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

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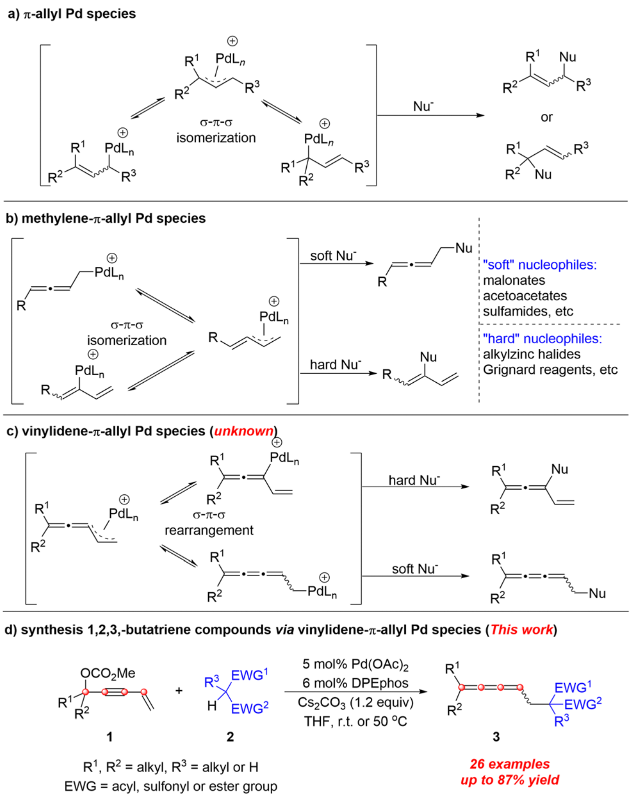
The reactivity of a new type of organometallic intermediate, vinylidene-π-allyl palladium species, has been demonstrated: the reaction between 4-alken-2-ynyl carbonates and stabilized carbon nucleophiles afforded functionalized 1,2,3,-butatriene compounds in moderate to high yields and excellent regioselectivities.

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 allenes[3] 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 PPh$_3$ (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 ^{1}H 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 Cs$_2$CO$_3$ was found to promote the reaction in 81% yield of **3aa** and 3% yield of **4aa.** Although *t*BuOLi provided a higher yield than Cs$_2$CO$_3$, 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 CH$_3$CN, 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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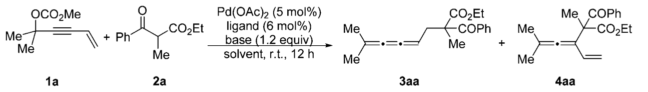
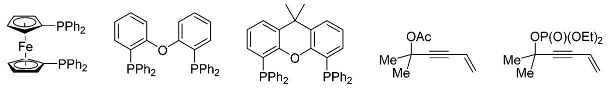
Table 1 Optimization of the reaction conditions[a]



1a **2a** **3aa** **4aa**

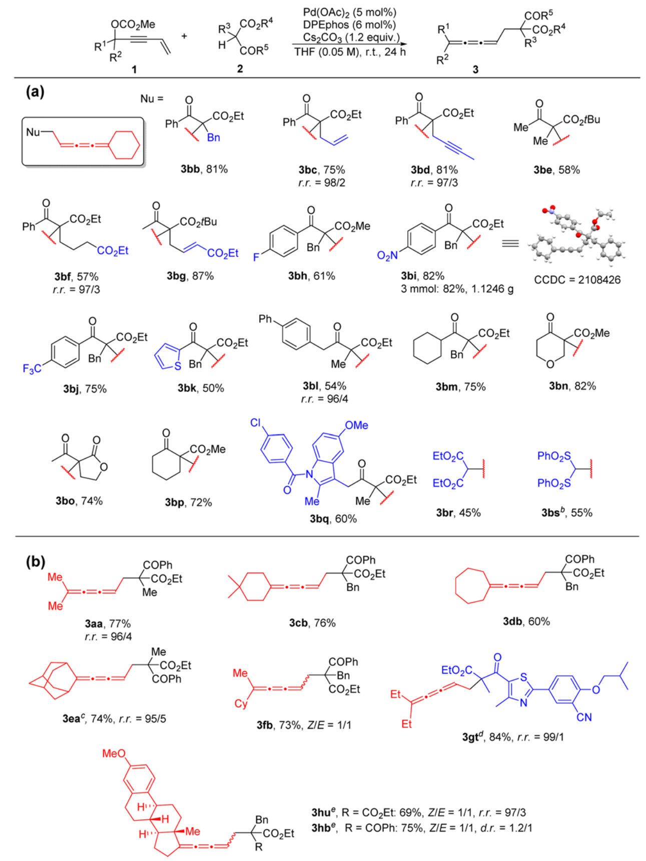
Entry	Ligand	Base	Solvent	Recovery of **1a**[b] (%)	Yield of **3aa**[b] (%)	Yield of **4aa**[b] (%)
1[c]	PPh_3	—	THF	80	—	—
2	DPPE	—	THF	83	—	—
3	DPPF	—	THF	—	53	5
4	DPEphos	—	THF	—	60	4
5	Xantphos	—	THF	—	17	24
6	DPEphos	K_2CO_3	THF	—	56	4
7	DPEphos	Cs_2CO_3	THF	—	81	3
8	DPEphos	K_3CO_4	THF	—	72	3
9	DPEphos	*t*BuOLi	THF	—	88	11
10[d]	DPEphos	Cs_2CO_3	THF	78[e]	8	—
11[f]	DPEphos	Cs_2CO_3	THF	2[g]	1	—
12	DPEphos	Cs_2CO_3	CH_3CN	—	75	4
13	DPEphos	Cs_2CO_3	EtOAc	—	69	4
14	DPEphos	Cs_2CO_3	DME	—	75	3
15	DPEphos	Cs_2CO_3	Dioxane	—	58	3
16	DPEphos	Cs_2CO_3	*n*-Hexane	—	69	3
17[h]	DPEphos	Cs_2CO_3	THF	—	56	6
18[i]	DPEphos	Cs_2CO_3	THF	—	80	4
19[j]	Xantphos	—	THF	—	10	23(20[k])



DPEphos DPEphos Xantphos **1a′** **1a″**

[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 CH_3NO_2 as the internal standard. [c] 12 mol% of PPh_3 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.

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



1 **2** **3**

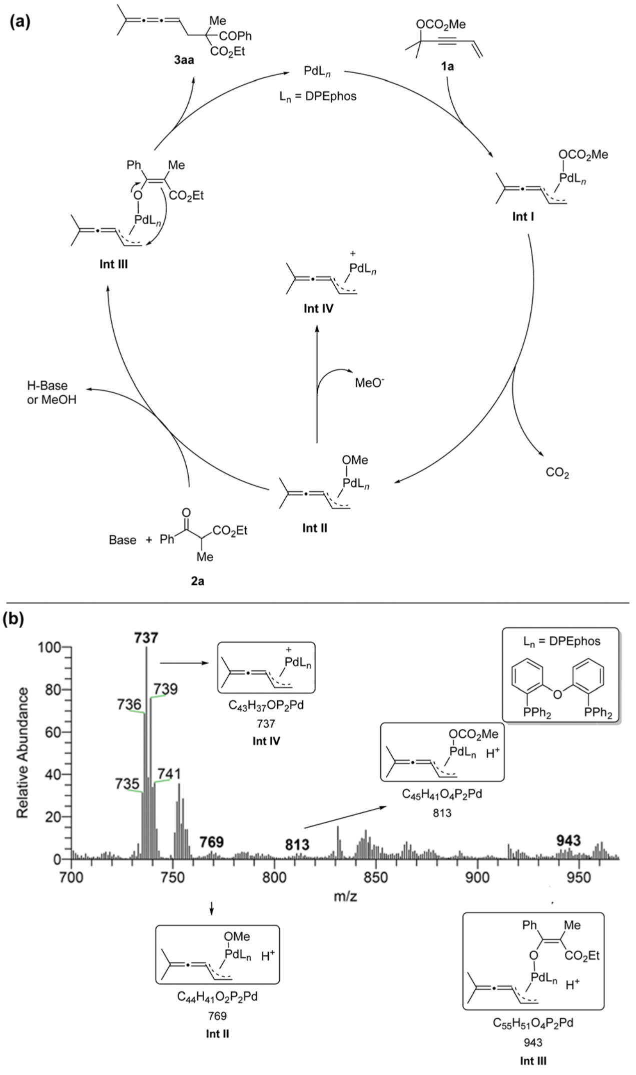
3bb, 81%
3bc, 75%, *r.r.* = 98/2
3bd, 81%, *r.r.* = 97/3
3be, 58%
3bf, 57%, *r.r.* = 97/3
3bg, 87%
3bh, 61%
3bi, 82%, 3 mmol: 82%, 1.1246 g
3bj, 75%
3bk, 50%
3bl, 54%, *r.r.* = 96/4
3bm, 75%
3bn, 82%
3bo, 74%
3bp, 72%
3bq, 60%
3br, 45%
3bs[b], 55%
3aa, 77%, *r.r.* = 96/4
3cb, 76%
3db, 60%
3ea[c], 74%, *r.r.* = 95/5
3fb, 73%, *Z*/*E* = 1/1
3gt[d], 84%, *r.r.* = 99/1
3hu[e], R = CO_2Et: 69%, *Z*/*E* = 1/1, *r.r.* = 97/3
3hb[e], R = COPh: 75%, *Z*/*E* = 1/1, *d.r.* = 1.2/1

[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 Cs_2CO_3 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.

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 (R^3) 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. R^5 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 R^5 group is a heteroaromatic group such as 2-thienyl, the reaction afforded **3bk** in 50% yield. Moreover, the R^5 group may also be an alkyl group affording the corresponding 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, Pd(0)L$_n$ would undergo S$_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$_2$CO$_3$. Then the carbon nucleophile would attack the terminal carbon atom *via* **Int III** to generate the linear selective products **3aa** and Pd(0)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), Pd(OAc)$_2$ (0.01 mmol), DPEphos (0.012 mmol), and Cs$_2$CO$_3$ (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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