OL | Organic Letters

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

Letter

pubs.acs.org/OrgLett

Vinylethylene Carbonates as α,β-Unsaturated Aldehyde Surrogates for Regioselective [3 + 3] Cycloaddition

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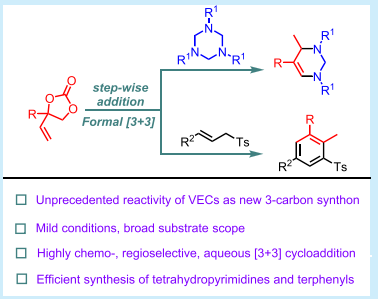
Supporting Information

ABSTRACT: Herein, we report a novel stepwise addition-controlled ring size method, to access tetrahydropyrimidines through an operationally simple [3 + 3] cycloaddition of vinylethylene carbonates with triazinanes. Interestingly, we could also use this method for a [3 + 3] oxidative cycloaddition, which allows the facile synthesis of polysubstituted terphenyls under mild conditions. Mechanistic studies suggest that vinylethylene carbonates could generate α,β-unsaturated aldehydes as 3-carbon synthons for cycloaddition via a combination process of Pd-catalyzed decarboxylation and β-H elimination.



The divergent cycloaddition of identical starting material by judicious choice of parameters, such as catalysts, ligands, solvents, etc., is a powerful approach to generate diverse molecular scaffolds and to expand the chemical space.[1] Despite the significant recent advances in divergent cycloaddition, the development of a new method to realize divergent cycloaddition still represents an important goal in organic synthesis and is highly appealing. As part of an overarching goal to develop new modes for divergent cycloaddition, we questioned whether the different intermediate species could be captured under stepwise addition. However, one fundamental challenge would be associated with the development of such a method. If intermediates species are thermodynamically unstable and reversible under stepwise addition mode, they could easily return to the starting state.[2]

Recently, vinylethylene carbonates (VECs) have emerged as promising dipole precursors to generate zwitterionic π-allyl palladium intermediates,[3] and they have been successfully used for various cycloadditions (Figure 1a). Seminal works from Zhang and co-workers took advantage of VECs as a *3-atom (3C, 5O) synthon* to engage in asymmetric [3 + 2] cycloadditions and constructed a series of useful five-membered heterocycles.[4] Subsequently, the group of Zhao,[5] Glorious,[6] Xiao/Lu,[7] Guo,[8] and others[3e,9] reported that VECs could serve as a 5-atom *(1C, 5O) synthon* for forming heterocyclic compounds with a challenging larger ring or medium-sized ring. Notably, all these reported synthons were exclusively generated via a single decarboxylation process.

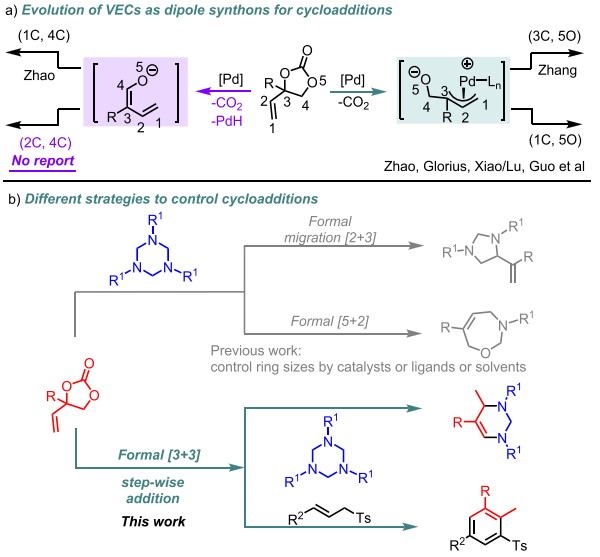


Figure 1. Evolution of VECs and our new discovery.

More recently, increasing attention has been devoted to explore VECs as novel synthons for cycloaddition through a combination process of decarboxylation and β-H elimination, thus enabling a diverse range of compound libraries to build.

Received: July 2, 2019

DOI: 10.1021/acs.orglett.9b02266
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Until now, only one elegant formal [4 + 2] cycloaddition of VECs by the utilization of a *(1C, 4C) synthon* formed via decarboxylation and β-H elimination was disclosed by Zhao.[10] However, to the best of our knowledge, the formal cycloaddition by utilizing VECs as a *3-atom (2C, 4C) synthon* via decarboxylation and β-H elimination has not yet been demonstrated. Undoubtedly, generating the intermediate with the reactivity of a 3-atom synthon *(2C, 4C) synthon* via *stepwise addition* would be a challenging issue because a *2-atom (1C, 2C) synthon* or *5-atom (1C, 5O) synthon* might become the predominant intermediate in the reaction.[5a,9c] Herein, we demonstrate how this method can be translated into the novel [3 + 3] cycloaddition between VECs and 1,3,5-triazinanes[1e,9c,11] or allylic sulfones that would be difficult to implement with other strategies (Figure 1b). Specifically, these reactions provide efficient and environmentally benign methods to synthesize tetrahydropyrimidines[12] and polysubstituted terphenyls[13] which represent two classes of therapeutic agents with multiple biological activities.

To validate the feasibility of aforementioned divergent cycloaddition via stepwise addition, our initial reaction was carried out by subjecting 4-phenyl-4-vinyl-1,3-dioxolan-2-one (**1a**) to our previous established conditions[9c] utilizing $Pd(COD)Cl_2$ as catalyst, Xantphos as ligand, AgTFA as additive in dichloromethane (DCM) at 80 °C for 2 h. After then, 1,3,5-triphenyl-1,3,5-triazinane (**2a**) was added into the above mixture and was stirred at 80 °C for additional 2 h. Gratifyingly, when we used this stepwise addition, the regioselectivity was totally changed and a formal [3 + 3] cycloaddition product **5aa** was obtained in 16% yield under the other identical conditions (Figure 2). The unexpected result

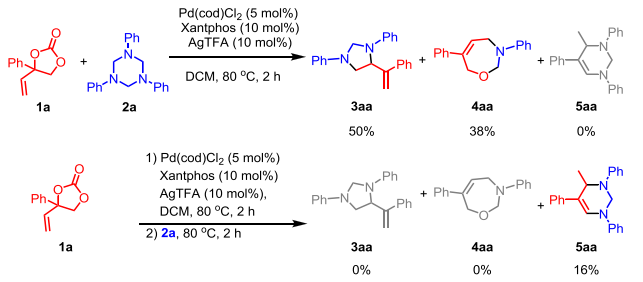
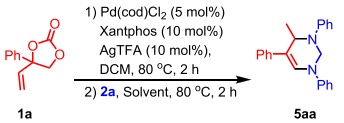


Figure 2. Initial discovery of formal [3 + 3] cycloaddition through stepwise addition mode.

could be attributed to the **2a**, which could suppress the key intermediate formation under previous conditions.[9c] This proof-of-principle result obviously demonstrated that using stepwise addition to control cycloaddition was feasible.

Encouraged by the preliminary results, we further attempted to increase the yield of the **5aa** by tuning reaction parameters under stepwise addition. It should be noted that the optimized conditions for the full conversion of **1a** in the first step have been established. Therefore, we only have to improve the efficiency of this formal [3 + 3] cycloaddition in the addition step of **2a** which is the rate-determining step. As summarized in Table 1, the reaction was profoundly affected by the solvents and the commonly used organic solvents including toluene, THF, and 1,4-dioxane are not suitable for this reaction. Conversely, the use of pure water or organic solvent with excess water is likely beneficial for **5aa** formation. It was found that the yield of **5aa** was significantly improved to 58% when the reaction was carried out in aqueous methanol (Table 1,

Table 1. Optimization of Pd-Catalyzed Formal [3 + 3] Cycloaddition[a]



entry	catalyst	**2a** (equiv)	solvent	yield (%)[b]
1	$Pd(COD)Cl_2$	0	DCM	–
2	$Pd(COD)Cl_2$	1.2	DCM	16
3	$Pd(COD)Cl_2$	1.2	toluene	10
4	$Pd(COD)Cl_2$	1.2	THF	15
5	$Pd(COD)Cl_2$	1.2	1,4-dioxane	20
6	$Pd(COD)Cl_2$	1.2	H_2O	52
7	$Pd(COD)Cl_2$	1.2	THF/H_2O (1/2)	40
8	$Pd(COD)Cl_2$	1.2	THF/H_2O (2/1)	30
9	$Pd(COD)Cl_2$	1.2	$DMSO/H_2O$ (1/2)	38
10	$Pd(COD)Cl_2$	1.2	DMF/H_2O (1/2)	55
11	$Pd(COD)Cl_2$	1.2	$EtOH/H_2O$ (1/2)	52
12	$Pd(COD)Cl_2$	1.2	*i*-$PrOH/H_2O$ (1/2)	41
13	$Pd(COD)Cl_2$	1.2	$MeOH/H_2O$ (1/2)	58
14	$Pd(COD)Cl_2$	1.5	$MeOH/H_2O$ (1/2)	64
15	$Pd(COD)Cl_2$	2	$MeOH/H_2O$ (1/2)	75(71)

[a]Reaction conditions: **1a** (0.05 mmol), **2a** (0.06 mmol), Pd catalyst (5 mol %), Xantphos (10 mol %), AgTFA (10 mol %), solvent (2 mL) at 80 °C for 2 h. [b]Yields were determined by the ^1H NMR using CH_2Br_2 as the internal standard; isolated yield was given in parentheses.

entry 13). Additionally, further examining the amounts of **2a** showed that 2 equiv of **2a** could give the best result, affording **5aa** in 71% isolated yield (Table 1, entry 15).

After establishing the optimal reaction conditions for the controllable formal [3 + 3] cycloaddition reaction, we next examined the substrate scope with respect to various VECs and 1,3,5-triazinanes (Scheme 1). This reaction was applicable to broad functional group substituted VEC substrates, including methyl (**5ca**, **5da**), methoxy (**5fa**), ether (**5ha**), chloro (**5na**), bromo (**5ma**), and ester groups (**5qa**). It should be noted that all products were formed through a formal [3 + 3] cycloaddition process, in which a zwitterionic π-allyl palladium intermediate as 3-carbon synthon was discovered for the first time. Inspired by the fact that physical and biological properties of fluorine atom are central to the function of many drugs, we treated the monofluoro (**5ja**, **5ka**), difluoro (**5la**), and trifluoromethyl (**5oa**) substituted VECs to the standard conditions, which provided the corresponding products in acceptable yields. It is worth mentioning that the deuterated substrate was effective for this transformation (**D-5aa**) as well, providing access to a product of pharmacokinetic value given the unique properties of the deuterium atom. Furthermore, triazinane partners bearing different functional groups were suitable substrates for this cycloaddition to furnish the desired **5ab**–**5ae** in good isolated yield. To demonstrate the practicability of this transformation, a gram-scale reaction was carried out and the corresponding product **5ab** was easily obtained in 51% yield.

Given that the polysubstituted terphenyls are prevalent in bioactive molecules and nature products, we next turned our attention to the construction of these compounds by using the same method (Scheme 2). After substrate **1a** was completely converted to the intermediate, the allylic sulfone **6a** was added

DOI: 10.1021/acs.orglett.9b02266
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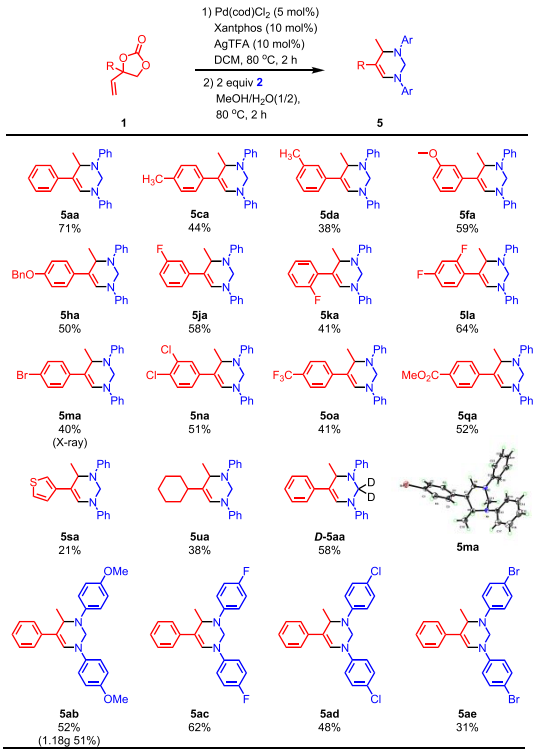
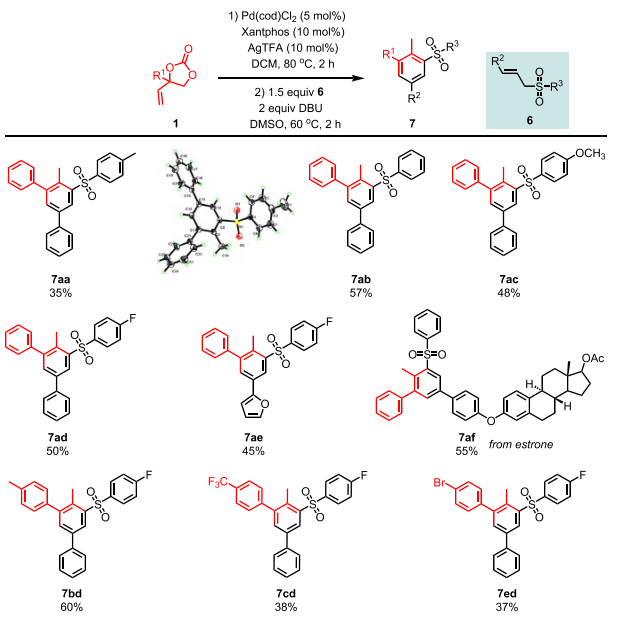
Scheme 1. Substrate Scope of Formal [3 + 3] Cycloaddition in the Synthesis of Tetrahydropyrimidines



[a]Isolated yields are indicated below each structure (Supporting Information gives the experimental details).

Scheme 2. Substrate Scope of Formal [3 + 3] Cycloaddition in the Synthesis of Polysubstituted Terphenyls

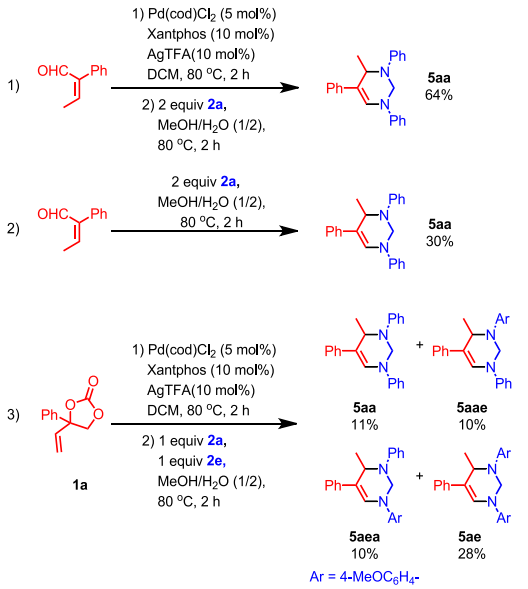


[a]Isolated yields are indicated below each structure (Supporting Information gives the experimental details).

and they were simply treated with the common organic base DBU in one pot. A highly regioselective [3 + 3] oxidative cycloaddition product **7aa** was isolated in 35% yield. This transformation proceeded smoothly with a range of allylic sulfones and VECs, and both substrates regardless of the electronic properties were tolerated and gave the desired products **7aa**–**7ed** in moderate to good yields (Scheme 2). A furan-containing allylic sulfone could also undergo efficient cycloaddition to produce **7ae** in a moderate yield. Next, we demonstrated the viability of this [3 + 3] oxidative cycloaddition in the late-stage modification of a natural product estrone derivative,[14] which was successfully incorporated with a terphenyl unit in a good isolated yield.

Several experiments were conducted to gain insight into the possible mechanism of these Pd-catalyzed cycloadditions (Scheme 3). The above distinct results were observed under

Scheme 3. Control Experiments



stepwise addition mode, implying a different intermediate formed in the reactions. Initially, we captured the intermediate and characterized it as an α,β-unsaturated aldehyde by NMR spectra. When the intermediate was reacted with **2a** under standard conditions, the desired product **5aa** was obtained in 64% yield. By contrast, the yield of **5aa** was significantly decreased to 30% under metal-free conditions. These results may indicate that the Pd/Ag active species could act not only as a catalyst to initiate the first step but also as a Lewis acid to activate the aldehyde in the second step. Second, we conducted a crossover experiment. The result is consistent with formal migration [2 + 3] cycloaddition[9c] and rules out the direct nucleophilic attack of triazinanes. The exact reason why formation of α,β-unsaturated aldehyde is favorable under the stepwise addition mode remains unclear at this stage. However, we speculated that triazinanes could prevent a π-allyl palladium intermediate from undergoing β-H elimination.

On the basis of the mechanistic experiments and relevant reports,[3a,15] a plausible mechanism was proposed in Figure 3. With regard to the stepwise addition cycloaddition mode, the zwitterionic π-allyl palladium intermediate (**A**) formed by decarboxylation could result in unsaturated enol through β-H elimination and then isomerizes to α,β-unsaturated aldehyde. Subsequently, it could react with an imine generated from triazinane (**2a**) and provide intermediate **D** via the Michael addition process, followed by hydrolysis losing one form-aldehyde together with attack of imine to afford intermediate

DOI: 10.1021/acs.orglett.9b02266
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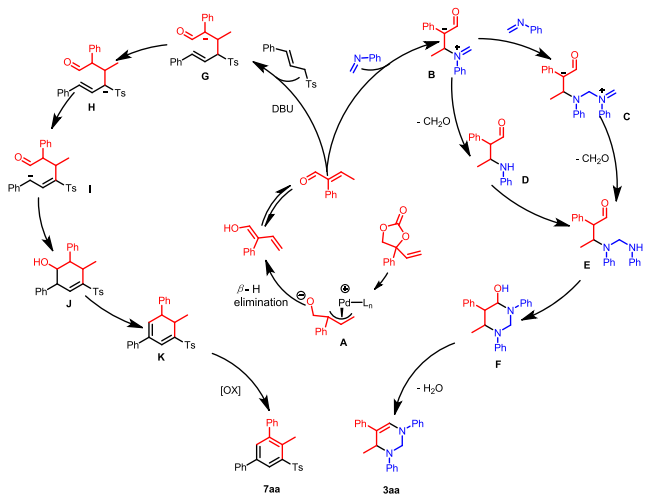

Figure 3. Plausible mechanism.

E. The opposite pathway could also be involved which cannot be excluded. Finally, a driving force for the formation of **3aa** through the formal [3 + 3] cycloaddition might be attributed to the loss of water caused by the intramolecular condensation. In a parallel [3 + 3] oxidative cycloaddition reaction, the allylic sulfone was first deprotonated by DBU. Subsequently, the 1,2-Michael addition occurs to generate intermediate **G**, followed by tautomerization, aldol condensation, and oxidative dehydrogenation to give the final product **7aa**.

In summary, a formal [3 + 3] cycloaddition reaction of VECs has been developed by stepwise addition. This reaction provides an efficient and aqueous method to synthesize polysubstituted tetrahydropyrimidines using VECs as *α,β*-unsaturated aldehyde surrogates. Additionally, the facile synthesis of polysubstituted terphenyls was realized by the same method via a [3 + 3] oxidative cycloaddition. More importantly, the zwitterionic *π*-allyl palladium intermediate as a novel 3-carbon synthon for cycloaddition generated by a combination process of decarboxylation and *β*-H elimination was disclosed for the first time. Finally, the new divergent synthesis method and insight of allylic chemistry will guide us to explore chemical space for drug discovery.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02266.

Experimental procedures and spectral data for all new compounds (PDF)

Accession Codes

CCDC 1852789 and 1937436 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the 100 talent program of the Chinese Academy of Sciences, Chinese NSF (21702217), "1000-Youth Talents Plan", Shanghai-Youth Talent, National Science & Technology Major Project "Key New Drug Creation and Manufacturing Program", China (Number: 2018ZX09711002-006), Shanghai-Technology innovation Action Plan (18JC1415300), and Shanghai "Phosphor" Science Foundation (Number: 19QA1410700) for financial support of this research.

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DOI: 10.1021/acs.orglett.9b02266
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