

Cite this: *Chem. Commun.*, 2023, 59, 3727

Received 17th December 2022,
Accepted 21st February 2023

DOI: 10.1039/d2cc06871k

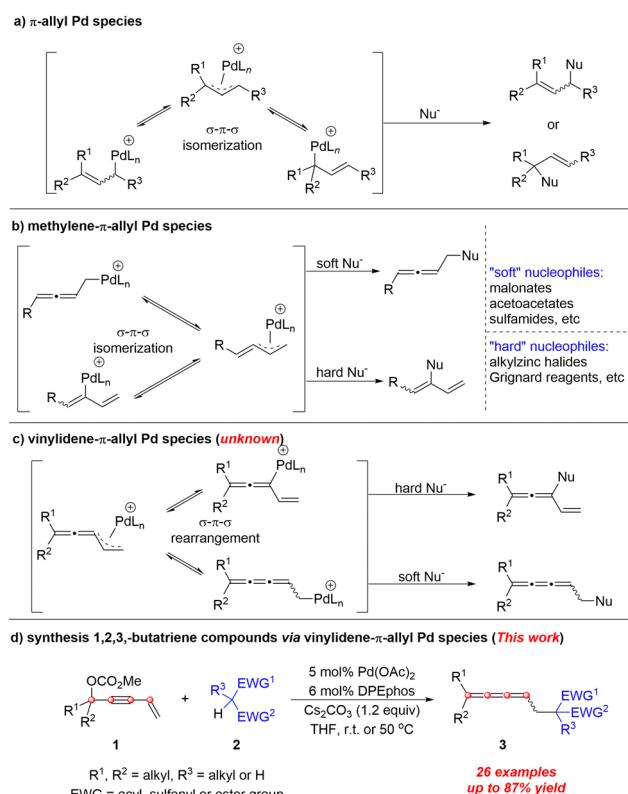
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The reactivity of a new type of organometallic intermediate, vinylidene- π -allyl palladium species, has been demonstrated: the reaction between 4-alken-2-ynyl carbonates and stabilized carbon nucleophiles afforded functionalized 1,2,3,-butatriene 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 $\text{Pd}(\text{OAc})_2$ (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 ^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 Cs_2CO_3 was found to promote the reaction in 81% yield of **3aa** and 3% yield of **4aa**. Although $t\text{BuOLi}$ provided a higher yield than Cs_2CO_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 $\text{Pd}(\text{OAc})_2$ (5 mol%) and DPEphos (6 mol%), replacing THF with other representative solvents such as CH_3CN , 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



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† Electronic supplementary information (ESI) available: General experimental procedures, characterization data, and copies of NMR spectra. CCDC 2108426. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d2cc06871k>

Scheme 1 Profiles of π -allyl palladium species.



Table 1 Optimization of the reaction conditions^a

Entry	Ligand	Base	Solvent	Recovery of 1a ^b (%)		Yield of 3aa ^b (%)	Yield of 4aa ^b (%)
				1a ^b (%)	3aa ^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	tBuOli	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	n-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)	
	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 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

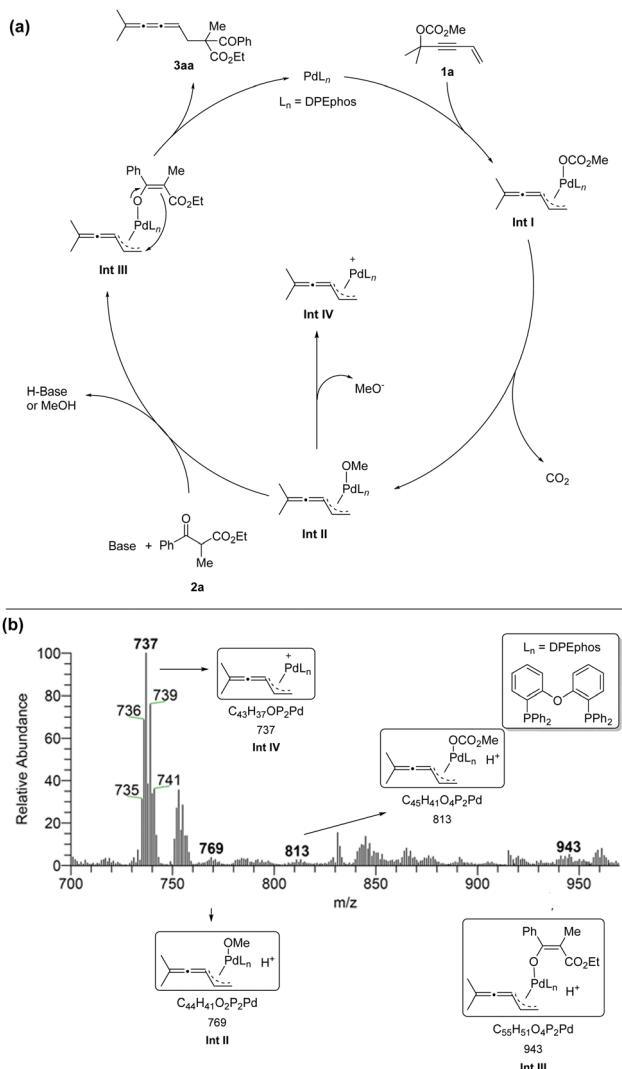
1	2	3
(a)		
(b)		

^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 -ketoster 2n–2p reacted smoothly with 72–82% yields. To our delight, commercially available drugs, such as Indomethacin and Febuxostat derived β -ketoster 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.

Financial support from the National Key R&D Program of China (No. 2021YFA1500100) is greatly appreciated. We also thank Jie Wang in our group for reproducing the results of **3aa**, **3be**, and **3br** presented in Table 2.

Conflicts of interest

There are no conflicts to declare.

Notes and references

- (a) J. Tsuji, H. Takahashi and M. Morikawa, *Tetrahedron Lett.*, 1965, **6**, 4387; (b) B. M. Trost and T. J. Dietsch, *J. Am. Chem. Soc.*, 1973, **95**, 8200.
- For selected reviews on π -allyl Pd species, see: (a) B. M. Trost and D. L. V. Vranken, *Chem. Rev.*, 1996, **96**, 395; (b) B. M. Trost and M. L. Crawley, *Chem. Rev.*, 2003, **103**, 2921; (c) B. M. Trost, M. R. Machacek and A. Aponick, *Acc. Chem. Res.*, 2006, **39**, 747; (d) Z. Lu and S. Ma, *Angew. Chem., Int. Ed.*, 2008, **47**, 258; (e) T. Jensen and P. Fristrup, *Chem. – Eur. J.*, 2009, **15**, 9632; (f) M. Diéguez and O. Pàmies, *Acc. Chem. Res.*, 2010, **43**, 312; (g) B. Sundararaju, M. Achard and C. Bruneau, *Chem. Soc. Rev.*, 2012, **41**, 4467; (h) B. M. Trost, *Org. Process Res. Dev.*, 2012, **16**, 185; (i) N. A. Butta and W. Zhang, *Chem. Soc. Rev.*, 2015, **44**, 7929; (j) B. M. Trost, *Tetrahedron*, 2015, **71**, 5708; (k) Y. Liu, S. Han, W. Liu and B. M. Stoltz, *Acc. Chem. Res.*, 2015, **48**, 740; (l) N. Butt, G. Yang and W. Zhang, *Chem. Rec.*, 2016, **16**, 2687; (m) R. L. Grangea, E. A. Clizbeeb and P. A. Evans, *Synthesis*, 2016, 2911; (n) Y. Wang, L. Lu and W. Xiao, *Chem. – Asian J.*, 2018, **13**, 2174; (o) O. Pàmies, J. Margalef, S. Cañellas, J. James, E. Judge, P. J. Guiry, C. Moberg, Jan-E. Bäckvall, A. Pfaltz, M. A. Pericàs and M. Diéguez, *Chem. Rev.*, 2021, **121**, 4373; For books, see: (p) Transition Metal Catalyzed Enantioselective Allylic Substitution, in *Organic Synthesis*, ed. U. Kazmaier, M. Beller, J. M. Brown, P. H. Dixneuf, A. Fürstner, L. Goofsen, L. S. Hegedus, P. Hofmann, T. Ikariya, L. A. Oro and Q.-L. Zhou, Springer, Heidelberg, 2012; (q) J. Tsuji, *Palladium reagents and catalysts: New perspectives for the 21st century*, Wiley, 2004.
- For the synthesis of allenes *via* methylene- π -allyl Pd species using “soft” nucleophiles, see: (a) M. Ogasawara, H. Ikeda, T. Nagano and T. Hayashi, *J. Am. Chem. Soc.*, 2001, **123**, 2089; (b) Y. Imada, K. Ueno, K. Kutsuwa and S.-I. Murahashi, *Chem. Lett.*, 2002, **140**; (c) M. Ogasawara, K. Ueyama, T. Nagano, Y. Mizuhata and T. Hayashi, *Org. Lett.*, 2003, **5**, 217; (d) M. Ogasawara, H. L. Ngo, T. Sakamoto, T. Takahashi and W. B. Lin, *Org. Lett.*, 2005, **7**, 2881; (e) M. Ogasawara, Y. H. Ge, K. Uetake and T. Takahashi, *Org. Lett.*, 2005, **7**, 5697; (f) M. Ogasawara, H. L. Ngo, T. Sakamoto and T. Takahashi, *J. Org. Chem.*, 2005, **70**, 5764; (g) B. M. Trost, D. R. Fandrick and D. C. Dinh, *J. Am. Chem. Soc.*, 2005, **127**, 14186; (h) Y. Imada, M. Nishida, K. Kutsuwa, S.-I. Murahashi and T. Naota, *Org. Lett.*, 2005, **7**, 5837; (i) M. Ogasawara, L. Y. Fan, Y. H. Ge and T. Takahashi, *Org. Lett.*, 2006, **8**, 5409; (j) Y. Imada, M. Nishida and T. Naota, *Tetrahedron Lett.*, 2008, **49**, 4915; (k) T. Nemoto, M. Kanematsu, S. Tamura and Y. Hamada, *Adv. Synth. Catal.*, 2009, **351**, 1773; (l) B. Q. Wan and S. Ma, *Angew. Chem., Int. Ed.*, 2013, **52**, 441; (m) Z. Wu, F. Berhal, M. M. Zhao, Z. G. Zhang, T. Ayad and V. Ratovelomanana-Vidal, *ACS Catal.*, 2014, **4**, 44; (n) J. X. Dai, X. Y. Duan, J. Zhou, C. L. Fu and S. Ma, *Chin. J. Chem.*, 2018, **36**, 387; (o) B. M. Trost, J. E. Schultz, T. W. Chang and M. R. Madubam, *J. Am. Chem. Soc.*, 2019, **141**, 9521; (p) H. C. Liu, Y. Z. Hu, Z. F. Wang, H. Y. Tao and C. J. Wang, *Chem. – Eur. J.*, 2019, **25**, 8681; (q) N. J. Adamson, H. Judd and S. J. Malcolmson, *J. Am. Chem. Soc.*, 2019, **141**, 8574; (r) H. Tsukamoto, T. Konno, K. Ito and T. Doi, *Org. Lett.*, 2019, **21**, 6811; (s) S. H. Song, J. Zhou, C. L. Fu and S. Ma, *Nat. Commun.*, 2019, **10**, 507; (t) S. H. Song and S. Ma, *Chin.*



- J. Chem.*, 2020, **38**, 1233; (u) S. Q. Yang, Y. F. Wang, W. C. Zhao, G. Q. Lin and Z. T. He, *J. Am. Chem. Soc.*, 2021, **143**, 7285; (v) J. Z. Xiao, H. B. Xu, X. H. Huo, W. B. Zhang and S. Ma, *Chin. J. Chem.*, 2021, **39**, 1958; (w) Y. C. Zhang, X. Zhang and S. Ma, *Nat. Commun.*, 2021, **12**, 2416; (x) C. F. Huang, F. C. Shi, Y. F. Cui, C. Li, J. Lin, Q. Liu, A. N. Qin, H. N. Wang, G. L. Wu, P. L. Wu, J. Z. Xiao, H. B. Xu, Y. Yuan, Y. Z. Zhai, W. F. Zheng, Y. Zheng, B. Yu and S. Ma, *Chem. Sci.*, 2021, **12**, 9347; (y) J. C. Zhang, X. H. Huo, J. Z. Xiao, L. Zhao, S. Ma and W. B. Zhang, *J. Am. Chem. Soc.*, 2021, **143**, 12622.
- 4 For the synthesis of 1,3-dienes *via* methylene- π -allyl Pd species using organic metal reagents as nucleophiles, see: (a) Y. D. Djahanbini, B. Cazes and J. Gore, *Tetrahedron Lett.*, 1984, **25**, 203; (b) J. S. Schneekloth Jr., M. Puchault and C. M. Crews, *Eur. J. Org. Chem.*, 2007, 40.
- 5 For the synthesis of 1,3-dienes *via* methylene- π -allyl Pd species using Organoboronic acids as nucleophiles, see: (a) M. Yoshida, T. Gotou and M. Ihara, *Chem. Commun.*, 2004, 1124; (b) T. Liu, J. Dong, S. J. Cao, L. C. Guo and L. Wu, *RSC Adv.*, 2014, **4**, 61722; (c) D. J. Lippincott, R. T. H. Linstadt, M. R. Maser and B. H. Lipshutz, *Angew. Chem., Int. Ed.*, 2017, **56**, 847; (d) D. J. Lippincott, R. T. H. Linstadt, M. R. Maser, F. Gallou and B. H. Lipshutz, *Org. Lett.*, 2018, **20**, 4719; (e) R. W. Brown, F. Zamani, M. G. Gardiner, H. B. Yu, S. G. Pyne and C. J. T. Hyland, *Chem. Sci.*, 2019, **10**, 9051.
- 6 For the synthesis of 1,3-dienes *via* carbonylation of methylene- π -allyl Pd species, see: (a) J. Nokami, A. Maihara and J. Tsuji, *Tetrahedron Lett.*, 1990, **31**, 5629; (b) K. Uemura and Y. Inoue, *Appl. Organomet. Chem.*, 2000, **14**, 8.
- 7 For the synthesis of 1,3-dienes *via* methylene- π -allyl Pd species using terminal alkynes as nucleophiles, see: (a) Y. Tao Xia, J. J. Wu, C. Y. Zhang, M. Mao, Y. G. Ji and L. Wu, *Org. Lett.*, 2019, **21**, 6383; (b) M. J. Sowden, J. S. Ward and M. S. Sherburn, *Angew. Chem., Int. Ed.*, 2020, **59**, 4145.
- 8 M. Mao, L. Zhang, Y. Z. Chen, J. Zhu and L. Wu, *ACS Catal.*, 2017, **7**, 181.
- 9 J. Lin, T. H. Zhu, M. Q. Jia and S. Ma, *Chem. Commun.*, 2019, **55**, 4523.
- 10 (a) Y. Wang, W. Zhang and S. Ma, *J. Am. Chem. Soc.*, 2013, **135**, 11517; (b) H. N. Wang, H. W. Luo, Z. M. Zhang, W. F. Zheng, Y. Yin, H. Qian, J. L. Zhang and S. Ma, *J. Am. Chem. Soc.*, 2020, **142**, 9763–9771.
- 11 J. T. Zhang, H. Y. Wang, W. Zhu, T. T. Cai and Y. L. Guo, *Anal. Chem.*, 2014, **86**, 8937.

