

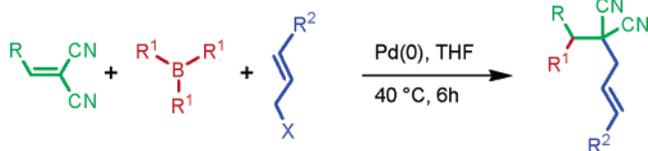
**β -Alkyl- α -allylation of Michael Acceptors
through the Palladium-Catalyzed
Three-Component Coupling between Allylic
Substrates, Trialkylboranes, and Activated
Olefins**

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The palladium-catalyzed three-component β -alkyl- α -allylation reaction of activated olefins has been achieved. For example, in the presence of 5 mol % of Pd(PPh₃)₄, the reaction of benzylidenemalononitrile **1a** with Et₃B and allyl acetate **2a** in THF proceeded smoothly at 40 °C to give the corresponding β -ethyl- α -allylated product **3a** in 81% yield.

The functionalization of Michael acceptors (activated olefins) through palladium-catalyzed carbon-carbon bond formation is becoming an important research area (Figure 1). These reactions generally proceed under milder conditions and with high atom economy.¹ The three-component coupling reactions such as alkoxy-allylation (path A),² bis-allylation (path B),³ cyano-allylation (path C),⁴ acetonation-allylation (path D),⁵ and amino-allylation (path E)⁶ gave the corresponding β , α -functionalized products in high yields. The palladium catalyzed [3 + 2] cycloaddition of vinylic oxirane and aziridine with activated olefins for the formation of five membered cyclic ether⁷ and pyrrolidine⁷ derivatives has also been reported in our laboratories (path F). The palladium-catalyzed reaction of activated olefins

(1) (a) Trost, B. M. *Science* **1991**, *254*, 1471–1477. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259–281. (c) Sheldon, R. A. *Pure Appl. Chem.* **2000**, *72*, 1233–1246.

(2) Nakamura, H.; Sekido, M.; Ito, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 6838–6839. It may be argued that this reaction is a two-component coupling, and not a three-component one. Since the addition to the Michael acceptors takes place both at β and α -positions, we would like to propose that this is also among the category of three component coupling.

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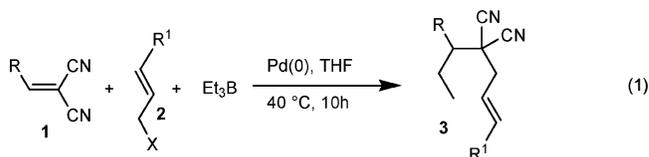
(5) Shim, J. G.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 8470–8474.

(6) Aoyagi, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 5977–5980.

(7) Shim, J.-G.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 3067–3071.

with allenes, bearing an activated methine at the carbon chain terminus, gave the cyclopentanes in good to excellent yields (path G).⁸ The palladium-catalyzed cycloaddition of activated olefins with the allylic carbonates having a hydroxy group at the terminus of the carbon chain gave the corresponding cyclic ethers (path H).⁹ Quite recently, we have reported the palladium-catalyzed hydrocarbonation, that is to say, β -hydro- α -allylation of activated olefins by the use of Bu₃SnH and allyl acetate.¹⁰ In all of the above cases, it was found that the reactions did not proceed when one of the two electron-withdrawing groups (E¹, E² = CN, CN; CN, COOEt; CN, SOOPh) was replaced by hydrogen, indicating the special nature of the olefin of type **1** in the palladium-catalyzed processes. Although these reactions are limited to highly activated olefins, the utility of the -CN group for further structural manipulation prompted us to continue research in this area. Several other researchers¹¹ also reported some interesting transformations using activated olefins; however, to the best of our knowledge the alkyl-allylation of activated olefins has not been reported yet.

We found that the palladium-catalyzed reaction of benzylidenemalononitrile **1a** (R = Ph, E¹ = E² = CN) with Et₃B and allyl acetate **2a** (R¹ = H, X = OAc) in THF proceeded smoothly at 40 °C to give the corresponding alkyl-allylation product **3a** in 81% yield (eq 1). Preliminary studies have been carried out using benzylidenemalononitrile **1a**, Et₃B (1.2 equiv) and allyl acetate **2a** (1.2 equiv) in the presence of a series of potential palladium catalysts (5 mol %) in THF (Table 1). The reaction was carried out in the presence of Pd(PPh₃)₄ (5 mol %) at 40 °C under an argon atmosphere (entry 1). The starting material **1a** was consumed within less than 6 h to give the desired alkyl-allylation product **3a** in 81% isolated yield. When Pd₂dba₃·CHCl₃ was employed alone as a palladium source, the reaction did not proceed (entry 2). The combination of Pd₂-dba₃·CHCl₃ and phosphine ligands (20 mol % for bisphosphines or 40 mol % for monophosphines) worked well, and the desired compound was obtained in good to moderate yields (entries 3–7). However, the use of dppe as a ligand proved unsatisfactory, and the product was obtained only in 10% yield as judged by ¹H NMR (entry 8). Thus, Pd(PPh₃)₄ was chosen as the catalyst for the alkyl-allylation of activated olefins. When the reaction of **1a** with either **2a** or **2c** was performed in the absence of Pd(PPh₃)₄ or in the presence of a catalytic amount of PPh₃,¹² instead of Pd(PPh₃)₄, no product **3a** was obtained at all. These control experiments clearly indicate that Pd(PPh₃)₄ is required for the reaction to proceed.



Once a suitable condition for the alkyl-allylation reaction was established, we investigated the scope of the three component

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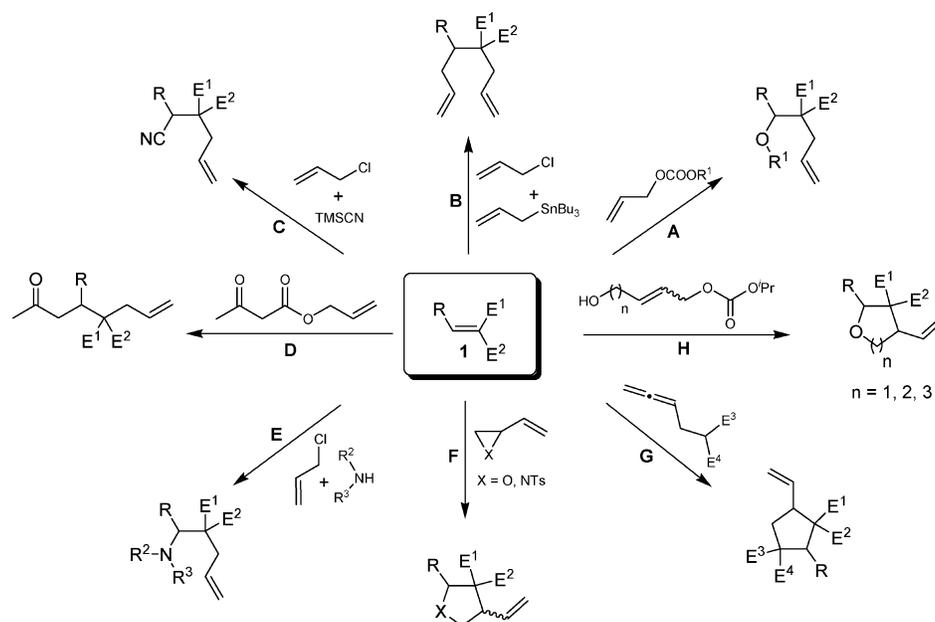


FIGURE 1. Palladium-catalyzed reactions of highly activated olefins.

coupling using various activated olefins. The results are summarized in Table 2. Treatment of the activated olefin **1b**, which has a methyl group at the para position of aromatic ring, with **2a** under the standard conditions gave the desired product **3b** in 78% yield (entry 1). The reaction of other aromatic olefins **1c** and **1d**, which have a strong electron-donating group such as methoxy and a strong electron-withdrawing group such as $-\text{NO}_2$ at the para position, gave the corresponding alkyl-allylation products **3c** and **3d**, respectively, in good yields (entries 2 and 3). The olefin **1e**, derived from 2-furaldehyde, also gave the desired product **3e** in 68% yield (entry 4). The reaction of isopropyl- and *tert*-butyl-substituted olefins **1f** and **1g** proceeded well to give the corresponding products **3f** and **3g** in 70% and 66% yield, respectively (entries 5 and 6). Not only activated olefins having two cyano groups but also the activated olefin **1h** bearing $-\text{CN}$ and $-\text{COOEt}$ groups under-

TABLE 1. Ligand Screen for the Alkyl-allylation Reaction^a

entry	Pd catalyst (5%)	phosphine	NMR yield ^b (%)
1	Pd(PPh ₃) ₄		87 (81) ^c
2	Pd ₂ dba ₃ ·CHCl ₃		0 ^d
3	Pd ₂ dba ₃ ·CHCl ₃	PPh ₃ (40 mol%)	81
4	Pd ₂ dba ₃ ·CHCl ₃	dppb (20 mol%)	71
5	Pd ₂ dba ₃ ·CHCl ₃	dppf (20 mol%)	82
6	Pd ₂ dba ₃ ·CHCl ₃	dppp (20 mol%)	60
7	Pd ₂ dba ₃ ·CHCl ₃	dppm (20 mol%)	78
8	Pd ₂ dba ₃ ·CHCl ₃	dpe (20 mol%)	10 ^d

^a The reactions of **1a** (0.3285 mmol) with Et₃B (1.2 equiv) and allyl acetate **2a** (1.2 equiv) in the presence of palladium catalysts (5 mol%) and phosphine ligands were carried out at 40 °C in THF for 6 h. ^b Yields were determined by ¹H NMR spectroscopy with dibromomethane as an internal standard. ^c Isolated yield is shown in parentheses. ^d The starting material was observed by TLC.

went the alkyl-allylation smoothly, giving the product **3h** in 81% yield; however, the diastereoselectivity was poor in this case (entry 7). The three-component coupling reaction also proceeded with cinnamyl acetate to give **3i** in a high yield (entry 8). It should be noted that the allylation with cinnamyl acetate took place exclusively at the α -position of the allyl acetate and no C–C bond-forming product at the γ -position was obtained. We also investigated the use of allyl chloride instead of **2a**, and virtually no difference in the rates of reaction or the overall yields has been observed (entry 9 compare to Table 1, entry 1). As mentioned in entry 10, tributylborane could also be used to produce butyl-allylation product **3j** in 62% yield. Similar to our previous reports, the present reaction worked well only for the doubly activated olefins and apparently with nitriles. The other olefins such as diethyl 2-benzylidenemalonate does not gave product under the standard condition.

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(12) It was thought that the presence of catalytic amounts of PPh₃, liberated from Pd(PPh₃)₄, would coordinate with triethylborane to form a more reactive tetracoordinate boron ate complex **I**. A delivery of one of the ethyl groups on boron to Michael acceptor would be then facilitated. The formation of similar complex **II**, from trialkylaluminum compounds (R₃Al) and phosphines, is known; see: (a) Schneider, C.; Brauner, J. *Eur. J. Org. Chem.* **2001**, 4445–4450. (b) Schneider, C.; Brauner, J. *Tetrahedron Lett.* **2000**, *41*, 3043–3046.

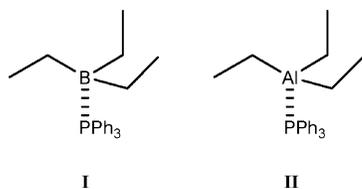


TABLE 2. Alkyl-allylation of Various Activated Olefins^a

entry	olefins (1)	allylic substrate (2)	product (3)	yield (%) ^b	entry	olefins (1)	allylic substrate (2)	product (3)	yield (%) ^b
1				78	6				66
2				79	7				81 ^c
3				61	8				82
4				68	9				80
5				70	10 ^d				62

^a The reactions of **1** (0.3285 mmol) with Et₃B (1.2 equiv) and allylic substrates **2** (1.2 equiv) in the presence of Pd(PPh₃)₄ (5 mol %) were carried out at 40 °C in THF for 6 h. ^b Isolated yields. ^c A mixture of diastereomers in a ratio of 6:4 was obtained. ^d Bu₃B was used, instead of Et₃B.

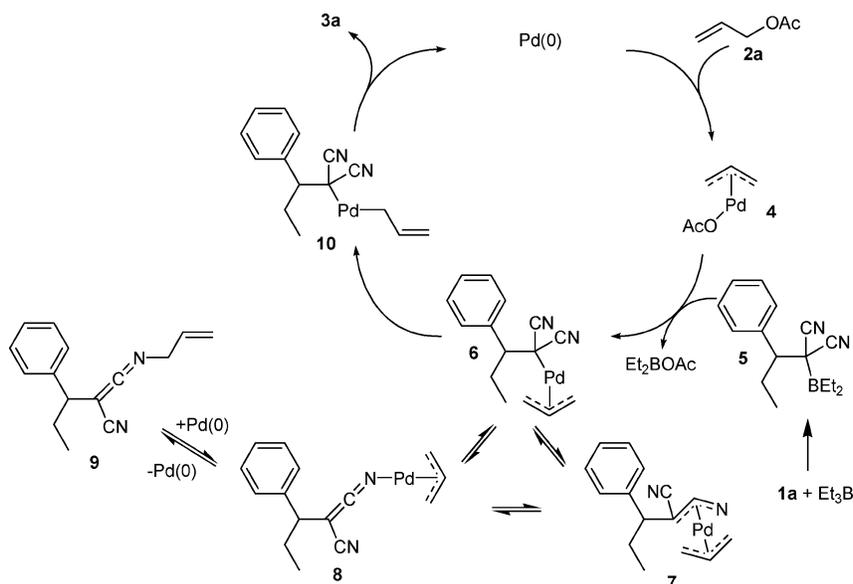


FIGURE 2. Proposed mechanism for the alkyl-allylation reaction.

A plausible mechanism for the three-component alkyl-allylation is shown in Figure 2. The oxidative addition of Pd(0) to allyl acetate **2a** leads to the formation of π -allylpalladium complex **4**. The π -allylpalladium complex **4** thus formed would react with the species **5**, formed by the Michael addition of one of the ethyl groups from Et₃B¹³ to **1a**, generating another

π -allylpalladium complex **6** with removal of Et₂BOAc. The conversion from the intermediate **5** to **6** proceeds in a way similar to the Tsuji–Trost allylation.¹⁴ The intermediate **6** could

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be in equilibrium with the intermediate **8**, which should more probably be represented as the bis- π -allylpalladium complex^{3,15} analogue **7**. The intermediate **8** might give the product **9** after reductive removal of Pd(0); however, it may again revert back to the intermediate **8** in the presence of Pd(0).¹⁶ The π -allylpalladium complex **6** is well represented as the intermediate **10**. The reductive elimination of Pd(0) from **10** gives the desired alkyl-allylation product **3a** with the regeneration of Pd(0).

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(15) (a) Szabo, K. J. *Chem. Eur. J.* **2004**, *10*, 5268–5275.

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In conclusion, we have developed a new procedure for the alkyl-allylation of activated olefins via the three component coupling reaction between activated olefins, Et₃B and allylic substrates in the presence of catalytic amounts of palladium. In combination with our previously reported methodologies on the activated olefins, this methodology provides a novel process for the 1,2 bis-functionalization of activated C–C bonds.

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Supporting Information Available: Experimental details, characterization data, ¹H and ¹³C spectra NMR of all compounds **3a–j**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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