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RESEARCH ARTICLE

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 ^tBuO₂H and H₂O₂ urea complex were ineffective for this transformation, but provided

Table 1 Optimization of the reaction conditions^a

Entry	[O]	Yield ^b
1	Phl(OPiv) ₂	26%
2	Phl(OAc) ₂	19%
3	$(NH_4)_2S_2O_8$	16%
4	$Na_2S_2O_8$	20%
5	^t BuOOH	$0(25\%)^{c}$
6	H ₂ O ₂ ·urea	$0(42\%)^{c}$
7	BQ	98%
8	$Cu(OAc)_2$	87%
9	CuÒ	$40\% (25\%)^c$
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 $Pd(OAc)_2$.

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 Ag₂O were also good oxidants for this reaction, but CuO and AgNO₃ 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).

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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 Table 2
 Pd-catalyzed cascade cyclization^{a,b}

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Entry	Substrate	Product	Yield (%)
		Ph Ph	
	PhNH	Ph	
1	≽o	N O	90%
1 2	R_2N 1a R = Me 1b R = Cy	R ₂ N	74%
3	1c $R_2 = (CH_2)_5$	3c	97%
	Dh. /	Ph Ph	
	Ph Ph	N	
4) =0 1d	Me N 3d	71%
	Me-N Ph	Ph	
	//	Ph Ph	
	Ph	Ph	
	Ph NH O	5-S=O	
5	Ph' \searrow NH O S'O 1e R = p-CH ₃ C ₆ H ₄ 1f R = NMe ₂	R O 3e	64% ^c
6	1f R = NMe ₂	3f Ph	84%
	Ph	Ph	
7	Ph NH 1g Boc	N 3g	27%
	Boc //	Boc Ph	
	Ph	Ph Ph	
8	Ph NH 1h	ON 3h	71%
	Ő′ `¹Pr ″	Pr ⁿ	
	Ph _	Me Ph	
	Me NH	N O	
9	≻⊝O 1i Me₂N	Me ₂ N O 3i	$73\% (3.7:1)^d$
	//		
		Ph	
10	NH	N 3i	60%
11	R_2N 1k R = Et	R ₂ N O 3k	69% 88%
	<u>//</u>	Ph	
12	` 'n	N 0 3I	72%
13	Me_2N 1m n = 2	Me ₂ N O 3m	70%
		Ph	
	× ,,,,		
	NH R >=O	R N O	
14	Me_2N 1n R = Me	Me ₂ N 3n	92% $(10:1)^d$
15 16	1o R = Bu ⁿ 1p R = Ph	3o 3p	95% $(11:1)^d$ 88% $(16:1)^d$
	- P	• •	

 $[^]a$ Reaction conditions: **1a** (0.2 mmol), Pd(OAc)₂ (5 mol%), benzoquinone (2 equiv.), PhCOCO₂H **2a** (2 equiv.), in CH₃CN (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 tertbutoxycarbonyl (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,Oacetal 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 11-1m 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)).

Table 3 Pd-catalyzed cascade cyclization^a

Entry	Acid	Product	Yield
1	Me OH 3q	Ph Me	94%
2	Et OH 3r	Me ₂ N O	89%
3	Bn OH 3s	Ph Ph NO Me ₂ NO	65%
4	O OH HN O 3t	Ph Ph Ne ₂ N O	82%
5 6	NHR 3u R = Ts 3v R = Ph	Ph Ph N N N N O Me ₂ N O	60% 0%

^a Reaction conditions are the same as in Table 2.

Next, several pyruvic acids were investigated for this Pdcatalyzed 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).

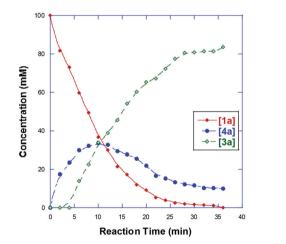


Fig. 2 Time course of reaction of 1a.

Scheme 1 Proposed mechanism.

Scheme 2 Proposed pathway for 4a formation.

For the formation of compound 4a, the reaction might involve a Wacker process. 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 BO 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(O₂CCOPh)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(O₂CCOPh)₂ or in the presence of PhCOCO₂H, 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

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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