



Palladium(0)-Catalyzed Allylic Substitution with Allylic Alkoxides as Substrates

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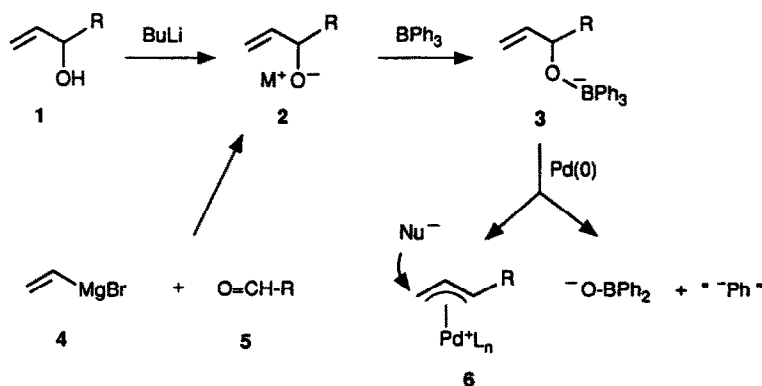
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Abstract: A new method has been developed which allows palladium(0)-catalyzed allylic substitution to occur between allylic alcohols and anionic C-nucleophiles: on reaction with Ph_3B , the allylic alkoxide **2** is first converted *in situ* into the more reactive species **3** which then undergoes a Pd(0)-catalyzed reaction with lithio diethyl malonate *via* the η^3 -complex **6**. Allylic alkoxides can be generated *in situ* either by deprotonation of the corresponding alcohol (**1** $\rightarrow$ **2**, e.g. with BuLi), *via* a vinylmagnesium halide addition to the corresponding aldehyde (**4** + **5** $\rightarrow$ **2**), or by hydride reduction (DIBAH) of α,β -unsaturated ketones (**31** $\rightarrow$ **32**). The whole sequence can be carried out as a one-pot procedure and is suitable for sensitive allylic alcohols that might be difficult to handle in pure state. While primary allylic alcohols (**7** and **18**) and their allylic isomers (**14** and **15**) give mixtures of mono- and bis-allylated products with $\text{LiCH}(\text{CO}_2\text{Et})_2$, exclusive monoallylation has been observed for secondary alcohols (**21**, **23**, and **26**).

Palladium(0)-catalyzed allylic substitution¹ is an established, efficient, highly stereoselective, and reliable method for C-C, C-N, and C-O bond formation, with hundreds of synthetic applications reported to date.^{1,2} Although esters,¹ carbonates,³ carbamates,⁴ phosphates,⁵ and related derivatives^{6,7} of allylic alcohols have frequently been used as substrates,⁸ the parent alcohols are generally much less reactive.^{9,10} This apparently stems from the poor capability of a non-activated hydroxyl to serve as a leaving group. Moreover, a C-nucleophile, such as sodio diethyl malonate, would first convert the allylic alcohol to the corresponding alkoxide, nucleophilic substitution of which can hardly be anticipated. Very few attempts have been made to generate palladium η^3 -complexes directly from allylic alcohols.⁹⁻¹⁴

In a preliminary communication,¹⁵ we have recently reported on the *in situ* transformation of allylic alkoxides **2** (generated by deprotonation of alcohols **1** with BuLi) by means of triphenylboron (Ph_3B)¹⁶ to the reactive species **3** that readily undergo Pd(0)-catalyzed substitution with lithiodiethyl malonate as a typical C-nucleophile (Scheme I). Herein we present an orchestration of this method and show that alkoxides of sensitive allylic alcohols can be generated *in situ* also by the reaction of the corresponding aldehyde with a Grignard reagent (**4** + **5** $\rightarrow$ **2**), or by the reduction of α,β -unsaturated ketones with *i*-Bu₂AlH (DIBAH), and reacted further in one pot.

Scheme I

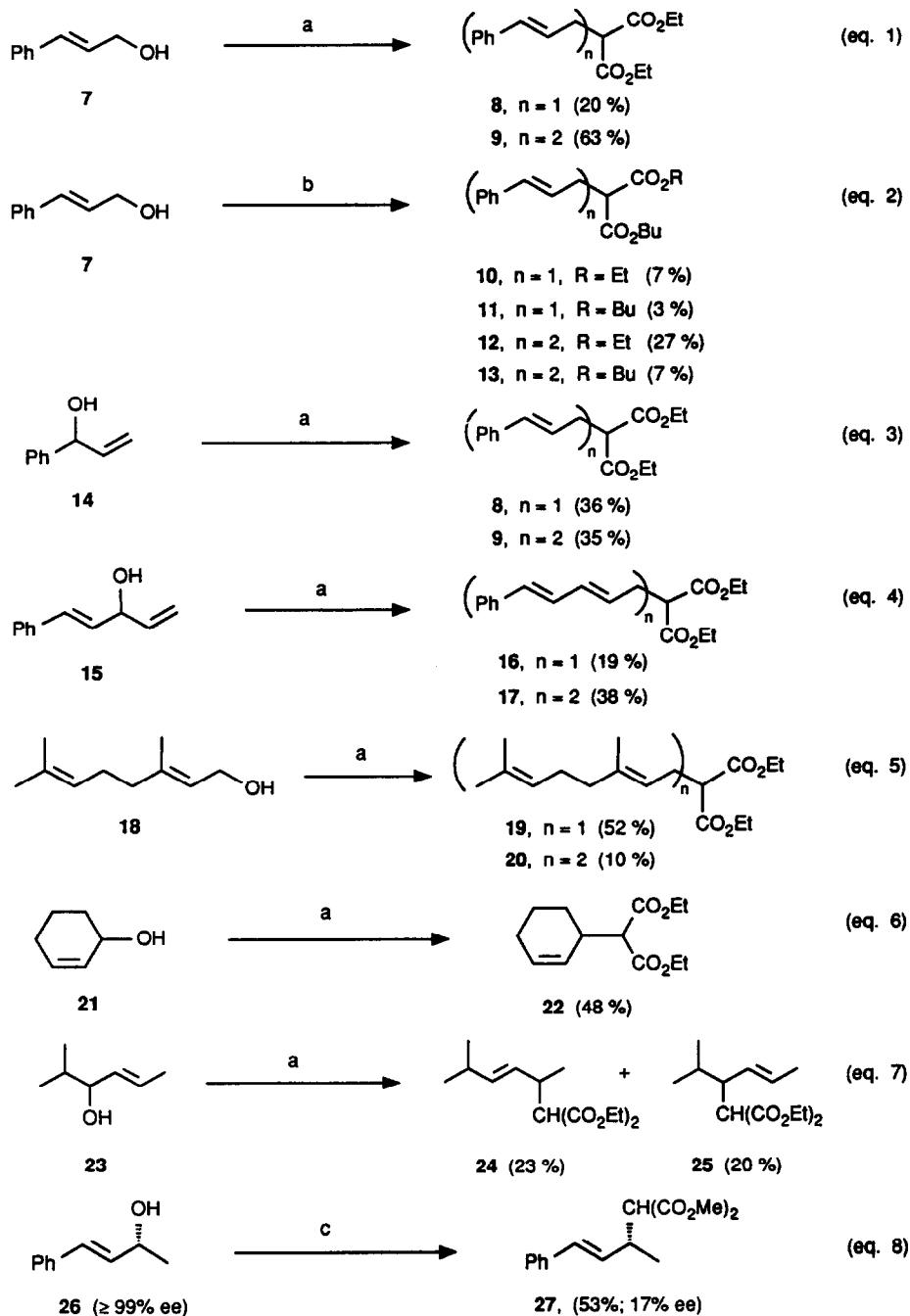


We have used cinnamyl alcohol (7) as a readily available model compound to develop optimal conditions. In contrast to its acetate, alcohol 7 is inert towards the standard conditions of Pd(0)-catalyzed substitution with lithiodiethyl malonate. We have now found, however, that addition of Ph₃B to the reaction mixture triggers the reaction (Scheme II). Optimized conditions are as follows: alkoxide ion is first generated from 7 by means of BuLi (1 equiv.) in THF and then converted *in situ* into an activated intermediate of type 3 by adding Ph₃B (1.1 equiv.) at r.t. Subsequently, (Ph₃P)₄Pd (5 mol%), and LiCH(CO₂Et)₂ (1.5 equiv.) are added and the reaction mixture is refluxed (THF) for 3 h.^{20,21} In case of 7, the mono- and bis-allylated products 8 and 9 were isolated in 20% and 63% yield, respectively (eq. 1).²² When Ph₃B was replaced by Bu₃B, incorporation of the butyl group into the products (10 - 13) was observed (eq. 2). In this case, formation of (PhCH=CHCH₂)₂O as a by-product (10%) was also observed.

A brief study of several other allylic alcohols was carried out (eq. 3-8) and fair to good yields of the expected products were obtained (Scheme II). 1-Hydroxy-1-phenyl-prop-2-en (14), its vinylogue 15, and geraniol (18) furnished the products of mono- and bis-allylation (eq. 3-5).²¹⁻²³ By contrast, only mono-allylation has been observed with secondary alcohols, such as cyclohex-1-en-3-ol (21) and 2-methyl-hex-4-en-3-ol (23), which can be attributed to steric hindrance (eq. 6 and 7).²⁴

We reasoned that lithiodiethyl malonate (used in a slight excess) should abstract a proton from the allylic alcohol (1 equiv.) anyway and, therefore, the initial generation of the alkoxide 2 by means of BuLi may not be necessary. Moreover, formation of the η³-complex 6 from 3 will release a strong base (Scheme I) which should also be capable of deprotonation of the starting material. Hence, another experiment was set up, in which the initial addition of BuLi was omitted; a mixture of the remaining components, i.e. alcohol 7 (1 equiv.), LiCH(CO₂Et)₂ (1.5 equiv.), Ph₃B (1.1 equiv.), (Ph₃P)₄Pd (5 mol%), and Ph₃P (10 mol%) was refluxed in THF for 3 h. To our delight, the reaction was found to give an almost quantitative yield of a mixture of mono- and bis-allylated derivatives 8 (49%) and 9 (50%).

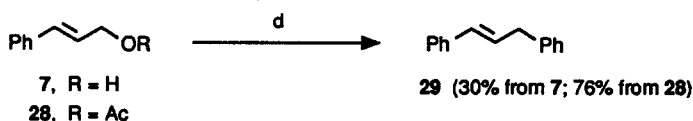
Scheme II: **a:** (i) BuLi (1 equiv.), THF, r.t., 5 min; (ii) Ph₃B (1.1 equiv.), r.t., 10 min; (iii) LiCH(CO₂Et)₂ (1.5 equiv.), (Ph₃P)₄Pd (5 mol%), Ph₃P (10 mol%), reflux 3–8 h. **b:** as in **a**; Ph₃B replaced by Bu₃B. **c:** as in **a**; LiCH(CO₂Et)₂ replaced by LiCH(CO₂Me)₂.



The stereochemical course of this reaction has been probed with the enantiomerically pure⁷ alcohol **26**. While the Pd(0)-catalyzed substitution performed on its acetate is highly stereoselective,²⁵ alcohol **26** was found to give a largely racemized product **27** (eq. 8), as evidenced by its optical rotation. This striking difference can be rationalized by taking into account a facial isomerization of the Pd- η^3 -complexes resulting from the attack of Pd(0) at higher temperatures.^{7b,26-28}

Since palladium η^3 -complexes have recently been found to undergo phenylation by NaBPh₄,¹⁷ it was of interest to carry out the reaction of the lithium alkoxide of **7** with Ph₃B in the absence of lithio diethyl malonate. In this case we have found (*E*)-1,3-diphenylprop-1-en (**29**) to be the major product (30%) which indicates that the Ph group can be transferred from the anionic species **3** arising in the initial step (Scheme III). Alternative transfer from the neutral molecule of Ph₃B is also possible.^{17a,19} Acetate **28** reacted in the same way (76%).

Scheme III: **d**, as in **a** (Scheme II), LiCH(CO₂Et)₂ omitted.

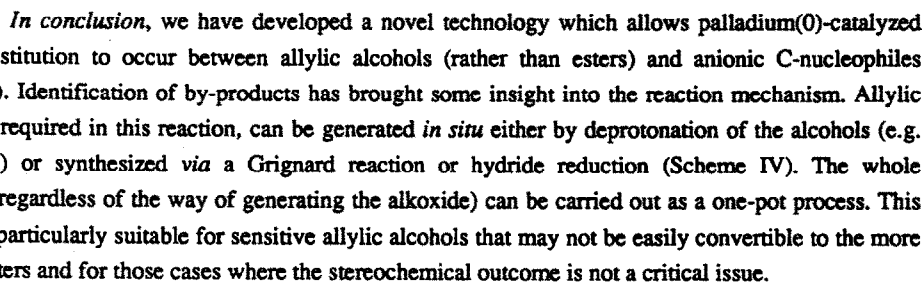


Allylic alcohols are often sensitive and, occasionally, cannot be easily synthesized (owing to the difficulties during workup) or esterified. Consequently, acetates of these alcohols often give high proportion of elimination on attempted allylic substitution. We reasoned that in cases when such alcohols are prepared by Grignard reaction (**4** + **5** → **2**), the alkoxide generated in the reaction mixture might be directly used for the substitution under the conditions described above. If successful, isolation of the unstable alcohol would then be avoided. To test this hypothesis, we generated the magnesium salt **30** by the reaction of benzaldehyde with vinylmagnesium bromide (Scheme IV). To the reaction mixture was then successively added Ph₃B (1.1 equiv.), (Ph₃P)₄Pd (5 mol%), and LiCH(CO₂Et)₂ (1.5 equiv.) at r.t. as before and the mixture was refluxed (THF) for 3 h. The reaction proceeded as expected and a mixture of mono- and bis-allylated products **8** (19%) and **9** (52%) was isolated in good yield.

Another method of generating the required alkoxide *in situ* is the hydride reduction of the corresponding α,β -unsaturated ketone. Indeed, the alkoxide **32**, generated from dibenzylidene acetone (**31**) by the DIBAH reduction, was converted into **33** (Scheme IV) although in poor yield (19%) and accompanied by several unidentified by-products. Similarly, cyclopent-2-en-1-one (**34**) afforded the substitution product **36** (28%) with the lithium salt of 2-ethoxycarbonyl-cyclopentan-1-one under the similar conditions in one pot. The latter experiment demonstrates that even sterically hindered β -dicarbonyls can be employed in this protocol.

In all the reactions using Ph₃B, formation of biphenyl and phenol as by-products (in ca. 1:1 ratio) has also been observed. Biphenyl may arise from the sequence involving release of "Ph-" from **3** (Scheme I) which would then attack a molecule of PhBR₂ (possibly with Pd-catalysis).²⁹ The mechanism of the formation of phenol is not clear but may be tentatively attributed to the reaction of Ph₂BO⁻ (generated along with **6** and "Ph-") with PhBR₂ to produce Ph₂B-O-B-PhR₂, followed by the B→O

Scheme IV: a, (i) Ph_3B (1.1 equiv.); (ii) $\text{LiCH}(\text{CO}_2\text{Et})_2$ (1.5 equiv.), $(\text{Ph}_3\text{P})_4\text{Pd}$ (5 mol%), Ph_3P (0.1 equiv.), THF, reflux 3 h. b, as in a; $\text{LiCH}(\text{CO}_2\text{Et})_2$ replaced by Li salt of 2-ethoxycarbonyl-cyclopentan-1-one.



Experimental Section

Materials and Equipment. Optical rotations were measured in CHCl_3 at 22 °C with an error of $\pm 1^\circ$. ^1H NMR spectra were measured on Varian XL-200 (4.7 T, FT mode) instruments for CDCl_3 solutions at 25 °C with Me_4Si as an internal standard. Chemical shifts are given in δ values (ppm) relative to the signal of the standard ($\delta = 0.00$). Coupling constants were obtained by decoupling experiments and are given in absolute values. Enantiomeric excess of **27** was determined by optical rotation.⁷ Mass spectra were measured on ZAB-EQ (VG Analytical) spectrometer: EI spectra were recorded at 75 eV using the lowest temperatures enabling evaporation (100-210 °C) and

perfluorokerosene for calibration. Elemental composition of the ions was determined by high resolution techniques. GC Analysis was carried out at Hewlett-Packard 5890 instrument using capillary columns (50% OV-17, 10m x 2.65 μ m). Petroleum ether refers to the fraction boiling in the range 40-60 °C. The identity of samples prepared by different routes was checked by TLC and GC and IR, mass, and NMR spectra. Yields are given for isolated product. Lithio diethyl malonate was prepared by addition of *n*-butyllithium (1.6 M solution in *n*-hexane; 630 μ L; 1.008 mmol) to a solution of diethyl malonate (160 μ L; 1.054 mmol) in dry THF (4 mL) at r.t. over 5 min. After stirring for another 10 min at r.t. the reagent was used. All reactions were carried out under argon.

General procedure for allylic substitution using alkoxides generated from alcohols by means of butyllithium. To a stirred solution of allylic alcohol (0.50 mmol) in dry THF (3 mL) was added *n*-butyllithium in hexane (0.50 mmol) and the mixture was stirred at r.t. for 5 min. A solution of triphenylboron (0.55 mmol) in THF (2 mL) was then added and the mixture was stirred at r.t. for 10 min. Then, a solution of lithio diethyl malonate (0.75 mmol) in THF (2 mL) was added, followed by a solution of $(\text{Ph}_3\text{P})_4\text{Pd}$ (5 mol%) and Ph_3P (10 mol%) in THF (2 mL). The mixture was then refluxed for 3-8 h and monitored by TLC. After completion of the reaction, the solvent was evaporated *in vacuo* and the residue flash-chromatographed on silica (10 g) with petroleum ether or a petroleum ether-ether (95:5) mixture, or a petroleum ether-ether-acetone mixture (93:5:2 or 90:5:5). The product was analyzed by GC and ^1H NMR.

General procedure for allylic substitution using alkoxides generated by Grignard addition. To a stirred solution of aldehyde (0.50 mmol) in dry THF (3 mL) was added a 1.0 M solution of vinylmagnesium bromide (0.50 mmol) in THF at 0 °C over a period of 5 min and the mixture was stirred at r.t. for 15 min. The alkoxide generated in this way was further reacted with Ph_3B and lithio diethyl malonate in the presence of $(\text{Ph}_3\text{P})_4\text{Pd}$ and Ph_3P as described above.

General procedure for allylic substitution using alkoxides generated by DIBALH reduction. To a stirred solution of enone (0.50 mmol) in dry THF (3 mL) was added a 1.2 M solution of diisobutylaluminum hydride (0.50 mmol) in THF at 0 °C over a period of 5 min. The mixture was stirred at r.t. for 15 min and then treated with Ph_3B , lithio diethyl malonate, and $(\text{Ph}_3\text{P})_4\text{Pd}$ and Ph_3P as above.

9: ^1H NMR δ 1.26 (t, J = 7.3 Hz, 6 H, $\text{CH}_3\text{CH}_2\text{O}$), 2.84 (d, J = 7.5 Hz, 4 H, 2 x $\text{PhCH}=\text{CH}-\text{CH}_2\text{C}$), 4.21 (q, J = 7.3 Hz, 4 H, $\text{CH}_3\text{CH}_2\text{O}$), 6.09 (dt, J = 15.6, 7.5, and 7.5 Hz, 2 H, 2 x $\text{PhCH}=\text{CHCH}_2$), 6.47 (d, J = 15.6 Hz, 2 H, 2 x $\text{PhCH}=\text{CH}$), 7.14-7.44 (m, 10 H, arom.).

10: ^1H NMR δ 0.94 (t, J = 7 Hz, 3 H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$), 1.27 (t, J = 7 Hz, 3 H, $\text{CH}_3\text{CH}_2\text{O}$), 1.40 (m, W = 38 Hz, 2 H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$), 1.61 (m, W = 38 Hz, 2 H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$), 2.81 (t, J = 7.5 Hz, 2 H, $\text{PhCH}=\text{CH}-\text{CH}_2\text{CH}$), 3.49 (t, J = 7.5 Hz, 1 H, $\text{PhCH}=\text{CHCH}_2-\text{CH}$), 4.16 (t, J = 7 Hz, 2 H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$), 4.21 (q, J = 7 Hz, 2 H, $\text{CH}_3\text{CH}_2\text{O}$), 6.16 (dt, J = 15.6, 7.5, and 7.5 Hz, 1 H, $\text{PhCH}=\text{CHCH}_2$), 6.47 (d, J = 15.6 Hz, 1 H, $\text{PhCH}=\text{CH}$), 7.13-7.45 (m, 5 H, arom.); HRMS m/z 305 $[(\text{M}+\text{H})^+]$, 13%, $\text{Cl}/\text{isobutane}$).

11: ^1H NMR δ 0.93 (t, J = 6.8 Hz, 6 H, 2 x CH_3CH_2), 1.37 (m, W = 41 Hz, 4 H, 2 x $\text{CH}_3\text{CH}_2\text{CH}_2$), 1.61 (m, W = 37 Hz, 4 H, 2 x $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$), 2.80 (t, J = 7.8 Hz, 2 H, $\text{PhCH}=\text{CH}-\text{CH}_2\text{CH}$), 3.50 (t, J = 7.8 Hz, 1, $\text{PhCH}=\text{CHCH}_2-\text{CH}$), 4.22 (t, J = 6.8 Hz, 4 H, 2 x $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$), 6.15 (dt, J = 15.6, 7.8, and 7.8 Hz, 1 H, $\text{PhCH}=\text{CHCH}_2$), 6.47 (d, J = 15.6 Hz, 1 H, $\text{PhCH}=\text{CH}$), 7.14-7.39 (m, 5 H, arom.); HRMS m/z 332 (M^+ , 2%, EI).

12: ^1H NMR δ 0.94 (t, J = 7 Hz, 3 H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$), 1.27 (t, J = 7 Hz, 3 H, $\text{CH}_3\text{CH}_2\text{O}$), 1.40 (m, W = 38 Hz, 2 H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$), 1.61 (m, W = 38 Hz, 2 H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$), 2.85 (d, J = 7.5 Hz, 4 H, 2 x $\text{PhCH}=\text{CH}-\text{CH}_2\text{C}$), 4.16 (t, J = 7 Hz, 2 H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$), 4.21 (q, J = 7 Hz, 2 H, $\text{CH}_3\text{CH}_2\text{O}$), 6.09 (dt, J = 15.6, 7.7, and 7.7 Hz, 2 H, 2 x $\text{PhCH}=\text{CHCH}_2$), 6.47 (d, J = 15.6 Hz, 2 H, 2 x $\text{PhCH}=\text{CH}$), 7.13-7.44 (m, 10 H, arom.).

13: ^1H NMR δ 0.93 (t, J = 6.8 Hz, 6 H, 2 x CH_3CH_2), 1.37 (m, W = 41 Hz, 4 H, 2 x $\text{CH}_3\text{CH}_2\text{CH}_2$), 1.61 (m, W = 37 Hz, 4 H, 2 x $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$), 2.84 (d, J = 7.8 Hz, 4 H, 2 x $\text{PhCH}=\text{CH}-\text{CH}_2\text{C}$), 4.22 (t, J = 6.8 Hz, 4 H, 2 x $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$), 6.08 (dt, J = 15.6, 7.8, and 7.8 Hz, 2 H, 2 x $\text{PhCH}=\text{CHCH}_2$), 6.47 (d, J = 15.6 Hz, 2 H, 2 x $\text{PhCH}=\text{CH}$), 7.14-7.39 (m, 10 H, arom.).

16: ^1H NMR δ 1.27 (t, J = 7 Hz, 6 H, 2 x $\text{CH}_3\text{CH}_2\text{O}$), 2.73 (t, J = 7.6 Hz, 2 H, $\text{CH}=\text{CH}-\text{CH}_2-\text{CH}$), 3.45 (t, J = 7.6 Hz, 1 H, $\text{PhCH}=\text{CHCH}_2-\text{CH}$), 4.19 (q, J = 7 Hz, 4 H, 2 x $\text{CH}_3\text{CH}_2\text{O}$), 5.57-6.38 (m, 2 H, $\text{PhCH}=\text{CH}-\text{CH}=\text{CH}-\text{CH}_2$), 6.74 (ddd, J = 15.6, 10.4, and 5.2 Hz, 1 H, $\text{PhCH}=\text{CH}-\text{CH}=\text{CH}$), 6.48 (d, J = 15.6 Hz, 1 H, $\text{PhCH}=\text{CH}$), 7.15-7.45 (m, 5 H, arom.).

17: ^1H NMR δ 1.27 (t, J = 7 Hz, 6 H, 2 x $\text{CH}_3\text{CH}_2\text{O}$), 2.75 (d, J = 7.3 Hz, 4 H, 2 x $\text{CH}=\text{CH}-\text{CH}_2-\text{CH}$), 4.19 (q, J = 7 Hz, 4 H, 2 x $\text{CH}_3\text{CH}_2\text{O}$), 5.57-6.38 (m, 4 H, 2 x $\text{PhCH}=\text{CH}-\text{CH}=\text{CH}-\text{CH}_2$), 6.74 (ddd, J = 15.6, 10.4, and 5.2 Hz, 2 H, 2 x $\text{PhCH}=\text{CH}-\text{CH}=\text{CH}$), 6.47 (d, J = 15.6 Hz, 2 H, 2 x $\text{PhCH}=\text{CH}$), 7.15-7.45 (m, 10 H, arom.).

33: ^1H NMR δ 1.20 (t, J = 7.1 Hz, 6 H, 2 x $\text{CH}_3\text{CH}_2\text{O}$), 3.60 (d, J = 9.4 Hz, 1 H, $\text{C}_2\text{H}_5\text{O}_2\text{C}-\text{CH}-\text{CO}_2\text{C}_2\text{H}_5$), 3.84 (dt, J = 9.4, 7.8, and 7.8 Hz, 1 H, $\text{CH}=\text{CH}-\text{CH}-\text{CH}=\text{CH}$), 4.16 (q, J = 7.1 Hz, 4 H, 2 x $\text{CH}_3\text{CH}_2\text{O}$), 6.24 (dd, J 15.9 and 7.8 Hz, 2 H, 2 x $\text{PhCH}=\text{CH}-\text{CH}$), 6.52 (d, J = 15.9 Hz, 2 H, 2 x $\text{PhCH}=\text{CH}$), 7.16-7.38 (m, 10 H, arom.).

36 (a 1:1 mixture of two diastereoisomers): ^1H NMR δ 1.25 and 1.26 (two t, J = 7.0 Hz, total 3 H, CH_3CH_2), 0.88-2.55 (m, 9 H, CH_2), 3.47-3.69 (m, 1 H, one of $\text{CH}_2-\text{CH}=\text{CH}$), 4.03-4.26 (m, 1 H, $\text{CH}-\text{CH}=\text{CH}$), 4.17 (q, J = 7.0 Hz, 2 H, $\text{CH}_3\text{CH}_2\text{O}$), 5.33 and 5.68 (two ddd, J = 5.8, 2.1, and 2.1 Hz, total 1 H, $\text{CH}-\text{CH}=\text{CH}-\text{CH}_2$), 5.80-5.89 (m, 1 H, $\text{CH}-\text{CH}=\text{CH}-\text{CH}_2$).

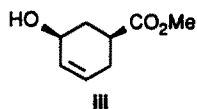
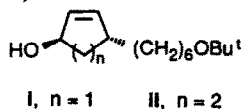
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- (8) Whereas with these groups the corresponding η^3 -complex is invariably formed in an *anti*-fashion,¹ the use of a leaving group capable of chelation with Pd may reverse this usual stereochemistry and generate the complex of opposite configuration.⁷
- (9) Only a handful of examples of the Pd-catalyzed reaction of allylic alcohols with nucleophiles have been described. These reactions proceed under extreme conditions: thus Pd(0)-catalyzed reactions of 2-propen-1-ol, (*E*)-but-2-en-1-ol, and 1-buten-3-ol with stabilized C-nucleophiles (β -ketoesters) occur in toluene at 100 °C over 4–96 h.¹⁰ Since this substitution occurs in the absence of a base, a mechanism involving activation of allylic hydroxyl by a Lewis or Brønsted acid (e.g. titanium isopropoxide^{10c}) may be suggested. Another formal allylic substitution of a

tertiary allylic hydroxyl by an amido group (N-nucleophile)¹¹ is catalyzed by (MeCN)₂PdCl₂ but proceeds via a different mechanism, involving a Pd(II)-initiated electrophilic addition across the double bond followed elimination of Pd(OH)₂.

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- (16) Phenylation of allylic acetates has been described via a Pd(0)-catalyzed reaction with NaBPh₄.¹⁷ Similarly, Pd-catalyzed arylation with NaBAR₄ has been reported for the Heck reaction¹⁸ and for vinyltriflates.¹⁹
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- (20) Less reactive substrates required up to 8 h.
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- (22) In all cases only *E*-isomers of the resulting olefins were detected. In our preliminary communication¹⁵ the mixture of **8** and **9** arising from **7** (eq. 1) was mistaken for an *E/Z* mixture of mono-alkylated products due to an incorrect interpretation of the low-field NMR and GC data.
- (23) (PhCH=CHCH₂)₂O was detected as a by-product: HRMS *m/z* 250 (*M*⁺, 2%, EI).
- (24) The starting material was recovered in two instances: **18** (18%), **21** (21%).
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- (27) The starting alcohol does not racemize under the reaction conditions as revealed by optical rotation of the recovered (26%) **18**.
- (28) Reactions of **i** - **iii** turned out to be non-selective as well, producing mixtures of all possible isomers (58-74%).



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