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Reactivity of vinylidene- π -allyl palladium(II) species†

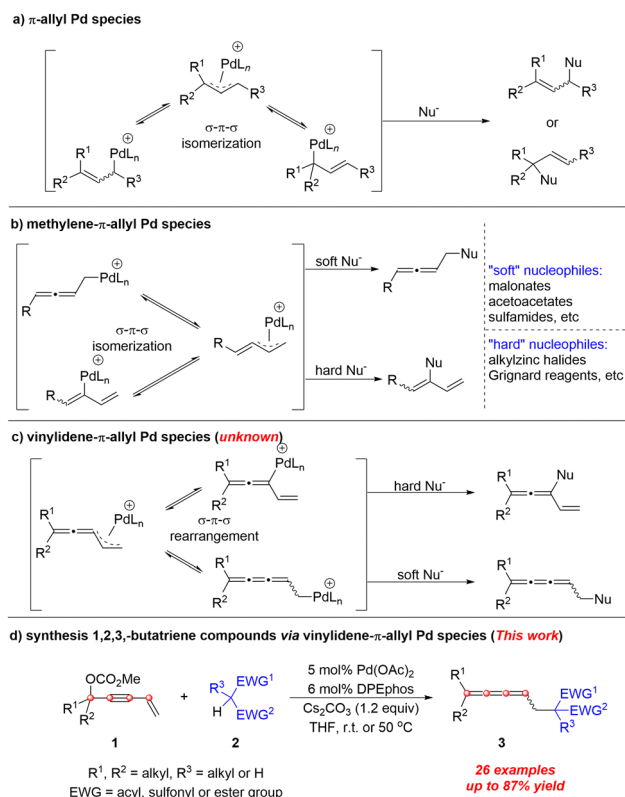
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The reactivity of a new type of organometallic intermediate, vinylidene- π -allyl palladium species, has been demonstrated: the reaction between 4-alken-2-ynyl carbonates and stabilized carbon nucleophiles afforded functionalized 1,2,3-,butatriene compounds in moderate to high yields and excellent regioselectivities.

π -Allyl palladium chemistry (Scheme 1a) has been well-established^{1,2} and has become a powerful protocol for the formation of carbon-carbon and carbon-heteroatom bonds. In analogy, methylene- π -allyl Pd species (Scheme 1b) also show attractive reactivity towards different types of nucleophiles affording allenes³ or 1,3-dienes,⁴⁻⁹ respectively. Here, we wish to report the first example of the reactivity of vinylidene- π -allyl palladium species (Scheme 1c) formed from 4-alken-2-ynyl carbonates with nucleophiles.

In our initial studies, the reaction of 4-alken-2-ynyl carbonate **1a** and ethyl 2-benzoylpropionate **2a** catalyzed by Pd(OAc)₂ (5 mol%) and PPh₃ (12 mol%) in THF at room temperature for 12 h afforded no product (Table 1, entry 1). Subsequent screening of various bisphosphine ligands (Table 1, entries 2–5) led to the formation of cumulated triene **3aa** as the major product together with a small amount of vinylallene **4aa** as determined by ¹H NMR analysis of the crude reaction mixture. The reaction with DPEphos gave product **3aa** in 60% yield with only 4% yield of **4aa** (Table 1, entry 4). To improve the yield of product **3aa**, a series of inorganic bases were screened (Table 1, entries 6–9) and Cs₂CO₃ was found to promote the reaction in 81% yield of **3aa** and 3% yield of **4aa**. Although *t*BuOLi provided a higher yield than Cs₂CO₃, the regioselectivity was lower (Table 1,

entry 9). As a comparison, the corresponding acetate **1a'** showed lower reactivity (entry 10) and the corresponding phosphate **1a''** was incompatible with this catalytic system (entry 11). Under the catalysis of Pd(OAc)₂ (5 mol%) and DPEphos (6 mol%), replacing THF with other representative solvents such as CH₃CN, EtOAc, DME, 1,4-dioxane and *n*-hexane resulted in poor yields and low regioselectivities (Table 1, entries 12–16). A reaction on the 0.5 mmol scale at a concentration of 0.1 M afforded product **3aa** in a lower yield and regioselectivity (56% of **3aa** with 6% of **4aa**) (Table 1, compare entry 7 with entry 17). After further



Scheme 1 Profiles of π -allyl palladium species.

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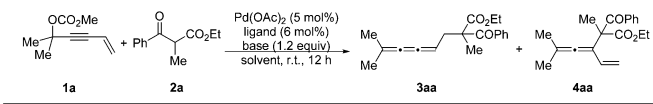
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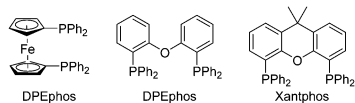
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Table 1 Optimization of the reaction conditions^a

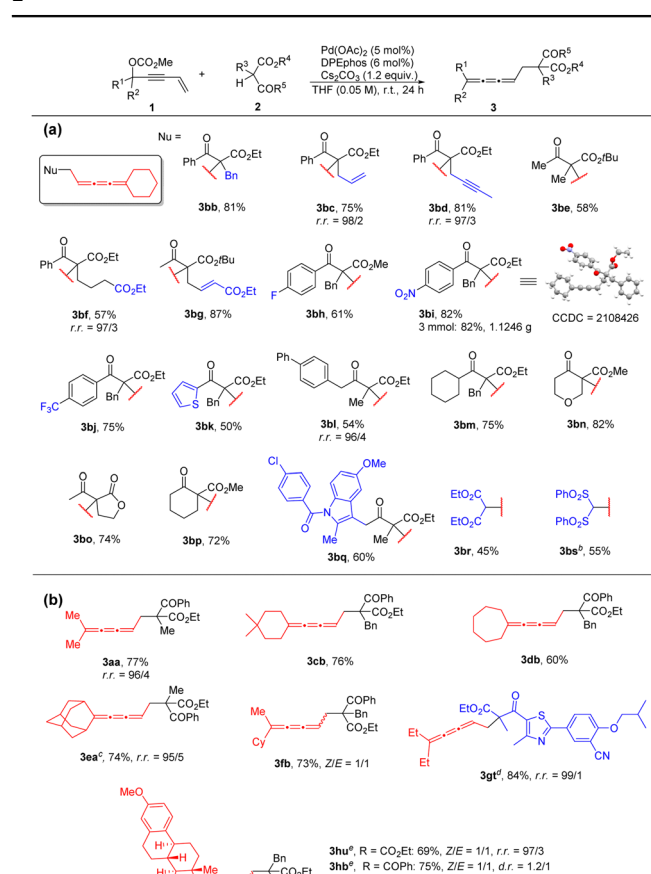
						
Entry	Ligand	Base	Solvent	Recovery of 1a ^b (%)	Yield of 3aa ^b (%)	Yield of 4aa ^b (%)
1 ^c	PPh ₃	—	THF	80	—	—
2	DPPE	—	THF	83	—	—
3	DPPF	—	THF	—	53	5
4	DPEphos	—	THF	—	60	4
5	Xantphos	—	THF	—	17	24
6	DPEphos	K ₂ CO ₃	THF	—	56	4
7	DPEphos	CS ₂ CO ₃	THF	—	81	3
8	DPEphos	K ₃ CO ₄	THF	—	72	3
9	DPEphos	<i>t</i> BuOLi	THF	—	88	11
10 ^d	DPEphos	CS ₂ CO ₃	THF	78 ^e	8	—
11 ^f	DPEphos	CS ₂ CO ₃	THF	2 ^g	1	—
12	DPEphos	CS ₂ CO ₃	CH ₃ CN	—	75	4
13	DPEphos	CS ₂ CO ₃	EtOAc	—	69	4
14	DPEphos	CS ₂ CO ₃	DME	—	75	3
15	DPEphos	CS ₂ CO ₃	Dioxane	—	58	3
16	DPEphos	CS ₂ CO ₃	<i>n</i> -Hexane	—	69	3
17 ^h	DPEphos	CS ₂ CO ₃	THF	—	56	6
18 ⁱ	DPEphos	CS ₂ CO ₃	THF	—	80	4
19 ^j	Xantphos	—	THF	—	10	23(20 ^k)



^a Reaction conditions: **1a** (0.2 mmol), **2a** (1.2 equiv.), Pd(OAc)₂ (5 mol%), ligand (6 mol%), and base (1.2 equiv.) in solvent (2 mL) unless otherwise noted. ^b Determined by ¹H-NMR analysis with CH₃NO₂ as the internal standard. ^c 12 mol% of PPh₃ was used. ^d The corresponding **1a'** was used instead of **1a**. ^e Recovery of **1a'**. ^f The corresponding **1a''** was used instead of **1a**. ^g Recovery of **1a''**. ^h The reaction was carried out on a 1 mmol scale in 10 mL of THF. ⁱ The reaction was carried out on a 0.5 mmol scale in 10 mL of THF for 24 h. ^j The reaction was carried out on a 1 mmol scale for 24 h. ^k Isolated yield.

optimization we observed that the reaction at a concentration of 0.05 M could improve the yield and regioselectivity (Table 1, entry 18). Thus, the reaction parameters for entry 18 have been defined as the standard conditions. Besides, the structure of the regioisomer **4aa** was confirmed by isolation based on a large scale experiment (entry 19).

With the optimal conditions in hand, we chose 1,1-pentamethylenepent-4-en-2-ynyl carbonate **1b** as a model substrate to explore the scope of β-ketocarbonyls **2** (Table 2a). Firstly, the substrates with substitution on the α-position of β-ketocarbonyls (R³) such as alkyl, alkenyl, alkynyl and ester groups all demonstrated high reactivity to afford the corresponding 1,2,3-butatrienes **3bb–3bg** in 57–87% yields. R⁵ of the phenyl group with an electron withdrawing group (fluoro (**2h**), nitro (**2i**), trifluoromethyl (**2j**)) may also be tolerated generating the products **3bh–3bj** smoothly in 61–82% yields. Three mmol scale reaction of **1b** with **2i** afforded 1.1246 g (82%) of product **3bi**, whose structure was further confirmed by single-crystal X-ray diffraction. When the R⁵ group is a heteroaromatic group such as 2-thienyl, the reaction afforded **3bk** in 50% yield. Moreover, the R⁵ group may also be an alkyl group affording the corresponding

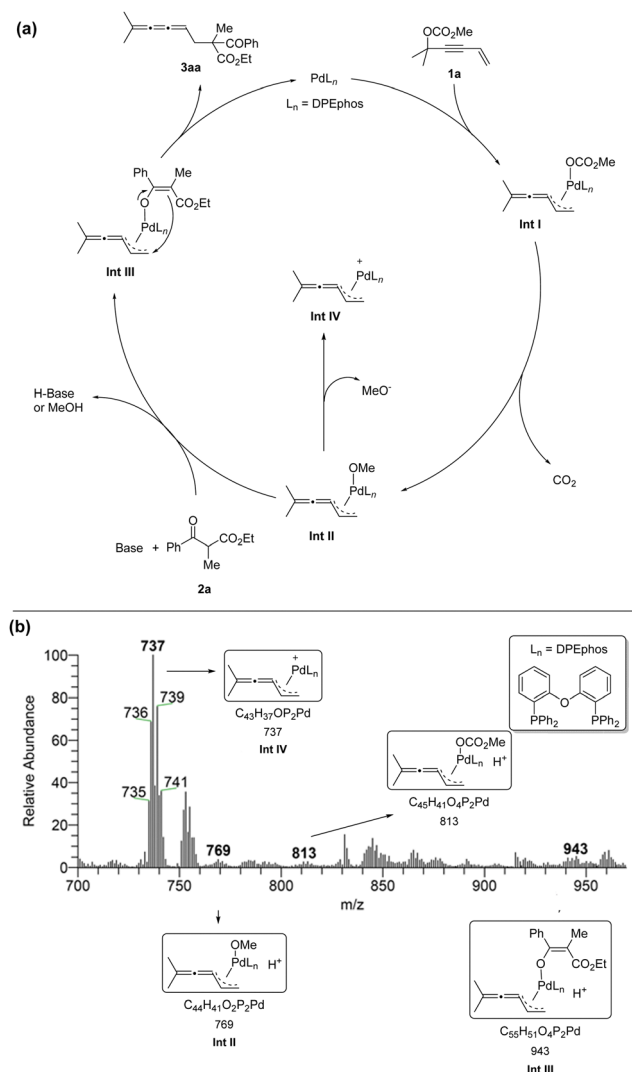
Table 2 Scope of 3-vinyl propargylic carbonates **1** and β-ketocarbonyls **2**^a

^a Unless otherwise indicated, the reaction was performed with 0.5 mmol of **1**, 1.2 equiv. of **2**, 5 mol% of Pd(OAc)₂, 6 mol% of DPEphos and 1.2 equiv. of CS₂CO₃ in THF (0.05 M) at room temperature for 24 h on a 0.5 mmol scale. Yields of isolated products are given. r.r. refers to the regioselectivity of the 1,2,3-butatriene product vs. vinylallene, which is determined by ¹H-NMR analysis of the crude product. ^b The reaction was carried out for 36 h. ^c The reaction was carried out at 50 °C for 42 h. ^d The reaction was carried out for 33 h. ^e The reaction was carried out at 50 °C for 48 h.

1,2,3-butatriene products **3bl** and **3bm**. In addition, the carbon- and oxygen-containing cyclic β-ketoesters **2n–2p** reacted smoothly with 72–82% yields. To our delight, commercially available drugs, such as Indomethacin and Febuxostat derived β-ketoesters **2q** and **2t** could also be incorporated into this reaction, resulting in the desired cumulated butatrienes **3bq** and **3gt**. In addition, diethyl malonate (**2r**) and bis(phenylsulfonyl)methane (**2s**) may also react with **1b** to afford the corresponding 1,2,3-triene products **3br** and **3bs** in moderate yields.

Next, we investigated the scope of 3-vinyl propargylic carbonates **1** (Table 2b). Cyclic ketone derived 3-vinyl propargylic carbonates **1b–1e** or acyclic ketone derived 3-vinyl propargylic carbonates **1a** and **1g** worked successfully under the standard reaction conditions. Non-symmetrical ketones such as cyclohexyl methyl ketone and estrone derived substrates **1f** and **1h** also gave the cumulated butatrienes **3fb**, **3hu** and **3hb** in decent yields.





Scheme 2 Plausible mechanism and SAESI-MS studies.

We proposed a possible mechanism as shown in Scheme 2a: Firstly, $\text{Pd}(0)\text{L}_n$ would undergo $\text{S}_{\text{N}}2'$ -type oxidative addition to form intermediate **Int I**.¹⁰ Followed by releasing one molecule of CO_2 , vinylidene- π -allyl palladium species **Int II** was generated. Subsequently, the enolate was formed with the help of MeO^- or Cs_2CO_3 . Then the carbon nucleophile would attack the terminal carbon atom *via* **Int III** to generate the linear selective products **3aa** and $\text{Pd}(0)\text{L}_n$ was regenerated. In order to identify possible intermediates in the reaction process, we carried out solvent-assisted electrospray ionization-mass spectrometry (SAESI-MS) and SAESI-MS/MS analysis (Scheme 2b).¹¹ A solution of **1a** (0.2 mmol), **2a** (0.24 mmol), $\text{Pd}(\text{OAc})_2$ (0.01 mmol), DPEphos (0.012 mmol), and Cs_2CO_3 (0.24 mmol) in THF (2 mL) was stirred at room temperature. After 2.5 hours, the reaction mixture was analyzed. **Ints I–IV** have been detected and further confirmed by a SAESI-MS/MS experiment (see ESI[†]), which firmly supports the above-mentioned mechanism.

In conclusion, we have developed a new strategy for the construction of functionalized 1,2,3-butatriene compounds *via*

a new vinylidene- π -allyl palladium species, which was formed from the oxidative addition reaction of the Pd -DPEphos complex with 4-alken-2-ynyl carbonates. We are actively pursuing other reactivity of this new vinylidene- π -allyl palladium species.

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Conflicts of interest

There are no conflicts to declare.

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