Palladium-Catalyzed Addition of Alcohol Pronucleophiles to Alkylidenecyclopropanes

Drexel H. Camacho, Itaru Nakamura, Shinichi Saito, and Yoshinori Yamamoto*

Department of Chemistry, Graduate School of Science and Institute for Chemical Reaction Science, Tohoku University, Sendai 980-8578, Japan

yoshi@yamamoto1.chem.tohoku.ac.jp

Received October 2, 2000

Palladium-catalyzed addition of alcohol pronucleophiles **1** to alkylidenecyclopropane derivatives **2** afforded the corresponding allylic ethers **3** in excellent to moderate yields. Catalyst optimization indicated the $Pd(PPh_3)_4-P(o\text{-tolyl})_3$ combination as the best system among all catalysts tested. Intramolecular reaction also proceeded smoothly. A plausible mechanism for this catalytic reaction was proposed.

Palladium has shown to be a versatile catalyst in carbon−carbon bond formation involving unactivated unsaturated systems and carbon pronucleophiles (Figure 1,a).[1−5] The palladium undergoes oxidative addition to the C−H bond of the pronucleophile and allows the regioselective addition to the C−C multiple bonds.[6,7] These hydrocarbonation processes have been proven to be efficient ecologically with high atom economy.[8] The addition of carbon−heteroatom bonds to unsaturated systems with the aid of palladium catalysts has likewise been developed where the hydroammination (Figues 1b),[9] hydrocarboxylation (Figure 1c)[10] and hydrosulfination (Figure 1d)[11] reactions with unactivated unsaturated systems occur efficiently.

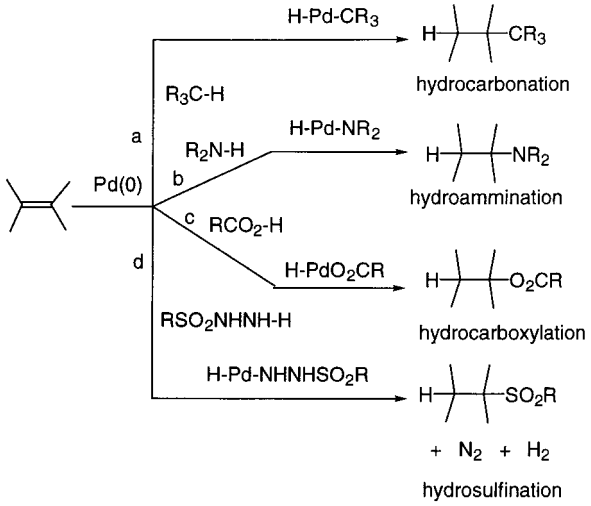


Figure 1. Carbon−carbon and carbon−heteroatom bond forming reactions.

The transition metal catalyzed addition of alcohols to unsaturated systems, however, has not been widely investigated. In the addition of alcohols to dienes (Figure 2a) [12] or allenes (Figure 2b),[13] the reactions proceed

* To whom correspondence should be addressed. Fax: +81-(22)217−6784.

(1) Yamamoto, Y. *Pure Appl. Chem.* **1996**, *68*, 9 and references therein.

(2) For hydrocarbonation of 1,3 dienes, see: (a) Takahashi, K.; Miyake, A.; Hata, G. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1183. (b) Andell, O. S.; Bäckvall, J.-E.; Moberg, C. *Acta Chem. Scand. Ser. B* **1986**, *40*, 184. (c) Baker, R.; Popplestone, R. J. *Tetrahedron Lett.* **1978**, *38*, 3575. (d) Jolly, P. W.; Kokel, N. *Synthesis* **1990**, 771. (e) Trost, B. M.; Zhi, L. *Tetrahedron Lett.* **1992**, *33*, 1831.

(3) For hydrocarbonation of 1,3 enynes, see: Salter, M. M.; Gevorgyan, V.; Saito, S.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1996**, 17.

(4) For hydrocarbonation of allenes, see: (a) Yamamoto, Y.; Al-Masum, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 6019. (b) Besson, L.; Goré, J.; Cazes, B. *Tetrahedron Lett.* **1995**, *36*, 3853. (c) Trost, B. M.; Gerusz, V. J. *J. Am. Chem. Soc.* **1995**, *117*, 5156. (d) Yamamoto, Y.; Al-Masum, M.; Fujiwara, N.; Asao, N. *Tetrahedron Lett.* **1995**, *36*, 2811. (e) Yamamoto, Y.; Al-Masum, M. *Synlett* **1995**, 969. (f) Yamamoto, Y.; Al-Masum, M.; Fujiwara, N. *J. Chem. Soc., Chem. Commun.* **1996**, 381. (g) Yamamoto, Y.; Al-Masum, M.; Takeda, A. *J. Chem. Soc., Chem. Commun.* **1996**, 831.

(5) For hydrocarbonation of alkynes, see: (a) Trost, B. M.; Chan, C.; Ruhter, G. *J. Am. Chem. Soc.* **1987**, *109*, 3486. (b) Trost, B. M.; Matsubara, S.; Caringi, J. J. *J. Am. Chem. Soc.* **1989**, *111*, 8745. (c) Trost, B. M.; Kottirsch, G. *J. Am. Chem. Soc.* **1990**, *112*, 2816.

(6) For C−H addition to C−C multiple bond via activation of the unsaturated system, see: Hegedus, L. S. *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1990; Vol. 4, pp 571−583.

(7) For C−H addition to multiple bond via carbometalation reactions, see: Knochel, P. *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1990; Vol. 4, pp 865−911.

(8) (a) Yamamoto, Y.; Radhakrishnan, U. *Chem. Soc. Rev.* **1999**, *28*, 199−207 and references therein. (b) Kamijo, S.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 1747. (c) Tsukada, N.; Shibuya, A.; Nakamura, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 8123. (d) Nakamura, I.; Saito, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 2661.

(9) (a) Al-Masum, M.; Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* **1997**, *38*, 6071. (b) Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 5421. (c) Besson, L.; Goré, J.; Cazes, B. *Tetrahedron Lett.* **1995**, *36*, 3857. (d) Armbruster, R. W.; Morgan, M. M.; Schmidt, J. L.; Lau, C. M.; Riley, R. M.; Zabrowski, D. L.; Dieck, H. A. *Organometallics* **1986**, *5*, 234. (e) Radhakrishnan, U.; Al-Masum, M.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 1037. (f) Nakamura, I.; Itagaki, H.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 6458. (g) Wolf, L. B.; Tjen, K. C. M. F.; Rutjes, F. P. J. T.; Hiemstra, H.; Schoemaker, H. E. *Tetrahedron Lett.* **1998**, *39*, 5081. (h) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9546.

(10) (a) Al-Masum, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 3809. (b) Rose, D.; Lepper, H. *J. Organomet. Chem.* **1973**, *49*, 473. (c) Trost, B. M.; Brieden, W.; Baringhaus, K. H. *Angew. Chem.* **1992**, *104*, 1392; *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1335. (d) Mitsudo, T.; Hori, Y.; Yamakawa, Y.; Watanabe, Y. *J. Org. Chem.* **1987**, *52*, 2230. (e) Lambert, C.; Utimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 5323.

(11) (a) Kamijo, S.; Al-Masum, M.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 691. (b) Julia, M.; Nel, M.; Saussine, L. *J. Organomet. Chem.* **1979**, *181*, C17.

(12) (a) Smutny, E. J. *J. Am. Chem. Soc.* **1967**, *89*, 6793. (b) Yagi, H.; Tanaka, E.; Ishiwatari, H.; Hidai, M.; Uchida, Y. *Synthesis* **1977**, 334.

10.1021/jo001428j CCC: $20.00
Published on Web 12/16/2000

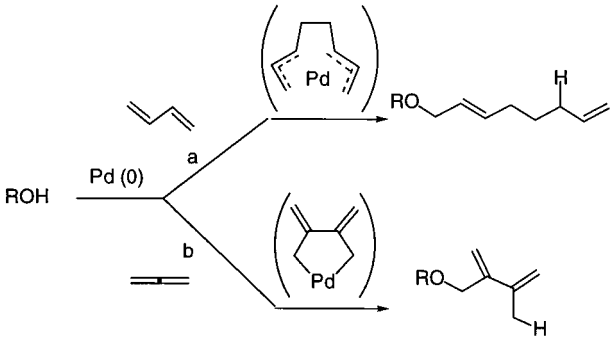


Figure 2. Pd-catalyzed addition of alcohol to butadiene and allene.

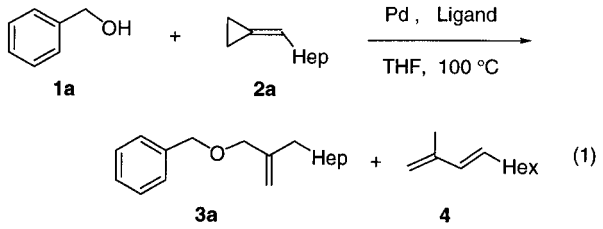
presumably via cyclic palladium intermediates[13b] where dimerization of the acceptors occurred. In these processes, the Pd activates the olefin for nucleophilic attack.

Recently, we have demonstrated that the Pd-catalyzed addition of alcohols to alkylidenecyclopropanes proceeds presumably via activation of the alcohols,[14] serving as a powerful tool in the synthesis of allylic ethers. We now report a detailed study on this reaction as well as the intramolecular version of the Pd-catalyzed addition of alcohols to alkylidenecyclopropanes.

Results and Discussion

Optimization of Catalyst System. The addition of benzyl alcohol (**1a**) to octylidenecyclopropane (**2a**) (eq 1, Table 1) to give **3a** was chosen as the standard substrates for the optimization of the catalyst system. Initial test experiments were carried out using the $[(\eta^3\text{-}C_3H_5)PdCl]_2$-dppp system which was shown to be the best condition in the addition of amine pronucleophiles to alkylidenecyclopropanes.[9f] Test results indicated that addition of the alcohol occurred giving 16% of **3a** (entry 1). The major product, however, was the diene **4**. The formation of **4** was deduced from the ring opening of the methylenecyclopropane. Combination of the $[(\eta^3\text{-}C_3H_5)PdCl]_2$ with monodentate ligand, P(*o*-tolyl)$_3$, also gave the ring opened product (entry 2). The use of $Pd_2(dba)_3{\cdot}CHCl_3$ with dppp (entry 3) and PPh_3 (entry 4) likewise gave similar results. In entry 5 the $Pd(OAc)_2$−P(*o*-tolyl)$_3$ system also gave mostly the diene product. In contrast, $Pd(PPh_3)_4$ catalyst in the absence of additional ligands (entry 6) appeared to be effective in producing the ether **3a** in 46% yield. The addition of excess PPh_3 (entry 7) somehow diminished the reaction products. The use of bidentate ligands such as dppe (entry 8) and dppb (entry 9) gave disappointing results as well. An increase in product yield, however, was observed when P(*o*-tolyl)$_3$ was employed as an additional ligand giving 59% yield of **3a** (entry 10). The formation of **4** was also minimized using this condition. Furthermore a decrease in the use of catalyst (from 10 to 5 mol %), as well as the use of 1 equiv of **2a** in toluene, increased the product yield of **3a** while it decreased the undesirable product **4** (entry 11). The role of P(*o*-tolyl)$_3$ was not clear, but it can be assumed that it increases the activity of $Pd(PPh_3)_4$ probably producing $Pd[P(o\text{-tolyl})_3]_2$ in situ.[15] When the reaction was carried out in the absence of both Pd catalyst and ligands, no reaction was observed (entry 12). Ring opening of the alkylidenecyclopropane did not even occur, indicating that the alkylidenecyclopropane is stable at 100 °C and that ring opening is catalyzed by palladium.

Table 1. Optimization of Catalyst System in the Addition of 1a to 2a[a]



entry	Pd	ligand	yield of **3a** (%)[b]	yield of **4** (%)[b]	recovery of **2** (%)[b]
1	$[(\eta^3\text{-}C_3H_5)PdCl]_2$	dppp[c]	16	51	29
2	$[(\eta^3\text{-}C_3H_5)PdCl]_2$	P(*o*-tolyl)$_3$	trace	58	35
3	$Pd_2(dba)_3{\cdot}CHCl_3$	dppp[c]	trace	59	29
4	$Pd_2(dba)_3{\cdot}CHCl_3$	PPh_3	trace	64	26
5	$Pd(OAc)_2$	P(*o*-tolyl)$_3$	trace	73	19
6	$Pd(PPh_3)_4$	−	46	21	22
7	$Pd(PPh_3)_4$	PPh_3	27	trace	51
8	$Pd(PPh_3)_4$	dppe[d]	21	26	39
9	$Pd(PPh_3)_4$	dppb[e]	17	28	49
10	$Pd(PPh_3)_4$	P(*o*-tolyl)$_3$	59	19	13
11[f]	$Pd(PPh_3)_4$	P(*o*-tolyl)$_3$	71	trace	6
12	−	−	NR	- -	∼99

[a] All reactions were carried out in a Wheaton microreactor with 0.5 mmol of **1a** and 1.0 mmol of **2a** in THF (0.25−0.5 M concentration) at 100 °C for 3 days using 10 mol % of Pd and 20 mol % of the ligand, unless otherwise indicated. [b] NMR yield using *p*-xylene as an internal standard. [c] dppp = 1,3 bis(diphenylphosphino)propane. [d] dppe = 1,2 bis-(diphenylphosphino)ethane. [e] dppb = 1,4 bis(diphenylphosphino)-butane. [f] The reaction was carried out in toluene using 1:1 mole ratio of the substrates, 5 mol % of Pd, and 10 mol % of the ligand.

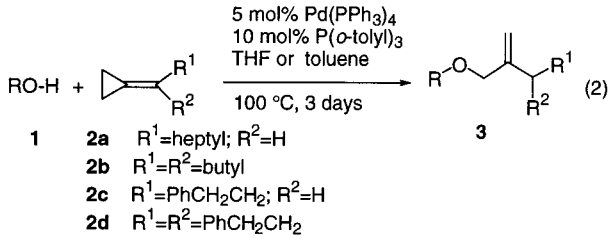
Palladium-Catalyzed Addition of Alcohols 1a−n to Alkylidenecyclopropane Derivatives 2a−d. We then examined the scope of alcohol pronucleophiles **1a−n** for the hydroalkoxylation reaction with alkylidenecyclopropanes **2a−d** using the optimized conditions (eq 2, Table 2). In the presence of 5 mol % of $Pd(PPh_3)_4$ and 10 mol % of P(*o*-tolyl)$_3$ in toluene at 100 °C, the reaction of benzyl alcohol **1a** with **2a** afforded the allyl ether **3a** in 69% isolated yield (entry 1). The use of 2,2,2-trifluroethanol **1b** also gave the hydroalkoxylated product **3b** (entry 2). The reaction of phenol **1c** with **2a** also proceeded smoothly (entry 3) but the initial product **3c** (Scheme 1) underwent further Claisen rearrangement to afford **3c′**. When the reaction was performed at 70 °C for 6 h, **3c** was isolated in 32% yield along with **3c′** and the starting material. 2,4,6-Trimethylphenol **1d** gave **3d** (entry 4) efficiently. The use of triethylsilanol **1e** as a pronucleophile also afforded the hydroalkoxylated product **3e** in moderate yield (entry 5). Moreover, water **1f** could effectively act as oxygen pronucleophile to give **3f** by double addition of O−H bond (entry 6). It is noteworthy that water as a substrate does not render the palladium catalyst inactive. The formation of **3g** from the addition of allyl alcohol **1g** to **2a** indicates that the hydroalkoxylation reaction essentially tolerates a C=C double bond (entry 7). The low yield, however, can be attributed to the possible elimination of the nonsubsti-

(13) Inoue, Y.; Ohtsuka, Y.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3345. (b) Coulson, D. R. *J. Org. Chem.* **1973**, *38*, 1483.

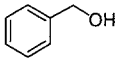
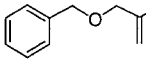
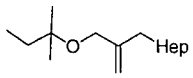
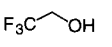
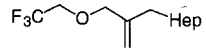
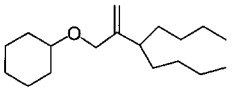
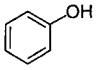
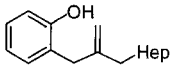
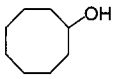
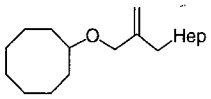
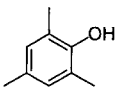
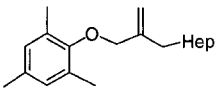
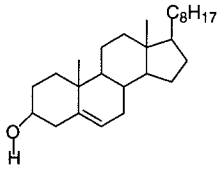
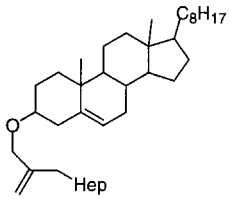
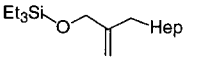
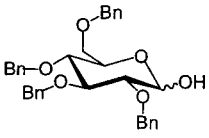
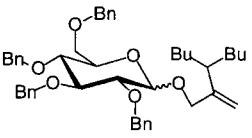
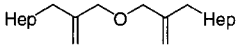
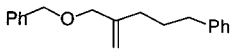
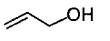
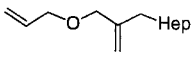
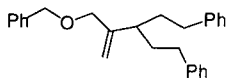
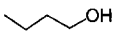
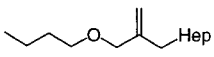
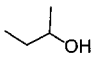
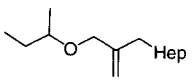
(14) Camacho, D. H.; Nakamura, I.; Saito, S.; Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3365.

(15) (a) Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2046. (b) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969.

Table 2. Palladium-Catalyzed Addition of Alcohols 1 to Alkylidenecylopropanes 2[a]

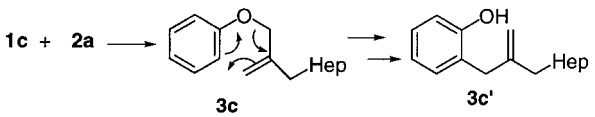


1 **2a** R^1=heptyl; R^2=H
2b R^1=R^2=butyl
2c R^1=$PhCH_2CH_2$; R^2=H
2d R^1=R^2=$PhCH_2CH_2$ **3**

entry	ROH 1	2	Product 3	Yield(%)[b]	entry	ROH 1	2	Product 3	Yield(%)[b]
1	 **1a**[c]	**2a**	 **3a**	69	10	 **1j**[f]	**2a**	 **3j**	25
2	 **1b**	**2a**	 **3b**	68	11	 **1k**	**2b**	 **3k**	28
3	 **1c**[c]	**2a**	 **3c'**[d]	56	12	 **1l**	**2a**	 **3l**	20
4	 **1d**	**2a**[e]	 **3d**	67	13	 **1m**	**2a**	 **3m**	24
5	Et_3SiOH **1e**	**2a**	 **3e**	49	14	 **1n**	**2b**	 **3n**	54
6	H_2O **1f**	**2a**	 **3f**	40	15	**1a**	**2c**	 **3o**	67
7	 **1g**	**2a**	 **3g**	30	16	**1a**	**2d**	 **3p**	80
8	 **1h**[f]	**2a**	 **3h**	63					
9	 **1i**[f]	**2a**	 **3i**	24					

[a] Unless otherwise specified, all reactions were carried out in 1:1 mole ratio (0.5 mmol) of the substrates using 5 mol % of $Pd(PPh_3)_4$, 10 mol % of P(*o*-tolyl)$_3$ in THF at 100 °C for 3 days. [b] Isolated yields. [c] Solvent used was toluene. [d] See text. [e] The reaction was carried out at 70 °C. [f] The alcohol was used as the solvent.

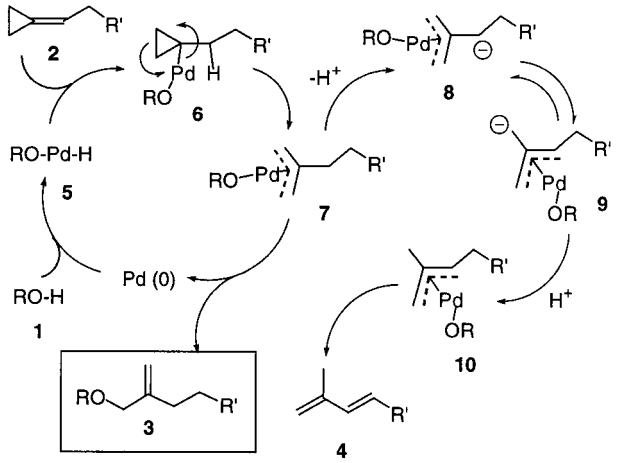
Scheme 1



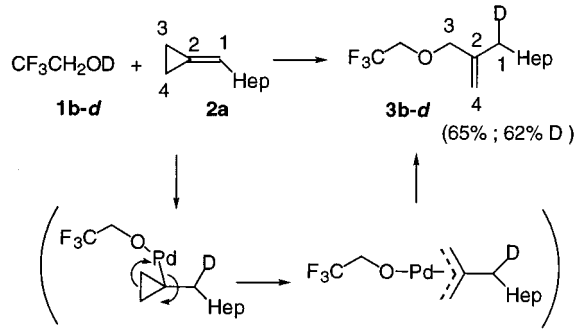
tuted allyl moiety in **3g** by the Pd catalyst.[16] In the case of propargyl alcohol, no addition product was observed. An aliphatic alcohol such as *n*-butanol **1h** likewise underwent the hydroalkoxylation reaction to afford **3h** (entry 8). The reaction however required an excess amount of the alcohol. When 1 equiv of **1h** was used in the reaction with **2a** in THF, **3h** was produced in poor yield indicating that the nucleophilicity of a normal aliphatic alcohol is lower than that of **1a**−**f**. Similarly, the use of *sec*-butanol **1i** and *tert*-amyl alcohol **1j** as solvents afforded **3i** and **3j**, respectively, in lower yields (entries 9 and 10). The bulky groups in **1i** and **1j** might have interfered in the reaction to produce lower yields. Cyclic alcohols such as **1k** and **1l** in the reactions with **2b** and **2a** also proceeded smoothly to give **3k** and **3l**,

(16) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*. John Wiley: Chichester, 1995; pp 364−366.

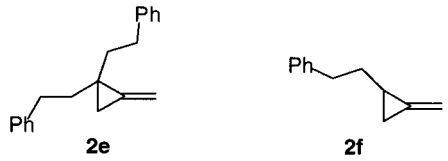
Scheme 2



Scheme 3



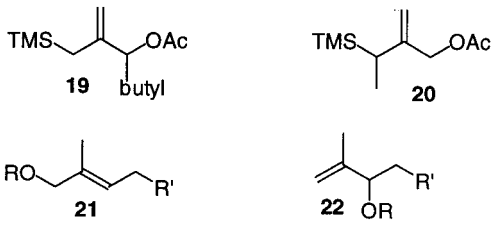
respectively, in lower yields (entries 11 and 12). Cholesterol **1m** likewise reacted with **2a** to give the corresponding allyl ether product **3m** (entry 13). Moreover, the protected sugar **1n**, 2,3,4,6-tetra-*o*-benzyl-D-glucopyranose, also underwent hydroglycosylation reaction with **2b** to give **3n** (entry 14). The presence of an electron-withdrawing ether group near the alcohol moiety in **1n** allows the reaction to proceed easily compared with the cyclic alcohols **1k**−**m**, indicating the higher reactivity of the more acidic alcohols. This observation is further supported by the facile reactions of the acidic alcohols **1b**−**d** compared with the less acidic aliphatic alcohols **1h**−**j**. The methylenecyclopropanes **2c** and **2d** with a 2-phenethyl substituent at the exocyclic methylene carbon atom also underwent hydroalkoxylation reactions with **1a** to give **3o** and **3p**, respectively (entries 15 and 16). However, the reactions of **2e** and **2f** with either **1a** or **1b** did not give the desired hydroalkoxylation products at all probably due to steric and electronic factors.



The examples shown in Table 1 indicate that the reaction shows excellent chemoselectivity where the regioselective distal bond cleavage of the cyclopropane ring occurs (see Scheme 2). The facile addition of phenols, silanols, as well as a wide range of alcohols to the alkylidenecyclopropanes proceeds smoothly. In the case of phenolic OH, the reaction of **1d** with **2a** proceeds very well even at 70 °C. Moreover, the formation of **3c** and **3c′** were observed within 6 h, suggesting the high reactivity of phenolic OH toward **2a**. As can be seen from these results, the chemoselectivity of **2a** for hydroxyl groups is in the following order: phenolic > benzylic > allylic > primary > cyclic ≈ secondary ≈ tertiary OH. Such selectivity is attributable to the easy formation of the H−Pd−OPh complex (or H−Pd^+ species) (see Scheme 2) owing to the greater acidity of the phenol compared to aliphatic alcohols which allows the facile transfer of hydrogen to the Pd as a proton.[18b] Moreover, the higher cationic property of the Pd in the H−Pd−OPh complex makes it more reactive toward alkylidenecyclopropanes compared to the H−Pd−OR complexes for alcoholic hydroxyl groups. Steric factor also contributes to the observed chemoselectivity and reactivity.

A plausible mechanism for this hydroalkoxylation reaction is illustrated in Scheme 2. The initial step would be oxidative addition of the Pd to the O−H bond.[17] This well-known type of oxidative addition produces the highly reactive H−Pd−OR complex **5**.[18] Hydropalladation to the alkylidenecyclopropane **2** would give the intermediate **6** which upon distal bond cleavage would afford the π-allyl complex **7**. Reductive elimination regenerates the Pd(0) and **3** is produced. The palladium catayzed ring opening of **2** can then be attributed to the possible β-hydride elimination to give **8** which would rearrange to give **9**. Protonation would afford **10** and further Pd-β-hydride elimination would give the diene **4**. The possible intermediacy of **4** in the formation of **3** was ruled out, since the reaction of **4** with **2a** using the described conditions, gave no adducts at all. Other products due to the possible cleavage of the cyclopropyl proximal bond was never observed. The mechanistic proposal of Markovnikov hydropalladation[19] and distal bond cleavage is in accordance with the palladium-catalyzed hydrocarbonation[8c] and hydroammination[9f] of alkylidenecyclopropanes. The hydoalkoxylation mechanism is further substantiated by the deuterium labeling experiment as shown in Scheme 3. Using the same conditions as described, the reaction of **1b-*d*** and **2a** gave **3b-*d*** smoothly. Deuterium incorporation occurred exclusively at C1. No deuterium labels were observed in the other carbons of **3b-*d***, indicating

(17) The possible activation of the alkylidenecyclopropane by Pd to form either bis(α−allyl)palladium or π−allyl-palladium complexes (see: ref 8d) was not entirely ruled out but is considered less likely to occur in light of the observed non addition of **1a** to the trimethylenemethyl (TMM) precursors **19** or **20** using the same conditions as described. Moreover, the possible formations of products **21** and **22** formed from either attacks of OR^- nucleophiles to the possible Pd−(TMM) complex were never observed.

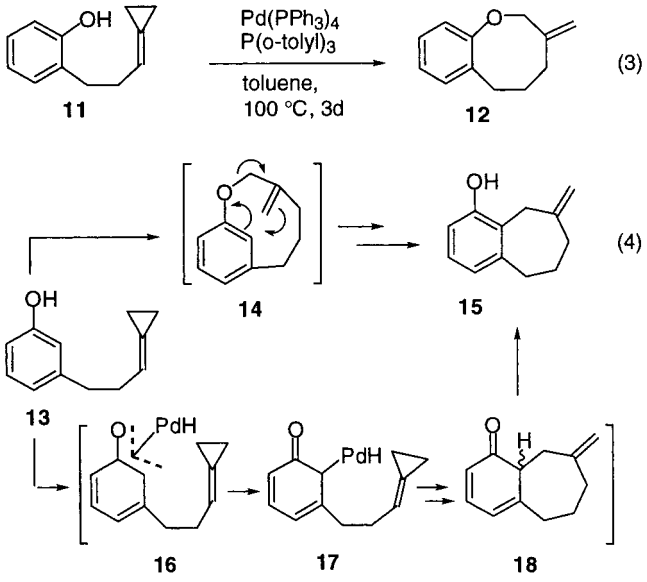


(18) [$Pd(PCy_3)_2$] reacted with phenol to give *trans*-[$(Cy_3P)_2Pd(H)$-(OPh)]·PhOH complex which was isolated and characterized unambiguously: (a) Braga, D.; Sabatino, P.; Di Bugno, C.; Leoni, P.; Pasquali, M. *J. Organomet. Chem.* **1987**, *334*, C46. (b) Di Bugno, C.; Pasquali, M.; Leoni, P.; Sabatino, P.; Braga, D. *Inorg. Chem.* **1989**, *28*, 1390. For a review see: (c) Grushin, V. V. *Chem. Rev.* **1996**, *96*, 2011.

(19) As one referee pointed out, the regioselectivity of the hydropalladation on a tetrasubstituted alkene system **2d** is probably controlled by steric factors.

the hydropalladation reaction to **2a** is highly regioselective. This reaction thus differs considerably from the proximal bond cleavage of methylenecyclopropanes observed in the Pd-catalyzed hydrostannation[20] and rhodium-catalyzed hydrosilylation[21] reactions.

Palladium-Catalyzed Intramolecular Hydroalkoxylation of Alkylidenecyclopropanes. Further, we examined the intramolecular version of the addition of alcohols to alkylidenecyclopropanes. In the reaction of the phenol-tethered alkylidenecyclopropane **11**, facile cyclization was observed affording the eight-membered exomethylene ether ring (**12**) in 54% yield in high regioselectivity. In the case of **13**, cyclization also proceeded, but presumably, the initial hydroalkoxylation product **14** underwent further Claisen rearrangement to give 47% of **15**.[22] Alternatively, π-oxoallyl Pd complex **16** could have been formed to give **17** which upon hydropalladation would lead to **18** and subsequent rearrangements would give **15**.



Conclusion

This type of transformation via catalytic process has not been known previously, and thus the present development provides a further example in the utility of Pd as an efficient catalyst in the addition of alcohol pronucleophiles to nonconjugated unsaturated systems. The excellent regioselectivity and the wide range of alcohols that serves as pronucleophiles provide a new and efficient route to the synthesis of allyl ethers.

Experimental Section

Materials. The alkylidenecyclopropanes **2a**−**d** were prepared from the corresponding aldehyde or ketone according to published procedures.[23] The methylenecylopropane derivatives **2e**,**f** [24] were prepared according to known procedures. All other compounds used were commercially available and purchased from Aldrich, Kanto, and TCI.

Palladium-Catalyzed Addition of Alcohols to Alkylidenecylopropanes (General Procedures). The alcohols (0.5 mmol) were added at room temperature to a stirring mixture of $Pd(PPh_3)_4$ (5 mol %; 0.0025 mmol; 0.0289 g) and P(*o*-tolyl)$_3$ (10 mol %; 0.05 mmol; 0.0152 g) in THF or toluene (1.5 mL) under Ar atmosphere in a Wheaton microreactor, followed by the addition of alkylidenecyclopropanes (0.5 mmol). The reaction was then heated to 100 °C for 3 days. The course of the reaction was monitored by TLC. The reaction was then filtered through a short column (silica gel) and concentrated. The product was isolated by column chromatography (silica gel), eluent: hexane/EtOAc 10/1, and further purified by MPLC.

2-(Benzyloxymethyl)dec-1-ene (3a): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.30 (m, 5H), 5.03 (s, 1H), 4.92 (s, 1H), 4.44 (s, 2H), 3.96 (s, 2H), 2.07 (t, J = 7.3 Hz, 2H,), 1.44 (m, J = 7.3 Hz, 2H), 1.27 (s, 10H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) 146.4, 138.5, 128.4, 127.7, 127.5, 111.4, 73.1, 71.9, 33.2, 31.9, 29.4, 29.4, 29.3, 27.6, 22.7, 14.1 ppm; IR (neat) 3066, 3030, 2954, 2925, 2854, 1651, 1496, 1465, 1454, 1379, 1361, 1253, 1203, 1093, 1074, 1028, 902, 734, 696, 665 cm^{-1}; HRMS calcd for $C_{18}H_{28}O$: 260.2140, found: 260.2142.

2-(Trifluoromethyloxymethyl)dec-1-ene (3b): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.97 (s, 1H), 4.92 (s, 1H), 4.06 (s, 2H), 3.78 (q, J = 8.8, 8.6 Hz, 2H), 2.05 (t, J = 7.3 Hz, 2H), 1.44 (m, J = 7.15 Hz, 2H), 1.27 (s, 10H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) 144.8, 112.9, 75.1, 67.0, 66.6, 32.8, 31.9, 29.4, 29.3, 29.2, 27.4, 22.7, 14.1 ppm; IR (neat) 3080, 2927, 2856, 1651, 1463, 1379, 1307, 1280, 1161, 1132, 1010, 966, 908, 848, 827, 723, 665 cm^{-1}. Anal. Calcd for $C_{13}H_{23}OF_3$ (%): calcd: C 61.90, H 9.19; found: C 62.29, H 9.22; HRMS calcd for $C_{13}H_{23}OF_3$: 252.1701, found: 252.1705.

2-(Phenoxymethyl)dec-1-ene (3c): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.24 (m, 2H), 6.96−6.82 (m, 2H), 5.12 (s, 1H), 4.98 (s, 1H), 4.45 (s, 2H), 2.13 (t, J = 7.7 Hz, 2H), 1.48 (t, J = 7.5 Hz, 2H), 1.27 (s, 10H), 0.88 (t, J = 6.4 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) 158.9, 145.1, 129.4, 120.7, 114.8, 111.7, 70.8, 33.1, 31.9, 29.9, 29.5, 29.4, 29.3, 27.7, 22.7, 14.1 ppm; IR (neat) 3060, 3020, 2925, 2854, 1654, 1598, 1587, 1496, 1299, 1242, 1170, 1153, 1078, 1031, 1018, 900, 786, 752, 690 cm^{-1}. Anal. Calcd for $C_{17}H_{26}O$ (%): calcd: C 82.86, H 10.64; found: C 82.40, H 10.98; HRMS calcd for $C_{17}H_{26}O$: 246.1984, found: 246.1985.

2-(2-Hydroxyphenylmethyl)dec-1-ene (3c′): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17−7.07 (m, 2H), 6.89−681 (m, 2H), 5.16(s, 1H), 4.92 (s, 1H), 4.86 (s, 1H), 3.39 (s, 2H), 2.01 (t, J = 7.5 Hz, 2H), 1.46 (t, J = 7.15 Hz, 2H), 1.26 (s, 10H), 0.87 (t, J = 6.5 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) 155.2, 148.8, 139.0, 128.0, 124.5, 120.8, 116.1, 111.3, 38.6, 35.5, 31.9, 29.4, 29.3, 29.2, 27.6, 22.6, 14.1 ppm; IR (neat) 3568−3200 (br), 3070, 3020, 2954, 2925, 2854, 1708, 1643, 1608, 1593, 1488, 1456, 1377, 1259, 1215, 1170, 1091, 1041, 891, 752, 721, 665 cm^{-1}; HRMS calcd for $C_{17}H_{26}O$: 246.1984, found: 246.1983.

2-(2,4,6-Trimethylphenoxymethyl)dec-1-ene (3d): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (s, 2H), 5.21 (s, 1H), 4.98 (s, 1H), 4.16 (s, 2H), 2.24 (s, 9H), 2.19 (t, J = 7.5 Hz, 2H), 1.50 (m, J = 7.5 Hz, 2H), 1.27 (s, 10H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) 153.7, 146.1, 133.0, 130.7, 129.5, 111.1, 74.8, 33.4, 31.9, 29.5, 29.4, 29.3, 27.8, 22.7, 20.7, 16.2, 14.1 ppm; IR (neat) 3074, 3010, 2943, 2925, 2854, 1726, 1651, 1598, 1483, 1465, 1375, 1307, 1213, 1147, 1114, 1002, 900, 852, 750, 721 cm^{-1}. Anal. Calcd for $C_{20}H_{32}O$ (%): calcd: C 83.20, H 11.10; found: C 82.60, H 11.00; HRMS calcd for $C_{20}H_{32}O$: 288.2453, found: 288.2459.

2-(Triethylsilyloxymethyl)dec-1-ene (3e): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.03 (s, 1H), 4.80 (s, 1H), 4.06 (s, 2H), 2.02 (t, J = 7.1 Hz, 7.9 Hz, 2H), 1.43 (m, J = 7.1 Hz, 7.7 Hz, 2H), 1.27 (s, 10H) 0.97 (t, J = 3.5 Hz, 7.7 Hz, 9H), 0.88 (t, J = 6.6 Hz, 3H), 0.64 (q, J = 3.7 Hz, 7.9 Hz, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) 148.8, 108.3, 65.6, 32.8, 31.9, 29.5, 29.3, 27.9, 22.7, 14.1, 6.8, 4.5 ppm; IR (neat) 3072, 2954−2856, 2732, 1654, 1458, 1413, 1379, 1240, 1120, 1087, 1016, 974, 896, 823, 744 cm^{-1}. Anal. Calcd for $C_{17}H_{36}OSi$ (%): calcd: C 71.83, H 12.68;

(20) Lautens, M.; Meyer, C.; Lorenz, A. *J. Am. Chem. Soc.* **1996**, *118*, 10676.

(21) Bessmertnykh, A. G.; Blinov, K. K.; Grishin, Y. K.; Donskaya, N. A.; Tveritinova, E. V.; Yur eva, N. M.; Beletskaya, I. P. *J. Org. Chem.* **1997**, *62*, 6069.

(22) For the ORTEP and X-ray data of **15**, see Supporting Information.

(23) (a) Utimoto, K.; Tamura, M.; Sisido, K. *Tetrahedron* **1973**, *29*, 1169. (b) Schweizer, E. E.; Berninger, C. J.; Thompson, J. G. *J. Org. Chem.* **1968**, *33*, 336.

(24) Arora, S.; Binger, P. *Synthesis* **1974**, 801.

found: C 71.59, H 12.75; HRMS calcd for $C_{17}H_{36}OSi$: 284.2536, found: 284.2535.

Bis(2-methylenedecyl) ether (3f): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.99 (s, 2H), 4.89 (s, 2H), 3.88 (s, 4H), 2.04 (t, J = 7.15, 7.9 Hz, 4H), 1.44 (m, 4H), 1.27 (s, 20 H), 0.88 (t, J = 6.4, 6.9 Hz, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) 146.5, 111.0, 72.8, 33.2, 31.9, 29.5, 29.4, 29.3, 27.6, 22.7, 14.1 ppm; IR (neat) 3074, 2956, 2925, 2854, 1615, 1465, 1396, 1377, 1350, 1255, 1089, 1028, 900, 721, 665 cm^{-1}. HRMS calcd for $C_{22}H_{42}O$: 322.3234, found: 322.3220.

2-(Allyloxymethyl)dec-1-ene (3g): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99−5.86 (m, 1H), 5.31−5.24 (dq, J = 1.65, 17 Hz, 1H), 5.20−5.15 (dq, J = 1.29, 10.4 Hz, 1H), 5.00 (d, J = 0.73 Hz, 1H), 4.89 (d, J = 0.74 Hz, 1H), 3.96 (dt, J = 1.47, 5.7 Hz, 2H), 3.91 (s, 2H), 2.05 (t, J = 7.51 Hz, 2H), 1.45 (t, J = 7.3 Hz, 2H), 1.27 (s, 10H), 0.88 (t, J = 6.4 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) 146.4, 134.9, 116.8, 111.1, 73.1, 70.9, 33.2, 31.9, 29.5, 29.4, 29.3, 27.6, 22.7, 14.1 ppm; IR (neat) 3080, 3014, 2956, 2925, 2854, 1649, 1465, 1379, 1348, 1087, 1020, 989, 920, 900, 665 cm^{-1}. Anal. Calcd for $C_{14}H_{26}O$ (%): calcd: C 80.00, H 12.37; found: C 80.06, H 12.42; HRMS calcd for $C_{14}H_{26}O$: 210.1984, found: 210.1957.

2-(Butoxymethyl)dec-1-ene (3h): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.98 (s, 1H), 4.87 (s, 1H) 3.89 (s, 2H), 3.39 (t, J = 6.4 Hz, 2H), 2.04 (t, J = 7.3 Hz, 2H), 1.58 (m, 2H), 1.54 (m, 2H), 1.27 (s, 12H), 0.92 (t, 3H), 0.88 (t, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) 146.7, 110.8, 73.8, 69.9, 33.1, 31.9, 29.5, 29.4, 29.3, 27.6, 22.7, 19.4, 14.1, 13.9 ppm; IR (neat) 3074, 2958, 2927, 2856, 2734, 1652, 1465, 1379, 1350, 1299, 1267, 1234, 1099, 1053, 1014, 964, 933, 898, 723 cm^{-1}. Anal. Calcd for $C_{15}H_{30}O$ (%): calcd: C 79.64, H 13.27; found: C 79.47, H 13.25; HRMS calcd for $C_{15}H_{30}O$: 226.2297, found: 226.2308.

2-(*sec*-Butoxymethyl)dec-1-ene (3i): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.0 (s, 1H), 4.85 (s, 1H), 3.96−3.83 (dd, J = 12.5, 16.5 Hz, 2H), 3.34 (m, J = 6.2, 6.0 Hz, 1H), 2.05 (t, J = 7.3 Hz, 2H), 1.50 (m, 2H), 1.44 (dm, J = 1.3, 6.2, 7.5 Hz, 2H), 1.27 (s, 10H), 1.13 (d, J = 6.2 Hz, 3H), 0.90 (overlapping t, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) 147.2, 110.6, 76.0, 71.2, 33.2, 31.9, 29.5, 29.5, 29.3, 29.2, 27.7, 22.7, 19.1, 14.1, 9.9 ppm; IR (neat) 3074, 2962, 2927, 2856, 1654 (d), 1465, 1373, 1338, 1174, 1137, 1116, 1078, 1024, 966, 898, 723 cm^{-1}. Anal. Calcd for $C_{15}H_{30}O$ (%): calcd: C 79.64, H 13.27; found: C 79.85, H 13.15; HRMS calcd for $C_{15}H_{30}O$: 226.2295, found: 226.2272.

2-(*tert*-Pentoxymethyl)dec-1-ene (3j): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.03 (s, 1H), 4.83 (s, 1H), 3.76 (s, 2H) 2.04 (t, J = 7.15 Hz, 2H), 1.51 (m, J = 7.4 Hz, 2H), 1.27 (s, 12H), 1.16 (s, 6H), 0.88 (t, J = 7.51, 6.6 Hz, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) 147.8, 109.8, 74.9, 64.3, 33.4, 32.9, 31.9, 29.5, 29.3, 27.8, 25.0, 22.7, 14.1, 8.3 ppm; IR (CCl_4) 3074, 2962, 2925, 2856, 1716, 1654, 1643, 1379, 1363, 1294, 1240, 1178, 1157, 1080, 896, 723 cm^{-1}. Anal. Calcd for $C_{16}H_{32}O$ (%): calcd: C 80.00, H 13.30; found: C 80.10, H 12.45; HRMS calcd for $C_{16}H_{32}O$: 240.2453, found: 240.2423.

2-(Cyclohexyloxymethyl)dec-1-ene (3k): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.09 (s, 1H), 4.83 (s, 1H), 3.89 (s, 2H), 3.29 (m, 1H), 1.99 (m, 2H), 1.73 (m, 2H), 1.53 (m, 1H), 1.37−1.17 (m, 18 H), 0.87 (t, J = 6.6 Hz, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) 149.6, 109.9, 76.9, 69.0, 43.4, 33.9, 32.2, 29.6, 25.9, 24.2, 22.9, 14.1 ppm; IR (neat) 3080, 2956, 2929, 2858, 1716, 1647, 1452, 1402, 1377, 1361, 1350, 1259, 1095, 1024, 954, 900, 804 cm^{-1}; HRMS calcd for $C_{18}H_{34}O$: 266.2610, found: 266.2590.

2-(Cyclooctyloxymethyl)dec-1-ene (3l): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.98 (s,1H), 4.85 (s, 1H), 3.88 (s, 2 H), 3.51−3.38 (m, 1H), 2.04 (t, J = 7.15, 7.8 Hz, 2H),1.85−1.42 (m, 15H), 1.27 (s,br, 11H), 0.88 (t, J = 6.4, 6.9 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) 147.2, 110.5, 78.8, 70.9, 33.2, 31.9, 31.5, 29.5, 29.4, 29.3, 27.7, 27.3, 25.5, 23.2, 22.7, 14.1 ppm; IR (neat) 3072, 2923, 2854, 2694, 1651, 1467, 1446, 1377, 1355, 1257, 1118, 1078, 896 cm^{-1}; HRMS calcd for $C_{19}H_{36}O$: 280.2766, found: 280.2758.

Cholesteryl ether 3m: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.35 (m, 1H), 4.99 (s, 1H), 4.86 (s, 1H), 3.94 (s, 2H), 3.21−3.14 (m, 1H), 2.37−2.34 (m, 1H), 2.25−2.17 (m, 1H), 2.07−1.76 (m, 9H), 1.64−1.23 (m, 24H), 1.19−1.00 (m, 8H), 0.92−0.87 (m, 14H), 0.67 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) 147.0, 141.1, 121.5, 110.7, 78.4, 76.8, 56.8, 56.1, 50.2, 42.3, 39.8, 39.5, 39.1, 37.3, 36.9, 36.2, 35.8, 33.2, 31.9, 31.9, 29.5, 29.4, 29.3, 28.4, 28.2, 28.0, 27.6, 24.3, 23.8, 22.8, 22.7, 22.6, 21.1, 19.4, 18.7, 14.1, 11.9 ppm; HRMS calcd for $C_{38}H_{66}O$: 538.5114, found: 538.5121.

Glucopyranosyl ether 3n: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.14 (m, 20H), 5.22 (ds, J = 1.5 Hz, 1H), 5.02−4.90 (m, 3H), 4.84−4.71 (m, 3H), 4.65−4.51 (m, 3H), 4.47−4.37 (m, 2H), 4.03 (d, J = 13.6 Hz, 1H), 3.77−3.44 (m, 6H), 2.04 (p, J = 6.7, 7.0, 6.9 Hz, 1H), 1.41−1.23 (m, 12H), 0.86 (t, 6H); ^{13}C NMR (300 MHz, $CDCl_3$) 147.8, 138.6, 138.3, 138.2, 138.1, 128.4, 128.3, 128.2, 128.0, 127.8, 127.7, 127.6, 127.5, 110.6, 102.8, 84.7, 82.3, 77.9, 75.7, 75.0, 74.9, 74.9, 73.4, 70.2, 68.9, 43.5, 33.8, 33.6, 29.6, 29.5, 22.9, 22.8, 14.1 ppm; IR (neat) 3087, 3060, 3030, 2956, 2925, 2858, 1730, 1647, 1604, 1496, 1454, 1398, 1361, 1328, 1261, 1207, 1155, 1089, 1072, 1063, 906, 802, 734, 696 cm^{-1}; HRMS calcd for $C_{46}H_{58}O_6$: 706.4243, found: 706.4236.

2-(Benzyloxymethyl)-5-phenylpent-1-ene (3o): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.16 (m, 10H), 5.07 (s, 1H), 4.95 (s, 1H), 4.81 (s, 2H), 3.96 (s, 2H), 2.62 (dt, J = 2.4, 7.14 Hz, 2H), 2.14 (t, J = 7.5, 7.15 Hz, 2H), 1.80 (dp, J = 2.4, 7.4 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) 145.8, 142.3, 138.4, 128.4, 128.4, 128.3, 127.7, 127.5, 125.7, 111.8, 73.1, 71.9, 35.6, 32.7, 29.3 ppm; IR (neat) 3062, 3026, 2935, 2856, 1651, 1602, 1496, 1452, 1203, 1097, 1074, 1028, 904, 736, 698 cm^{-1}. Anal. Calcd for $C_{19}H_{22}O$ (%): calcd: C 85.66, H 8.33; found: C 85.37, H 8.54; HRMS calcd for $C_{19}H_{22}O$: 266.1671, found: 266.1670.

2-(Benzyloxymethyl)-3-phenethyl-5-phenylpent-1-ene (3p): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.11 (m, 15H), 5.29 (s, 1H), 5.04 (s, 1H), 4.54 (s, 2H), 3.99 (s, 2H), 2.56 (m, J = 7.15, 8.1 Hz 4H), 2.19 (p, J = 7.15, 6.97 Hz 1H), 1.76 (q, J = 6.97, 8.1 Hz 4H); ^{13}C NMR (300 MHz, $CDCl_3$) 147.6, 142.5, 138.3, 128.4, 128.3, 127.6, 127.5, 125.6, 112.5, 72.4, 71.6, 43.1, 35.8, 33.6 ppm; IR (neat) 3084, 3062, 3026, 2929, 2856, 1645, 1602, 1494, 1454, 1361, 1203, 1099, 1028, 906, 746, 698 cm^{-1}. Anal. Calcd for $C_{27}H_{30}O$ (%): calcd: C 87.51, H 8.17; found: C 87.36, H 8.07; HRMS calcd for $C_{27}H_{30}O$: 370.2297, found: 370.2297.

12: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20−6.82 (m, 4H), 4.79 (s, 1H), 4.71 (s, 1H), 4.48 (s, 2H), 2.75 (m, 2H), 2.28 (m, 2H), 1.76 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) 157.0, 147.2, 137.2, 130.0, 127.5, 124.4, 121.6, 116.2, 81.3, 34.3, 32.7, 31.3 ppm; IR (neat) 3072, 3020, 2977, 2927, 2850, 1645, 1602, 1583, 1490, 1456, 1438, 1404, 1352 (d), 1288 (d), 1255, 1234, 1209, 1182, 1147, 1101, 1051, 1008, 997, 968, 935, 906, 819 cm^{-1}. Anal. Calcd for $C_{12}H_{14}O$ (%): calcd: C 82.71, H 8.10; found: C 82.62, H 8.21; HRMS calcd for $C_{12}H_{14}O$: 174.1045, found: 174.1049.

15: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (t, J = 7.69, 7.72 Hz, 1H), 6.68 (d, J = 7.33 Hz, 1H), 6.59 (d, J = 7.90 Hz, 1H), 4.81 (s, 1H), 4.71 (qs, 2H), 3.52 (s, 2H), 2.85 (m, 2H), 2.45 (t, J = 6.43, 6.22 Hz, 2H), 1.71 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) 151.9, 147.2, 144.4, 126.4, 121.8, 113.6, 111.1, 39.9, 35.0, 33.5, 28.3 ppm; HRMS calcd for $C_{12}H_{14}O$: 174.1045, found: 174.1059.

Supporting Information Available: Copies of ^{1}H NMR spectra of **3a**, **3b**, **3c**, **3c′**, **3d**, **3e**, **3f**, **3g**, **3h**, **3i**, **3j**, **3k**, **3l**, and **12**, preparation of compounds **11** and **13**, ORTEP and X-ray data of **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO001428J