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Palladium-catalyzed cascade cyclization for the construction of *spiro*-*N*,*O*-acetals†

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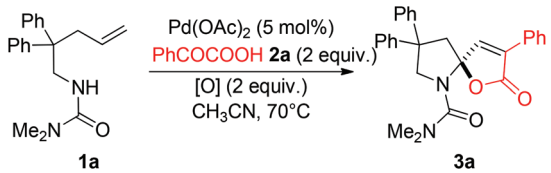
A facile Pd-catalyzed cascade cyclization of *N*-alkenylamine and pyruvic acids has been developed to construct *spiro*-*N*,*O*-acetals. This transformation was initiated by an intramolecular oxidative amination of alkenes, followed by hydrolysis to give a ketone intermediate, which further reacts with pyruvic acid to deliver the final *spiro*-*N*,*O*-acetals.

The rich variety of nitrogen-containing molecules that occur as natural and pharmaceutical compounds has inspired considerable interest in the development of new methods for their syntheses.[1] For instance, the moiety of *spiro*-*N*,*O*-acetal is a core of bioactive natural products.[2] This skeleton was generally obtained from oxidative spirocyclization of furan derivatives.[3] Herein, we report a highly efficient synthetic approach to construct this *spiro*-*N*,*O*-acetal from simple alkenes by using palladium as a catalyst.

In 2009, our group reported a palladium-catalyzed intramolecular aminofluorination of *N*-tosyl alkenes to give fluorinated pipyridine derivatives with high regioselectivity.[4] Quite recently, the regioselectivity could be switched from *endo*- to *exo*-cyclization by replacing a tosyl group at nitrogen with a chelating group, such as the aminocarbonyl group.[5] A variety of monofluoromethyl containing heterocycles were efficiently obtained with good substrate scope and functional group compatibility. In this study, we observed that the addition of an acidic proton is beneficial for the aminofluorination. During the screening of acidic additives, a *spiro*-*N*,*O*-acetal product **3a** was detected from the reaction of **1a** with benzoylformic acid **2a** as an additive, *albeit* in low yield (<10%). The highly efficient construction of a *spiro*-*N*,*O*-acetal product inspired us to optimize the reaction conditions, and a series of oxidants were screened in the absence of AgF. As shown in Table 1, the reaction of **1a** afforded product **3a** in a slightly low yield (~30%) using a hypervalent iodine oxidant (entries 1 and 2), and the aminooxygenation product was the major product. Strong oxidants $(NH_4)_2S_2O_8$ and $Na_2S_2O_8$ also gave **3a** in low yields (entries 3 and 4). Other oxidants $^tBuO_2H$ and H_2O_2 urea complex were ineffective for this transformation, but provided alkene isomerization products (entries 5 and 6). Excitingly, the reaction afforded product **3a** in 98% yield with benzoquinone (BQ) as an oxidant (entry 7). $Cu(OAc)_2$ and Ag_2O were also good oxidants for this reaction, but CuO and $AgNO_3$ gave inferior results (entries 8–11). Dioxygen was proven to be a less effective oxidant (entry 12). Importantly, no reaction occurred in the absence of palladium catalyst (entry 13).

Table 1 Optimization of the reaction conditions[a]



1a **3a**

Entry	[O]	Yield[b]
1	$PhI(OPiv)_2$	26%
2	$PhI(OAc)_2$	19%
3	$(NH_4)_2S_2O_8$	16%
4	$Na_2S_2O_8$	20%
5	^tBuOOH	0 (25%)[c]
6	H_2O_2·urea	0 (42%)[c]
7	BQ	98%
8	$Cu(OAc)_2$	87%
9	CuO	40% (25%)[c]
10	Ag_2O	86%
11	$AgNO_3$	13% (26%)[c]
12	O_2 (1 atm)	30% (17%)[c]
13[d]	BQ	—

[a] Reaction conditions: **1a** (0.1 mmol), $Pd(OAc)_2$ (5 mol%), [O] (2 equiv.), $PhCOCO_2H$ (2 equiv.) in CH_3CN (0.5 mL). [b] ^1H NMR yield with CF_3-DMA as an internal standard. [c] Yield of the isomer of **1a**. [d] Without $Pd(OAc)_2$.

With the above optimized reaction conditions in hand, substrate scope was further investigated. Firstly, different protecting groups on nitrogen were surveyed. As shown in Table 2, substrates **1a–1d** bearing an aminocarbonyl group on nitrogen were compatible with these reaction conditions to afford

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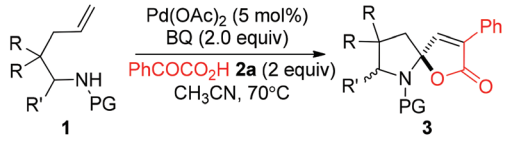
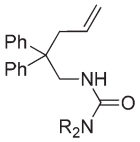
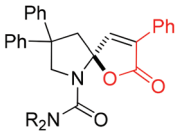
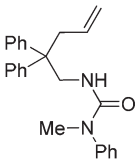
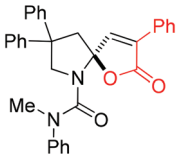
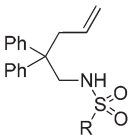
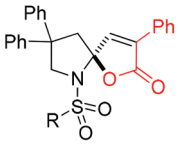
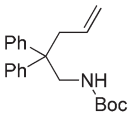
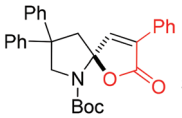
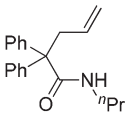
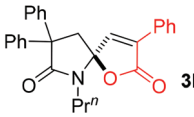
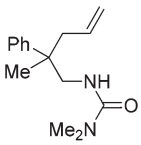
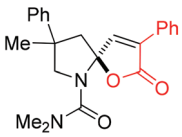
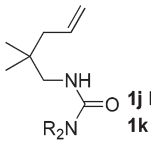
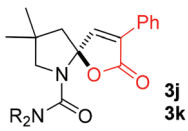
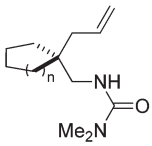
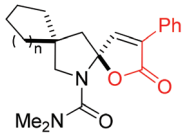
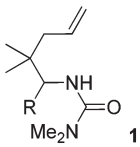
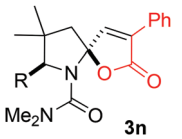
†Electronic supplementary information (ESI) available. See DOI: 10.1039/c4qo00002a

Table 2 Pd-catalyzed cascade cyclization[a,b]



Entry	Substrate	Product	Yield (%)
1	 **1a** R = Me	 **3a**	90%
2	**1b** R = Cy	**3b**	74%
3	**1c** R_2 = $(CH_2)_5$	**3c**	97%
4	 **1d**	 **3d**	71%
5	 **1e** R = p-$CH_3C_6H_4$	 **3e**	64%[c]
6	**1f** R = NMe_2	**3f**	84%
7	 **1g**	 **3g**	27%
8	 **1h**	 **3h**	71%
9	 **1i**	 **3i**	73% (3.7 : 1)[d]
10	 **1j** R = Me	 **3j**	69%
11	**1k** R = Et	**3k**	88%
12	 **1l** n = 1	 **3l**	72%
13	**1m** n = 2	**3m**	70%
14	 **1n** R = Me	 **3n**	92% (10 : 1)[d]
15	**1o** R = Bu^n	**3o**	95% (11 : 1)[d]
16	**1p** R = Ph	**3p**	88% (16 : 1)[d]

[a] Reaction conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (5 mol%), benzoquinone (2 equiv.), $PhCOCO_2H$ **2a** (2 equiv.), in CH_3CN (1.0 mL) at 70 °C for 16 h. [b] Isolated yield. [c] At 90 °C. [d] *d.r.* Ratio of crude product.

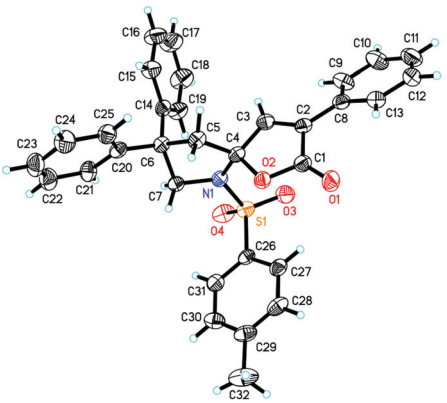
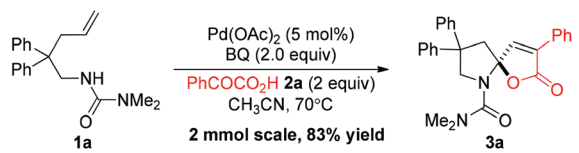


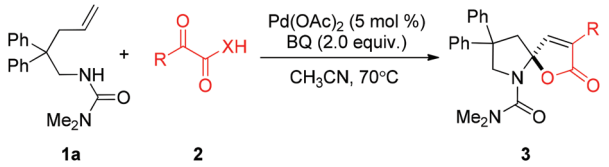
Fig. 1 The X-ray of compound **3e**.

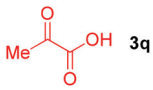
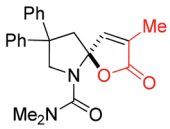
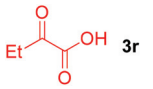
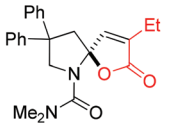
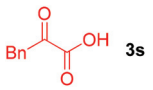
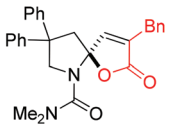
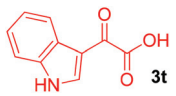
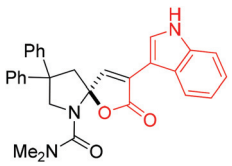
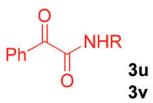
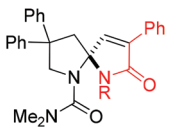
products **3a–3d** in good yields (entries 1–4). In addition, the sulfonyl group proved to be a good protecting group. For instance, the reaction of substrate **1e** bearing a *p*-toluenesulfonyl group afforded the corresponding product **3e** in 64% yield, and the structure of **3e** was confirmed by X-ray crystallization spectroscopy (Fig. 1). The reaction of **1f** bearing a sulfonylamide group gave product **3f** in 84% yield (entries 5 and 6). Compared to the aforementioned substrates, substrate **1g** installing a *tert*-butoxycarbonyl (Boc) protecting group was incompatible with the reaction conditions to give product **3g** in 27% yield (entry 7). However, amide substrate **1h** was suitable for this transformation to produce **3h** in 71% yield (entry 8). The above results demonstrated that diverse protecting groups were compatible with the standard conditions to deliver the *spiro-N,O*-acetal products. Next, we turned our attention to explore the substrate scope of alkenes. The substrate **1i** bearing methyl and phenyl groups on the carbon chain afforded product **3i** in 73% yield but with moderate diastereoselectivity (3.7 : 1, entry 9). Substrates **1j** and **1k** bearing the dimethyl group provided corresponding products **3j–3k** in good yields (entries 10 and 11). In addition, cyclic substrates **1l–1m** proved to be compatible for this reaction to give *bis-spiro-N,O*-acetal products **3l–3m** in good yields (entries 12 and 13). Finally, substrates **1n–1p** bearing a substituent on the adjacent position to nitrogen were tested. Gratifyingly, high diastereoselectivities were observed in these reactions, and products **3o–3p** were delivered in excellent yields (entries 14–16).[6] It was worth noting that the reaction of **1a** on the 2 mmol scale also provided the desired product **3a** in 83% yield (eqn (1)). However, significant Thorpe–Ingold effect was observed in this cyclization reaction. No desired product was obtained in the reaction of substrate **1q** without substituents on the carbon chain (eqn (2)).



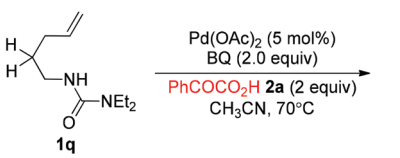
(1)

Table 3 Pd-catalyzed cascade cyclization[a]



Entry	Acid	Product	Yield
1	 **3q**		94%
2	 **3r**		89%
3	 **3s**		65%
4	 **3t**		82%
5	 **3u** R = Ts		60%
6	**3v** R = Ph		0%

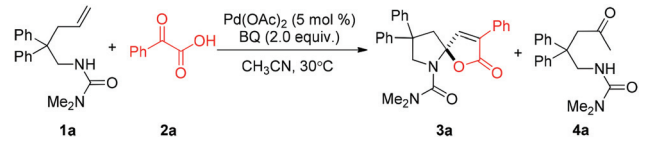
[a] Reaction conditions are the same as in Table 2.

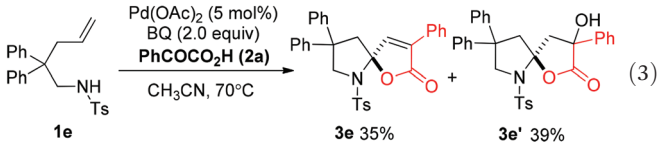


(2)

Next, several pyruvic acids were investigated for this Pd-catalyzed cascade cyclization. As shown in Table 3, pyruvic acids **2b–2d** exhibited a similar reactivity as **2a** to form *spiro-N,O*-acetals **3q–3s** in moderate to excellent yields (entries 1–3). Very excitingly, 3-indoleglyoxylic acid **2e** without the protecting group on nitrogen was also compatible with current reaction conditions to afford the corresponding product **3t** in good yield (82%). Furthermore, the amide derivatives from phenylpyruvic acid were surveyed. We were delighted to find that substrate **2f** with the tosyl group was also suitable for this transformation to give *spiro-N,N*-acetal **3u** in 60% yield (entry 5). However, the less acidic substrate **2g** proved to be ineffective (entry 6).

In order to understand the mechanism, the reaction of **1a** was monitored by ^{1}H NMR at 30 °C. As shown in Fig. 2, we found that an intermediate **4a** was initially formed, and then gradually transformed to product **3a** (Fig. 2). An independent experiment demonstrated that compound **4a** could be easily reacted with **2a** to produce **3a** in the absence of $Pd(OAc)_2$ in high yield (86%). In addition, in the case of **1e**, when the reaction was conducted at 70 °C, product **3e′** was obtained in 39% yield, combined with 35% yield of **3e** (eqn (3)). These results indicate that the reaction is possibly initiated to give a ketone product **4a**, followed by a sequential aldol reaction[7] and condensation to give intermediate **III**, which undergoes dehydration to deliver the final product **3a** (Scheme 1).[8]





(3)

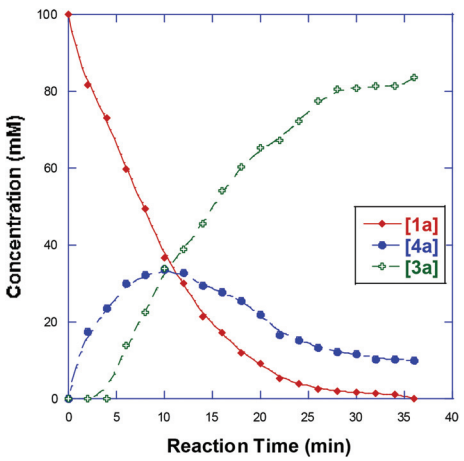
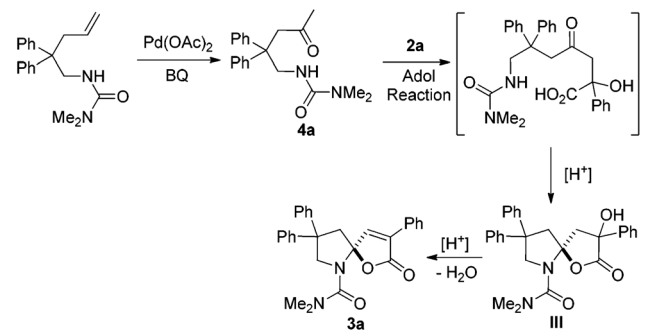
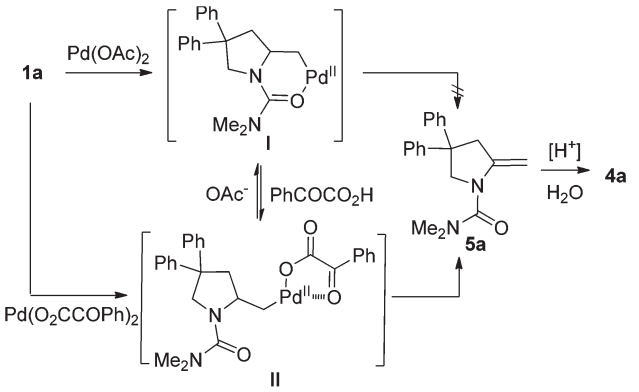


Fig. 2 Time course of reaction of **1a**.

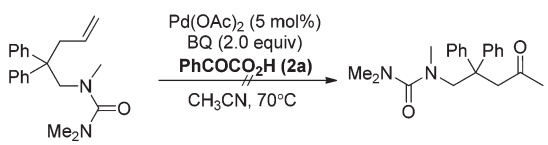


Scheme 1 Proposed mechanism.

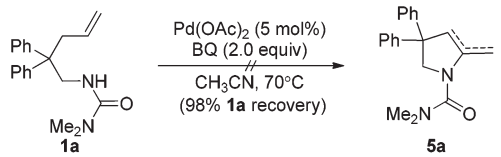


Scheme 2 Proposed pathway for **4a** formation.

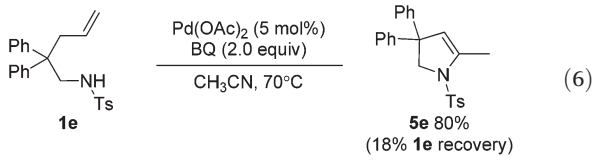
For the formation of compound **4a**, the reaction might involve a Wacker process.[9] However, when the substrate *N*-Me-**1a** was treated under standard reaction conditions, the corresponding Wacker product *N*-Me-**4a** was not observed (eqn (4)).[10] The result revealed that this pathway is unlikely.[11] Alternatively, **4a** might be derived from the hydrolysis of enamide **5a**, which was generated from an intramolecular Aza-Wacker reaction catalyzed by Pd catalyst.[12] When the reaction of **1a** was treated with $Pd(OAc)_2$ in the presence of BQ but without acid, no reaction occurred, and **1a** was recovered quantitatively (eqn (5)). In contrast, the reaction of **1e** afforded oxidative amination product **5e** in 80% yield (eqn (6)). The possible reason is that, after aminopalladation of alkenes, β-H elimination was inhibited due to the chelation of palladium intermediate **I**. However, the final β-H elimination occurs in the reaction of **1e** due to the very weak chelation of the tosyl group, followed by alkene isomerization to give enamine **5e** (Scheme 2). Very interestingly, when the catalyst $Pd(OAc)_2$ was replaced with $Pd(O_2CCOPh)_2$, the reaction of **1a** yielded product **4a** in 15% yield, combined with a small amount of *spiro* product **3a** (eqn (7)).[13] This result implied that palladium intermediate **I** could be equilibrated with intermediate **II** in the case of $Pd(O_2CCOPh)_2$ or in the presence of $PhCOCO_2H$, and palladium intermediate **II** could undergo β-H elimination to afford **5a** (Scheme 2). With further hydrolysis, compound **5a** could be converted to ketone product **4a** in the presence of a strong acid (such as **2a**).[14]



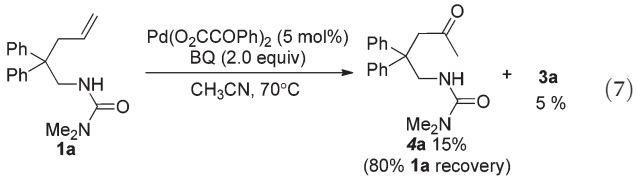
(4)



(5)



(6)



(7)

In conclusion, we have discovered a facile Pd-catalyzed cascade cyclization to synthesize a variety of *spiro-N,O*-acetals from simple alkenylamines. Further mechanistic study indicated that the reaction involves a palladium-catalyzed intramolecular oxidative Aza-Wacker cyclization and the following hydrolysis, aldol reaction, cyclization, and dehydration. Among these transformations, strongly acidic properties of pyruvic acid play an important role.

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