Palladium-Catalyzed Cascade Cyclization for the Construction of spiro-N,O-Acetals

Journal:	*Organic Chemistry Frontiers*
Manuscript ID:	QO-RES-01-2014-000002.R1
Article Type:	Research Article
Date Submitted by the Author:	26-Jan-2014
Complete List of Authors:	Liu, Guosheng; Shanghai Institute of Organic Chemistry, State Key Laboratory of Organometallic Chemistry Cheng, Jiashun; Shanghai Institute of Organic Chemistry, State Key Laboratory of Organometallic Chemistry Chen, Pinhong; Shanghai Institute of Organic Chemistry, State Key Laboratory of Organometallic Chemistry

Org.Chem.Front Organic Chemistry Frontiers Dynamic Article Links ►

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/orgchemfront

COMMUNICATION

Palladium-Catalyzed Cascade Cyclization for the Construction of *spiro*-N,O-Acetals†

Jiashun Cheng, Pinhong Chen and Guosheng Liu*[a]

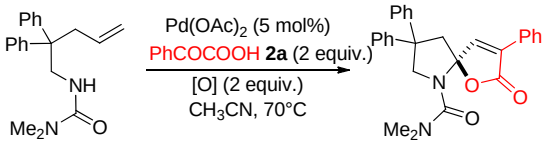
Received (in XXX, XXX) Xth XXXXXXXXX 30XX, Accepted Xth XXXXXXXXX 30XX
DOI: 10.1039/b000000x

A facile Pd-catalyzed cascade cyclization of N-alkenylamine and pyruvic acids was discovered to construct *spiro*-N,O-acetals. This transformation was intiated by a intramolecular oxidative amination alkenes, followed by hydrolysis to give 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 have 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 reported a highly efficient synthetic approach to construct this *spiro*-N,O-acetals from simple alkenes by using palladium as catalyst.

In 2009, our group reported a palladium-catalyzed intramolecular aminofluorination of *N*-tosyl alkenes to give fluorinated pipyridine derivatives with highly regioselectivity.[4] Quite recently, the regioselectivity could be switched from *endo*- to *exo*-cyclization by replacing tosyl group at nitrogen with a chelating group, such as 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 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 additive, *albelt* in low yield (< 10%). The highly efficient construction of *spiro*-N,O-acetal product inspired us to optimize the reaction condition, 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 slightly low yield (~ 30%) using hypervalent iodine oxidant (entries 1-2), and aminooxygenation product was the major product. Strong oxidants $(NH_4)_2S_2O_8$ and $Na_2S_2O_8$ also gave **3a** in low yields (entry 3-4). Other oxidants $^tBuO_2H$ and H_2O_2 urea complex were ineffective for this transformation, but provided alkene isomerization product (entries 5-6). 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]



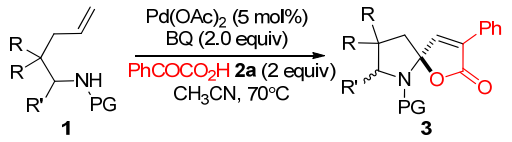
1a **3a**

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 internal standard. [c] Yield of isomer of **1a**. [d] without $Pd(OAc)_2$.

With above optimized reaction condition in hand, substrate scope was further investigated. Firstly, different protecting groups on nitrogen was surveyed. As shown in Table 2, substrates **1a-1d** bearing a aminocarbonyl group on nitrogen were compatibile to this reaction condition to afford products **3a-3d** in good yields (entries 1-4). In addition, sulfonyl group was proved to be a good protecting group. For instance, the reaction of substrate **1e** bearing a *p*-toluenesulfonyl group afforded corresponding product **3e** in 64% yield, and the structure of **3e** was confirmed by X-Ray crystallazation spectroscopy. The reaction of **1f** bearing a sulfonylamide group gave product **3f** in 84% yield (entries 5-6). Compared to aforementioned substrates, substrate **1g** installing a *tert*-butoxycarbonyl (Boc) protecting group was incompatible with the reaction condition to give product **3g** in 27% yield (entry 7). However, amide substrate **1h**

Table 2. Pd-Catalyzed Cascade Cyclization.[a,b]



1 3

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**	96% (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 16h. [b]Isolated yield. [c] at 90 °C. [d]*d.r.* ratio of crude product.

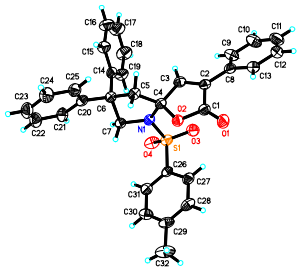
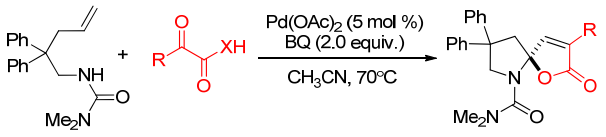


Figure 1. The X-Ray of Compound **3e.**

was suitable for this transformation to produce **3h** in 71% yield (entry 8). Above results demonstrated that diverse protecting group was compatible to the standard condition to deliver the *spiro-N,O*-acetal products. Next, we turned our attention to explore substrate scope of alkenes. For the substrate **1i** bearing methyl and phenyl group on the carbon chain afforded product **3i** in 73% yield but with moderate diastereoselectivity (3.7:1, entry 9). Substrates **1j** and **1k** bearing dimethyl group provided corresponding products **3j-3k** in good yields (entries 10-11). In addition, cyclic substrates **1l-1m** were proved to be compatible for this reaction to give *bis-spiro-N,O*-acetal products **3l-3m** in

Table 3. Pd-Catalyzed Cascade Cyclization.[a]

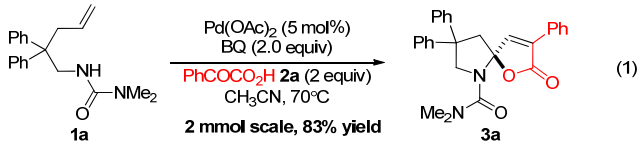


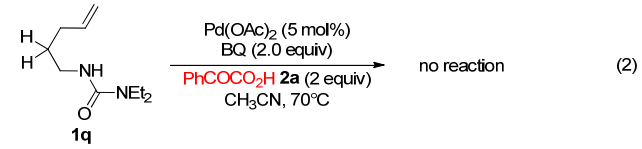
1a 2 3

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

[a] Reaction condition is same with Table 2.

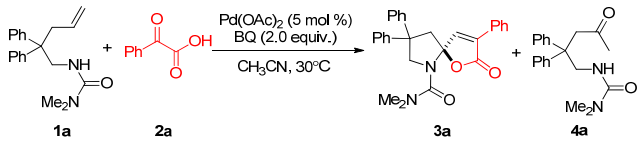
good yields (entries 12-13). Finally, substrates **1n-1p** bearing a substituent on the adjecent position of nitrogen were tested. Gratifyingly, high diastereoselectivities were observed in these reaction, and products **3o-3p** were delivered in excellent yields (entries 14-16).[6] It was worthy noting that the reaction of **1a** in 2 mmol scale also provided desired product **3a** in 83% yield (eq 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 (eq 2).





Next, several pyruvic acids were investigated for this Pd-catalyzed cascade cyclization. As shown in Table 3, pyruvic acids **2b-2d** were exhibited a similar reactivity as **2a** to form *spiro*-*N*,*O*-acetals **3q-3s** in moderate to excellent yileds (entries 1-3). Very excitingly, 3-indoleglyoxylic acid **2e** without protecting group on nitrogen was also compatible to current reaction condition 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 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** was 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 Figure 2, we found that a intermediate **4a** was initially formed, and then gradually transformed to product **3a** (Figure 1). 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, for the case of **1e**, when reaction was conducted at 70 °C, product **3e'** did obtain in 39% yield, combined with 35% yield of **3e** (eq 3). Those results indicationed that the reaction is possibly initiated to give a ketone product **4a**, followed by a seqential aldol reaction[7] and condensation to give intermediate **III**, which undergoes dehydration to deliver final product **3a** (Scheme 1).[8]



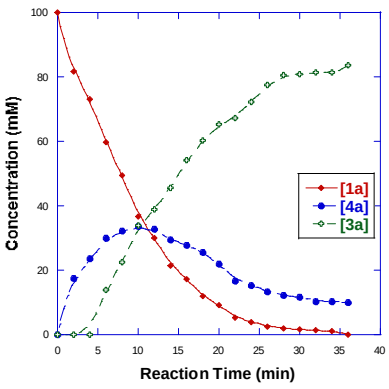
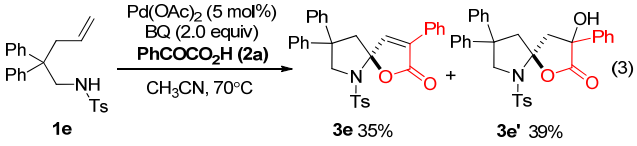
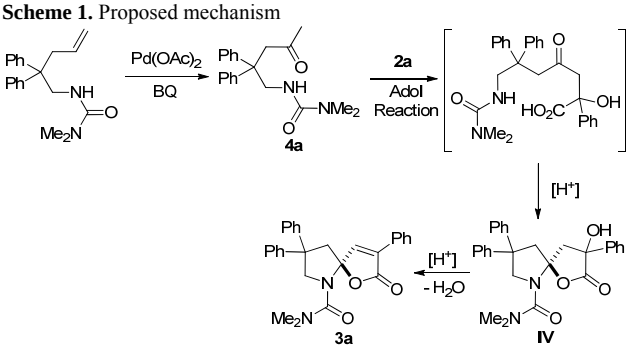


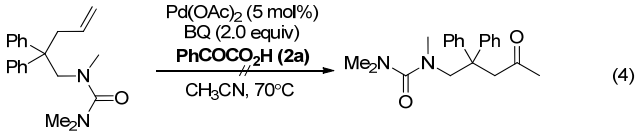
Figure 2. Time Course of Reaction of **1a**.

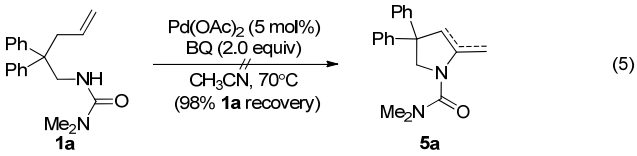


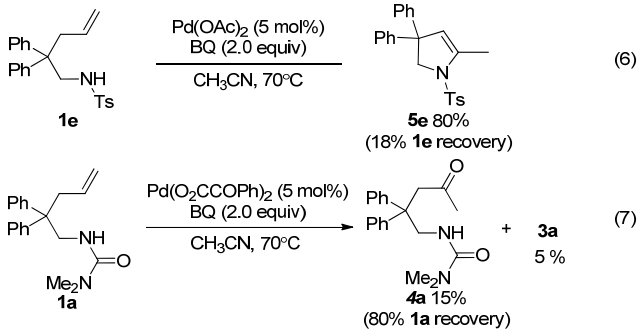
Scheme 1. Proposed mechanism



For the formation of compound **4a**, the reaction might involve a Wacker process.[9] However, when substrate *N*-Me-**1a** was treated under standard reaction condition, the corresponding Wacker product *N*-Me-**4a** was not observed (eq 4).[10] The result revealed that this pathway is unlikely.[11] Alternatively, **4a** might be derived from the hydrolysis of enamide **5a**, which generated from intramolecular Aza-Wacker reaction catalyzed by Pd catalyst.[12] When reaction of **1a** was treated by $Pd(OAc)_2$ in the presence of BQ but without acid, no reaction occurred, and **1a** was recovered quantitatively (eq 5). In contrast, the reaction of **1e** afforded oxidative amination product **5e** in 80% yield (eq 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 tosyl group, and followed by alkene isomerization to give emamine **5e** (Scheme 2). Very interesting, when catalyst $Pd(OAc)_2$ was replaced $Pd(O_2CCOPh)_2$, the reaction of **1e** yielded product **4a** in 15% yield, combined with small amount of *spiro* product **3a** (eq 7).[13] This result implied that palladium intermediate **I** could be equilibrated with intermediate **II** in the case of $Pd(O_2CCOPh)_2$ or

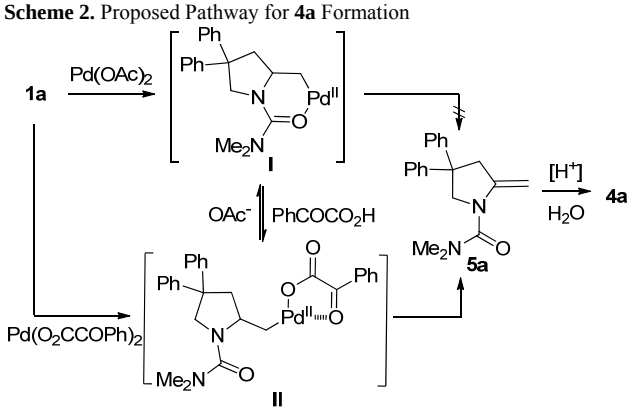






in the presence of $PhCOCO_2H$, and palladium intermediate **II** could undergo β-H elimination to afford **5a** (Scheme 2). With further hydrolysis, compound **5a** could be converted to ketone product **4a** in the presence of strong acid (such as **2a**).[14]

Scheme 2. Proposed Pathway for **4a** Formation



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 following hydrolysis, Adol reaction, cyclization, and dehydration. Among these transformations, strong acidic property of pyruvic acid plays an important role.

We are grateful for financial support from 973 program (NO. 2011CB808700), NSFC (Nos. 21225210, 20923005 and 21121062), STCSM (11JC1415000), and the CAS/SAFEA International Partnership Program for Creative Research Teams.

Notes and references

1 (a) R. F. Heck, *Palladium Reagents in Organic Synthesis*. Ed.; Academic: New York, 1985; (b) A. Ricci, *Modern Amination Methods*. Ed.; Wiley-VCH: Weinheim, 2000; (c) K.C. Nicolaou, E. J. Sorensen, *Classics in Total Synthesis: Targets, Strategies, Methods.* Ed.; Wiley-VCH: Weinheim, 1996; (d) E. Negishi, *Handbook of Organopalladium Chemistry for Organic Synthesis*. Ed.; John Wiley & Sons: New York, 2002; (e) B. M. Trost, I. Fleming, *Comprehensive Organic Synthesis*. Eds.; Pergamon: Oxford, 1991.

2 (a) E. Breuer, S. Zbaida, *Tetrahedron.* 1975, **31**, 499; (b) E. Leete, G. B. Bodem, *J. Am. Chem. Soc*. 1976, **98**. 6321; (c) F. He, Y. Bo, J. D. Altom, E. J. Corey, *J. Am. Chem. Soc*. 1999, **121**. 6771; (d) K. C. Nicolaou, S. M. Dalby, S. Li, T. Suzuki, D. Y.-K. Chen, *Angew. Chem. Int. Ed*, 2009, **48**, 7616; (e) H. Satoh, H. Ueda, H. Tokuyama, *Tetrahedron*, 2013, **69**, 89; (f) S. Sumi, K. Matsumoto, H. Tokuyama, T. Fukuyama, *Tetrahedron*, 2003, **59**, 8571.

3 (a) S. Naud, S. J. Macnaughton, B. S. Dyson, D. J. Woollaston, J. W. P. Dallimore, J. Robertson, *Org. Biomol. Chem*. 2012 , **10**, 3506; (b) J. L. Bullington,; J. H. Dodd, *J. Heterocyclic. Chem*. 1998, **35**, 397.

4 T. Wu, G. Yin, G. Liu, *J. Am. Chem. Soc.* 2009, **131**, 16354.

5 T. Wu, J. Cheng, P. Chen, G. Liu, *Chem. Comm.* 2013, **49**, 8707.

6 The detailed configurations of **3n**-**3p** were not clear at the moment.

7 (a) J. Liu, Z. Yang, Z. Wang, F. Wang, X. Chen, X. Liu, X. Feng, Z. Su, C. Hu, *J. Am. Chem. Soc*. 2008, **130**, 5654; (b) X. Zhu, A. Lin, L. Fang, W. Li, C. Zhu, Y. Cheng, *Chem.- Eur. J*. 2011, **17**, 8281; (c) X. Xu, Z. Tang, Y. Wang, S. Luo, L. Cun, L. Gong, *J. Org. Chem*, 2007, **72**, 9905. (d) A. Bender, D. Gtlnther und R. Wingen, *Liebigs Ann. Chem*. 1985, 579; (f) R. B. Salem, G. Jenner, *Tetrahedron Lett*. 1986, **27**. 1575.

8 (a) P. Wang, W.J. Asbell, Patent: US4968812 A1, 1990; (b) J. S. Yadav, K. V. Raghavendra, A. Kavita, D. K. Mohapatra, *Eur. J. Org. Chem*. 2013, 2849; (c) L. N. Aldrich, C. B. Berry, B. S. Bates, L. C. Konkol, M. So, C. W. Lindsley, *Eur. J. Org. Chem.* 2013, 4215; (d) G. Spagnol, A. Rajca, S. Rajca, *J. Org. Chem*, 2007, **72**, 1867; (e) Y. Fu, F. Ye, W. Xu, *Heterocycl. Commun*. 2011, **16**, 43.

9 (a) P. M. Henry, *Palladium Catalyzed Oxidation of Hydrocarbons*; D. Reidel, Dordrecht: Holland, 1980, p. 41. (b) P. M. Henry, In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley & Sons: New York, 2001; p. 209

10 The reaction of *N*-Me-**1a** afforded allylic acetoxylation product in 93% yield with 2.3:1 linear:branch ratio. For selective examples, see: (a) Y. Wu, G. Liu, *Top. Cur. Chem.* 2010, **292**, 195; (b) M. S. Chen, M. C. White, *J. Am. Chem. Soc.* 2004, **126**, 1346; (c) A. N. Campell, P. B. White, I. A. Guzei, S. S. Stahl, *J. Am. Chem. Soc.* 2010, **132**, 15116.

11 When some simple alkenes, such as styrene and 1-Octene, were treated under standard reaction, no any ketone products were observed. These results also against the Wacker process pathway.

12 (a) V. Kotov, C. C. Scarborough, S. S. Stahl. *Inorg. Chem.* 2007, **46**, 1910; (b) M. M. Rogers, Va. Kotov, J. Chatwichien, S. S. Stahl, *Org. Lett*. 2007, **9**, 4331; (c) J. E. Redford, R. I. McDonald, M. L. Rigsby, J. D. Wiensch, S. S. Stahl, *Org. Lett*. 2012, **14**, 1242; (d) A. B. Weinstein, D. P. Schuman, Z. X. Tan, S. S. Stahl, *Angew. Chem. Int. Ed.* 2013, **52**, 11867. (e) Michael, F. E.; Cochran, B. M. *J. Am. Chem. Soc*. 2006, **128**, 4246.

13 The low conversion is possibly due to the exhausted of benzoyl-formic acid **2a**, which reacted with **4a** to give **3a**.

14 (a) P. J. A. Demoen, P. A. J. Janssen, J. L. M. Loomans. *J. Am. Chem. Soc.* 1959, **81**, 6286; (b) D. H. R. Barton, N. J. A. Gutteridge, R. H. Hesse, M. M. Pechet, *J. Org. Chem.* 1969, **34**, 1473; (c) H.-Y. Lee, Y.-H. Lee, *Synlett* 2001, 1656.

