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Et₃B-promoted, Pd(0)-catalyzed allylation of active methylene compounds with allylic alcohols

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Abstract

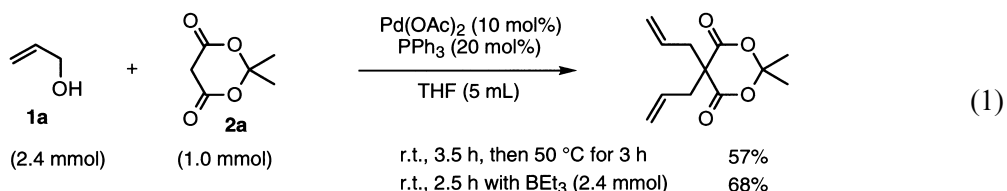
Triethylborane promotes the Pd(0)-catalyzed allylation of active methylene compounds (Meldrum's acid and malonates) with a variety of allylic alcohols. The reaction proceeds smoothly at room temperature and provides the allylation products in good yield. © 2000 Elsevier Science Ltd. All rights reserved.

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Palladium-catalyzed allylation of active methylene compounds is an established, efficient method for C–C bond formation.¹ In most cases, carboxylic acid esters,² carbonates,³ phosphates,¹ and related compounds of allylic alcohols have been utilized as substrates. Apparently the direct use of allylic alcohols as substrates is more desirable; however, the poor capability of the hydroxyl group to serve as a leaving group has limited their use.⁴

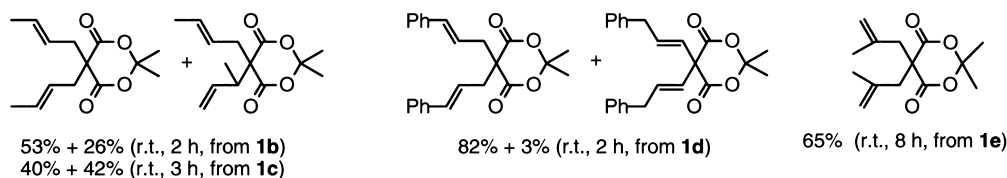
In 1970, Atkins et al.⁵ reported that allylic alcohols and acetylacetone (p*K*_a = 9) combined to give 3-allylacetylacetones in good yield when heated to 85°C in the presence of catalytic amounts of Pd(acac)₂ and PPh₃. Later, Bergbreiter et al.⁶ and Chauvin et al.⁷ revealed that even less nucleophilic β-ketoesters (p*K*_a = ca. 11) and malonates (p*K*_a = ca. 13) also underwent direct palladium-catalyzed allylation with allylic alcohols, although under rather harsh conditions (heating at around 100°C). Meanwhile, several methods have been developed that enable the allylation to proceed under milder conditions (room temperature–refluxing THF), where allylic alcohols are activated in situ through transformation into the esters of inorganic acids, such as As₂O₃,⁸ B₂O₃,⁹ and CO₂.¹⁰

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Here we would like to disclose that Et₃B greatly promotes the palladium-catalyzed allylation of active methylene compounds with allylic alcohols with a wide structural variety; allylation of Meldrum's acid (**2a**, pK_a = 5.2) and even diethyl malonate (**2b**) and diethyl benzylmalonate (**2c**) proceeds smoothly at room temperature and gives rise to the expected products in good isolated yield.

In accord with the previous report,⁵ **2a** was reluctant to undergo the allylation with allyl alcohol (**1a**) at room temperature (Eq. (1)). For the reaction to proceed at a reasonable rate, a higher temperature was required. To our surprise, however, in the presence of Et₃B (2.4 equiv. relative to **2a**), under otherwise identical conditions, the reaction proceeded smoothly at room temperature and was completed within 2.5 h (Eq. (1)). The results obtained for other allylic alcohols under the conditions shown in Eq. (1) (in the presence of 2.4 equiv. of Et₃B) are summarized in Scheme 1. All the reactions, so far examined, furnished the diallylation products in good yield.



Scheme 1. Et₃B-promoted Pd(0)-catalyzed bis-allylation of Meldrum's acid with allylic alcohols. For the structures of allylic alcohols, see Table 1

Next, we tested the ability of Et₃B as a promoter by using less nucleophilic **2b** and **2c** as a probe (Eqn. (2)). The results are summarized in Table 1. Under the conditions established for **2a**, however, **2b** was unwilling to undergo allylation; no allylation took place even under forcing conditions (run 13, Table 1). We found that NaH was very effective to restore the reactivity; in the presence of NaH (0.5 equiv. relative to **2b**), the allylation of **2b** with **1g** was completed at room temperature within 4 h and provided **3h** in 74% isolated yield (run 10, Table 1). The results of runs 10–13 clearly indicate that both Et₃B and NaH are indispensable for a smooth and successful allylation. It is also apparent from Table 1 that the conditions thus established are applicable quite satisfactorily to many other allylic alcohols, which encompass primary, secondary, and dienyl alcohols with a variety of substitution patterns on the double bond.¹¹

We usually applied Pd(OAc)₂ (10 mol%) and PPh₃ (20 mol%) as the catalyst; however, the amounts may be reduced to one-half without causing any noticeable differences in the reaction time and in the yield of the product (runs 6 and 7). Interestingly, crotyl alcohol (**1c**) turned out to be more reactive than, or at least as reactive as, the corresponding acetate (runs 3 and 4, Table 1).

Table 1
Et₃B-promoted, palladium(0)-catalyzed allylation of malonates **2b,c** with allyl alcohols **1a-j**^a

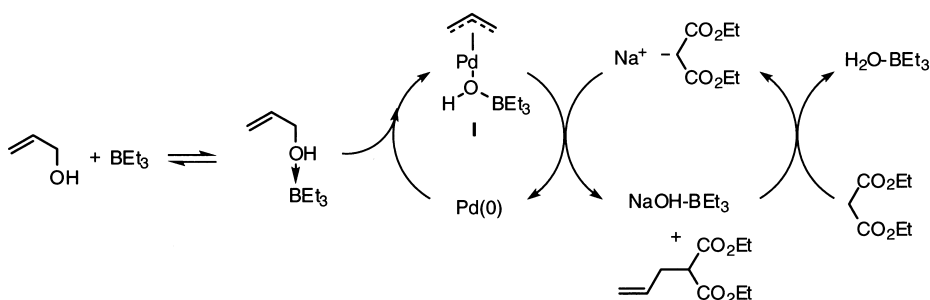
R' $\text{CH}_2=\text{CH}-\text{CH}_2-\text{OH}$ 1 (0.9 mmol) $\text{R}-\text{CH}(\text{CO}_2\text{Et})-\text{CH}_2-\text{CO}_2\text{Et}$ 2b: R = H, 2c: R = CH₂Ph (1.0 mmol) Pd(OAc)₂ (10 mol%) PPh₃ (20 mol%) THF (5 mL) R' $\text{CH}_2=\text{CH}-\text{CH}_2-\text{CH}(\text{R})-\text{CH}_2-\text{CO}_2\text{Et}$ 3 (2)						
run	allyl alcohol 1	malonate 2	Et ₃ B (mmol)	NaH (mmol)	temp (°C)/ time (h)	% isolated yield of product 3 ^b
1	1a	2c	1.2	0.5	25/27	3a : 80
2	1b	2c	1.2	0.5	25/6	3b : 51 3c : 26
3	1c	2c	1.2	0.5	25/4	3b : 64, 3c : 12
4	(the acetate of 1c)	2c	1.2	0.5	25/7	3b : 65, 3c : 15
5	1d	2b	1.2	0.5	25/4	3d : 84
6	1d	2c	1.2	0.5	25/4	3e : 84
7 ^c	1d	2c	1.2	0.5	25/5	3e : 84
8	1e	2c	1.2	0.5	25/48	3f : 80
9	1f	2c	1.2	0.5	25/75	3g : 75
10	1g	2b	1.2	0.5	25/4	3h : 74
11	1g	2b	0.25	0.5	25/100	3h : 50
12	1g	2b	0	0.5	50/18	3h : 13
13	1g	2b	1.2	0	50/41	3h : 0
14	1g	2c	1.2	0.5	25/20	3i : 55
15	1h	2b	1.2	0.5	25/48	3j : 75
16	1i	2c	1.2	0.5	25/5	3k : 55 3l : 5
17	1j	2b	1.2	0.5	50/20	3m : 31 3n : 4

a) Standard conditions: **1** (0.9 mmol), **2b** or **2c** (1.0 mmol), Pd(OAc)₂ (0.09 mmol), PPh₃ (0.18 mmol), Et₃B (1M hexane solution, indicated amount), NaH (indicated amount) in THF (5 mL) under N₂. b) All the products were fully characterized by ¹H NMR, IR, HRMS, and/or elemental analyses. Regio- and stereoisomers were not separated and the ratio was determined by ¹H NMR (400 MHz) and/or GLC. c) With Pd(OAc)₂ (0.045 mmol, 5 mol%) and PPh₃ (0.09 mmol, 10 mol%) under otherwise standard conditions.

Regioselectivity is just as is expected for the reactions via π -allylpalladium complexes as a reactive intermediate; straight chain products are produced preferentially over branched isomers (e.g., **3b** > **3c** from both **1b** and **1c**, runs 2–4; only **3d** and **3e** from **1d**, runs 5–7; **3m** > **3n** from **1j**, run 17). Dienyl alcohol **1i** reacted regioselectively at the least substituted allylic terminus, but non-stereoselectively, providing a mixture of isomers **3k** and **3l** in a ratio of ca. 10 to 1 (run 16).

The combination of the reagents used in the present reaction is quite similar to that reported by Stary et al.,¹² who employed Ph_3B , in place of Et_3B , as a promoter. Thus, a complex, $[\text{Ph}_3\text{B}-\text{O-allyl}]^- \text{Li}^+$, generated from Ph_3B (1.1 equiv.), an allylic alcohol (1.0 equiv.), and $n\text{-BuLi}$ (1.0 equiv.), was allowed to react with $\text{LiCH}(\text{CO}_2\text{Et})_2$ (1.5 equiv.) in the presence of $\text{Pd}(\text{PPh}_3)_4$ (5 mol%) and PPh_3 (10 mol%) in refluxing THF for 3–8 h. Allylmalonates were obtained in modest to good yields. For example, **3d** and **3h** were isolated in 80% and 48% yield, respectively. Judging from the reaction conditions (room temperature vs refluxing THF, NaH (0.5 equiv.) vs $n\text{-BuLi}$ (2.5 equiv.), volatile vs. heavy, bulky organic borane), the yields of products, and their structural versatility, Et_3B seems to be the reagent of choice.

In Scheme 2 our working hypothesis is outlined for the present Et_3B -promoted, $\text{Pd}(0)$ -catalyzed allylation of diethyl malonate with allyl alcohol. Et_3B may reduce $\text{Pd}(\text{II})$ into $\text{Pd}(0)$ through a few steps: ethyl group(s) transfer from B to $\text{Pd}(\text{II})$, followed by either reductive elimination from Et_2Pd or $\beta\text{-H}$ elimination from EtPdOAc and/or Et_2Pd . On the other hand, Et_3B may coordinate to the oxygen atom of allyl alcohol to help it undergo oxidative addition to $\text{Pd}(0)$. The thus-formed π -allylpalladium intermediate **I** reacts with diethyl sodiomalonate to produce a mixture of diethyl allylmalonate and $\text{NaOH}-\text{Et}_3\text{B}$, and $\text{Pd}(0)$ complexes.¹³ The $\text{Pd}(0)$ complexes may enter into a new catalytic cycle as described above, and the $\text{NaOH}-\text{Et}_3\text{B}$ complex may serve as a base to regenerate diethyl sodiomalonate.¹⁴



Scheme 2. A plausible catalytic cycle for the Et_3B -promoted $\text{Pd}(0)$ -catalyzed allylation of diethyl malonate with allyl alcohol

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11. Typical reaction procedure (run 1, Table 1): Into a N₂ purged flask containing Pd(OAc)₂ (20.2 mg, 0.09 mmol) and PPh₃ (47.2 mg, 0.18 mmol), were added successively THF (2.5 mL), allyl alcohol (**1a**, 52.2 mg, 0.9 mmol), and **2c** (a stock solution of 0.2 M in **2c** and 0.2 M in Na⁺-**2c**⁻ in THF, 2.5 mL, 1.0 mmol), and finally Et₃B (1 M in hexane, 1.2 mL, 1.2 mmol) via a syringe. The homogeneous mixture was stirred at ambient temperature for 27 h, during which the reaction was monitored by means of TLC. After dilution with ethyl acetate (50 mL), the mixture was washed with 2N HCl (10 mL) and then with brine (2×10 mL). The organic layer was dried (MgSO₄) and the solvent was removed in vacuo. Purification of the residue by column chromatography over silica gel (hexane–ethyl acetate 32/1, v/v) provided **3a**: 209.0 mg (80% yield).
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14. This mechanism suggests that the reaction should be catalytic with respect to Et₃B; however the catalytic efficiency of it is only moderate (turnover number=ca. 2, run 11, Table 1). Accordingly, we usually used Et₃B in a stoichiometric amount in order to obtain the better yields and to promote the reaction at a reasonable rate.