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Cite this: *Chem. Sci.*, 2023, **14**, 7709

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 8th April 2023
Accepted 20th June 2023

DOI: 10.1039/d3sc01849k

rsc.li/chemical-science

A Pd-catalyzed highly selective three-component protocol for trisubstituted allenes†

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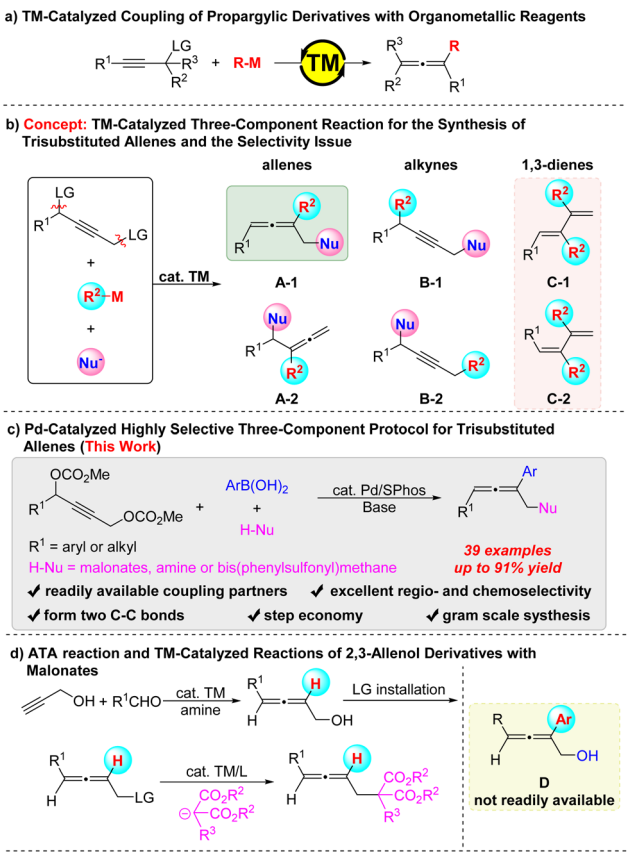
Herein we report the first example of a Pd-catalyzed highly selective three-component reaction of alkynyl-1,4-diol dicarbonates, organoboronic acids, and malonate anions for the efficient synthesis of trisubstituted 2,3-allenyl malonates not readily available by the known protocols. The reaction demonstrates an excellent regio- and chemo-selectivity for both the oxidative addition referring to the two C–O bonds and the subsequent coupling with the nucleophile with a remarkable functional group compatibility. A series of control experiments confirm a unique mechanism involving β-O elimination forming alka-1,2,3-triene and the subsequent insertion of its terminal C=C bond into the Ar–Pd bond.

Introduction

Allenes have attracted significant attention[1] in the fields of natural products,[2] modern organic synthesis,[3,4] medicinal chemistry,[5] and materials science,[6] and thus, much attention has been paid to the development of new methodologies for the syntheses of allenes from readily available starting chemicals.[7] Among them, a two-component reaction between readily available alkynes with an appropriate propargylic leaving group and organometallic reagents has been developed as a straightforward method for the syntheses of allenes[8] (Scheme 1a). We envisioned a new concept of Pd-catalyzed reaction of readily available 2-alkynyl-1,4-diol dicarbonate with an organometallic reagent and a nucleophile for allene synthesis (Scheme 1b). As we know the Pd-catalyzed reaction of 2-alkynyl-1,4-diol dicarbonate with organometallic reagents would afford the double coupling products, 1,3-dienes **C**.[9] Thus, the challenges of this strategy are (1) the regioselectivity of the oxidative additions of the two different C–O bonds in the dicarbonate; (2) the selectivity issue for the formation of different allenes **A-1** or **A-2**, alkynes **B-1** or **B-2**, or 1,3-conjugated dienes **C-1** or **C-2** (Scheme 1b). Herein, we report our realization of the first example of a Pd-catalyzed three-component reaction of 2-alkynyl-1,4-diol dicarbonates with organoboronic acids and malonates, affording trisubstituted allenes **4** (ref. 10 and 11) exclusively, enjoying an excellent regio- and chemo-selectivity with an unprecedented mechanism (Scheme 1c). Such **A-1**-type allenyl malonates have been demonstrated as highly versatile building blocks for natural allene product synthesis[12] and are traditionally prepared *via*



Scheme 1 Approaches to trisubstituted allenes.

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† Electronic supplementary information (ESI) available: General experimental procedures, characterization data, and copies of NMR spectra. CCDC 2202991. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d3sc01849k

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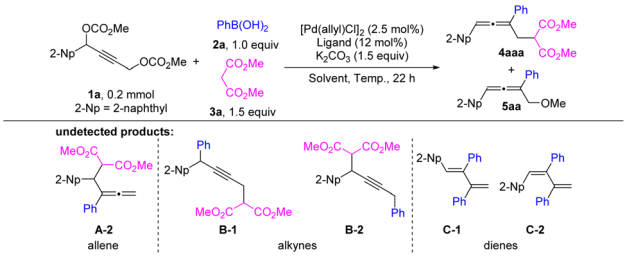
the transition metal catalyzed reactions of 2,3-allenol derivatives with malonates.[13,14] Although the precursors for 2,4-disubstituted 2,3-allenol derivatives, 2,3-allenols, are conveniently available *via* allenation of the propargyl alcohol (ATA) with aldehydes[15,16] (Scheme 1d), the current method is highly efficient and diverse due to the readily availability of the three starting materials and irreplaceable due to the inaccessibility of **D**-type allenols *via* the ATA reaction.

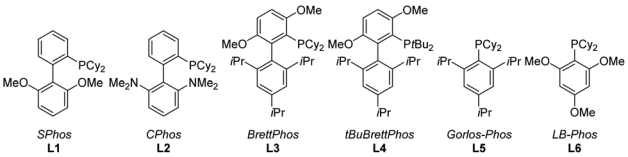
Results and discussion

At the outset, we examined the reaction of 2-alkynyl-1,4-diol dicarbonate **1a**, phenylboronic acid **2a**, and dimethyl malonate **3a** in the presence of $[Pd(allyl)Cl]_2$, SPhos (**L1**),[9a] and K_2CO_3 (Table 1, entry 1) at room temperature in THF for 22 h. To our delight, the allene product **4aaa** was obtained albeit in only 36% yield with 56% yield of an unexpected by-product, 2,3-allenyl methyl ether **5aa**. Other allenes **A-2**, alkynes **B-1** and **B-2**, or conjugated dienes **C-1** and **C-2** were not detected, indicating exclusive chemo- and regio-selectivity. It is quite surprising to note that the oxidative addition occurred with the sterically more crowded secondary C–O bond. The study on the ligand effect indicated that although **L2** or **L3** led to a better yield for allene product **4aaa**, a small amount of dicarbonate **1a** was also recovered (Table 1, entries 2 and 3). No reaction occurred with bulkier ligand **L4** (Table 1, entry 4). Since Gorlos-Phos (**L5·HBF$_4$**) and LB-Phos (**L6·HBF$_4$**)[17] were fully ineffective for this reaction (Table 1, entries 5 and 6), **L1** was applied for further screening. The base was proven to be essential (Table 1, entry 7) and slightly increasing the loading of K_2CO_3 would improve the yield of **4aaa** to 41% (Table 1, entry 8). By running the reaction at 50 °C, the yield of **4aaa** could be improved to 77% together with 15% of 2,3-allenyl methyl ether **5aa** (Table 1, entries 9–11). Solvent screening led to the observation that DCE was the best furnishing product **4aaa** in 88% yield (Table 1, entries 12–16). A reaction with 1.0 mmol furnished a slightly better result with **4aaa** being isolated in 91% yield (Table 1, entry 17).

Table 1 Optimization of the reaction conditions[a]



Entry	Ligand	Solvent	Temp.	Yield of **4aaa**/**1a** recovered/yield of **5aa**[b] %
1	**L1**	THF	r.t.	36/0/56
2	**L2**	THF	r.t.	49/10/24
3	**L3**	THF	r.t.	48/23/12
4	**L4**	THF	r.t.	0/71/0
5	**L5·HBF$_4$**	THF	r.t.	0/90/0
6	**L5·HBF$_4$**	THF	r.t.	0/84/0
7[c]	**L1**	THF	r.t.	0/99/0
8[d]	**L1**	THF	r.t.	41/0/53
9[d]	**L1**	THF	30 °C	46/0/49
10[d]	**L1**	THF	40 °C	64/0/26
11[d]	**L1**	THF	50 °C	77/0/15
12[d,e]	**L1**	DCE	50 °C	88/0/0
13[d,e]	**L1**	Toluene	50 °C	32/0/53
14[d,e]	**L1**	EtOAc	50 °C	83/0/4
15[d,e]	**L1**	CH_3CN	50 °C	69/0/0
16[d,e]	**L1**	1,4-Dioxane	50 °C	80/0/0
17[d,e,f]	**L1**	DCE	50 °C	94 (91)[g]/0/0



[a] Reaction conditions: **1a** (0.2 mmol), **2a** (1.0 equiv.), **3a** (1.5 equiv.), $[Pd(allyl)Cl]_2$ (2.5 mol%), ligand (12 mol%), and base in solvent unless otherwise noted. [b] Determined by ^1H NMR analysis of the crude product using CH_2Br_2 as the internal standard. [c] The reaction was run in the absence of K_2CO_3. [d] 2.0 equiv. of K_2CO_3 were used. [e] The reaction was run for 24 h. [f] The reaction was carried out on a 1 mmol scale. [g] Isolated yield.

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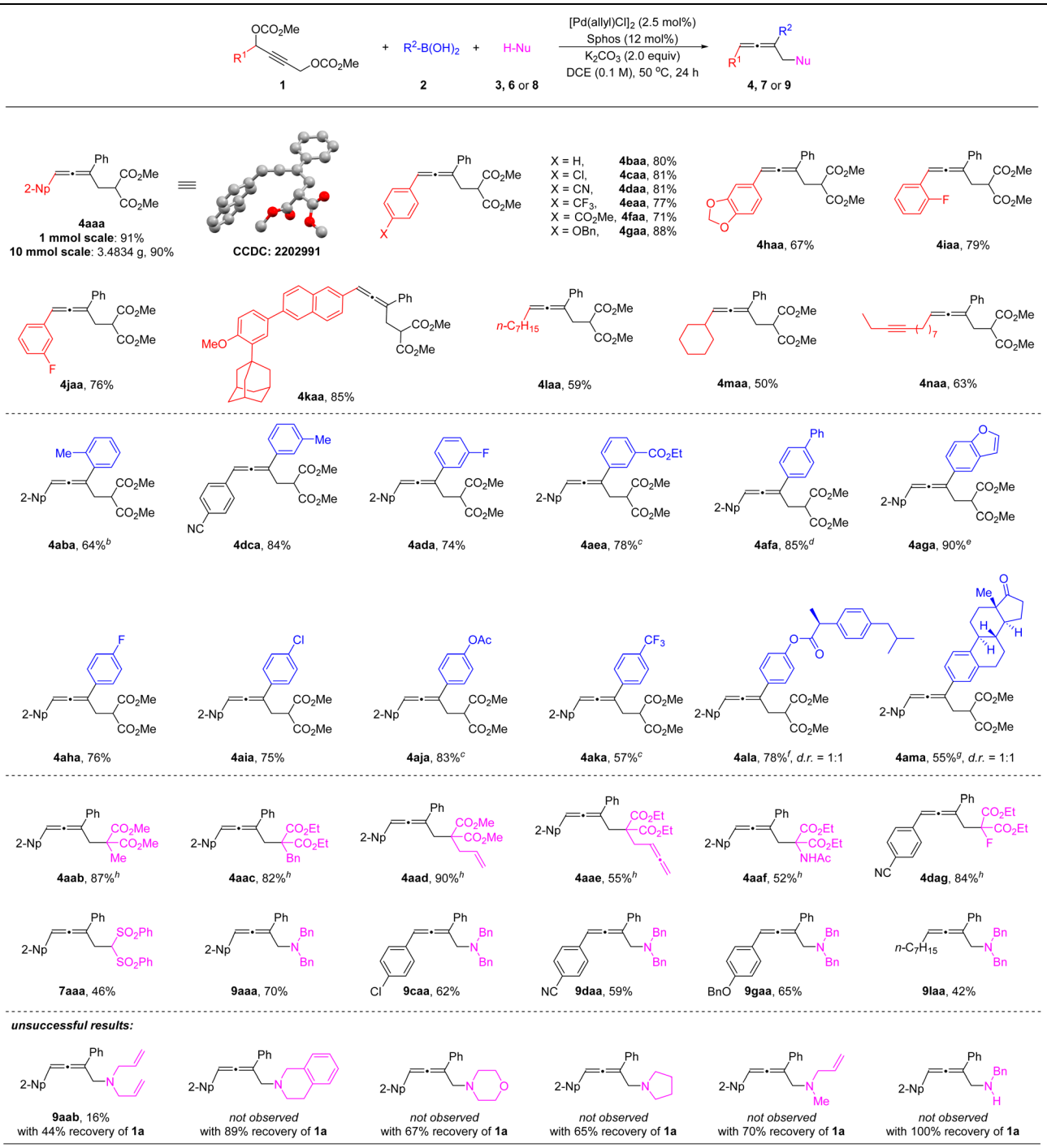
After establishing the optimal conditions, we turned to investigate the scope of 2-alkynyl-1,4-diol dicarbonates **1** (Table 2). The reaction could be applied to a wide range of substrates **1** bearing either electron-poor (**1c–1f**) or electron-rich (**1g–1h**) aryl groups (R^1) generating the corresponding allene products **4** in 67–88% yields. Interestingly, *ortho*-fluoro (**1i**) and

Table 2 The scope studies[a]



[a] Unless otherwise indicated, the reaction was performed with 1 mmol of **1**, 1.0 equiv. of **2**, 1.5 equiv. of **3**, **6** or **8**, 2.5 mol% of $[Pd(allyl)Cl]_2$, 12 mol% of SPhos, and 2.0 equiv. of K_2CO_3 in DCE (0.1 M) at 50 °C for 24 h. Yields of isolated products are given. [b] 5 mol% of $[Pd(allyl)Cl]_2$ and 24 mol% of SPhos were used. The reaction was run for 48 h. [c] 3.5 mol% of $[Pd(allyl)Cl]_2$ and 15 mol% of SPhos were used. The reaction was run for 36 h. [d] 3.5 mol% of $[Pd(allyl)Cl]_2$, 15 mol% of SPhos, and 2.0 equiv. of **3a** were used. The reaction was run for 36 h. [e] The reaction was run for 36 h. [f] 3.5 mol% of $[Pd(allyl)Cl]_2$ and 15 mol% of SPhos were used. The reaction was run for 48 h. [g] 2.0 equiv. of Cs_2CO_3 were used instead of K_2CO_3. The reaction was run for 48 h. [h] The reaction was performed with 1 mmol of **1**, 1.0 equiv. of **2a**, 2 equiv. of **3**, 3.5 mol% of $[Pd(allyl)Cl]_2$, 15 mol% of SPhos, and 2.0 equiv. of Cs_2CO_3 in DCE (0.1 M) at 50 °C for 48 h.

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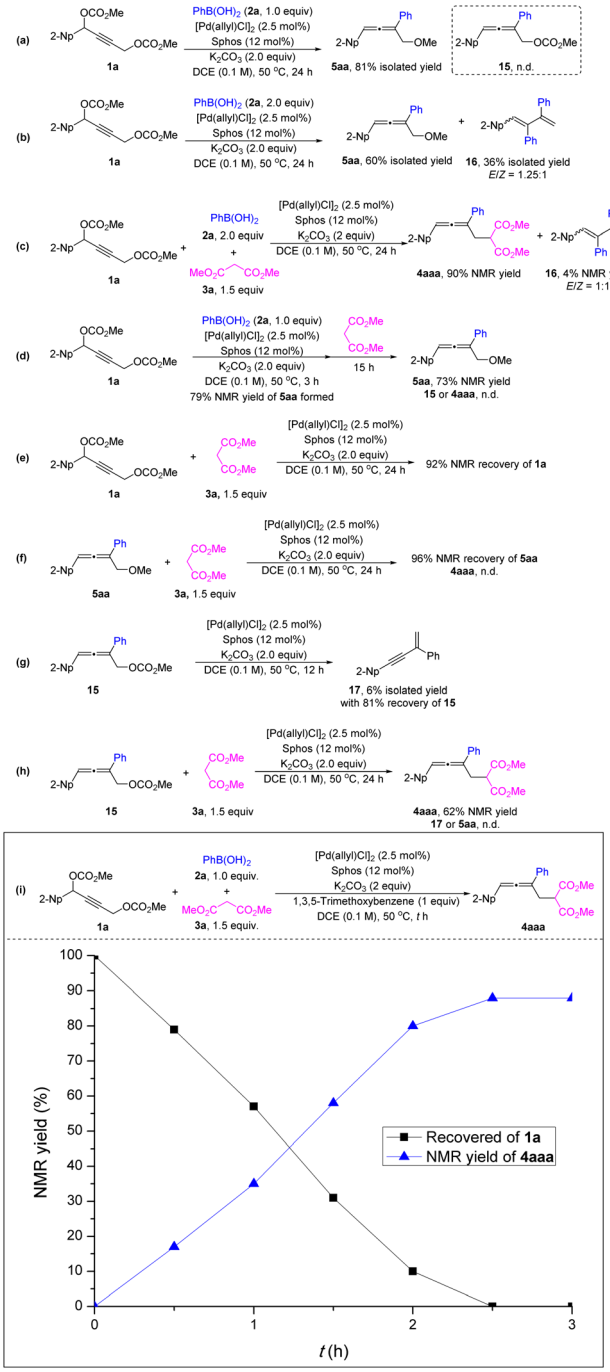
meta-fluoro (**1j**) substituted substrates were accommodated to afford the multi-functionalized allene products **4iaa** and **4jaa**. Delightedly, commercial drug adapalene derived 2-alkynyl-1,4-diol dicarbonate **1k** could also afford the desired allene **4kaa** in an excellent yield. Moreover, R^1 may also be an alkyl group (**4laa–4naa**). Next, the substrate scope of the organoboronic acid **2** was studied. Obviously, the electronic nature of the organoboronic acids has a limited impact on the reactivity affording the allene products **4aba–4aka** in up to 90% yields. Bioactive molecules, such as ibuprofen and estrone, modified organoboronic acids could also be applied, delivering products **4ala** and **4ama** in moderate yields. The practicality was demonstrated by the gram scale reaction of **1a** with **2a** and **3a** affording 3.5 g of product **4aaa** in 90% yield under 50 °C for 24 h. The structure of **4aaa** was further confirmed by single-crystal X-ray diffraction.[18]

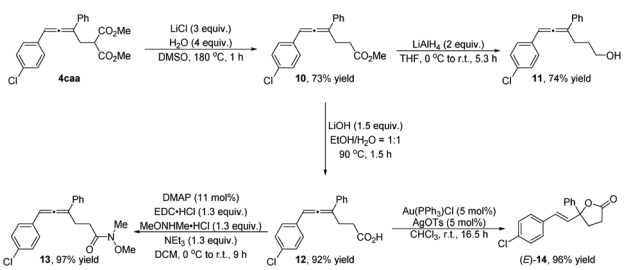
With 2-substituted malonates **3**, K_2CO_3 should be replaced with Cs_2CO_3 for complete transformation obviously due to the steric effect. Methyl, benzyl, allyl and 2,3-allenyl groups may be introduced into the 2-position of malonates to prepare allenes **4aab–4aac**, 1,6-vinylallene **4aad**, and bisallene **4aae** in moderate to excellent yields. The protocol also works for 2-acetamidomalonate **3f** and 2-fluoromalonate **3g**. Besides, bis(phenylsulfonyl)methane **6a** and dibenzylamine **8a**[19] could also serve as suitable nucleophiles to deliver the desired products **7** and **9** in moderate to high yields (42–73%). Diallylamine **8b** could provide the desired product **9aab** in 16% yield with 44% recovery of **1a**. Other amines such as tetrahydroisoquinoline, morpholine, pyrrolidine, *N*-allylmethylamine and benzylamine were also studied; however, no corresponding allenyl amine products were obtained.

To demonstrate the synthetic potential of this methodology, synthetic transformations of **4caa** have been demonstrated (Scheme 2): firstly, Krapcho decarboxylation was achieved, affording 4,5-allenoate **10** in 73% yield;[20] reduction of **10** with $LiAlH_4$ formed 4,5-allenol **11** in 74% yield; 4,5-allenoic acid **12** could be yielded by its treatment with LiOH; next, Weinreb amide **13** could be obtained in high yield by using *N*,*O*-dimethylhydroxylamine hydrochloride; gold(I)-catalyzed butyrolactone (*E*)-**14** in 96% yield with an exclusive *E*-selectivity.[21]

To gain insight into the mechanism, a couple of control experiments were performed (Scheme 3): at first, the reaction of 2-alkynyl-1,4-diol dicarbonate **1a** with 1 equiv. of phenylboronic acid **2a** under the standard conditions for 24 h afforded 2,3-allenyl methyl ether **5aa** in 81% yield (Scheme 3(a)); by



Scheme 3 Mechanistic studies.



Scheme 2 Synthetic applications.

increasing the loading of **2a** to 2 equiv., the conjugated diene **16** was obtained in 36% yield ($E/Z = 1.25:1$) together with 60% yield of allenylic ether **5aa** (Scheme 3(b)); a control experiment showed that only 4% yield ($E/Z = 1:1$) of conjugated diene **16** was formed when 2 equiv. of **2a** were applied under the standard reaction conditions together with allenylic malonate **4aaa** being formed in 90% yield (Scheme 3(c)); interestingly, when **1a** was treated with phenylboronic acid **2a** (1 equiv.) for 3 h, ether **5aa** was already formed in 79% NMR yield. The subsequent addition of malonate **3a** (1.5 equiv.) led to the formation of ether

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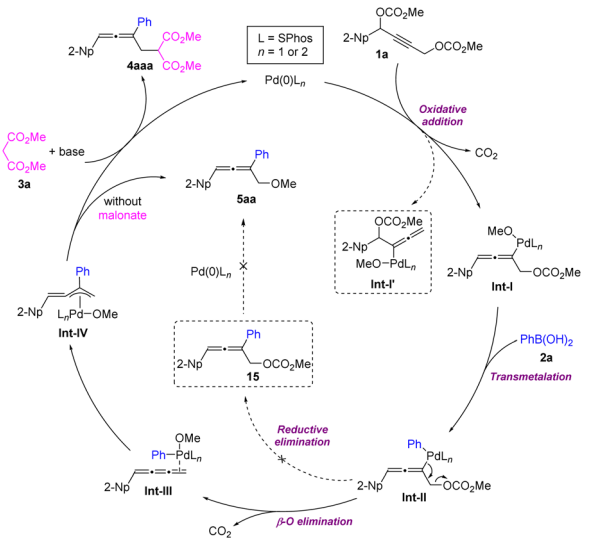
5aa in 73% yield, exclusively (Scheme 3(d)); when the reaction of 2-alkynyl-1,4-diol dicarbonate **1a** and malonate **3a** was conducted in the absence of phenylboronic acid **2a**, no products were observed with complete recovery of **1a**, indicating the importance of phenylboronic acid for the transformation (Scheme 3(e)). Furthermore, the reaction of ether **5aa** with 1.5 equiv. of **3a** under the standard conditions failed to afford the product **4aaa**, indicating that 2,3-allenyl methyl ether **5aa** is certainly not the intermediate for the formation of **4aaa** (Scheme 3(f)). We then deliberately prepared the envisioned intermediate, methyl 2,3-allenyl carbonate **15**. Its reaction under the standard conditions afforded 6% yield of 1,3-enyne **17** with 81% recovery (Scheme 3(g)); the reaction of allenylic carbonate **15** with malonate **3a** under the standard conditions in 24 h afforded **4aaa** in a lower yield of 62% without the formation of 1,3-enyne **17** or allenylic ether **5aa**, as compared with the three-component reaction (Scheme 3(h)). The reaction of **1a** in the presence of phenylboronic acid **2a** and malonate **3a** was also monitored and the formation of **15** was not observed during the whole reaction time (Scheme 3(i)). These experiments (Scheme 3(g)–(i)) indicated that **15** is not the intermediate product for the formation of either **4aaa** or ether **5aa** under the current reaction conditions.

Based on these experimental mechanistic studies, we proposed a plausible mechanism as shown in Scheme 4: initially, the oxidative addition occurred unexpectedly with the sterically more crowded secondary C–O bond exclusively to afford the allenyl palladium species **Int-I** rather than its regioisomer **Int-I′**, most probably due to the steric effect in these two intermediates. **Int-I** would undergo transmetalation exclusively with boronic acid **2a** to generate the intermediate **Int-II**. **Int-II** would prefer β-O elimination over reductive elimination, affording 1,2,3-butatriene-coordinated palladium intermediate **Int-III**. Reductive elimination could be ruled out by the monitoring experiment showing that the formation of **15** was not observed during the whole reaction time. Subsequently, highly regioselective insertion of the terminal C=C bond of the 1,2,3-butatriene into Ph-PdL$_n$OMe formed methylene-π-allyl Pd species **Int-IV**. After deprotonation of malonate **3a** and nucleophilic attack, product allene **4aaa** was afforded and the catalytically active Pd(0) species was regenerated, finishing the catalytic cycle. In the absence of malonate, reductive elimination would afford the methyl ether **5aa**.



Scheme 4 Proposed mechanism.

Conclusions

In conclusion, a novel protocol to synthesize trisubstituted allenes from 2-alkynyl-1,4-diol dicarbonate with organoboronic acid and malonate has been developed. The method utilizes readily available coupling partners, affording trisubstituted double functionalized allenes in an excellent regio- and chemoselectivity while enjoying a broad substrate scope and step-economy. It should be noted that such 2,2,4-trisubstituted allenyl malonates require lengthy steps *via* known protocols (see Scheme S1†). A unique mechanism involving β-O elimination forming 1,2,3-alkatrienes has been proposed. This reaction provides a new entity for the syntheses of multiple substituted allenes. Further studies, including the asymmetric version of this reaction, are being conducted in our laboratory.

Data availability

All experimental data and detailed procedures are available in the ESI.†

Author contributions

S. M. directed the research and developed the concept of the reaction with C. L., who also performed most of the experiments and prepared the ESI. Z. Z. also performed some of the experiments. C. L. and S. M. checked the experimental data. C. L. and S. M. wrote the manuscript with contributions from the other authors.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Financial support from the National Natural Science Foundation of China (No. 21988101) and National Key R&D Program of China (No. 2021YFA1500100) is greatly appreciated. We also thank Weiyi Wang in our group for reproducing the results of **4baa**, **4laa**, and **4aab** presented in Table 2.

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