

With compliments of the Author

Bis-Functionalization of 1,3-Dienes through 1,4-Conjugate Addition of Amphiphilic Bis- π -Allyl and Related Palladium Intermediates

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Abstract: Palladium-catalyzed three-component coupling of allylstannane, allyl chloride and a functionalized diene is described. Regioselective 1,4-functionalization of the Michael acceptor 1,3-diene is accomplished by the amphiphilic bis- π -allylpalladium complex. To the best of our knowledge, this is the first time a functionalized 1,3-butadiene has been used as a Michael acceptor. The scope of the present strategy is further extended to 1,4-allylation–oxyallylation of functionalized dienes.

Key words: palladium, allylation, allyl complexes, coupling, Michael addition

Strategies for 1,4-functionalization of 1,3-dienes through classical methods include cycloaddition reactions involving singlet oxygen,¹ and heterodienophiles such as nitroso compounds² and azodicarboxylates.³ Cycloadducts are further transformed into target molecules through suitable synthetic manipulations. Pioneering work on palladium-catalyzed 1,4-functionalization of 1,3-dienes was reported by Backvall and co-workers,⁴ and transition-metal-catalyzed transformations of 1,3-dienes have attracted the attention of a number of organic chemists.⁵ Synthetic transformations of 1,3-dienes using nickel,⁶ palladium,⁷ iron,⁸ and rhodium⁹ have been reported, and Hilt et al. have utilized the cobalt-catalyzed 1,4-hydrovinylation of 1,3-dienes for the synthesis of functionalized 1,4-dienes.¹⁰ RajanBabu and co-workers have carried out detailed in-

vestigations on asymmetric hydrovinylation of linear and cyclic 1,3-dienes.¹¹ Very recently, Sigman and co-workers achieved palladium-catalyzed 1,4-addition across the commodity chemical 1,3-butadiene to afford skipped polyene products.¹²

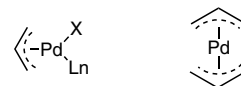
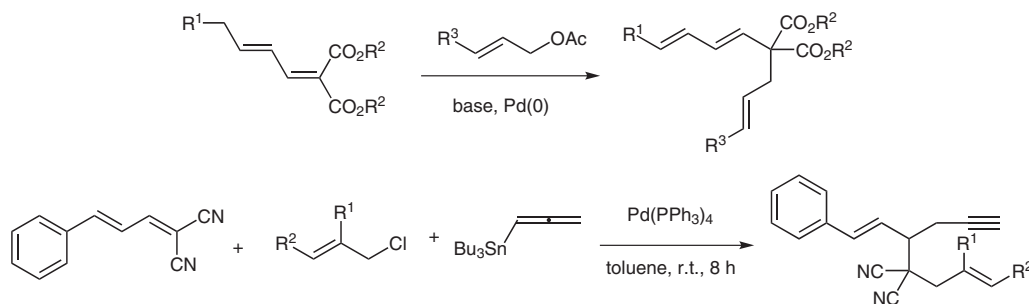


Figure 1 π -Allyl and bis- π -allyl palladium complexes

Bis- π -allylpalladium (Figure 1) and related intermediates show amphiphilic reactivity on reaction with activated olefins¹³ and benzynes.¹⁴ Inter- and intramolecular reactions of aldehydes, imines and activated olefins with bis- π -allylpalladium complexes have paved the way toward the synthesis of a number of highly functionalized organic molecules.^{13,15} Recently we have reported the bis-functionalization of isatylidenes by using the bis- π -allylpalladium complex as a facile route toward spiro-indol-2-ones.¹⁶ With the highly conjugated heptafulvene, the bis- π -allylpalladium complex undergoes 1,8-conjugate addition leading to bis-functionalized cycloheptatriene derivatives.¹⁷ A palladium-catalyzed deconjugative allylation reaction of 1,3-diene was reported for the first time by Sato and co-workers.¹⁸ Cheng et al. reported the reaction



Scheme 1 Reports by Sato et al.¹⁸ (top) and Cheng et al.¹⁹ (bottom)

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of a bis- π -allylpalladium complex generated from allyl chloride and allenylstannane with 1,3-diene, which afforded 1,2-addition products with exclusive regio- and chemoselectivity (Scheme 1).¹⁹

As part of our continuing interest in utilizing the amphiphilic nature of the bis- π -allylpalladium complex in organic synthesis, we undertook an investigation of its reactivity with highly functionalized 1,3-butadienes.²⁰ Our preliminary experiments involved the reaction of 1,3-butadiene derivative **1a** with allyl chloride (**2**) and allyltributylstannane (**3**) in the presence of $[\text{PdCl}_2(\text{PPh}_3)_2]$ in THF at room temperature (Table 1, entry 1).²¹ The reaction afforded 1,4-bis-allylated product **4a** in 78% yield, the structure of which was established on the basis of a range of spectroscopic techniques.²²

The reaction was then optimized to establish the best catalytic conditions (see the Supporting Information). Based on these studies, the optimal conditions for the transformation was found to be diene (1.0 equiv.), allyl chloride (2.0 equiv), allyltributylstannane (2.0 equiv), and 5 mol% $[\text{PdCl}_2(\text{PPh}_3)_2]$ in THF (2 mL) at room temperature.

The substrate scope for the bis-allylation strategy was investigated by utilizing various functionalized 1,3-butadienes. It should be noted that a variety of the highly functionalized 1,3-butadienes derived from substituted benzylidene malononitriles (**1b–d**, **1g** and **1h**) and heteroaryl malononitriles (**1e** and **1f**) can be used in this approach (Table 1). The use of highly substituted 1,3-butadienes makes this method potentially valuable for the synthesis of a number of biologically important targets.

Table 1 Palladium-Catalyzed Bis-Allylation of 1,3-Butadiene^a

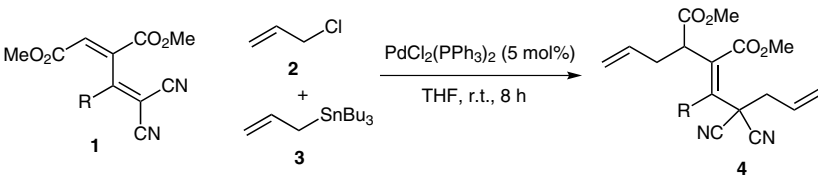
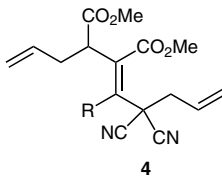
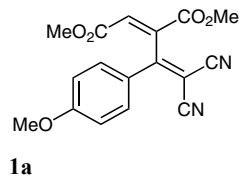
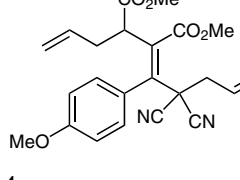
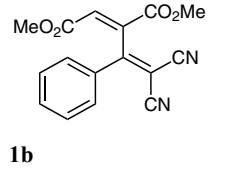
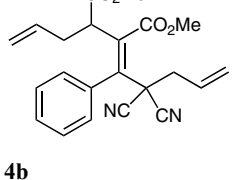
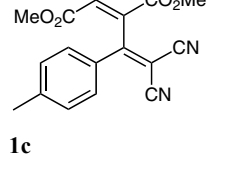
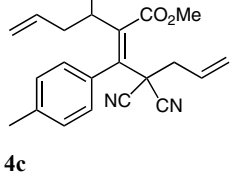
Entry	Substrate	Product	Yield (%)
1	 1	 4a	78
2	 1b	 4b	69
3	 1c	 4c	76
4	 1d	 4d	49

Table 1 Palladium-Catalyzed Bis-Allylation of 1,3-Butadiene^a (continued)

Entry	Substrate	Product	Yield (%)
5	 1e	 4e	61
6	 1f	 4f	71
7	 1g	 4g	30
8	 1h	 4h	47

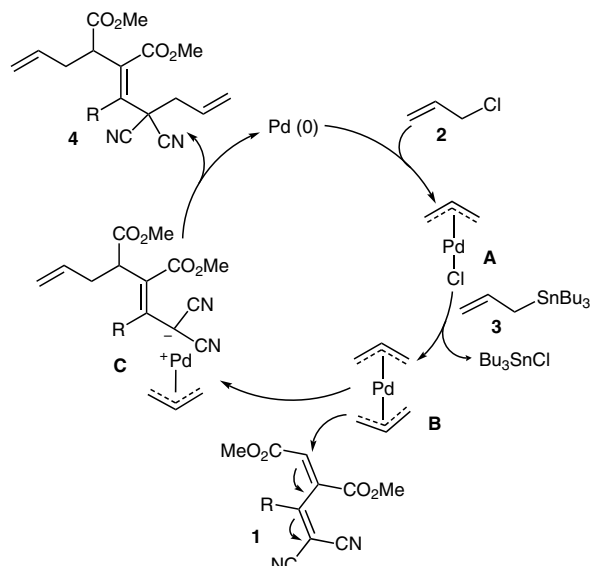
^a Reaction conditions: 1,3-diene **1** (1.0 equiv), allyl chloride **2** (2.0 equiv), allyl tributylstannane **3** (2.0 equiv), [PdCl₂(PPh₃)₂] (5 mol%), THF (2 mL), r.t., 8 h.

A plausible mechanistic pathway for bis-allylation is illustrated in Scheme 2. The initial event involves oxidative addition of allyl chloride **2** to a palladium(0) species to produce the η^3 -allylpalladium intermediate **A**. This intermediate undergoes ligand exchange with allyltributylstannane **3** to generate bis- η^3 -allylpalladium intermediate **B**, which subsequently undergoes nucleophilic 1,4-addition with diene **1** to form intermediate **C**, which, on reductive elimination, forms 1,4-bis-allylated product **4**.

To demonstrate the use of related π -allyl palladium intermediates, we initiated our investigations with the allylation-oxyallylation reaction of **1a** and diallylcarbonate **5** by the use of [Pd(PPh₃)₄] as the catalyst and THF as the solvent. To our delight, the desired allylated-oxyallylated product **6a** was obtained in 71% yield (Table 2, entry 1).

The structure of the allylated-oxyallylated product was unambiguously confirmed by single-crystal X-ray analysis of **6b** (from the reaction of **1b** and **5**; Figure 2).²³ The reaction presumably proceeds through oxidative addition of palladium to the diallyl carbonate, followed by loss of CO₂ to give intermediate **D**. Nucleophilic 1,4-addition followed by reductive elimination results in the formation of product **6**.

To develop conditions that were suitable for this transformation, we surveyed a variety of palladium catalysts and solvents (see the Supporting Information) and found that the optimal conditions for this reaction were: a mixture of 1,3-diene/diallyl carbonate (1:2) with 5 mol% [Pd(PPh₃)₄] in THF (2 mL) with a reaction time of 8 hours.



Scheme 2 Mechanistic rationale of palladium-catalyzed bis-allylation of 1,3-butadiene

A detailed study to expand the 1,4-allylation–oxyallylation strategy to other 1,3-dienes (**1b–f**) was undertaken, the results of which demonstrated that a wide range of substitution patterns are tolerated (Table 2).

In conclusion, we have developed a simple and efficient strategy for the bis-functionalization of 1,3-butadiene de-

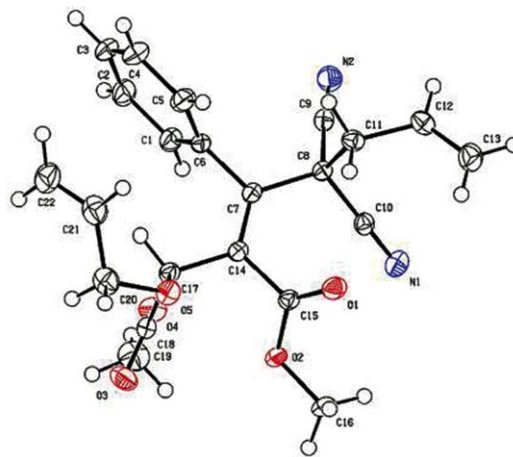
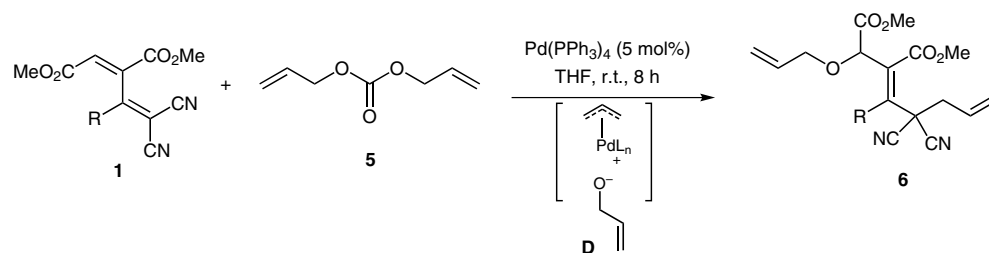


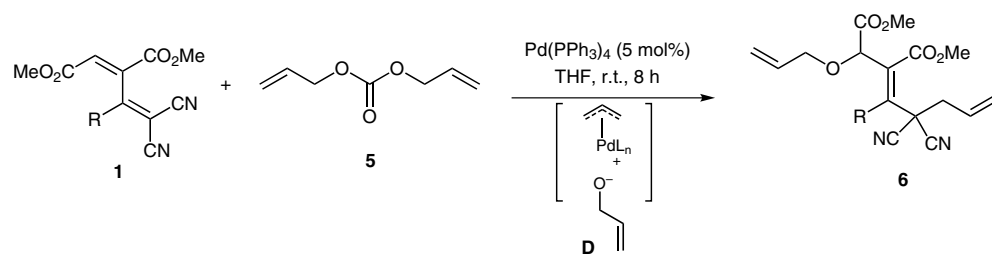
Figure 2 Single-crystal X-ray structure of **6b**

rivatives by a palladium-catalyzed three-component coupling reaction. To the best of our knowledge, this is the first report on a palladium-catalyzed 1,4-conjugate addition reaction of 1,3-butadiene derivatives via amphiphilic bis- π -allylpalladium and related complexes. Further synthetic manipulations of the synthesized trienes and investigations on the scope of other related palladium intermediates are under way and will be reported in due course.

Table 2 Palladium-Catalyzed Allylation–Oxyallylation Reaction of 1,3-Dienes^a



Entry	Substrate	Product	Yield (%)
1	<p>1a</p>	<p>6a</p>	71
2	<p>1b</p>	<p>6b</p>	55

Table 2 Palladium-Catalyzed Allylation–Oxyallylation Reaction of 1,3-Dienes^a

Entry	Substrate	Product	Yield (%)
3	 1c	 6c	66
4	 1d	 6d	31
5	 1e	 6e	69
6	 1f	 6f	43

^a Reaction conditions: 1,3-diene **1** (1.0 equiv.), diallyl carbonate **5** (2.0 equiv.), [Pd(PPh₃)₄] (5 mol%), THF (2 mL), r.t., 8 h

Acknowledgment

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Supporting Information for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synlett>.

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- (21) **Typical Procedure (Compound 4a):** To a degassed solution of [PdCl₂(PPh₃)₂] (4.4 mg, 0.0064 mmol) in anhydrous THF (2 mL) in a Schlenk tube, allyltributylstannane **3** (85.2 mg, 0.25 mmol) was added followed by allyl chloride **2** (19.6 mg, 0.25 mmol). To this, **1a** (42.02 mg, 0.12 mmol) was added (in THF) and the mixture was stirred at room temperature for 8 h. After the completion of the reaction (as evident by TLC), the solvent was removed under reduced pressure and the residue was purified by using silica gel (100–200 mesh) column chromatography (EtOAc–hexane, 12%) to afford **4a** (41.1 mg, 78%).
- (22) **Spectral Data of 4a:** *R_f* = 0.46 (EtOAc–hexane, 4:6); IR (neat): 3079, 2955, 2919, 2850, 2313, 2246, 1734, 1604, 1510, 1461, 1376, 1290, 1248, 1177, 1118, 1032 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 7.26–7.24 (m, 1 H), 7.08 (d, *J* = 8.5 Hz, 1 H), 6.98–6.94 (m, 2 H), 5.94–5.86 (m, 1 H), 5.56–5.47 (m, 1 H), 5.42–5.35 (m, 2 H), 5.05–4.98 (m, 2 H), 3.89 (s, 3 H), 3.84 (s, 3 H), 3.72 (s, 3 H), 3.18–3.15 (m, 1 H), 2.87–2.75 (m, 2 H), 2.63–2.58 (m, 1 H), 2.27–2.21 (m, 1 H); ¹³C NMR (125 MHz, CDCl₃): δ = 171.0, 166.0, 160.4, 137.4, 136.6, 134.0, 131.1, 130.1, 128.7, 126.0, 123.5, 118.1, 114.5, 114.3, 113.7 (2C), 55.3, 52.6, 52.5, 48.2, 42.7, 42.5, 33.8; HRMS (ESI): *m/z* [M + Na]⁺ calcd for C₂₃H₂₄N₂NaO₅: 431.15829; found: 431.15646.
- (23) CCDC-933875.