ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2018, **54**, 12182

Received 27th August 2018,
Accepted 1st October 2018

DOI: 10.1039/c8cc06945j

rsc.li/chemcomm

Divergent synthesis of N-heterocycles by Pd-catalyzed controllable cyclization of vinylethylene carbonates†

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Here, we report a palladium-catalyzed controllable cyclization of vinyl ethylene carbonates that proceeds through formal migration [2+3] and [5+2] cycloadditions, respectively, under mild conditions. The transformation described here affords a series of synthetically versatile 5,7-membered N-heterocycles which are found in natural products and pharmaceuticals with biological and medicinal properties.

Nitrogen heterocycle units, the most privileged and significant structures, are found in many small-molecule drugs and they are highly crucial for their potency and efficacy expression (Fig. 1).[1] Accordingly, the development of reliable methodologies for the efficient and concise construction of these structural motifs is attracting considerable attention in the field of transition metal catalysis.[2] While the transition metal-catalyzed cyclization made significant contribution to the building of various and versatile nitrogen heterocycle compound libraries, divergent synthesis with controllable ring sizes from the same starting materials is a long-standing challenge.[2d,3]

The allylic substitution reaction, which was originally discovered by Tsuji[4] and further developed by Trost[5] and others,[6] represents a powerful approach for the expeditious synthesis of allylic derivatives and diversified heterocycles through a π-allyl metal intermediate. Recently, Zhang,[7] Kleij,[8] Zhao,[9] Glorious,[10] and others[11] developed vinylethylene carbonates (VECs) as more stable and readily available substrates for Pd-catalyzed decarboxylative allylic substitution[7a,b,8] and cycloaddition[7c–g,9–11] with nucleophiles or unsaturated dipoles to construct allylic

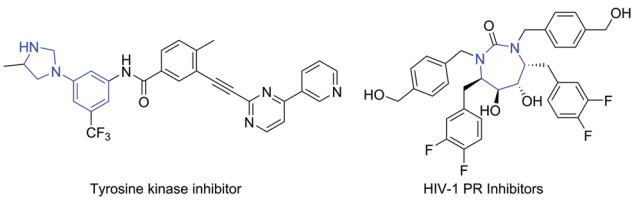

Fig. 1 Biologically active compounds of diversified N-heterocycles.

substituted and functional heterocyclic products. Notably, a π-allyl metal intermediate usually serves as either a 5-atom (1C, 5O) synthon or a 3-atom (3C, 5O) synthon to engage the cross-partners, which would lower the entropic and enthalpic costs with the aid of catalysts and ligands to achieve medium-sized ring formation (Fig. 2a). Very recently, Zhao and his co-workers realized an interesting Pd/Lewis acid co-catalyzed cycloaddition of VECs by the utilization of a (1C, 4C) synthon to construct spiro heterocycles. However, to the best of our knowledge, the formal cycloaddition by utilizing π-allyl Pd as a

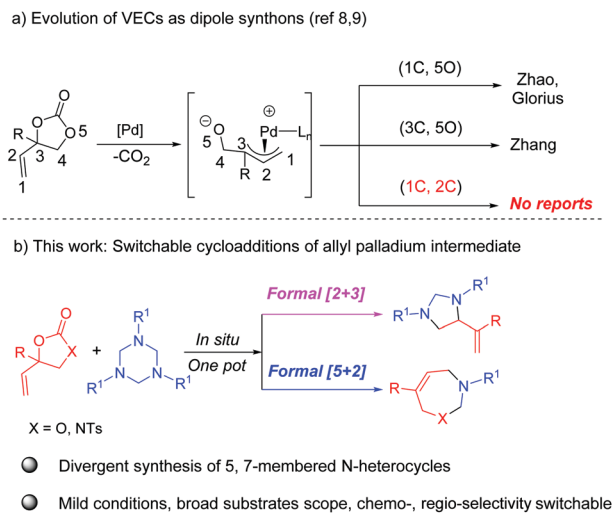

Fig. 2 Evolution of VECs and our new discovery.

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† Electronic supplementary information (ESI) available: Data for new compounds and experimental procedures. CCDC 1852787 and 1852788. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8cc06945j

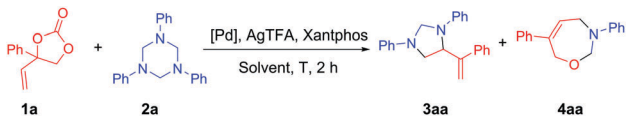
2-atom (1C, 2C) synthon has never been described to date. In this sense, using a zwitterionic π-allyl palladium intermediate as a new synthon would not only improve our ever-growing knowledge in allylic cycloaddition, but also provide a new opportunity for diversity-oriented controllable synthesis. Herein, we successfully realize these ideas and report an unprecedented Pd-catalyzed controllable cyclization of VECs *via* formal migration [2+3] and [5+2] cycloaddition pathways, respectively. An array of diversified 5,7-membered N-heterocycles was systematically constructed by judicious choice of additives from identical starting materials.

Our initial reaction was conducted with 4-phenyl-4-vinyl-1,3-dioxolan-2-one (**1a**) and 1,3,5-triphenyl-1,3,5-triazinane (**2a**) in the presence of $Pd(cod)Cl_2$ as a catalyst, Xantphos as a ligand, and AgTFA as an additive in dichloromethane (DCM) at 80 °C. Gratifyingly, the reaction proceeded smoothly and generated two different cycloaddition products **3aa** and **4aa** in 50% and 38% yields (Table 1, entry 1), respectively. The structure of **4aa** was further unambiguously confirmed by X-ray crystallographic analysis.

Encouraged by the preliminary results, we further systematically optimized the conditions and attempted to realize this reaction in a switchable mode. After a deep investigation on reaction parameters, the optimal conditions for **3aa** were ultimately identified as follows: $Pd(cod)Cl_2$ (5 mol%) as a catalyst, Xantphos (10 mol%) as a ligand, and AgTFA (10 mol%) as an additive in aqueous methanol solvent at 80 °C. It exclusively provided the desired product **3aa** in quantitative NMR yield and 85% isolated yield (Table 1, entry 11). In order to realize the switchable cyclization goal, we then turned our attention to tune the formal [5+2] cycloaddition product **4aa**, which is a considerable challenge in organic synthesis due to unfavorable entropy effects. Interestingly, conducting the reaction at mild temperature (60 °C) is likely beneficial for **4aa** formation. Switching the catalyst $Pd(cod)Cl_2$ to $[Pd(allyl)Cl]_2$ and choosing DCM as the solvent, **3aa** was suppressed and **4aa** became the major product. The isolated yield of **4aa** was increased dramatically to 81% (Table 1, entry 14). Finally, a control experiment was also conducted to understand the role of silver salts. The control experiment showed that the additive AgTFA was crucial to this controllable cyclization reaction (Table 1, entries 18 and 19). No [5+2] product was formed and the yield of the [2+3] product was significantly decreased to 23% in the absence of silver salts. Presumably, the cationic silver as a scavenger could capture anionic chloride and form a new trifluoroacetyl (TFA) anion, which promotes the cleavage of the C–N bond[12] from 1,3,5-triphenyl-1,3,5-triazinane (**2a**).

With the optimal conditions in hand, the generality of the Pd-catalyzed controllable formal migration [2+3] cycloaddition reaction was firstly explored. As illustrated in Table 2, a range of VECs containing electron-donating as well as electron-withdrawing groups at the *para*-, *meta*-, and *ortho*-positions of the aryl performed well and delivered the corresponding 5-membered ring products in good to excellent yield. Additionally, a dichloro substituent (**3na**) as a potential handle was also amenable to the standard conditions, thus offering a product suitable for further structural elaboration. Beyond the tolerance to the above-mentioned simple aromatic ring systems, the reaction is also compatible with naphthalene (**3ba**), heterocyclic (**3sa** and **3wa**), and non-aromatic substrates (**3ta**, **3ua**, and **3va**) commonly

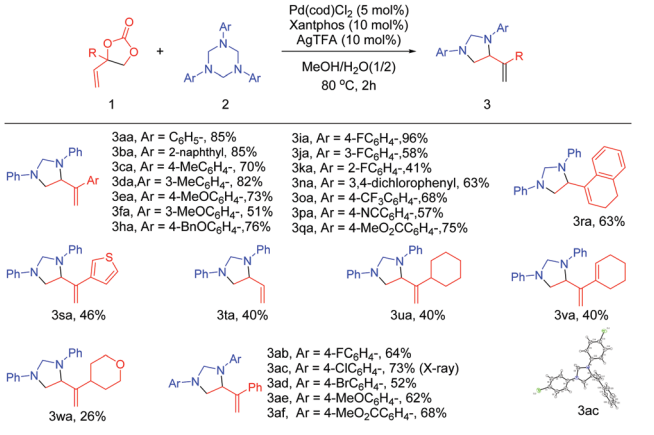
Table 1 Optimization of Pd-catalyzed controllable cycloaddition of VECs[a]



Entry	Catalyst	Solvent	Yield[b] (%) 3aa	4aa
1	$Pd(COD)Cl_2$	DCM	50	38
2	$Pd(OAc)_2$	DCM	16	13
3	$Pd(PPh_3)_4$	DCM	Trace	10
4	$Pd(COD)Cl_2$	Toluene	21	56
5	$Pd(COD)Cl_2$	H_2O	84	N.D.
6	$Pd(COD)Cl_2$	MeOH	20	28
7	$Pd(COD)Cl_2$	DMSO/H_2O (1/1)	55	N.D.
8	$Pd(COD)Cl_2$	DMF/H_2O (1/1)	67	N.D
9[c]	$Pd(COD)Cl_2$	MeOH/H_2O (1/1)	71	12
10[c]	$Pd(COD)Cl_2$	MeOH/H_2O (2/1)	89	N.D.
11[c]	$Pd(COD)Cl_2$	MeOH/H_2O (1/2)	99(85)	N.D.
12[d]	$[Pd(allyl)Cl]_2$	DCM	10	74
13[e]	$[Pd(allyl)Cl]_2$	DCM	3	81
14[f]	$[Pd(allyl)Cl]_2$	DCM	Trace	85(81)
15[d]	$Pd(COD)Cl_2$	DCM	13	64
16[e]	$Pd(COD)Cl_2$	DCM	8	66
17[f]	$Pd(COD)Cl_2$	DCM	15	81
18[fg]	$[Pd(allyl)Cl]_2$	DCM	N.D.	N.D.
19[g]	$Pd(COD)Cl_2$	MeOH/H_2O (1/2)	23	N.D.
20[f]	$Pd(TFA)_2$	DCM	8	84
21	$Pd(TFA)_2$	MeOH/H_2O (1/2)	87	N.D.

[a] Reaction conditions: **1a** (0.05 mmol), **2a** (0.06 mmol), Pd catalyst (5 mol%), Xantphos (10 mol%), AgTFA (10 mol%), solvent (0.5 mL) at 80 °C for 2 h; for more reaction conditions, see the ESI. [b] Yields were determined *via* ^1H NMR using CH_2Br_2 as the internal standard; isolated yield is given in parentheses. [c] Solvent (1 mL). [d] **1a** (0.1 mol), **2a** (0.05 mmol), solvent (1.0 mL) at 60 °C for 1 h. [e] **1a** (0.1 mol), **2a** (0.045 mmol), solvent (1.0 mL) at 60 °C for 1 h. [f] **1a** (0.1 mol), **2a** (0.06 mmol), solvent (1.0 mL) at 60 °C for 1 h. [g] No AgTFA.

Table 2 Substrate scope of formal migration [2+3] cycloadditions[a]



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

encountered in target-oriented synthesis. Furthermore, various triazinane partners also engaged in efficient cycloaddition regardless of the electronic properties on the substrates to deliver **3ab–3af** in good isolated yield. However, benzylic amine substituted triazinanes were unreactive under the reaction conditions.

As shown in Table 3, various *para*-, *meta*-, or *ortho*-substituents of both electron-rich and electron-poor characters at the aryl group on the substituted VECs could be well tolerated to provide the desired oxazepine products in moderate to very good yield. Notably, reactions of substrates with aromatic functional groups attached to VECs afforded higher yields than those with non-aromatic functional groups. Possibly, the aromatic functional groups could stabilize the zwitterionic π-allyl palladium intermediate and prevent it from losing activity. To our delight, the thienyl substituted VEC worked out smoothly to provide **4sa** in very good isolated yield. As an important extension of scope for this formal [5+2] cycloaddition, vinyloxazolidin-2-one was employed in this catalytic system, which could lead to the formation of 7-membered ring diazepine which is a privileged structure in pharmaceutical drugs. Gratifyingly, the diazepine product **4xa** could be accessed in moderate yield. Given that the benzylic amine protecting group is easily cleaved to free amine by hydrogenation and could be manipulated for functional group installation, we revisited the benzylic amine substituted triazinanes. In contrast to the formal migration [2+3] cycloaddition, it displayed good reactivity in the present system (**4ag**), furnishing the desired product in synthetically useful yield.

Several experiments were conducted to gain insight into the possible mechanism of this Pd-catalyzed controllable cyclization (Fig. 3). Initially, we carried out a cross-over experiment by treating VEC **1a** with a 1 : 1 mixture of **2a** and **2e** under the standard formal migration [2+3] cycloaddition conditions, and four different products with a ratio of 1 : 1 : 1 : 1 were obtained. This interesting result suggests that imine as a nucleophilic reagent is generated *in situ* from triazinanes *via* C–N bond cleavage. Besides, we also performed the reaction of **4ae** with **2a** and found a similar result to the cross-over experiment, thus indicating that the C–N bond cleavage event of the seven-membered

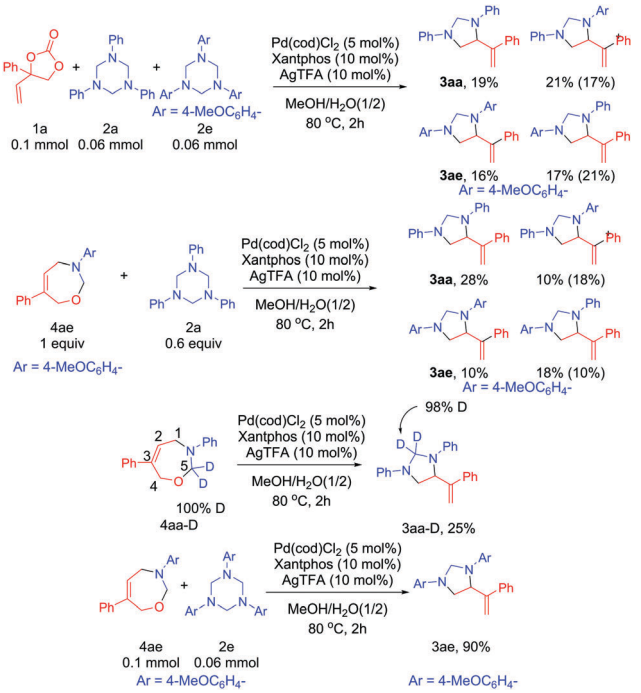
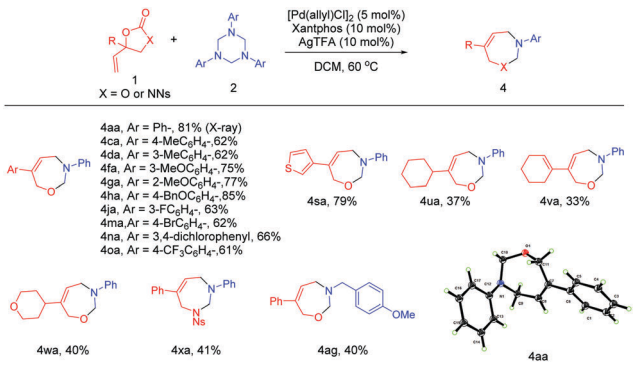


Fig. 3 Control experiments for mechanism identification.

ring occurs *via* oxidative addition of Pd(0) and releases one imine. Notably, a further D-labelling experiment could strongly support the C1–N bond cleavage instead of the C5–N bond cleavage. Additionally, the treatment of seven-membered ring **4ae** with **2e** resulted in **3ae** in 90% excellent yield under the standard formal migration [2+3] cycloaddition conditions, which demonstrated that the 7-membered ring diazepine could be an intermediate for 5-membered ring formation.

On the basis of the above results and relevant reports,[3a,13] a plausible mechanism is proposed in Fig. 4. The reaction begins with the oxidative addition of Pd(0) to VEC (**1a**), generating the zwitterionic π-allyl palladium intermediate **A** by releasing carbon dioxide. Meanwhile, three imines are generated *in situ* from triazinane (**2a**) *via* C–N bond cleavage, which would attack

Table 3 Substrate scope of formal [5+2] cycloadditions[a]



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

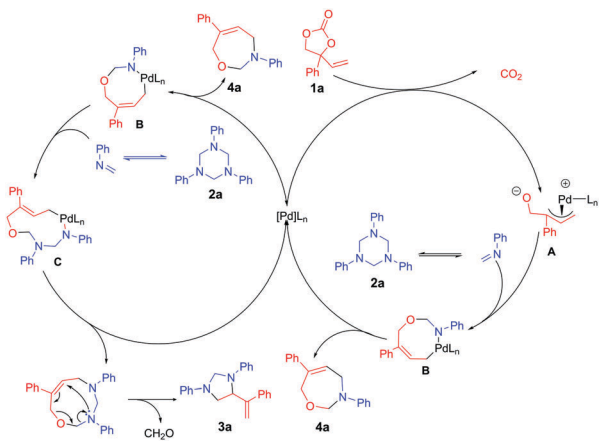


Fig. 4 Proposed mechanism of the controllable mode.

A followed by reductive elimination to produce the formal [5+2] cycloaddition product **4a** and regenerate Pd(0) species. Under controllable conditions, the 7-membered ring product **4a** could further undergo oxidative addition with Pd(0) species to give intermediate **B**, which is then captured by imine and delivers the ten-membered palladacycle **C**. Subsequently, reductive elimination and intramolecular aza [3,3]-sigmatropic rearrangement events take place to furnish the formal migration [2+3] cycloaddition product **3a** with extrusion of formaldehyde.

In summary, a diversity-oriented Pd-catalyzed regio-selectivity switchable cycloaddition of VECs has been developed under mild conditions. The judicious choice of the catalyst and solvent enables the efficient synthesis of two different types of 5-, 7-membered N-heterocycles from an identical starting material through formal migration [2+3] and [5+2] cycloadditions, and potentially contributes in expediting the search for lead compounds. Further studies on new reactivities of VECs and bioactive assessments of the above N-heterocycles are under progress in our lab.

We gratefully acknowledge the 100 Talent Program of Chinese Academy of Sciences, the Chinese NSF (21702217), the ''1000-Youth Talents Plan'', the Shanghai-Youth Talent, and the Shanghai-Technology Innovation Action Plan (18JC1415300) for financial support of this research.

Conflicts of interest

There are no conflicts to declare.

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