.6 equiv)	time (h)	product	isolated yield (%)
1[a]		**1**	3	 **4**	54
2		**1**	8	 **5**	33
3		 **6**	7.5	 **7**	59
4[b]		**1**	1	 **8**	64
5	 **9**	**6**	5	 **10**	53[c]
6		**1**	8	 **11**	88
7	 **12**	**1**	6.5	 **13**	46
8	**12**	**6**	5	 **14**	52
9	**2**	**6**	8	 **15**	69
10	**2**	 **16**	6.5	 **17**	82
11	**2**	 **18**	8	 **19**	82
12	**2**	 **20**	7	 **21**	81
13	**2**	 **22**	10	 **23**	57
14	**2**	 **24** (Ar = *o*-NO_2-Ph)	10	 **25**	52
15		**6**	2.5	 **26**	86
16		**6**	3	**26**	88
17	 **27** (er = >40:1)	**16**	2.5	 **28** (er = 9:1)	63–79[d]

[a] 0.2 equiv of AgOTf was used. [b] 0.05 equiv of AgOTf was used. [c] dr = 2:1 (unassigned). [d] dr = 1:1. [e] Reagents and conditions: silver acetylide (1.6 equiv), Cp_2ZrCl_2 (1.2 equiv), AgOTf (0.5 equiv), CH_2Cl_2, 23 °C.

SCHEME 2. Proposed Mechanism

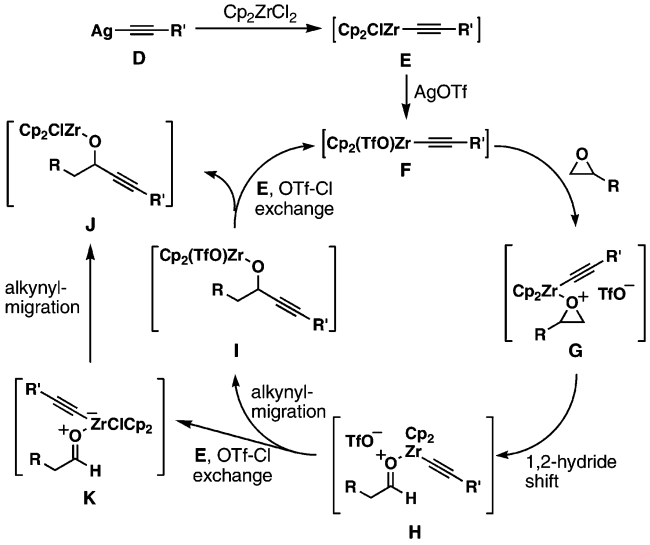
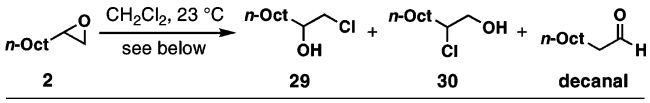


TABLE 3. Control Experiments



entry	reagents (equiv)	chlorohydrins, isolated yield (%)	decanal
1	Cp_2ZrCl_2 (1.6)	83	none
2	AgOTf (0.5)	none	none
3	Cp_2ZrCl_2 (1.2), AgOTf (0.5)	87	trace
4	**1** (1.6), Cp_2ZrCl_2 (1.2)	22	none

is based on the literature.[14] The observed specificity is remarkable because related 1,1-disubstituted epoxides exhibited poor to no stereospecificity under different reaction conditions.[15]

Our proposed mechanism is shown in Scheme 2. Transmetalation of silver acetylide **D** and Cp_2ZrCl_2 gives zirconium acetylide **E**, which then reacts with AgOTf to give the more Lewis acidic zirconium acetylide **F**.[16] This acetylide coordinates with an epoxide to form complex **G**. Subsequent 1,2-hydride shift gives the aldehyde−zirconium complex **H**, allowing for the carbonyl alkynylation to afford zirconium alkoxide **I**. This complex can then undergo triflate−chloride exchange with zirconium acetylide **E**, explaining the need for a substoichiometric amount of AgOTf. Alternatively, **E** and **H** could undergo triflate−chloride exchange to form **F** and ate complex **K**, which undergoes carbonyl alkynylation to form alkoxide **J**. This alternative mechanism may explain why the use of stoichiometric AgOTf resulted in lower yield (Table 1, entry 4) due to the poor availability of chloride ions.

On the basis of this proposed mechanism, we examined the role of the additives (Table 3). Treatment of **2** with Cp_2ZrCl_2 generated chlorohydrins **29** and **30** in 83% combined yield in a 5:1 ratio with no formation of decanal (entry 1). We also

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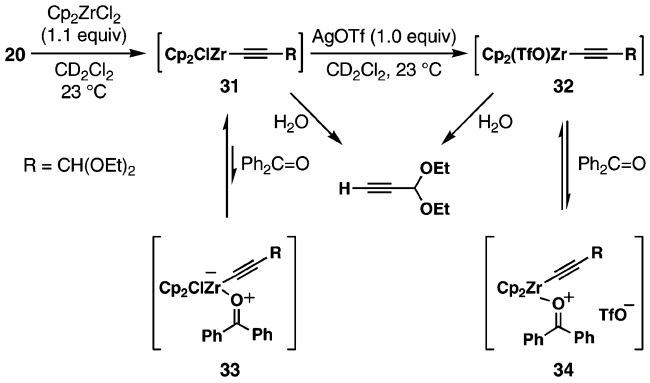
(15) (a) Karame, I.; Tommasino, M. L.; Lemaire, M. *Tetrahedron Lett.* **2003**, *44*, 7687−7689. (b) Hara, N.; Mochizuki, A.; Tatara, A.; Fujimoto, Y. *Tetrahedron*: *Asymmetry* **2000**, *11*, 1859−1868.

(16) Maeta, H.; Hashimoto, T.; Hasegawa, T.; Suzuki, K. *Tetrahedron Lett.* **1992**, *33*, 5965−5968.

SCHEME 3. Characterized Species



subjected the same epoxide to AgOTf and found no reaction (entry 2). Therefore, neither Cp_2ZrCl_2 nor AgOTf were able to induce the 1,2-hydride shift. Exposure of **2** to Cp_2ZrCl_2 and AgOTf gave **29** and **30** in 87% combined yield in a 1:1 ratio with a trace amount of decanal (entry 3). Although the combination of Cp_2ZrCl_2 and AgOTf presumably generates $Cp_2ZrCl(OTf)$ in situ and allows for the 1,2-hyride shift to occur, chlorohydrin formation promoted by Cp_2ZrCl_2 and/or $Cp_2ZrCl(OTf)$ is strongly preferred. Treatment of **2** to the mixture of **1** and Cp_2ZrCl_2, precursors to $[Cp_2ClZr-C\equiv C-CO_2Me]$, provided **29** and **30** in 22% combined yield in a 3:1 ratio (entry 4). This result shows that zirconium acetylide $[Cp_2ClZr-C\equiv C-CO_2Me]$ is not responsible for the transformation of **2** to **3** but suppresses chlorohydrin formation to some extent. To test whether chlorohydrin formation is reversible under the reaction conditions, **29** and **30** were subjected to the alkynylation reaction conditions. However, neither **3** nor decanal were observed, indicating that chlorohydrin formation is irreversible under the reaction conditions. Therefore, silver acetylide, Cp_2ZrCl_2, and AgOTf are all needed for the 1,2-hyride shift−alkynylation sequence in accordance with our proposed mechanism.

We proceeded to study the mechanism by NMR (Scheme 3). First, we were able to characterize **20**[17] by ^1H and ^{13}C NMR (Supporting Information). Addition of Cp_2ZrCl_2 to **20** generated zirconium acetylide **31** via transmetalation, which was corroborated by ^1H and ^{13}C NMR. Treatment of this zirconium acetylide with AgOTf (1 equiv) generated a new species showing downfield chemical shifts compared to **31** (Supporting Information), which we believe is **32**. Both **31** and **32** were sensitive toward moisture and could not be isolated after aqueous workups, only giving 3,3-diethoxypropyne. To probe the Lewis acidities of **31** and **32**, we used $Ph_2C{=}O$ as a Lewis base due to its attenuated reactivity. Treatment of **31** with $Ph_2C{=}O$ resulted in the slight upfield chemical shifts observed in ^{13}C NMR spectrum of $Ph_2C{=}O$, implying an equilibrium between the starting material and the plausible complex **33**. When **32** and $Ph_2C{=}O$ were mixed, the observed ^{13}C chemical shifts for $Ph_2C{=}O$ were now shifted downfield, which we interpret as **34**. These results show that the Zr atoms in both **31** and **32** are Lewis acidic, and **34** contains a Zr-bound electrophile in a higher population. This is also consistent with our previous observations that AgOTf was required to induce 1,2-hydride shift.

(17) Many silver acetylides including **1** could not be used due to its poor solubility in organic solvents, but acetylide **20** was soluble in organic solvents and thus used.

Conclusions

We have developed the first general method to couple epoxides with terminal alkynes to form propargylic alcohols. Various functional groups are compatible with these newly developed alkynylation conditions. Synthetic use of silver acetylides has been limited to only a few types of reactions.[10a,18] This study shows that the formation of silver acetylides followed by zirconium acetylides of electron-deficient electron-and rich alkynes is a powerful method to couple functionalized alkynes to epoxides.

Experimental Section

General Procedure for the Preparation of the Silver Acetylides. To a stirred solution of $AgNO_3$ (2.1−283 mmol, 2.1 equiv) in deionized H_2O (1.0−84 mL) and MeOH[19] (0.4−50 mL) was added NH_4OH (28−30%, 0.4−54 mL) until the solution became clear again at 23 °C under ambient light. After 30 min at the same temperature, terminal alkynes (1.0−138 mmol, 1 equiv) in MeOH (0.3−6 mL) were added dropwise. After an additional 10−30 min of vigorous stirring at the same temperature, the reaction mixture was filtered through a frit, then thoroughly rinsed with deionized H_2O (8 × 5−250 mL) and MeOH (5−250 mL). The resulting solids were dried under high vacuum overnight over P_2O_5 to give the appropriate silver acetylides (79%−quantitative yield) as powders. Although the silver acetylides shown in this paper were powders, we noted that more hydrophobic silver acetylides were oils. In these instances, we diluted the reaction mixture with H_2O and extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the silver acetylides as oils.

General Procedure for the Addition of Silver Acetylides to Epoxides. To a stirred solution (or suspension for poorly soluble silver acetylides) of silver acetylide (0.8−16 mmol, 1.6 equiv) in CH_2Cl_2 (1.8−30 mL) was added epoxide (0.5−9.9 mmol, 1 equiv) followed by the addition of Cp_2ZrCl_2 (0.6−12 mmol, 1.2 equiv) and AgOTf (0.025−5.0 mmol, 0.05−0.5 equiv) in one portion at 23 °C under ambient light. After vigorous stirring at the same temperature for 1−10 h the solution was quenched with saturated aqueous NH_4Cl or saturated aqueous $NaHCO_3$ (0.5−6 mL). After stirring for 15−30 min at the same temperature, the reaction mixture was filtered through a pad of Celite 545 and Na_2SO_4, rinsed with Et_2O (2 × 5−30 mL), and concentrated under reduced pressure. The resulting residues were purified by flash chromatography (EtOAc/hexanes) on silica gel to afford the corresponding alcohols.

Data for 3: colorless oil; R_f 0.29 (20% EtOAc in hexanes); IR (neat) 3419 (br, O−H), 2924, 2855, 2237, 1717, 1436, 1251, 1065, 752 cm^{-1}; ^1H NMR (300 MHz, 293 K, $CDCl_3$) δ 4.50 (br app q, 1H, J = 6.4 Hz), 3.80 (s, 3H), 1.91 (d, 1H, J = 5.8 Hz), 1.82−1.73 (m, 2H), 1.53−1.22 (m, 14H), 0.89 (t, 3H, J = 6.7 Hz); ^{13}C NMR (75 MHz, 293 K, $CDCl_3$) δ 153.8, 88.4, 76.1, 62.1, 52.8, 36.8, 31.8, 29.44, 29.39, 29.2, 29.1, 24.9, 22.6, 14.0; HRMS (EI+) calcd for $C_{14}H_{24}O_3$ $[M]^+$ 240.1725, found 240.1735.

Procedure and Data for the Preparation of 1-Oxaspiro[2.5]-octane. See ref 20.

Data for 4: see ref 8.

Data for 5: colorless oil; R_f 0.40 (30% EtOAc in hexanes); IR (neat) 3412 (br, O−H), 2952, 2237, 1718, 1436, 1254, 1068, 914, 752 cm^{-1}; ^1H NMR (300 MHz, 293 K, 1% CD_3OD in $CDCl_3$) δ 5.79 (dddd, 1H, J = 16.8, 10.2, 6.6, 6.6 Hz), 5.06−4.94 (m, 2H), 4.46 (app t, 1H, J = 6.6 Hz), 3.78 (s, 3H), 2.13−2.04 (m, 2H), 1.80−1.51 (m, 4H); ^{13}C NMR (75 MHz, 293 K, $CDCl_3$) δ 153.9, 138.0, 115.0, 88.6, 75.9, 61.6, 52.7, 36.1, 33.1, 24.0; LRMS (EI+)

(18) Dillinger, S.; Bertus, P.; Pale, P. *Org. Lett.* **2001**, *3*, 1661−1664.

(19) EtOH was used instead of MeOH for the preparation of the silver acetylide **20** from 3,3-diethoxypropyne.

(20) Michnik, T. J.; Matteson, D. S. *Synlett* **1991**, 631−632.

$C_{10}H_{11}O_2$ [M − H_3O]$^+$ 163 (58%), $C_9H_9O_2$ [M − CH_5O]$^+$ 149 (14%), $C_7H_{11}O$ [M − $C_2H_4O_2$]$^+$ 122 (26%).

Data for 7: colorless oil; R_f 0.27 (15% EtOAc in hexanes); IR (neat) 3345 (br O−H), 2933, 2863, 2232, 1641, 1459, 996, 911 cm^{-1}; ^{1}H NMR (300 MHz, 293 K, 1% CD_3OD in $CDCl_3$) δ 5.79 (dddd, 1H, J = 17.2, 10.0, 6.5, 6.5 Hz), 4.99 (dddd, 1H, J = 17.2, 1.5, 1.5, 1.5 Hz), 4.93 (br d, 1H, J = 10.0 Hz), 4.31 (br app t, 1H, J = 3.9 Hz), 2.18 (app td, 2H, J = 7.0, 2.0 Hz), 2.06 (br app q, 2H, J = 7.5 Hz), 1.71−1.58 (m, 2H), 1.56−1.33 (m, 6H), 0.88 (t, 3H, J = 7.3 Hz); ^{13}C NMR (125 MHz, 293 K, $CDCl_3$) δ 138.5, 114.6, 85.3, 81.1, 62.2, 37.4, 33.2, 30.7, 24.4, 21.8, 18.2, 13.5; LRMS (EI+) $C_{12}H_{19}O$ [M − H]$^+$ 179 (5%), $C_9H_{13}O$ [M − C_3H_7]$^+$ 137 (75%), $C_7H_{11}O$ [M − C_5H_9]$^+$ 111 (100%).

Data for 8: see ref 8.

Procedure for the Preparation of 9. See ref 20.

Data for 9: see ref 21.

Data for 10: colorless oil; R_f 0.28 (15% EtOAc in hexanes); IR (neat) 3360 (br O−H), 2931, 2862, 2224, 1451, 1379, 1140, 1047, 725 cm^{-1}; ^{1}H NMR (300 MHz, 293 K, 1% CD_3OD in $CDCl_3$) δ 5.90−5.66 (m, 2H), 4.19 (br app s, 1H), 2.40−2.28 (m, 1H), 2.21 (app t, 2H, J = 6.5 Hz), 2.06−1.94 (m, 2H), 1.92−1.73 (m, 2H), 1.64−1.35 (m, 6H), 0.90 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, 293 K, $CDCl_3$) δ 130.1, 129.9, 127.2, 126.5, 86.2, 86.1, 80.2, 80.0, 66.2, 66.0, 42.4, 30.7, 25.18, 25.16, 24.5, 21.8, 21.4, 21.0, 18.3, 13.5; HRMS (EI+) calcd for $C_{13}H_{20}O$ [M]$^+$ 192.1514, found 192.1508.

Data for 11: see ref 22.

Procedure for the Preparation of 12. To a stirred solution of 1-*tert*-butyldimethylsiloxy-3-butene (935 mg, 5.02 mmol) in CH_2Cl_2 (17 mL) was added *m*CPBA (70%, 2.47 g, 10.0 mmol) at 0 °C. After 10 min at the same temperature, the reaction was allowed to warm to 23 °C. After 14 h at the same temperature, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous Na_2SO_3 (10 mL). The reaction mixture was then vigorously stirred for an additional 15 min, then diluted with hexanes (25 mL), and the layers were separated. The organic layer was then washed with saturated aqueous $NaHCO_3$ (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (1−5% EtOAc in hexanes) on silica gel (50 mL) to afford **12** (964 mg, 95%) as a colorless oil.

Data for 12: see ref 23.

Data for 13: pale yellow oil; R_f 0.30 (20% EtOAc in hexanes); IR (neat) 3411 (br O−H), 2954, 2858, 2237, 1720 (C=O), 1436, 1255, 1100, 837 cm^{-1}; ^{1}H NMR (300 MHz, 293 K, 1% CD_3OD in $CDCl_3$) δ 4.53 (br app t, 1H, J = 5.3 Hz), 3.77 (s, 3H), 3.76−3.60 (m, 2H), 1.96−1.64 (m, 4H), 0.90 (s, 9H), 0.083 (s, 3H), 0.079 (s, 3H); ^{13}C NMR (75 MHz, 293 K, $CDCl_3$) δ 153.9, 88.6, 76.0, 63.0, 61.5, 52.6, 34.5, 28.3, 25.8, 18.3, −5.48, −5.53; HRMS (ESI+) calcd for $C_{14}H_{27}O_4Si$ [M + H]$^+$ 287.1679, found 287.1675.

Data for 14: colorless oil; R_f 0.31 (15% EtOAc in hexanes); IR (neat) 3385 (br O−H), 2931, 2859, 2235, 1468, 1387, 1254, 1103, 837 cm^{-1}; ^{1}H NMR (300 MHz, 293 K, 1% CD_3OD in $CDCl_3$) δ 4.39 (br s, 1H), 3.71−3.63 (m, 2H), 2.24−2.16 (m, 2H), 1.82−1.64 (m, 4H), 1.51−1.23 (m, 4H), 0.93−0.87 (m, 12H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, 293 K, $CDCl_3$) δ 85.2, 81.1, 63.2, 62.2, 35.5, 30.7, 28.5, 25.9, 21.9, 18.34, 18.27, 13.5, −5.4; HRMS (ESI+) calcd for $C_{16}H_{32}O_2NaSi$ [M + Na]$^+$ 307.2069, found 307.2070.

Data for 15: colorless oil; R_f 0.40 (15% EtOAc in hexanes); IR (neat) 3384 (br, O−H), 2926, 2855, 2233, 1466, 1379, 1026, 722 cm^{-1}; ^{1}H NMR (300 MHz, 293 K, 1% CD_3OD in $CDCl_3$) δ 4.35 (br app t, 1H, J = 6.4 Hz), 2.22 (app td, 2H, J = 6.9, 1.8 Hz), 1.72−1.60 (m, 2H), 1.55−1.24 (m, 18H), 0.96−0.85 (m, 6H); ^{13}C NMR (75 MHz, 293 K, $CDCl_3$) δ 85.4, 81.4, 62.8, 38.2, 31.9 30.8, 29.52, 29.48, 29.27, 29.26, 25.2, 22.7, 21.9, 18.4, 14.1, 13.5; HRMS (EI+) calcd for $C_{16}H_{30}O$ [M]$^+$ 238.2297, found 238.2288.

Data for 17: pale yellow oil; R_f 0.31 (15% EtOAc in hexanes); IR (neat) 3329 (br, O−H), 2924, 2855, 2229, 1599, 1490, 1070, 1027, 755 cm^{-1}; ^{1}H NMR (300 MHz, 293 K, 1% CD_3OD in $CDCl_3$) δ 7.45−7.39 (m, 2H), 7.34−7.28 (m, 3H), 4.57 (app t, 1H, J = 6.6 Hz), 1.83−1.74 (m, 2H), 1.57−1.23 (m, 14H), 0.87 (t, 3H, J = 6.6 Hz); ^{13}C NMR (75 MHz, 293 K, $CDCl_3$) δ 131.7, 128.3, 128.2, 122.7, 90.3, 84.8, 63.0, 37.9, 31.9, 29.5, 29.3, 25.2, 22.7, 14.1; HRMS (EI+) calcd for $C_{18}H_{26}O$ [M]$^+$ 258.1984, found 258.1975.

Data for 19: colorless oil; R_f 0.14 (15% EtOAc in hexanes); IR (neat) 3423 (br, O−H), 2924, 2854, 1466, 1343, 1201, 1120, 1024, 902 cm^{-1}; ^{1}H NMR (300 MHz, 293 K, 1% CD_3OD in $CDCl_3$) δ 4.81 (br s, 1H), 4.40−4.33 (m, 1H), 4.33 (dd, 1H, J = 15.6, 1.5 Hz), 4.25 (dd, 1H, J = 15.6, 1.2 Hz), 3.88−3.79 (m, 1H), 3.56−3.49 (m, 1H), 1.88−1.20 (m, 22H), 0.87 (t, 3H, J = 5.9 Hz); ^{13}C NMR (75 MHz, 293 K, $CDCl_3$) δ 96.9, 87.4, 80.2, 62.1, 62.0, 54.3, 37.6, 31.8, 30.1, 29.47, 29.45, 29.22, 29.21, 25.2, 25.1, 22.6, 18.9, 14.0; HRMS (ESI+) calcd for $C_{18}H_{32}O_3$ [M + Na]$^+$ 319.2249, found 319.2250.

Data for 21: colorless oil; R_f 0.22 (15% EtOAc in hexanes); IR (neat) 3425 (br, O−H), 2925, 2856, 2241, 1467, 1328, 1145, 1054, 1012 cm^{-1}; ^{1}H NMR (300 MHz, 293 K, 1% CD_3OD in $CDCl_3$) δ 5.29 (d, 1H, J = 1.2 Hz), 4.39 (br app t, 1H, J = 6.6 Hz), 3.81−3.68 (m, 2H), 3.63−3.56 (m, 2H), 1.75−1.66 (m, 2H), 1.52−1.18 (m, 20H), 0.87 (t, 3H, J = 6.8 Hz); ^{13}C NMR (75 MHz, 293 K, $CDCl_3$) δ 91.2, 86.5, 80.0, 62.2, 60.9, 60.8, 37.4, 31.8, 29.5, 29.3, 29.2, 25.1, 22.6, 15.0, 14.1; HRMS (EI+) calcd for $C_{15}H_{27}O_2$ [M − OEt]$^+$ 239.2011, found 239.2007.

Data for 23: colorless oil; R_f 0.24 (20% EtOAc in hexanes); IR (neat) 3424 (br, O−H), 2925, 2855, 1750, 1457, 1379, 1226, 1028 cm^{-1}; ^{1}H NMR (300 MHz, 293 K, 1% CD_3OD in $CDCl_3$) δ 4.73 (d, 1H, J = 18.2 Hz), 4.67 (d, 1H, J = 18.2 Hz), 4.37 (br app t, 1H, J = 6.3 Hz), 2.10 (s, 3H), 1.73−1.64 (m, 2H), 1.48−1.21 (m, 14H), 0.87 (t, 3H, J = 6.6 Hz); ^{13}C NMR (75 MHz, 293 K, $CDCl_3$) δ 170.3, 88.0, 78.6, 62.3, 62.2, 53.3, 37.5, 31.8, 29.5, 29.3, 29.2, 25.1, 22.6, 20.7, 14.1; HRMS (ESI+) calcd for $C_{15}H_{26}O_3$ [M + Na]$^+$ 277.1780, found 277.1829.

Procedure for the Preparation of *p*-Nitrophenyl Propargyl Selenide. To a stirred solution of 2-nitrophenylselenocyanate (2.27 g, 10.0 mmol) and propargyl alcohol (650 μL, 11.2 mmol) in THF (35 mL) was added ^{n}Bu$_3$P (3.0 mL, 12 mmol) dropwise at 0 °C. After 40 min at the same temperature, the reaction was poured onto saturated aqueous $NaHCO_3$ (300 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (1→ 5% Et_2O in hexanes) on silica gel (250 mL) to afford *p*-nitrophenyl propargyl selenide (1.90 g, 79%) as a yellow solid.

Data for *p*-nitrophenyl propargyl selenide: yellow solid; mp 85−86 °C; R_f 0.29 (15% EtOAc in hexanes); IR (KBr pellet) 3272, 3088, 2925, 1589, 1565, 1497, 1352, 1306, 1100, 1038, 731 cm^{-1}; ^{1}H NMR (300 MHz, 293 K, $CDCl_3$) δ 8.37 (dd, 1H, J = 8.4, 1.2 Hz), 7.69 (dd, 1H, J = 8.1, 1.2 Hz), 7.62 (ddd, 1H, J = 8.1, 6.9, 1.5 Hz), 7.39 (ddd, 1H, J = 8.4, 6.9, 1.5 Hz), 3.55 (d, 2H, J = 2.7 Hz), 2.28 (t, 1H, J = 2.7 Hz); ^{13}C NMR (75 MHz, 293 K, $CDCl_3$) δ 146.0, 134.0, 132.9, 128.8, 126.4, 125.9, 79.5, 72.1, 11.4; HRMS (EI+) calcd for $C_9H_7NO_2{}^{80}Se$ [M]$^+$ 240.9642, found 240.9633.

Data for 25: pale yellow solid; mp 71−72 °C; R_f 0.34 (30% EtOAc in hexanes); IR (KBr pellet) 3332 (br, O−H), 2923, 2850, 1589, 1567, 1503, 1330, 1306, 1038, 729 cm^{-1}; ^{1}H NMR (300 MHz, 293 K, 1% CD_3OD in $CDCl_3$) δ 8.34 (dd, 1H, J = 8.3, 1.3 Hz), 7.65 (dd, 1H, J = 8.1, 1.3 Hz), 7.58 (ddd, 1H, J = 8.1, 7.2, 1.5 Hz), 7.36 (ddd, 1H, J = 8.3, 7.2, 1.5 Hz), 4.33 (br app t, 1H, J = 6.6 Hz), 3.62−3.55 (m, 2H), 1.71−1.15 (m, 16H), 0.87 (t, 3H, J = 6.8 Hz); ^{13}C NMR (75 MHz, 293 K, $CDCl_3$) δ 146.2, 133.9, 133.2, 129.0, 126.4, 125.8, 85.2, 80.2, 62.6, 37.8, 31.8, 29.5

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(22) Pchelka, B. K.; Loupy, A. *Tetrahedron* **2006**, *62*, 10968−10979.
(23) Lawson, E. N.; Jamie, J. F.; Kitching, W. J. *J. Org. Chem.* **1992**, *57*, 353−358.

(2 carbons overlapped), 29.25, 29.20, 25.1, 22.6, 14.1, 12.0; HRMS (EI+) calcd for $C_{19}H_{27}NO_3{}^{80}Se$ $[M]^+$ 397.1156, found 397.1141.

Data for 26: R_f 0.40 (20% EtOAc in hexanes); IR (neat) 3420 (br, O−H), 3028, 2931, 2228, 1495, 1452, 1032, 746 cm^{-1}; ^1H NMR (300 MHz, 293 K, 1% CD_3OD in $CDCl_3$) δ 7.42−7.18 (m, 10H), 5.02 (ddd, 1H, J = 7.2, 1.8, 1.8 Hz), 4.20 (br d, 1H, J = 7.2 Hz), 2.16−1.95 (m, 3H), 1.40−1.16 (m, 4H), 0.82 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, 293 K, 1% CD_3OD in $CDCl_3$) δ 141.2, 140.6, 128.9, 128.8, 128.3, 128.1, 126.7, 126.6, 87.6, 79.9, 65.2, 58.2, 30.4, 21.6, 18.2, 13.4; HRMS (ESI+) calcd for $C_{20}H_{22}ONa$ $[M + Na]^+$ 301.1568, found 301.1579.

Procedure for the Preparation of *rac*-27. To a stirred solution of cyclohexylmethyl ketone (1.4 mL, 10 mmol) and CH_2Br_2 in THF (30 mL) was added ^{n}BuLi (1.6 M in hexanes, 7.0 mL) down the flask sides over 15 min at −78 °C. After an additional 30 min at the same temperature, the reaction was warmed to 23 °C. After 2.75 h at the same temperature, the reaction mixture was poured onto saturated aqueous NH_4Cl (40 mL) and concentrated under reduced pressure to remove most of the THF. The resulting aqueous residue was extracted with Et_2O (2 × 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (2→ 4% EtOAc in hexanes) on silica gel (50 mL) to afford *rac*-**27** (1.08 g, 77%) as a colorless oil.

Procedure and Data for the Preparation of (*R*)-27. See ref 13.

Data for 28: R_f 0.27 (10% EtOAc in hexanes); IR (neat) 3417 (br, O−H), 2924, 1637, 1490, 1447, 1000, 755 cm^{-1}; ^1H NMR (300 MHz, 293 K, 1% CD_3OD in $CDCl_3$) δ 7.41−7.38 (m), 7.33−7.28 (m), 4.61 (d, J = 5.7 Hz), 1.82−1.52 (m), 1.36−1.10 (m), 1.06 (t, J = 6.6 Hz), 1.03 (t, J = 6.9 Hz); ^{13}C NMR (75 MHz, 293 K, $CDCl_3$) δ 131.7, 131.6, 128.3, 122.8, 90.2, 89.2, 85.9, 85.3, 65.40, 65.35, 45.0, 44.8, 39.5, 35.0, 31.6, 31.4, 29.2, 28.7, 26.71, 26.64, 26.59, 26.47, 11.43, 11.40; HRMS (EI+) calcd for $C_{17}H_{22}O$ $[M]^+$ 242.1671, found 242.1676.

General Procedure for the Preparation of 29, 30, and Decanal from 2. To a stirred solution of **2** (45 μL, 0.24 mmol) in CH_2Cl_2 (1.0 mL) were added the other reaction components (equivalents based on optimized alkynylation reaction conditions) at 23 °C. After 3.5−19 h at the same temperature, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (0.3 mL). After stirring for 15−30 min at the same temperature, the reaction mixture was filtered through a pad of Celite 545 and Na_2SO_4, rinsed with Et_2O (3 × 5 mL), and concentrated under reduced pressure. The resulting residues were purified by flash chromatography (EtOAc/hexanes) on silica gel to afford the corresponding products.

Data for 29 and 27: see ref 24.

Procedure for the Preparation of 31 and 33 from 20. To an NMR tube was added **20** (35−49 mg, 0.15−0.20 mmol) followed by CD_2Cl_2 (0.8 mL) under Ar at 23 °C. To the homogeneous solution was added Cp_2ZrCl_2 (1.1 equiv) and the resulting mixture was vortexted for 5 min. NMR experiments were then performed on the rapidly generated acetylide **31**. To this solution was added benzophenone (1.0 equiv) and the mixture was vortexed for 2 min. NMR experiments were then performed on equilibrium between **31** and **33**. See Tables S1 and S2 in the Supporting Information for NMR data.

Procedure for the Preparation of 32 and 34 from 31. To an NMR tube containing **31** (0.15−0.20 mmol) in CD_2Cl_2 (0.8 mL) was added AgOTf (1.0 equiv) under Ar at 23 °C, and the mixture was then vortexed for 5 min. NMR experiments were immediately performed on the rapidly generated acetylide **32**. To this solution was added benzophenone (1.0 equiv) and the mixture was vortexed for 2 min. NMR experiments were then performed on equilibrium between **32** and **34** (see Tables S1 and S2 in the Supporting Information for data).

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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