Pergamon

Tetrahedron Letters 42 (2001) 3113–3116

TETRAHEDRON LETTERS

Et_3B-promoted, Pd-catalyzed *C*-allylation of *o*-hydroxyacetophenone and its derivatives with allyl alcohols

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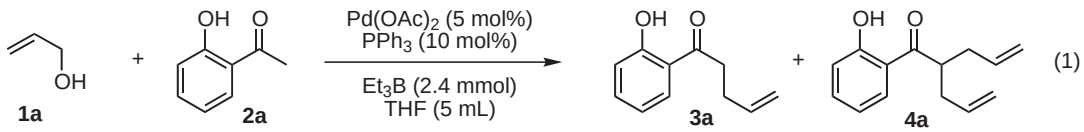
Received 8 February 2001; accepted 19 February 2001

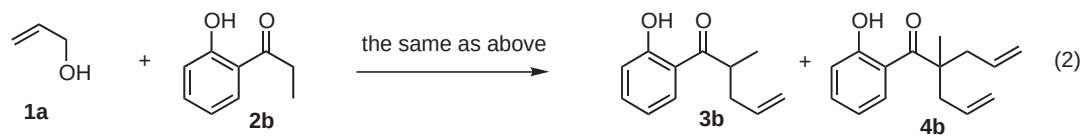
Abstract—Triethylborane promotes the Pd-catalyzed selective *C*-diallylation of *o*-hydroxyacetophenone and *C*-monoallylation of *o*-hydroxypropiophenone with a variety of ally alcohols. The reaction proceeds smoothly at 25–50°C and provides the allylation products in excellent yields. © 2001 Elsevier Science Ltd. All rights reserved.

Palladium-catalyzed allylic alkylation of active methylene compounds such as β-ketoesters and malonates is an established, efficient method for C–C bond formation reactions.[1] In most cases, carboxylic acid esters, carbonates, phosphates and related compounds of allyl alcohols have been utilized as the alkylation agents. In a limited number of cases, however, the reaction has proven to be successful with direct use of allyl alcohols.[2] On the other hand, the α-allylic alkylation of non-stabilized ketones and esters is still to be explored. The alkylation reported so far is rather sophisticated and requires both reaction partners to be pre-activated: allyl alcohols as their ester derivatives and ketones and esters as their metal and metalloid enolates[3] or as their enol ethers.[4]

Here we would like to disclose that *o*-hydroxylphenyl alkyl ketones and allyl alcohols react to provide the *C*-allylation products in excellent yields when they are treated with Et_3B in the presence of a catalytic amount of $Pd(OAc)_2$. Significantly, no pre-activation of either reaction partner is required. Thus, the reaction of *o*-



	allyl alcohol	ketones	reaction conditions	product (isolated yield)	
1	**1a** (1.2 mmol)	**2a** (1.0 mmol)	r.t., 24 h	**3a** (1%)	**4a** (43%)
2	**1a** (2.4 mmol)	**2a** (1.0 mmol)	r.t., 24 h	**3a** (0%)	**4a** (82%)
3	**1a** (1.2 mmol)	**3a** (1.0 mmol)	r.t., 2 h	**3a** (0%)	**4a** (80%)



4	**1a** (1.2 mmol)	**2b** (1.0 mmol)	r.t., 5 h	**3b** (81%)	**4b** (0%)
5	**1a** (2.4 mmol)	**2b** (1.0 mmol)	r.t., 5 h	**3b** (83%)	**4b** (3%)

Scheme 1.

Keywords: alcohols; allylation; boron and compounds; palladium and compounds.

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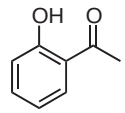
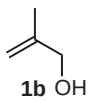
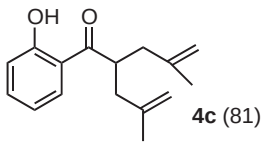
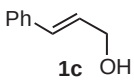
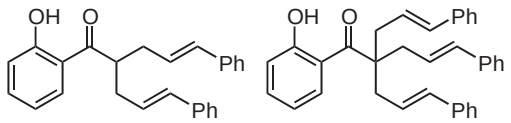
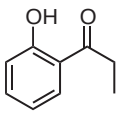
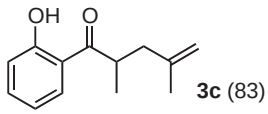
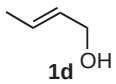
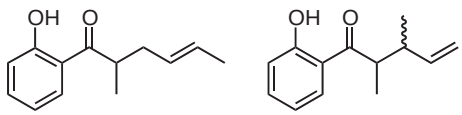
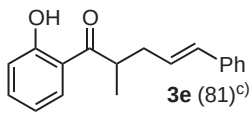
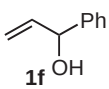
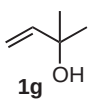
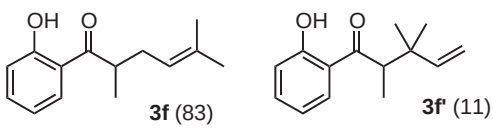
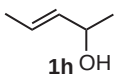
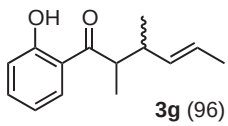
PII: S0040-4039(01)00381-1

hydroxyacetophenone (**2a**, 1.0 mmol) and allyl alcohol (**1a**, 1.2 mmol) in the presence of Et_3B (2.4 mmol), $Pd(OAc)_2$ (0.05 mmol), and PPh_3 (0.10 mmol) at room temperature for 24 h provided mono-**3a** (1%) and diallylation product **4a** (43%) with recovery of **2a** in 45% yield (run 1, Scheme 1). The same reaction with 2.4 mmol of **1a** provided **4a** in 82% isolated yield with no recovery of **2a** (run 2, Scheme 1). The selective formation of **4a** in good yield (run 1, Scheme 1; 78% based on 55% conversion of **2a**) suggests that the second alkylation (**3a**→**4a**) proceeds much faster than the first one (**2a**→**3a**). Indeed, the alkylation of **3a** with **1a** completed in a remarkably shorter reaction time and provided **4a** in excellent yield (run 3, Scheme 1). *o*-Hydroxypropiophenone (**2b**) displayed similar reaction features: **2b** smoothly reacted with **1a** and provided **3b** in good yield (run 4). Interestingly, a further alkylation of **3b** leading to **4b** proceeded to a negligible extent even when the reaction was undertaken in the presence of an excess amount of **1a** (run 5). All these results indicate that the present alkylation displays a strong tendency to selectively provide α-disubstituted alkyl ketones.

Table 1. Pd-catalyzed *C*-diallylation of **2a** and *C*-monoallylation of **2b** with allyl alcohols **1b**–**h**[a)]

run	ketones **2**	allyl alcohol **1**	temp (°C)/time (h) (% conversion)	% isolated yield of proudcts **3**, **4**, and **5**[b)]
1	 **2a**	 **1b**	25/48 (100)	 **4c** (81)
2	**2a**	 **1c**	25/48; 50/6 (100)	 **4d** (80) **5a** (10)[c)]
3	 **2b**	**1b**	25/22 (77)	 **3c** (83)
4	**2b**	 **1d**	25/20 (100)	 **3d** (66) **3d'** (24) [1:1.1][d)]
5	**2b**	 **1e**	25/20 (100)	**3d** (63) **3d'** (25) [1:1.1][d)]
6	**2b**	**1c**	25/4 (100)	 **3e** (81)[c)]
7	**2b**	 **1f**	25/8 (100)	**3e** (88)[c)]
8	**2b**	 **1g**	25/45; 50/5 (81)	 **3f** (83) **3f'** (11)
9	**2b**	 **1h**	25/30; 50/8 (100)	 **3g** (96) [1:1.1][d)]

a) Typical reaction conditions: A mixture of **1** (2.4 mmol for **2a**, 1.2 mmol for **2b**), **2** (1.0 mmol), Et_3B (2.4 mmol, 1 M solution in hexane), $Pd(OAc)_2$ (0.05 mmol) and PPh_3 (0.10 mmol) in THF (5 ml) was stirred for the period of time and at the temperature indicated in the Table.
b) Isolated yield for the spectroscopically homogenous products (based on conversion).
c) A mixture of 1,6- and 1,4-diphenyl-1,5-hexadienes (24% in run 2, 4% in run 6, 6% in run 7) was also produced.
d) Ratios of two diastereomers determined on the basis of ^1H NMR spectra (400 MHz).

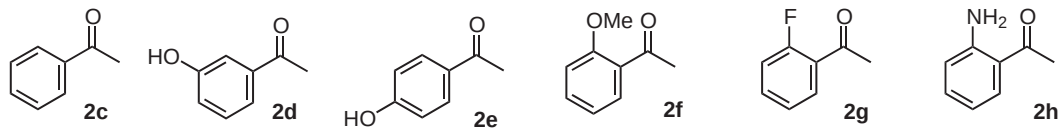
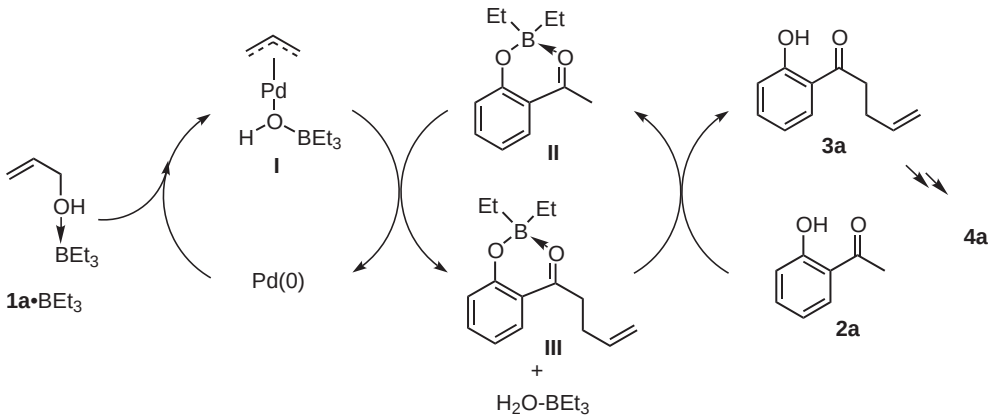


Figure 1. A list of acetophenone derivatives that provide no *C*-allylation products for the reaction with **1a** under standard conditions.



Scheme 2. A plausible catalytic cycle for the Et_3B-promoted, Pd-catalyzed *C*-allylation of **2a** with **1a**.

Results obtained for the reaction of **2a** and **2b** with other allyl alcohols **1b–h** (2.4 equiv. for **2a** and 1.2 equiv. for **2b**) are summarized in Table 1, which reveals that the present allylative alkylation is successfully applicable to primary, secondary and tertiary allyl alcohols with a wide variety of substitution patterns on the double bond.[5] Regioselectivity is just as is expected for the reactions via π-allylpalladium complexes as intermediates; unsymmetrical allyl alcohols react at the least substituted allylic termini either exclusively (runs 2, 6 and 7 Table 1) or selectively (runs 4, 5 and 8).

o-Hydroxyphenyl alkyl ketones seem to be unique substrates that undergo the present alkylation; acetophenone, *m*- and *p*-hydroxyacetophenones were all unreactive under similar reaction conditions (Fig. 1). These results suggest the importance of activation of alkyl ketones through either intramolecular hydrogen bonding or coordination of some borane species bound to the *o*-hydroxyl group. Accordingly, we examined various *o*-heteroatom substituted acetophenones (**2f–h**).[6] However, none of them turned out to be reactive; **2h** provided *N*-allylaminoacetophenone in low yield (29% based on 31% conversion). As reported recently from these laboratories,[2a] the Et_3B-promoted, Pd-catalyzed alkylation of malonates with allyl alcohols proceeds only in the presence of bases such as NaH. In sharp contrast to this, *o*-hydroxyphenyl alkyl ketones smoothly undergoes the alkylation in the absence of a base even though the acidity of these ketones is expected to be lower than that of malonates.

In Scheme 2 our working hypothesis for the present Pd-catalyzed allylic alkylation using **1a** and **2a** as typical reaction partners is outlined, where Et_3B serves in many ways to promote the reaction. Et_3B may reduce Pd(II) to Pd(0) through a few steps: ethyl group(s) transfer from B to Pd(II), followed by either reductive elimination from Et_2Pd or β-H elimination from EtPdOAc and/or Et_2Pd. Et_3B may coordinate to the oxygen atom of **1a** to help it undergo oxidative addition to Pd(0). Furthermore, a small portion of Et_3B may be hydrolyzed by **1a** or **2a** to produce an intermediate **II**.[7] The intermediate **II** would react through its enol form with π-allylpalladium species **I** and produce a mixture of **III**, H_2O–BEt_3 and Pd(0) complexes. The thus-formed **III** may undergo transesterification with **2a**, regenerating **II** and liberating **3a**. In a similar way, **3a** may be alkylated further to finally provide **4a**.

The mechanism suggests that the reaction could be catalytic with respect to Et_3B. Indeed, the reactions of **1a** (1.2 mmol) and **2b** (1.0 mmol) performed with reduced amounts of Et_3B (1.2 and 0.6 mmol) completed in 5 h at room temperature and provided **3b** in 92 and 96% yields, respectively (cf. run 4, Scheme 1). In the absence of Et_3B, no reaction was observed and **2b** was recovered quantitatively.

Acknowledgements

Financial support from the Ministry of Education, Science, Sports and Culture, Japanese Government, Grant-in-Aid for Scientific Research B, is acknowledged.

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5. Typical reaction procedure (run 1, Table 1): Into an N_2 purged flask containing $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) and PPh_3 (26.2 mg, 0.10 mmol), THF (5.0 mL), β-methylallyl alcohol (**1b**, 172.8 mg, 2.4 mmol), **2a** (136.2 mg, 1.0 mmol) and Et_3B (2.4 mmol, 1 M in hexane) were added successively via a syringe. The homogeneous mixture was stirred at ambient temperature for 48 h, during which the reaction was monitored by means of TLC. After dilution with ethyl acetate, the mixture was washed with 2 M HCl and then with brine. The organic layer was dried ($MgSO_4$) and the solvent was removed in vacuo. Purification of the residue by column chromatography over silica gel (hexane) provided **4c**: 196.5 mg (81% yield). R_f (**2a**) = 0.55, R_f (**4c**) = 0.71 (hexane–EtOAc, 4:1).
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