

Cationic Pd(II)-Catalyzed Tandem Reaction of 2-Arylethynylanilines and Aldehydes: An Efficient Synthesis of Substituted 3-Hydroxymethyl Indoles

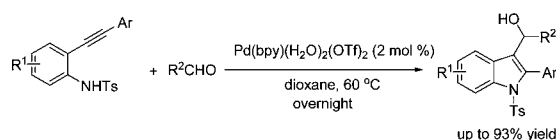
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ABSTRACT



An efficient cationic palladium(II)-catalyzed synthesis of substituted 3-hydroxymethylindoles from readily accessible starting materials is developed. This tandem reaction involves an intramolecular aminopalladation of an alkyne and an addition to the carbonyl group to quench the carbon–palladium bond to complete the catalytic cycle without the necessity of a redox system.

Heterocyclic compounds, particularly indoles, are of interest because they widely occur in nature as partial structures of alkaloids and have unique biological activities.¹ As synthetic procedures, palladium(0)- or palladium(II)-catalyzed heteroannulations are now emerging as a unique, powerful, and versatile synthetic approach toward a variety of structural cores of complex heterocycles.² Among them, Pd(II)-catalyzed annulation reactions of 2-alkenyl- or 2-alkynylaniline derivatives are often used for the synthesis of

substituted indoles.³ From the literature, it can be seen that reactions of 2-alkynylaniline derivatives are more useful because the starting materials can be easily prepared from 2-haloanilines and terminal alkynes by the palladium-catalyzed Sonogashira cross-coupling reaction. Another advantage of utilizing these substrates is that no redox system is required in their annulation reactions (compare eqs 1 and 2).

In addition, tandem reactions cannot occur for alkylpalladium species (the intermediate in eq 1) due to the rapidly occurring β -hydride elimination reaction, but the indolylpalladium species as the intermediate (eq 2) can undergo further tandem reactions such as insertion of carbon–carbon double bonds⁴ or carbon monoxide⁵ to form multiply functionalized indoles. In the latter cases, the only drawback is that a redox

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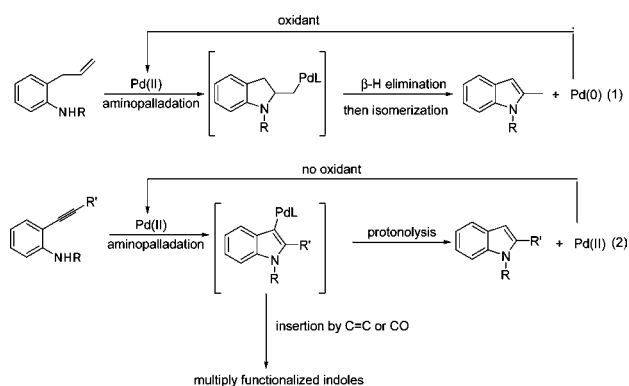
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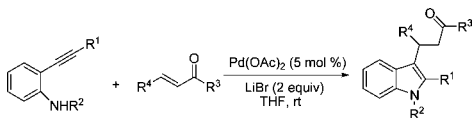
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system is required for the regeneration of the catalytic palladium species.



In our previous work, we reported an efficient method for the synthesis of 2,3-disubstituted indoles with high selectivity from 2-alkynylaniline derivatives and α,β -unsaturated carbonyl compounds under the catalysis of $\text{Pd}(\text{OAc})_2$ in the presence of bromide ion (Scheme 1).^{4d,e} This is a tandem

Scheme 1. Palladium(II)-Catalyzed Tandem Reaction for the Synthesis of Substituted Indoles from 2-Alkynylanilines and α,β -Unsaturated Carbonyl Compounds



reaction involving *trans*-aminopalladation of an alkyne (similar to eq 2), insertion of an enone, and protonolysis of the carbon–palladium bond. The divalent palladium species was regenerated in the protonolysis step to complete the catalytic cycle without the necessity of a redox system. Recently, our group also established some cationic palladium-catalyzed procedures for the addition of carbon–palladium species to carbon–heteroatom multiple bonds.⁶ As compared with the neutral palladium species, such as $\text{Pd}(\text{OAc})_2$ or $\text{PdCl}_2(\text{CH}_3\text{CN})_2$, the cationic palladium(II) species facilitate the addition to carbon–heteroatom multiple bonds due to its vacant coordination sites and harder metal property.⁷ Also, a divalent palladium species was regenerated for the catalytic cycle. As part of our continuing studies on the scope of cationic palladium-catalyzed addition reactions of arylpalladium or vinylpalladium species to carbon–heteroatom multiple bonds,

(6) Cationic Pd(II)-catalyzed addition reactions of arylboronic acids to carbon-heteroatom bonds, see: (a) Liu, G.; Lu, X. *J. Am. Chem. Soc.* **2006**, *128*, 16504. (b) Zhao, B.; Lu, X. *Tetrahedron Lett.* **2006**, *47*, 6765. (c) Zhao, B.; Lu, X. *Org. Lett.* **2006**, *8*, 5987. (d) Dai, H.; Lu, X. *Org. Lett.* **2007**, *9*, 3077. (e) Liu, G.; Lu, X. *Adv. Synth. Catal.* **2007**, *349*, 2247. (f) Lin, S.; Lu, X. *J. Org. Chem.* **2007**, *72*, 9757. (g) Dai, H.; Lu, X. *Adv. Synth. Catal.* **2008**, *350*, 249. (h) Yang, M.; Zhang, X.; Lu, X. *Org. Lett.* **2007**, *9*, 5131. (i) Song, J.; Shen, Q.; Xu, F.; Lu, X. *Org. Lett.* **2007**, *9*, 2947. (j) Yu, X.; Lu, X. *Org. Lett.* **2009**, *11*, 4366. (k) Han, X.; Lu, X. *Org. Lett.* **2010**, *12*, 108.

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we explored a new annulation route for the preparation of substituted 3-hydroxymethyl indoles in one step employing substituted 2-arylethynylanilines and aldehydes as starting materials. In the literature, such compounds are usually synthesized from indoles and aldehydes by a Friedel–Crafts reaction.⁸

The reaction of *N*-tosyl-2-phenylethynylaniline (**1a**) with *p*-nitrobenzaldehyde (**2a**) was first conducted to screen the optimal reaction conditions, and the results are summarized in Table 1. Initially, the catalysts and temperature

Table 1. Optimization of the Reaction Conditions^a

entry	catalyst (mol %)	yield ^b (%)	
		3aa	4aa
1	$\text{Pd}(\text{OAc})_2$ (5)/bpy (5.5)	16	70
2	$\text{Pd}(\text{COOCF}_3)_2$ (5)/bpy (5.5)	trace	10
3	$\text{Pd}(\text{MeCN})_4(\text{BF}_4)_2$ (5)/bpy (5.5)		NR
4	$\text{Pd}(\text{OTf})_2 \cdot 2\text{H}_2\text{O}$ (5)/bpy (5.5)	trace	trace
5	$\text{Pd}(\text{dppp})(\text{H}_2\text{O})_2(\text{OTf})_2$ (2)	trace	88
6	$\text{Pd}(\text{dppp})(\text{H}_2\text{O})_2(\text{BF}_4)_2$ (2)	16	62
7	$\text{Pd}(\text{bpy})(\text{H}_2\text{O})_2(\text{OTf})_2$ (2)	60	30
8	$\text{Pd}(\text{bpy})(\text{H}_2\text{O})_2(\text{BF}_4)_2$ (2)	50	29
9	$[(\text{bpy})\text{Pd}(\mu\text{-OH})_2](\text{OTf})_2$ (2)	42	28
10 ^c	$\text{Pd}(\text{bpy})(\text{H}_2\text{O})_2(\text{OTf})_2$ (2)	21	25
11 ^d	$\text{Pd}(\text{bpy})(\text{H}_2\text{O})_2(\text{OTf})_2$ (2)	46	30
12 ^e	$\text{Pd}(\text{bpy})(\text{H}_2\text{O})_2(\text{OTf})_2$ (2)	75	17

^a **1a** (0.1 mmol), **2a** (0.12 mmol, 1.2 equiv), and the catalyst were stirred in dioxane at 60 °C overnight. ^b Isolated yields. ^c The reaction was carried out at 25 °C for 40 h. ^d The reaction was carried out at 100 °C for 6 h. ^e The amount of **2a** was 2.0 equiv with respect to **1a**.

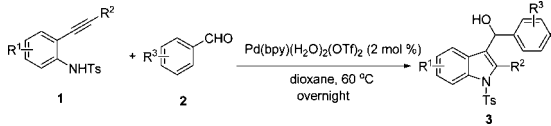
effects on the reaction were examined. It was found that $\text{Pd}(\text{OAc})_2/\text{bpy}$ or some in situ prepared cationic palladium salts/bpy were ineffective to catalyze the reaction, giving product **3aa** in very low yields together with the byproduct **4aa**, which came from protonolysis of the intermediate (Table 1, entries 1–4). Then, some isolated cationic palladium complexes bearing bipyridine or dppp as ligands were used. It was exciting that the catalyst $\text{Pd}(\text{bpy})(\text{H}_2\text{O})_2(\text{OTf})_2$ was the best one to catalyze this tandem aminopalladation–addition reaction in dioxane (60% yield, Table 1, entry 7). However, when the reaction temperature was lowered to 25 °C or raised to 100 °C, the yield of **3aa** was decreased to 21% and 46%, respectively (Table 1, entries 9 and 10). Some other solvents such as toluene, CH_3NO_2 , THF, $\text{ClCH}_2\text{CH}_2\text{Cl}$, and DMSO were also tried, but most of them were ineffective or

(8) For reviews of Friedel–Crafts reactions, see: (a) Olah, G. A. *Friedel–Crafts Chemistry*; Wiley-Interscience: New York, 1973. (b) Roberts, R. M.; Khalaf, A. A. *Friedel–Crafts Alkylation Chemistry. A Century of Discovery*; Marcel Dekker: New York, 1984. (c) Heaney, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 2, p 733. (d) Smith, M. B. *Organic Synthesis*; McGraw-Hill: New York, 1994; p 1313.

produced a lower yield of **3aa**. Finally, the best yield was obtained by increasing the amount of substrate **2a** to 2.0 equiv with respect to **1a** (75% yield, Table 1, entry 12).

Under the optimized reaction conditions as shown in Table 1, entry 12, a series of substituted 2-alkynylanilines and aromatic aldehydes were chosen to test this annulation reaction as shown in Table 2. Aldehydes with strong electron-

Table 2. Tandem Annulation Reaction of 2-Arylethynylanilines with Substituted Benzaldehydes^a



entry	1		2	yield ^b (%)
	R ¹	R ²	R ³	
1	H	Ph (1a)	<i>p</i> -NO ₂ (2a)	75 (3aa)
2	H	Ph (1a)	<i>m</i> -NO ₂ (2b)	63 (3ab)
3	H	Ph (1a)	5-Cl-4-NO ₂ (2c)	93 (3ac)
4 ^c	H	Ph (1a)	<i>p</i> -COCH ₃ (2d)	trace
5 ^d	H	Ph (1a)	<i>p</i> -CN (2e)	trace
6	H	Ph (1a)	H (2f)	complex mixture
7	4-Me	Ph (1b)	<i>p</i> -NO ₂ (2a)	65 (3ba)
8	4-F	Ph (1c)	<i>p</i> -NO ₂ (2a)	64 (3ca)
9	4-Cl	Ph (1d)	<i>p</i> -NO ₂ (2a)	62 (3da)
10	5-Cl	Ph (1e)	<i>p</i> -NO ₂ (2a)	49 (3ea)
11	H	<i>p</i> -MeC ₆ H ₄ (1f)	<i>p</i> -NO ₂ (2a)	78 (3fa)
12	H	<i>p</i> -BrC ₆ H ₄ (1g)	<i>p</i> -NO ₂ (2a)	62 (3ga)
13	H	<i>n</i> -Hexyl (1h)	<i>p</i> -NO ₂ (2a)	trace
14	H	CH ₃ OCH ₂ (1i)	<i>p</i> -NO ₂ (2a)	trace

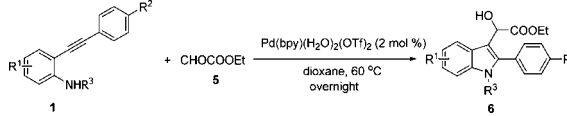
^a A mixture of **1** (0.1 mmol), **2** (0.2 mmol, 2.0 equiv), and the catalyst Pd(bpy)(H₂O)₂(OTf)₂ (2 mol %) was stirred in dioxane at 60 °C overnight. ^b Isolated yields. ^c A 35% yield of **4aa** can be achieved in a complex reaction mixture. ^d Almost no reaction occurred.

withdrawing groups such as a nitro group on the benzene ring and anilines with tosyl group on the nitrogen atom provided good results (Table 2, entries 1–3). If the substituent on the aryl aldehyde was an acetyl or nitrile group, only a trace of the products could be obtained (Table 2, entries 4 and 5). When benzaldehyde was utilized, the reaction became complicated (Table 2, entry 6). This might be due to the change of the electrophilicity of the aldehyde. For anilines **1**, alkynes bearing aryl groups with halo- or methyl substituents all reacted smoothly with *p*-nitrobenzaldehyde to provide the desired products in moderate yields (Table 2, entries 7–12). If the substituent R² was changed from phenyl to *n*-hexyl or methoxymethyl, the reaction became sluggish and only a trace of the products can be obtained (Table 2, entries 13 and 14). No reaction occurred for anilines with other *N*-substituted groups (such as mesyl or trifluoroacetyl). This may be due to the requirement of a strong electron withdrawing group on the nitrogen atom to facilitate the aminopalladation step.

Next, we turned our attention to extend this new palladium-catalyzed annulation reaction by using other active aldehydes such as ethyl glyoxylate. Similarly, it can react

with **1a** successfully to afford the expected product α -hydroxyindolyl acetate (**6**) in the same conditions as shown in Table 2. Then, a series of substituted *N*-tosyl-2-phenylethynylanilines were also tested. With the exception of **1k**, all of them, including **1j**, which has no reactivity with *p*-nitrobenzaldehyde, can react smoothly to provide the corresponding α -hydroxyindolyl acetates **6** in good yields (Table 3). In the literature, such compounds usually can be obtained from the reaction of indoles and ethyl glyoxylate.⁹

Table 3. Annulation Reaction of 2-Arylethynylanilines with Ethyl Glyoxylate^a



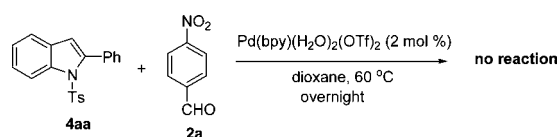
entry	R ¹	R ²	R ³	yield ^b (%)
1	H	H	Ts (1a)	89 (6a)
2	4-Me	H	Ts (1b)	80 (6b)
3	4-F	H	Ts (1c)	81 (6c)
4	4-Cl	H	Ts (1d)	73 (6d)
5	5-Cl	H	Ts (1e)	67 (6e)
6	H	Me	Ts (1f)	83 (6f)
7	H	Br	Ts (1g)	81 (6g)
8	H	H	Ms (1j)	51 (6j)
9	H	H	COCF ₃ (1k)	NR

^a A mixture of **1** (0.1 mmol), **5** (0.2 mmol, 2.0 equiv), and the catalyst Pd(bpy)(H₂O)₂(OTf)₂ (2 mol %) was stirred in dioxane at 60 °C overnight. ^b Isolated yields.

Then some other activated ketones such as ethyl 3,3,3-trifluoropyruvate or ethyl benzoylformate were used to react with substrate **1a**, and it was disappointing that no reaction occurred for these ketones.

Some control experiments were also run to gain further insight into the mechanistic details of this sequential process. Because indoles such as **4aa** can be easily produced in many metal-catalyzed cyclization reactions of 2-alkynylaniline derivatives,^{2,3} and they were also the main byproducts in our reactions, a question arose as to whether products such as **4aa** were formed first in our reactions and they subsequently transferred to products **3** by palladium(II)-catalyzed Friedel–Crafts type reaction.^{9a} To test this hypothesis, **4aa** was employed to react with *p*-nitrobenzaldehyde in the same conditions as Table 2, but no reaction occurred at all (Scheme 2), indicating that our reaction is a new tandem reaction,

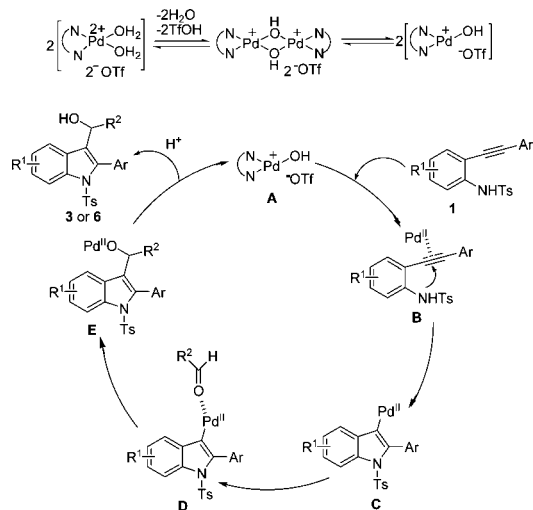
Scheme 2. Reaction of 2-Phenyl-*N*-tosylindole with *p*-Nitrobenzaldehyde



not a one pot, two step process. This may be due to the fact that our reaction can only proceed for the substrates with a tosyl group on the nitrogen atom (Tables 2 and 3) which will decrease the nucleophilicity of C3 in indoles to make the Friedel–Crafts type reaction impossible.

A possible mechanism that accounts for the formation of 3-hydroxymethylindoles **3** or α -hydroxyindolyl acetates **6** is illustrated in Scheme 3. First, the active palladium species

Scheme 3. Proposed Mechanism for the Formation of **3** or **6**



A is formed by dissociation of $\text{Pd}(\text{bpy})(\text{H}_2\text{O})_2(\text{OTf})_2$, followed by an intramolecular aminopalladation on the palladium(II)-coordinated alkyne via intermediate **B** to generate

the intermediate **C**. Then the carbon–palladium bond in **C** adds to the carbonyl group of aldehydes to produce palladium alkoxide intermediate **E**, and finally, the product **3** or **6** is formed by protonolysis of **E** with regeneration of the palladium species to make the catalytic cycle possible.

In summary, we have disclosed a novel synthesis of multiply substituted 3-hydroxymethyl indoles under the catalysis of cationic palladium(II) complex $\text{Pd}(\text{bpy})(\text{H}_2\text{O})_2(\text{OTf})_2$, which is the first example of a tandem reaction initiated by an aminopalladation of an alkyne and an addition to the carbonyl group as the quenching step of the carbon–palladium bond. This will regenerate the Pd(II) species without the necessity of a redox system. This tandem reaction provided an efficient way for the construction of functionalized indoles in one step and only Pd(II) was used in the catalytic cycle. This strategy may find further applications in the future for rapidly constructing other useful heterocycles.

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Supporting Information Available: Experimental procedures, characterization data, and copies of NMR spectra of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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