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Allylic Alcohols as Substrates for the Palladium(0)-Catalyzed Allylic Substitution

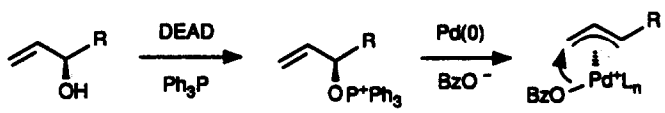
Ivo Starý,[a,*] Irena G. Stará,[a] and Pavel Kočovský [b,*]

[a] *Institute of Organic Chemistry and Biochemistry ČSAV, CS-166 10 Prague 6, Czechoslovakia*
[b] *Department of Chemistry, University of Leicester, Leicester LE1 7RH, UK*

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 **7** is first converted *in situ* into the more reactive species **8** which then undergoes a Pd(0)-catalyzed reaction with lithiodiethyl malonate *via* the η^3-complex **9**.

Palladium(0)-catalyzed allylic substitution[1] is an established, efficient, and highly stereoselective method for the C-C, C-N, and C-O bond formation, synthetic applications of which are numerous.[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 sodiodiethyl 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 η^3-complexes directly from allylic alcohols and Pd(0).[9]

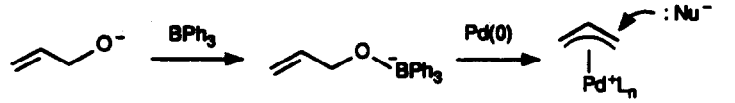
In one of the reports,[13] allylic alcohol **1** was first activated by forming the Mitsunobu-type intermediate **2** which then reacted with Pd(0) to give rise to the complex **3** (eq. 1). The subsequent internal migration of the BzO group from Pd effected an overall allylic substitution with an O-nucleophile (eq. 1); no attempt has been made to apply this methodology to other nucleophiles.[13] Alternatively, the η^3-complex **5** has been generated from allylic alcohol **4** on reaction with $SnCl_2$/Pd(II) and converted to the allyltin species **6** (eq. 2) which then reacted with aldehydes and ketones.[14] In this case, the role of $SnCl_2$ may also have been to activate **4**. In summary, a direct generation of an electrophilic palladium η^3-complex from allylic alcohol in the presence of a strong base has not yet been described.



1 2 3 (eq. 1)

4 5 6 (eq. 2)

Herein, we report on an *in situ* transformation of allylic alkoxides **7** by means of triphenyl boron (Ph_3B)[15] to the reactive species **8** that readily undergo Pd(0)-catalyzed substitution with lithiodiethyl malonate as a typical C-nucleophile (eq. 3).



(eq. 3)

7 **8** **9**

Cinnamyl alcohol (**10**), in contrast to its acetate, is inert towards the standard conditions of Pd(0)-catalyzed substitution with lithiodiethyl malonate. We have now found, however, that addition of Ph_3B to the reaction mixture triggers the reaction (Scheme I). Optimized conditions are as follows: alkoxide ion is first generated from **10** by means of BuLi (1 equiv.) in THF and then converted *in situ* into an activated intermediate of type **8** by adding Ph_3B (1.1 equiv.) at r.t. Subsequently, $(Ph_3P)_4Pd$ (5 mol%) and $LiCH(CO_2Et)_2$ (1.5 equiv.) is added and the reaction mixture is refluxed (THF) for 3 h.[19,20] In case of **10**, the product **11** was isolated in 80% yield as a 4:1 mixture of *E* and *Z* isomers (eq. 4).

A brief study of several other allylic alcohols was also carried out (eq. 5-7) and fair to good yields were obtained (Scheme I). Thus, both geraniol (**12**) and cyclohex-1-en-3-ol (**14**) furnished the expected products **13** and **15**, respectively.[20-22] The stereochemical course of this reaction has been probed with the enantiomerically pure[7] alcohol **16**. While the Pd(0)-catalyzed substitution performed on its acetate is highly stereoselective,[23] alcohol **16** was found to give a largely racemized product **17** (eq. 7) as evidenced by its optical rotation. This striking difference can be rationalized by taking into account facial isomerization of the Pd-η^3-complexes resulting from the attack of Pd(0) at higher temperatures.[7b,24-26]

Since palladium η^3-complexes have recently been found to undergo phenylation by $NaBPh_4$,[16] it was of interest to carry out the reaction of the lithium alkoxide of **10** with Ph_3B in the absence of lithiodiethyl malonate. In this case we have found (*E,E*)-1,3-diphenylprop-1-en to be the major product (30%) which indicates that the Ph group can be transferred from the anionic species **8** arising in the initial step. Alternative transfer from the neutral molecule of Ph_3B is also possible.[16a,18]

In conclusion, we have developed a novel technology which allows the palladium(0)-catalyzed allylic substitution to occur between allylic alcohols (rather than esters) and anionic C-nucleophiles (eq. 3). This method, at the present stage, may be successfully applied to compounds where the stereochemical outcome is not a critical issue.

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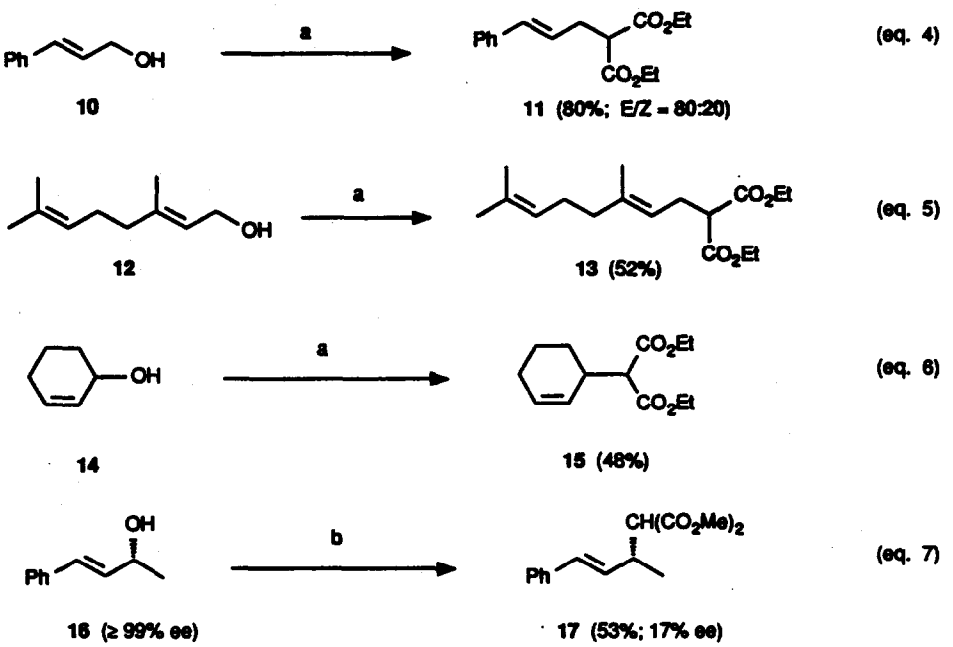
Scheme I. a : (i) BuLi (1 equiv.), THF, r.t., 5 min; (ii) Ph_3B (1.1 equiv.), r.t., 10 min; (iii) $LiCH(CO_2Et)_2$ (1.5 equiv.), $(Ph_3P)_4Pd$ (5 mol%), Ph_3P (10 mol%), reflux 3-8 h. b: as in a; $LiCH(CO_2Et)_2$ replaced by $LiCH(CO_2Me)_2$.



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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 of 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 occur 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) occurs in toluene at 100 °C over 4-96h.[10] Since this substitution occurs in the absence of a base, a mechanism involving an activation of allylic hydroxyl by a Lewis or Brønsted acid may be suggested. Another formal allylic substitution of a tertiary allylic hydroxyl by amido group (*N*-nucleophile)[11] is catalyzed by $(MeCN)_2PdCl_2$ and proceeds *via* a different mechanism, involving a Pd(II)-initiated electrophilic addition across the double bond followed elimination of $Pd(OH)_2$. The Pd(II)-catalyzed reaction of allylic alcohols with diethyl malonate[12] may be attributed to the electrophilic activation of the hydroxy group.

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(15) Phenylation of allylic acetates has been described *via* a Pd(0)-catalyzed reaction with $NaBPh_4$.[16] Similarly, Pd-catalyzed arylation with $NaBAr_4$ has been reported for the Heck reaction[17] and for vinyltriflates.[18]

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(19) Less reactive substrates required up to 8 h.

(20) Biphenyl and phenol have been identified as by products in all reactions.

(21) Aside from **13**, a bis-allylation product (6%) has also been detected.

(22) The starting material (18% and 21%, respectively) was recovered.

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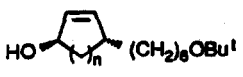
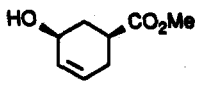
(25) The starting alcohol does not racemize under the reaction conditions as revealed by optical rotation of the recovered (26%) **16**.

(26) Reactions of i - iii turned out to be non-selective as well, producing mixtures of all possible isomers (58-74%).



i, n = 1 ii, n = 2



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