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Cationic Pd(II)-catalyzed cyclization of *N*-tosyl-aniline tethered alkynyl ketones initiated by hydropalladation of alkynes: a facile way to 1,2-dihydro or 1,2,3,4-tetrahydroquinoline derivatives†

Kun Shen, Xiuling Han,* Guoqin Xia and Xiyun Lu*

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A cationic Pd(II)-catalyzed intramolecular alkyne-carbonyl reductive coupling reaction of *N*-tosyl-aniline tethered alkynyl ketones under transfer hydrogenation conditions to give hydroquinolines is developed.

Hydrogenated quinoline derivatives, 1,2-dihydroquinolines and 1,2,3,4-tetrahydroquinolines, are ubiquitous in biochemical, biological and medicinal structures. They are an important class of compounds in the pharmaceutical and agrochemical industries, as well as building blocks for the total synthesis of natural products.¹ In the past few decades, numerous studies have been conducted to evaluate their potential utilities such as antifungal and anticancer activity,² antioxidant effects,³ and their role as ligands in some asymmetric synthesis.⁴ Consequently, a number of strategies have been developed for the synthesis of these scaffolds including partial hydrogenation of quinolines, Lewis acids, transition-metal- or organo-catalyzed intra- and intermolecular cyclization reactions.^{1d,5} Although many methods for the synthesis of these hydroquinolines have been established, there still exist some drawbacks such as harsh reaction conditions, prolonged reaction time, limited scope of substrates and modest selectivity, which promote chemists to explore other novel reactions to produce them more efficiently and conveniently.

In designing a new method for the synthesis of these hydroquinolines, palladium(II)-catalyzed cyclization of *N*-tosyl-aniline-tethered alkynyl ketones was selected. As we know, palladium(II)-catalyzed tandem reactions have emerged as a powerful and efficient tool for the rapid construction of C–C bonds, which have been widely used in the synthesis of many complex molecules.⁶ For the cyclization of alkynyl ketones,

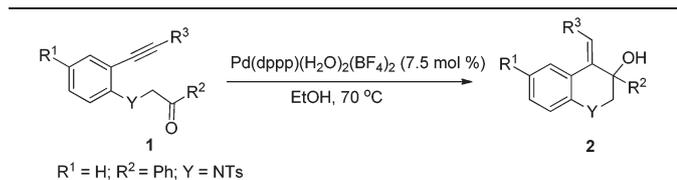
there are mainly two modes for the initiation of the palladium(II)-catalyzed reactions: nucleopalladation of alkynes and transmetallation of boron reagents with palladium(II). In these reactions, the nucleopalladation of alkynes or the insertion of alkynes into the C–Pd bond (formed from the transmetallation of boron reagents with palladium(II) complexes) can produce an alkenylpalladium species which consequently adds to the carbonyl group to offer a class of hydroxyl-bearing carbo- or heterocyclic compounds in an atom economical way. Using this methodology, our group has developed some novel tandem reactions in a redox-free way.⁷ Recently, we have found that the Pd–H species generated from cationic palladium complexes and ethanol can also realize similar cyclization reactions⁸ which have not been reported in the literature.⁹ Following our ongoing interest in palladium(II)-catalyzed tandem reactions, we wish to report now a cationic palladium(II)-catalyzed intramolecular alkyne-carbonyl reductive coupling reaction by using *N*-tosyl-aniline tethered alkynyl ketones as the substrates, allowing access to functionalized 1,2-dihydro or 1,2,3,4-tetrahydroquinolines.

In our previous work, it was found that the steric effect of the substituents on alkynes was important for the reductive cyclization.⁸ Thus, the steric effect of substituent R³ in substrates **1** for this new reaction was studied first. As can be seen from Table 1, the sterically hindered group such as ^tBu or SiMe₃ favored the transformation, which is in accordance with the previous work (Table 1, entries 1–4). Owing to the easy further transformation of the silicon moiety, compound **1e** was chosen as the model substrate for reaction condition screening.

In our initial study, substrate **1e** was reacted in ethanol (0.1 M) in the presence of 7.5 mol% of [Pd(dppp)(H₂O)₂](BF₄)₂ at 70 °C for 6 h (Table 2, entry 1). The reductive cyclization products **2e** and **3e** were isolated in 95% total yield. When the

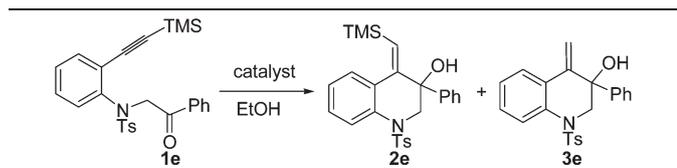
State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, P. R. China. E-mail: xlhan@mail.sioc.ac.cn, xylu@mail.sioc.ac.cn

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Table 1 Steric effect of the substituent R³ for the reductive cyclization reaction^a

Entry	R ³	Substrate	Time (h)	Products	Yield ^b (%)
1	H	1a	24	2a	Trace
2	ⁿ Bu	1b	24	2b	Trace
3	Ph	1c	24	2c	17
4	^t Bu	1d	12	2d	80
5 ^c	SiMe ₃	1e	6	2e	62

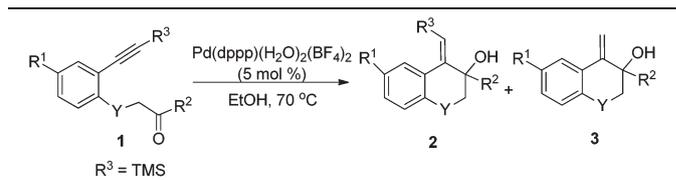
^a Conditions: reactions were carried out with **1** (0.20 mmol) and the catalyst (7.5 mol%) in EtOH (2.0 mL) at 70 °C. ^b Isolated yield. ^c Desilylation product **3e** was also isolated (see Table 2, entry 1).

Table 2 Screening of reaction conditions^a

Entry	Catalyst ^b	Temp. (°C)	Time (h)	Yield ^c (%)		
				2e	3e	Total
1	Cat. I	70	6	62	33	95
2	Cat. I	50	8	68	22	90
3 ^d	Cat. I	70	6	58	34	92
4	Cat. II	70	24	29	25	54
5 ^e	Cat. I	70	10	66	32	98
6 ^e	Cat. III	70	10	24	69	93
7	Cat. III	70	18	0	75	75
8	Cat. IV	70	24	N.R.		

^a Conditions: reactions were carried out with **1e** (0.20 mmol) and the catalyst (7.5 mol%) in EtOH (2 mL). ^b Cat. I: [Pd(dppp)(H₂O)₂](BF₄)₂; Cat. II: [Pd(*rac*-binap)(H₂O)₂](BF₄)₂; Cat. III: [Pd(dppp)(H₂O)₂](OTf)₂; Cat. IV: [Pd(bpy)(μ-OH)₂](OTf)₂. ^c Isolated yield. ^d ^tPrOH was used as the solvent. ^e Catalyst (5 mol%) was added.

reaction temperature was decreased to 50 °C, a slightly lower yield was obtained (90%, Table 2, entry 2). ^tPrOH also gave a good total yield, whereas the amount of desilylation product **3e** was increased (Table 2, entry 3). The use of [Pd(*rac*-binap)(H₂O)₂](BF₄)₂ as the catalyst lowered the total yield to 54% (Table 2, entry 4). Reducing the amount of the catalyst [Pd(dppp)(H₂O)₂](BF₄)₂ to 5 mol% did not compromise the yield (Table 2, entry 5). Interestingly, under the catalysis of [Pd(dppp)(H₂O)₂](OTf)₂, **3e** was obtained as the major product and **2e** could transfer to **3e** completely with a long reaction time (Table 2, entries 6 and 7). The catalyst [Pd(bpy)(μ-OH)₂](OTf)₂ was totally ineffective to the reaction (Table 2, entry 8). On the basis of the above investigation, the optimal conditions for this reductive cyclization reaction are as follows:

Table 3 Cationic Pd(II)-catalyzed synthesis of 1,2,3,4-tetrahydroquinolines **2** and **3**^a

Entry	Substrate			Y	T (h)	Yield ^b (%)	
	R ¹	R ²	Y			2	3
1	H	Ph	NTs	1e	10	66 2e	32 3e
2	F	Ph	NTs	1f	6	63 2f	29 3f
3	Cl	Ph	NTs	1g	8	76 2g	14 3g
4	Me	Ph	NTs	1h	10	75 2h	20 3h
5	H	<i>p</i> -NO ₂ -C ₆ H ₄	NTs	1i	10	62 2i	27 3i
6	H	<i>p</i> -Me-C ₆ H ₄	NTs	1j	12	59 2j	33 3j
7	H	<i>p</i> -OMe-C ₆ H ₄	NTs	1k	8	46 2k	26 3k
8	H	<i>p</i> -Cl-C ₆ H ₄	NTs	1l	10	71 2l	26 3l
9	H	<i>o</i> -Me-C ₆ H ₄	NTs	1m	12	Trace	0
10	H	Me	NTs	1n	6	33 2n	31 3n
11	H	^t Bu	NTs	1o	12	N.R.	
12	H	Ph	NMs	1p	4	47 2p	38 3p
13	H	Ph	O	1q	4	53 2q	24 3q

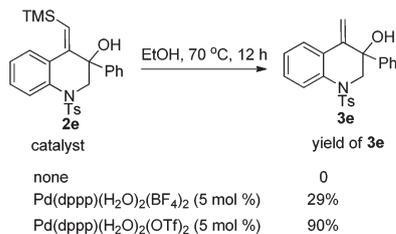
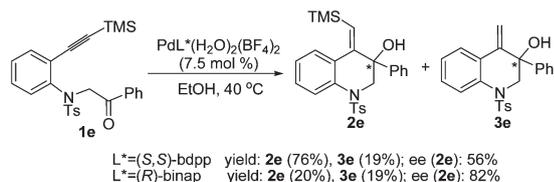
^a Conditions: reactions were carried out with **1** (0.20 mmol) and the catalyst (5 mol%) in EtOH (2 mL) at 70 °C. ^b Isolated yield.

1e (0.2 mmol) and [Pd(dppp)(H₂O)₂](BF₄)₂ (5 mol%) in EtOH (2 mL) at 70 °C (Table 2, entry 5).

Under the optimal conditions, the substrate scope of the reaction was examined with a variety of *N*-tosyl-aniline tethered alkyne ketones and the results are summarized in Table 3. Substrates bearing a methyl group, fluoro or chloro atom on the benzene ring also gave good results which were similar to that of **1e** (Table 3, entries 2–4). Reactions occurred successfully when R² was an aromatic ring bearing a nitro, methyl group or chlorine atom, whereas a methoxy group had a deleterious effect (Table 3, entries 5–8). Ketones with a bulky group had no reactivity at all (Table 3, entries 9 and 11). Methyl ketone (**1n**) only provided a moderate total yield (Table 3, entry 10). NMs or O tethered substrates also reacted well for this cyclization (Table 3, entries 12 and 13). The structures of the products were confirmed by X-ray crystallography of **2g** as a typical example.

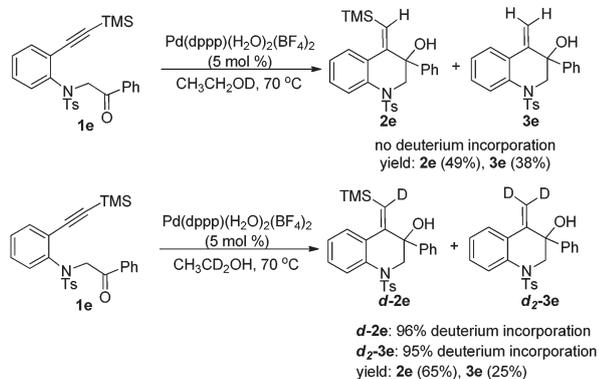
For the formation of products **3**, some control experiments were then conducted. Treatment of **2e** in ethanol without the catalyst did not give product **3e**. However, a transformation occurred in the presence of the catalyst [Pd(dppp)(H₂O)₂](BF₄)₂ or [Pd(dppp)(H₂O)₂](OTf)₂ and the latter could give a better result, indicating that **3e** might be generated from **2e** under the catalysis of the palladium(II) catalyst (Scheme 1).¹⁰

Next, the asymmetric version of this process using chiral phosphine ligands was carried out (Scheme 2). When the reaction was catalyzed by [Pd(*S,S*-bdpp)(H₂O)₂](BF₄)₂, a high total yield (95%) was obtained with substrate **1e**, whereas the asymmetric induction was moderate (**2e**, 56% ee). Under the catalysis of [Pd(*R*-binap)(H₂O)₂](BF₄)₂, the reaction gave **2e** in a higher ee value (82%), but the yield was low (39%).

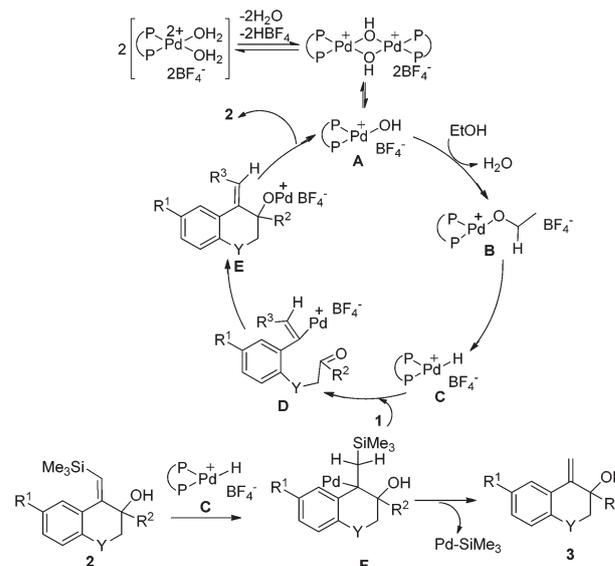
Scheme 1 Transformation of **2e** to **3e**.Scheme 2 Asymmetric reductive cyclization of **1e**.

To gain mechanistic insight, the reaction was then conducted in deuterated ethanol. Subjecting **1e** to the reductive cyclization reaction conditions in $\text{CH}_3\text{CH}_2\text{OD}$ gave products **2e** and **3e** in 87% total yield with no deuterium incorporation into the products. However, when $\text{CH}_3\text{CD}_2\text{OH}$ was used, the reaction could afford *d*-**2e** and *d*₂-**3e** with deuterium at the vinyl position in 90% total yield (Scheme 3). Thus, it was concluded that the vinyl hydrogen in the products was from the α -hydrogen of ethanol.

On the basis of the above results, a possible mechanism of this reductive cyclization reaction is shown in Scheme 4. The Pd hydroxy complex **A** is presumed to be the active catalytic species and it reacts with ethanol to generate Pd ethoxide complex **B**, which subsequently gives the Pd hydride complex **C** via β -hydride elimination.¹¹ Hydropalladation of the alkyne affords a vinylpalladium intermediate **D** followed by intramolecular addition to the carbonyl group to give the intermediate **E**. The protonolysis of the newly formed intermediate **E** generates products **2** and the Pd(II) species **A** to complete the catalytic cycle.



Scheme 3 Deuterium-labeling studies.

Scheme 4 Proposed mechanism for the formation of **2** and **3**.

On the other hand, the insertion of the C=C double bond of products **2** into Pd-H species (intermediate **C**) can produce intermediate **F**, which then undergoes β -desilylation to afford another products **3**.¹⁰ In Scheme 3, when $\text{CH}_3\text{CD}_2\text{OH}$ was used as the hydrogen source, both of the two vinyl hydrogens in the product **3e** were replaced by deuterium, which further verified that it was a palladium-catalyzed desilylation process in our reaction.

Having synthesized some 1,2,3,4-tetrahydroquinolines successfully by using our new reactions, we next studied the cyclization of another type of aniline tethered alkynyl ketones such as substrate **4a** under similar conditions. When **4a** was reacted in the presence of 5 mol% of $[\text{Pd}(\text{dppp})(\text{H}_2\text{O})_2](\text{BF}_4)_2$ in ethanol (0.1 M) at 70 °C for 24 h, the cyclization product 1,2-dihydroquinoline **5a** was formed, albeit in a low yield (38%, Table 4, entry 1). Excitingly, the yield of **5a** was increased to 85% using $[\text{Pd}(\text{dppp})(\text{H}_2\text{O})_2](\text{OTf})_2$ as the catalyst (Table 4, entry 2). The catalyst $[\text{Pd}(\text{rac-binap})(\text{H}_2\text{O})_2](\text{OTf})_2$ can also give a moderate yield of **5a** (72%, Table 4, entry 3). The yield decreased at a lower temperature (Table 4, entry 4). Only 12% yield was obtained while using 4 Å molecular sieves as the additive (Table 4, entry 5). The reaction did not occur under the catalysis of $\text{Pd}(\text{OAc})_2$ or $\text{Pd}(\text{CF}_3\text{COO})_2$ (Table 4, entries 6 and 7). Thus, the optimal reductive cyclization conditions for this kind of compound were as follows: **4a** (0.2 mmol) and $[\text{Pd}(\text{dppp})(\text{H}_2\text{O})_2](\text{OTf})_2$ (5 mol%) in EtOH (2 mL) at 70 °C.

With the optimal reaction conditions in hand, we studied the scope of this cyclization reaction (Table 5). For carbonyl groups in the substrates, phenyl alkyl ketones had higher reactivity than that of diphenyl ones (Table 5, **5a–5d**). Sterically hindered groups on the alkyne benefited the cyclization, which was similar to the results in Table 3 (Table 5, **5e–5h**). Substrates with the benzene ring substituted by a chlorine or bromine atom gave the corresponding products in good yields,

Table 4 Screening of reaction conditions^a

Entry	Catalyst	Yield ^b (%)
1	[Pd(dppp)(H ₂ O) ₂](BF ₄) ₂	38
2	[Pd(dppp)(H ₂ O) ₂](OTf) ₂	85
3	[Pd(<i>rac</i> -binap)(H ₂ O) ₂](OTf) ₂	72
4 ^c	[Pd(dppp)(H ₂ O) ₂](OTf) ₂	33
5 ^d	[Pd(dppp)(H ₂ O) ₂](OTf) ₂	12
6	Pd(OAc) ₂ + dppp	0
7	Pd(CF ₃ COO) ₂ + dppp	0

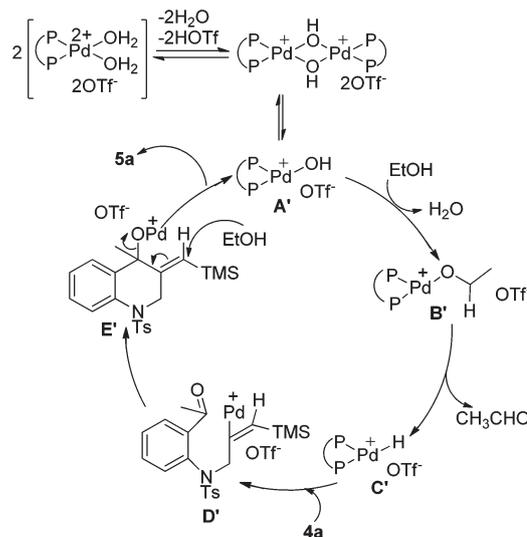
^a Conditions: reactions were carried out with **4a** (0.20 mmol) and the catalyst (5 mol%) in EtOH (2 mL) at 70 °C for 24 h, unless otherwise mentioned. ^b Isolated yield. ^c The reaction was performed at 50 °C. ^d 4 Å molecular sieves were added.

Table 5 Cationic Pd(II)-catalyzed synthesis of 1,2-dihydroquinolines **5**^{a,b}

Substrate 4	Product 5	Yield (%)
		85%
		87%
		63%
		42%
		25%
		35%
		95%
		82%
		76%
		82%
		42%
		55%
		0
		83%

^a Conditions: reactions were carried out with substrates **4** (0.20 mmol) and the catalyst (5 mol%) in alcohol (2 mL) at 70 °C until the consumption of the substrates as monitored by TLC. ^b Isolated yield.

but the methoxyl group deteriorated the reaction (Table 5, **5i–5k**). The naphthalene-ring tethered substrate **4l** also underwent cyclization with a moderate yield (Table 5, **5l**). When NTs in the substrate was changed to O, no reaction occurred at all (Table 5, **5m**). Finally, a similar reactivity was found when EtOH was replaced by *i*PrOH, indicating that the alcohols used in the cyclization not only provided the hydrogen source, but also acted as substrates in the subsequent transformation

**Scheme 5** Proposed mechanism for the formation of **5a**.

(Table 5, **5n**). The structures of the products were confirmed by X-ray crystallography of **5l** as a typical example.

A plausible mechanism is outlined in Scheme 5 and the process for the formation of intermediate **E'** is similar to that of intermediate **E** as shown in Scheme 4. Then intermediate **E'** is attacked by ethanol to promote the cleavage of the C–O bond to give the product and regenerate the palladium(II) species. Comparing with the reactions in Table 3, intermediate **E'** in this reaction can be attacked by the alcohol to undergo further transformation, which may be due to the stability of the conjugated double bond formed in the product.

In conclusion, two cationic Pd(II)-catalyzed intramolecular alkyne-carbonyl reductive coupling reactions under transfer hydrogenation conditions are developed. The reactions offer an environmentally benign method for the synthesis of 1,2-dihydro or 1,2,3,4-tetrahydroquinoline derivatives in high yields. Further studies on the asymmetric version of the reaction are in progress in our laboratory.

Acknowledgements

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