RSC Advances

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Cite this: *RSC Adv.*, 2023, **13**, 27158

Palladium-catalyzed intramolecular aza-Wacker-type cyclization of vinyl cyclopropanecarboxamides to access conformationally restricted aza[3.1.0]bicycles†

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Received 11th August 2023
Accepted 6th September 2023

DOI: 10.1039/d3ra05440c

rsc.li/rsc-advances

A palladium(II)-catalyzed intramolecular oxidative aza-Wacker-type reaction of vinyl cyclopropanecarboxamides to access a series of conformationally restricted highly substituted aza[3.1.0]bicycles is reported. The transformation proceeded through a typical aza-Wacker reaction mechanism to forge a new C–N bond with oxygen as the terminal oxidant. The desired fused heterocycles were obtained in moderate yields. The process is tolerant of a range of functional aryl groups under mild conditions.

Introduction

The rigid 3-azabicyclo[3.1.0]hexane moiety is an essential three-dimensional building block found in alicyclic amine-based fragments of several pharmaceuticals, including the hepatitis C virus drug Victrelis, potent gyrase inhibitor Trovafloxacin, and the pesticide procymidone (Fig. 1).[1] This type of small molecule is also useful as an organic synthon for the selective functionalization of a variety of bioactive molecules and is suitable for late-stage modification of drug candidates in medicinal chemistry.[2]

The palladium(II)-catalyzed aza-Wacker-type reaction of olefins is an important transformation given that amines, carbazoles, carbamates, and amides are commonly utilized in intermolecular palladium-catalyzed oxidative amination reactions.[3] It has found widespread application in the construction of natural products and synthetic bioactive compounds. From a mechanistic aspect, after nucleopalladation of the olefin bond, a key carbon-bonded Pd(II) intermediate is generated, which can partake in subsequent reaction steps. Alkyl substituents with low steric hindrance are usually pre-attached to the terminal position of the alkene group to facilitate subsequent β-hydride elimination, rather than β′-hydride elimination (Scheme 1a).[4] In particular, aryl-involved and terminal alkene-involved transformations always involve an amidopalladation intermediate or a π-allylpalladium complex to the alkylpalladium species, resulting in multiple fused products through the formation of C–C bonds *via* reductive elimination of the palladacycle (Scheme 1b, path a).[5] Alternatively, the alkylpalladium species may afford the enamide product *via* a β′-hydride elimination. In addition, because the elimination occurs at locations with high steric resistance, the yields of such reactions are generally not higher than those of using non-terminal alkenes (Scheme 1b, path b).[6] Several examples of transformation *via* path a in Scheme 1b have been established by different research groups. For example, in 2011, Yang *et al.*[5h] obtained indole derivatives **3** *via* Pd-catalyzed intramolecular

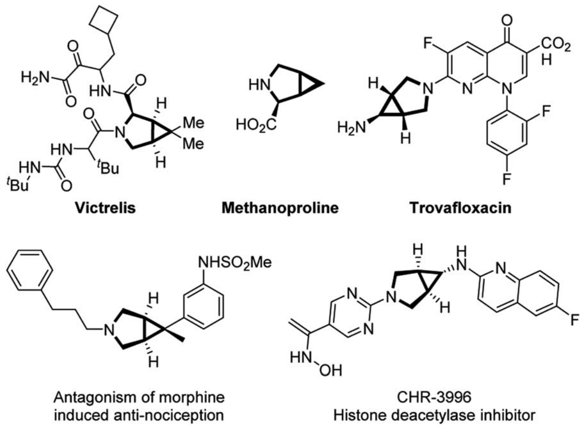

Fig. 1 Examples of aza[3.1.0]bicycles-containing bioactive pharmacophores.

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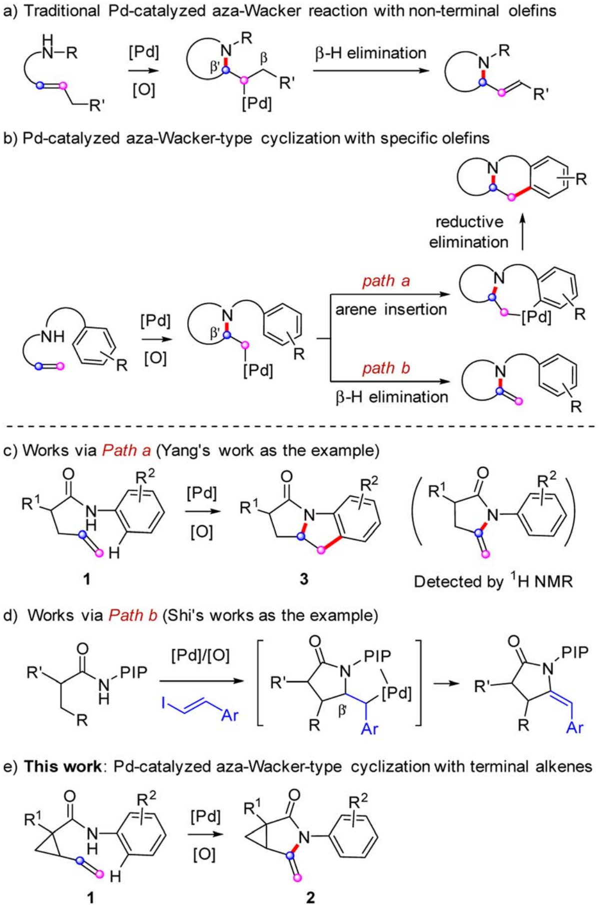
† Electronic supplementary information (ESI) available: NMR spectra, HRMS, and single-crystal X-ray diffraction data (PDF). CCDC 2142480. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d3ra05440c



Scheme 1 Reaction of allylic compounds in intramolecular aza-Wacker-type reaction.

amidoarylation of alkenes starting from α-allyl-substituted acetanilides **1**. They observed a trace amount of β-hydrogen eliminated enamide by-product by ^{1}H NMR spectroscopy (Scheme 1c). Recently, Shi's group[6b–d] developed a series of works on Pd(II)-catalyzed intermolecular cascade methylene C(sp^3)–H alkenylation/aza-Wacker cyclization to access α/β-stereospecific γ-lactams *via* a π-allyl-Pd intermediate. The presence of an aryl group forces the hydrogen elimination reaction to occur regiospecifically at the β′-position (Scheme 1d).

Although remarkable process has been made in intramolecular aza-Wacker-type reactions in recent decades, the construction of structurally diverse heterocyclic compounds, including fused and bridged ring compounds, using this strategy remains challenging.[7] To the best of our knowledge, the synthesis of conformationally restricted aza[3.1.0]bicycles from vinyl cyclopropanecarboxamides *via* intramolecular aza-Wacker oxidation or oxidative amination is not reported in the literature. Herein, we describe our recent efforts toward the Pd-catalyzed ligand-free intramolecular oxidative amidation of vinyl cyclopropanecarboxamides **1** to access conformationally restricted aza[3.1.0]bicycle core **2** *via* aza-Wacker-type reaction (Scheme 1e).

Results and discussion

Combined with our studies on derivatization reactions of amides and previous reports,[8] we envisioned that fused-heterocycles **3** may be accessed by treating vinyl cyclopropanecarboxamides **1** with Pd salts to give the important cyclopropa[3,4]pyrrolo[1,2-*a*]indolone core **2** of natural products and prodrugs *via* the aza-Wacker-type oxidation amidation reaction.[9] With this assumption in hand, we attempted all reaction conditions described by previous reports with model reagent **1a**,[10] but we found that all efforts failed to give the fused heterocycles **3**, indicating that these conditions are not fit for this type of vinyl cyclopropanecarboxamide to undergo the formal [3 + 2] cyclization reaction. Fortunately, the crystal structure of the aza[3.1.0]bicycle **2a**, was unambiguously confirmed by X-ray diffraction (CCDC no. 2142480, Fig. 2). This result suggests that the transformation proceeded *via* cascade amidopalladation/β-hydride elimination, rather than through the amidoarylation pathway. Subsequent optimization indicated that 5 mol% of Pd(PPh$_3$)$_2$Cl$_2$ can promote complete consumption of the substrate in 24 h, affording **2a** in 60% yield in the presence of 1.0 equiv. of K$_2$CO$_3$ in dimethylformamide (DMF) in a sealed tube at 50 °C using molecular oxygen as the terminal oxidant (Table 1, entry 1). Lowering the loading of the Pd(PPh$_3$)$_2$Cl$_2$ catalyst to 3 mol% still furnished a 58% yield of **2a**, but the reaction time was prolonged to 44 h (Table 1, entry 2). In contrast, increasing the catalyst loading to 10 mol% resulted in a yield of only 59% (Table 1, entry 3). Further efforts to increase the yield of **2a** were unsuccessful, including performance of the reaction with Pd(OAc)$_2$, Pd(TFA)$_2$, PdCl$_2$, PdCl$_2$(MeCN)$_2$, PdCl$_2$(dppe), and Pd(dba)$_2$ as alternative catalysts. All of these reactions gave yields of **2a** that were less than that observed with Pd(PPh$_3$)$_2$Cl$_2$ catalyst (Table 1, entries 4–9). Oxidant was shown to be necessary for the reaction, and a high concentration of oxygen clearly favored the rapid turn-over of the metal catalyst (Table 1, entries 10 and 11). When the reactions were carried out at slightly higher or lower temperatures, the yields were not improved (Table 1, entries 12 and 13). In addition, lowering or increasing the amount of K$_2$CO$_3$ also failed to improve the yield of **2a** (Table 1, entries 14 and 15). Other bases including AcOK, K$_3$PO$_4$, and Cs$_2$CO$_3$ were proven less efficient than K$_2$CO$_3$ (Table 1, entries 16–18). Solvent screening indicated that DMF was the most appropriate solvent. Use of *N*-methyl-2-pyrrolidone (NMP), acetonitrile, dioxane, toluene, dimethyl sulfoxide (DMSO), or tetrahydrofuran (THF) as solvent provided diminished yields or trace amounts of the product (Table 1, entries 19–24). The conversion performed in ethanol gave a poor yield of product **2a**.

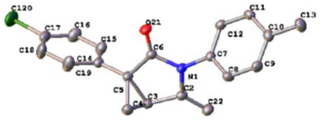
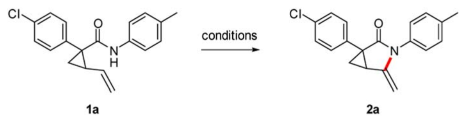


Fig. 2 ORTEP drawing of **2a**.

Table 1 Optimization of reaction conditions[a]

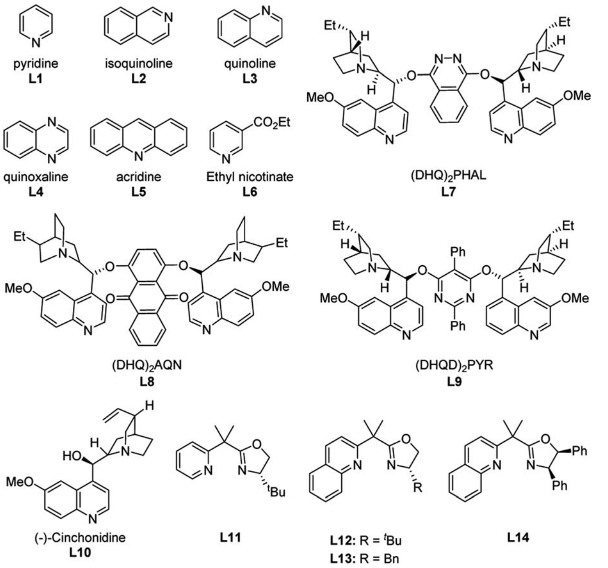


Entry	[Pd]/mol%	Solvent	Time/h	Yield/%[b]
1	$Pd(PPh_3)_2Cl_2$ (5)	DMF	24	60
2	$Pd(PPh_3)_2Cl_2$ (3)	DMF	44	58
3	$Pd(PPh_3)_2Cl_2$ (10)	DMF	24	59
4	$Pd(OAc)_2$ (5)	DMF	8	46
5	$Pd(TFA)_2$ (5)	DMF	24	21 (31)
6	$PdCl_2$ (5)	DMF	24	19 (42)
7	$PdCl_2(MeCN)_2$ (5)	DMF	24	25 (27)
8	$PdCl_2$(dppe) (5)	DMF	24	44
9	$Pd(dba)_2$ (5)	DMF	24	13 (45)
10	$Pd(PPh_3)_2Cl_2$ (5)	DMF	24	Trace[c]
11	$Pd(PPh_3)_2Cl_2$ (5)	DMF	24	Trace[d]
12	$Pd(PPh_3)_2Cl_2$ (5)	DMF	33	58 (10)[e]
13	$Pd(PPh_3)_2Cl_2$ (5)	DMF	17	53[f]
14	$Pd(PPh_3)_2Cl_2$ (5)	DMF	24	39 (30)[g]
15	$Pd(PPh_3)_2Cl_2$ (5)	DMF	24	60[h]
16	$Pd(PPh_3)_2Cl_2$ (5)	DMF	24	26[i]
17	$Pd(PPh_3)_2Cl_2$ (5)	DMF	24	45 (17)[j]
18	$Pd(PPh_3)_2Cl_2$ (5)	DMF	24	49 (18)[k]
19	$Pd(PPh_3)_2Cl_2$ (5)	NMP	24	45 (13)
20	$Pd(PPh_3)_2Cl_2$ (5)	MeCN	24	24 (43)
21	$Pd(PPh_3)_2Cl_2$ (5)	Dioxane	24	Trace (90)
22	$Pd(PPh_3)_2Cl_2$ (5)	Toluene	24	Trace (88)
23	$Pd(PPh_3)_2Cl_2$ (5)	DMSO	24	37 (39)
24	$Pd(PPh_3)_2Cl_2$ (5)	THF	24	Trace (94)
25	$Pd(PPh_3)_2Cl_2$ (5)	EtOH	24	29 (41)

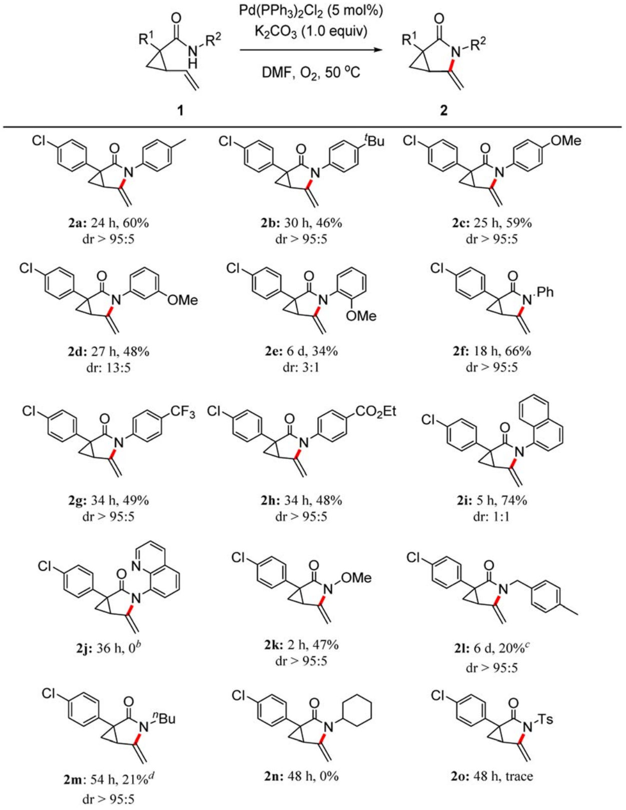
[a] Unless otherwise indicated, the reaction was conducted with **1a** (0.5 mmol, 1.0 equiv.), [Pd] salt (5 mol%), K_2CO_3 (1.0 equiv.) and solvent (2 mL) at 50 °C under O_2 in a sealed tube. [b] Recovered **1a** shown in parentheses after purification by column chromatography. [c] N_2. [d] Air. [e] 40 °C. [f] 60 °C. [g] K_2CO_3 (0.5 equiv.). [h] K_2CO_3 (1.5 equiv.). [i] AcOK. [j] K_3PO_4. [k] Cs_2CO_3.

Related researches have already indicated the importance of pyridine and amine ligands for this aza-Wacker-type reaction.[5h,10d,10e,11] Accordingly, some representative ligands **L1–L14** (Scheme 2) were employed to the reaction, with 40 mol% loading under the optimal reaction conditions (Table 1, entry 1). Unfortunately, all attempts to improve the yield were unsuccessful, ligands inhibit the process, with yields of **2a** not exceeding 31%, along with most of starting material was recovered after 24 h. Especially, the yield of **2a** given by **L4** and **L6** was not higher than 31% even at 10% ligand dosage.

With the optimized reaction conditions in hand (Table 1, entry 1), the substrate scope and limitation of this palladium-catalyzed intramolecular aza-Wacker-type oxidation amidation of vinyl cyclopropanecarboxamides were studied. As shown in Scheme 3, various aryl R^2 groups were examined, demonstrating that the reaction could tolerate aryl groups bearing an electron-donor group (EDG) (**2a–e:** Me, ^{t}Bu, and OMe) at the *para-*, *meta-*, and *ortho*-position or electron-withdrawing group (EWG) at the *para*-position (**2g:** CF_3 and **2h:** CO_2Et), as well as the unsubstituted phenyl group (**2f**). Notably, given that the substrate featuring an *ortho*-substituted methoxy group gave a relatively low yield of desired product **2e**, further use of substrates with EDG at the *ortho*-position was not attempted. To our delight,



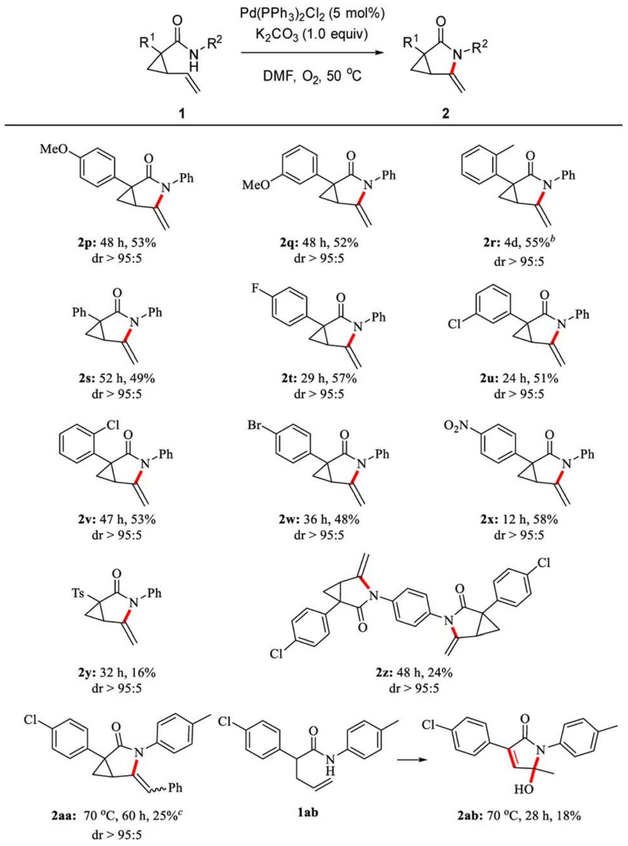
Scheme 2 Structures of generally used ligands.



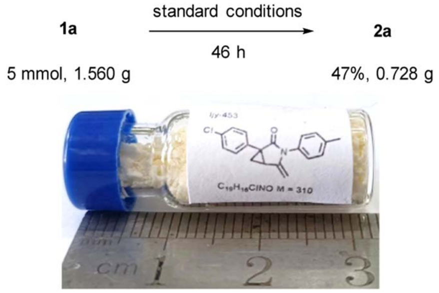
Scheme 3 Extension of reaction scope with various R^2 groups.[a] [a] Unless otherwise indicated, all reactions were conducted with **1** (0.5 mmol, 1.0 equiv.), $Pd(PPh_3)_2Cl_2$ (5 mol%), K_2CO_3 (1.0 equiv.) and DMF (2 mL) at 50 °C under O_2 in a sealed tube, and the dr values were determined from the ^1H NMR analysis of the crude reaction mixture. [b] 91% of **1j** was recovered. [c] 58% of **1l** was recovered. [d] 71% of **1m** was recovered.

product **2i** bearing a naphthyl group on the nitrogen atom of the amide moiety was isolated in 74% yield after 5 h. However, the transformation from **1j** with an aminoquinoline (AQ) group failed to give compound **2j**, with 91% of the starting material recovered. We presumed that this lack of reaction was caused by poisoning of the Pd catalyst by coordination with the bidentate AQ ligand.[12] However, given that steric hindrance might also be partially responsible for the low yield of the aforementioned products, we tested the reaction with the *N*–OMe substituted substrate **1k**. Product **2k** was isolated in 47% yield, indicating that steric hindrance may not be the cause of low yields. The reactions with benzyl- and ^{n}Bu-substituted substrates **1l** and **1m** afforded products **2l** and **2m**, respectively, in 20% and 21% yields. Unfortunately, our efforts to expand the protocol with substrate featuring a cyclohexyl group (**1n**) met with failure even at high temperatures and with long reaction times, whereas the tosylate-substituted starting material (**1o**) gave a trace amount of desired product **2o**.

The reaction scope was further explored with a series of substrates with varied R^1 substituents see Scheme 4. The transformation was favored for various 1-aryl substituted vinyl cyclopropanecarboxamides bearing a OMe (**2p** and **2q**), Me (**2r**), F (**2t**), Cl (**2u** and **2v**), or Br (**2w**) group at the *para*-, *meta*- or *ortho*-position, along with the phenyl-substituted cyclopropane derivative (**2s**). The target compounds **2p–w** were isolated in 48–57% yields. Notably, the bromobenzene moiety of product **2w** remained intact as a site for further functionalization by methods including the Suzuki–Miyaura,[13] Buchwald–Hartwig,[14] and the Sonogashi coupling reactions.[15] In addition, the starting material **1x** with an EWG at the *para*-position readily provided the product **2x** in 58% yield. Unfortunately, the reaction of **1y** furnished the desired product **2y** only in 16% yield. A novel alkene bisamidation product **2z** with a benzene ring as the linker was also obtained in 24% yield. We also noted that all reactions were accompanied by mixtures of unidentified byproducts, which is the reason for the low yield of product **3**. The reaction using terminal substituted alkene **1aa** bearing a phenyl group did not reach completion after 60 h, affording **2aa** in 25% yield along with 63% of recovered starting material **1aa**. Notably, allyl-substituted chain substrate **1ab** underwent this aza-Wacker-type cyclization reaction before oxidation and hydroxylation tandem processes formed compound **2ab**, which features a hydroxyl group that is likely to be derived from symbiotic water of the reaction.



Scheme 4 Extension of reaction scope with various R^1 groups.[a] [a] Unless otherwise indicated, all reactions were conducted with **1** (0.5 mmol, 1.0 equiv.), Pd(PPh$_3$)$_2$Cl$_2$ (5 mol%), K$_2$CO$_3$ (1.0 equiv.) and DMF (2 mL) at 50 °C under O$_2$ in a sealed tube, and the dr values were determined from the ^{1}H NMR analysis of the crude reaction mixture. [b] 21% of **1r** was recovered. [c] 63% of **1aa** was recovered.



Scheme 5 Gram-scale preparation of compound **2a**.

To our delight, we found that the reaction can be readily scaled up: 5 mmol of 1-(4-chlorophenyl)-*N*-(*p*-tolyl)-2-vinylcyclopropane-1-carboxamide (**1a**) was treated with 5 mol% Pd(PPh$_3$)$_2$Cl$_2$, 1.0 equiv. of K$_2$CO$_3$, and O$_2$ in DMF to smoothly furnish a 47% yield of **2a** after 46 h (Scheme 5).

Experimental

General information

Unless stated otherwise, reactions were conducted in flame-dried Schlenk under a positive pressure of O$_2$. All reagents were purchased from commercial sources and used without further treatment and all substrates are homogeneous, unless otherwise indicated. Starting materials **1** were synthesized following the literature.[16] DMF, MeCN, and toluene solvents were distilled under an atmosphere of dry N$_2$. Petroleum ether (PE) used here refers to the 60–90 °C boiling point fraction of petroleum. Ethyl acetate is abbreviated as EA. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance/600 (^{1}H: 600 MHz, ^{13}C: 150 MHz at 25 °C) or Bruker Avance/400 (^{1}H: 400 MHz, ^{13}C: 100 MHz at 25 °C). Fluorine nuclear magnetic resonance (^{19}F NMR) spectra were recorded on a Bruker Avance/600 or Bruker Avance/400. NMR data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, and m = multiplet), and coupling constants in Hertz (Hz). All high-resolution mass spectra (HRMS) were measured on a mass spectrometer by using electrospray ionization orthogonal acceleration time-of-flight (ESI-OA-TOF), and the purity of all samples used for HRMS (>95%) was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopic analysis. Melting points were measured on a melting point apparatus equipped with a thermometer and were uncorrected. All reactions were monitored by thin-layer chromatography (TLC) with GF254 silica gel-coated plates. Flash chromatography was carried out on SiO_2 (silica gel 200–300 mesh). The single crystal of **2a** suitable for X-ray analysis was obtained by slowly volatilizing a mixed solution of PE and dichloromethane of **2a** in a semi-sealed penicillin glass vial bottle (7 mL) at room temperature (10 mg of **2a** was dissolved with 5 drops of dichloromethane before *ca.* 2 mL of PE was added).

General procedures for 2 (2a as an example)

In a flame-dried 10 mL Schlenk tube was added **1a** (156 mg, 0.5 mmol), $Pd(PPh_3)_2Cl_2$ (17 mg, 5 mol%), K_2CO_3 (69 mg, 1.0 equiv.), the mixture was stirred well in DMF (2 mL) and stir at 50 °C in sand bath under O_2 (the whole process was closely monitored by TLC). After the completion of the reaction, the mixture was added saturated aqueous NaCl and extracted with DCM (10 mL × 3). Then the organic solvent was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography with PE/EA (50 : 1) as eluent to give **2a** as a white solid (93 mg, 60%).

Conclusions

In summary, we developed a palladium-catalyzed intramolecular aza-Wacker-type oxidation amidation reaction starting from readily available vinyl cyclopropanecarboxamides. The transformation proceeded smoothly under mild conditions to provide a series of highly substituted aza[3.1.0]bicycles in moderate yields (27 examples). These compounds, which were conformationally restricted by their structural elements, have high potential for biological activity. The process is tolerant of a range of functional aryl groups. As the key intermediate, an alkylpalladium species, derived from an amidopalladation underwent β-hydride elimination to access the desired bicyclic 3-azabicyclo[3.1.0]hexan-2-ones. Notably, the enamide and cyclopropane moieties are valuable units for the subsequent construction of structurally diverse biologically valuable organic molecules. In addition, the interesting alkene bisamidation product **2z** was synthesized for the first time. Although the yield of this product was not high in this case, this compound may prove valuable in the fields of chemical biology and medicinal chemistry. Currently, our laboratory is performing further studies aimed at improving reaction yields and exploring the reactivity of aza[3.1.0]bicyclic compounds.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the NSFC (21772032, 21877206, and 22101074), the 111 Project (D17007), Excellent Youth Foundation of Henan Scientific Committee (222300420012), China Postdoctoral Science Foundation (2019M660173), the Natural Science Foundation of Henan Province (202300410233), and Henan Key Laboratory of Organic Functional Molecules and Drug Innovation for financial support.

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